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Medicinrådet

Application for the assessment of inclisiran (Leqvio®) for adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

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1. Basic information

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Overview of the pharmaceutical	
Proprietary name	Leqvio®
Generic name	inclisiran
Marketing authorization holder in Denmark	Novartis Europharm Limited Vista Building Elm Park, Merrion Road Dublin 4 Ireland
ATC code	C10AX16
Pharmacotherapeutic group	Cardiovascular System. Lipid modifying agents.
Active substance(s)	inclisiran
Pharmaceutical form(s)	Solution for injection (injection).
Mechanism of action	The active substance of Leqvio® is inclisiran, a lipid-modifying agent (ATC code: C10AX16). Inclisiran is a small interfering RNA (siRNA). It reduces the intrahepatic PCSK9 enzyme and increases recycling of LDL-C receptor and its expression on the hepatocyte cell surface, thereby increasing LDL-C uptake and lowering LDL-C levels in the circulation.
Dosage regimen	The recommended dosage of inclisiran is 284 mg administered as a single subcutaneous injection initially, again at 3 months and then every 6 months.

Overview of the pharmaceutical	
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Leqvio® 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.
Other approved therapeutic indications	None
Will dispensing be restricted to hospitals?	Prescription status is NBS (card, endo, neuro).
Combination therapy and/or co-medication	Statins or other lipid-lowering therapies as described in the indication for Leqvio®.
Packaging – types, sizes/number of units, and concentrations	Leqvio® 284 mg solution for injection in prefilled pen. 1x1.5 ml. This medicinal product does not require any special storage conditions. Do not freeze.
Orphan drug designation	No

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2. Abbreviations

ACC	American College of Cardiology
AE	Adverse event
apoB	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular disease
CHD	Coronary heart disease
CM	Cost minimization
CrI	Credible interval
CSR	Clinical study report
CV	Cardiovascular
DMC	Danish Medicines Council
FE	Fixed effects
FH	Familial hypercholesterolemia
GalNAc	N-acetyl galactosamine
HeFH	Heterozygous familial hypercholesterolemia
HoFH	Homozygous familial hypercholesterolemia
HSUV	Health state utility values
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LLT	Lipid lowering therapy
MACE	Major adverse cardiovascular events
MD	Mean difference
MI	Myocardial infarction
MTD	Maximally tolerated dose
NMA	Network meta-analysis
OR	Odds ratio
PAD	Peripheral artery disease
PCSK9	Proprotein convertase subtilisin/kexin type 9
PICO	Population, intervention, comparator, outcomes
PSA	Probabilistic sensitivity analysis
Q2W	Once every 2 weeks
RADS	Rådet for Anvendelse af Dyr Sygehusmedicin
RE	Random effects
SC	Subcutaneously
siRNA	Small interfering ribonucleic acid
SmPC	Summary of Product Characteristics

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4. Summary

Indication and population covered in this application

Inclisiran is indicated in adults with primary hypercholesterolemia (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.

Elevated LDL-C is a major risk factor for the development of cardiovascular disease [1]. Elevated LDL-C levels promote the formation of atherosclerotic plaques and when the plaque ruptures, it can cause occlusion of the arteries leading to ischaemic events that are characteristic of ASCVD. Total atherosclerotic plaque burden can be approximated by both the concentration of LDL-C (and other apoB-containing lipoproteins) and the duration of exposure [2].

Cardiovascular disease is the most common cause of death globally and second most common in Denmark with 12,048 deaths in 2018 alone [3]. The patient group is very resource consuming and is in frequent contact with both primary and specialist care and the health economic disease burden for cardiovascular diseases is substantial. There is thus an unmet need for optimizing treatment of LDL-C levels (e.g. through less frequent administration) which may lead to better adherence and control and thereby prevent cardiovascular diseases.

The total costs in relation to hospitalisation for cardiovascular disease amounted to almost 5.3 billion DKK in 2017 [4], the yearly cost of treatment and care in relation to atherosclerosis is estimated to 1.76 billion DKK [5] and the yearly loss of productivity due to atherosclerosis is estimated to 1.87 billion DKK [5].

It is estimated that 2 million 20-70 year old Danes have hypercholesterolemia (LDL >3 mmol/L) and in 2017 646.000 Danes were in treatment with lipid lowering treatment [6]. Statins are first choice in the pharmacologic treatment of hypercholesterolaemia, and if the target LDL-C is not reached with the maximal tolerated dose of statins, ezetimibe may be added. In cases where patients experience intolerance to statins the guideline recommends dose reductions and/or change to another statin (2-3 statins). Patients who do not achieve the target LDL-C with a statin with or without ezetimibe, or who are intolerant to statin may be referred to cardiologic hospital lipid clinics, where they are evaluated for eligibility for treatment with PCSK9 inhibitors.

Inclisiran is expected to be used if statin and other lipid lowering is not enough - as for the PCSK9 inhibitors alirocumab and evolocumab. Thus the size of the patient population eligible for inclisiran is expected to be in line with the estimated population for the PCSK9 inhibitors, i.e. 2499 patients in 2021 increasing to 6937 patients in 2025.

The intervention

Inclisiran is a small interfering RNA (siRNA). It reduces the intrahepatic PCSK9 enzyme which increases recycling of LDL-C receptor and its expression on the hepatocyte cell surface, thereby increasing LDL-C uptake and lowering LDL-C levels in the circulation [7].

RNAi medicines are special in the sence that they target a specific gene and can down-regulate it, or turn it off, in a way that is reversible and adjustable, by using an already existing process in the body. Inclisiran is conjugated with triantennary N-acetyl galactosamine (GalNAc) to facilitate uptake specifically by hepatocytes [7, 8]. Due to the GalNAc conjugation, inclisiran uptake is specific to the liver. Based on computational searches against the human transcriptome and subsequent analysis in liver cells there is a low likelihood of off-target binding of inclisiran [9].

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In the liver cells, inclisiran is internalized in the hepatocytes by endocytosis, with plasma concentrations of inclisiran declining within 24 hours reaching undetectable levels within 48 hours [7, 8, 10, 11]. The endosomes slowly release inclisiran into the cytoplasm, where the guide strand of inclisiran remains stable for weeks, contributing to its duration of action, however it is progressively diluted with every cell division [12]. Inclisiran is primarily metabolized by nucleases, it undergoes slow exonuclease degradation to shorter nucleotides of varying length or are excreted renally [7]. In general mimicking the body's process of RNA interference should not impact the cell's DNA, as RNA interference in human cells is restricted to the cytoplasm, i.e. the target mRNA is subject to degradation in the cytoplasm and not in the nucleus [13].

The recommended dose is 284 mg inclisiran administered as a single subcutaneous injection initially, again at 3 months, and then followed by every 6 months. Inclisiran is intended for administration by a healthcare professional. A benefit of clinical significance with inclisiran compared to PCSK9 inhibitors is the infrequent dosing intervals. Twice yearly injections administered by a health care professional have the potential to reduce resource usage in the hospitals and to optimize treatment adherence, thereby enabling better control of LDL-C levels over a considerable period of time. The twice yearly administration by a health care professional could be an advantage for patients who either cannot or are not willing to frequent self-injections.
The administrative burden for the lipid clinics related to the distribution of PCSK9 inhibitors to patients for home administration is substantial. In addition, the PCSK9 inhibitors must be stored at 2 °C to 8 °C , (alirocumab may be kept at less than 25 °C for up to 30 days), whereas inclisiran does not require any special storage conditions, except that it must not be frozen [7, 14, 15].

A pooled analysis of ORION-9, -10 and -11 across the different patient populations showed that the placebo-corrected change in LDL-C with inclisiran at day 510 was -50.7% (95% confidence interval: -52.9% to -48.4%; p <0.0001) [16].

It is worth noticing the safety profile of inclisiran, with "injection site reaction" registered as the only adverse event in the approved SmPC [7]. As of October 20, 2020, a total of 5107 patients had 5701.8 patient years of inclisiran exposure in clinical trials. Currently approximately 1250 patients have been treated in clinical studies with 8 injections or more, equivalent to 3 years and 9 months (data on file).

Comparators
Inclisiran is a treatment alternative to PCSK9 inhibitors (alirocumab (Praluent®) or evolocumab (Repatha®)). Both PCSK9 inhibitors and inclisiran are 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.

Inclisiran as well as the PCSK9 inhibitors all target PCSK9 in their mode of action, and have also shown similar efficacy on LDL-C reduction [7, 14, 15].

The PCSK9 inhibitors have been evaluated by the Danish Medicines Council, based on the following dosing:

- Praluent (alirocumab) 150 mg subcutaneously (SC) biweekly
- Repatha (evolocumab) 140 mg SC biweekly

Evolocumab is currently recommended as first choice for 80% of patients [17].

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Efficacy Outcomes

The efficacy comparisons between inclisiran and the PCSK9 inhibitors are based on percentage and absolute change in LDL-C from baseline to week 24. Percentage change in LDL-C was the primary endpoint in all included studies except for the outcomes studies ODYSSEY OUTCOMES [18] and FOURIER [19].

Lowering of LDL-C is broadly accepted as a valid surrogate endpoint for effect on cardiovascular events [20] and was considered a valid surrogate endpoint for PSCK9 inhibitors before results from the cardiovascular outcomes studies were available [21]. Thus, during the time gap between the publication of the cardiovascular outcomes trials for evolocumab [19] and alirocumab [[18], the two PSCK9 inhibitors were considered to be equally effective by RADS, based on comparable LDL-C lowering efficacy. The Medicines Council has also extrapolated outcome results to sub-populations, such as HeFH patients, that were not included in the the PCSK9 inhibitor outcomes studies (ODYSSEY OUTCOMES and FOURIER) by applying the same rationale of similar LDL-C lowering efficacy [22]. In line with the Medicines Council's approach, the percentage change in LDL-C therefore seems to be the most appropriate efficacy endpoint, until cardiovascular outcomes data is available from the 5-year ORION-4, an ongoing long term cardiovascular outcomes trial with inclisiran including 15,000 patients [23].

Method of analyses

In the absence of head-to-head trials versus the PCSK9 inhibitors, Novartis conducted a Bayesian NMA comparing the relative efficacy of the treatments. The NMA was made by Evidera, and subsequently submitted to NICE in the UK. The use of the NMA in relation to this application was discussed at the dialogue meeting with the Medicines Council before submitting this application. The NMA was provided to the secretariat by Novartis in due time prior to the meeting, and there were no objections to this approach raised at the meeting.

Although the primary efficacy endpoints in all ORION trials were percent change in LDL-C at day 510 and time-adjusted change in LDL-C, these longer duration timepoints, and specifically time-adjusted analyses, were not available from any of the comparator studies. The most commonly reported timepoint across comparator PCSK9 inhibitor studies was 24 weeks, and in some cases for evolocumab, only 12week results were available. Therefore, in order to maximize the available comparator evidence, 24 weeks was selected as the main timepoint of interest for the NMA analyses. This ensured that up-titration of alirocumab, which occurred at week 12, was complete prior to outcome assessment. This was felt to be a conservative approach with respect to the results of the comparator studies, which, like the ORION trials, tended to show the most favourable results at 24 weeks.

Efficacy results

For all populations studied - HeFH on MTD statin, ASCVD and risk equivalent populations on MTD statin, and ASCVD and risk equivalent intolerant to statin - inclisiran demonstrated a statistically significant benefit over placebo in terms of reduction in LDL-C. The findings from the NMA suggest that inclisiran provides outcomes that are expected to be comparable to alirocumab and evolocumab across various hypercholesteremia patient populations.

A pooled analysis of ORION-9, -10 and -11 across the different patient populations showed that the placebo-corrected change in LDL-C with inclisiran at day 510 was -50.7% (95% confidence interval: -52.9% to -48.4%; p <0.0001). The Mean absolute change in LDL-C from baseline to day 510 was -1.43 mmol/L (95% confidence interval: -2.00 to -1.36; p <0.0001) [16].

It is not possible in published literature to define the minimum reduction in LDL-C that gives a clinical significant change on cardiovascular outcomes. There are several factors besides LDL lowering that influence the total risk of cardiovascular outcomes. Besides that, the population is a heterogenic group with different risk factors, baseline LDL-C and LDL-C targets [24]. For instance for secondary prevention the high risk groups should according to guidelines

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aim for a 50% decrease of LDL-C [20]. In primary prevention even smaller changes in LDL-C might be clinically significant, if the time with the LDL-C reduction and treatment is long enough, as both the concentration of LDL-C as well as time of exposure are defining the total plaque burden [2].

Safety of inclisiran

The following safety outcomes were compared: Withdrawal for any reason, withdrawal due to adverse events, AE and SAEs. There were no statistical difference between inclisiran and comparators for any of the safety outcomes which indicates similar safety profiles. Though, based on the SmPCs, inclisiran seems to have a more favourable safety profile compared to PCSK9 inhibitors, with injection site reactions as the only adverse drug reaction [7].

As of October 20, 2020, a total of 5107 patients had 5701.8 patient years of inclisiran exposure in clinical trials. Currently approximately 1250 patients have been treated in clinical studies with 8 injections or more, equivalent to 3 years and 9 months (data on file). Longer term data are, however, still limited. Currently the follow-up studies ORION-3 and ORION-8 are ongoing in addition to the cardiovascular outcomes trial, ORION-4, which includes approximately 15.000 patients who will be treated for a median length of 5 years [23].

PCSK9 inhibitors are self-administered by the patient or a caregiver every two weeks. In contrast, inclisiran is administered as a single subcutaneous injection initially, again at 3 months and then every 6 months by a health care professional. Twice yearly injections administered by a health care professional have the potential to optimize treatment adherence, thereby enabling better control of LDL-C levels over a considerable period of time. The twice yearly administration by a health care professional could also be an advantage for patients who either cannot or are not willing to frequent self-injections.

Cardiovascular outcomes

Similar to the development program for the PCSK9 inhibitors, the pivotal studies ORION-9, ORION-10 and ORION-11 studies were not powered to investigate the effect of Inclisiran on overall major adverse cardiovascular events (MACE). The cardiovascular outcomes study, ORION-4, is expected to have results in 2025 [23].

Cardiovascular outcomes of inclisiran have been explored in a meta-analysis which included the three inclisiran studies ORION-9, ORION-10 and ORION-11. Rate of MACE was a co-primary endpoint and was defined as a composite of cardiac death, any signs or symptoms of cardiac arrest, nonfatal MI and stroke. Inclisiran decreased the MACE rate by 24% (RR = 0.76; 95% CI, 0.61 to 0.94, p = 0.01) compared with placebo. The meta-analysis suggests inclisiran is associated with a statistically significant reduction in MACE rate which is in alignment with the acknowledged correlation between LDL-C reduction and mortality and morbidity outcomes [20]. However the studies were not designed to address the question on cardiovascular outcome, the analysis was not predefined and is based on reported AEs from publications [25]. Confirmation by the ORION-4 study is required.

Relevance to the Danish context

The populations included in the clinical studies in this application were generally comparable with the Danish patients for whom inclisiran is indicated. This applies both to the HeFH and the ASCVD and risk equivalent populations when it comes to age, atherosclerotic cardiovascular disease, use of MTD or high dose statin (except by those intolerant to statin), and baseline LDL-C. The only exception is that the use of ezetimibe was generally lower than what would be expected in Danish patients eligible for treatment with inclisiran. However, subgroup data for percent change in LDL-C presented by two of the included trials did not suggest background/baseline ezetimibe use to be a treatment-effect modifier (see Table 8), and the results of the clinical studies are thus considered relevant in a Danish context.

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Structure and results of the health economic analysis

As no significant differences in efficacy and safety between inclisiran and the relevant comparators (alirocumab and evolocumab) were demonstrated, a simple cost-minimization (CM) analysis was agreed with the Medicines Council during the dialogue meeting and thus conducted. The model was developed in Microsoft Excel 365 as a simple cohort model. Weekly model cycles have been used to align with the posology of the treatment regimens. The model reflects the treatment course of the interventions and estimates the costs associated with each intervention and the associated incremental costs. No efficacy parameters were included in the model with the objective of model parsimony. The model considered costs associated with drug acquisition, administration, and monitoring of the treatment, i.e., drug costs, administration costs, monitoring cost and patient costs. A 10-year time horizon was applied in the base-case in line the health economic analysis conducted by the Medicines Council for the treatment guideline for PCSK9 inhibitors in Denmark.

At AIP-level, inclisiran is associated with savings when compared to alirocumab (DKK -63.128,22) and evolocumab (DKK -53.722,66). The savings of inclisiran at AIP-level are the results of a lower drug cost and a lower patient cost and transportation cost over the time horizon. No differences in hospital cost between the interventions included in the model are expected. The results were sensitive to change in the time horizon. This is explained by the posology of inclisiran, where 3 administrations are required during the first year, and 2 administrations are required in the subsequent years. Consequently, higher drug cost for inclisiran are accrued in the first year, compared to the PCSK9 inhibitors.

The budget impact analysis at AIP-level indicated that a recommendation of inclisiran for the full eligible population would result in savings of DKK 1.673.657 in year 5 compared to the scenario, where inclisiran is not recommended.

Potential RWE project with the Phase IV Unit in Bispbebjerg Hospital

A collaboration with Phase 4 CPH is considered to be initiated, if inclisiran is recommended for usage by the Danish Medicines Council. The purpose is an assessment of patients treated with inclisiran in clinical practice.
The objective will be to describe the demographics and clinical characteristics of inclisiran patients and assess the effect on LDL-reduction in clinical practice stratified by ASCVD, ASCVD risk equivalent and FH patients over a 5-year time (evaluated every year). The study will be descriptive, non-interventional, retrospective cohort study using secondary data from the health care registries in Denmark from 4th quarter of 2021 to 4th quarter of December 2026.

Conclusion

Findings from the NMA show that the addition of inclisiran to current standard of care for patients with HeFH and ASCVD results in statistically significant and clinically meaningful improvements in LDL-C and comparable tolerability. In addition, the findings suggest that inclisiran provides outcomes that are expected to be comparable to alirocumab and evolocumab across various hypercholesteremia patient populations.

A high degree of disease control for high risk patients is possible due to inclisiran's proven and sustained LDL-C reduction over the course of the extended dosing interval. With a favorable safety profile and as an injection administered by healthcare professionals only twice yearly in the maintenance phase, it has the potential to reduce resource spending and remove the adherence challenges that may be encountered with self-administered treatments and thus on the long term potentially result in better cardiovascular disease disease control.

At AIP-level, inclisiran is associated with savings when compared to alirocumab (DKK -63.128,22) and evolocumab (DKK -53.722,66). The budget impact analysis at AIP-level indicated that a recommendation of inclisiran for the full eligible population would result in savings of DKK 1.673.657 in year 5 compared to the scenario, where inclisiran is not recommended.

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5. The patient population, the intervention and choice of comparators

5.1 The medical condition and patient population

Hyperlipidaemia is a heterogeneous group of disorders characterized by an excess of lipids (i.e. cholesterol, phospholipids, triglycerides) in the bloodstream. Hypercholesterolemia, a type of hyperlipidaemia, specifically refers to the presence of high levels of cholesterol, including LDL-C. Mixed dyslipidaemia is defined as elevated LDL-C, triglycerides, and/or high-density lipoprotein-cholesterol.

Hypercholesterolemia can be divided into two groups; familial hypercholesterolemia (FH) which has an underlying genetic cause, and non-familial hypercholesterolemia which does not have a clear genetic aetiology. FH is a dominant genetic disorder that causes high levels of LDL-C in the blood and is characterized by premature cardiovascular disease [26]. It is caused by mutations in genes encoding proteins which regulate LDL receptor-mediated clearance of LDL-C, including its receptor (LDLR), apolipoprotein B (Apo B) and proprotein convertase subtilisin/kexin type 9 (PCSK9) [27]. There are two clinical manifestations depending on the presence of one or two affected alleles in these genes. The milder heterozygous form (heterozygous familial hypercholesterolemia, HeFH) results from a single affected allele. The more severe homozygous form (homozygous familial hypercholesterolemia, HoFH) results from biallelic pathogenic variants in one of these genes, or one pathogenic variant in each of two different genes [27].

Patients with non-familial hypercholesterolemia have elevated LDL-C levels related to factors such as diet, smoking and physical inactivity, as well as disorders like diabetes, chronic kidney disease and elevated blood pressure.

Elevated LDL-C is a major risk factor for the development of cardiovascular disease [1]. Regardless of genetic aetiology, hypercholesterolemia patients have higher risk of ASCVD events, such as myocardial infarction (MI), ischaemic stroke and peripheral artery disease (PAD), and patients with a prior ASCVD event have increased risk of recurrent events. Elevated LDL-C levels promote the formation of atherosclerotic plaques, and when the plaque ruptures they can cause occlusion of the arteries leading to ischaemic events that are characteristic of ASCVD. Total atherosclerotic plaque burden can be approximated by both the concentration of LDL-C (and other apoB-containing lipoproteins) and the duration of exposure [2].

ASCVD is the leading cause of cardiovascular morbidity and mortality [28]. The cumulative exposure to LDL-C is causal to ASCVD, hence lowering LDL-C may halt the progression of the atherosclerotic plaque and reduce the incidence of ASCVD [2]. The correlation between LDL-C and ASCVD risk has been demonstrated in numerous randomized controlled trials, as well as in several meta-analyses [29, 30]. Overall, greater absolute LDL-C reduction leads to greater cardiovascular risk reduction, and a recent meta-analysis of 28 statin trials reported a 21% reduction in major vascular events per 1.0 mmol/L reduction in LDL cholesterol, as shown in Figure 1 [31].

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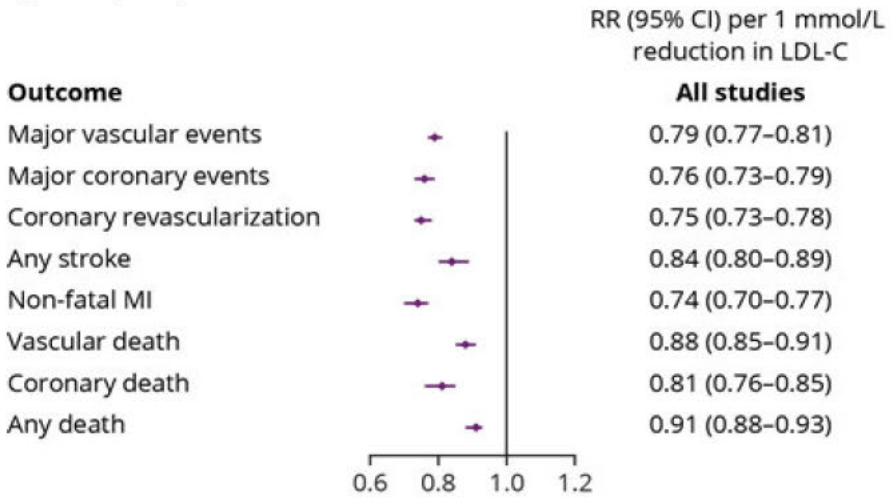
Figure 1 Effects on major CV-events per 1.0 mmol/L reduction in LDL-C at different levels of risk estimated from meta-analyses. Figure adapted by Novartis.



Based on extensive evidence generation over the last decades, the recently updated European dyslipidaemia guidelines stated that:

> *"... there is no longer an 'LDL-C hypothesis', but established facts that increased LDL-C values are causally related to ASCVD, and that lowering LDL particles and other ApoB-containing lipoproteins as much as possible reduces CV events"* [20].

It is estimated that 2 million 20-70 year old Danes have hypercholesterolemia (LDL >3 mmol/L) and in 2017 646.000 Danes were in treatment with lipid lowering treatment [6].

Cardiovascular disease is the most common cause of death globally and second most common in Denmark with 12,048 deaths in 2018 alone [3]. The patient group is very resource consuming and is in frequent contact with both primary and specialist care and the health economic disease burden for cardiovascular diseases is substantial. The total costs in relation to hospitalisation for cardiovascular disease amounted to almost 5.3 billion DKK in 2017 [4], the yearly cost of treatment and care in relation to atherosclerosis is estimated to 1.76 billion DKK [5] and the yearly loss of productivity due to atherosclerosis is estimated to 1.87 billion DKK [5].

The below paragraphs aim to summarize the incidence and prevalence of ASCVD and HeFH in Denmark, as shown in Table 1. The numbers for the ASCVD population include the following total numbers from Hjertetal.dk: ischemic heart disease (AMI and angina pectoris), ischaemic stroke, PAD regardless of their LDL levels. Many patients have multiple manifestations of ASCVD, so overlap may be expected.

Table 1 ASCVD: Incidence and prevalence in the past 5 years

Year	2016	2017	2018	2019	2020
Incidence in Denmark	41.140	40.523	38.639	37.500[1]	36.750[1]
Prevalence in Denmark	314.888	316.906	318.305	320.000[1]	321.500[1]

[1]Numbers for 2019 and 2020 are estimated based on the numbers from 2016-2018

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It is expected that 80% of HeFH patients have had a cardiovascular event and would for that reason be reflected in the table for ASCVD patients. A specialist estimate concludes that 2.500 HeFH patients are identified as of today out of a total group of 25,000 HeFH patients [32].

It is assumed that 60% of the ASCVD population are men, 17% have diabetes and the average age is 60 years for ASCVD patients, 50 years for secondary HeFH and 35 years for primary HeFH [32].

The expected number of patients eligible for the new treatment during the next 5 years is shown in Table 2 below [32]:

Table 2 Estimated number of patients eligible for treatment

Year	2021	2022	2023	2024	2025
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	2.499	3.543	4.631	5.761	6.937

Estimates on number of patients on inclisiran are provided in the health economic part of this application.

5.2 Patient populations relevant for this application

The patient populations relevant for this application are:

- Patients with HeFH with hypercholesterolemia, not adequately controlled with statins and/or other lipid lowering therapies.
- Patients with ASCVD and risk equivalent with hypercholesterolemia, not adequately controlled with statins and/or other lipid lowering therapies.

An important part of this application is built on the NMA used for the submission to NICE in the UK. In this NMA the two above mentioned patient populations were split into two subgroups: patients on MTD statin and patients who are statin intolerant. This distinction will thus also be made in this application.

For the health economic part of this application, relevant patients are patients from the two populations described above who are in scope for treatment with PCSK9 inhibitors in Denmark, according to the treatment guideline for PCSK9 inhibitors by the Medicines Council [17], see below.

5.3 Current treatment options and choice of comparators

5.3.1 Current treatment options

Danish patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia are treated according to the treatment guideline for dyslipidaemia from the Danish Society of Cardiology [33]. The treatment involves a stepwise approach starting with changes in lifestyle, including diet, weight control, physical exercise, smoking cessation and alcohol intake.

Statins are first choice in the pharmacologic treatment of hypercholesterolaemia, and if the target LDL-C is not reached with the maximal tolerated dose of statins, ezetimibe may be added. In cases where patients experience intolerance to statins the guideline recommends dose reductions and/or change to another statin (2-3 statins).

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Patients who do not achieve the target LDL-C with a statin with or without ezetimibe, or who are intolerant to statin may be referred to cardiologic hospital lipid clinics, where they are evaluated for eligibility for treatment with PCSK9 inhibitors.

The criteria for starting treatment with PCSK9 inhibitors are described in the treatment recommendation from the Medicines Council for PCSK9 inhibitors for hyperlipidaemia, February 2021 [17], as outlined in Table 3 and Table 4.

Table 3 Criteria for treatment with PCSK9 inhibitors for patients with FH

Consider starting treatment with a PCSK9 inhibitor for patients with FH, who despite maximally tolerated* lipid lowering treatment still have a LDL-C level of:		
FH – primary prophylaxis		FH. Secondary prophylaxis
LDL-C > 4 mmol/L	LDL-C > 3.5 mmol/L	≥ 2.6 mmol/L
< 2 risk factors	≥ 2 of the following risk factors: • Family disposition: Cardiovascular disease in a 1st degree relative < 60 years for women and < 55 years for men • Male gender • Smoker • Hypertension • Diabetes (type 1 and 2) • Lp(a) > 50 mg/L • HDL <1.0 for men, 1.2 for women • < 50% LDL-reduction on ordinary treatment	Manifest cardiovascular disease** or diabetes with microvascular complications

*Maximally tolerated dose meaning that the patient as a minimum has tried high dose statin in combination with ezetimibe (unless there are contraindications or adverse reactions). In patients who are near the treatment goal (missing by 10-15% LDL reduction), it can be considered to add one anion exchanger, before starting a PCSK9 inhibitor.

** previous myocardial infarction, angina pectoris, peripheral arterial disease, stroke or TCI due to arteriosclerosis.

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Table 4 Criteria for treatment with PCSK9 inhibitors for patients without FH, who are in high risk of cardiovascular events

Consider starting treatment with a PCSK9 inhibitor for patients who despite maximally tolerated* lipid lowering treatment still have a LDL-C level of:		
Speciality	LDL-C ≥ 2.6 mmol/L	LDL-C > 3.0 mmol/L
Cardiology/Vascular Surgery	• Acute coronary syndrome < 1 year • Previous acute myocardial infarction and ≥ 1 risk factor** • Peripheral artery disease (PAD) (amputation, revascularized, or claudicatio AND ankle-brachial index (ABI) < 0.85) and ≥ 1 risk factor	• Previous myocardial infarction without other risk factors • Peripheral artery disease (PAD) (amputation, revascularized, or claudicatio AND ankle-brachial index (ABI) < 0.85) without other risk factors • Stabil angina pectoris***
Endocrinology		• Diabetes mellitus with micro-/macro-albuminuria
Neurology	• Iscaemic stroke/transistoric cerebral iscaemia (TCI) due to artherosclerosis***	• Non-cardioembolic ischaemic stroke/TCI and ≥ 1 risk factor** and/or stenoses in the pre- or intracerebral vessels
*Maximally tolerated dose meaning that the patient as a minimum has tried high dose statin in combination with ezetimibe (unless there are contraindications or adverse reactions). In patients who are near the treatment goal (missing by 10-15% LDL reduction), it can be considered to add one anion exchanger, before starting a PCSK9 inhibitor., **Diabetes mellitus, active smoking, poly-vascular disease, > 1 AMI, age > 65 years *** Relevant pre-cerebellar stenoses in the carotids or intra-cranially identified by ultrasound, CT-angio or MR-angio scan, **** Defined as positive ischemia test, coronary ateriographia with significant stenoses or coronary revascularization.		

5.3.2 Choice of comparators

Inclisiran is a treatment alternative to PCSK9 inhibitors (alirocumab (Praluent®) or evolocumab (Repatha®)). Both PCSK9 inhibitors and inclisiran are 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.

Inclisiran as well as the PCSK9 inhibitors all target PCSK9 in their mode of action, and have also shown similar efficacy on LDL reduction [7, 14, 15].

The PCSK9 inhibitors have been evaluated by the Danish Medicines Council, based on the following dosing:

- Praluent (alirocumab) 150 mg SC biweekly
- Repatha (evolocumab) 140 mg SC biweekly

Evolocumab is currently recommended as first choice for 80% of patients [17].

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5.3.3 Description of the comparators

The two comparators, alirocumab and evolocumab are described in Table 5 below.

Table 5 Description of comparators [14, 15, 17]

	Praluent	Repatha
Generic name (ATC-code)	Alirocumab (C10AX14)	Evolocumab (C10AX13)
Mode of action	Alirocumab is a fully human IgG1 monoclonal antibody that binds with high affinity and specificity to proprotein convertase subtilisin kexin type 9 (PCSK9). PCSK9 binds to the low-density lipoprotein receptors (LDLR) on the surface of hepatocytes to promote LDLR degradation within the liver. LDLR is the primary receptor that clears circulating LDL, therefore the decrease in LDLR levels by PCSK9 results in higher blood levels of LDL-C. By inhibiting the binding of PCSK9 to LDLR, alirocumab increases the number of LDLRs available to clear LDL, thereby lowering LDL-C levels.	Evolocumab binds selectively to PCSK9 and prevents circulating PCSK9 from binding to the low density lipoprotein receptor (LDLR) on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation. Increasing liver LDLR levels results in associated reductions in serum LDL-cholesterol (LDL-C).
Pharmaceutical form	Solution for injection (injection)	Solution for injection (injection)
Method of administration	Subcutaneous use (sc.)	Subcutaneous use
Dosing	75 mg sc. once every 2 weeks, or 150 mg sc. once every 2 weeks, or 300 mg sc. once every 4 weeks (monthly).	140 mg sc. every two weeks, or 420 mg sc. once monthly.
Should the pharmaceutical be administered with other medicines?	Alirocumab is to be administered 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.	Evolocumab it to be administered 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.

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Treatment duration/criteria for end of treatment	Treatment duration is life-long. According to the treatment recommendation by the Danish Medicines Council for PCSK9 inhibitors the treatment should be stopped in case of: • Lack of effect on LDL-C • Development of severe renal or hepatic disease • Other serious adverse events or for the patient unacceptable adverse events • The treatment should also be discontinued in the event of terminal illness and / or expected short remaining life.	
Necessary monitoring, both during administration and during the treatment period	According to the treatment recommendation by the Danish Medicines Council for PCSK9 inhibitors the following monitoring is required: The patient should be followed up one month after the first injection with following actions: • Inspection of injection site • Patients are asked about injection site reactions and any other adverse events. • Patients are asked specifically if they had any symptoms from muscle and joints, neurocognitive symptoms, cold and influenza. • Control of lipids (total, LDL, HDL-C and triglycerides), liver and renal parameters and hemoglobin A1c (HbA1c). If unproblematic, patients should be seen every 6 months. After 1-2 years the interval between controls may be changed to once yearly. Same procedure at all controls.	
Need for diagnostics or other tests (i.e. companion diagnostics)	Measurement of LDL-C	Measurement of LDL-C
Packaging	Praluent 75 mg solution for injection in prefilled pen, 2 pens Praluent 75 mg solution for injection in prefilled pen, 6 pens Praluent 150 mg solution for injection in prefilled pen, 2 pens Praluent 150 mg solution for injection in prefilled pen, 6 pens	Repatha 140 mg solution for injection in prefilled pen, 1 pen Repatha 140 mg solution for injection in prefilled pen, 2 pens Repatha 140 mg solution for injection in prefilled pen, 6 pens

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5.4 The intervention

Inclisiran is a small interfering RNA (siRNA). It reduces the intrahepatic PCSK9 enzyme which increases recycling of LDL-C receptor and its expression on the hepatocyte cell surface, thereby increasing LDL-C uptake and lowering LDL-C levels in the circulation [7].

RNAi medicines are special in the sence that they target a specific gene and can down-regulate it, or turn it off, in a way that is reversible and adjustable, by using an already existing process in the body. Inclisiran is conjugated with triantennary GalNAc to facilitate uptake specifically by hepatocytes [7, 8]. Due to the GalNAc conjugation, inclisiran uptake is specific to the liver. Based on computational searches against the human transcriptome and subsequent analysis in liver cells there is a low likelihood of off-target binding of inclisiran [9].

In the liver cells, inclisiran is internalized in the hepatocytes by endocytosis, with plasma concentrations of inclisiran declining within 24 hours reaching undetectable levels within 48 hours [7, 8, 10, 11]. The endosomes slowly release inclisiran into the cytoplasm, where the guide strand of inclisiran remains stable for weeks, contributing to its duration of action, however it is progressively diluted with every cell division [12]. Inclisiran is primarily metabolized by nucleases, it undergoes slow exonuclease degradation to shorter nucleotides of varying length or are excreted renally [7]. In general mimicking the body's process of RNA interference should not impact the cell's DNA as RNA interference in human cells is restricted to the cytoplasm, i.e. the target mRNA is subject to degradation in the cytoplasm and not in the nucleus [13].

Inclisiran is as previously mentioned indicated in adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

The recommended dose is 284 mg inclisiran administered as a single subcutaneous injection initially, again at 3 months, and then followed every 6 months. Inclisiran is intended for administration by a healthcare professional. Treatment with inclisiran is potentially life-long, with criteria for treatment discontinuation expected to be the same as for the PCSK9 inhibitors according to the Medicines Council [17] (see Table 5 above).

Monitoring of the treatment can take place during the visit where the administration of inclisiran takes place.

It is worth noticing the safety profile of inclisiran, with "injection site reaction" registered as the only adverse event in the approved SmPC [7].

Inclisiran is expected to be used if statin and other lipid lowering is not enough - as for the PCSK9 inhibitors alirocumab and evolocumab. These are usually administered every 2 weeks by subcutaneous injection by the patient or a care giver, and monitored at the hospital clinic after one month and then every 6 months the first 1-2 years, and, if unproblematic, yearly thereafter.

A benefit of clinical significance with inclisiran compared to PCSK9 inhibitors is the infrequent dosing intervals. Twice yearly injections administered by a health care professional have the potential to optimize treatment adherence, thereby enabling better control of LDL-C levels over a considerable period of time. The twice yearly administration by

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a health care professional could be an advantage for patients who either cannot or are not willing to frequent self-injections.

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6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

Systematic literature searches were performed 08-10 May 2020 and again 16-17 February 2021, the latter searching for records published after the first search was performed. The searches were performed in MEDLINE (Ovid), Embase (Ovid), Cochrane Central Register of Controlled Trials (Wiley), PubMed (NLM) and Web of Science (SCI-Expanded and CPCI-S). To identify information on trials in progress, searches were performed in Clinicaltrials.gov (via https://clinicaltrials.gov/) and EU clinical trials register (via https://www.clinicaltrialsregister.eu/). The first search was performed on 09 May 2020 and the update search on 17 February 2021.

Conference searching was undertaken through a search of Embase and CPCI-S and by a hand search of title followed by a keyword search of conference content of the six conferences, identified with clinical input (Heart UK, Annual Scientific Session and Expo of the American-College-of-Cardiology (ACC), Congress of the European-Atherosclerosis-Society (EAS), International Symposium on Atherosclerosis (ISA), Scientific sessions of the American Heart Association (AHA), Congress of the European Society of Cardiology (ESC)). The conference hand searching for the original search was undertaken on 03-04 April and 08-09 May 2020, and for the update search in a single round in February 2021. Search strategies are provided in Appendix A – Literature search for efficacy and safety of intervention and comparators.

In the first search (May 2020), 7574 records were identified through database searching and 960 records were identified through other searches, in total 8534 records, that were reduced to 6150 after duplicates were removed. A primary screening based on title and abstract and a secondary screening based on full text read was undertaken by three reviewers independently, with two votes required for each record to be included. If there was uncertainty about the relevance of a record based on the abstract in the primary screening, it was included and taken forward to secondary screening. In the secondary screening, where researchers disagreed regarding the inclusion or exclusion of a record, reasons for disagreement were discussed and if a consensus was not reached, the third researcher was involved to reach a decision.

In the updated search (February 2021), 928 records were identified through database searching and 100 records were identified through other sources, in total 1028 records, that were reduced to 616 after duplicates were removed. Selection was undertaken by three reviewers independently as described for the first search.

Both the first and updated literature searches originally included bempedoic acid, ezetimibe and icosapent ethyl in addition to inclisiran, alirocumab and evolocumab. Later, the comparators were narrowed to only include inclisiran, alirocumab and evolocumab. In the first search, 1035 were excluded with reason after full text screening. In the update search, 170 records were excluded with reason after full text screening. For a list of studies excluded with reason refer to Appendix A – Literature search for efficacy and safety of intervention and comparators. The record selection process is summarised in Figure 17 and Figure 18.
The literature search resulted in 22 records to be included covering 24 studies as two records describe 2 studies each: 3 trials of inclisiran, 15 trials of alirocumab and 6 trials of evolocumab (Table 6). There were no head-to-head trials identified between inclisiran, alirocumab and evolocumab. The majority of trials had a placebo comparator, which was often given in addition to background statins and/or other lipid lowering therapy (LLTs), in patients who were tolerant. The update search did not identify any studies or publications to be included.
The search in clnicaltrials.gov and the EU Clinical Trials Register for ongoing or completed studies from which results has not been published yet also didn't identify any records to be included, refer to Table 37.

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6.2 List of relevant studies

Relevant studies are listed in Table 6. For detailed information about included studies, refer to Appendix B Main characteristics of included studies.

Table 6 Relevant studies included in the assessment

Reference	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
Alirocumab studies				
Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial. Stein, Lancet 2012 [34]	NCT01266876	NCT01266876	Start date: January 2011 Completion date: November 2011	Inclisiran vs. alirocumab for HeFH
Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia and LDL-C of 160 mg/dl or Higher. Ginsberg, Cardiovasc Drugs Ther. 2016 [35]	ODYSSEY HIGH FH	NCT01617655	Start date: June 2012 Completion date: January 2015	Inclisiran vs. alirocumab for HeFH
ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. Kastelein, Eur Heart J. 2015 [22] [36]	ODYSSEY FH I	NCT01623115	Start date: July 2012 Completion date: December 2014	Inclisiran vs. alirocumab for HeFH
	ODYSSEY FH II	NCT01709500	Start date: December 2012 Completion date: January 2015	Inclisiran vs. alirocumab for HeFH
Alirocumab and cardiovascular outcomes after acute coronary syndrome. Schwartz, N Engl J Med. 2018 [18]	ODYSSEY OUTCOMES	NCT01663402	Start date: October 2012 Completion date: January 2018	Inclisiran vs. alirocumab for ASCVD and risk equivalent, on MDT statin

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Reference	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. Robinson, N Engl J Med. 2015 [37]	ODYSSEY Long Term	NCT01507831	Start date: January 2012 Completion date: November 2014	Inclisiran vs. alirocumab for HeFH subgroup Inclisiran vs. alirocumab for ASCVD and risk equivalent, on MDT statin
A phase III randomized trial evaluating alirocumab 300 mg every 4 weeks as monotherapy or add-on to statin: ODYSSEY CHOICE I. Roth, Atherosclerosis 2016 [38]	ODYSSEY CHOICE I	NCT01926782	Start date: September 2013 Completion date: April 2015	Inclisiran vs. alirocumab for ASCVD and risk equivalent, on MDT statin
Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. McKenney, J Am Coll Cardiol. 2012 [39]	NTC01288443	NCT01288443	Start date: January 2011 Completion date: December 2011	
Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: The ODYSSEY COMBO I study. Kereiakes, Am Heart J. 2015 [40]	ODYSSEY COMBO I	NCT01644175	Start date: July 2012 Completion date: April 2014	Inclisiran vs. alirocumab for ASCVD and risk equivalent, on MDT statin
A randomized trial evaluating the efficacy and safety of alirocumab in South Korea and Taiwan (ODYSSEY KT). Koh, J Clin Lipidol. 2018 [41]	ODYSSEY KT	NCT02289963	Start date: January 2015 Completion date: April 2016	Inclisiran vs. alirocumab for ASCVD and risk equivalent, on MDT statin
Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on	ODYSSEY COMBO II	NCT01644188	Start date: May 2014 Completion date: July 2015	Inclisiran vs. alirocumab for ASCVD and risk equivalent, on MDT statin

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Reference	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. Cannon, Eur Heart J. 2015 [42]				
ODYSSEY EAST: Alirocumab efficacy and safety vs ezetimibe in high cardiovascular risk patients with hypercholesterolemia and on maximally tolerated statin in China, India, and Thailand. Han, J Clin Lipidol. 2020 [43]	ODYSSEY EAST	NCT02715726	Start date: July 2016 Completion date: August 2018	Inclisiran vs. alirocumab for ASCVD and risk equivalent, on MDT statin
Efficacy and Safety of Alirocumab 150 mg Every 4 Weeks in Patients With Hypercholesterolemia Not on Statin Therapy: The ODYSSEY CHOICE II Study. Stroes, J Am Heart Assoc. 2016 [44]	ODYSSEY CHOICE II	NCT02023879	Start date: December 2013 Completion date: June 2017	Inclisiran vs. alirocumab for ASCVD and risk equivalent, statin intolerant
Efficacy and safety of alirocumab 150mg every 4 weeks in hypercholesterolemic patients on non-statin lipid-lowering therapy or lowest strength dose of statin: ODYSSEY NIPPON. Teramoto, J Cardiol. 2019 [45]	ODYSSEY NIPPON	NCT02584504	Start date: November 2015 Completion date: January 2018	Inclisiran vs. alirocumab for ASCVD and risk equivalent, statin intolerant
Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. Moriarty, J Clin Lipidol. 2015 [46]	ODYSSEY ALTERNATIVE	NCT01709513	Start date: September 2012 Completion date: May 2017	Inclisiran vs. alirocumab for ASCVD and risk equivalent, statin intolerant
Evolocumab studies				
PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia	RUTHERFORD-2	NCT01763918	Start date: February 2013 Completion date: December 2013	Inclisiran vs. evolocumab for HeFH

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Reference	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
(RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Raal, Lancet 2015 [47]				
Evolocumab and clinical outcomes in patients with cardiovascular disease. Sabatine, N Engl J Med. 2017 [19]	FOURIER	NCT01764633	Start date: February 2013 Completion date: November 2016	Inclisiran vs. evolocumab for ASCVD and risk equivalent, on MDT statin
Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. Robinson, JAMA 2014 [48]	LAPLACE-2	NCT01763866	Start date: January 2013 Completion date: December 2013	Inclisiran vs. evolocumab for ASCVD and risk equivalent, on MDT statin
Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study. Giugliano, Lancet 2012 [49]	LAPLACE-TIMI57	NCT01380730	Start date: July 2011 Completion date: April 2012	Inclisiran vs. evolocumab for ASCVD and risk equivalent, on MDT statin
Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. Stroes, J Am Coll Cardiol. 2014 [50]	GAUSS-2	NCT01763905	Start date: January 2013 Completion date: November 2013	Inclisiran vs. evolocumab for ASCVD and risk equivalent, statin intolerant
Evolocumab vs. Ezetimibe in Statin-Intolerant Hyperlipidemic Japanese Patients: Phase 3 GAUSS-4 Trial.	GAUSS-4	NCT02634580	Start date: February 2016 Completion date: May 2018	Inclisiran vs. evolocumab for ASCVD and risk equivalent, statin intolerant

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Reference	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
Koba, J Atheroscler Thromb. 2020 [51]				
Inclisiran studies				
Inclisiran for the treatment of heterozygous familial hypercholesterolemia. Raal, N Engl J Med. 2020 [52]	ORION-9	NCT03397121	Start date: November 2017 Completion date: September 2019	Inclisiran vs. alirocumab for HeFH Inclisiran vs. evolocumab for HeFH
Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. Ray, N Engl J Med. 2020 [9]	ORION-10	NCT03399370	Start date: December 2017 Completion date: September 2019	Inclisiran vs. alirocumab for ASCVD and risk equivalent, on MDT statin Inclisiran vs. evolocumab for ASCVD and risk equivalent, on MDT statin Inclisiran vs. alirocumab for ASCVD and risk equivalent, statin intolerant subgroup Inclisiran vs. evolocumab for ASCVD and risk equivalent, statin intolerant subgroup
	ORION-11	NCT03400800	Start date: November 2017 Completion date: August 2019	Inclisiran vs. alirocumab for ASCVD and risk equivalent, on MDT statin Inclisiran vs. evolocumab for ASCVD and risk equivalent, on MDT statin Inclisiran vs. alirocumab for ASCVD and risk equivalent, statin intolerant subgroup Inclisiran vs. evolocumab for ASCVD and risk equivalent, statin intolerant subgroup

Some studies include treatment arms that are not relevant for analysis. A list of treatment arms excluded and reason for exclusion are shown in Table 36 in Appendix A – Literature search for efficacy and safety of intervention and comparators.

Ongoing studies and studies that are completed but not published have been identified via clinicaltrials.gov and are listed in Table 37 in Appendix A – Literature search for efficacy and safety of intervention and comparators.

For detailed information about included studies, see Appendix B Main characteristics of included studies.

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7. Efficacy and safety

In the absence of a head-to-head trials versus the PCSK9 inhibitors, Novartis conducted a Bayesian Network Meta-Analysis (NMA) comparing the relative efficacy of the treatments. The NMA was made by Evidera, and subsequently submitted to NICE in the UK. Separate analyses were made for patients on maximally tolerated dose (MTD) of statin and patients who were statin-intolerant. For the HeFH population, the analysis for the statin-intolerant subgroup was not feasible, as only one relevant study was identified. For the ASCVD and risk equivalent population data for the two subgroups are presented separately.

The use of the NMA in relation to this application was discussed at the dialogue meeting with the Medicines Council before submitting this application. The NMA was provided to the secretariat by Novartis in due time prior to the meeting, and there were no objections to this approach raised at the meeting.

Data for alirocumab and evolocumab are presented in the same sections in this application, since

- the results presented are derived from an NMA, where one comparator influences the results for other comparators and,
- the two comparators, alirocumab and evolocumab have the same mode of action and are considered to have similar efficacy and safety profiles.

7.1 Efficacy and safety of inclisiran compared to alirocumab and evolocumab for patients with HeFH

7.1.1 Relevant studies for the HeFH population

Seven studies were included for the HeFH population on MTD statin, as shown in Figure 2. Since only ORION-9 was identified for the HeFH statin-intolerant population, no comparisons were made for this subpopulation.

Figure 2 Network diagram for the HeFH population on MTD

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* Subgroup data for patients with HeFH were used in the analysis.

Only data from treatment arms that are relevant for this application are included, i.e., alirocumab 75 mg up titrated to 150 mg Q2W or 150 mg Q2W and evolocumab 140 mg Q2W.

Some studies include treatment arms with dosing regimens that are not relevant for this application. These treatment arms have been excluded from the analysis. A list of excluded treatment arms with reason for exclusion are shown in Table 36, Appendix A – Literature search for efficacy and safety of intervention and comparators.

The main characteristics for the included studies are shown in Table 7. In addition, the table shows results by study in order to provide an optimal overview. Results are discussed in Section 7.1.2.

Detailed study characteristics for each study separately are described in Appendix B Main characteristics of included studies. For baseline characteristics of patients included in each study see Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety.

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Table 7 HeFH population on MTD statin. Main study characteristics and results by study

Study ID	Trial population and criterion for LDL-C at baseline	Duration of treatment/ Time of LDL-C assessment (if different from duration of treatment)	Eligible intervention arms	N randomized (eligible treatment arms)	LDL-C at baseline, mean (SD) (mmol/L)	Percent Change in LDL-C, mean (SD)	Absolute Change in LDL-C, mean (SD), (mmol/L)	SAE n (%)	Withdrawn (all causes) n (%)	Withdrawn due to AE n (%)
Alirocumab studies										
NCT01266876 [34]	HeFH on stable statin dose with or without ezetimibe therapy	12 weeks	ALI 150mg Q2W	16	3.8 (0.8)	-67.9 (19.4)	-2.7 (0.8)	0	NR	0
mITT population	LDL-C of 2.6 mmol/L or higher		Placebo	15	3.9 (0.9)	-10.65 (19.5)	-0.5 (0.8)	1 (6.6)	2 (13.3)	0
						Difference % change in LDL-C vs placebo: p<0.0001				
						Difference abs. change in LDL-C vs placebo: p<0.0001				
Odyssey Long term [37] Subgroup[1] *(data from full study population is in italics)*	Patients at high risk for cardiovascular events on MTD statin with or without other LLT. A subgroup of patients had HeFH LDL-C levels of 1.8 mmol/L or more.	78 weeks/24 weeks	ALI 150 mg Q2W	271	*3.2 (1.1)[2]*	-56.3 (31.3)	NR	*290 (18.7)*	*437 (28.1*)*	*111 (7.2)[3]*
			Placebo	145	*3.2 (1.1)[2]*	7.0 (28.9)	NR	*154 (19.5)*	*193 (24.5*)*	*46 (5.8)[3]*
						Difference % change in LDL-C vs placebo: -63.3 (2 9)[4], p=0.6038				
						Difference abs. change in LDL-C vs placebo: NR				

Study ID	Trial population and criterion for LDL-C at baseline	Duration of treatment/ Time of LDL-C assessment (if different from duration of treatment)	Eligible intervention arms	N randomized (eligible treatment arms)	LDL-C at baseline, mean (SD) (mmol/L)	Percent Change in LDL-C, mean (SD)	Absolute Change in LDL-C, mean (SD), (mmol/L)	SAE n (%)	Withdrawn (all causes) n (%)	Withdrawn due to AE n (%)
Odyssey HIGH FH [35]	HeFH on MDT statin with or without other LLT	78 weeks/24 weeks	ALI 150 mg Q2W	71	5.1 (1.5)[2]	-45.7 (29.5)	-2.3 (1.5)[2]	10 (13.9)	29 (40.3*)	3 (4.2)
ITT population	LDL-C ≥4.6 mmol/L.		Placebo	35	5.2 (1.1)[2]	-6.6 (29.0)	-0.4 (1.5)[2]	4 (11.4)	9 (25.7*)	2 (5.7)
						Difference % change in LDL-C vs placebo: -39.1 (6.0)[4], [-51.1;-27.1], p<0.0001				
						Difference abs. change in LDL-C vs placebo: -1.9 (0.3)[5], [-2.5;-1.3], p<0.0001				
Odyssey FH I [36]	HeFH on MDT statin with or without other LLT	78 weeks/24 weeks	ALI 75 mg Q2W-150 mg Q2W	322	3.7 (0.1)[4]	-48.8 (28.7)	NR	44 (13.7)	76 (23.6)	11 (3.4)
ITT population	LDL-C not at goal for primary (≥2.6 mmol/L) or secondary (≥1.8 mmol/L) prevention.		Placebo	163	3.7 (0.1)[4]	9.1 (28.1)	NR	22 (13.5)	33 (20.3)	10 (6.1)
						Difference % change in LDL-C vs placebo: -57.9 (2.7)[4], [-63.3;-52.6], p<0.0001				
						Difference abs. change in LDL-C vs placebo: NR				

Study ID	Trial population and criterion for LDL-C at baseline	Duration of treatment/ Time of LDL-C assessment (if different from duration of treatment)	Eligible intervention arms	N randomized (eligible treatment arms)	LDL-C at baseline, mean (SD) (mmol/L)	Percent Change in LDL-C, mean (SD)	Absolute Change in LDL-C, mean (SD), (mmol/L)	SAE n (%)	Withdrawn (all causes) n (%)	Withdrawn due to AE n (%)
Odyssey FH II [36] ITT population	HeFH on MDT statin with or without other LLT LDL-C not at goal for primary (≥2.6 mmol/L) or secondary (≥1.8 mmol/L) prevention.	78 weeks/24 weeks	ALI 75 mg Q2W-150 mg Q2W	166	3.5 (0.1)[4]	-48.7 (24.5)	NR	15 (9)	17 (10.2)	6 (3.6)
			Placebo	81	3.5 (0.1)[4]	2.8 (25.2)	NR	8 (9.9)	10 (12.4)	1 (1.2)
						Difference % change in LDL-C vs placebo: -51.4 (3.4)[4], [-58.1;-44.8], p<0.0001 Difference abs. change in LDL-C vs placebo: NR				
Evolocumab studies										
RUTHERFORD-2 [47] Population NR	HeFH on a stable dose of statin with or without other LLT Fasting LDL-C of 2.6 mmol/L or higher.	12 weeks	EVO 140 mg Q2W	110	4.2 (1.3)	-61.3 (18.5)	-2.6 (0.8)	3 (3)	NR	0
			Placebo	54	3.9 (0.9)	-2.0 (18.4)	-0.2 (0.7)	2 (4)	NR	0
						Difference % change in LDL-C vs placebo: -59.23 [-65.1;-53.4], p<0.0001 Difference abs. change in LDL-C vs placebo: -2.43 [-2.7;-2.1], p<0.0001				

Study ID	Trial population and criterion for LDL-C at baseline	Duration of treatment/ Time of LDL-C assessment (if different from duration of treatment)	Eligible intervention arms	N randomized (eligible treatment arms)	LDL-C at baseline, mean (SD) (mmol/L)	Percent Change in LDL-C, mean (SD)	Absolute Change in LDL-C, mean (SD), (mmol/L)	SAE n (%)	Withdrawn (all causes) n (%)	Withdrawn due to AE n (%)
Inclisiran studies										
ORION-9 [52], Novartis, data on file. ITT population	HeFH on MTD statin with or without ezetimibe LDL-C level of at least 2.6 mmol/L.	540 days/day 150	Inclisiran 284 mg	242	3.9 (1.3)[5]	-45.5 (24.2)	-1.8 (1.0)	NR	NR	NR
			Placebo	240	4.0 (1.5)[5]	5.0 (24.5)	0.1 (1.0)	NR	NR	NR
						Difference % change in LDL-C vs placebo: -50.50 [-54.8; -46.2, p<0.0001				
						Difference abs. change in LDL-C vs placebo: **-1.90 [-2.1; -1.7], p<0.0001**				
		540 days/ day 510	Inclisiran 284 mg	231	3.9 (1.3)[5]	-39.7 (-43.7;-35.7)[6]		18 (7.5)	7* (2.9*)	3 (1.2)
			Placebo	229	4.0 (1.5)[5]	8.2 (4.3;12.2)[6]		33 (13.8)	10* (4.2*)	0
						Difference % change in LDL-C vs placebo: -47.9 [-53.5;-42.3], p<0.001				
						Difference abs. change in LDL-C vs placebo: **1.8 [-2.0;-1.6], p<0.001**				

[1] Baseline LDL-C and N are shown for the full population.
[2] Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.02586. Conversion factor was not reported in the publication.
[3] Values reported in the table from the publication but do not match those reported in the text (113 and 47 for the alirocumab and placebo arms respectively).
[4] LS mean (SE).
[5] Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.02586, as requested in the publication.
[6] (CI 95%).
*Calculated value.

ALI, alirocumab; CI, Confidence interval; EVO, evolocumab; EZE, ezetimibe; LDL-C, low density lipoprotein cholesterol; LSM, least square mean; NR, Not reported; SE, standard error; Q2W, once every second week; SE, Standard error.

7.1.1.1 Differences between studies

Important prognostic factors and effect modifying variables that may affect the efficacy and safety of inclisiran and the comparators on the individual level may include background ezetimibe and statins, cardiovascular risk and severity (including LDL-C level), and the time point at which the effect is assessed. Differences between studies regarding these factors and variables are discussed below.

Background ezetimibe

Subgroup data for percent change in LDL-C presented by two of the included trials did not suggest background/baseline ezetimibe use to be a treatment-effect modifier (Table 8).

Table 8 Percent Change in LDL-C stratified by baseline ezetimibe use

Trial	Comparison	LS Mean (SE)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: LDL-C = low-density lipoprotein-cholesterol; LS = least squares; SE = standard error

Background statins

Some differences were observed across the trials with regards to inclusion and exclusion criteria based on previous statin exposure. For studies not explicitly recruiting patients on MTD statin, the proportion of patients receiving high-intensity vs. moderate-intensity statins were compared with the ORION trials to determine appropriateness for NMA. Studies in which patients on placebo were administered twice the statin dose of patients in the active intervention arm were excluded from the analysis (see Appendix A – Literature search for efficacy and safety of intervention and comparators for further details). For the remaining studies, wherein patients were receiving MTD statin or similar distributions of high-/moderate-intensity statins, it was assumed that individual statins (e.g. atorvastatin, rosuvastatin, simvastatin) would have similar efficacy as background therapy, regardless of the specific statin and dosage. It was also assumed that differences in background statin therapy (when balanced across treatment arms) would not bias the results of the NMA. ORION-9 was the only study to also include a small proportion of statin-intolerant patients (25%) [52].

Cardiovascular risk and severity

Stratifications based on the presence or risk of cardiovascular (CV) disease and severity of hypercholesterolaemia were explored in detail. Inconsistent and limited reporting of data across the included studies with regards to CV history, prior CV events, and CV risk factors were observed.

Subgroup data based on factors that could be used to define CV risk were limited and inconsistent. One exception was the availability of subgroup data based on baseline LDL-C which were reported based on consistent cut-offs for two comparator trials [36], although these cut-offs were not consistent with the predefined subgroups from the ORION trials.

ODYSSEY HIGH FH [35] was identified as an outlier among trials of patients with HeFH, given the inclusion criteria (LDL-C ≥4.1 mmol/L) and observed mean baseline LDL-C (5.0-5.2 mmol/L) which were higher than in comparator trials.

Timepoints
Although total study follow-up of the ORION trials was 540 days (approximately 77 weeks), several PCSK9 inhibitor studies had a much shorter duration of follow-up (i.e., 12 weeks for RUTHERFORD-2). With regards to efficacy outcomes of interest, the most commonly reported timepoints were 12 or 24 weeks which closely align with the 90-day and 150-day outcomes reported by the ORION trials.

Visual inspection of the graphical results of LDL-C for ORION and comparator trials demonstrated a plateau in percent change in LDL-C over time, with relative treatment effects decreasing slightly in most studies. Given the observed plateau, the fact that up-titration of alirocumab typically occurred at week 12, and the fact that most studies reported efficacy outcomes of interest at 24 weeks (with the exception of the evolocumab study [47], 24 weeks (or 150 days for inclisiran) was selected as the preferred timepoint of interest for the base case, with 12-week data only included in cases wherein 24-week data are not reported.

For safety outcomes of interest, results are presented at end of study. Given the variation in follow-up, end of study outcomes as withdrawal due to any reason and due to adverse event were considered comparable, if the duration of follow-up was 24 weeks or longer.

For adverse events and serious adverse events results were considered comparable, if the duration of follow-up was one year or longer.

7.1.1.2 Validity of studies

A summary of the risk of bias for each study included in the NMA is included in Table 38, Appendix A – Literature search for efficacy and safety of intervention and comparators.
The following studies provided sufficient information to ascertain that they represented a low risk of bias: the ORION-9 study of inclisiran [52], and ODYSSEY FH I, ODYSSEY FH II, and ODYSSEY LONG-TERM studies of alirocumab [36, 37].

RUTHERFORD-2 study of evolocumab [47] represented an overall low-moderate risk of bias increased only by a lack of concealment of treatment during the randomization process.

NCT01266876 study of alirocumab [34] had a moderate risk of bias due to an imbalance in baseline characteristics of prognostic variables between arms. The ODYSSEY HIGH FH study of alirocumab reported imbalances in discontinuation rates between arms, as well as unclear reporting of the randomization process and concealment of treatment, thereby also representing a medium risk of bias overall [35].

7.1.2 Efficacy and safety – results per study

The following outcomes are included:

Reduction in LDL-C
Reduction in LDL-C from baseline is regarded as the most important outcome. Although avoidance of ASCVD morbidity and mortality is the clinically relevant outcome for lowering therapy, interventional studies of lipid-lowering agents have consistently shown that reductions in LDL-C levels reduce ASCVD morbidity and mortality. This has been demonstrated in individual studies (studies of statins, non-statins, and most recently PCSK9 inhibitors) as well as in meta-analyses of statin trials. For example, a meta-analysis of 28 statin trials published in 2010 reported a 21% reduction in major coronary events, coronary revascularization and stroke for every 1 mmol/L reduction in LDL-C levels [31], while a meta-analysis of 49 trials of different LDL-C-lowering therapies, including statin and non-statin therapies, acting via upregulation of LDLR expression, showed a 23% reduction in the risk of major vascular events for every 1 mmol/L reduction in LDL- C levels [53]. Another meta-analysis which involved 19 trials including those of

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statins, ezetimibe and PCSK9 inhibitors showed that each 1 mmol/L reduction in LDL-C levels was associated with a 19% reduction in major vascular outcomes [54].

Lowering of LDL-C is broadly accepted as a valid surrogate endpoint for effect on cardiovascular events [20] and was considered a valid surrogate endpoint for PSCK9 inhibitors, before results from the cardiovascular outcomes studies were available [21]. Thus, during the time gap between the publication of the cardiovascular outcomes for evolocumab [19] and alirocumab [18], the two PSCK9 inhibitors were considered to be equally effective by RADS based on comparable LDL-C lowering efficacy. The Medicines Council has also extrapolated outcome results to sub-populations, such as HeFH patients, that were not included in the the PCSK9 inhibitor outcomes studies (ODYSSEY OUTCOMES and FOURIER) by applying the same rationale of similar LDL-C lowering efficacy [22]. In line with the Medicines Council's approach, the percentage change in LDL-C therefore seems to be the most appropriate efficacy endpoint, until cardiovascular outcomes data is available from ORION-4.

ORION-4 is an ongoing long term cardiovascular outcomes trial which includes approximately 15,000 patients who will be treated with Inclisiran for a median length of 5 years [23]. Results for ORION-4 are expected in 2025. The goal of the trial is to demonstrate a cardiovascular outcomes benefit (>26% reduction in Major Adverse Cardiac Events (MACE) over 5 years). The trial has 5 years follow-up to ensure statistical power and full therapeutic effect. In comparison the PCSK9 inhibitor cardiovascular outcomes trials were shorter than 3 years and showed 15% reduction in MACE, but no statistical significant benefit for CV death [18, 19].

Results from both percentage and absolute reduction in LDL-C from baseline are presented, but the emphasis will be on the percentage reduction. Firstly, the baseline LDL-C differs somewhat between studies, and secondly, percentage reduction in LDL-C is the primary endpoint in all included studies, except for ODYSSEY OUTCOMES and FOURIER. In addition, RADS evaluated the effect for alirocumab and evolocumab based on percentage reduction in LDL-C in 2016 [22]. Outcomes by study are summarized in Table 7 above.

Safety outcomes

Following the Guidance from the Medicines Council for assessment of new drugs, the proportion of patients experiencing the following outcomes are presented by study:

- Any adverse event
- Serious adverse events
- Discontinuation due to adverse event
- Discontinuation for any reason

There are limited published data on the proportion of patients experiencing adverse drug reactions, and it is therefore not included as an outcome in this application.

Safety outcomes by study are summarized in Table 7 above. Proportion of patients with any adverse event is listed in Table 47, Appendix E Safety data for intervention and comparators.

In addition, an overview of CV adverse events and all-cause mortality reported by study is shown inTable 53, Appendix E Safety data for intervention and comparators.

For detailed efficacy and safety results, including references, see Appendix D Efficacy and safety results per study and Appendix E Safety data for intervention and comparators.

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7.1.3 Comparative analyses of efficacy and safety

Method of synthesis

Most outcomes are compared by a network meta-analysis (NMA), however AEs and SAEs were not included in the NMA, and therefore an indirect comparion a.m. Bucher has been applied.

In the absence of head-to-head trials versus the PCSK9 inhibitors, Novartis conducted a Bayesian Network Meta-Analysis (NMA) comparing the relative efficacy of the treatments. The NMA was made by Evidera, and subsequently submitted to NICE in the UK. The use of the NMA in relation to this application was discussed at the dialogue meeting with the Medicines Council before submitting this application. The NMA was provided to the secretariat by Novartis in due time prior to the meeting, and there were no objections to this approach raised at the meeting. The NMA report is attached as Appendix L – NMA report. Novartis intends to publish two articles on this NMA by October 2021. Until published, the information below and in the separate attachment should be redacted in public documents.

The data from the NMA have been used for this application with a few exceptions:

[redacted]

Table 9 below shows the eligible populations, comparators and outcomes for this application.

Table 9 Eligible Populations, Comparators and Outcomes for the base case, relevant for this application

Disease Category	Population*	Comparators	Outcomes
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE = adverse event; CFB = change from baseline; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol;; Q2W = every two weeks; SC = subcutaneously

* Further stratification of populations based on background ezetimibe, risk of cardiovascular disease, and severity of hypercholesterolaemia were considered

[1]Not feasible as only one relevant study was identified

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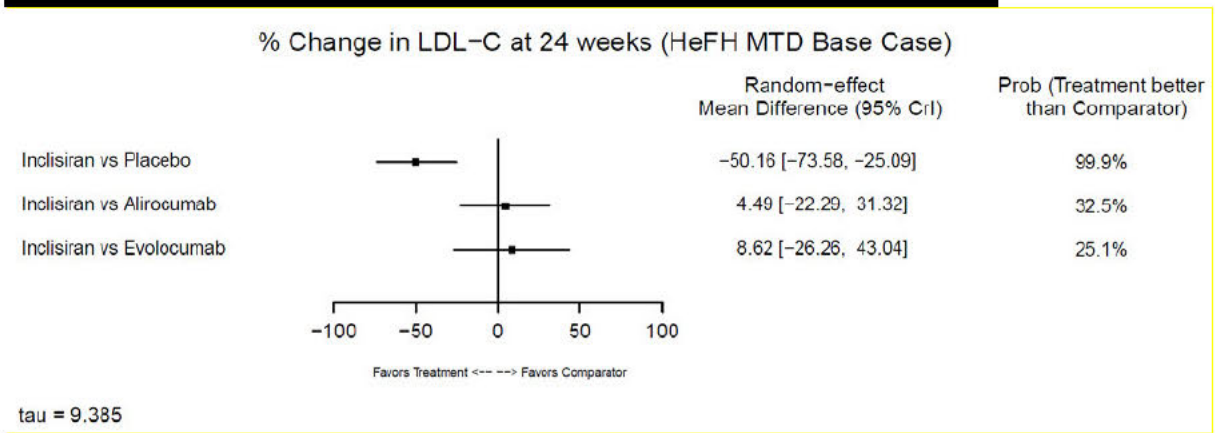
[redacted]

Duration of treatment in the ORION studies with inclisiran was 540 days, i.e., 77 weeks. For proportion of patients experiencing an AE and an SAE the comparison is considered appropriate when the treatment length in the comparator study is approximately the same or longer. As AEs and SAEs were not included in the NMA, indirect comparison a.m. Bucher was made and results are shown in Table 57 in Appendix F Comparative analysis of efficacy and safety. In addition, a narrative comparison of the safety profile of inclisiran vs. the PCSK9 inhibitors, mainly based on the approved Summary of Product Characteristics (SmPC), will be presented in Table 56 in Appendix E Safety data for intervention and comparators.

Results from the comparative analysis

7.1.3.1 Percent change in LDL-C at 24 weeks

[redacted]



[redacted]

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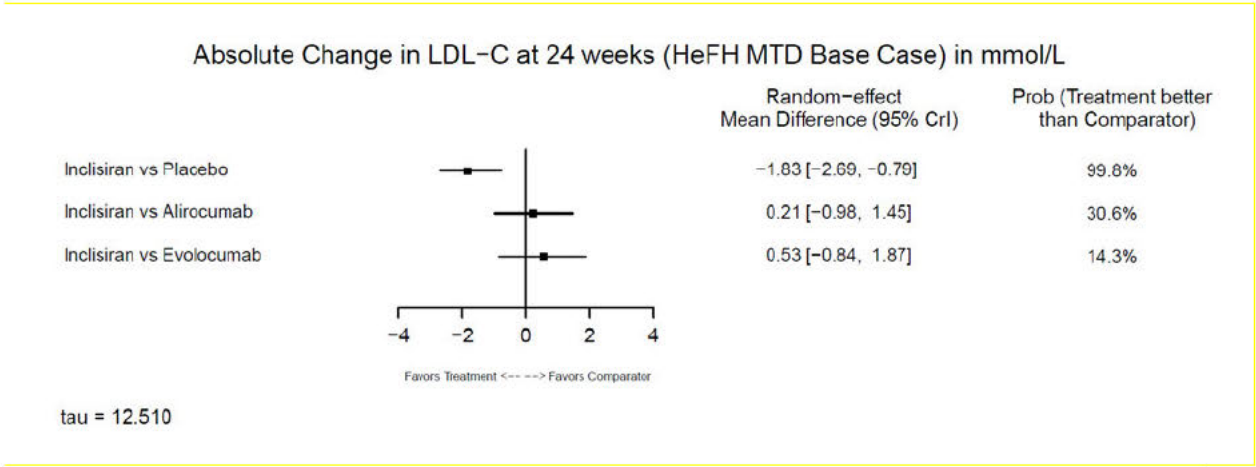
7.1.3.2 Absolute change in LDL-C at 24 weeks

[redacted]



[redacted]

7.1.3.3 Total discontinuations at ≥24 weeks

[redacted]

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7.1.3.4 Discontinuation due to AEs at ≥24 weeks

[redacted]

7.1.3.5 Adverse events and Serious adverse events

Treatment duration in the inclisiran study ORION-9 was 540 days (77 weeks). For proportion of patients experiencing an AE and an SAE a comparison is considered appropriate, when the treatment length in the comparator study is approximately the same or longer. Three studies (ODYSSEY High FH, ODYSSEY FH I and ODYSSEY FH II [35, 36] with alirocumab lasted 78 weeks, which allows a comparison between inclisiran and alirocumab with regard to proportion of patients who experienced an AE and an SAE (Table 10). The only study in the HeFH population with evolocumab was RUTHERFORD-2, with a treatment duration of only 12 weeks.

Table 10 Indirect comparisons of inclisiran vs. alirocumab for patients with HeFH

Results per outcome	Absolute difference in effect Inclisiran vs. alirocumab			Relative difference in effect Inclisiran vs. alirocumab		
	Difference	CI	P value	RR	CI	P value
Proportion of patients with AEs	6.610	-3.110;16.329	NA	1.091	0.960;1.241	0.1822
Proportion of patients with SAEs	-6.356	-13.544;0.832	NA	0.537	0.275;1.047	0.0680

Source: Table 57

The indirect comparison shows that the risk of experiencing an AE with inclisiran was numerically higher compared to alirocumab, and the risk of experiencing an SAE with inclisiran was numerically lower compared to alirocumab. The differences were not statistically significant. For details regarding statistical methods please see Appendix M – Statistical methods.

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Based on the SmPC, (total population with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia) inclisiran has a favourable safety profile, with adverse reactions at the injection site as the only adverse reaction (8.2%) [7].

In comparison, the most common adverse reactions at recommended doses of alirocumab are local injection site reactions (6.1%), upper respiratory tract signs and symptoms (2.0%), and pruritus (1.1%) [15]. For evolocumab, the most commonly reported adverse reactions at the recommended doses are nasopharyngitis (7.4%), upper respiratory tract infection (4.6%), back pain (4.4%), arthralgia (3.9%), influenza (3.2%), and injection site reactions (2.2%) [14]. For further comparisons regarding posology, special populations, contraindications, special warnings and precautions for use and interaction see Table 56, Appendix E Safety data for intervention and comparators. According to the treatment recommendation by the Danish Medicines Council for PCSK9 inhibitors, patients on PCSK9 inhibitors should be asked specifically if they had any symptoms from muscle and joints, neurocognitive symptoms, cold and influenza [17]. Based on the safety profile this specific questions may not be necessary for inclisiran.

Inclisiran has a favourable safety profile, with the only known adverse reaction being injection site reaction [7]. The ORION-4 study will contribute with further data when completed in 2025. As of October 20, 2020, a total of 5107 patients had 5701.8 patient years of inclisiran exposure in clinical trials. Currently approximately 1250 patients have been treated in clinical studies with 8 injections or more, equivalent to 3 years and 9 months (data on file). The latest safety review by an independent monitoring board took place in January 2021, with no changes to the known safety profile.

Cardiovascular outcomes

The incidence of overall major adverse cardiovascular events (MACE), and of individual events including CV death, non-fatal MI, stroke, and requirement for a revascularisation process was similar across all interventions, however the range of incidence within each comparator was very broad and MACE results were not reported in all trials (see Table 53, Table 54 and Table 55 in Appendix E Safety data for intervention and comparators. There was also variation in the definition of cardiac events and the length of randomized treatment periods varied between trials. Apart from FOURIER and ODYSSEY OUTCOMES which were designed as longer term cardiovascular outcomes trials, most trials reported CV events only as adverse events and some trials reported adjudicated events whereas others, including the inclisiran trials, reported non-adjudicated data which may provide elevated incidence data. No formal statistical analysis between inclisiran and the PCSK9 inhibitors for CV outcome data was deemed feasible.

Cardiovascular outcomes of inclisiran have been explored in a meta-analysis which included the three inclisiran studies ORION-9, ORION-10 and ORION-11. Rate of major adverse cardiovascular events (MACE) was a co-primary endpoint and was defined as a composite of cardiac death, any signs or symptoms of cardiac arrest, nonfatal myocardial infarction, and stroke. Inclisiran decreased the MACE rate by 24% (RR = 0.76; 95% CI, 0.61 to 0.94, p = 0.01) compared with placebo. The meta-analysis suggests inclisiran is associated with a statistically significant reduction in MACE rate, which is in alignment with the acknowledged correlation between LDL-C reduction and mortality and morbidity outcomes [16]. However the studies were not designed to address the question on cardiovascular outcome, the analysis was not predefined, and is based on reported adverse events from publications [25]. Confirmation by the ORION-4 study is required.

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7.1.3.6 Conclusion on efficacy and safety of inclisiran vs alirocumab and evolocumab for patients with HeFH

Findings from the NMA demonstrate the comparative efficacy and safety of inclisiran versus currently approved and recommended PCSK9 inhibitors (alirocumab and evolocumab) when added to MTD statin therapy with or without other LLT.

In patients with HeFH, inclisiran demonstrated a statistically significant benefit over placebo in terms of reduction in LDL-C. Differences in LDL-C compared to PCSK9 inhibitors were not statistically significant.

There was no statistical difference between inclisiran and comparators for any of the safety outcomes which indicates similar safety profiles. Though, based on the SmPCs, inclisiran seems to have a more favourable safety profile compared to PCSK9 inhibitors, with injection site reactions as the only adverse drug reaction [7]. Long term data are, however, still limited.

Findings from the NMA show that the addition of inclisiran to current standard of care for patients with HeFH generally results in statistically significant and clinically meaningful improvements in LDL-C and comparable tolerability. In addition, the findings suggest that inclisiran provides outcomes that are expected to be comparable to alirocumab and evolocumab across various hypercholesteremia patient populations.

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7.2 Efficacy and safety of inclisiran compared to alirocumab and evolocumab for patients with ASCVD and risk equivalent

7.2.1 Relevant studies for the ASCVD and risk equivalent population

13 studies were included for the subgroup on MTD statin, and seven studies were included for the subgroup intolerant to statin as shown in Figure 7 and Figure 8.

Figure 7 Network diagram for ASCVD and risk equivalent population on MTD statin

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Only data from treatment arms that are relevant for this application are included, i.e., alirocumab 75 mg up titrated to 150 mg Q2W or 150 mg Q2W and evolocumab 140 mg Q2W.

Some studies included treatment arms with dosing regimens that are not relevant for this application. These treatment arms have been excluded from the analysis, except from the FOURIER study, where the analysis is based on the full IIT, including 10.1% of patients on evolocumab 420 mg QM, due to data availability and timepoint of assessment. A list of excluded treatment arms with reason for exclusion is shown in Table 36, Appendix A – Literature search for efficacy and safety of intervention and comparators.

Relevant studies and results by study are shown in Table 11 for the subgroup on MTD statin in Table 12 and for the subgroup intolerant to statin. Results are discussed in Section 7.2.2.

Detailed study characteristics for each study separately are described in Appendix B Main characteristics of included studies. For baseline characteristics of patients included in each study see Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety.

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Table 11 ASCVD and risk equivalent population on MTD statin. Main study characteristics and results by study

Study ID	Trial population and criterion for LDL-C at baseline	Duration of treatment/ Time of LDL-C assessment (if different from duration of treatment)	Eligible intervention arms	N randomized (eligible treatment arms)	LDL-C at baseline, mean (SD) (mmol/L)	Percent Change in LDL-C, mean (SD)	Absolute Change in LDL-C, mean (SD), (mmol/L)	SAE n (%)	Withdrawn (all causes) n (%)	Withdrawn due to AE n (%)
Alirocumab studies										
Odyssey Outcomes [18] ITT population	Acute coronary syndrome 1 to 12 months earlier on statin therapy at a high-intensity dose or at the maximum tolerated dose. LDL-C at least 1.8 mmol per liter, a non–high-density lipoprotein (HDL) cholesterol level of at least 100 mg per deciliter, or an apolipoprotein B level of at least 80 mg per deciliter.	2.8 years (median)	ALI 75 mg Q2W SC-150 mg Q2W	8,602	2.4 (0.8)[1]	NR	NR	2202 (23.3)	1343 (14.2)	343 (3.6)
			Placebo	8,750	2.4 (0.8)[1]	NR	NR	2350 (24.9)	1496 (15.8)	324 (3.4)
						Difference % change in LDL-C vs placebo: NR Difference abs. change in LDL-C vs placebo: NR				

Study ID	Trial population and criterion for LDL-C at baseline	Duration of treatment/ Time of LDL-C assessment (if different from duration of treatment)	Eligible intervention arms	N randomized (eligible treatment arms)	LDL-C at baseline, mean (SD) (mmol/L)	Percent Change in LDL-C, mean (SD)	Absolute Change in LDL-C, mean (SD), (mmol/L)	SAE n (%)	Withdrawn (all causes) n (%)	Withdrawn due to AE n (%)
Odyssey Long [37] ITT population	High risk for cardiovascular events who were receiving treatment with statins at the maximum tolerated dose with or without other LLT. LDL-C levels of 1.8 mmol/L or more.	78 weeks/24 weeks	ALI 150 mg Q2W	1,530	3.2 (1.1)[1]	-61 (27.4)	-1.9 (0.9)[1]	290 (18.7)	437 (28.1*)	111 (7.2)[2]
			Placebo	780	3.2 (1.1)[1]	0.8 (27.9)	-0.1 (0.9)[1]	154 (19.5)	193 (24.5*)	46 (5.8)[2]
						Difference % change in LDL-C vs placebo: -61.9 (1.3) [-64.3;-59.4], p<0.001 Difference abs. change in LDL-C vs placebo: 1,80 [-1.9; -1.7], p<0.0001				
Odyssey Choice I [38] ITT population	(a) Moderate-to-very-high cardiovascular disease (CVD) risk receiving the maximally tolerated dose of statin, (b) moderate-to very-high CVD risk and with statin-associated muscle symptoms, or (c)moderate CVD risk and not receiving statin. LDL-C ≥1.8 mmol/L for patients at very high CVD risk or ≥2.6 mmol/L for patient at high or moderate CVD risk.	48 weeks/24 weeks	ALI 75 mg Q2W	76	3.0 (0.9)	–51.6 (28.8)	NR	9 (11.5)	13* (16.7*)	4 (5.1)
			Placebo	156	2.9 (1.0)	–0.1 (28.7)	NR	23 (14.6)	28* (17.8*)	13 (8.3)
						Difference % change in LDL-C vs placebo: -51.51 (4.0)[3], p<0.0001 Difference abs. change in LDL-C vs placebo: NR				
NTC01288443 [39] mITT population	Patients with LDL-C ≥2.59 mmol/L receiving a stable dose of atorvastatin 10, 20, or 40 mg daily for ≥6 weeks. LDL-C ≥2.9 mmol/L.	12 weeks	ALI 150mg Q2W	29	3.2 (0.7)[4]	–72.4 (17.2)	NR	0	4 (12.9*)	1 (3.2)
			Placebo	31	3.4 (0.7)[2]	–5.1 (17.3)	NR	1 (3.2)	0	0
						Difference % change in LDL-C vs placebo: p<0.0001 Difference abs. change in LDL-C vs placebo: NR				

Study ID	Trial population and criterion for LDL-C at baseline	Duration of treatment/ Time of LDL-C assessment (if different from duration of treatment)	Eligible intervention arms	N randomized (eligible treatment arms)	LDL-C at baseline, mean (SD) (mmol/L)	Percent Change in LDL-C, mean (SD)	Absolute Change in LDL-C, mean (SD), (mmol/L)	SAE n (%)	Withdrawn (all causes) n (%)	Withdrawn due to AE n (%)
Odyssey Combo I [40] ITT population	Established CVD or coronary heart disease (CHD) risk equivalents (eg, diabetes mellitus with other risk factors or chronic kidney disease). On MTD statin with or without other LLT. LDL-C ≥2.0 mmol/L and established CVD or LDL-C ≥2.9 mmol/L with coronary heart disease (CHD) risk equivalents (e.g., diabetes mellitus with other risk factors or chronic kidney disease).[4]	24 weeks	ALI 75 mg Q2W SC-150 mg Q2W	205	2.6 (0.8)[4]	–48.2 (27.8)	–1.3 (0.9)[4]	26 (12.6)	51 (24.6*)	13 (6.3)
			Placebo	106	2.7 (0.9)[4]	–2.3 (28.1)	–0.1 (0.8)[4]	14 (13.1)	32 (29.9*)	8 (7.5)
						Difference % change in LDL-C vs placebo: **-45.9**[5] [-52.5;-39.3], p<0.0001				
						Difference abs. change in LDL-C vs placebo: -1.20 [-1.4; -1.0], p<0.0001				
Odyssey KT [41] ITT population	High CV risk, defined as history of CV disease (CVD), moderate chronic kidney disease, or diabetes with multiple risk factors. On MTD statin. LDL-C ≥2.0 mmol/L in patients with a history of documented CVD, or LDL-C ≥2.9 mmol/L in patients without such history.[4]	24 weeks	ALI 75 mg Q2W SC-150 mg Q2W	97	2.5 (0.7)[4]	–57.1 (29.6)	–1.4 (0.8)[4]	17 (17.5)	10 (10.3)	2 (2.1)
			Placebo	102	2.6 (0.7)[4]	6.3 (29.3)	0.1 (0.8)[4]	10 (9.8)	5 (4.9)	1 (1)
						Difference % change in LDL-C vs placebo: **-63.4 (4.2)**[3], [-71.6;-55.2], p<0.0001				
						Difference abs. change in LDL-C vs placebo: **-1.6 (0.1)**[3], **[-1 8;-1.3]**, p<0.0001				
Odyssey Combo II [42] ITT population	Established CHD or CHD risk equivalents (ischaemic stroke, peripheral artery disease, moderate chronic kidney disease, or diabetes mellitus plus ≥2 additional risk factors), and treated with MTD statin. Other LLT was not permitted.	104 weeks/24 weeks	ALI 75 mg Q2W SC-150 mg Q2W	467	2.8 (0.9)	–50.6 (30.3)	–1.5 (0.7)	124 (25.9)	71 (14.8*)	44 (9.2)
			EZE	240	2.7 (0.9)	–20.7 (29.4)	–0.7 (0.8)	60 (24.9)	35 (14.5*)	19 (7.9)

Study ID	Trial population and criterion for LDL-C at baseline	Duration of treatment/ Time of LDL-C assessment (if different from duration of treatment)	Eligible intervention arms	N randomized (eligible treatment arms)	LDL-C at baseline, mean (SD) (mmol/L)	Percent Change in LDL-C, mean (SD)	Absolute Change in LDL-C, mean (SD), (mmol/L)	SAE n (%)	Withdrawn (all causes) n (%)	Withdrawn due to AE n (%)
	Documented cardiovascular disease (CVD) and LDL-C ≥1.8 mmol/L or no documented history of CVD but at high cardiovascular risk and LDL-C ≥2.6 mmol/L.					Difference % change in LDL-C vs ezetimibe: **-29.8 (2.3)**[3], **[-34.4;-25.3]**, p<0.0001 Difference abs. change in LDL-C vs ezetimibe: - 0.80 [-0.9; -0.7], p<0.0001				
Odyssey EAST [43] ITT population	History of CV disease (defined as CHD or CHD risk equivalents) and LDL-C levels ≥1.8 mmol/L despite current lipid-lowering therapy or without a history of CV disease (but with other risk factors) and LDL-C ≥2.6 mmol/L. On MTD statin.	24 weeks	ALI 75 mg Q2W SC/ 150 mg Q2W	**403**	2.9 (1.3)	**–56.0 (30.1)**	**–1.6 (0.8)**	41 (10.1)	NR	6 (1.5)
			EZE	**208**	2.9 (1.3)	**–20.3 (28.8)**	**–0.6 (0.8)**	23 (11.2)	NR	3 (1.5)
						Difference % change in LDL-C vs ezetimibe: **-35.6 (2.5)** [3], [-40.6;-30.7], p<0.0001 Difference abs. change in LDL-C vs ezetimibe: -1.00 [-1.1; -0.9], p<0.0001				
Evolocumab studies										
FOURIER [19] ITT population	Patients with atherosclerotic cardiovascular disease on statin (preferably high-intensity, at least 20 mg atorvastatin or equivalent daily), with or without ezetimibe. LDL cholesterol levels ≥ 1.8 mmol/L.	Median duration 2.2 years/24 weeks	EVO 140 mg Q2W or 420 mg QM	**12,964**	2.4 (2.1-2.8)[1,6]	**–62 (24.1)**	**–1.8 (0.9)**[1]	3140 (24.8)	1682 (12)	226 (1.6)
			Placebo	**12,954**	2.4 (2.1-2.8)[1,6]	**–1.0 (28.0)**	**–0.3 (0.8)**[1]	3404 (24.7)	1746 (13)	201 (1.5)
						Difference % change in LDL-C vs placebo: **61**, p<0.001 Difference abs. change in LDL-C vs placebo: **1.5**[1]				

Study ID	Trial population and criterion for LDL-C at baseline	Duration of treatment/ Time of LDL-C assessment (if different from duration of treatment)	Eligible intervention arms	N randomized (eligible treatment arms)	LDL-C at baseline, mean (SD) (mmol/L)	Percent Change in LDL-C, mean (SD)	Absolute Change in LDL-C, mean (SD), (mmol/L)	SAE n (%)	Withdrawn (all causes) n (%)	Withdrawn due to AE n (%)
LAPLACE-2 [48] Pooled from the treated population[8]	Patients with hypercholesterolaemia. Patients were randomised to different statin treatment regimens in addition to evolocumab, ezetimibe or placebo. LDL-C level of 3.9 mmol/L or greater (no statin at screening), 2.6 mmol/L or greater (non-intensive statin at screening), or 2.1 mmol/L or greater (intensive statin at screening).[7]	12 weeks	EVO 140 mg Q2W[4]	555[8]	2.8 (1.1)[7,8]	–61.7 (27.0)[8]	–1.8 (1.0)[7,8]	23 (2.1)	NR	21 (1.9)
			EZE 10 mg[4]	112[8]	2.8 (1.0)[7,8]	–18.3 (27.0)[8]	–0.5 (0.9)[7,8]	2 (0.9)	NR	4 (1.8)
			Placebo[4]	281[8]	2.8 (1.0)[7,8]	9.3 (26.0)[8]	0.2 (0.9)[7,8]	13 (2.3)	NR	12 (2.2)
						Difference % change in LDL-C vs placebo (EVO): -71.00 [74.8; -67.2], p<0.0001				
						Difference % change in LDL-C vs placebo (EZE): -27.60 (-33.5; -21.7), p<0.0001				
						Difference abs. change in LDL-C vs placebo (EVO): -2.00 [-2.1; -1.9], p<0.0001				
						Difference abs. change in LDL-C vs placebo (EZE): -0,70 [-0.9; -0.5], p<0.0001				
LAPLACE-TIMI57 [49] mITT population	Hypercholesterolaemia while on a stable dose of statin, with or without ezetimibe. LDL-C >2.2 mmol/L.	12 weeks	EVO 140 mg Q2W	78	3.1 (0.6)	–63.34 (21.2)	–2.1 (0.8)	4 (5)	2 (2.6*)	2 (3)
			Placebo	78	3.2 (0.7)	2.76 (21.1)	–0.0 (0.8)	4 (5)	0	0
						Difference % change in LDL-C vs placebo: **-66.1 (2.7)[3]**, [-71.5;-60.7], p<0.0001				
						Difference abs. change in LDL-C vs placebo: **-2.0 (0,1)[3], [-2.2;-1.8], p<0.0001**				

Study ID	Trial population and criterion for LDL-C at baseline	Duration of treatment/ Time of LDL-C assessment (if different from duration of treatment)	Eligible intervention arms	N randomized (eligible treatment arms)	LDL-C at baseline, mean (SD) (mmol/L)	Percent Change in LDL-C, mean (SD)	Absolute Change in LDL-C, mean (SD), (mmol/L)	SAE n (%)	Withdrawn (all causes) n (%)	Withdrawn due to AE n (%)
Inclisiran studies										
ORION-10 [9] ITT population	Patients with atherosclerotic cardiovascular disease. On MTD statin or with documented statin intolerance, with or without other LLT. LDL-C 1.8 mmol/L or higher.	540 days/day 150	Inclisiran 284 mg	781	2.7 (1.0)[1]	–59.5 (26.4)	–1.6 (0.7)[1]	NR	NR	NR
			Placebo	780	2.7 (1.0)[1]	0.9 (26.4)	–0.0 (0.7)[1]	NR	NR	NR
						Difference % change in LDL-C vs placebo: -60.40 [-63.0; -57.8], p<0.0001				
						Difference abs. change in LDL-C vs placebo: -1.60 [NR], p<0.0001				
		540 days/day 510	Inclisiran 284 mg	691	2.7 (1.0)[1]	-51.3[9]	-1.5[1,9]	175 (22.4)	60* (7.7*)	19 (2.4)
			Placebo	666	2.7 (1.0)[1]	1.0[9]	-0.1[1,9]	205 (26.3)	85*	17 (2.2)
						Difference % change in LDL-C vs placebo: -52.3 [-55.7;-48 8], p<0.001				
						Difference abs. change in LDL-C vs placebo: -1.5 [-1.48;-1.32], p<0.001				
ORION-11 [9] ITT population	Patients with atherosclerotic cardiovascular disease (ASCVD) or risk equivalents ((type 2 diabetes, familial hypercholesterolemia, or a 10-year risk of a cardiovascular event of ≥20% as assessed by the Framingham Risk Score for Cardiovascular Disease or equivalent).	540 days/day 150	Inclisiran 284 mg	810	2.8 (1.1)[1]	–45.9 (47.9)	–1.3 (1.2)[1]	NR	NR	NR
			Placebo	807	2.7 (0.9)[1]	8.3 (47.8)	0.1 (1.3)[1]	NR	NR	NR
						Difference % change in LDL-C vs placebo: -49.9 [-53.1;-46 6], p<0.001				
						Difference abs. change in LDL-C vs placebo: -1.40 [-1.5; -1.3], p<0.0001				

Study ID	Trial population and criterion for LDL-C at baseline	Duration of treatment/ Time of LDL-C assessment (if different from duration of treatment)	Eligible intervention arms	N randomized (eligible treatment arms)	LDL-C at baseline, mean (SD) (mmol/L)	Percent Change in LDL-C, mean (SD)	Absolute Change in LDL-C, mean (SD), (mmol/L)	SAE n (%)	Withdrawn (all causes) n (%)	Withdrawn due to AE n (%)
	On MTD statin or with documented statin intolerance, with or without other LLT. LDL-C ≥1.8 mmol/L if ASCVD. LDL-C ≥2.6 mmol/L if risk equivalent.	540 days/day 510	Inclisiran 284 mg	724	2.8 (1.1)[1]	-45.8[9]	-1.3[1,9]	181 (22.3)	N=810 38 (4.7)	23 (2.8)
			Placebo	739	2.7 (0.9)[1]	4.0[9]	0.0[1,9]	181 (22.5)	N=807 37 (4.6)	18 (2.2)
									Difference % change in LDL-C vs placebo: **-49.9** [-53.1;-46 6], p<0.001 Difference abs. change in LDL-C vs placebo: **-1,3** [-1.42;-1.26], p<0.001	

[1] Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.02586, as requested in the publication.
[2] values reported in the table from the publication but do not match those reported in the text (113 and 47 for the alirocumab and placebo arms respectively)
[3] LSM (SE)
[4] Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.02586. Conversion factor was not reported in the publication.
[5] Estimated mean (95% CI) change from baseline (%)
[6] Values represent median (IQR).
[7] Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.0259, as requested in the publication.
[8] Treatment arms were pooled for patients who received placebo, ezetimibe or evolocumab, respectively. N represents patients in these groups who received treatment every second week. Baseline LDL-C values are reported for all patients who received placebo, ezetimibe or evolocumab irrespective of treatment regimen. To assure that LAPLACE-2 was given its proper weight in analyses, before analysis, we mathematically combined each group (i.e., the placebo arms, the ezetimibe 10 mg arms, and the evolocumab 140 mg arm) to calculate a group mean and group SD for each. The pooled mean was n-weighted mean across all arms within group. For the pooled SD, the following formula was used, and modified as necessary by number of arms with data; it accounts for individual arm variation and variation in the means across arms (where, for instance, σ_1^2 is the within-group variance for group 1, μ_1 is the mean for group 1, μ is the estimate of the global mean, and σ is the estimate of the global SD). σ=√((n_1 σ_1^2+n_2 σ_2^2+n_1 (μ_1-μ)^2+n_2 (μ_2-μ)^2)/(n_1+n_2))
[9] LSM, SE was not reported.
* Calculated value.

ALI, alirocumab; CHD, coronary heart disease; CI, Confidence interval; CV, cardiovascular; CVD, cardiovascular disease; EVO, evolocumab; EZE, ezetimibe; IQR, interquartile range; LDL-C, low density lipoprotein cholesterol; LSM, Least square mean; NR, Not reported; Q2W, once every second week; QM, once every month; SE, standard error.

Table 12 ASCVD and risk equivalent population intolerant to statin. Main study characteristics and results by study

Study ID	Trial population and criterion for LDL-C at baseline	Duration of treatment/ Time of LDL-C assessment (if different from duration of treatment)	Eligible intervention arms	N randomized (eligible treatment arms)	LDL-C at baseline, mean (SD) (mmol/L)	Percent Change in LDL-C, mean (SD)	Absolute Change in LDL-C, mean (SD), (mmol/L)	SAE n (%)	Withdrawn (all causes) n (%)	Withdrawn due to AE n (%)
Alirocumab studies										
Odyssey Choice II (NCT02023879) Stroes, 2016 [44] ITT population	Patients with hypercholesterolemia receiving fenofibrate or ezetimibe or diet alone. LDL-C ≥2.0 mmol/L if very high cardiovascular risk, or LDL-C ≥2.9 mmol/L if high or moderate risk. For patients with statin intolerance or on diet alone, LDL-C had to be ≥2.9 mmol/L and <4.6 mmol/L.	24 weeks	ALI 75 mg Q2W	115	4.0 (1.2)[1]	–53.5 (17.2)	-2.1 (0.7)[1]	6 (5.2)	8* (6.9*)	2 (1.7)
			Placebo	57	4.1 (1.2)[1]	4.7 (17.4)	0.1 (0.7)[1]	4 (6.9)	6* (10.3*)	2 (3.4)
						Difference % change in LDL-C vs placebo: -58.2 (2.8)[2], p<0.0001 Difference abs. change in LDL-C vs placebo: -2.20 [-2.4; -2.0], p<0.0001				
Odyssey NIPPON (NCT02584504) Teramoto, 2019 [45] ITT population	(HeFH or non-familial hypercholesterolaemia with or without coronary heart disease on low-dose statin or non-statin lipid-lowering therapy (LLT). LDL-C ≥2.9 mmol/L mg/dL (heterozygous familial hypercholesterolemia or non-familial hypercholesterolemia with coronary heart disease) or ≥3.4 mmol/L (non-familial hypercholesterolemia, Japan Atherosclerosis Society category III).	12 weeks blinded + 52 weeks open-label/12 weeks	ALI 150 mg Q2W	53	3.9 (0.8)[1]	–70.1 (16.7)	-2.6 (0.7)[1]	2 (3.8)	3 (5.7*)	1 (1.9)
			Placebo	56	4.9 (1.9)[1]	–4.3 (16.5)	-0.1 (0.8)[1]	1 (1.8)	1 (1.8*)	0
						Difference % change in LDL-C vs placebo: -65.8 (3.1)[2], [-72.9;-58.7], p<0.0001 Difference abs. change in LDL-C vs placebo: -2.50 [-2 8; -2.2], p<0.0001				

Study ID	Trial population and criterion for LDL-C at baseline	Duration of treatment/ Time of LDL-C assessment (if different from duration of treatment)	Eligible intervention arms	N randomized (eligible treatment arms)	LDL-C at baseline, mean (SD) (mmol/L)	Percent Change in LDL-C, mean (SD)	Absolute Change in LDL-C, mean (SD), (mmol/L)	SAE n (%)	Withdrawn (all causes) n (%)	Withdrawn due to AE n (%)
Odyssey ALTERNATIVE (NCT01709513) Moriarty, 2015 [46] ITT population	Moderate or high cardiovascular risk with statin intolerance. LDL-C ≥2.6 mmol/L or very high risk LDL-C ≥1.8 mmol/L.	24 weeks	ALI 75 mg Q2W SC-150 mg Q2W	**126**	5.0 (1.8)[3]	**–45.0 (24.7)**	**-2.6 (0.7)[3]**	12 (9.5)	30 (23.8*)	23 (18.3)
			EZE	**122**	4.8 (1.5)[3]	**–14.6 (24.3)**	**-1.0 (0.9)[3]**	10 (8.1)	42 (33.9*)	31 (25)
						Difference % change in LDL-C vs ezetimibe: -30.4 (3.1)[2], [-36.6;-24.2], p<0.0001				
						Difference abs. change in LDL-C vs ezetimibe: **-1.60 [-1.8; -1.4], p<0.0001**				
Evolocumab studies										
GAUSS-2 (NCT01763905) Stroes, 2014 [50] Population NR	Patients with hypercholesterolaemia on low-dose or no statin. LDL-C above their National Cholesterol Education Program (NCEP) Adult Treatment Panel III goal.	12 weeks	EVO 140 mg Q2W	**103**	5.0 (1.5)[1]	**–56.1 (19.4)**	**-2.7 (1.1)[1]**	5 (5)	NR	6 (6)
			EZE 10 mg daily	**51**	5.0 (1.7)[1]	**–18.1 (18.2)**	**-0.9 (1.0)[1]**	1 (2)	NR	4 (8)
						Difference % change in LDL-C vs ezetimibe: -38.12 [-43.7;-32.4], p<0.001				
						Difference abs. change in LDL-C vs ezetimibe: **-1.82 [-2.1;-1.5], p<0.001**				

Study ID	Trial population and criterion for LDL-C at baseline	Duration of treatment/ Time of LDL-C assessment (if different from duration of treatment)	Eligible intervention arms	N randomized (eligible treatment arms)	LDL-C at baseline, mean (SD) (mmol/L)	Percent Change in LDL-C, mean (SD)	Absolute Change in LDL-C, mean (SD), (mmol/L)	SAE n (%)	Withdrawn (all causes) n (%)	Withdrawn due to AE n (%)
GAUSS-4 (NCT02634580) Koba, 2020 [51] Population NR	Patients with hypercholesterolaemia and statin intolerance. LDL-C threshold based on their management category in the 2012 Japan Atherosclerosis Society Guidelines for the Diagnosis and Prevention of ASCVD in Japan.	12 weeks blinded + open-label extension to 1 year (12 weeks)	EVO 140 mg Q2W/420 QM	40	5.0 (1.4)[4]	–59.5 (17.1)	-2.9 (0.8)[4]	0	3 (7.5*)	2 (5)
			EZE 10 mg daily	21	4.7 (1.5)[4]	–19.0 (13.7)	-0.9 (0.8)[4]	2 (9.5)	1 (4.8*)	0
						Difference % change in LDL-C vs ezetimibe: -40.12 [-48.7;-31.6], p<0.0001				
						Difference abs. change in LDL-C vs ezetimibe: **-2.00 [-2.4; -1.6], p<0.0001**				
Inclisiran studies										
ORION-10 (NCT03399370) Ray, 2020 [9], Novartis, data on file. Subgroup[5] (day 150) *(data from full study population is in italics, day 510)*	Patients with atherosclerotic cardiovascular disease. On MTD statin or with documented statin intolerance, with or without other LLT. LDL-C 1.8 mmol/L or higher.	540 days/day 150	Inclisiran 284 mg	115 *(781)*	*2.7 (1.0)*[2]	–55.0 (29.0)	-1.9 (0.8)[2]	NR	NR	NR
			Placebo	117 *(780)*	*2.7 (1.0)*[2]	5.1 (29.3)	0.0 (0.8)[2]	NR	NR	NR
						Difference % change in LDL-C vs placebo: -60.10 [-67.6; -52.6], p<0.0001				
						Difference abs. change in LDL-C vs placebo: **-1.90 [-2.1; -1.7], p<0.0001**				
		540 days/*day 510*	Inclisiran 284 mg	80 *(781)*	*2.7 (1.0)*[2]	–55.0 (29.0)	-1.9 (0.8)[2]	*175 (22.4)*	*60* (7.7*)*	*19 (2.4)*
			Placebo	88 *(780)*	*2.7 (1.0)*[2]	5.1 (29.3)	0.0 (0.8)[2]	*205 (26.3)*	*85**	*17 (2.2)*
						Difference % change in LDL-C vs placebo: -60.10 [-67.6; -52.6], p<0.0001				
						Difference abs. change in LDL-C vs placebo: **-1.90 [-2.1; -1.7], p<0.0001**				

Study ID	Trial population and criterion for LDL-C at baseline	Duration of treatment/ Time of LDL-C assessment (if different from duration of treatment)	Eligible intervention arms	N randomized (eligible treatment arms)	LDL-C at baseline, mean (SD) (mmol/L)	Percent Change in LDL-C, mean (SD)	Absolute Change in LDL-C, mean (SD), (mmol/L)	SAE n (%)	Withdrawn (all causes) n (%)	Withdrawn due to AE n (%)
ORION-11 (NCT03400800) Ray, 2020 [9], Novartis, data on file. Subgroup[5] (day 150) *(data from full study population is in italics, day 510)*	Patients with atherosclerotic cardiovascular disease (ASCVD) or risk equivalents ((type 2 diabetes, familial hypercholesterolemia, or a 10-year risk of a cardiovascular event of ≥20% as assessed by the Framingham Risk Score for Cardiovascular Disease or equivalent). On MTD statin or with documented statin intolerance, with or without other LLT. LDL-C ≥1.8 mmol/L if ASCVD. LDL-C ≥2.6 mmol/L if risk equivalent.	540 days/day 150	Inclisiran 284 mg	53 *(810)*	*2.8 (1.1)*[2]	−45.4 (20.6)	-1.7 (0.7)	NR	NR	NR
			Placebo	53 *(807)*	*2.7 (0.9)*[2]	−2.7 (20.8)	-0.2 (0.7)	NR	NR	NR
						Difference % change in LDL-C vs placebo: -42.70 [-50.6; -34.8], p<0.0001				
						Difference abs. change in LDL-C vs placebo: -1.50 [-1.8; -1.2], p<0.0001				
		540 days/*day 510*	Inclisiran 284 mg	44 *(724)*	*2.8 (1.1)*[2]	NR	NR	*181 (22.3)*	*38 (4.7)*	*23 (2.8)*
			Placebo	41 *(739)*	*2.7 (0.9)*[2]	NR	NR	*181 (22.5)*	*37 (4.6)*	*18 (2.2)*
						Difference % change in LDL-C vs placebo: -41.64 [-51.1;-32.14], p<0.0001				
						Difference abs. change in LDL-C vs placebo: NR				

[1] Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.02586. Conversion factor was not reported in the publication.
[2] LSM (SE).
[3] Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.02586, as requested in the publication.
[4] Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.0259, as requested in the publication.
[5] Values are reported for the sub-group with no statin treatment at baseline.
* Calculated value.

ALI, alirocumab; CI, Confidence interval; EVO, evolocumab; EZE, ezetimibe; LDL-C, low density lipoprotein cholesterol; LSM, Least square mean; NR, Not reported; Q2W, once every second week; QM, once every month; SE, Standard error.

7.2.1.1 Differences between studies

Important prognostic factors and effect modifying variables that may affect the efficacy and safety of inclisiran and the comparators on the individual level may include background ezetimibe and statins, cardiovascular risk and severity (including LDL-C level), and the time point at which the effect is assessed. Differences between studies regarding these factors and variables are discussed below.

Background ezetimibe

Subgroup data for percent change in LDL-C presented by two of the included trials did not suggest background/baseline ezetimibe use to be a treatment-effect modifier (Table 13).

Table 13 Percent change in LDL-C stratified by baseline ezetimibe use

Trial	Comparison	LS Mean (SE)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: LDL-C = low-density lipoprotein-cholesterol; LS = least squares; SE = standard error

Background statins

Some differences were observed across the trials with regards to inclusion and exclusion criteria based on previous statin exposure. For studies not explicitly recruiting patients on MTD statin, the proportion of patients receiving high-intensity vs. moderate-intensity statins were compared with the ORION trials to determine appropriateness for NMA. Studies in which patients on placebo were administered twice the statin dose of patients in the active intervention arm were excluded from the analysis (see Appendix A – Literature search for efficacy and safety of intervention and comparators for further details). For the remaining studies, wherein patients were receiving MTD statin or similar distributions of high-/moderate-intensity statins, it was assumed that individual statins (e.g. atorvastatin, rosuvastatin, simvastatin) would have similar efficacy as background therapy, regardless of the specific statin and dosage. It was also assumed that differences in background statin therapy (when balanced across treatment arms) would not bias the results of the NMA. The ORION studies were the only studies to also include a small proportion of statin-intolerant patients (ORION-10 [22%], ORION-11 [12%] [9]).

For trials that recruited statin-intolerant patients there were small proportions of patients across several studies who remained on low-dose background statin therapy, including the partially intolerant patients in the ORION trials. The proportions of patients in the ORION trials were in line with other trials.

Cardiovascular risk and severity

Stratifications based on the presence or risk of CV disease and severity of hypercholesterolaemia were explored in detail. Inconsistent and limited reporting of data across the included studies with regards to CV history, prior CV events, and CV risk factors were observed. Specifically, definitions of risk equivalence varied between the ORION and comparator trials. Populations in the ORION trials included patients considered to be ASCVD 'risk equivalent', defined by the presence of type 2 diabetes, FH, or a ≥20% 10-year risk of a CV event as assessed by the Framingham Risk Score for Cardiovascular Disease or equivalent. Other trials defining risk equivalence included patients with coronary heart disease (CHD) risk equivalent, including one or more of the following: ischaemic stroke, PAD, chronic kidney disease,

or diabetes mellitus, and two or more additional risk factors. The various components used to define risk equivalent patients in the ORION trials were also not consistently reported across the comparator trials. However, the number of risk equivalent patients was relatively low across included trials.

Furthermore, subgroup data based on these factors and others that could be used to define CV risk were limited and inconsistent. One exception was the availability of subgroup data based on baseline LDL-C which were reported based on consistent cut-offs for six comparator trials [37, 38, 42, 44, 46, 49], although these cut-offs were not consistent with the predefined subgroups from the ORION trials.

ODYSSEY OUTCOMES [18] was deemed an outlier amongst trials of ASCVD patients receiving MTD statin. In this trial, the median time since a recent acute coronary event was 2.6 months, which, based on clinical expert feedback, may result in highly variable LDL-C values at baseline due to plaque rupture, and subsequently unreliable results.

Timepoints

Although total study follow-up of the ORION trials was 540 days (approximately 77 weeks), several PCSK9 inhibitor trials had a much shorter duration of follow-up (i.e., 12 weeks for the GAUSS trials, LAPLACE-TIMI 57 [49] and 24 weeks for ODYSSEY ALTERNATIVE [46]). With regards to efficacy outcomes of interest, the most commonly reported timepoints were 12 or 24 weeks which closely align with the 90-day and 150-day outcomes reported by the ORION trials.

Visual inspection of the graphical results of LDL-C for ORION and comparator trials demonstrated a plateau in percent change in LDL-C over time, with relative treatment effects decreasing slightly in most studies. Given the observed plateau, the fact that up-titration of alirocumab typically occurred at week 12 and the fact that most studies reported efficacy outcomes of interest at 24 weeks (with the exception of two evolocumab studies [48, 49], 24 weeks (or 150 days for inclisiran) was selected as the preferred timepoint of interest for the base case, with 12-week data only included in cases wherein 24-week data are not reported.

For safety outcomes of interest, results are presented at end of study. Given the variation in follow-up, end of study outcomes as withdrawal due to any reason and due to adverse event were considered comparable if the duration of follow-up was 24 weeks or longer.

For adverse events and serious adverse events results were considered comparable if the duration of follow-up was one year or longer.

7.2.1.2 Validity of studies

A summary of the risk of bias for each study included in the NMA is included in Table 38, Appendix A – Literature search for efficacy and safety of intervention and comparators.

The following studies provided sufficient information to ascertain that they represented a low risk of bias; the ORION-10, and ORION-11 studies of inclisiran [9]; ODYSSEY COMBO II and ODYSSEY LONG-TERM studies of alirocumab [37, 42], and FOURIER, and LAPLACE TIMI-57 studies of evolocumab [19, 49].

Several studies presented an overall low-moderate risk of bias increased only by a lack of clarity over the randomization process, concealment of treatment during the randomization process and/or reasons for discontinuation, these included: the ODYSSEY CHOICE I, ODYSSEY CHOICE II, ODYSSEY OUTCOMES, ODYSSEY ALTERNATIVE, ODYSSEY KT, ODYSSEY EAST and ODYSSEY COMBO I studies of alirocumab [18, 38, 40, 41, 43, 44, 46], and the LAPLACE-2, and GAUSS-4 studies of evolocumab [48, 51].

The ODYSSEY NIPPON study of alirocumab had a moderate risk of bias due to an imbalance in discontinuation rates between arms [45]. The NCT01288443 study of alirocumab and the GAUSS-2 trial of evolocumab both reported

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imbalances in discontinuation rates between arms, as well as unclear reporting of the randomization process and concealment of treatment, thereby also representing a medium risk of bias overall [39, 50].

7.2.2 Efficacy and safety – results per study

The following outcomes are included:

Reduction in LDL-C

Reduction in LDL-C from baseline is regarded as the most important outcome. Although avoidance of ASCVD morbidity and mortality is the clinically relevant outcome for lowering therapy, interventional studies of lipid-lowering agents have consistently shown that reductions in LDL-C levels reduce ASCVD morbidity and mortality. This has been demonstrated in individual studies (studies of statins, non-statins, and most recently PCSK9 inhibitors) as well as in meta-analyses of statin trials. For example, a meta-analysis of 28 statin trials published in 2010 reported a 21% reduction in major coronary events, coronary revascularization and stroke for every 1 mmol/L reduction in LDL-C levels [31], while a meta-analysis of 49 trials of different LDL-C-lowering therapies, including statin and non-statin therapies, acting via upregulation of LDLR expression, showed a 23% reduction in the risk of major vascular events for every 1 mmol/L reduction in LDL- C levels [53]. Another meta-analysis which involved 19 trials including those of statins, ezetimibe and PCSK9 inhibitors showed that each 1 mmol/L reduction in LDL-C levels was associated with a 19% reduction in major cardiovascular outcomes [54].

Lowering of LDL-C is broadly accepted as a valid surrogate endpoint for effect on cardiovascular events [20] and was considered a valid surrogate endpoint for PSCK9 inhibitors before results from the cardiovascular outcomes studies were available [2]. Thus, during the time gap between the publication of the cardiovascular outcomes for evolocumab [19] and alirocumab [18], the two PSCK9 inhibitors were considered to be equally effective by RADS, based on comparable LDL-C lowering efficacy. The Medicines Council has also extrapolated outcome results to sub-populations, such as HeFH patients, that were not included in the the PCSK9 inhibitor outcomes studies (ODYSSEY OUTCOMES and FOURIER) by applying the same rationale of similar LDL-C lowering efficacy [22]. In line with the Medicines Council's approach, the percentage change in LDL-C therefore seems to be the most appropriate efficacy endpoint, until cardiovascular outcomes data is available from ORION-4.

ORION-4 is an ongoing long term cardiovascular outcomes trial which includes approximately 15,000 patients who will be treated with Inclisiran for a median length of 5 years [23]. Results for ORION-4 are expected in 2025. The goal of the trial is to demonstrate a cardiovascular outcomes benefit (>26% reduction in Major Adverse Cardiac Events over 5 years). The trial has 5 years follow-up to ensure statistical power and full therapeutic effect. In comparison the PCSK9 inhibitor cardiovascular outcomes trials were shorter than 3 years and showed 15% reduction in MACE, but no statistical significant benefit for CV death [18, 19].

Results from both percentage and absolute reduction in LDL-C from baseline are presented, but the emphasis will be on percentage reduction of LDL. Firstly, the baseline LDL-C differs somewhat between studies, and secondly, percentage reduction in LDL-C is the primary endpoint in all included studies, except for ODYSSEY OUTCOMES and FOURIER. In addition, RADS evaluated the effect of alirocumab and evolocumab based on percentage reduction in LDL-C in 2016 [22]. Outcomes by study are summarized in Table 11 and Table 12 above.

Safety outcomes

Following the Guidance from the Medicines Council for assessment of new drugs, the proportion of patients experiencing the following outcomes are presented by study:

- Any adverse event
- Serious adverse events

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- Discontinuation due to adverse event
- Discontinuation for any reason

There are limited published data on the proportion of patients experiencing adverse drug reactions, and it is therefore not included as an outcome in this application.

Safety outcomes by study are summarized in Table 7 above. Proportions of patients with any AE is listed in Table 47, Appendix E Safety data for intervention and comparators.

In addition, an overview of CV AEs and all-cause mortality reported by study is shown in Table 53, Appendix E Safety data for intervention and comparators.

For detailed efficacy and safety results, including references, see Appendix D Efficacy and safety results per study and Appendix E Safety data for intervention and comparators.

7.2.3 Comparative analyses

Method of synthesis

Most outcomes are compared by a network meta-analysis (NMA). However AEs and SAEs were not included in the NMA, and therefore an indirect comparion a.m. Bucher has been applied.

In the absence of head-to-head trials versus the PCSK9 inhibitors, Novartis conducted a Bayesian NMA comparing the relative efficacy of the treatments. The NMA was made by Evidera, and subsequently submitted to NICE in the UK. The use of the NMA in relation to this application was discussed at the dialogue meeting with the Medicines Council before submitting this application. The NMA was provided to the secretariat by Novartis in due time prior to the meeting, and there were no objections to this approach raised at the meeting. The NMA report is attached as Appendix L – NMA report. Novartis intends to publish two articles on this NMA by October 2021. Until published, the information below and in the separate attachment should be redacted in public documents. Novartis intends to publish two articles on this NMA by October 2021. Until published, the information below and in the separate attachment should be redacted in public documents.

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Table 14 Eligible populations, comparators and outcomes for the base case, relevant for this application

Disease Category	Population*	Comparators	Outcomes
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Duration of treatment in the ORION studies with inclisiran was 540 days, i.e., 77 weeks. For the proportion of patients experiencing an AE and an SAE a comparison is considered appropriate when the treatment length in the comparator study is approximately the same or longer. As AEs and SAEs were not included in the NMA, indirect comparison a.m. Bucher was made and results are shown in Appendix F Comparative analysis of efficacy and safety. In addition, a narrative comparison of the safety profile of inclisiran vs. the PCSK9 inhibitors, mainly based on the approved Summary of Product Characteristics (SmPC), will be presented.

Results from the comparative analysis

7.2.3.1 Percentage change in LDL-C at 24 weeks

[redacted]

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7.2.3.5 Adverse events and serious adverse events

Treatment duration in the inclisiran studies ORION-10 and ORION-11 was 540 days (77 weeks). For proportion of patients experiencing an AE or an SAE a comparison is considered appropriate when the treatment length in the comparator study is approximately the same or longer. Only studies with patients on MTD statin are included, as patients on inclisiran who were intolerant to statin (a subgroup in the ORION-10 and ORION-11) were not accounted for separately. Three placebo-controlled studies (ODYSSEY OUTCOMES, ODYSSEY LONG TERM, and ODYSSEY COMBO I with alirocumab lasted 2.8 years, 78 weeks and 62 weeks, respectively, and one placebo-controlled study (FOURIER) with evolocumab lasted 2.2 years, which allows a comparison between inclisiran and PCSK9 inhibitors with regard to proportion of patients who experienced an AE or an SAE (Table 15 and Table 16).

Table 15 Indirect comparisons of inclisiran vs. alirocumab for patients with ASCVD and risk equivalent

Results per outcome	Absolute difference in effect Inclisiran vs. alirocumab			Relative difference in effect Inclisiran vs. alirocumab		
	Difference	CI	P value	RR	CI	P value
Proportion of patients with AEs	1.482	-1.569;4.533	NA	1.020	0.981;1.061	0.3128
Proportion of patients with SAEs	-0.503	-3.656;2.650	NA	0.976	0.853;1.118	0.7294

Source: Table 58 and Table 59

Table 16 Indirect comparisons of inclisiran vs. evolocumab for patients with ASCVD and risk equivalent

Results per outcome	Absolute difference in effect Inclisiran vs.evolocumab			Relative difference in effect Inclisiran vs. evolocumab		
	Difference	CI	P value	RR	CI	P value
Proportion of patients with AEs	0.100	-2.902;3.101	NA	1.002	0.965;1.041	0.916
Proportion of patients with SAEs	-2.003	5.116;1.110	NA	0.915	0.801;1.045	0.190

Source: Table 58 and Table 59

The indirect comparisons show that the risk of experiencing an AE with inclisiran is numerically higher compared to alirocumab and evolocumab, and the risk of experiencing an SAE with inclisiran was numerically lower compared to alirocumab and evolocumab. The differences were not statistically signifiant. For details regarding statistical methods please see Appendix M – Statistical methods.

Based on the SmPC, (total population with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia), inclisiran has a favourable safety profile, with adverse reactions at the injection site as the only adverse reaction (8.2%) [7].

In comparison, the most common adverse reactions at recommended doses of alirocumab are local injection site reactions (6.1%), upper respiratory tract signs and symptoms (2.0%), and pruritus (1.1%) [15]. For evolocumab, the most commonly reported adverse reactions at the recommended doses are nasopharyngitis (7.4%), upper respiratory tract infection (4.6%), back pain (4.4%), arthralgia (3.9%), influenza (3.2%), and injection site reactions (2.2%)[14]. For further comparisons regarding posology, special populations, contraindications, special warnings and precautions for use and interaction see Table 56, Appendix E Safety data for intervention and comparators. According to the treatment recommendation by the Danish Medicines Council for PCSK9 inhibitors, patients on PCSK9 inhibitors should be asked specifically if they had any symptoms from muscle and joints, neurocognitive symptoms, cold and influenza [17]. Based on the safety profile these specific questions may not be necessary for inclisiran.

Inclisiran has a favourable safety profile, with the only known adverse reaction being injection site reaction [7]. The ORION-4 study will contribute with further data when completed in 2025. As of October 20, 2020, a total of 5107 patients had 5701.8 patient years of inclisiran exposure in clinical trials. Currently approximately 1250 patients have been treated in clinical studies with 8 injections or more, equivalent to 3 years and 9 months (data on file). The latest safety review by an independent monitoring board took place in January 2021, with no changes to the known safety profile.

Cardiovascular outcomes

The incidence of overall major adverse cardiovascular events (MACE), and of individual events including CV death, non-fatal MI, stroke, and requirement for a revascularisation process was similar across all interventions, however the range of incidence within each comparator was very broad and MACE results were not reported in all trials (see see Table 53, Table 54 and Table 55 in Appendix E Safety data for intervention and comparators). There was also variation in the definition of cardiac events, and the length of randomized treatment periods varied between trials. Apart from FOURIER and ODYSSEY OUTCOMES which were designed as longer term cardiovascular outcomes trials, most trials reported CV events only as adverse events and some trials reported adjudicated events whereas others, including the inclisiran trials, reported non-adjudicated data which may provide elevated incidence data. No formal statistical analysis between inclisiran and the PCSK9 inhibitors for CV outcome data was deemed feasible.

Cardiovascular outcomes of inclisiran have been explored in a meta-analysis which included the three inclisiran studies ORION-9, ORION-10 and ORION-11. Rate of MACE was a co-primary endpoint and was defined as a composite of cardiac death, any signs or symptoms of cardiac arrest, nonfatal MI, and stroke. Inclisiran decreased the MACE rate by 24% (RR = 0.76; 95% CI, 0.61 to 0.94, p = 0.01) compared with placebo. The meta-analysis suggests inclisiran is associated with a statistically significant reduction in MACE rate which is in alignment with the acknowledged correlation between LDL-C reduction and mortality and morbidity outcomes [16].However the studies were not designed to address the question on cardiovascular outcome, the analysis was not predefined, and is based on reported AEs from publications [25]. Confirmation by the ORION-4 study is required.

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7.2.3.6 Conclusion on efficacy and safety for patients with ASCVD

Findings from the NMA demonstrate the comparative efficacy and safety of inclisiran versus currently approved and recommended PCSK9 inhibitors (alirocumab and evolocumab) in patients with ASCVD and risk equivalent, when added to MTD statin therapy with or without other LLT or when statins are contraindicated or not tolerated.

For ASCVD and risk equivalent populations on MTD statin, inclisiran demonstrated a statistically significant benefit over placebo in terms of reduction in LDL-C. Differences in LDL-C compared to PCSK9 inhibitors were not statistically significant.

For ASCVD and risk equivalent populations intolerant or contraindicated to statins, inclisiran was significantly better than placebo in terms of change in LDL-C. Differences in LDL-C compared to PCSK9 inhibitors were not statistically significant.

There were no statistical difference between inclisiran and comparators for any of the safety outcomes which indicates similar safety profiles. Though, based on the SmPCs, inclisiran seems to have a more favourable safety profile compared to PCSK9 inhibitors with injection site reactions as the only adverse drug reaction [7]. Long term data are, however, still limited.

Findings from the NMA show that the addition of inclisiran to current standard of care for patients with ASCVD and risk equivalent generally results in statistically significant and clinically meaningful improvements in LDL-C and comparable tolerability. In addition, the findings suggest that inclisiran provides outcomes that are expected to be comparable to alirocumab and evolocumab across various hypercholesteremia patient populations.

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8. Health economic analysis

Findings from the NMA demonstrate comparative efficacy and safety of inclisiran versus currently approved and recommended PCSK9 inhibitors (alirocumab and evolocumab), as no statistical difference between inclisiran and comparators for any of the efficacy and safety outcomes were observed. Consequently, in accordance with the guidelines from the Medicines Council, a cost-minimization (CM) analysis has been conducted.

8.1 Model

The CM analysis was conducted as a simple cost-per-patient analysis for inclisiran compared to alirocumab and evolocumab. As the evidence demonstrates non-significant differences in efficacy or safety outcomes between the interventions, the model only considered costs associated with drug acquisition, administration, and monitoring of the treatment, i.e., drug costs, administration costs, monitoring cost and patient costs.
The model was developed in Microsoft Excel 365 as a simple cohort model. In order to allow the model to align with the treatment regimens, weekly model cycles have been used in the model. The model reflects the treatment course based on the posology of each intervention included as per the SmPC [7, 14, 15]. The model reflects the treatment course of the interventions and estimates the costs associated with each intervention and the associated incremental costs. As there are no differences in efficacy between the interventions, no mortality is modelled, and the patients will remain on treatment throughout the time horizon.

8.1.1 Perspective, time horizon and discounting

The model applies a Danish restricted societal perspective, in line with the guidelines presented by the the Medicines Council [57].
A 10-year time horizon was applied in the base-case, as this was used in the health economic evaluation of PCSK9 inhibitors by the Medicines Council [32]. The impact on the results of varying the time horizons to 5 and 20 years, respectively, was explored in scenario analyses.
A discount rate of 3,5% was applied to the costs, as defined by the Danish Ministry of Finance and in the guidelines from the Medicines Council [57, 58].

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

Not applicable. As this comparison is between three interventions that are assumed to be equivalent in terms of efficacy and safety, no relative efficacy parameters have been included in the model. In addition, no efficacy parameters are included with the objective of model parsimony.

8.2.1 Presentation of input data used in the model and how they were obtained

Not applicable. Please find the rationale in section 8.2.

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

Not applicable. Please find the rationale in section 8.2.

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8.2.2.1 Patient population

The intended patient population for this analysis have been based on the populations described in the treatment guidelines released by the Medicines Council for PCSK9 inhibitors [59].
As the model is a CM analysis and all interventions are fixed-dose, no patient characteristics have been applied in this model, as these would not have an impact on the results.

8.2.2.2 Intervention

The intervention, inclisiran, is intended for administration by a healthcare professional. The recommended dose is 284 mg administered as a single subcutaneous injection: initially, again at 3 months, followed by every 6 months. The dosing of inclisiran is summarized in Table 17.

Table 17. Intervention: Inclisiran

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	284 mg s.c: initially, again at 3 months, followed by every 6 months [7].	284 mg s.c: initially, again at 3 months, followed by every 6 months [7].	284 mg s.c: initially, again at 3 months, followed by every 6 months [7].

8.2.2.3 Comparators

In the recommendation of PCSK9 inhibitors for the treatment of hyperlipidemia from the Medicines Council, two interventions are included, evolocumab and alirocumab [59]. Both interventions are included in the model as comparators.
As the treatments are assumed clinically equivalent, no clinical documentation is included in this model and only the posology for both comparators have been included for the model to enable estimation of drug and administration costs.
Both comparators are self-administered by the patient every other week. The posology of both comparators are listed in Table 18 and Table 19.

Table 18. Comparator: Alirocumab

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	150 mg s.c every other week [59]	150 mg s.c every other week [59]*	150 mg s.c every other week[59]
The comparator's position in the Danish clinical practice	2nd choice [59]	2nd choice [59]	2nd choice [59]

* The model includes an option to select a dosing of 300 mg s.c. every fourth week. The distribution between the two dosing options is user modifiable.

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Table 19. Comparator: Evolocumab

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	140 mg s.c every other week [14]	140 mg s.c every other week [14]	140 mg s.c every other week [14]
The comparator's position in the Danish clinical practice	1st choice [59]	1st choice [59]	1st choice [59]

8.2.2.4 Relative efficacy outcomes

Not applicable. Please find the rationale in section 8.2.

8.2.2.5 Adverse reaction outcomes

Not applicable. Please find the rationale in section 8.2.

8.3 Extrapolation of relative efficacy

Not applicable. Please find the rationale in section 8.2.

8.3.1 Time to event data – summarized:

Not applicable. Please find the rationale in section 8.2.

8.4 Documentation of health-related quality of life (HRQoL)

Not applicable. Please find the rationale in section 8.2.

8.4.1 Overview of health state utility values (HSUV)

Not applicable. Please find the rationale in section 8.2.

8.4.2 Health state utility values used in the health economic model

Not applicable. Please find the rationale in section 8.2.

8.5 Resource use and costs

8.5.1 Drug costs

Drug costs have been estimated using pharmacy purchase prices (AIP). The AIP for inclisiran, alirocumab and evolocumab have been sourced from Medicinpriser.dk [60] and are listed in
Table 20. In the model, drug costs are applied at every cycle, where an administration occurs based on the posology presented in section 8.2.2.2 and 8.2.2.3.

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Table 20. Drug costs

Drug	Price per pack (DKK)	Formulation	Source
Inclisiran	16.850,00	284 mg per pen, 1 pen	Medicinpriser.dk [60]
Alirocumab	9.696,32	150 mg per pen, 6 pens	Medicinpriser.dk [60]
Evolocumab	9.444,16	140 mg per pen, 6 pens	Medicinpriser.dk [60]

8.5.2 Administration cost and resource use in relation to monitoring (Hospital cost)

Inclisiran is intended for administration by healthcare professionals, and to reflect this in the model a cost has been applied at each administration for inclisiran in the model (see Table 21).

Both alirocumab and evolocumab are intended for self-administration by the patients and therefore no administration cost has been applied for the two interventions throughout the model. This aligns with the assumptions made in the health economic evaluation of PCSK9 inhibitors made by the Medicines Council [32]. Based on Danish KOL input, patients on treatment with PCSK9 inhibitors will visit the hospital prior to the first administration for the training of self-administration (clinical expert, see List of experts). Therefore, an administration cost visit has been applied in the first model cycle for the PCSK9 inhibitors.

All alirocumab and evolocumab, patients are assumed to have a visit at the hospital 1 month following the first administration and then every 6 months for monitoring of efficacy and safety of the treatments. This frequency has been based on the recommendation in the Danish treatment guidelines for PCSK9 inhibitors [59]. We acknowledge that the guideline considers that monitoring potentially can be reduced to once a year after 1-2 years of treatment. However, since this is not the current practice this is not reflected in the base case. A DRG tariff has been included for the cost of a monitoring visit at the hospital (see Table 18).

To avoid double-counting, no further additional monitoring cost have been included for inclisiran, as the patients are monitored during their administration visit. This assumption has been validated with a Danish clinical expert (see List of experts).

It is assumed that the basic blood samples are included in the DRG tariffs, therefore, the cost of additional blood samples has not been included. Furthermore, based input from a Danish clinical expert, the blood samples taken for patient treated with inclisiran and PCSK9, respectively, are not expected to differ (see List of experts).

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Table 21. Administration

Type	Price (DKK)	Note	Source
Administration of inclisiran + monitoring	1.518	DRG 2021, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DE780: Hyperkolesterolæmi Procedure: BWAA31: Medicingivning ved subkutan injektion, ZZ9010: Medikamentel behandling, kontrol af	Interaktiv DRG 2021
Administration of alirocumab and evolocumab (one-off cost)	1.518	DRG 2021, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DE780: Hyperkolesterolæmi Procedure: BWAA31: Medicingivning ved subkutan injektion	Interaktiv DRG 2021
Monitoring visit (PCSK9 inhibitors)	1.518	DRG 2021, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DE780: Hyperkolesterolæmi Procedure: ZZ9010: Medikamentel behandling, kontrol af	Interaktiv DRG 2021

8.5.3 Patient cost and transportation cost

Patient costs (defined as patient costs in guidelines from the Medicines Council [61] are included in the model in line with the Medicines Council's method guidelines [61]. The unit cost per hour is assumed to be DKK 179 in line with the guidelines from the Medicines Council [61]. The time usage for the administration of inclisiran was assumed to be 30 min per administration. The duration of a self-administration of a PCSK9 inhibitor has been assumed to be 15 mins per administration. Patient costs are reported in Table 22.

Transportation costs are included in the model in line with Medicines Council's guidelines [61]. An average rate of DKK 3,52 per km is assumed with an average distance of 28 km per hospital visit in line with Medicines Council's methods guidelines [61]. In the model, transportation cost is applied at the occurrence of hospital visits, e.g. administration of inclisiran and monitoring visits. The transportation costs are reported in Table 22.

Based on Danish KOL input (clinical expert, see List of experts), it is expected that patients will visit the hospital every 6th month for the dispensing of all the interventions, this aligns with the monitoring visits. Therefore, no additional patient cost or transportation cost for drug dispensing have been applied in the base case. To test the impact of this assumption, a dispensing frequency of every 3rd month has been explored in a scenario analysis. The model also allows for a user-defined dispensing frequency in the cell, 'disp_freq', on the 'Drug cost'-sheet.

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Table 22. Patient cost

Type	Price (DKK)	Note	Source
Administration of inclisiran (0,5 hour)	89,50	Applied on every occurrence of administration of inclisiran in the model	DMC unit cost list [61]
Monitoring visit (1 hour)	179,00	Applied on the occurrence of a monitoring visit in the model, monitoring is assumed to be included at every inclisiran administration visit	DMC unit cost list [61]
Self-administration of PCSK9 inhibitor	44,75	Applied on every occurrence of administration of alirocumab and evolocumab in the model	DMC unit cost list [61]
Dispensing of PCSK9 inhibitors	89,50	Applied, if a dispensing visit does not fall in the same cycles as a monitoring visit for alirocumab and evolocumab	DMC unit cost list [61]
Transportation cost associated with a hospital visit	98,56	DKK 3,52 per km with an average distance of 28 km per visit. Applied on every occurrence of a hospital visit in the model, e.g. administration of inclisiran or monitoring visits	DMC unit cost list [61]

DMC, Danish Medicines Council

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8.6 Results

8.6.1 Base case overview

Table 23 Base case overview

Intervention	- inclisiran
Comparators	- alirocumab - evolocumab
Type of model	CM model
Time horizon	10 years (120 months)
Discount rate	3,5%
Included costs	- Drug costs - Hospital costs (administration of inclisiran & monitoring cost) - Patient costs
Dosage of pharmaceutical	- inclisiran: Fixed-dose - alirocumab: Fixed-dose - evolocumab: Fixed-dose
Discontinuation	No treatment discontinuation assumed
Other key assumptions	- No additional monitoring costs are included, as it is expected that there are not differences between the interventions in scope of this assessment. This has been validated by Danish KOLs

8.6.2 Base case results

Table 24 and Table 25 present the total cost for the inclisiran, alirocumab and evolocumab arm, respectively, and the incremental cost of inclisiran compared to the two comparators. At AIP prices, the total cost was estimated to be DKK 341.266,11 for inclisiran, DKK 404.394,77 for alirocumab and DKK 394.988,77 for evolocumab. The incremental cost of inclisiran vs. alirocumab was estimated to be DKK -63.128,22 and for the comparison vs. evolocumab, the incremental cost of inclisiran was estimated to be DKK -53.722,66. Over a time horizon of 10 years, the use of inclisiran is associated with savings compared to the use of alirocumab or evolocumab at AIP-level.

Table 24. Base-case results inclisiran vs. alirocumab

Per patient	Inclisiran	Alirocumab	Difference
Drug costs	DKK 306.929,04	DKK 361.672,49	DKK -54.743,46
Hospital costs	DKK 27.650,94	DKK 27.650,94	DKK 0,00

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Per patient	Inclisiran	Alirocumab	Difference
Patient time and transport costs	DKK 6.686,14	DKK 15.070,91	DKK -8.384,77
Total cost	**DKK 341.266,11**	**DKK 404.394,77**	**DKK -63.128,22**

Table 25. Base-case results for inclisiran vs. evolocumab

	Inclisiran	Evolocumab	Difference
Drug costs	DKK 306.929,04	DKK 352.266,93	DKK -45.337,90
Hospital costs	DKK 27.650,94	DKK 27.650,94	DKK 0,00
Patient time and transport costs	DKK 6.686,14	DKK 15.070,91	DKK -8.384,77
Total cost	**DKK 341.266,11**	**DKK 394.988,33**	**DKK -53.722,66**

8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

Scenario analyses have been conducted for the time horizon and for the assumption applied to the dispensing frequency (Table 26). The scenario analyses indicate that the results were not sensitive to the changes in the dispensing frequency. The results were sensitive to change in the time horizon, however, the scenario analyses indicated that inclisiran would be a cost-saving intervention at a time horizon of 2.42 years (29 months). With a time horizon shorter than 29 months, inclisiran would no longer be a cost-saving intervention vs. the cheapest comparator, evolocumab at AIP-level. However, as treatment with both inclisiran and PCSK9 inhibitors are either life-long or at least for 10 years (as assumed in the health economic assessment for PCSK9 inhibitors for hyperlipidaemia conducted by the Medicines Council), a mean time horizon of only 2.42 years is not appropriate to apply.

Table 26. Scenario analyses

	Change	Reason / Rational / Source	Incremental cost vs alirocumab (DKK)	Incremental cost vs evolocumab (DKK)
Base case	-	-	**DKK -63.128,22**	**DKK -53.722,66**
Time horizon	2.42 years (29 months)	The time horizon from where inclisiran becomes cost saving vs. cheapest comparator	DKK -2.579,99	DKK -10,68

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	Change	Reason / Rational / Source	Incremental cost vs alirocumab (DKK)	Incremental cost vs evolocumab (DKK)
	5 years (60 months)	Test impact of time horizon, lower bound	DKK -26.528,95	DKK -21.422,71
	20 years (240 months)	Test impact of time horizon, upper bound	DKK -119.889,74	DKK -103.816,40
Dispensing frequency of PCSK9 inhibitors	Every 3rd month	Test impact of dispensing	DKK -66.365,75	DKK -56.960,19

8.7.2 Probabilistic sensitivity analyses

Not applicable. Since this is a CM analysis no ICERs are estimated. Consequently, a PSA is not meaningful to conduct.

9. Budget impact analysis

The budget impact model was developed to estimate the expected budget impact of recommending inclisiran as a possible standard treatment in Denmark. The budget impact analysis has been embedded within the CM model and therefore any changes in the settings of the cost per patient model would affect the results of the budget impact model. The budget impact result is representative of the population in the cost per patient model.
The costs included in the budget impact model are undiscounted, and patient cost and transportation cost have not been included as per the guidelines by the Medicines Council [57].
The analysis compares the costs for the Danish regions per year over five years in the scenario where inclisiran is recommended as possible standard treatment and the scenario where inclisiran is not recommended as a possible standard treatment. The total budget impact per year is the difference between the two scenarios.

9.1 Number of patients

The total number of patients have been based on the patient populations included in the budget impact analyses in the economic evaluation of PCSK9 inhibitors by the Medicines Council [32]. The number of patients used for the base case analysis is the sum of all subpopulations (See Table 27). Subgroup analyses have been conducted with the subpopulations included in the economic evaluation of PCSK9 inhibitors by the Medicines Council, and the patient numbers have been derived from the same report [32].

Table 27. Total number of patients over the next five-year period (total population)

	Year 1	Year 2	Year 3	Year 4	Year 5
Total number of patients	2.499	3.543	4.631	5.761	6.937

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9.2 Market share

It is stated in the current recommendation that evolocumab will be the 1st line therapy used for 80% of the patients. Alirocumab is the current alternative for the last 20%. Evolocumab is expected to have the highest market share in all years.

If inclisiran is not recommended, it is assumed that inclisiran can be used as an alternative to PCSK9 inhibitor for relatively few patients (Table 28). These patients will be those who experience side effects, absent effect or lacking adherence with PCSK9 inhibitors.

If inclisiran is recommended, it is assumed that inclisiran will be considered clinically equivalent to the PCSK9 inhibitor and inclisiran will become 2nd line treatment and achieve up to 15% market share (Table 29).

Table 28. Market share over the next five-year period - if the inclisiran is not recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Inclisiran	1%	2%	3%	4%	5%
Alirocumab	39%	28%	17%	16%	15%
Evolocumab	60%	70%	80%	80%	80%

Table 29. Market share over the next five-year period - if inclisiran is recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Inclisiran	3%	6%	9%	12%	15%
Alirocumab	37%	24%	11%	8%	5%
Evolocumab	60%	70%	80%	80%	80%

9.3 Budget impact

Based on the base case settings, the estimated budget impact of recommending inclisiran as a treatment option for treatment of hyperlipemia in Denmark at AIP was DKK 426.460 in year 1 and DKK -1.673.657 in year 5 as shown in Table 30. Inclisiran is associated with an increased budget impact in year 1, due to the initial loading dosing in year 1. However, over time a recommendation of inclisiran will result in a saving in year 4 and 5, due to a lower cost for the subsequent treatment years.

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Table 30. Expected budget impact of recommending inclisiran in the total population

	Year 1	Year 2	Year 3	Year 4	Year 5
Total cost of scenario with a recommendation of inclisiran	DKK 115.383.201	DKK 159.162.373	DKK 206.737.444	DKK 255.181.419	DKK 305.659.467
Total cost of scenario without a recommendation of inclisiran	DKK 114.956.741	DKK 158.682.492	DKK 206.547.893	DKK 255.857.180	DKK 307.333.123
Budget impact of the recommendation	**DKK 426.460**	**DKK 479.882**	**DKK 189.550**	**DKK -675.762**	**DKK -1.673.657**

9.4 Subgroup analyses

To estimate the budget impact of recommending inclisiran in the various subpopulations, the patient numbers for each subpopulation have been sourced from the economic evaluation of PCSK9 inhibitors conducted by the Medicines Council (see Table 31) [32]. For the subgroup analyses, the market shares have been assumed to be the same as in the base case analysis, as these are not expected to vary across the different populations. The budget impact in year 5 of recommending inclisiran for each subpopulation has been reported in Table 32.

Table 31. Patient subpopulations defined by the Medicines Council [32]

	Year 1	Year 2	Year 3	Year 4	Year 5
Total population	2.499	3.543	4.631	5.761	6.937
HeFH patients, primary prevention	681	1.205	1.729	2.254	2.778
HeFH patients, secondary prevention	1.266	1.551	1.837	2.122	2.408
ACS, subpopulation	248	399	570	760	971
Polyvascular Disease, subpopulation	234	273	322	380	448
Diabetes, subpopulation	56	72	87	102	117
Ischemic apoplexy, subpopulation, large vessels	7	22	44	73	110
Ischemic apoplexy, subpopulation, small vessels	7	21	42	70	105

Table 32. Subgroup analyses of the estimated budget impact at year 5

	Estimated budget impact at year 5
Total population	**DKK -1.673.657**

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	Estimated budget impact at year 5
HeFH patients, primary prevention	DKK -605.156
HeFH patients, secondary prevention	DKK -730.874
ACS, subpopulation	DKK -177.368
Polyvascular Disease, subpopulation	DKK -117.835
Diabetes, subpopulation	DKK -34.158
Ischemic apoplexy, subpopulation, large vessels	DKK -4.029
Ischemic apoplexy, subpopulation, small vessels	DKK -4.236

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10. Discussion on the submitted documentation

Findings from the NMA demonstrate the comparative efficacy and safety of inclisiran versus currently approved and recommended PCSK9 inhibitors (alirocumab and evolocumab) when added to MTD statin therapy with or without other LLT or when statins are contraindicated or not tolerated for patients with HeFH as well as ASCVD and risk equivalent.

Outcomes and method of analyses

The efficacy comparisons between inclisiran and the PCSK9 inhibitors are based on percentage change in LDL-C from baseline to week 24. Percentage change in LDL-C was the primary endpoint in all included studies except for the outcomes studies ODYSSEY OUTCOMES and FOURIER [18, 19]. Lowering of LDL-C is broadly accepted as a valid surrogate endpoint for effect on cardiovascular events [20] and was considered a valid surrogate endpoint for PSCK9 inhibitors before results from the cardiovascular outcomes studies were available [21]. Thus, during the time gap between the publication of the cardiovascular outcomes for evolocumab [19] and alirocumab [18], the two PSCK9 inhibitors were considered to be equally effective by RADS, based on comparable LDL-C lowering efficacy. The Medicines Council has also extrapolated outcome results to sub-populations, such as HeFH patients, that were not included in the the PCSK9 inhibitor outcomes studies (ODYSSEY OUTCOMES and FOURIER) by applying the same rationale of similar LDL-C lowering efficacy [62]. In line with the Medicines Council's approach, we therefore think that percentage change in LDL-C is the most appropriate efficacy endpoint, until cardiovascular outcomes data is available from ORION-4.

In the absence of head-to-head trials versus the PCSK9 inhibitors, Novartis conducted a Bayesian NMA comparing the relative efficacy of the treatments. The NMA was made by Evidera, and subsequently submitted to NICE in the UK. The use of the NMA in relation to this application was discussed at the dialogue meeting with the Medicines Council before submitting this application. The NMA was provided to the secretariat by Novartis in due time prior to the meeting, and there were no objections to this approach raised at the meeting.

Although the primary efficacy endpoints in all ORION trials were percent change in LDL-C at day 510 and time-adjusted change in LDL-C, these longer duration timepoints, and specifically time-adjusted analyses, were not available from any of the comparator studies. The most commonly reported timepoint across comparator PCSK9 inhibitor studies was 24 weeks, and in some cases for evolocumab, only 12week results were available. Therefore, in order to maximize the available comparator evidence, 24 weeks was selected as the main timepoint of interest for the NMA analyses. This ensured that up-titration of alirocumab, which occurred at week 12, was complete prior to outcome assessment. This was felt to be a conservative approach with respect to the results of the comparator studies, which, like the ORION trials, tended to show the most favourable results at 24 weeks.

Efficacy

For all populations studied, HeFH on MTD statin, ASCVD and risk equivalent population on MTD statin, and ASCVD and risk equivalent intolerant to statin, inclisiran demonstrated a statistically significant benefit over placebo in terms of reduction in LDL-C. The findings from the NMA suggest that inclisiran provides outcomes that are expected to be comparable to alirocumab and evolocumab across various hypercholesteremia patient populations.

A pooled analysis across of ORION-9, -10 and -11 across the different patient populations showed that the placebo-corrected change in LDL-C with inclisiran at day 510 was -50.7% (95% confidence interval: -52.9% to -48.4%; p <0.0001). The Mean absolute change in LDL-C from baseline to day 510 was -1.43 mmol/L (95% confidence interval: -2.00 to -1.36; p <0.0001) [16].

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It is not possible in published literature to define the minimum reduction in LDL-C that gives a clinical significant change on cardiovascular outcomes. There are several factors besides LDL lowering that influence the total risk of cardiovascular outcomes. Besides that, the population is a heterogenic group with different risk factors, baseline LDL-C and LDL-C targets [24]. For instance for secondary prevention the high risk groups should according to guideline aim for a 50% decrease of LDL-C [20]. In primary prevention even smaller changes in LDL-C might be clinically significant if the time with the reduction and treatment is long enough, as both the concentration of LDL-C as well as time of exposure are defining the total plaque burden [2].

Safety

There were no statistical difference between inclisiran and comparators for any of the safety outcomes which indicates similar safety profiles. Though, based on the SmPCs, inclisiran seems to have a more favourable safety profile compared to PCSK9 inhibitors with injection site reactions as the only adverse drug reaction [7]. Long term data are, however, still limited. Currently there is a cardiovascular outcomes trial, ORION-4, ongoing which includes approximately 15.000 patients who will be treated for a median length of 5 years.

PCSK9 inhibitors are self-administered by the patient or a caregiver every two weeks. In contrast, inclisiran is administered as a single subcutaneous injection initially, again at 3 months and then every 6 months by a health care professional. Twice yearly injections administered by a health care professional have the potential to optimize treatment adherence, thereby enabling better control of LDL-C levels over a considerable period of time. The twice yearly administration by a health care professional could also be an advantage for patients who either cannot or are not willing to frequent self-injections.

Relevance to the Danish context

The populations included in the clinical studies in this application were generally comparable with the Danish patients for whom inclisiran is indicated. This applies both to the HeFH and the ASCVD and risk equivalent populations when it comes to age, atherosclerotic cardiovascular disease, use of MTD or high dose statin (except by those intolerant to statin), and baseline LDL-C. The only exception is that the use of ezetimibe was generally lower than what would be expected in Danish patients eligible for treatment with inclisiran. However, subgroup data for percent change in LDL-C presented by two of the included trials did not suggest background/baseline ezetimibe use to be a treatment-effect modifier (see Table 8), and the results of the clinical studies are thus considered relevant in a Danish context.

Strengths and weaknesses of the health economic model

A CM analysis was conducted, and at the AIP-level, inclisiran is associated with savings when compared to alirocumab and evolocumab. The savings of inclisiran at AIP-level are the results of a lower drug cost and a lower patient cost and transportation cost over the time horizon. The model does not estimate any differences in hospital cost between all 3 interventions included in the model. The results were sensitive to change in the time horizon. This is explained by the posology of inclisiran, where 3 administrations are required during the first year, and 2 administrations are required in the subsequent years. Therefore, more drug cost is accrued in the first year, compared to the PCSK9 inhibitors. The results were not sensitive to scenarios, where the dispensing of PCSK9 inhibitors was more frequent (every 3rd month). The budget impact analysis at AIP-level indicated that a recommendation of inclisiran would result in saving in year 5 compared to the scenario, where inclisiran is not recommended.

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Conclusion

Findings from the NMA show that the addition of inclisiran to current standard of care for patients with HeFH and ASCVD generally results in statistically significant and clinically meaningful improvements in LDL-C and comparable tolerability. In addition, the findings suggest that inclisiran provides outcomes that are expected to be comparable to alirocumab and evolocumab across various hypercholesteremia patient populations.

A high degree of control for high risk patients is possible due to inclisiran's proven and sustained LDL-C reduction over the course of the extended dosing interval. With a favorable safety profile and as an injection administered by healthcare professionals biannually in the maintenance phase, it has the potential to remove the adherence challenges that may be encountered with self-administered treatments and thus on the long term potentially result in better disease control.

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11. Other considerations

Novartis has established a research collaboration with Phase 4 CPH (Fase 4 Kliniske Farmakologi) at Bispebjerg Hospital to do the following study: An assessment of patient characteristics and treatment patterns among ASCVD patients with hypercholesterolemia, ASCVD-risk equivalent patients with hypercholesterolemia and FH patients in Denmark.

The study design is a descriptive, non-interventional, retrospective cohort study of ASCVD patients with hypercholesterolemia, ASCVD-risk equivalent patients with hypercholesterolemia, or FH patients in Denmark using a secondary source of data from several registries; The Danish National Patient Registry, The Danish National Prescription Registry, The Danish Civil Registration System, The Register of Laboratory Results for Research for the study period 2005-2019 if data is available or else 2018.

The data collected will characterize and describe the population in details not seen in current publications. Unfortunately approvals from health authorities have been delayed due to COVID-19. Data and publications are expected to be available later in 2021.

An additional collaboration with Phase 4 CPH is in scope and is considered to be initiated, if inclisiran is recommended for usage by the Danish Medicines Council. The purpose is an assessment of patients treated with inclisiran in clinical practice.

The objective will be to describe the demographics and clinical characteristics of inclisiran patients and assess the effect on LDL-reduction in clinical practice stratified by ASCVD, ASCVD risk equivalent and FH patients over a 5-year time (evaluated every year). The study will be descriptive, non-interventional, retrospective cohort study using secondary data from the health care registries in Denmark from 4th quarter of 2021 to 4th quarter of December 2026. A minimum specified number of patients treated with incisiran must be defined to be able to perform the analysis.

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Appendix A – Literature search for efficacy and safety of intervention and comparators

The objective of the literature search was to answer the following:
"What is the comparative efficacy and safety of inclisiran versus other pharmacologic agents for the management of primary hypercholesterolaemia (heterozygous familial and non-familial) and 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 in patients who are statin-intolerant, or for whom a statin is contraindicated?"

The objectives more specifically were to:

- Identify published and unpublished reports of the efficacy, safety and tolerability of inclisiran, and comparators in RCTs, for the treatment of hypercholesterolaemia;
- Present a narrative synthesis of outcome data reported in relevant studies of inclisiran, and other comparators;
- Identify evidence to be used to assess the feasibility of an indirect treatment comparison to synthesise relevant data;
- Identify evidence to inform a cost-effectiveness (CE) model for inclisiran for the treatment of hypercholesterolaemia.

Systematic literature searches were performed 08-10 May 2020 and again 16-17 February 2021, the latter searching for records published after the first search was performed. The searches were performed in MEDLINE (Ovid), Embase (Ovid), Cochrane Central Register of Controlled Trials (Wiley), PubMed (NLM) and Web of Science (SCI-Expanded and CPCI-S).
To identify information on trials in progress, searches were performed in Clinicaltrials.gov (via https://clinicaltrials.gov/) and EU clinical trials register (via https://www.clinicaltrialsregister.eu/). The first search was performed on 09 May 2020 and the update search on 17 February 2021.
Conference searching was undertaken through a search of Embase and CPCI-S and by a hand search of title followed by a keyword search of conference content of the six conferences, identified with clinical input (Heart UK, Annual Scientific Session and Expo of the American-College-of-Cardiology (ACC), Congress of the European-Atherosclerosis-Society (EAS), International Symposium on Atherosclerosis (ISA), Scientific sessions of the American Heart Association (AHA), Congress of the European Society of Cardiology (ESC)). The conference hand searching for the original search was undertaken on 03-04 April and 08-09 May 2020, and for the update search in a single round in February 2021.

Database	Platform	Relevant period for the search	Date of search completion
Medline	Ovid	1946 to 07 May 2020 1946 to 16 February 2021	08 May 2020 17 February 2021 (update search)
Embase	Ovid	1980 to 2020 Week 18	08 May 2020 17 February 2021 (update search)
Cochrane Central Register of Controlled Trials	Wiley	Issue 5 of 12, May 2020	10 May 2020 17 February 2021 (update search)

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Database	Platform	Relevant period for the search	Date of search completion
PubMed (for e-publications)	NLM		08 May 2020 17 February 2021 (update search)

Abbreviations: NLM, National Library of Medicine

Table 33 Registers included in the search

Database	Platform	Search strategy	Date of search
US NIH registry & results database	https://clinicaltrials.gov	Search string run in expert search	09 May 2020 17 February 2021 (update search)
EU Clinical Trials Register	EU Clinical Trials Register	Search string run in the basic search box	09 May 2020 18 February 2021 (update search)

Abbreviatons:US NIH, United States National Institute of Health; EU, European Union.

Table 34 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched
Embase	Website	Search string	
CPCI-S	Website	Search string	
Heart UK	Conference content	Hand search of title followed by a keyword search of conference content.	
Annual Scientific Session and Expo of the American-College-of-Cardiology (ACC)	Conference content	Hand search of title followed by a keyword search of conference content.	
Congress of the European-Atherosclerosis-Society (EAS)	Conference content	Hand search of title followed by a keyword search of conference content.	
International Symposium on Atherosclerosis (ISA)	Conference content	Hand search of title followed by a keyword search of conference content.	
Scientific sessions of the American Heart Association (AHA)	Conference content	Hand search of title followed by a keyword search of conference content.	

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Conference	Source of abstracts	Search strategy	Words/terms searched
Congress of the European Society of Cardiology (ESC)	Conference content	Hand search of title followed by a keyword search of conference content.	

For the original literature search, conference hand search was performed in two rounds. The first round of handsearching was performed in April 2020 for inclisiran, alirocumab, evolocumab, and ezetimibe (conferences: Heart UK, ACC, EAS, ISA), and later expanded for a second round of handsearching to include two further conferences (conferences: AHA, ESC) and two further interventions (bempedoic acid and icosapent ethyl). For the update literature search, conference handsearching for SLR update was conducted at a single round only and was performed in February 2021.

Heart UK 2020 got cancelled, ACC 2020 is already included in original SLR as conducted in March 2020, ISA was not planned for 2020. Abstracts from AHA and ESC were included which happened in late 2020.

In addition to the above mentioned searches, supplementary searches were undertaken:

- Web searching: Handsearching by intervention was performed on key regulatory and Health Technology Assessment (HTA) websites. These records were reviewed and only eligible if they reported data not published elsewhere.
- Citation chasing: Studies meeting inclusion at full text were citation chased. Backwards citation chasing was undertaken manually through a review of the bibliographies of included studies and forwards citation chasing was undertaken using Web of Science (Clarivate Analytics).
- Company data on file was also accessed and four clinical study reports (CSRs) were identified for the inclisiran trials, ORION-1, ORION-9, ORION-10 and ORION-11.

Search strategy

The search strategy developed to meet the objective of the literature search was defined by the following inclusion and exclusion criteria.

Population:
The target population of patients include people with heterozygous familial hypercholesterolaemia or non-familial hypercholesterolaemia/mixed dyslipidaemia and established ASCVD or risk equivalents whose LDL-C is not adequately controlled with maximally tolerated statin background therapy, in addition to those that are intolerant to statin.
Subpopulations of participants eligible for inclusion include:

- Hypercholesterolaemia subpopulations (HeFH, Non-FH (ASCVD/ ASCVD risk-equivalent), primary / secondary prevention)
- Background therapy:
    - Patients on maximally tolerated dose background statin therapy (with or without ezetimibe);
    - Patients on stable high/ medium-dose background statin therapy representative of proportions seen in MTD trials
    - Statin intolerant patients
    - Differential baseline LDL-C levels thresholds

Studies conducted exclusively in homozygous familial hypercholesterolaemia (HoFH) or in patients on low-dose or unstable doses of statins are ineligible (unless intolerant), but where there is a mixed population it was included where eligible patients were reported separately. Equally, studies conducted exclusively in diabetes or hypertension populations were ineligible, while mixed populations including those patients would be eligible.

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Interventions:
Alirocumab and evolocumab are licenced for use in hypercholesterolaemia populations in the US and Europe. Inclisiran has marketing authorization pending with both the EMA and FDA. Eligible interventions are inclisiran, evolocumab (Repatha®) and alirocumab (Praluent®). Trials evaluating any of these interventions are eligible either as monotherapy or in combination regimens with any of the other interventions, or other lipid modifying therapy. All interventions are only eligible at their US and/ or EU recommended dose and frequency of their licensing (current or pending). The literature search strategies also included ezetimibe (Ezetrol®), bempedoic acid (Nexletol®/ Nilemdo®) and icosapent ethyl (Vascepa®), and therefore these are included in the below search strings. Later it was later decided to exclude these interventions from the PICO and the records were excluded during the selection process.

Comparators:
Interventions listed above and other pharmacologic agents will all be considered as eligible comparators, as will placebo (with or without background therapy).

Outcomes:
Studies providing data on any of the efficacy outcomes listed below in the relevant patient populations were eligible for inclusion:

- Percentage change from baseline in LDL-C;
- Absolute change from baseline in LDL-C;
- Time adjusted LDL-C change from baseline;
- Proportion of patients achieving LDL-C targets as defined in individual trials;
- Absolute and/ or percentage change from baseline in other lipids, lipoproteins, apolipoproteins and PCSK9, inclusive of: non-HDL-cholesterol; apolipoprotein-B (ApoB); lipoprotein-a (Lp[a]); total cholesterol (TC); triglycerides; very- low-density lipoprotein cholesterol (VLDL-C); apolipoprotein-A1 (Apo-A1); high sensitivity C-reactive protein (hsCRP);
- Requirement of procedures including apheresis and revascularisation;
- Cardiovascular events (fatal and non-fatal).

The safety outcomes of interest are:

- Any adverse event (AE);
- Treatment-related AE (TRAE);
- Serious AE (SAE);
- CV-related and non-CV related mortality;
- Discontinuation due to AEs.

Health related quality of life (HRQoL):

- Change in HRQoL from baseline.

Study design:
Randomized trials of any phase were eligible for inclusion. Only studies with ≥12 weeks of follow-up and ≥10 patients per group will be included.

Publication types:
Full-text, peer-reviewed publications of trials was the most desirable form of evidence eligible for inclusion. Abstracts or oral conference presentations from 2018-2020 reporting clinical trials were eligible for inclusion if sufficient data were reported or if they supplemented data from another relevant publication. Unpublished CSRs for inclisiran were also available and eligible for inclusion. HTA documents were also be eligible for inclusion and used to supplement any missing data from published reports.

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The following publication types will be identified to enable hand-searching for additional references but will not form part of the data synthesis: Systematic reviews with or without meta-analysis and guidelines. The following study designs and publication types will not be eligible for inclusion: Non-systematic reviews, expert opinion pieces, letters, editorials, press releases, case studies of individuals, in vitro studies, animal model studies.

Limits:
Bibliographic databases, and the trials registry and trials platform, were searched from inception to present. Conferences were hand searched from 2018-2020. Study identification was limited to studies reporting randomized trials. No other limits (language, publication type or status) were applied to the search.

Search strings for the individual searches are provided in the following.

Bibliographic databases:

MEDLINE search, 08 May 2020

#	Searches	Results
1	exp hyperlipidemias/	65699
2	(hypercholesterol?emi$ or hypercholesterin?emi$ or cholester?emi$ or cholesterin?emi$ or hyperlipid?emi$ or hyperlipoprotein?emia$ or lip?emia$ or lipid?emi$ or hyperlip?emi$ or HeFH or "Heterozygous Familial Hypercholesterolemia" or hofh or "Homozygous Familial Hypercholesterolaemia" or fh or "familial hypercholesterolemia" or hypertriglycerid?emia$ or "mckusick 14575" or triglycerid?emia$ or (triglyceride adj1 storage adj1 disease$)).ti,ab,ot,hw.	110550
3	((cholesterol$ or lipid$ or LDL) adj3 (elevat$ or ascend$ or increas$ or high or rais$ or low$)).ti,ab,ot,hw.	150857
4	1 or 2 or 3	229665
5	(Inclisiran* or ALN 60212 or ALN60212 or ALN-60212 or ALN PCS or ALNPCS or ALN-PCS or ALNPCSsc or ALN-PCSsc or "ALN be,PCSsc" or "UNII-UOW2C71PG5" or "1639324-58-5").af.	73
6	(Alirocumab* or Praluent* or regn 727 or regn727 or regn-727 or sar 236553 or sar236553 or sar-236553 or HSDB 8280 or PP0SHH6V16 or 1245916-14-6).af.	622
7	(Evolocumab* or Repatha* or AMG 145 or AMG145 or AMG-145 or D10557 or HSDB 8307 or LKC0U3A8NJ or 1256937-27-5).af.	671
8	Ezetimibe/	1979
9	(Ezetimibe* or Ezetimiba* or Ezetimibum* or Absorcol* or Ach-ezetimibe* or Ag-ezetimibe* or Apo-ezetimibe* or Auro-ezetimibe* or Bio-ezetimibe* or Ezedoc* or Ezetib* or Ezetimib* or Ezetrol* or Gln-ezetimibe* or Ipg-ezetimibe* or Jamp-ezetimibe* or Liptruzet* or M-ezetimibe* or Mar-ezetimibe* or Mint-ezetimibe* or Mylan-ezetimibe* or Nexlizet* or Nra-ezetimibe* or PMS-ezetimibe* or Priva-ezetimibe* or Ran-ezetimibe* or Riva-	4392

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#	Searches	Results
	ezetimibe* or Viemm* or Vytorin* or Zetia* or Zient* or sch 582235 or sch58235 or sch-58235 or "MK 0653" or MK0653 or MK-0653 or HSDB 7737 or HSDB7737 or HSDB-7737 or EOR26LQQ24 or 163222-33-1).af.	
10	(Bempedoic* or Nexletol* or Nexlizet* or Nilemdo* or Nustendi or ESP 55016 or ESP55016 or ESP-55016 or ETC 1002 or ETC1002 or ETC-1002 or AK499358 or 1EJ6Z6Q368 or 738606-46-7).af.	68
11	(Icosapent ethyl* or Epadel* or Vascepa* or Vp-pnv-dha* or Lcosapent* or Miraxion* or AMR 101 or AMR101 or AMR-101 or Lax 101 or lax101 or lax-101 or mnd 21 or mnd21 or mnd-21 or 6GC8A4PAYH or 86227-47-6).af.	382
12	5 or 6 or 7 or 8 or 9 or 10 or 11	5537
13	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	597269
14	Randomized Controlled Trial/	505204
15	exp Randomized Controlled Trials as Topic/	135594
16	"Randomized Controlled Trial (topic)"/	0
17	Controlled Clinical Trial/	93660
18	exp Controlled Clinical Trials as Topic/	140855
19	"Controlled Clinical Trial (topic)"/	0
20	Randomization/	102678
21	Random Allocation/	102678
22	Double-Blind Method/	157463
23	Double Blind Procedure/	0
24	Double-Blind Studies/	157463
25	Single-Blind Method/	28470
26	Single Blind Procedure/	0
27	Single-Blind Studies/	28470
28	Placebos/	34859
29	Placebo/	0

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#	Searches	Results
30	Control Groups/	1667
31	Control Group/	1667
32	(random* or sham or placebo*).ti,ab,hw,kf,kw.	1483933
33	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	235067
34	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	996
35	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.	972919
36	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	43539
37	allocated.ti,ab,hw.	64855
38	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	34129
39	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	8102
40	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	402
41	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	4959
42	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	7681
43	("Phase 3" or "phase3" or "phase III" or P3 or "PIII" or "Phase 2" or "phase2" or "phase II" or P2 or "PII").ti,ab,hw,kf,kw.	183731
44	(trial or trail).ti.	223085
45	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44	2293404
46	(systematic$ adj3 review$).ti,ab,ot,hw,kw.	198423
47	meta anal$.ti,ab,kw.	170633
48	46 or 47	289191
49	45 or 48	2447607
50	4 and 12 and 49	1422

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MEDLINE search, 17 February 2021 (update search)

#	Searches	Results
1	exp hyperlipidemias/	67038
2	(hypercholesterol?emi$ or hypercholesterin?emi$ or cholester?emi$ or cholesterin?emi$ or hyperlipid?emi$ or hyperlipoprotein?emia$ or lip?emia$ or lipid?emi$ or hyperlip?emi$ or HeFH or "Heterozygous Familial Hypercholesterolemia" or hofh or "Homozygous Familial Hypercholesterolaemia" or fh or "familial hypercholesterolemia" or hypertriglycerid?emia$ or "mckusick 14575" or triglycerid?emia$ or (triglyceride adj1 storage adj1 disease$)).ti,ab,ot,hw.	114531
3	((cholesterol$ or lipid$ or LDL) adj3 (elevat$ or ascend$ or increas$ or high or rais$ or low$)).ti,ab,ot,hw.	158143
4	1 or 2 or 3	239868
5	(Inclisiran* or ALN 60212 or ALN60212 or ALN-60212 or ALN PCS or ALNPCS or ALN-PCS or ALNPCSsc or ALN-PCSsc or "ALN be,PCSsc" or "UNII-UOW2C71PG5" or "1639324-58-5").af.	115
6	(Alirocumab* or Praluent* or regn 727 or regn727 or regn-727 or sar 236553 or sar236553 or sar-236553 or HSDB 8280 or PP0SHH6V16 or 1245916-14-6).af.	718
7	(Evolocumab* or Repatha* or AMG 145 or AMG145 or AMG-145 or D10557 or HSDB 8307 or LKC0U3A8NJ or 1256937-27-5).af.	788
8	Ezetimibe/	2105
9	(Ezetimibe* or Ezetimiba* or Ezetimibum* or Absorcol* or Ach-ezetimibe* or Ag-ezetimibe* or Apo-ezetimibe* or Auro-ezetimibe* or Bio-ezetimibe* or Ezedoc* or Ezetib* or Ezetimib* or Ezetrol* or Gln-ezetimibe* or Ipg-ezetimibe* or Jamp-ezetimibe* or Liptruzet* or M-ezetimibe* or Mar-ezetimibe* or Mint-ezetimibe* or Mylan-ezetimibe* or Nexlizet* or Nra-ezetimibe* or PMS-ezetimibe* or Priva-ezetimibe* or Ran-ezetimibe* or Riva-ezetimibe* or Viemm* or Vytorin* or Zetia* or Zient* or sch 582235 or sch58235 or sch-58235 or "MK 0653" or MK0653 or MK-0653 or HSDB 7737 or HSDB7737 or HSDB-7737 or EOR26LQQ24 or 163222-33-1).af.	4697
10	(Bempedoic* or Nexletol* or Nexlizet* or Nilemdo* or Nustendi or ESP 55016 or ESP55016 or ESP-55016 or ETC 1002 or ETC1002 or ETC-1002 or AK499358 or 1EJ6Z6Q368 or 738606-46-7).af.	138
11	(Icosapent ethyl* or Epadel* or Vascepa* or Vp-pnv-dha* or Lcosapent* or Miraxion* or AMR 101 or AMR101 or AMR-101 or Lax 101 or lax101 or lax-101 or mnd 21 or mnd21 or mnd-21 or 6GC8A4PAYH or 86227-47-6).af.	476
12	5 or 6 or 7 or 8 or 9 or 10 or 11	6109

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#	Searches	Results
13	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	618931
14	Randomized Controlled Trial/	525882
15	exp Randomized Controlled Trials as Topic/	145192
16	"Randomized Controlled Trial (topic)"/	0
17	Controlled Clinical Trial/	94111
18	exp Controlled Clinical Trials as Topic/	150688
19	"Controlled Clinical Trial (topic)"/	0
20	Randomization/	104940
21	Random Allocation/	104940
22	Double-Blind Method/	163162
23	Double Blind Procedure/	0
24	Double-Blind Studies/	163162
25	Single-Blind Method/	29917
26	Single Blind Procedure/	0
27	Single-Blind Studies/	29917
28	Placebos/	35401
29	Placebo/	0
30	Control Groups/	1727
31	Control Group/	1727
32	(random* or sham or placebo*).ti,ab,hw,kf,kw.	1576187
33	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	244885
34	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	1150
35	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.	1041937

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#	Searches	Results
36	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	46667
37	allocated.ti,ab,hw.	70232
38	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	37090
39	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	9281
40	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	453
41	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	5851
42	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	8785
43	("Phase 3" or "phase3" or "phase III" or P3 or "PIII" or "Phase 2" or "phase2" or "phase II" or P2 or "PII").ti,ab,hw,kf,kw.	194450
44	(trial or trail).ti.	242802
45	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44	2430513
46	(systematic$ adj3 review$).ti,ab,ot,hw,kw.	234919
47	meta anal$.ti,ab,kw.	197572
48	46 or 47	333282
49	45 or 48	2610140
50	4 and 12 and 49	1552
51	limit 51 to yr="2020 -Current"	217

Embase search, 08 May 2020

#	Searches	Results
1	exp hyperlipidemia/	149359
2	(hypercholesterol?emi$ or hypercholesterin?emi$ or cholester?emi$ or cholesterin?emi$ or hyperlipid?emi$ or hyperlipoprotein?emia$ or lip?emia$ or lipid?emi$ or hyperlip?emi$ or HeFH or "Heterozygous Familial Hypercholesterolemia" or hofh or "Homozygous Familial	184595

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#	Searches	Results
	Hypercholesterolaemia" or fh or "familial hypercholesterolemia" or hypertriglycerid?emia$ or "mckusick 14575" or triglycerid?emia$ or (triglyceride adj1 storage adj1 disease$)).ti,ab,ot,hw.	
3	((cholesterol$ or lipid$ or LDL) adj3 (elevat$ or ascend$ or increas$ or high or rais$ or low$)).ti,ab,ot,hw.	269982
4	1 or 2 or 3	398243
5	inclisiran/	162
6	(Inclisiran* or ALN 60212 or ALN60212 or ALN-60212 or ALN PCS or ALNPCS or ALN-PCS or ALNPCSsc or ALN-PCSsc or "ALN be,PCSsc" or UNII-UOW2C71PG5 or 1639324-58-5).af.	217
7	alirocumab/	1610
8	(Alirocumab* or Praluent* or regn 727 or regn727 or regn-727 or sar 236553 or sar236553 or sar-236553 or HSDB 8280 or PP0SHH6V16 or 1245916-14-6).af.	1718
9	evolocumab/	1750
10	(Evolocumab* or Repatha* or AMG 145 or AMG145 or AMG-145 or D10557 or HSDB 8307 or LKC0U3A8NJ or 1256937-27-5).af.	1910
11	ezetimibe/	9806
12	(Ezetimibe* or Ezetimiba* or Ezetimibum* or Absorcol* or Ach-ezetimibe* or Ag-ezetimibe* or Apo-ezetimibe* or Auro-ezetimibe* or Bio-ezetimibe* or Ezedoc* or Ezetib* or Ezetimib* or Ezetrol* or Gln-ezetimibe* or Ipg-ezetimibe* or Jamp-ezetimibe* or Liptruzet* or M-ezetimibe* or Mar-ezetimibe* or Mint-ezetimibe* or Mylan-ezetimibe* or Nexlizet* or Nra-ezetimibe* or PMS-ezetimibe* or Priva-ezetimibe* or Ran-ezetimibe* or Riva-ezetimibe* or Viemm* or Vytorin* or Zetia* or Zient* or sch 582235 or sch58235 or sch-58235 or "MK 0653" or MK0653 or MK-0653 or HSDB 7737 or HSDB7737 or HSDB-7737 or EOR26LQQ24 or 163222-33-1).af.	12004
13	bempedoic acid/	142
14	(Bempedoic* or Nexletol* or Nexlizet* or Nilemdo* or ESP 55016 or ESP55016 or ESP-55016 or ETC 1002 or ETC1002 or ETC-1002 or AK499358 or 1EJ6Z6Q368 or 738606-46-7).af.	181
15	icosapentaenoic acid ethyl ester/	676

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#	Searches	Results
16	(Icosapent ethyl* or Epadel* or Vascepa* or Vp-pnv-dha* or Lcosapent* or Miraxion* or AMR 101 or AMR101 or AMR-101 or Lax 101 or lax101 or lax-101 or mnd 21 or mnd21 or mnd-21 or 6GC8A4PAYH or 86227-47-6).af.	550
17	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	14254
18	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	0
19	Randomized Controlled Trial/	597076
20	exp Randomized Controlled Trials as Topic/	177964
21	"Randomized Controlled Trial (topic)"/	177964
22	Controlled Clinical Trial/	464140
23	exp Controlled Clinical Trials as Topic/	185138
24	"Controlled Clinical Trial (topic)"/	10661
25	Randomization/	86516
26	Random Allocation/	82737
27	Double-Blind Method/	144450
28	Double Blind Procedure/	168832
29	Double-Blind Studies/	129428
30	Single-Blind Method/	36698
31	Single Blind Procedure/	38692
32	Single-Blind Studies/	38692
33	Placebos/	279312
34	Placebo/	335555
35	Control Groups/	110457
36	Control Group/	110457

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#	Searches	Results
37	(random* or sham or placebo*).ti,ab,hw,kw.	2000630
38	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kw.	294904
39	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kw.	1306
40	(control* adj3 (study or studies or trial* or group*)).ti,ab,kw.	1333689
41	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kw.	54068
42	allocated.ti,ab,hw.	82886
43	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kw.	62520
44	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kw.	12029
45	(pragmatic study or pragmatic studies).ti,ab,hw,kw.	582
46	((pragmatic or practical) adj3 trial*).ti,ab,hw,kw.	5273
47	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kw.	12081
48	("Phase 3" or "phase3" or "phase III" or P3 or "PIII" or "Phase 2" or "phase2" or "phase II" or P2 or "PII").ti,ab,hw,kw.	324269
49	(trial or trail).ti.	298138
50	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49	3182751
51	(systematic$ adj3 review$).ti,ab.	227319
52	meta$ anal$.ti,ab.	237663
53	51 or 52	371952
54	50 or 53	3382368
55	4 and 17 and 54	4490
56	(conference abstract or conference review).pt.	3776509
57	55 not 56	3626

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Embase search, 17 February 2021 (update search)

#	Searches	Results
1	exp hyperlipidemia/	163270
2	(hypercholesterol?emi$ or hypercholesterin?emi$ or cholester?emi$ or cholesterin?emi$ or hyperlipid?emi$ or hyperlipoprotein?emia$ or lip?emia$ or lipid?emi$ or hyperlip?emi$ or hefh or "Heterozygous Familial Hypercholesterolemia" or hofh or "Homozygous Familial Hypercholesterolaemia" or fh or "familial hypercholesterolemia" or hypertriglycerid?emia$ or "mckusick 14575" or triglycerid?emia$ or (triglyceride adj1 storage adj1 disease$)).ti,ab,ot,hw.	202977
3	((cholesterol$ or lipid$ or LDL) adj3 (elevat$ or ascend$ or increas$ or high or rais$ or low$)).ti,ab,ot,hw.	291216
4	1 or 2 or 3	433921
5	inclisiran/	239
6	(Inclisiran* or ALN 60212 or ALN60212 or ALN-60212 or ALN PCS or ALNPCS or ALN-PCS or ALNPCSsc or ALN-PCSsc or "ALN be,PCSsc" or UNII-UOW2C71PG5 or 1639324-58-5).af.	302
7	alirocumab/	1852
8	(Alirocumab* or Praluent* or regn 727 or regn727 or regn-727 or sar 236553 or sar236553 or sar-236553 or HSDB 8280 or PP0SHH6V16 or 1245916-14-6).af.	1976
9	evolocumab/	2067
10	(Evolocumab* or Repatha* or AMG 145 or AMG145 or AMG-145 or D10557 or HSDB 8307 or LKC0U3A8NJ or 1256937-27-5).af.	2246
11	ezetimibe/	10547
12	(Ezetimibe* or Ezetimiba* or Ezetimibum* or Absorcol* or Ach-ezetimibe* or Ag-ezetimibe* or Apo-ezetimibe* or Auro-ezetimibe* or Bio-ezetimibe* or Ezedoc* or Ezetib* or Ezetimib* or Ezetrol* or Gln-ezetimibe* or Ipg-ezetimibe* or Jamp-ezetimibe* or Liptruzet* or M-ezetimibe* or Mar-ezetimibe* or Mint-ezetimibe* or Mylan-ezetimibe* or Nexlizet* or Nra-ezetimibe* or PMS-ezetimibe* or Priva-ezetimibe* or Ran-ezetimibe* or Riva-ezetimibe* or Viemm* or Vytorin* or Zetia* or Zient* or sch 582235 or sch58235 or sch-58235 or "MK 0653" or MK0653 or MK-0653 or HSDB 7737 or HSDB7737 or HSDB-7737 or EOR26LQQ24 or 163222-33-1).af.	12916
13	bempedoic acid/	255

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#	Searches	Results
14	(Bempedoic* or Nexletol* or Nexlizet* or Nilemdo* or ESP 55016 or ESP55016 or ESP-55016 or ETC 1002 or ETC1002 or ETC-1002 or AK499358 or 1EJ6Z6Q368 or 738606-46-7).af.	302
15	icosapentaenoic acid ethyl ester/	801
16	(Icosapent ethyl* or Epadel* or Vascepa* or Vp-pnv-dha* or Lcosapent* or Miraxion* or AMR 101 or AMR101 or AMR-101 or Lax 101 or lax101 or lax-101 or mnd 21 or mnd21 or mnd-21 or 6GC8A4PAYH or 86227-47-6).af.	702
17	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	15632
18	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	0
19	Randomized Controlled Trial/	655430
20	exp Randomized Controlled Trials as Topic/	200707
21	"Randomized Controlled Trial (topic)"/	200707
22	Controlled Clinical Trial/	467714
23	exp Controlled Clinical Trials as Topic/	208727
24	"Controlled Clinical Trial (topic)"/	11618
25	Randomization/	90893
26	Random Allocation/	87083
27	Double-Blind Method/	159214
28	Double Blind Procedure/	183555
29	Double-Blind Studies/	142879
30	Single-Blind Method/	40537
31	Single Blind Procedure/	42554
32	Single-Blind Studies/	42554
33	Placebos/	310857
34	Placebo/	366653

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#	Searches	Results
35	Control Groups/	110568
36	Control Group/	110568
37	(random* or sham or placebo*).ti,ab,hw,kw.	2184103
38	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kw.	321285
39	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kw.	1533
40	(control* adj3 (study or studies or trial* or group*)).ti,ab,kw.	1466414
41	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kw.	59105
42	allocated.ti,ab,hw.	91478
43	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kw.	69089
44	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kw.	13765
45	(pragmatic study or pragmatic studies).ti,ab,hw,kw.	582
46	((pragmatic or practical) adj3 trial*).ti,ab,hw,kw.	5273
47	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kw.	14190
48	("Phase 3" or "phase3" or "phase III" or P3 or "PIII" or "Phase 2" or "phase2" or "phase II" or P2 or "PII").ti,ab,hw,kw.	351407
49	(trial or trail).ti.	334134
50	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49	3471458
51	(systematic$ adj3 review$).ti,ab.	270577
52	meta$ anal$.ti,ab.	276307
53	51 or 52	431572
54	50 or 53	3705077
55	4 and 17 and 54	4826

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#	Searches	Results
56	(conference abstract or conference review).pt.	4082647
57	55 not 56	3884
58	limit 58 to yr="2020 - 2021"	311

The Cochrane Library search, 10 May 2020

ID	Search	Hits
#1	MeSH descriptor: [Hyperlipidemias] explode all trees	6311
#2	(hypercholesterol?emi* or hypercholesterin?emi* or cholester?emi* or cholesterin?emi* or hyperlipid?emi* or hyperlipoprotein?emia* or lip?emia* or lipid?emi* or hyperlip?emi* or HeFH or "Heterozygous Familial Hypercholesterolemia" or hofh or "Homozygous Familial Hypercholesterolaemia" or fh or "familial hypercholesterolemia" or hypertriglycerid?emia* or "mckusick 14575" or triglycerid?emia* or (triglyceride NEAR/1 storage Near/1 disease*)):ti,ab,kw	15622
#3	((cholesterol* or lipid* or LDL) near/3 (elevat* or ascend* or increase* or high or rais* or low*)):ti,ab,kw	24634
#4	#1 or #2 or #3	33208
#5	(Inclisiran* or ALN 60212 or ALN60212 or ALN-60212 or ALN PCS or ALNPCS or ALN-PCS or ALNPCSsc or ALN-PCSsc or "ALN be,PCSsc" or "UNII-UOW2C71PG5" or "1639324-58-5"):ti,ab,kw	33
#6	(Alirocumab* or Praluent* or regn 727 or regn727 or regn-727 or sar 236553 or sar236553 or sar-236553 or HSDB 8280 or PP0SHH6V16 or "1245916-14-6"):ti,ab,kw	343
#7	(Evolocumab* or Repatha* or AMG 145 or AMG145 or AMG-145 or D10557 or HSDB 8307 or LKC0U3A8NJ or "1256937-27-5"):ti,ab,kw	328
#8	MeSH descriptor: [Ezetimibe] this term only	690
#9	(Ezetimibe* or Ezetimiba* or Ezetimibum* or Absorcol* or Ach-ezetimibe* or Ag-ezetimibe* or Apo-ezetimibe* or Auro-ezetimibe* or Bio-ezetimibe* or Ezedoc* or Ezetib* or Ezetimib* or Ezetrol* or Gln-ezetimibe* or Ipg-ezetimibe* or Jamp-ezetimibe* or Liptruzet* or M-ezetimibe* or Mar-ezetimibe* or Mint-ezetimibe* or Mylan-ezetimibe* or Nexlizet* or Nra-ezetimibe* or PMS-ezetimibe* or Priva-ezetimibe* or Ran-ezetimibe* or Riva-ezetimibe* or Viemm* or Vytorin* or Zetia* or Zient* or sch 582235 or sch58235 or sch-58235 or "MK 0653" or MK0653 or MK-0653 or HSDB 7737 or HSDB7737 or HSDB-7737 or EOR26LQQ24 or "163222-33-1"):ti,ab,kw	1647
#10	(Bempedoic* or Nexletol* or Nexlizet* or Nilemdo* or Nustendi or ESP 55016 or ESP55016 or ESP-55016 or ETC 1002 or ETC1002 or ETC-1002 or AK499358 or 1EJ6Z6Q368 or "738606-46-7"):ti,ab,kw	58
#11	(Icosapent ethyl* or Epadel* or Vascepa* or Vp-pnv-dha* or Lcosapent* or Miraxion* or AMR 101 or AMR101 or AMR-101 or Lax 101 or lax101 or lax-101 or mnd 21 or mnd21 or mnd-21 or 6GC8A4PAYH or "86227-47-6"):ti,ab,kw	114
#12	#5 or #6 or #7 or #8 or #9 or #10 or #11	2280
#13	#4 and #12	1800

The Cochrane Library search, 17 February 2021 (update search)

ID	Search	Hits
#1	MeSH descriptor: [Hyperlipidemias] explode all trees	6484
#2	(hypercholesterol?emi* or hypercholesterin?emi* or cholester?emi* or cholesterin?emi* or hyperlipid?emi* or hyperlipoprotein?emia* or lip?emia* or lipid?emi* or hyperlip?emi* or HeFH or "Heterozygous Familial Hypercholesterolemia" or	

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hofh or "Homozygous Familial Hypercholesterolaemia" or fh or "familial hypercholesterolemia" or hypertriglycerid?emia* or "mckusick 14575" or triglycerid?emia* or (triglyceride NEAR/1 storage Near/1 disease*)):ti,ab,kw		16462
#3	((cholesterol* or lipid* or LDL) near/3 (elevat* or ascend* or increase* or high or rais* or low*)):ti,ab,kw	26036
#4	#1 or #2 or #3	35170
#5	(Inclisiran* or ALN 60212 or ALN60212 or ALN-60212 or ALN PCS or ALNPCS or ALN-PCS or ALNPCSsc or ALN-PCSsc or "ALN be,PCSsc" or "UNII-UOW2C71PG5" or "1639324-58-5"):ti,ab,kw	49
#6	(Alirocumab* or Praluent* or regn 727 or regn727 or regn-727 or sar 236553 or sar236553 or sar-236553 or HSDB 8280 or PP0SHH6V16 or "1245916-14-6"):ti,ab,kw	390
#7	(Evolocumab* or Repatha* or AMG 145 or AMG145 or AMG-145 or D10557 or HSDB 8307 or LKC0U3A8NJ or "1256937-27-5"):ti,ab,kw	389
#8	MeSH descriptor: [Ezetimibe] this term only	717
#9	(Ezetimibe* or Ezetimiba* or Ezetimibum* or Absorcol* or Ach-ezetimibe* or Ag-ezetimibe* or Apo-ezetimibe* or Auro-ezetimibe* or Bio-ezetimibe* or Ezedoc* or Ezetib* or Ezetimib* or Ezetrol* or Gln-ezetimibe* or Ipg-ezetimibe* or Jamp-ezetimibe* or Liptruzet* or M-ezetimibe* or Mar-ezetimibe* or Mint-ezetimibe* or Mylan-ezetimibe* or Nexlizet* or Nra-ezetimibe* or PMS-ezetimibe* or Priva-ezetimibe* or Ran-ezetimibe* or Riva-ezetimibe* or Viemm* or Vytorin* or Zetia* or Zient* or sch 582235 or sch58235 or sch-58235 or "MK 0653" or MK0653 or MK-0653 or HSDB 7737 or HSDB7737 or HSDB-7737 or EOR26LQQ24 or "163222-33-1"):ti,ab,kw	1748
#10	(Bempedoic* or Nexletol* or Nexlizet* or Nilemdo* or Nustendi or ESP 55016 or ESP55016 or ESP-55016 or ETC 1002 or ETC1002 or ETC-1002 or AK499358 or 1EJ6Z6Q368 or "738606-46-7"):ti,ab,kw	81
#11	(Icosapent ethyl* or Epadel* or Vascepa* or Vp-pnv-dha* or Lcosapent* or Miraxion* or AMR 101 or AMR101 or AMR-101 or Lax 101 or lax101 or lax-101 or mnd 21 or mnd21 or mnd-21 or 6GC8A4PAYH or "86227-47-6"):ti,ab,kw	140
#12	#5 or #6 or #7 or #8 or #9 or #10 or #11	2514
#13	#4 and #12	1967
#14	#13 with Publication Year from 2020 to 2021, in Trials	138

PubMed search, 08 May 2020

((Inclisiran* or Evolocumab* or Repatha* or Alirocumab* or Praluent* or Ezetimibe* or Ezetrol* or Bempedoic* or Nexletol* or Nilemdo* or Icosapent ethyl* or Vascepa*)) AND ((((pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]))))	495

PubMed search, 17 February 2021 (update search)

((Inclisiran* or Evolocumab* or Repatha* or Alirocumab* or Praluent* or Ezetimibe* or Ezetrol* or Bempedoic* or Nexletol* or Nilemdo* or Icosapent ethyl* or Vascepa*)) AND ((((pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]))))	196

Trial registers

Clinicaltrials.gov search, 09 May 2020

Records retrieved: 578

(EXPAND[Concept] "Heterozygous Familial Hypercholesterolemia" OR EXPAND[Concept] "Homozygous Familial Hypercholesterolaemia" OR EXPAND[Concept] "familial hypercholesterolemia" OR hypercholesterolaemia OR hypercholesterolemia OR hypercholesterolaemi OR hypercholesterolemi OR hyperlipoproteinemia OR hyperlipoproteinaemia OR hyperlipoproteinemi OR hyperlipoproteinaemi OR hypercholesterinemia OR hypercholesterinaemia OR hypercholesterinemi OR hypercholesterinaemi OR hyperlipidemia OR hyperlipidaemia OR hyperlipidemi OR hyperlipidaemi OR cholesteremia OR cholesteraemia OR cholesteremi OR cholesteraemi OR cholesterinemia OR cholesterinaemia OR cholesterinemi OR cholesterinaemi OR lipemia OR lipaemia OR lipemi OR lipaemi OR lipidemia OR lipidaemia OR lipidemi OR lipidaemi OR hyperlipemia OR hyperlipaemia OR hyperlipemi OR hyperlipaemi OR HeFH OR hofh OR fh OR hypertriglyceridemia OR hypertriglyceridaemia OR

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EXPAND[Concept] "mckusick 14575" OR triglyceridemia OR triglyceridaemia OR EXPAND[Concept] "triglyceride storage" OR (cholesterol OR lipid OR LDL) AND (elevate OR elevated or ascend OR ascended OR increase OR increasing OR increased OR high OR raise OR raised OR raising OR low OR lower or lowered)) AND ((Inclisiran OR Inclisirantm OR Inclisiranr OR “ALN 60212” OR ALN60212 OR ALN-60212 OR “ALN PCS” OR ALNPCS OR ALN-PCS OR ALNPCSsc OR ALN-PCSsc OR EXPAND[Concept] "ALN be,PCSsc" OR EXPAND[Concept] "UNII-UOW2C71PG5" OR EXPAND[Concept] "1639324-58-5") OR (Alirocumab OR Alirocumabtm OR Alirocumabr OR Praluent OR “regn 727” OR regn727 OR regn-727 OR “sar 236553” OR sar236553 OR sar-236553 OR “HSDB 8280” OR PP0SHH6V16 OR 1245916-14-6) OR (Evolocumab OR Evolocumabtm OR Evolocumabr OR Repatha OR “AMG 145” OR AMG145 OR AMG-145 OR D10557 OR “HSDB 8307” OR LKC0U3A8NJ OR 1256937-27-5) OR (Ezetimibe OR Ezetimiba OR Ezetimibetm OR Ezetimibatm OR Ezetimiber OR Ezetimibar OR Ezetimibum OR Absorcol OR Ach-ezetimibe OR Ag-ezetimibe OR Apo-ezetimibe OR Auro-ezetimibe OR Bio-ezetimibe OR Ezedoc OR Ezetib OR Ezetimib OR Ezetrol OR Gln-ezetimibe OR Ipg-ezetimibe OR Jamp-ezetimibe OR Liptruzet OR M-ezetimibe OR Mar-ezetimibe OR Mint-ezetimibe OR Mylan-ezetimibe OR Nexlizet OR Nra-ezetimibe OR PMS-ezetimibe OR Priva-ezetimibe OR Ran-ezetimibe OR Riva-ezetimibe OR Viemm OR Vytorin OR Zetia OR Zient OR “sch 582235” OR sch58235 OR sch-58235 OR EXPAND[Concept] "MK 0653" OR MK0653 OR MK-0653 OR “HSDB 7737” OR HSDB7737 OR HSDB-7737 OR EOR26LQQ24 OR 163222-33-1) OR (Bempedoic OR Bempedoictm OR Bempedoicr OR Nexletol OR Nexlizet OR Nilemdo OR “ESP 55016” OR ESP55016 OR ESP-55016 OR “ETC 1002” OR ETC1002 OR ETC-1002 OR AK499358 OR 1EJ6Z6Q368 OR 738606-46-7) OR (Icosapent OR Icosapenttm OR Icosapentr OR Epadel OR Vascepa OR Vp-pnv-dha OR Lcosapent OR Miraxion OR EXPAND[Concept] "AMR 101" OR AMR101 OR AMR-101 OR EXPAND[Concept] "Lax 101" OR lax101 OR lax-101 OR EXPAND[Concept] "mnd 21" OR mnd21 OR mnd-21 OR 6GC8A4PAYH OR 86227-47-6))

Clinicaltrials.gov search, 17 February 2021 (update search)

Records retrieved: 70 (from January 2020 to present, previously identified citations from original search were removed)

(EXPAND[Concept] "Heterozygous Familial Hypercholesterolemia" OR EXPAND[Concept] "Homozygous Familial Hypercholesterolaemia" OR EXPAND[Concept] "familial hypercholesterolemia" OR hypercholesterolaemia OR hypercholesterolemia OR hypercholesterolaemi OR hypercholesterolemi OR hyperlipoproteinemia OR hyperlipoproteinaemia OR hyperlipoproteinemi OR hyperlipoproteinaemi OR hypercholesterinemia OR hypercholesterinaemia OR hypercholesterinemi OR hypercholesterinaemi OR hyperlipidemia OR hyperlipidaemia OR hyperlipidemi OR hyperlipidaemi OR cholesteremia OR cholesteraemia OR cholesteremi OR cholesteraemi OR cholesterinemia OR cholesterinaemia OR cholesterinemi OR cholesterinaemi OR lipemia OR lipaemia OR lipemi OR lipaemi OR lipidemia OR lipidaemia OR lipidemi OR lipidaemi OR hyperlipemia OR hyperlipaemia OR hyperlipemi OR hyperlipaemi OR HeFH OR hofh OR fh OR hypertriglyceridemia OR hypertriglyceridaemia OR EXPAND[Concept] "mckusick 14575" OR triglyceridemia OR triglyceridaemia OR EXPAND[Concept] "triglyceride storage" OR (cholesterol OR lipid OR LDL) AND (elevate OR elevated or ascend OR ascended OR increase OR increasing OR increased OR high OR raise OR raised OR raising OR low OR lower or lowered)) AND ((Inclisiran OR Inclisirantm OR Inclisiranr OR “ALN 60212” OR ALN60212 OR ALN-60212 OR “ALN PCS” OR ALNPCS OR ALN-PCS OR ALNPCSsc OR ALN-PCSsc OR EXPAND[Concept] "ALN be,PCSsc" OR EXPAND[Concept] "UNII-UOW2C71PG5" OR EXPAND[Concept] "1639324-58-5") OR (Alirocumab OR Alirocumabtm OR Alirocumabr OR Praluent OR “regn 727” OR regn727 OR regn-727 OR “sar 236553” OR sar236553 OR sar-236553 OR “HSDB 8280” OR PP0SHH6V16 OR 1245916-14-6) OR (Evolocumab OR Evolocumabtm OR Evolocumabr OR Repatha OR “AMG 145” OR AMG145 OR AMG-145 OR D10557 OR “HSDB 8307” OR LKC0U3A8NJ OR 1256937-27-5) OR (Ezetimibe OR Ezetimiba OR Ezetimibetm OR Ezetimibatm OR Ezetimiber OR Ezetimibar OR Ezetimibum OR Absorcol OR Ach-ezetimibe OR Ag-ezetimibe OR Apo-ezetimibe OR Auro-ezetimibe OR Bio-ezetimibe OR Ezedoc OR Ezetib OR Ezetimib OR Ezetrol OR Gln-ezetimibe OR Ipg-ezetimibe OR Jamp-ezetimibe OR Liptruzet OR M-ezetimibe OR Mar-ezetimibe OR Mint-ezetimibe OR Mylan-ezetimibe OR Nexlizet OR Nra-ezetimibe OR PMS-ezetimibe OR Priva-ezetimibe OR Ran-ezetimibe OR Riva-ezetimibe OR Viemm OR Vytorin OR Zetia OR Zient OR “sch 582235” OR sch58235 OR sch-58235 OR EXPAND[Concept] "MK 0653" OR MK0653 OR MK-0653 OR “HSDB 7737” OR HSDB7737 OR HSDB-7737 OR EOR26LQQ24 OR 163222-33-1) OR (Bempedoic OR Bempedoictm OR Bempedoicr OR Nexletol OR Nexlizet OR Nilemdo OR “ESP 55016” OR ESP55016 OR ESP-55016 OR “ETC 1002” OR ETC1002 OR ETC-1002 OR AK499358 OR 1EJ6Z6Q368 OR

738606-46-7) OR (Icosapent OR Icosapenttm OR Icosapentr OR Epadel OR Vascepa OR Vp-pnv-dha OR Lcosapent OR Miraxion OR EXPAND[Concept] "AMR 101" OR AMR101 OR AMR-101 OR EXPAND[Concept] "Lax 101" OR lax101 OR lax-101 OR EXPAND[Concept] "mnd 21" OR mnd21 OR mnd-21 OR 6GC8A4PAYH OR 86227-47-6))

EU Clinical Trials Register search, 09 May 2020

Retrieved records: 117

117 result(s) found for: (((hypercholesterolaemia OR hypercholesterolemia OR hypercholesterolaemi OR hypercholesterolemi OR hyperlipoproteinemia OR hyperlipoproteinaemia OR hyperlipoproteinemi OR hyperlipoproteinaemi OR hypercholesterinemia OR hypercholesterinaemia OR hypercholesterinemi OR hypercholesterinaemi OR hyperlipidemia OR hyperlipidaemia OR hyperlipidemi OR hyperlipidaemi OR cholesteremia OR cholesteraemia OR cholesteremi OR cholesteraemi OR cholesterinemia OR cholesterinaemia OR cholesterinemi OR cholesterinaemi OR lipemia OR lipaemia OR lipemi OR lipaemi OR lipidemia OR lipidaemia OR lipidemi OR lipidaemi OR hyperlipemia OR hyperlipaemia OR hyperlipemi OR hyperlipaemi OR HeFH OR hofh OR fh OR hypertriglyceridemia OR hypertriglyceridaemia OR "mckusick 14575" OR triglyceridemia OR triglyceridaemia OR "triglyceride storage" OR "Heterozygous Familial Hypercholesterolemia" OR "Homozygous Familial Hypercholesterolaemia" OR "familial hypercholesterolemia") OR ((cholesterol OR lipid OR LDL) AND (elevate OR elevated or ascend OR ascended OR increase OR increasing OR increased OR high OR raise OR raised OR raising OR low OR lower or lowered))) AND (Inclisiran OR Inclisirantm OR Inclisiranr OR "ALN 60212" OR ALN60212 OR ALN-60212 OR "ALN PCS" OR ALNPCS OR ALN-PCS OR ALNPCSsc OR ALN-PCSsc OR "ALN be PCSsc" OR "UNII-UOW2C71PG5" OR "1639324-58-5" OR Alirocumab OR Alirocumabtm OR Alirocumabr OR Praluent OR "regn 727" OR regn727 OR regn-727 OR "sar 236553" OR sar236553 OR sar-236553 OR "HSDB 8280" OR PP0SHH6V16 OR 1245916-14-6 OR Evolocumab OR Evolocumabtm OR Evolocumabr OR Repatha OR "AMG 145" OR AMG145 OR AMG-145 OR D10557 OR "HSDB 8307" OR LKC0U3A8NJ OR 1256937-27-5 OR Ezetimibe OR Ezetimiba OR Ezetimibetm OR Ezetimibatm OR Ezetimiber OR Ezetimibar OR Ezetimibum OR Absorcol OR Ach-ezetimibe OR Ag-ezetimibe OR Apo-ezetimibe OR Auro-ezetimibe OR Bio-ezetimibe OR Ezedoc OR Ezetib OR Ezetimib OR Ezetrol OR Gln-ezetimibe OR Ipg-ezetimibe OR Jamp-ezetimibe OR Liptruzet OR M-ezetimibe OR Mar-ezetimibe OR Mint-ezetimibe OR Mylan-ezetimibe OR Nexlizet OR Nra-ezetimibe OR PMS-ezetimibe OR Priva-ezetimibe OR Ran-ezetimibe OR Riva-ezetimibe OR Viemm OR Vytorin OR Zetia OR Zient OR "sch 582235" OR sch58235 OR sch-58235 OR "MK 0653" OR MK0653 OR MK-0653 OR "HSDB 7737" OR HSDB7737 OR HSDB-7737 OR EOR26LQQ24 OR 163222-33-1 OR Bempedoic OR Bempedoictm OR Bempedoicr OR Nexletol OR Nexlizet OR Nilemdo OR "ESP 55016" OR ESP55016 OR ESP-55016 OR "ETC 1002" OR ETC1002 OR ETC-1002 OR AK499358 OR 1EJ6Z6Q368 OR 738606-46-7 OR Icosapent OR Icosapenttm OR Icosapentr OR Epadel OR Vascepa OR Vp-pnv-dha OR Lcosapent OR Miraxion OR "AMR 101" OR AMR101 OR AMR-101 OR "Lax 101" OR lax101 OR lax-101 OR "mnd 21" OR mnd21 OR mnd-21 OR 6GC8A4PAYH OR 86227-47-6)).

EU Clinical Trials Register search, 18 February 2021 (update search)

Retrieved records: 11 (from January 2020 to present)

11 result(s) found for: (((hypercholesterolaemia OR hypercholesterolemia OR hypercholesterolaemi OR hypercholesterolemi OR hyperlipoproteinemia OR hyperlipoproteinaemia OR hyperlipoproteinemi OR hyperlipoproteinaemi OR hypercholesterinemia OR hypercholesterinaemia OR hypercholesterinemi OR hypercholesterinaemi OR hyperlipidemia OR hyperlipidaemia OR hyperlipidemi OR hyperlipidaemi OR cholesteremia OR cholesteraemia OR cholesteremi OR cholesteraemi OR cholesterinemia OR cholesterinaemia OR cholesterinemi OR cholesterinaemi OR lipemia OR lipaemia OR lipemi OR lipaemi OR lipidemia OR lipidaemia OR lipidemi OR lipidaemi OR hyperlipemia OR hyperlipaemia OR hyperlipemi OR hyperlipaemi OR HeFH OR hofh OR fh OR hypertriglyceridemia OR hypertriglyceridaemia OR "mckusick 14575" OR triglyceridemia OR triglyceridaemia OR "triglyceride storage" OR "Heterozygous Familial Hypercholesterolemia" OR "Homozygous Familial Hypercholesterolaemia" OR "familial hypercholesterolemia") OR ((cholesterol OR lipid OR LDL) AND (elevate OR elevated or ascend OR ascended OR increase OR increasing OR increased OR high OR raise OR raised OR raising OR low OR lower or lowered))) AND (Inclisiran OR Inclisirantm OR Inclisiranr OR "ALN 60212" OR ALN60212 OR ALN-60212 OR "ALN PCS" OR ALNPCS OR ALN-PCS OR ALNPCSsc OR ALN-PCSsc OR "ALN be PCSsc" OR "UNII-UOW2C71PG5" OR "1639324-58-5" OR Alirocumab OR Alirocumabtm OR Alirocumabr OR Praluent OR

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"regn 727" OR regn727 OR regn-727 OR "sar 236553" OR sar236553 OR sar-236553 OR "HSDB 8280" OR PP0SHH6V16 OR 1245916-14-6 OR Evolocumab OR Evolocumabtm OR Evolocumabr OR Repatha OR "AMG 145" OR AMG145 OR AMG-145 OR D10557 OR "HSDB 8307" OR LKC0U3A8NJ OR 1256937-27-5 OR Ezetimibe OR Ezetimiba OR Ezetimibetm OR Ezetimibatm OR Ezetimiber OR Ezetimibar OR Ezetimibum OR Absorcol OR Ach-ezetimibe OR Ag-ezetimibe OR Apo-ezetimibe OR Auro-ezetimibe OR Bio-ezetimibe OR Ezedoc OR Ezetib OR Ezetimib OR Ezetrol OR Gln-ezetimibe OR Ipg-ezetimibe OR Jamp-ezetimibe OR Liptruzet OR M-ezetimibe OR Mar-ezetimibe OR Mint-ezetimibe OR Mylan-ezetimibe OR Nexlizet OR Nra-ezetimibe OR PMS-ezetimibe OR Priva-ezetimibe OR Ran-ezetimibe OR Riva-ezetimibe OR Viemm OR Vytorin OR Zetia OR Zient OR "sch 582235" OR sch58235 OR sch-58235 OR "MK 0653" OR MK0653 OR MK-0653 OR "HSDB 7737" OR HSDB7737 OR HSDB-7737 OR EOR26LQQ24 OR 163222-33-1 OR Bempedoic OR Bempedoictm OR Bempedoicr OR Nexletol OR Nexlizet OR Nilemdo OR "ESP 55016" OR ESP55016 OR ESP-55016 OR "ETC 1002" OR ETC1002 OR ETC-1002 OR AK499358 OR 1EJ6Z6Q368 OR 738606-46-7 OR Icosapent OR Icosapenttm OR Icosapentr OR Epadel OR Vascepa OR Vp-pnv-dha OR Lcosapent OR Miraxion OR "AMR 101" OR AMR101 OR AMR-101 OR "Lax 101" OR lax101 OR lax-101 OR "mnd 21" OR mnd21 OR mnd-21 OR 6GC8A4PAYH OR 86227-47-6)).

Conferences

Conference searching results

Database/ conference	N of studies identified		SLR Update
Embase	188		62
CPCI-S	43		4
Heart UK	2	24	-
Annual Scientific Session and Expo of the American-College-of-Cardiology (ACC)	2	41	-
Congress of the European-Atherosclerosis-Society (EAS)	1	42	6
International Symposium on Atherosclerosis (ISA)	0	18	-
Scientific sessions of the American Heart Association (AHA)	81		4
Congress of the European Society of Cardiology (ESC)	54		9
Total	496		85

Heart UK 2020 got cancelled, ACC 2020 is already included in original SLR as conducted in March 2020, ISA was not planned for 2020

Embase conference search, 08 May 2020

#	Searches	Results
1	exp hyperlipidemia/	149359
2	(hypercholesterol?emi$ or hypercholesterin?emi$ or cholester?emi$ or cholesterin?emi$ or hyperlipid?emi$ or hyperlipoprotein?emia$ or lip?emia$ or lipid?emi$ or hyperlip?emi$ or HeFH or "Heterozygous Familial Hypercholesterolemia" or hofh or "Homozygous Familial Hypercholesterolaemia" or fh or "familial hypercholesterolemia" or hypertriglycerid?emia$ or "mckusick 14575" or triglycerid?emia$ or (triglyceride adj1 storage adj1 disease$)).ti,ab,ot,hw.	184595

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#	Searches	Results
3	((cholesterol$ or lipid$ or LDL) adj3 (elevat$ or ascend$ or increas$ or high or rais$ or low$)).ti,ab,ot,hw.	269982
4	1 or 2 or 3	398243
5	inclisiran/	162
6	(Inclisiran* or ALN 60212 or ALN60212 or ALN-60212 or ALN PCS or ALNPCS or ALN-PCS or ALNPCSsc or ALN-PCSsc or "ALN be,PCSsc" or "UNII-UOW2C71PG5" or "1639324-58-5").af.	217
7	alirocumab/	1610
8	(Alirocumab* or Praluent* or regn 727 or regn727 or regn-727 or sar 236553 or sar236553 or sar-236553 or HSDB 8280 or PP0SHH6V16 or 1245916-14-6).af.	1718
9	evolocumab/	1750
10	(Evolocumab* or Repatha* or AMG 145 or AMG145 or AMG-145 or D10557 or HSDB 8307 or LKC0U3A8NJ or 1256937-27-5).af.	1910
11	ezetimibe/	9806
12	(Ezetimibe* or Ezetimiba* or Ezetimibum* or Absorcol* or Ach-ezetimibe* or Ag-ezetimibe* or Apo-ezetimibe* or Auro-ezetimibe* or Bio-ezetimibe* or Ezedoc* or Ezetib* or Ezetimib* or Ezetrol* or Gln-ezetimibe* or Ipg-ezetimibe* or Jamp-ezetimibe* or Liptruzet* or M-ezetimibe* or Mar-ezetimibe* or Mint-ezetimibe* or Mylan-ezetimibe* or Nexlizet* or Nra-ezetimibe* or PMS-ezetimibe* or Priva-ezetimibe* or Ran-ezetimibe* or Riva-ezetimibe* or Viemm* or Vytorin* or Zetia* or Zient* or sch 582235 or sch58235 or sch-58235 or "MK 0653" or MK0653 or MK-0653 or HSDB 7737 or HSDB7737 or HSDB-7737 or EOR26LQQ24 or 163222-33-1).af.	12004
13	bempedoic acid/	142
14	(Bempedoic* or Nexletol* or Nexlizet* or Nilemdo* or ESP 55016 or ESP55016 or ESP-55016 or ETC 1002 or ETC1002 or ETC-1002 or AK499358 or 1EJ6Z6Q368 or 738606-46-7).af.	181
15	icosapentaenoic acid ethyl ester/	676
16	(Icosapent ethyl* or Epadel* or Vascepa* or Vp-pnv-dha* or Lcosapent* or Miraxion* or AMR 101 or AMR101 or AMR-101 or Lax 101 or lax101 or lax-101 or mnd 21 or mnd21 or mnd-21 or 6GC8A4PAYH or 86227-47-6).af.	550
17	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	14254
18	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	0

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#	Searches	Results
19	Randomized Controlled Trial/	597076
20	exp Randomized Controlled Trials as Topic/	177964
21	"Randomized Controlled Trial (topic)"/	177964
22	Controlled Clinical Trial/	464140
23	exp Controlled Clinical Trials as Topic/	185138
24	"Controlled Clinical Trial (topic)"/	10661
25	Randomization/	86516
26	Random Allocation/	82737
27	Double-Blind Method/	144450
28	Double Blind Procedure/	168832
29	Double-Blind Studies/	129428
30	Single-Blind Method/	36698
31	Single Blind Procedure/	38692
32	Single-Blind Studies/	38692
33	Placebos/	279312
34	Placebo/	335555
35	Control Groups/	110457
36	Control Group/	110457
37	(random* or sham or placebo*).ti,ab,hw,kw.	2000630
38	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kw.	294904
39	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kw.	1306
40	(control* adj3 (study or studies or trial* or group*)).ti,ab,kw.	1333689
41	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kw.	54068

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#	Searches	Results
42	allocated.ti,ab,hw.	82886
43	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kw.	62520
44	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kw.	12029
45	(pragmatic study or pragmatic studies).ti,ab,hw,kw.	582
46	((pragmatic or practical) adj3 trial*).ti,ab,hw,kw.	5273
47	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kw.	12081
48	("Phase 3" or "phase3" or "phase III" or P3 or "PIII" or "Phase 2" or "phase2" or "phase II" or P2 or "PII").ti,ab,hw,kw.	324269
49	(trial or trail).ti.	298138
50	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49	3182751
51	(systematic$ adj3 review$).ti,ab.	227319
52	meta$ anal$.ti,ab.	237663
53	51 or 52	371952
54	50 or 53	3382368
55	4 and 17 and 54	4490
56	(conference abstract or conference review).pt.	3776509
57	55 and 56	864
58	(2018* or 2019* or 2020*).yr.	3733132
59	57 and 58	188

Embase conference search, 17 February 2021 (update search)

#	Searches	Results
1	exp hyperlipidemia/	163270

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#	Searches	Results
2	(hypercholesterol?emi$ or hypercholesterin?emi$ or cholester?emi$ or cholesterin?emi$ or hyperlipid?emi$ or hyperlipoprotein?emia$ or lip?emia$ or lipid?emi$ or hyperlip?emi$ or HeFH or "Heterozygous Familial Hypercholesterolemia" or hofh or "Homozygous Familial Hypercholesterolaemia" or fh or "familial hypercholesterolemia" or hypertriglycerid?emia$ or "mckusick 14575" or triglycerid?emia$ or (triglyceride adj1 storage adj1 disease$)).ti,ab,ot,hw.	202977
3	((cholesterol$ or lipid$ or LDL) adj3 (elevat$ or ascend$ or increas$ or high or rais$ or low$)).ti,ab,ot,hw.	291216
4	1 or 2 or 3	433921
5	inclisiran/	239
6	(Inclisiran* or ALN 60212 or ALN60212 or ALN-60212 or ALN PCS or ALNPCS or ALN-PCS or ALNPCSsc or ALN-PCSsc or "ALN be,PCSsc" or "UNII-UOW2C71PG5" or "1639324-58-5").af.	302
7	alirocumab/	1852
8	(Alirocumab* or Praluent* or regn 727 or regn727 or regn-727 or sar 236553 or sar236553 or sar-236553 or HSDB 8280 or PP0SHH6V16 or 1245916-14-6).af.	1976
9	evolocumab/	2067
10	(Evolocumab* or Repatha* or AMG 145 or AMG145 or AMG-145 or D10557 or HSDB 8307 or LKC0U3A8NJ or 1256937-27-5).af.	2246
11	ezetimibe/	10547
12	(Ezetimibe* or Ezetimiba* or Ezetimibum* or Absorcol* or Ach-ezetimibe* or Ag-ezetimibe* or Apo-ezetimibe* or Auro-ezetimibe* or Bio-ezetimibe* or Ezedoc* or Ezetib* or Ezetimib* or Ezetrol* or Gln-ezetimibe* or Ipg-ezetimibe* or Jamp-ezetimibe* or Liptruzet* or M-ezetimibe* or Mar-ezetimibe* or Mint-ezetimibe* or Mylan-ezetimibe* or Nexlizet* or Nra-ezetimibe* or PMS-ezetimibe* or Priva-ezetimibe* or Ran-ezetimibe* or Riva-ezetimibe* or Viemm* or Vytorin* or Zetia* or Zient* or sch 582235 or sch58235 or sch-58235 or "MK 0653" or MK0653 or MK-0653 or HSDB 7737 or HSDB7737 or HSDB-7737 or EOR26LQQ24 or 163222-33-1).af.	12916
13	bempedoic acid/	255
14	(Bempedoic* or Nexletol* or Nexlizet* or Nilemdo* or ESP 55016 or ESP55016 or ESP-55016 or ETC 1002 or ETC1002 or ETC-1002 or AK499358 or 1EJ6Z6Q368 or 738606-46-7).af.	302
15	icosapentaenoic acid ethyl ester/	801

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#	Searches	Results
16	(Icosapent ethyl* or Epadel* or Vascepa* or Vp-pnv-dha* or Lcosapent* or Miraxion* or AMR 101 or AMR101 or AMR-101 or Lax 101 or lax101 or lax-101 or mnd 21 or mnd21 or mnd-21 or 6GC8A4PAYH or 86227-47-6).af.	702
17	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	15632
18	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	0
19	Randomized Controlled Trial/	655430
20	exp Randomized Controlled Trials as Topic/	200707
21	"Randomized Controlled Trial (topic)"/	200707
22	Controlled Clinical Trial/	467714
23	exp Controlled Clinical Trials as Topic/	208727
24	"Controlled Clinical Trial (topic)"/	11618
25	Randomization/	90893
26	Random Allocation/	87083
27	Double-Blind Method/	159214
28	Double Blind Procedure/	183555
29	Double-Blind Studies/	142879
30	Single-Blind Method/	40537
31	Single Blind Procedure/	42554
32	Single-Blind Studies/	42554
33	Placebos/	310857
34	Placebo/	366653
35	Control Groups/	110568
36	Control Group/	110568
37	(random* or sham or placebo*).ti,ab,hw,kw.	2184103

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#	Searches	Results
38	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kw.	321285
39	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kw.	1533
40	(control* adj3 (study or studies or trial* or group*)).ti,ab,kw.	1466414
41	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kw.	59105
42	allocated.ti,ab,hw.	91478
43	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kw.	69089
44	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kw.	13765
45	(pragmatic study or pragmatic studies).ti,ab,hw,kw.	680
46	((pragmatic or practical) adj3 trial*).ti,ab,hw,kw.	6246
47	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kw.	14190
48	("Phase 3" or "phase3" or "phase III" or P3 or "PIII" or "Phase 2" or "phase2" or "phase II" or P2 or "PII").ti,ab,hw,kw.	351407
49	(trial or trail).ti.	334134
50	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49	3471458
51	(systematic$ adj3 review$).ti,ab.	270577
52	meta$ anal$.ti,ab.	276307
53	51 or 52	431572
54	50 or 53	3705077
55	4 and 17 and 54	4826
56	(conference abstract or conference review).pt.	4082647
57	55 and 56	942
58	(2018* or 2019* or 2020*).yr.	5084170
59	57 and 58	263

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#	Searches	Results
60	limit 60 to yr="2020 - 2021"	62

CPCI-S conference search, 08 May 2020

# 12	43	#10 AND #3 **Refined by: PUBLICATION YEARS:** (2020 OR 2019 OR 2018) *Indexes=CPCI-S Timespan=All years*
# 11	241	#10 AND #3 *Indexes=CPCI-S Timespan=All years*
# 10	825	#9 OR #8 OR #7 OR #6 OR #5 OR #4 *Indexes=CPCI-S Timespan=All years*
# 9	29	**TOPIC:** ((Icosapent ethyl* or Epadel* or Vascepa* or Vp-pnv-dha* or Lcosapent* or Miraxion* or AMR 101 or AMR101 or AMR-101 or Lax 101 or lax101 or lax-101 or mnd 21 or mnd21 or mnd-21 or 6GC8A4PAYH or "86227-47-6")) *Indexes=CPCI-S Timespan=All years*
# 8	22	**TOPIC:** ((Bempedoic* or Nexletol* or Nexlizet* or Nilemdo* or Nustendi or ESP 55016 or ESP55016 or ESP-55016 or ETC 1002 or ETC1002 or ETC-1002 or AK499358 or 1EJ6Z6Q368 or "738606-46-7")) *Indexes=CPCI-S Timespan=All years*
# 7	550	**TOPIC:** ((Ezetimibe* or Ezetimiba* or Ezetimibum* or Absorcol* or Ach-ezetimibe* or Ag-ezetimibe* or Apo-ezetimibe* or Auro-ezetimibe* or Bio-ezetimibe* or Ezedoc* or Ezetib* or Ezetimib* or Ezetrol* or Gln-ezetimibe* or Ipg-ezetimibe* or Jamp-ezetimibe* or Liptruzet* or M-ezetimibe* or Mar-ezetimibe* or Mint-ezetimibe* or Mylan-ezetimibe* or Nexlizet* or Nra-ezetimibe* or PMS-ezetimibe* or Priva-ezetimibe* or Ran-ezetimibe* or Riva-ezetimibe* or Viemm* or Vytorin* or Zetia* or Zient* or sch 582235 or sch58235 or sch-58235 or "MK 0653" or MK0653 or MK-0653 or HSDB 7737 or HSDB7737 or HSDB-7737 or EOR26LQQ24 or "163222-33-1")) *Indexes=CPCI-S Timespan=All years*
# 6	103	**TOPIC:** ((Evolocumab* or Repatha* or AMG 145 or AMG145 or AMG-145 or D10557 or HSDB 8307 or LKC0U3A8NJ or "1256937-27-5")) *Indexes=CPCI-S Timespan=All years*
# 5	120	**TOPIC:** ((Alirocumab* or Praluent* or regn 727 or regn727 or regn-727 or sar 236553 or sar236553 or sar-236553 or HSDB 8280 or PP0SHH6V16 or "1245916-14-6")) *Indexes=CPCI-S Timespan=All years*
# 4	22	**TOPIC:** ((Inclisiran* or ALN 60212 or ALN60212 or ALN-60212 or ALN PCS or ALNPCS or ALN-PCS or ALNPCSsc or ALN-PCSsc or "ALN be,PCSsc" or "UNII-UOW2C71PG5" or "1639324-58-5")) *Indexes=CPCI-S Timespan=All years*
# 3	13,754	#2 OR #1 *Indexes=CPCI-S Timespan=All years*
# 2	10,481	**TOPIC:** (((cholesterol* or lipid* or LDL) near/4 (elevat* or ascend* or increase* or high or rais* or low*))) *Indexes=CPCI-S Timespan=All years*

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# 1	3,669	**TOPIC:** ((hypercholesterol?emi* or hypercholesterin?emi* or cholester?emi* or cholesterin?emi* or hyperlipid?emi* or hyperlipoprotein?emia* or lip?emia* or lipid?emi* or hyperlip?emi* or HeFH or "Heterozygous Familial Hypercholesterolemia" or hofh or "Homozygous Familial Hypercholesterolaemia" or fh or "familial hypercholesterolemia" or hypertriglycerid?emia* or "mckusick 14575" or triglycerid?emia* or (triglyceride NEAR/1 storage NEAR/1 disease*))) *Indexes=CPCI-S Timespan=All years*

CPCI-S conference search, 17 February 2021 (update search)

# 12	4	#10 AND #3 **Refined by: PUBLICATION YEARS:** (2020 OR 2019 OR 2018) *Indexes=CPCI-S Timespan=All years*
# 11	249	#10 AND #3 *Indexes=CPCI-S Timespan=All years*
# 10	859	#9 OR #8 OR #7 OR #6 OR #5 OR #4 *Indexes=CPCI-S Timespan=All years*
# 9	34	**TOPIC:** ((Icosapent ethyl* or Epadel* or Vascepa* or Vp-pnv-dha* or Lcosapent* or Miraxion* or AMR 101 or AMR101 or AMR-101 or Lax 101 or lax101 or lax-101 or mnd 21 or mnd21 or mnd-21 or 6GC8A4PAYH or "86227-47-6")) *Indexes=CPCI-S Timespan=All years*
# 8	26	**TOPIC:** ((Bempedoic* or Nexletol* or Nexlizet* or Nilemdo* or Nustendi or ESP 55016 or ESP55016 or ESP-55016 or ETC 1002 or ETC1002 or ETC-1002 or AK499358 or 1EJ6Z6Q368 or "738606-46-7")) *Indexes=CPCI-S Timespan=All years*
# 7	556	**TOPIC:** ((Ezetimibe* or Ezetimiba* or Ezetimibum* or Absorcol* or Ach-ezetimibe* or Ag-ezetimibe* or Apo-ezetimibe* or Auro-ezetimibe* or Bio-ezetimibe* or Ezedoc* or Ezetib* or Ezetimib* or Ezetrol* or Gln-ezetimibe* or Ipg-ezetimibe* or Jamp-ezetimibe* or Liptruzet* or M-ezetimibe* or Mar-ezetimibe* or Mint-ezetimibe* or Mylan-ezetimibe* or Nexlizet* or Nra-ezetimibe* or PMS-ezetimibe* or Priva-ezetimibe* or Ran-ezetimibe* or Riva-ezetimibe* or Viemm* or Vytorin* or Zetia* or Zient* or sch 582235 or sch58235 or sch-58235 or "MK 0653" or MK0653 or MK-0653 or HSDB 7737 or HSDB7737 or HSDB-7737 or EOR26LQQ24 or "163222-33-1")) *Indexes=CPCI-S Timespan=All years*
# 6	111	**TOPIC:** ((Evolocumab* or Repatha* or AMG 145 or AMG145 or AMG-145 or D10557 or HSDB 8307 or LKC0U3A8NJ or "1256937-27-5")) *Indexes=CPCI-S Timespan=All years*
# 5	132	**TOPIC:** ((Alirocumab* or Praluent* or regn 727 or regn727 or regn-727 or sar 236553 or sar236553 or sar-236553 or HSDB 8280 or PP0SHH6V16 or "1245916-14-6")) *Indexes=CPCI-S Timespan=All years*
# 4	22	**TOPIC:** ((Inclisiran* or ALN 60212 or ALN60212 or ALN-60212 or ALN PCS or ALNPCS or ALN-PCS or ALNPCSsc or ALN-PCSsc or "ALN be,PCSsc" or "UNII-UOW2C71PG5" or "1639324-58-5")) *Indexes=CPCI-S Timespan=All years*
# 3	14,022	#2 OR #1 *Indexes=CPCI-S Timespan=All years*
# 2	10,657	**TOPIC:** (((cholesterol* or lipid* or LDL) near/4 (elevat* or ascend* or increase* or high or rais* or low*)))

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		Indexes=CPCI-S Timespan=All years
# 1	3,741	**TOPIC:** ((hypercholesterol?emi* or hypercholesterin?emi* or cholester?emi* or cholesterin?emi* or hyperlipid?emi* or hyperlipoprotein?emia* or lip?emia* or lipid?emi* or hyperlip?emi* or HeFH or "Heterozygous Familial Hypercholesterolemia" or hofh or "Homozygous Familial Hypercholesterolaemia" or fh or "familial hypercholesterolemia" or hypertriglycerid?emia* or "mckusick 14575" or triglycerid?emia* or (triglyceride NEAR/1 storage NEAR/1 disease*))) *Indexes=CPCI-S Timespan=All years*

Systematic selection of studies

After duplicates were removed from the total search result, a primary screening based on title and abstract and a secondary screening based on full text read was undertaken by three reviewers independently, with two votes required for each record to be included. If there was uncertainty about the relevance of a record based on the abstract in the primary screening, it was included and taken forward to secondary screening. In the secondary screening, where researchers disagreed regarding the inclusion or exclusion of a record, reasons for disagreement were discussed and if a consensus was not reached, the third researcher was involved to reach a decision. The selections for the first and the update search are shown in Figure 17 and Figure 18.

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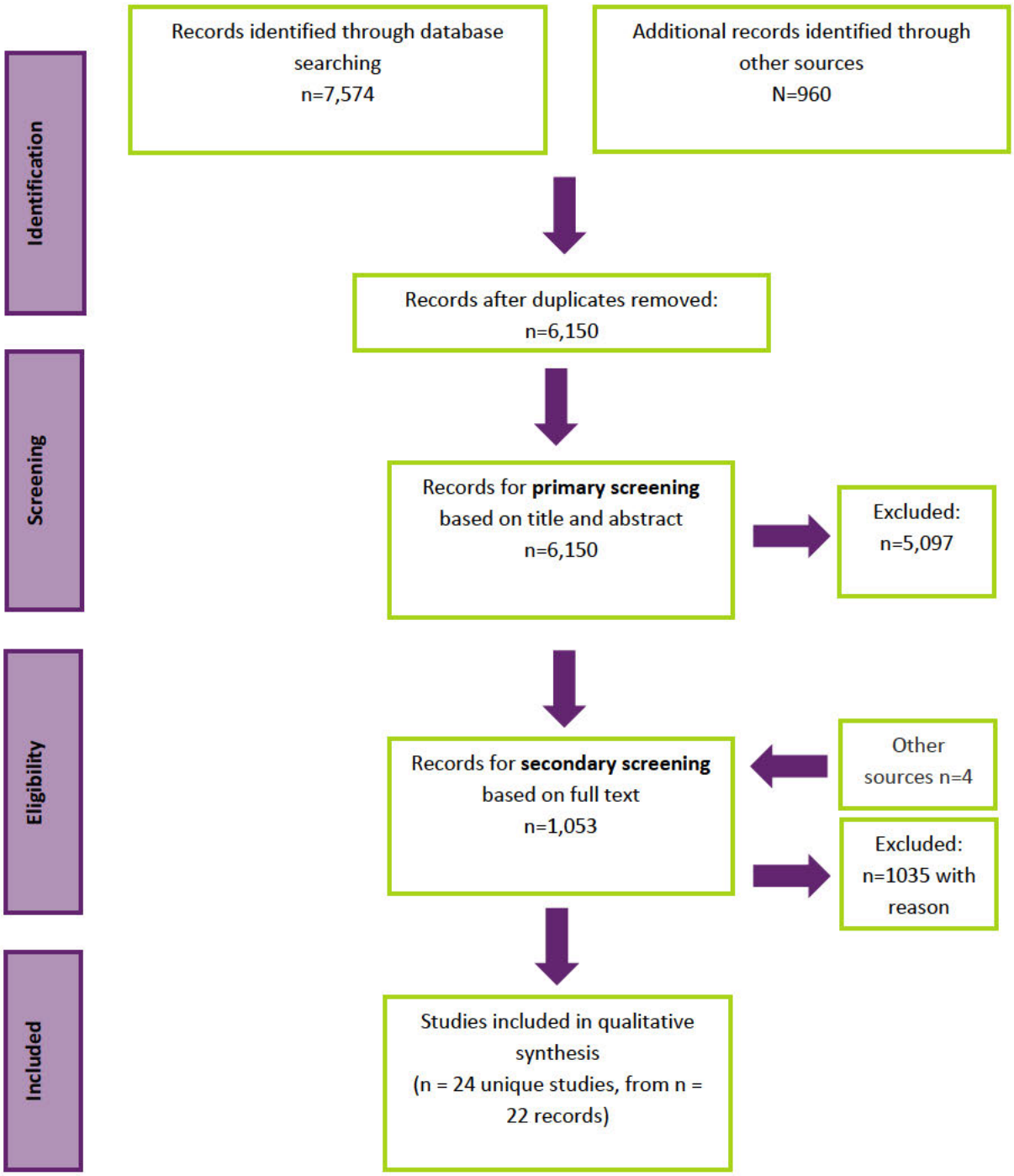
Figure 17 PRISMA diagram of the study selection process (May 2020)



Exclusions by reason: *Abstract only with insufficient information (n=12); Abstract pre-218 (n=135); Eligible patients not reported separately (n=2); Eligible trial yet to report (n=21); Ineligible interventions (n=35); Ineligible population (n=185); Ineligible publication type (n=101); Ineligible study design (n=136); Ineligible patient subgroup of eligible trial (n=17); Ineligible subgroup analysis of eligible trials (n=36); No eligible outcomes (n=20); Pooled analysis trials not reported separately (n=62); Non-relevant SLR (n=20); SLR pre-2015 (n=18); Unable to locate record (n=5); Vascepa trials, ineligible population (n=16), narrow PICO (excluding e.g. ezetimibe, bempedoic acid and icosapent ethy): n=152 records.*

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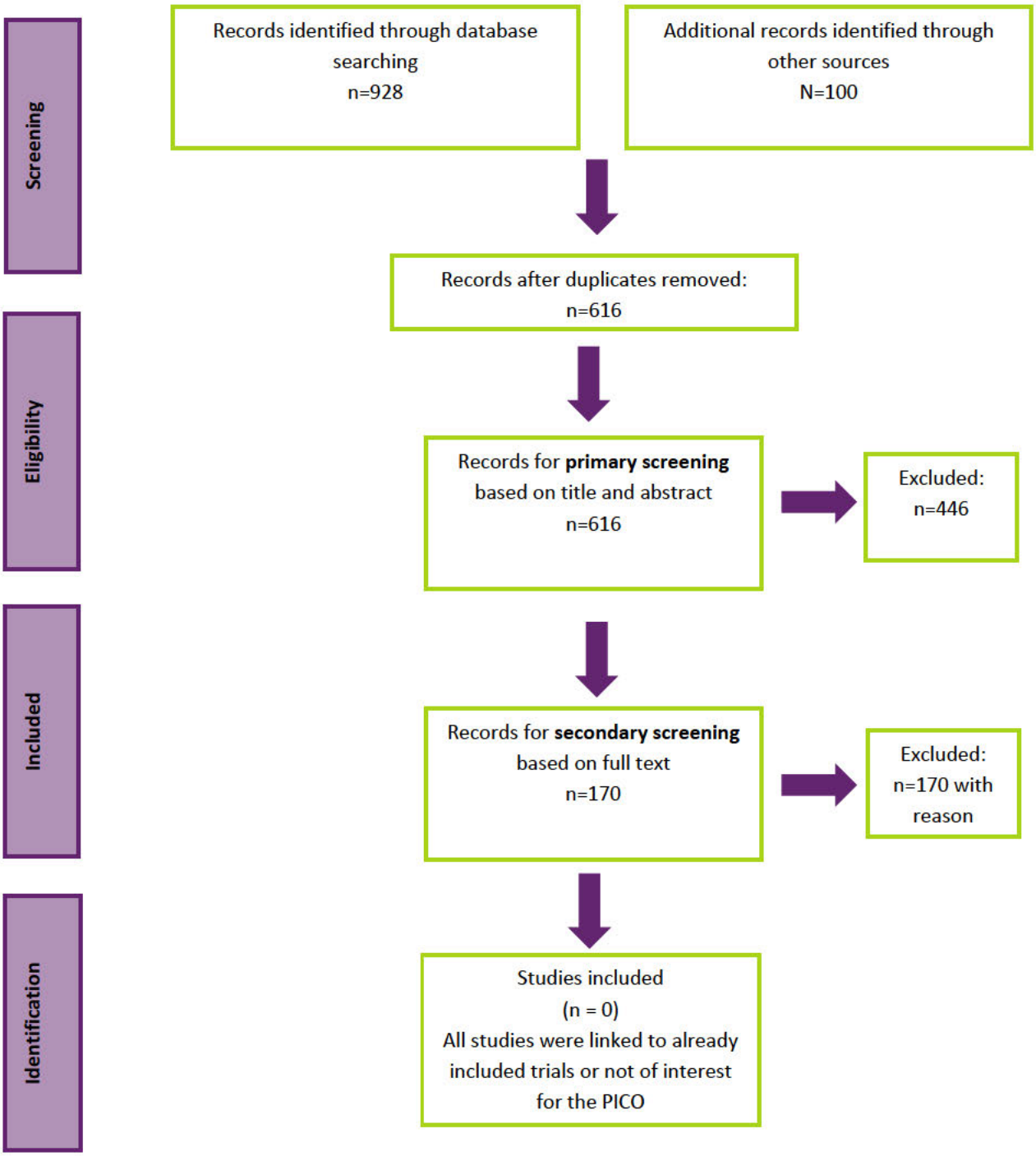
Figure 18 PRISMA flow chart of study selection process, update literature search (February 2021)



Exclusions by reason: *Abstract only with insufficient information (n=23); Eligible trial yet to report (n=2); Ineligible population (n=255); Ineligible publication type (n=17); Ineligible study design (n=12); No eligible outcomes (n=23); Pooled analysis trials not reported separately (n=19); Non-relevant SLR (n=41); Vascepa trials, ineligible population (n=5).*

A list of excluded records with reasons is provided in the embedded document, Table 35.

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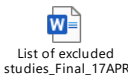
Table 35 List of excluded studies



The table is submitted as a separate file.

Treatment arms excluded from the analysis

Table 36 below lists the treatment arms from the included trials that were excluded from the analysis, and the reason.

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Table 36 Treatment arms from included studies which are excluded from the analysis

	Treatment arms excluded	Reason for exclusion
NCT01266876 [34]	Alirocumab 300 mg sc Q4W Alirocumab 200 mg sc Q4W Alirocumab 150 mg sc Q4W	Not relevant dose regimens
RUTHERFORD-2 [47]	Evolocumab 420 mg sc QM Placebo sc QM	Not relevant dose regimens
ODYSSEY CHOICE I [38]	Patients receiving statin: Alirocumab 300 mg sc Q4W Patients not receiving statin: All treatment arms	Not relevant dose regimen Data for sub-group of pts not receiving statin (statin intolerant) was not included because this sub-group included mixed population: • Patients with moderate- to very-high CVD risk and with statin associated muscle symptoms (defined in protocol as muscle related statin intolerance) • Patients with moderate CVD risk and **not receiving statin** The second group of patients were not necessarily statin intolerant and thus data for this sub-group was not included in NMA.
NTC01288443 [39]	Alirocumab 50 mg sc Q2W Alirocumab 100 mg sc Q2W Alirocumab 200 mg sc Q4W/alternating placebo Alirocumab 300 mg sc Q4W/alternating placebo	Not relevant dose regimens
LAPLACE-2 [48]	Atorvastatin groups 10 mg po QD or 80 mg po QD: • Placebo sc QM + placebo po QD • Placebo sc QM + ezetimibe po 10 mg QD • Evolocumab 420 mg QM + placebo po QD Rosuvastatin 5 mg po QD or rosuvastatin 40 mg po QD or simvastatin 40 mg po QD: • Placebo sc QM • Evolocumab 420 mg QM	Not relevant dose regimens

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LAPLACE-TIMI 57 [49]	Evolocumab 70 mg sc Q2W Evolocumab 105 mg sc Q2W Placebo sc Q4W Evolocumab 280 mg sc Q4W Evolocumab 350 mg sc Q4W Evolocumab 420 mg sc Q4W	Not relevant dose regimens
ODYSSEY CHOICE II [44]	Alirocumab 150 mg sc Q4W	Not relevant dose regimen
ODYSSEY NIPPON [45]	Alirocumab 150 mg sc Q4W	Not relevant regimen
ODYSSEY ALTERNATIVE [46]	Atorvastatin 20 mg po QD	Atorvastatin not relevant
GAUSS-2 [50]	Evolocumab 420 mg QM + placebo po QD Ezetimibe po QD + placebo sc QM	Not relevant dose regimens

Abbreviations: po, by mouth; sc, sub cutaneous; Q2W, every second week; Q4W, every four weeks; QD, daily.

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Ongoing studies and studies that are completed but not published yet

A search was undertaken in clinicaltrials.gov on 14 April 2021 to identify ongoing studies and studies that were completed but had not yet been published. To identify ongong studies, the filters “Not yet recruiting”, “Recruiting”, “Enrolling by invitation” and “Active, not recruiting” were applied. To identify completed but not yet published studies, the filter “completed” was applied, and for the studies with a stop date in 2020 a search was done for the NCT number in PubMed to identify potential publications.

Table 37 Studies that are ongoing or completed but not yet published

Alirocumab studies, completed but not published

ClinicalTrials.gov Search Results 04/14/2021

	NCT Number	Title	Other Names	Status	Study Results	Conditions	Interventions	Dates
1	NCT03510715	An Efficacy and Safety Study of Alirocumab in Children and Adolescents With Homozygous Familial Hypercholesterolemia		Completed	Has Results	•Hypercholesterolemia	•Drug: Alirocumab SAR236553 (REGN727) •Drug: Atorvastatin •Drug: Simvastatin •Drug: Fluvastatin •Drug: Pravastatin •Drug: Lovastatin •Drug: Rosuvastatin •Drug: Ezetimibe •Drug: Cholestyramine •Drug: Nicotinic acid •Drug: Fenofibrate •Drug: Omega-3 fatty acids	Study Completion: February 17, 2020
2	NCT02957682	Evaluating Effect of the Study Drug Praluent (Alirocumab) on Neurocognitive Function When Compared to Placebo		Completed	No Results Available	•Hypercholesterolemia	•Drug: Praluent (Alirocumab) •Drug: Placebo	Study Completion: March 5, 2020

Alirocumab studies, ongoing

ClinicalTrials.gov Search Results 04/14/2021

	NCT Number	Title	Other Names	Status	Study Results	Conditions	Interventions	Dates
1	NCT03480568	Alirocumab in Patients on a Stable Dialysis Regimen		Recruiting	No Results Available	•Hemodialysis •Peritoneal Dialysis •Hypercholesterolemia •Atherosclerotic Disease	•Drug: Alirocumab 150 MG/ML [Praluent]	Study Start: May 1, 2018 Primary Completion: August 31, 2020
2	NCT03552432	The Efficacy of Alirocumab for Thin-cap fibroatheroma in Patients With Coronary Artery Disease Estimated by Optical Coherence Tomography	Title Acronym: ALTAIR	Recruiting	No Results Available	•Coronary Artery Disease •Thin-cap fibroatheroma	•Drug: Alirocumab	Study Start: August 23, 2017 Primary Completion: September 30, 2020
3	NCT03344692	Effect of Alirocumab on Postprandial Hyperlipemia in Patients With Type 2 Diabetes	Title Acronym: EUTERPE	Recruiting	No Results Available	•Type2 Diabetes	•Drug: Alirocumab •Other: Placebo	Study Start: February 12, 2019 Primary Completion: April 30, 2022
4	NCT04781322	Safety, Tolerability, and Bioeffects of Alirocumab in Non-treatment Seeking Heavy Drinkers		Recruiting	No Results Available	•Alcohol Associated Liver Disease •Heavy Drinking Behavior	•Drug: Alirocumab •Other: Placebo	Study Start: April 19, 2021 Primary Completion: December 31, 2022
5	NCT02959047	A Trial of Alirocumab and Plaque Regression in Peripheral Arterial Disease		Active, not recruiting	No Results Available	•Peripheral Arterial Disease	•Drug: Alirocumab •Drug: Matching placebo	Study Start: July 17, 2017 Primary Completion: January 17, 2021
6	NCT04193306	Efficacy and Safety Of Alirocumab to Prevent Early Cardiac Allograft Vasculopathy in Recent Heart Transplant Recipients	Title Acronym: ACAV	Recruiting	No Results Available	•Cardiac Allograft Vasculopathy	•Drug: Alirocumab •Other: Placebo	Study Start: November 18, 2019 Primary Completion: December 2022
7	NCT03067844	Vascular Effects of Alirocumab in Acute MI-Patients	Title Acronym: PACMAN-AMI	Active, not recruiting	No Results Available	•Coronary Vessel •Coronary Circulation •Atheroma; Myocardial	•Drug: Alirocumab	Study Start: April 25, 2017 Primary Completion: September 2021
8	NCT04790513	Trial to Evaluate Efficacy and Safety of LIB003, Evolocumab and Alirocumab in High-risk CVD Patients	Title Acronym: LIBerate-H2H	Not yet recruiting	No Results Available	•Hypercholesterolemia •Cardiovascular Diseases	•Biological: lerodalcibep •Biological: evolocumab •Biological: alirocumab	Study Start: April 1, 2021 Primary Completion: September 30, 2021

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	NCT Number	Title	Other Names	Status	Study Results	Conditions	Interventions	Dates
9	NCT03510884	An Efficacy and Safety Study of Alirocumab in Children and Adolescents With Heterozygous Familial Hypercholesterolemia		Active, not recruiting	No Results Available	•Hypercholesterolaemia	•Drug: Alirocumab SAR236553 (REGN727) •Drug: Rosuvastatin •Drug: Atorvastatin •Drug: Simvastatin •Drug: Pravastatin •Drug: Lovastatin •Drug: Fluvastatin •Drug: Ezetimibe •Drug: Cholestyramine •Drug: Nicotinic acid •and 3 more	Study Start: May 31, 2018 Primary Completion: January 14, 2021
10	NCT03718286	Effects of Acute, Rapid Lowering of LDL Cholesterol With Alirocumab in Patients With STEMI Undergoing Primary PCI	Title Acronym: EPIC STEMI	Recruiting	No Results Available	•ST Elevation Myocardial Infarction •Acute Coronary Syndrome •Hypercholesterolemia •Hyperlipidemias •Dyslipidemias •Physiological Effects of Drugs	•Drug: Alirocumab •Other: Sham Control	Study Start: March 11, 2019 Primary Completion: March 2021
11	NCT04189484	Pharmacodynamic Biomarkers to Support Biosimilar Development: PCSK9 Inhibitors		Recruiting	No Results Available	•Healthy Subjects •Pharmacokinetics •Pharmacodynamics	•Biological: Evolocumab •Biological: Alirocumab •Biological: Placebo	Study Start: January 6, 2020 Primary Completion: April 2021
12	NCT03537742	PCSK9 Inhibition After Heart Transplantation		Enrolling by invitation	No Results Available	•Vasculopathy	•Biological: alirocumab •Biological: placebo	Study Start: May 13, 2019 Primary Completion: September 2023
13	NCT03355027	Investigating the Lowest Threshold of Vascular Benefits From LDL Cholesterol Lowering in Patients With Stable CV Disease	Title Acronym: INTENSITY-HIGH	Active, not recruiting	No Results Available	•Atherosclerosis •Cardiovascular Diseases	•Drug: Alirocumab 150 MG/ML •Drug: Ezetimibe 10Mg Tablet •Drug: Atorvastatin 40Mg Tablet •Drug: Atorvastatin 80Mg Tablet •Drug: Rosuvastatin 20Mg Tablet •Drug: Rosuvastatin 40Mg Tablet •Drug: Simvastatin 80mg	Study Start: November 30, 2017 Primary Completion: September 30, 2019
14	NCT03207945	Effect of PCSK9 Inhibition on Cardiovascular Risk in Treated HIV Infection (EPIC-HIV Study)	Title Acronym: EPIC-HIV	Recruiting	No Results Available	•Dyslipidemias •Cardiovascular Diseases •HIV Infections	•Drug: Alirocumab •Other: Placebo	Study Start: April 30, 2018 Primary Completion: November 2021

	NCT Number	Title	Other Names	Status	Study Results	Conditions	Interventions	Dates
15	NCT04613167	Markers of Cardiovascular Risk in Patients With Premature Coronary Artery Disease and Treatment	Title Acronym: GEBI	Recruiting	No Results Available	•Acute Coronary Syndrome •Premature Coronary Heart Disease •Lipoproteinemia •Inflammation •Genetic Polymorphisms	•Drug: Alirocumab •Drug: Evolocumab •Drug: Control group	Study Start: November 10, 2020 Primary Completion: June 30, 2021
16	NCT04731155	Impact of Early PCSK9 Inhibitor on Heart After Acute Myocardium Infarction	Title Acronym: PERFECT-AMI	Recruiting	No Results Available	•Early PCSK9 Inhibitor on Ventricular Remodling	•Drug: PCSK9 inhibitor #Alirocumab#plus standard medications •Drug: standard medications	Study Start: February 1, 2021 Primary Completion: May 2021
17	NCT04073797	PET Imaging of Inflammation and Lipid Lowering Study	Title Acronym: PIILL	Not yet recruiting	No Results Available	•Hypercholesterolemia •Hypercholesterolemia, Familial	•Drug: PCSK9 inhibitor •Diagnostic Test: 68Ga-DOTATATE PET-MRI	Study Start: October 1, 2019 Primary Completion: October 1, 2023
18	NCT04656028	Genetic Testing and Motivational Counseling for FH	Title Acronym: GENMOTIV-FH	Recruiting	No Results Available	•Hypercholesterolemia, Familial •Hypercholesterolemia, Familial, 1 •Hypercholesterolemia, Familial, 2 •Hypercholesterolemia, Familial, 3 •Hypercholesterolemia, Familial, 4 •Hypercholesterolemia, Familial, 4, Autosomal Recessive •Familial Hypercholesterolemia With Hyperlipemia •Hypercholesterolemia, Autosomal Dominant, Type B •Hypercholesterolemia, Autosomal Dominant •Hypercholesterolemia, Autosomal Dominant, 3 •and 16 more	•Genetic: Genetic Testing •Behavioral: Motivational Counseling •Diagnostic Test: Lipid analysis •Other: Consultation with a cardiologist-lipidologist (correction of therapy, lifestyle, diet) •Other: Visit 1 •Other: Visit 2 •Other: Visit 3	Study Start: June 15, 2020 Primary Completion: October 31, 2021

Evolocumab studies, completed but not published

ClinicalTrials.gov Search Results 04/14/2021

	NCT Number	Title	Other Names	Status	Study Results	Conditions	Interventions	Dates
1	NCT04665830	PCSK 9 Inhibition as Secondary Prevention in Renal Transplant Patients		Completed	No Results Available	•Kideny Transplant Recipients With High Cardiovascular Risk Score	•Drug: Evolocumab	Study Completion: May 1, 2020
2	NCT03096288	Impact of Evolocumab on the Effects of Clopidogrel in Patients With High On-Treatment Platelet Reactivity		Completed	No Results Available	•Atherosclerotic Cardiovascular Disease	•Drug: Evolocumab •Other: Placebo	Study Completion: November 2, 2020

Evolocumab studies, ongoing

ClinicalTrials.gov Search Results 04/14/2021

	NCT Number	Title	Other Names	Status	Study Results	Conditions	Interventions	Dates
1	NCT04306081	Effect of Evolocumab in Functional Status and LDL Oxidation of Patients With Peripheral Arterial Disease	Title Acronym: Evol-PAD	Recruiting	No Results Available	•Peripheral Arterial Disease	•Drug: Evolocumab 140 mg/mL Subcutaneous Injection 1 milliliter (mL) pre-filled injector Pen x 3 for a monthly dose of 420 mg for 6 months. •Other: Placebo 1milliliter (mL) Subcutaneous Injection pre-filled injector Pen x 3 monthly for 6 months.	Study Start: December 14, 2017 Primary Completion: December 30, 2020
2	NCT04303377	Early Treatment With Evolocumab in Patients With ST-elevation Myocardial Infarction	Title Acronym: ExOTIC	Recruiting	No Results Available	•ST-elevation Myocardial Infarction	•Biological: Evolocumab	Study Start: November 18, 2019 Primary Completion: November 18, 2020
3	NCT04306471	Effect of Evolocumab in Patients With Critical Limb Ischemia (Evol-CLI)	Title Acronym: Evol-CLI	Recruiting	No Results Available	•Critical Limb Ischemia	•Drug: Evolocumab 140mg/mL Injector 1milliliter (mL) Pen x 3 for a monthly dose of 420 mg for 12 months. •Other: Placebo 1 milliliter (mL) Injector Pen x 3 monthly for 12 months	Study Start: February 24, 2020 Primary Completion: February 4, 2021
4	NCT04719221	Impact of Evolocumab as an Additional Lipid-lowering Therapy to Changes in Lipid Core Burden Index of Non-culprit Vulnerable Plaque in Patients Who Underwent Percutaneous Coronary Intervention for the Acute Coronary Syndrome		Recruiting	No Results Available	•Clinical Trial •Acute Coronary Syndrome	•Drug: Evolocumab •Device: NIRS IVUS	Study Start: March 2021 Primary Completion: June 2023
5	NCT04730973	CARotid plaqUe StabilizatiOn and Regression With Evolocumab.	Title Acronym: CARUSO	Recruiting	No Results Available	•Carotid Artery Disease	•Drug: Evolocumab •Other: lipid-lowering therapy (LLT)	Study Start: February 1, 2021 Primary Completion: January 31, 2022
6	NCT03515304	Evolocumab in Acute Coronary Syndrome	Title Acronym: EVACS	Active, not recruiting	No Results Available	•Acute Coronary Syndrome	•Drug: Evolocumab •Drug: Placebo	Study Start: May 20, 2018 Primary Completion: January 15, 2022
7	NCT03734211	Cholesterol Lowering With EVOLocumab to Prevent Cardiac Allograft Vasculopathy in De-novo Heart Transplant Recipients	Title Acronym: EVOLVD	Recruiting	No Results Available	•Cardiac Allograft Vasculopathy	•Drug: Evolocumab •Drug: Placebo	Study Start: June 10, 2019 Primary Completion: November 30, 2021
8	NCT03931161	Effect of Evolocumab on Carotid Plaque Composition in Asymptomatic Carotid Artery Stenosis (EVOCAR-1)	Title Acronym: EVOCAR-1	Recruiting	No Results Available	•Carotid Artery Stenosis	•Drug: Evolocumab Auto-Injector [Repatha] •Drug: Placebo Auto-Injector	Study Start: September 4, 2019 Primary Completion: September 4, 2023
9	NCT03900026	Effect of Evolocumab on Saphenous Vein Graft Patency Following Coronary Artery Bypass Surgery	Title Acronym: NEWTON-CABG	Recruiting	No Results Available	•Coronary Artery Bypass Graft Surgery •Atherosclerosis •Vein Occlusion	•Drug: Evolocumab •Other: Placebo	Study Start: May 30, 2019 Primary Completion: December 1, 2023

	NCT Number	Title	Other Names	Status	Study Results	Conditions	Interventions	Dates
10	NCT04710368	Effect of Evolocumab on Coronary Plaque Characteristics	Title Acronym: YELLOW III	Not yet recruiting	No Results Available	•Coronary Artery Disease	•Drug: Evolocumab Injections	Study Start: February 2021 Primary Completion: February 2024
11	NCT03791593	EVOlocumab in Stable Heart Failure With Reduced Ejection Fraction of Ischemic Etiology: EVO-HF Pilot	Title Acronym: EVO-HF	Recruiting	No Results Available	•Heart Failure With Reduced Ejection Fraction	•Drug: Evolocumab	Study Start: December 3, 2018 Primary Completion: March 2021
12	NCT04082442	Evolocumab in Patients With Acute MI	Title Acronym: EVACS II	Recruiting	No Results Available	•Acute Coronary Syndrome	•Drug: Evolocumab •Drug: Placebos	Study Start: September 1, 2019 Primary Completion: December 2021
13	NCT04397653	Evolocumab Plus Ezetimibe in High Risk Haemodialized Statin Intolerant Patients		Recruiting	No Results Available	•Hypercholesterolemia •Chronic Kidney Disease Requiring Chronic Dialysis	•Drug: Evolocumab •Drug: Placebo •Drug: Ezetimibe	Study Start: May 4, 2020 Primary Completion: November 19, 2020
14	NCT03944577	Impact of Evolocumab in Cardiac Transplant Patients With CAV		Recruiting	No Results Available	•Heart Transplant	•Drug: Evolocumab (Repatha)	Study Start: July 15, 2019 Primary Completion: December 31, 2021
15	NCT02624869	Open Label Study to Evaluate Safety, Tolerability and Efficacy of Evolocumab (AMG 145) in Pediatric Subjects (10 to 17 Years of Age) With Heterozygous Familial Hypercholesterolemia (HeFH) or Homozygous Familial Hypercholesterolemia (HoFH).	Title Acronym: HAUSER-OLE	Active, not recruiting	No Results Available	•Familial Hypercholesterolemia	•Biological: evolocumab (AMG 145)	Study Start: September 10, 2016 Primary Completion: June 7, 2021
16	NCT04100434	Effect of Evolocumab Added to Moderate-Intensity Statin Therapy on LDL-C Lowering and Cardiovascular Adverse Events in Patients With Acute Coronary Syndrome	Title Acronym: EMSIACS	Recruiting	No Results Available	•Acute Coronary Syndrome •Proprotein Convertase Subtilisin/ Kexin Type 9 Inhibitor	•Drug: Evolocumab	Study Start: January 1, 2021 Primary Completion: June 1, 2022
17	NCT04510844	Evolocumab In Advanced Chronic Kidney Disease Trial	Title Acronym: EVO-CKD	Not yet recruiting	No Results Available	•Chronic Kidney Diseases •High Cholesterol	•Drug: Evolocumab •Other: Placebo	Study Start: October 2020 Primary Completion: February 2023
18	NCT03869073	Evolocumab for PCSK9 Lowering in Early Acute Sepsis (The PLEASe Study)	Title Acronym: PLEASe	Recruiting	No Results Available	•Sepsis	•Drug: Evolocumab •Drug: Placebo	Study Start: February 11, 2019 Primary Completion: February 11, 2021
19	NCT04539223	A Study of Evolocumab on Carotid Artery Atherosclerotic Plaque Morphology Prior to Carotid EndArterectomy	Title Acronym: SLICE-CEA	Recruiting	No Results Available	•Carotid Artery Stenosis •Asymptomatic Carotid Artery Stenosis	•Drug: Evolocumab	Study Start: August 28, 2020 Primary Completion: April 2022

	NCT Number	Title	Other Names	Status	Study Results	Conditions	Interventions	Dates
20	NCT04659525	Evolocumab Plus Ezetimibe in Haemodialized Statin-intolerant Patients With Hypercholesterolemia		Recruiting	No Results Available	•Hypercholesterolemia •CKD Stage 5 •Chronic Kidney Disease Requiring Chronic Dialysis	•Drug: Evolocumab •Drug: Ezetimibe •Drug: Placebo	Study Start: November 1, 2020 Primary Completion: November 30, 2021
21	NCT03872401	Effect of Evolocumab in Patients at High Cardiovascular Risk Without Prior Myocardial Infarction or Stroke	Title Acronym: VESALIUS-CV	Recruiting	No Results Available	•Coronary Heart Disease (CHD)	•Drug: Evolocumab •Drug: Placebo	Study Start: June 11, 2019 Primary Completion: June 20, 2025
22	NCT04608474	Lipid Management in Renal Transplant Recipients Using Evolocumab.		Not yet recruiting	No Results Available	•Hyperlipidemias	•Drug: Evolocumab •Drug: Statins (Cardiovascular Agents)	Study Start: March 1, 2021 Primary Completion: February 2022
23	NCT03060577	An Extension Trial of Inclisiran Compared to Evolocumab in Participants With Cardiovascular Disease and High Cholesterol	Title Acronym: ORION-3	Active, not recruiting	No Results Available	•Atherosclerotic Cardiovascular Disease •Symptomatic Atherosclerosis •Type2 Diabetes •Familial Hypercholesterolemia	•Drug: Inclisiran •Drug: Evolocumab	Study Start: March 24, 2017 Primary Completion: December 31, 2021
24	NCT03689946	Effect of Evolocumab on Coronary Artery Plaque Volume and Composition by CCTA and Microcalcification by F18-NaF PET		Recruiting	No Results Available	•Cardiovascular Disease •Hyperlipidemia	•Drug: Evolocumab •Diagnostic Test: 18F-NaF PET •Diagnostic Test: CCTA	Study Start: March 22, 2019 Primary Completion: December 31, 2021
25	NCT03932721	EXpanded Combination of Evolocumab Plus Empagliflozin on Diabetes: EXCEED-BHS3 Trial	Title Acronym: EXCEED-BHS3	Recruiting	No Results Available	•Dyslipidemia Associated With Type II Diabetes Mellitus •Diabetes Mellitus, Type 2 •Hypertension Arterial	•Drug: Evolocumab 140 MG/ML	Study Start: October 1, 2018 Primary Completion: June 30, 2020
26	NCT04790513	Trial to Evaluate Efficacy and Safety of LIB003, Evolocumab and Alirocumab in High-risk CVD Patients	Title Acronym: LIBerate-H2H	Not yet recruiting	No Results Available	•Hypercholesterolemia •Cardiovascular Diseases	•Biological: lerodalcibep •Biological: evolocumab •Biological: alirocumab	Study Start: April 1, 2021 Primary Completion: September 30, 2021
27	NCT03080935	Fourier Open-label Extension Study in Subjects With Clinically Evident Cardiovascular Disease in Selected European Countries		Active, not recruiting	No Results Available	•Dyslipidemia	•Drug: Evolocumab	Study Start: March 13, 2017 Primary Completion: December 11, 2022
28	NCT03829046	The Effects of Evolocumab in Patients With Diabetes and Atherosclerotic Vascular Disease		Recruiting	No Results Available	•Atherosclerotic Vascular Disease •Type2 Diabetes •Microvascular Dysfunction	•Drug: Placebo •Drug: Evolocumab	Study Start: June 3, 2019 Primary Completion: December 2021
29	NCT02867813	Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk Open-label Extension	Title Acronym: FOURIER OLE	Active, not recruiting	No Results Available	•Dyslipidemia	•Biological: Evolocumab	Study Start: September 2, 2016 Primary Completion: December 23, 2021

	NCT Number	Title	Other Names	Status	Study Results	Conditions	Interventions	Dates
30	NCT04034485	Phase 3 Study to Evaluate the Efficacy and Safety of LIB003 With Evolocumab in HoFH		Enrolling by invitation	No Results Available	•Homozygous Familial Hypercholesterolemia	•Drug: LIB003 (lerodalcibep) •Drug: evolocumab	Study Start: December 7, 2019 Primary Completion: May 30, 2022
31	NCT04073134	The CHORAL Flow Study	Title Acronym: CHORAL	Recruiting	No Results Available	•Coronary Artery Disease •Atherosclerosis •Hyperlipidemias	•Biological: Evolocumab •Drug: Placebo	Study Start: September 11, 2019 Primary Completion: March 27, 2022
32	NCT03626831	Effect of Evolocumab on Vascular Function	Title Acronym: EVO	Recruiting	No Results Available	•Atherosclerotic Cardiovascular Disease	•Drug: Evolocumab Prefilled Syringe •Drug: Placebos	Study Start: April 4, 2019 Primary Completion: December 2020
33	NCT04189484	Pharmacodynamic Biomarkers to Support Biosimilar Development: PCSK9 Inhibitors		Recruiting	No Results Available	•Healthy Subjects •Pharmacokinetics •Pharmacodynamics	•Biological: Evolocumab •Biological: Alirocumab •Biological: Placebo	Study Start: January 6, 2020 Primary Completion: April 2021
34	NCT04101643	PCSK9 Inhibitor Treatment for Patients With SPG5		Recruiting	No Results Available	•Hereditary Spastic Paraplegia Type 5	•Drug: evolocumab	Study Start: September 29, 2019 Primary Completion: January 3, 2021
35	NCT04141579	Functional Improvement of Coronary Artery Narrowing by Cholesterol Reduction With a PCSK9 Antibody	Title Acronym: FITTER	Active, not recruiting	No Results Available	•Coronary Artery Disease •Atherosclerosis of Coronary Artery	•Drug: Evolocumab 140 MG/ML [Repatha]	Study Start: February 11, 2020 Primary Completion: September 2022
36	NCT04573777	Reducing Intracranial atheroSclErosis With Repatha	Title Acronym: RISER	Recruiting	No Results Available	•Ischemic Stroke	•Drug: Repatha	Study Start: April 6, 2021 Primary Completion: December 1, 2023
37	NCT04338165	Impact of PCSK9 Inhibitors on Coronary Microvascular Dysfunction in Patients With Atherosclerotic Cardiovascular Disease Proved by Myocardial Ischemia and Needing Coronarography	Title Acronym: MICROPROTECT	Not yet recruiting	No Results Available	•Atherosclerotic Cardiovascular Disease	•Drug: Evolocumab 140 MG/ML [Repatha]	Study Start: June 2020 Primary Completion: November 2022
38	NCT04613167	Markers of Cardiovascular Risk in Patients With Premature Coronary Artery Disease and Treatment	Title Acronym: GEBI	Recruiting	No Results Available	•Acute Coronary Syndrome •Premature Coronary Heart Disease •Lipoproteinemia •Inflammation •Genetic Polymorphisms	•Drug: Alirocumab •Drug: Evolocumab •Drug: Control group	Study Start: November 10, 2020 Primary Completion: June 30, 2021

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	NCT Number	Title	Other Names	Status	Study Results	Conditions	Interventions	Dates
39	NCT04314167	Effect of Serum LDL Cholesterol Concentration on Pancreatic Insulin Secretion		Recruiting	No Results Available	•Hypercholesterolemia •Insulin Resistance •Insulin Secretion	•Drug: Lowering cholesterol concentrations by PCSK-9 inhibitor	Study Start: July 28, 2020 Primary Completion: March 15, 2022
40	NCT04073797	PET Imaging of Inflammation and Lipid Lowering Study	Title Acronym: PIILL	Not yet recruiting	No Results Available	•Hypercholesterolemia •Hypercholesterolemia, Familial	•Drug: PCSK9 inhibitor •Diagnostic Test: 68Ga-DOTATATE PET-MRI	Study Start: October 1, 2019 Primary Completion: October 1, 2023
41	NCT04369664	CHOlesterol Lowering and Residual Risk in Type 2 Diabetes	Title Acronym: CHORD	Recruiting	No Results Available	•Type 2 Diabetes	•Drug: Statin •Drug: PCSK9 inhibitor •Drug: Ezetimibe 10mg	Study Start: June 22, 2020 Primary Completion: November 2023
42	NCT04701242	Ezetimibe Utilization Early After Acute Myocardial Infarction, "EzAMI Trial"	Title Acronym: EzAMI	Not yet recruiting	No Results Available	•Acute Myocardial Infarction •Dyslipidemias	•Drug: Ezetimibe 10mg	Study Start: March 2021 Primary Completion: December 2023
43	NCT04656028	Genetic Testing and Motivational Counseling for FH	Title Acronym: GENMOTIV-FH	Recruiting	No Results Available	•Hypercholesterolemia, Familial •Hypercholesterolemia, Familial, 1 •Hypercholesterolemia, Familial, 2 •Hypercholesterolemia, Familial, 3 •Hypercholesterolemia, Familial, 4 •Hypercholesterolemia, Familial, 4, Autosomal Recessive •Familial Hypercholesterolemia With Hyperlipemia •Hypercholesterolemia, Autosomal Dominant, Type B •Hypercholesterolemia, Autosomal Dominant •Hypercholesterolemia, Autosomal Dominant, 3 •and 16 more	•Genetic: Genetic Testing •Behavioral: Motivational Counseling •Diagnostic Test: Lipid analysis •Other: Consultation with a cardiologist-lipidologist (correction of therapy, lifestyle, diet) •Other: Visit 1 •Other: Visit 2 •Other: Visit 3	Study Start: June 15, 2020 Primary Completion: October 31, 2021

Inclisiran studies, ongoing

ClinicalTrials.gov Search Results 04/14/2021

	NCT Number	Title	Other Names	Status	Study Results	Conditions	Interventions	Dates
1	NCT03814187	Trial to Assess the Effect of Long Term Dosing of Inclisiran in Subjects With High CV Risk and Elevated LDL-C	Title Acronym: ORION-8	Active, not recruiting	No Results Available	•ASCVD •Elevated Cholesterol •Heterozygous Familial Hypercholesterolemia •Homozygous Familial Hypercholesterolemia	•Drug: Inclisiran Sodium	Study Start: April 16, 2019 Primary Completion: August 2023
2	NCT03060577	An Extension Trial of Inclisiran Compared to Evolocumab in Participants With Cardiovascular Disease and High Cholesterol	Title Acronym: ORION-3	Active, not recruiting	No Results Available	•Atherosclerotic Cardiovascular Disease •Symptomatic Atherosclerosis •Type2 Diabetes •Familial Hypercholesterolemia	•Drug: Inclisiran •Drug: Evolocumab	Study Start: March 24, 2017 Primary Completion: December 31, 2021
3	NCT04774003	Study of Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of Inclisiran in Chinese Participants With Elevated Serum LDL-C	Title Acronym: ORION-14	Recruiting	No Results Available	•Hyperlipidemia	•Drug: 100 mg inclisiran sodium (equivalent to 94.5 mg inclisiran) •Drug: Placebo •Drug: 300 mg inclisiran sodium (equivalent to 284 mg inclisiran)	Study Start: February 26, 2021 Primary Completion: September 24, 2021
4	NCT04659863	Study to Evaluate Efficacy and Safety of Inclisiran in Adolescents With Homozygous Familial Hypercholesterolemia	Title Acronym: ORION-13	Recruiting	No Results Available	•Homozygous Familial Hypercholesterolemia	•Drug: Inclisiran •Drug: Placebo	Study Start: February 16, 2021 Primary Completion: September 5, 2022
5	NCT04652726	Study to Evaluate Efficacy and Safety of Inclisiran in Adolescents With Heterozygous Familial Hypercholesterolemia	Title Acronym: ORION-16	Recruiting	No Results Available	•Heterozygous Familial Hypercholesterolemia	•Drug: Inclisiran •Drug: Placebo	Study Start: January 27, 2021 Primary Completion: July 22, 2022
6	NCT04807400	Study in Primary Care Evaluating Inclisiran Delivery Implementation + Enhanced Support	Title Acronym: SPIRIT	Not yet recruiting	No Results Available	•Atherosclerotic Cardiovascular Disease •Atherosclerotic Cardiovascular Disease Risk Equivelents •Elevated Low Density Lipoprotein Cholesterol	•Drug: Inclisiran •Behavioral: Behavioural Support	Study Start: March 29, 2021 Primary Completion: June 15, 2022
7	NCT04666298	Study of Efficacy and Safety of Inclisiran in Japanese Participants With High Cardiovascular Risk and Elevated LDL-C		Not yet recruiting	No Results Available	•Hypercholesterolemia •Heterozygous Familial Hypercholesterolemia	•Drug: Inclisiran sodium •Drug: Placebo	Study Start: January 29, 2021 Primary Completion: April 11, 2022
8	NCT03851705	A Study of Inclisiran in Participants With Homozygous Familial Hypercholesterolemia (HoFH)	Title Acronym: ORION-5	Active, not recruiting	No Results Available	•Homozygous Familial Hypercholesterolemia	•Drug: Inclisiran for injection •Drug: Placebo	Study Start: February 6, 2019 Primary Completion: March 2, 2020
9	NCT04765657	Study of Efficacy and Safety of Inclisiran in Asian Participants With Atherosclerotic Cardiovascular Disease (ASCVD) or ASCVD High Risk and Elevated Low Density Lipoprotein Cholesterol (LDL-C)		Not yet recruiting	No Results Available	•Hypercholesterolemia	•Drug: inclisiran sodium •Drug: Placebo	Study Start: March 15, 2021 Primary Completion: July 18, 2022

	NCT Number	Title	Other Names	Status	Study Results	Conditions	Interventions	Dates
10	NCT03705234	A Randomized Trial Assessing the Effects of Inclisiran on Clinical Outcomes Among People With Cardiovascular Disease	Title Acronym: ORION-4	Recruiting	No Results Available	•Atherosclerotic Cardiovascular Disease	•Drug: Inclisiran •Drug: Placebo	Study Start: October 30, 2018 Primary Completion: December 2024

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Risk of bias by study

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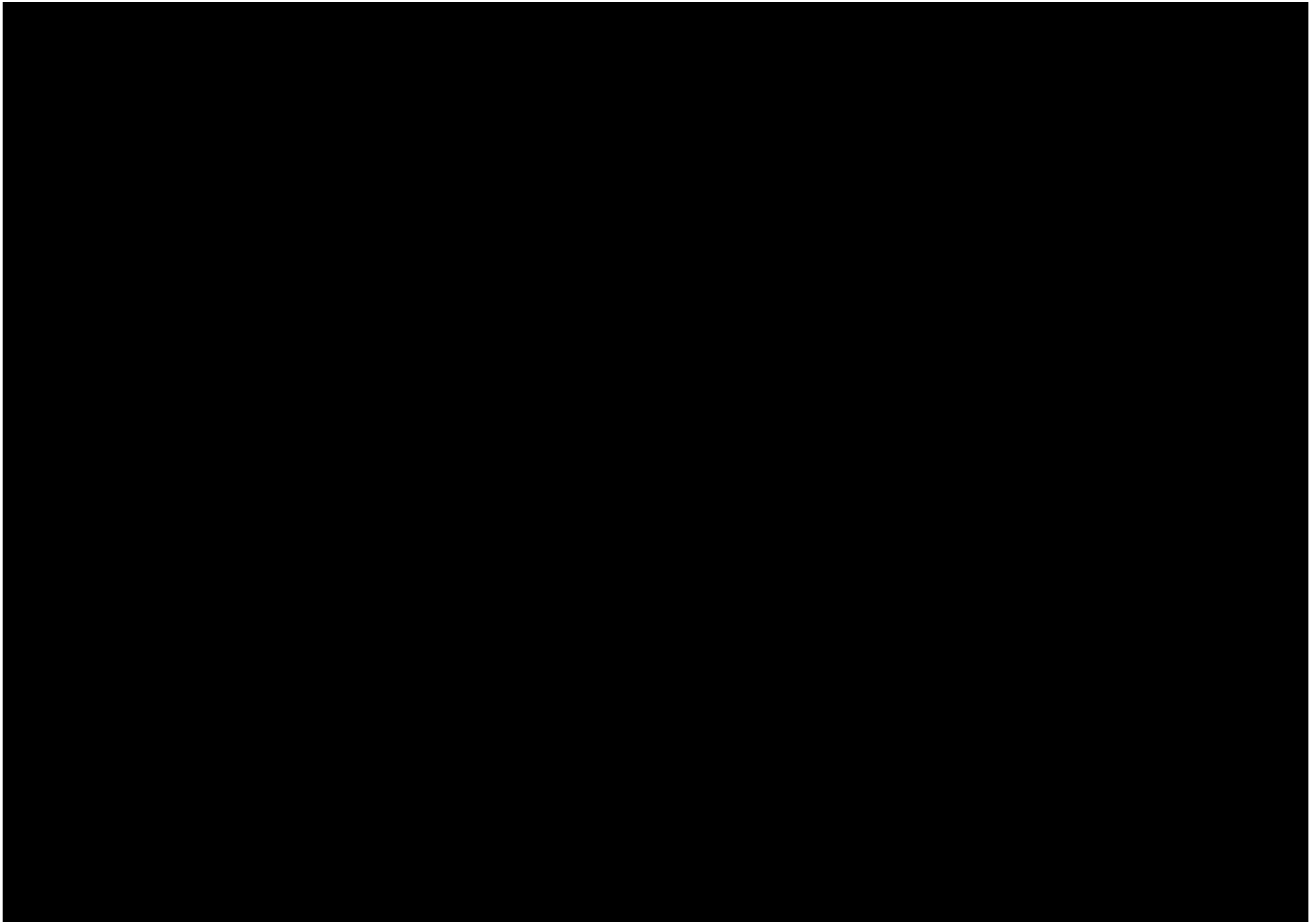

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Quality assessment

The literature search was performed by Novartis Global in May 2020 with an update in February 2021. The literature search has in general been performed and documented in accordance with the methodology recommended by the Medicines Council. However additional comparators and outcomes were initially included and the seardh has been broarder, eg. Including conference abstracts,

Unpublished data

Unpublished day 150 data from the ORION studies has been included in this application and is included in the NMA. Pulictation of the NMA is planned and expected prior to October 2021, i.e. prior to the final decision by the Medicines Council. [redacted]

Other data on file included in the application is exposure to inclisiran in ongoing clinical studies. As of October 20, 2020, a total of 5107 patients had 5701.8 patient years of inclisiran exposure in clinical trials. The data is shown in Table 39, and based on the assumption that half of the patients in the ongoing follow-up studies ORION-3 and ORION -8 were treated with inclisiran in the original study. [redacted]

[redacted]

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Appendix B Main characteristics of included studies

Alirocumab studies	
Trial name: NCT01266876	**NCT number: NCT01266876**
Objective	To assess the efficacy and safety of alirocumab in participants diagnosed with HeFH
Publications – title, author, journal, year	Effect of a monoclonal antibody to PCSK9, REGN727/ SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial. Stein et al. Lancet 2012 [34]
Study type and design	Phase 2, placebo-controlled trial. The trial is now completed.
Sample size (n)	46
Main inclusion and exclusion criteria	Inclusion criteria: • Must meet the World Health Organization criteria for HeFH • Participants must be on a stable statin dose, with or without ezetimibe, for at least 6 weeks before screening • Serum LDL-C levels ≥ 100 mg/dL at screening • Willing to follow the NCEP ATPIII TLC diet, or an equivalent diet plan, starting at screening and continuing until the last study visit • A negative urine/serum pregnancy test at each screening visit and start of the study, for women of childbearing potential Exclusion criteria: • Participants with homozygous FH (clinically or by previous genotyping) • Use of a medication (other than a statin or EZE) to alter serum lipids within 42 days (6 weeks) before screening including, but not limited to: o Fibrates o Niacin (>500 mg/day) o Omega-3 fatty acids (>1000 mg/day of DHA/EPA) o Bile acid resins • Use of nutraceuticals or OTC medications that may alter lipid levels that are not stable for at least 6 weeks before screening and are not planned to remain constant throughout the study. Examples include: o Omega-3 fatty acids (≤1000 mg/day of DHA/EPA) o Niacin (≤500 mg/day) o Plant stanols, such as found in Benecol, flax seed oil, psyllium o Red yeast rice • Disorders known to influence lipid levels, such as nephrotic syndrome, significant liver disease, Cushing's disease, untreated hypothyroidism (patients on stable thyroid replacement for at least 12 weeks before the full screening visit, who are metabolically euthyroid by thyroid-stimulating hormone (TSH) testing are allowed) • Use of thyroid medications (except for replacement therapy which has been stable for at least 12 weeks before the full screening visit) • Fasting serum TG >350 mg/dL screening • LDL apheresis within 12 months before screening
Intervention	Alirocumab 150mg Q2W (n=16)
Comparator	Placebo Q2W (n=15)

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Follow-up time	12-week treatment period plus an 8-week follow-up period to week 20
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary outcomes: • Percent change in LDL-C from baseline to week 12 Secondary outcomes: • Absolute change in LDL-C from baseline to week 12 • All AEs, SAEs, withdrawal from the study due to AEs, and all-cause mortality **Other endpoints:** The following secondary endpoints were included in the study but results are not included in this application: • Proportions of patients achieving an LDL-C concentration lower than 2·6 mmol/L and lower than 1·8 mmol/L at week 12 • Percent change in triglycerides, total cholesterol, HDL-cholesterol, non-HDL-cholesterol, apo-B, apo-A1 and Lp(a) from baseline to week 12 • Absolute change in triglycerides, total cholesterol, HDL-C, and non-HDL-C from baseline to week 12
Method of analysis	Modified intention-to-treat analysis. The percent change in LDL-C from baseline to week 12 was analysed using an ANCOVA model with treatment group and randomisation strata of ezemitimibe use as fixed effects, and the corresponding baseline value as covariate. Continuous secondary efficacy variables were analysed using the same ANCOVA model as for the primary endpoint.
Subgroup analyses	None

Trial name: Odyssey HIGH FH	**NCT number: NCT01617655**
Objective	To evaluate the effect of alirocumab on LDL-C levels after 24 weeks of treatment in comparison with placebo
Publications – title, author, journal, year	Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia and LDL-C of 160 mg/dl or higher. Ginsberg et al. Cardiovasc Drugs Ther 2016 [35]
Study type and design	Phase 3, placebo-controlled, double-blind trial. The trial is now completed.
Sample size (n)	107
Main inclusion and exclusion criteria	Inclusion criteria: • Participants with heterozygous familial hypercholesterolemia who were not adequately controlled with their lipid-modifying therapy. Exclusion criteria: • Age < 18 years • LDL-C < 160 mg/dL (< 4.14 mmol/L) at the screening visit (week-3). • Fasting serum triglycerides > 400 mg/dL (> 4.52 mmol/L) during the screening period. • Known history of homozygous familial hypercholesterolemia.

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Trial name: Odyssey HIGH FH	NCT number: NCT01617655
Intervention	Alirocumab 150mg Q2W (n=72)
Comparator	Placebo Q2W (n=35)
Follow-up time	78-week treatment period. At the end of the 78-week double-blind treatment period, patients could enter an open-label extension study, during which they all received alirocumab 150 mg Q2W. Those patients opting out of the open-label treatment period underwent an 8-week follow-up.
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary outcomes: • Percent change in LDL-C from baseline to week 24 Secondary outcomes: • Absolute change in LDL-C from baseline to week 24 • All AEs, SAEs, withdrawal from the study for any reason, withdrawal from the study due to AEs, cardiovascular events, and all-cause mortality **Other endpoints:** The following secondary endpoints were included in the study but results are not included in this application: • LDL-C percent change from baseline to week 24 (on-treatment analysis) and from baseline to weeks 12, 52, and 78 • Percent change in non-HDL cholesterol, total cholesterol, HDL-cholesterol, apo-B, Lp(a), and triglycerides • Proportion of patients achieving LDL-C < 70 mg/dl (1.81 mmol/L) or < 100 mg/dl (2.59 mmol/L) • Proportion of patients with LDL-C < 70 mg/dl and/or a ≥ 50 % reduction in calculated LDL-C
Method of analysis	Intention-to-treat analysis. A mixed effect model with repeated measures approach to account for missing data was used to provide LS means estimates within each treatment arm and for the comparison between treatment arms for the primary and continuous secondary efficacy endpoints with a hierarchical procedure used to control type I error and handle multiple secondary endpoint analyses.
Subgroup analyses	None

Trial name: Odyssey FH I	NCT number: NCT01623115
Objective	To evaluate the effect of alirocumab on LDL-C levels after 24 weeks of treatment in comparison with placebo.
Publications – title, author, journal, year	ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. Kastelein et al. Eur Heart J 2015 [36]

Trial name: Odyssey FH I	NCT number: NCT01623115
Study type and design	Phase 3, placebo-controlled, double-blind trial. The trial is now completed, though a 3-year open-label extension study is currently ongoing.
Sample size (n)	486
Main inclusion and exclusion criteria	Inclusion criteria: • Participants with HeFH who were not adequately controlled with their lipid-modifying therapy. Exclusion criteria: • Age < 18 years or legal age of adulthood, whichever is greater • LDL-C < 70 mg/dL (1.81 mmol/L) and with cardiovascular disease • LDL-C < 100 mg/dL (2.59 mmol/L) and without cardiovascular disease • Fasting serum triglycerides > 400 mg/dL (4.52 mmol/L) • Known history of homozygous familial hypercholesterolemia.
Intervention	Alirocumab 75mg Q2W (n=323)
Comparator	Placebo Q2W (n=163)
Follow-up time	78-week treatment period. At the end of the 78 week treatment period, patients were given the option to enter a 3 year open-label extension study (currently ongoing) in which all patients are administered alirocumab. If patients decided not to enter the open-label treatment period, they were followed up for 8 weeks post-treatment.
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary outcomes: • Percent change in LDL-C from baseline to week 24 Secondary outcomes: • All AEs, SAEs, withdrawal from the study for any reason, withdrawal from the study due to AEs, cardiovascular events, and all-cause mortality **Other endpoints:** The following secondary endpoints were included in the study but results are not included in this application: • Percent change in LDL-C levels in an on-treatment analysis (using measurements that were collected while patients were still receiving treatment) • Proportion of patients reaching calculated LDL-C ,2.6 mmol/L (for those without prior CV events) and <1.8 mmol/L (for those with prior CV events) at week 24 • Proportion of patients reaching LDL-C ,1.8 mmol/L regardless of prior CV events
Method of analysis	Intention-to-treat analysis. The primary efficacy analysis was conducted using a mixed effects model with repeated measures. The LS mean difference between alirocumab and placebo was calculated using all LDL-C values regardless of adherence to treatment.

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Trial name: Odyssey FH I	NCT number: NCT01623115
Subgroup analyses	Subgroup analyses of LDL-C reductions from baseline to week 24 (alirocumab vs. placebo) were conducted according to various demographics and baseline characteristics, statin/LLT use, and baseline lipids [36]. The analyses are not included in this application.

Trial name: Odyssey FH II	NCT number: NCT01709500
Objective	To evaluate the effect of alirocumab on LDL-C levels after 24 weeks of treatment in comparison with placebo.
Publications – title, author, journal, year	ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. Kastelein et al. Eur Heart J 2015 [36]
Study type and design	Phase 3, placebo-controlled, double-blind trial. The trial is now completed, though a 3-year open-label extension study is currently ongoing.
Sample size (n)	249
Main inclusion and exclusion criteria	Inclusion criteria: • Participants with HeFH who were not adequately controlled with their lipid-modifying therapy • Provide signed informed consent Exclusion criteria: • Patient without diagnosis of HeFH made either by genotyping or by clinical criteria • LDL-C <70 mg/dL (<1.81 mmol/L) at the screening visit (week-2) in patients with history of documented cardiovascular disease • LDL-C <100 mg/dL (<2.59 mmol/L) at the screening visit (week -2) in patients without history of documented cardiovascular disease • Not on a stable dose of lipid-modifying therapy (including statin) for at least 4 weeks and/or fenofibrate for at least 6 weeks, as applicable, prior to the screening visit (week -2) and from screening to randomization • Currently taking another statin than simvastatin, atorvastatin, or rosuvastatin • Simvastatin, atorvastatin, or rosuvastatin is not taken daily or not taken at a registered dose • Daily doses above atorvastatin 80 mg, rosuvastatin 40 mg, or simvastatin 40 mg (except for patients on simvastatin 80 mg for more than 1 year, who are eligible) • Use of fibrates, other than fenofibrate within 6 weeks of the screening visit (week-2) or between screening and randomization visits • Use of nutraceutical products or over-the-counter therapies that may affect lipids which have not been at a stable dose/amount for at least 4 weeks prior to the screening visit (week -2) or between screening and randomization visits • Use of red yeast rice products within 4 weeks of the screening visit (week-2), or between screening and randomization visits • Patient who has received plasmapheresis treatment within 2 months prior to the screening visit (week -2), or has plans to receive it during the study • Recent (within 3 months prior to the screening visit [week -2] or between screening and randomization visits) MI, unstable angina leading to hospitalization, percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), uncontrolled cardiac arrhythmia, stroke, transient ischemic attack (TIA), carotid revascularization, endovascular procedure or surgical intervention for peripheral vascular disease.
Intervention	Alirocumab 75mg Q2W (n=167)

Trial name: Odyssey FH II	NCT number: NCT01709500
Comparator	Placebo Q2W (n=82)
Follow-up time	78-week treatment period. At the end of the 78 week treatment period, patients were given the option to enter a 3 year open-label extension study (currently ongoing) in which all patients are administered alirocumab. If patients decided not to enter the open-label treatment period, they were followed up for 8 weeks post-treatment.
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary outcomes: • Percent change in LDL-C from baseline to week 24 Secondary outcomes: • All AEs, SAEs, withdrawal from the study for any reason, withdrawal from the study due to AEs, cardiovascular events, and all-cause mortality **Other endpoints:** The following secondary endpoints were included in the study but results are not included in this application: • Percent change in LDL-C levels in an on-treatment analysis (using measurements that were collected while patients were still receiving treatment) • Proportion of patients reaching calculated LDL-C ,2.6 mmol/L (for those without prior CV events) and <1.8 mmol/L (for those with prior CV events) at week 24 • Proportion of patients reaching LDL-C ,1.8 mmol/L regardless of prior CV events
Method of analysis	Intention-to-treat analysis. The primary efficacy analysis was conducted using a mixed effects model with repeated measures. The LS mean difference between alirocumab and placebo was calculated using all LDL-C values regardless of adherence to treatment.
Subgroup analyses	Subgroup analyses of LDL-C reductions from baseline to week 24 (alirocumab vs. placebo) were conducted according to various demographics and baseline characteristics, statin/LLT use, and baseline lipids [36]. The analyses are not included in this application.

Trial name: Odyssey Outcomes	NCT number: NCT01663402
Objective	To compare the effect of alirocumab with placebo on the occurrence of CV events (composite endpoint of CHD death, non-fatal MI, fatal and non-fatal ischaemic stroke, UA requiring hospitalization) in participants who experienced an ACS event 4 to 52 weeks prior to randomization and were treated with evidence-based medical and dietary management of dyslipidaemia.
Publications – title, author, journal, year	Alirocumab and cardiovascular outcomes after acute coronary syndrome. Schwartz et al. N Engl J Med 2018 [18]
Study type and design	Phase 3, placebo-controlled, double-blind trial. The trial is now completed.

Trial name: Odyssey Outcomes	NCT number: NCT01663402
Sample size (n)	18,924
Main inclusion and exclusion criteria	Inclusion criteria: • Recently (< 52 weeks) hospitalized for ACS Exclusion criteria: • Age < 40 years • ACS event occurring more than 52 weeks prior to randomization visit • LDL-C likely to be <70 mg/dL (<1.81 mmo/L), and apo-B <80 mg/dL (<0.8 g/L), and non - HDL-C) <100 mg/dL (<2.59 mmol/L) with evidence-based medical and dietary management of dyslipidaemia
Intervention	Alirocumab 75mg Q2W (n=9462)
Comparator	Placebo Q2W (n=9462)
Follow-up time	Patients were followed for a median of 2.8 years (interquartile range, 2.3 to 3.4)
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Secondary outcomes: • Percent change in LDL-C from baseline to month 4 • All AEs, SAEs, withdrawal from the study for any reason, withdrawal from the study due to AEs, cardiovascular events, and all-cause mortality **Other endpoints:** The following endpoints were included in the study but results are not included in this application: • The primary end point was a composite of death from CHD, nonfatal MI, fatal or nonfatal ischemic stroke, or UA requiring hospitalization • Prespecified secondary end points included: any CHD event (death from coronary heart disease, nonfatal MI, UA requiring hospitalization, or an ischemia-driven coronary revascularization procedure); major CHD event (death from CHD or nonfatal MI); any CV event (death from cardiovascular causes, nonfatal ischaemic stroke, nonfatal MI, unstable angina requiring hospitalization, or an ischaemia-driven coronary revascularization procedure); a composite of death from any cause, nonfatal MI, or nonfatal ischaemic stroke; death from CHD; death from cardiovascular causes; and death from any cause • Individual components of the primary end point, an ischemia-driven coronary revascularization procedure, and hospitalization for congestive heart failure were additional secondary end points
Method of analysis	Not applicable
Subgroup analyses	Subgroup analyses of the primary endpoint were conducted according to various demographics and baseline characteristics, statin/LLT use, and baseline lipids [18]. The analyses are not included in this application.

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Trial name: Odyssey Long Term	NCT number: NCT01507831
Objective	To evaluate the long-term safety and tolerability of alirocumab in high cardiovascular risk participants with hypercholesterolemia not adequately controlled with their current LMT
Publications – title, author, journal, year	Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. Robinson et al. N Engl J Med 2015 [37]
Study type and design	Phase 3, placebo-controlled, double-blind, parallel group trial. The trial is now completed.
Sample size (n)	2,341
Main inclusion and exclusion criteria	Inclusion criteria: • Either A or B who were not adequately controlled with their LMT. A) Participants with HeFH with or without established CHD or CHD risk equivalents; or B) Participants with hypercholesterolemia together with established CHD or CHD risk equivalents Exclusion criteria: • Age < 18 years • LDL-C <70 mg/dL (< 1.81 mmol/L) • Fasting serum triglycerides > 400 mg/dL (>4.52 mmol/L)
Intervention	Alirocumab 150mg Q2W (n=1553)
Comparator	Placebo (n=788)
Follow-up time	78 weeks of treatment. The mean duration of follow-up (regardless of adherence to the study drug) in the safety population was 80.9 weeks in the alirocumab group and 80.1 weeks in the placebo group.
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary outcomes: • Percent change in LDL-C from baseline to week 24 Secondary outcomes: • Absolute change in LDL-C from baseline to week 24 • All AEs, SAEs, withdrawal from the study for any reason, withdrawal from the study due to AEs, cardiovascular events, and all-cause mortality **Other endpoints:** The following secondary endpoints were included in the study but results are not included in this application: • Percent change in LDL-C level while the study drug was being taken, as well as other lipoprotein variables at weeks 12 and 24 in both the intention-to-treat analysis and the analysis that included only patients who were receiving the study drug
Method of analysis	Intention-to-treat analysis. The primary and secondary LDL-C outcome was analysed using a mixed-effects model for repeated measures.

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Trial name: Odyssey Long Term	NCT number: NCT01507831
Subgroup analyses	Subgroup analyses of the primary endpoint were conducted according to various demographics and baseline characteristics, statin/LLT use, and baseline lipids [37]. The analyses are not included in this application.

Trial name: Odyssey Choice I	NCT number: NCT01926782
Objective	To determine the efficacy, long-term safety, and tolerability of alirocumab 300 mg every 4 weeks (Q4W), in comparison with placebo, as well as its potential as a starting regimen.
Publications – title, author, journal, year	A phase III randomized trial evaluating alirocumab 300 mg every 4 weeks as monotherapy or add-on to statin: ODYSSEY CHOICE I. Roth et al. Atherosclerosis 2016 [38]
Study type and design	Phase 3, placebo-controlled, double-blind trial. The trial is now completed.
Sample size (n)	547
Main inclusion and exclusion criteria	Inclusion criteria: • Men and women > age 18 or legal age of majority with elevated LDL-C • Patients not having adequate control of their hypercholesterolemia based on their individual level of CVD risk • Willing and able to comply with clinic visits and study-related procedures • Provided signed informed consent Exclusion criteria: • Recent (within 3 months prior to the screening visit) MI, UA leading to hospitalization, percutaneous coronary intervention, coronary artery bypass graft surgery, uncontrolled cardiac arrhythmia, stroke, transient ischemic attack, carotid revascularization, endovascular procedure or surgical intervention for peripheral vascular disease • Known history of positive test for human immunodeficiency virus (HIV) • Any clinically significant abnormality identified at the time of screening that in the judgment of the investigator or any sub-investigator would preclude safe completion of the study or constrain assessment of endpoints, such as major systemic diseases or participants with short life expectancy. • Participants considered by the investigator or any sub-investigator to be inappropriate for this study (e.g, geographic or social), actual or anticipated, that the investigator felt would restrict or limit the participant's participation for the duration of the study. • Certain laboratory findings obtained during the screening period
Intervention	Alirocumab 75mg Q2W (n=78)
Comparator	Placebo Q2W (n=157)
Follow-up time	The study comprised a 3-week screening period, followed by 48 weeks of double-blind treatment and 8 weeks of follow-up (off treatment).
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary outcomes: • Percent change in LDL-C from baseline to week 24

Trial name: Odyssey Choice I	NCT number: NCT01926782
	Secondary outcomes: • All AEs, SAEs, withdrawal from the study for any reason, withdrawal from the study due to AEs, and cardiovascular events **Other endpoints:** The following endpoints were included in the study but results are not included in this application: • Co-primary endpoint percent change in calculated LDL-C from baseline to the average over weeks 21-24 (alirocumab 300 mg Q4W vs. placebo, according to randomization) using all LDL-C values regardless of adherence to treatment • Key secondary endpoint: Percent change in calculated LDL-C from baseline to week 24 assessed using all LDL-C values during the efficacy treatment period (on-treatment approach); percent change in calculated LDL-C from baseline to week 12; the proportion of patients achieving LDL-C targets of <70 mg/dL (1.8 mmol/L; very high cardiovascular risk) or <100 mg/dL (2.6 mmol/L) at week 24 (moderate or high cardiovascular risk); and the percent change in apo-B, non-HDL-C, total cholesterol, Lp(a), fasting triglycerides, HDL-C, and apo-A1 from baseline to weeks 12 and 24 • Other secondary endpoints: Percent change in calculated LDL-C from baseline to week 48, and the proportion of patients achieving LDL-C targets at weeks 12 and 48
Method of analysis	Intention-to-treat analysis. The primary endpoints were analysed using a mixed-effects model with repeated measures, with parameters to account for missing data. Key secondary endpoints were analysed as for the primary endpoint.
Subgroup analyses	Subgroup analyses of the primary endpoint were conducted according to various demographics and baseline characteristics, statin/LLT use, and baseline lipids [38]. The analyses are not included in this application.

Trial name: NTC01288443	NCT number: NTC01288443
Objective	To evaluate the effect of alirocumab (SAR236553/REGN727) on LDL-C levels after 12 weeks of treatment in comparison with placebo in participants with LDL-C ≥ 100 mg/dL (≥ 2.59 mmol/L) on ongoing stable atorvastatin therapy.
Publications – title, author, journal, year	Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. McKenney et al. J Am Coll Cardiol 2012 [39]
Study type and design	Phase 2, double-blind, parallel-group, placebo-controlled trial. The trial is now completed.
Sample size (n)	92
Main inclusion and exclusion criteria	Inclusion criteria: • Participants with primary hypercholesterolemia receiving a lipid-lowering treatment other than atorvastatin or not at stable dose of atorvastatin 10 mg, 20 mg, or 40 mg for at least 6 weeks prior to screening period or drug naive participants if they are likely to have LDL-C ≥ 100 mg/dL (≥ 2.59 mmol/L) at the end of the 6-week run-in treatment period on atorvastatin therapy

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Trial name: NTC01288443	NCT number: NTC01288443

	• OR
	• Participants with primary hypercholesterolemia treated with atorvastatin at stable dose of 10 mg, 20 mg, or 40 mg for at least 6 weeks prior to screening period and likely to have LDL-C ≥ 100 mg/dL (≥ 2.59 mmol/L) at the screening visit
	
	Exclusion criteria:
	• LDL-C < 100 mg/dL (< 2.59 mmol/L): 1) After the run-in period on atorvastatin (10 mg, 20 mg, or 40 mg) for participants receiving a lipid-lowering treatment other than atorvastatin or not at stable dose of atorvastatin 10 mg, 20 mg, or 40 mg for at least 6 weeks prior to the screening, or drug naive participant; OR 2) At the first visit for participants who were being treated with stable dose of atorvastatin (10 mg, 20 mg, or 40 mg) for at least 6 weeks prior to screening
	• Participants not previously instructed on a cholesterol-lowering diet
	• Participants with type 1 diabetes
	• Participants with type 2 diabetes treated with insulin
	• Participants with type 2 diabetes and with an glycated haemoglobin (HbA1c) ≥ 8.5% at screening visit (considered poorly controlled)
	• Laboratory findings measured before randomization:
	  ○ Triglycerides >350 mg/dL at screening visit
	  ○ positive serum or urine pregnancy test in females of childbearing potential
	• Pregnant or breast-feeding women
	• Women of childbearing potential with no effective contraceptive method

Intervention	Alirocumab 150mg Q2W (n=29)
Comparator	Placebo Q2W (n=31)
Follow-up time	The study comprised 3 periods: screening, 12-week double-blind treatment, and 8-week follow-up period.
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary outcomes: • Percent change in LDL-C from baseline to week 24 Secondary outcomes: • All AEs, SAEs, withdrawal from the study for any reason, and withdrawal from the study due to AEs **Other endpoints:** The following secondary endpoints were included in the study but results are not included in this application: • Absolute change from baseline in calculated LDL-C (mmol/L) at week 12 - on-treatment analysis • Absolute change from baseline in calculated LDL-C mg/dL) at week 12 - on-treatment analysis • Percentage of participants achieving calculated LDL-C <100 mg/dL (2.59 mmol/L) and <70 mg/dL (1.81 mmol/L) at week 12 - on-treatment analysis • Percent change from baseline in total cholesterol, HDL-C, non-HDL-C and apo-B at week 12 - on-treatment analysis

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Trial name: NTC01288443	NCT number: NTC01288443
	• Percent change from baseline in fasting triglycerides and Lp(a) at week 12 - on-treatment analysis • Absolute change in the ratio apo-B/apo-A-1) from baseline to week 12 - on-treatment analysis
Method of analysis	Modified intent-to-treat population, defined as all randomized patients with an evaluable primary endpoint, using an analysis of covariance model with treatment group and randomization strata of atorvastatin dose as fixed effects, and baseline LDL-C as covariate. The primary and secondary endpoints were analysed using an ANCOVA model with treatment group and randomization strata of atorvastatin dose as fixed effects, and baseline LDL-C as covariate.
Subgroup analyses	None

Trial name: Odyssey Combo I	NCT number: NCT01644175
Objective	To demonstrate the reduction of LDL-C by alirocumab as add-on therapy to stable maximally tolerated daily statin therapy with or without other LMT in comparison with placebo after 24 weeks of treatment in high CV risk participants with hypercholesterolemia
Publications – title, author, journal, year	Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: The ODYSSEY COMBO I study. Kereiakes et al. Am Heart J 2015 [40]
Study type and design	Phase 3, randomized (2:1 alirocumab vs placebo), double-blind, 52-week trial. The trial is now completed.
Sample size (n)	316
Main inclusion and exclusion criteria	Inclusion criteria: • Participants with hypercholesterolemia and established CHD or CHD risk equivalents who were not adequately controlled with a maximally tolerated daily dose of statin with or without other LMT, both at stable dose for at least 4 weeks to 6 weeks prior to screening (week -2) Exclusion criteria: • Age <18 or legal age of adulthood, whichever was greater • Participants without established CHD or CHD risk equivalent • LDL-C <70 mg/dL (<1.81 mmol/L) and participants with a history of documented cardiovascular disease • LDL-C <100 mg/dL (<2.59 mmol/L) and participants without a history of documented cardiovascular disease • Not on a stable dose of LMT (including statin) for at least 4 weeks and/or fenofibrate for at least 6 weeks, as applicable, prior to the screening visit (Week -2) and from screening to randomization • Fasting serum triglycerides > 400 mg/dL (>4.52 mmol/L)
Intervention	Alirocumab 75mg Q2W (n=209)
Comparator	Placebo Q2W (n=107)

Trial name: Odyssey Combo I	NCT number: NCT01644175
Follow-up time	52-week treatment period and and 8-week follow-up period
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary outcomes: • Percent change in LDL-C from baseline to week 24 Secondary outcomes: • Absolute change in LDL-C from baseline to week 24 • All AEs, SAEs, withdrawal from the study for any reason, withdrawal from the study due to AEs, cardiovascular events, and all-cause mortality **Other endpoints:** The following secondary endpoints were included in the study but results are not included in this application: • Percent change in LDL-C from baseline to week 24 (on-treatment analysis), percent change in LDL-C at other defined time points, percent changes in other lipid parameters, and proportion of patients reaching LDL-C b70 mg/dL
Method of analysis	Intention-to-treat analysis. The primary and secondary endpoints were analysed using a mixed-effects model with repeated measures, with parameters to account for missing data.
Subgroup analyses	Subgroup analyses of the primary endpoint were conducted according to various demographics and baseline characteristics, statin/LLT use, and baseline lipids [40]. The analyses are not included in this application.

Trial name: Odyssey KT	NCT number: NCT02289963
Objective	To demonstrate the reduction of LDL-C by alirocumab as add-on therapy to stable maximally tolerated daily statin therapy with or without other LMT in comparison with placebo after 24 weeks of treatment in high CV risk participants with hypercholesterolemia in South Korea and Taiwan.
Publications – title, author, journal, year	A randomized trial evaluating the efficacy and safety of alirocumab in South Korea and Taiwan (ODYSSEY KT). Koh et al. J Clin Lipidol 2018 [41]
Study type and design	Phase 3, placebo-controlled, double-blind, parallel group trial. The trial is now completed.
Sample size (n)	199
Main inclusion and exclusion criteria	Inclusion criteria: • Participants with hypercholesterolemia and established CHD or CHD risk equivalents who are not adequately controlled with a maximally tolerated daily dose of statin with or without other LMT, both at stable dose for at least 4 weeks prior to screening visit (week -3)

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Trial name: Odyssey KT	NCT number: NCT02289963
	Exclusion criteria: • Aged <18 years or legal age of adulthood, whichever was greater. • Participants without established CHD or CHD risk equivalent. • LDL-C <70 mg/dL (<1.81 mmol/L) in participants with a history of documented CV disease. • LDL-C <100 mg/dL (<2.59 mmol/L) in participants without a history of documented CV disease. • Not on a stable dose of LMT (including statin) for at least 4 weeks prior to the screening visit (week -3) or between screening to randomization visits. • Currently taking a statin other than atorvastatin, rosuvastatin or simvastatin. • Atorvastatin, rosuvastatin or simvastatin was not taken daily or not taken at a registered dose. • Daily doses above atorvastatin 80 mg, rosuvastatin 20 mg or simvastatin 40 mg. • Fasting serum triglycerides >400 mg/dL (>4.52 mmol/L) at the screening period
Intervention	Alirocumab 75mg Q2W (n=97)
Comparator	Placebo Q2W (n=102)
Follow-up time	The study comprised an up to 3-week screening period, followed by 24 weeks of double-blind treatment and 8 weeks of follow-up (off treatment).
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary outcomes: • Percent change in LDL-C from baseline to week 24 Secondary outcomes: • Absolute change in LDL-C from baseline to week 24 • All AEs, SAEs, withdrawal from the study for any reason, withdrawal from the study due to AEs, cardiovascular events, and all-cause mortality **Other endpoints:** The following secondary endpoints were included in the study but results are not included in this application: • Percent change in calculated LDL-C from baseline to week 24 assessed using an on-treatment approach • Percent change in calculated LDL-C from baseline to week 12, the percent change in apo-B, non-HDL-C, total cholesterol, Lp(a), HDL-C, triglycerides, and apo-A1 from baseline to weeks 12 and 24 • Proportion of patients reaching calculated LDL-C ,70 mg/dL at week 24
Method of analysis	Intention-to-treat analysis. The primary and secondary endpoints were analysed using a mixed-effects model with repeated measures, with parameters to account for missing data.
Subgroup analyses	None.

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Trial name: Odyssey Combo II	NCT number: NCT01644188
Objective	To demonstrate the reduction of LDL-C by alirocumab as add-on therapy to stable maximally tolerated daily statin therapy in comparison with ezetimibe after 24 weeks of treatment in participants with hypercholesterolemia at high CV risk.
Publications – title, author, journal, year	Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. Cannon et al. Eur Heart J 2015 [42]
Study type and design	Double-blind, double-dummy, active-controlled, parallel-group, 104-week study of alirocumab vs. ezetimibe. The trial is now completed.
Sample size (n)	720
Main inclusion and exclusion criteria	Inclusion criteria: • Participants with hypercholesterolemia and established CHD or CHD risk equivalents who were not adequately controlled with a maximally tolerated daily dose of statin at stable dose for at least 4 weeks prior to the screening visit (week -2) Exclusion criteria: • Age < 18 or legal age of adulthood, whichever was greater • Participants without established CHD or CHD risk equivalents • LDL-C <70 mg/dL (<1.81 mmol/L) and participants with a history of documented CV disease • LDL-C <100 mg/dL (<2.59 mmol/L) and participants without a history of documented CV disease • Fasting serum triglycerides >400 mg/dL (>4.52 mmol/L)
Intervention	Alirocumab 75mg Q2W (n=479)
Comparator	Placebo Q2W (n=241)
Follow-up time	104-week treatment period followed by an 8-week post-treatment observational period.
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary outcomes: • Percent change in LDL-C from baseline to week 24 Secondary outcomes: • Absolute change in LDL-C from baseline to week 24 • All AEs, SAEs, withdrawal from the study for any reason, withdrawal from the study due to AEs, cardiovascular events, and all-cause mortality **Other endpoints:** The following secondary endpoints were included in the study but results are not included in this application: • Percent change in calculated LDL-C from baseline to week 24 (on-treatment analysis), and from baseline to weeks 12 (ITT/on-treatment analysis) or 52 (ITT analysis) • Percent change in apo-B, non-HDL-C, total cholesterol, Lp(a), HDL-C, fasting triglycerides, and apo-A-1 from baseline to week 24 (ITT analysis)

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Trial name: Odyssey Combo II	NCT number: NCT01644188
	• Proportion of patients reaching calculated LDL-C ,1.8 mmol/L at week 24 (ITT/on-treatment analysis)
Method of analysis	Intention-to-treat analysis. The primary and secondary endpoints were analysed using a mixed-effects model with repeated measures, with parameters to account for missing data.
Subgroup analyses	Subgroup analyses of the primary endpoint were conducted according to various demographics and baseline characteristics, statin/LLT use, and baseline lipids [42]. The analyses are not included in this application.

Trial name: Odyssey EAST	NCT number: NCT02715726
Objective	To demonstrate the reduction of LDL-C by alirocumab as add-on therapy to stable maximally tolerated daily statin therapy in comparison to ezetimibe 10 mg daily after 24 weeks of treatment in Asia in participants with hypercholesterolemia at high CV risk.
Publications – title, author, journal, year	ODYSSEY EAST: Alirocumab efficacy and safety vs ezetimibe in high cardiovascular risk patients with hypercholesterolemia and on maximally tolerated statin in China, India, and Thailand. Han et al. J Clin Lipidol 2020 [43]
Study type and design	Phase 3, parallel-group, double blind trial. The trial is now completed.
Sample size (n)	615
Main inclusion and exclusion criteria	Inclusion criteria: • Participants with hypercholesterolemia and established CHD or CHD risk equivalents who were not adequately controlled with a maximally tolerated daily dose of statin at stable dose for at least 4 weeks prior to the screening visit (week -3) Exclusion criteria: • Participants without established CHD or CHD risk equivalents. • LDL-C <70 mg/dL (<1.81 mmol/L) at the screening visit (week -3) in participants with history of documented CV disease. • LDL-C <100 mg/dL (<2.59 mmol/L) at the screening visit (week -3) in participants without history of documented CV disease. • Change in statin dose or dose regimen from screening to randomization. • Currently taking a statin other than atorvastatin, rosuvastatin, or simvastatin. • Atorvastatin, rosuvastatin, or simvastatin was not taken daily or not taken at a registered dose. • Daily doses above atorvastatin 80 mg, rosuvastatin 40 mg, or simvastatin 40 mg. • Use of cholesterol absorption inhibitor (ie, ezetimibe), omega-3 fatty acid (at doses ≥1000 mg daily), nicotinic acid, fibrates, bile acid-binding sequestrant, or red yeast rice products in the past 4 weeks prior to screening visit (week -3). • Fasting serum triglycerides >400 mg/dL (>4.52 mmol/L) at the screening period
Intervention	Alirocumab 75mg Q2W (n=407)
Comparator	Ezetimibe 10 mg/day (n=208)

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Trial name: Odyssey EAST	NCT number: NCT02715726
Follow-up time	After randomization, patients entered a double-blind, double-dummy treatment period lasting 104 weeks followed by an 8-week post-treatment observational period.
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary outcomes: • Percent change in LDL-C from baseline to week 24 Secondary outcomes: • Absolute change in LDL-C from baseline to week 24 • All AEs, SAEs, withdrawal from the study due to AEs, cardiovascular events, and all-cause mortality **Other endpoints:** The following secondary endpoints were included in the study but results are not included in this application: • Percent change in calculated LDL-C from baseline to week 24 (on-treatment analysis), and from baseline to weeks 12 (ITT/on-treatment analysis) or 52 (ITT analysis) • Percent change in apo-B, non-HDL-C, total cholesterol, Lp(a), HDL-C, fasting triglycerides, and apo-A-1 from baseline to week 24 (ITT analysis) • Proportion of patients reaching calculated LDL-C ,1.8 mmol/L at week 24 (ITT/on-treatment analysis)
Method of analysis	Intention-to-treat analysis. The primary and secondary endpoints were analysed using a mixed-effects model with repeated measures, with parameters to account for missing data.
Subgroup analyses	Subgroup analyses of the primary endpoint were conducted according to various demographics and baseline characteristics, statin/LLT use, and baseline lipids [43]. The analyses are not included in this application.

Trial name: Odyssey Choice II	NCT number: NCT02023879
Objective	To demonstrate the reduction of LDL-C by a regimen of alirocumab including a starting dose of 150 mg Q4W as add-on to non-statin lipid modifying background therapy or as monotherapy in comparison with placebo in participants with primary hypercholesterolemia not treated with a statin
Publications – title, author, journal, year	Efficacy and safety of alirocumab 150 mg every 4 weeks in patients with hypercholesterolemia not on statin therapy: The ODYSSEY CHOICE II study. Stroes et al. J Am Heart Assoc 2016 [44]
Study type and design	Phase 3, placebo-controlled, double-blind trial. The trial is now completed.
Sample size (n)	233
Main inclusion and exclusion criteria	Inclusion criteria:

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Trial name: Odyssey Choice II	NCT number: NCT02023879
	• Participants with primary hypercholesterolemia (HeFH or non-FH) not adequately controlled with their non-statin LMT (either ezetimibe or fenofibrate) or diet alone Exclusion criteria: • LDL-C <70 mg/dL (1.81 mmol/L) at screening for statin intolerant participants at very high CV risk • LDL-C <100 mg/dL (<2.59 mmol/L) at screening for statin intolerant participants at high or moderate CV risk or, participants not fulfilling the statin intolerant definition at moderate CV risk • LDL-C ≥160 mg/dL (≥4.1 mmol/L) at screening for participants receiving diet only or, participants not fulfilling the statin intolerant definition at moderate CV risk and receiving a non-statin LMT
Intervention	Alirocumab 75mg Q2W (n=116)
Comparator	Placebo Q2W (n=58)
Follow-up time	The study comprised a 3-week screening period, followed by 24 weeks of double-blind treatment and 8 weeks of follow-up (off treatment) for those patients who did not enter the open-label treatment period
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary outcomes: • Percent change in LDL-C from baseline to week 24 Secondary outcomes: • Absolute change in LDL-C from baseline to week 24 • All AEs, SAEs, withdrawal from the study for any reason, withdrawal from the study due to AEs, cardiovascular events, and all-cause mortality **Other endpoints:** The following secondary endpoints were included in the study but results are not included in this application: • Percentage change in calculated LDL-C from baseline to week 24 using the on-treatment approach • Percentage change in calculated LDL-C from baseline to week 12 (also averaged for weeks 9-12) • Proportion of patients achieving predefined LDL-C targets of <70 or <100 mg/dL, depending on CV risk, at weeks 12 and 24 • Percentage change in other lipid parameters such as apo-B, non-HDL cholesterol, total cholesterol, Lp(a), fasting triglycerides, HDL-C, and apo-A1 from baseline to weeks 12 and 24
Method of analysis	Intention-to-treat analysis. The primary and secondary endpoints were analysed using a mixed-effects model with repeated measures, with parameters to account for missing data.

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Trial name: Odyssey Choice II	NCT number: NCT02023879
Subgroup analyses	Subgroup analyses of the primary endpoint were conducted according to various demographics and baseline characteristics, statin/LLT use, and baseline lipids [44]. The analyses are not included in this application.

Trial name: Odyssey NIPPON	NCT number: NCT02584504
Objective	To demonstrate the reduction of LDL-C by alirocumab administration as add-on therapy to non-statin LMT including diet therapy alone or the lowest strength of statin in comparison with placebo after 12 weeks of treatment in participants with hypercholesterolaemia.
Publications – title, author, journal, year	Efficacy and safety of alirocumab 150mg every 4 weeks in hypercholesterolemic patients on non-statin lipid-lowering therapy or lowest strength dose of statin: ODYSSEY NIPPON. Teramoto et al. J Cardiol 2019 [45]
Study type and design	Phase 3, placebo-controlled, double-blind, parallel group trial. The trial is now completed
Sample size (n)	163
Main inclusion and exclusion criteria	Inclusion criteria: • Participants with hypercholesterolaemia (HeFH or non-FH) receiving non statin LMTs or the lowest strength of statin Exclusion criteria: • LDL-C <100 mg/dL (<2.59 mmol/L) at the screening visit (week -3) in participants with HeFH or in participants with non-FH who have a history of documented CHD • LDL-C <120 mg/dL (<3.10 mmol/L) at the screening visit (week -3) in participants with non-FH participants who had a history of documented diseases or other risk factors classified as primary prevention category III as defined in JAS Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2012 • Not on a stable dose of LMT (including diet therapy alone) in the run-in period or the screening period • Fasting serum triglycerides >400 mg/dL (>4.52 mmol/L) at the screening period • Systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg at the run-in visit (week -7) or the screening visit (week -3) or the randomization visit (week 0)
Intervention	Alirocumab 150mg Q2W (n=53)
Comparator	Placebo Q2W (n=56)
Follow-up time	The study consisted of a run-in period of 4 weeks, a screening period of up to 3 weeks, a double-blind treatment period of 12 weeks, and an open-label treatment period of 52 weeks.
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary outcomes: • Percent change in LDL-C from baseline to week 12 Secondary outcomes: • Absolute change in LDL-C from baseline to week 12

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Trial name: Odyssey NIPPON	NCT number: NCT02584504
	• All AEs, SAEs, withdrawal from the study for any reason, withdrawal from the study due to AEs, cardiovascular events, and all-cause mortality **Other endpoints:** The following secondary endpoints were included in the study but results are not included in this application: • Percentage change in calculated LDL-C from baseline to week 12 (on-treatment analysis) • Percentage change in calculated LDL-C from baseline to average week 10–12 (ITT/on-treatment analysis) • Percent change from baseline to week 12 in apo-B (ITT/on-treatment analysis), non-HDL-C (ITT/on-treatment analysis), total cholesterol (ITT analysis), Lp(a) (ITT analysis), HDL-C (ITT analysis), fasting triglycerides (ITT analysis), apo-A-1 (ITT analysis) • Proportion of patients who reached the LDL-C goal at week 12 (ITT/on-treatment analysis)
Method of analysis	Intention-to-treat analysis. The primary and secondary endpoints were analysed using a mixed-effects model with repeated measures, with parameters to account for missing data.
Subgroup analyses	Subgroup analyses of the primary endpoint were conducted according to various demographics and baseline characteristics, statin/LLT use, and baseline lipids [45]. The analyses are not included in this application.

Trial name: Odyssey ALTERNATIVE	NCT number: NCT01709513
Objective	To compare alirocumab (REGN727/SAR236553) versus ezetimibe in participants with primary hypercholesterolemia and moderate, high, or very high CV risk, who are intolerant to statin.
Publications – title, author, journal, year	Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. Moriarty et al. J Clin Lipidol 2015 [46]
Study type and design	Phase 3, double-blind, double-dummy, active-controlled, parallel-group trial. The trial is now completed.
Sample size (n)	314
Main inclusion and exclusion criteria	Inclusion criteria: • Patients with primary hypercholesterolemia (HeFH or non-FH] with moderate, high or very high CV risk and a history of statin intolerance • Provide signed informed consent Exclusion criteria: • Calculated serum LDL-C <70 mg/dL (1.81 mmol/L) and very high CV risk at the screening visit • Calculated serum LDL-C <100 mg/dL (2.59 mmol/L) and high or moderate CV risk at the screening visit • A 10-year fatal CV disease risk score <1% at the screening visit)
Intervention	Alirocumab 75mg Q2W (n=126)
Comparators	Ezetimibe 10 mg/day (n=125)

Trial name: Odyssey ALTERNATIVE	NCT number: NCT01709513
	Atorvastatin 20 mg/day (n=63)
Follow-up time	The study comprised 5 periods: 1-week screening; 2-week washout of ezetimibe, statins (for patients taking a less than lowest-approved daily starting dose or regimen), and red yeast rice; 4-week single-blind placebo run-in to exclude patients with non-statin–related muscle symptoms; 24-week double-blind treatment; and 8-week off-treatment follow-up period.
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary outcomes: • Percent change in LDL-C from baseline to week 24 Secondary outcomes: • Absolute change in LDL-C from baseline to week 24 • All AEs, SAEs, withdrawal from the study for any reason, withdrawal from the study due to AEs, and cardiovascular events **Other endpoints:** The following secondary endpoints were included in the study but results are not included in this application: • Change from baseline to 24 weeks using on-treatment (modified ITT) LDL-C values • Percent change from baseline to 12 and 24 weeks in LDL-C, apo-B, non-HDL-C), total cholesterol, Lp(a), HDL-C, apo-A1 and fasting triglyceride concentrations
Method of analysis	Intention-to-treat analysis. The primary and secondary endpoints were analysed using a mixed-effects model with repeated measures, with parameters to account for missing data.
Subgroup analyses	Subgroup analyses of the primary endpoint were conducted according to various demographics and baseline characteristics, statin/LLT use, and baseline lipids [46]. The analyses are not included in this application.

Abbreviations: ACS, acute coronary syndrome; AE, adverse event; ANCOVA, analysis of covariance; apo-B; apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CV, cardiovascular; HDL, high density lipoprotein; HeFH, heterozygous familial hypercholesterolaemia; ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol; LLT, lipid-lowering therapy; Lp(a), lipoprotein(a); LS, least-squares; MI, myocardial infarction; non-FH, non-familial hypercholesterolemia; NYHA, New York Heart Association; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every two weeks; Q4W, every four weeks; SAE, serious adverse event: UA, unstable angina; VLDL-C , very low density lipoprotein-cholesterol.

Evolocumab studies	
Trial name: RUTHERFORD-2	**NCT number: NCT01763918**
Objective	The primary objective was to evaluate the effect of 12 weeks of evolocumab subcutaneously Q2W and QM, compared with placebo, on percent change from baseline in LDL-C in adults with HeFH.

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Publications – title, author, journal, year	PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Raal et al. Lancet. 2015 [47]
Study type and design	Phase 3, double-blind, placebo-controlled trial. The trial is now completed.
Sample size (n)	331
Main inclusion and exclusion criteria	Inclusion criteria: • Male or female ≥ 18 to ≤ 80 years of age • Diagnosis of HeFH • On a stable dose of an approved statin and lipid regulating medication • Fasting LDL-C ≥ 100 mg/dL (2.6 mmol/L) • Fasting triglycerides ≤ 400 mg/dL (4.5 mmol/L) Exclusion criteria: • Homozygous familial hypercholesterolemia • LDL or plasma apheresis • NYHA III or IV heart failure • Uncontrolled cardiac arrhythmia • Uncontrolled hypertension • Type 1 diabetes, poorly controlled type 2 diabetes • Uncontrolled hypothyroidism or hyperthyroidism
Intervention	Evolocumab 140mg Q2W (n=110)
Comparator	Placebo Q2W (n=54)
Follow-up time	12-week treatment period
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary outcomes: • Percent change in LDL-C from baseline to week 12 Secondary outcomes: • Absolute change in LDL-C from baseline to week 12 • All AEs, SAEs, withdrawal from the study due to AEs, and all-cause mortality **Other endpoints:** The following endpoints were included in the study but results are not included in this application: • Coprimary endpoint of percentage change in plasma LDL cholesterol from baseline to the mean of weeks 10 and 12 • Secondary endpoints: percentage of patients achieving a target of LDL-C lower than 1·8 mmol/L at the same timepoints as above • Mean percentage change from baseline in other lipids, apolipoproteins, high-sensitivity C-reactive protein, and unbound PCSK9
Method of analysis	Intention-to-treat analysis.

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	The primary and secondary endpoints were analysed using a mixed-effects model with repeated measures, with parameters to account for missing data.
Subgroup analyses	A post-hoc exploratory subgroup analysis of the percentage change from baseline in LDL cholesterol and other lipid parameters by genotype status (confirmed or unconfirmed) and by LDL receptor class (defective, negative, or unclassified) or apolipoprotein B mutation status [47]. The analyses are not included in this application.

Trial name: FOURIER	**NCT number: NCT01764633**
Objective	The primary objective was to evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for CV death, MI, stroke, hospitalization for UA, or coronary revascularization, whichever occurs first, in patients with clinically evident CV disease.
Publications – title, author, journal, year	Evolocumab and clinical outcomes in patients with cardiovascular disease. Sabatine et al. N Engl J Med 2017 [19]
Study type and design	Phase 3, double-blind, placebo-controlled trial. The trial is now completed.
Sample size (n)	27,564
Main inclusion and exclusion criteria	Inclusion criteria: • Male or female ≥ 40 to ≤ 85 years of age • History of clinically evident CV disease at high risk for a recurrent event • Fasting LDL-C ≥ 70 mg/dL (≥ 1.8 mmol/L)) or non-HDL-C ≥ 100 mg/dL (> 2.6 mmol/L) • Fasting triglycerides ≤ 400 mg/dL (4.5 mmol/L) Exclusion criteria: • NYHA class III or IV, or last known left ventricular ejection fraction < 30% • Uncontrolled hypertension • Uncontrolled or recurrent ventricular tachycardia • Untreated hyperthyroidism or hypothyroidism • Homozygous familial hypercholesterolemia • LDL or plasma apheresis
Intervention	Evolocumab 420mg or 140mg Q2W or Q4W (n=13784)
Comparator	Placebo Q2W or Q4W (n=13780)
Follow-up time	The median duration of follow-up was 26 months (interquartile range, 22 to 30), which resulted in 59,865 patient-years of follow-up.
Is the study used in the health economic model?	No

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Trial name: FOURIER	NCT number: NCT01764633
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Secondary outcomes: • Percent change in LDL-C from baseline to week 24 • Absolute change in LDL-C from baseline to week 24 • All AEs, SAEs, withdrawal from the study for any reason, withdrawal from the study due to AEs, cardiovascular events, and all-cause mortality **Other endpoints:** The following endpoints were included in the study but results are not included in this application: • Time to CV death, MI, hospitalization for UA, stroke, or coronary revascularization (primary) • Secondary: Time to CV death; time to all cause death; time to first MI; time to first stroke; time to first coronary revascularization; time to CV death or first hospitalization for worsening heart failure; and time to CV death or first hospitalization for worsening heart failure
Method of analysis	Intention-to-treat analysis. Between group differences in lipid parameters were calculated using a repeated measures linear mixed effects model using all measurements from baseline up to the end of the study, reported as LS means. The model included terms for treatment group, stratification factors, scheduled visit and the interaction of treatment with scheduled visit.
Subgroup analyses	Subgroup analyses were conducted according to various demographics and baseline characteristics [19]. The analyses are not included in this application.

Trial name: LAPLACE-2	NCT number: NCT01763866
Objective	To evaluate the effect of 12 weeks of evolocumab administered subcutaneously Q2W and QM when used in combination with a statin, compared with placebo, on percent change from baseline in LDL-C in patients with primary hypercholesterolemia and mixed dyslipidaemia.
Publications – title, author, journal, year	Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. Robinson et al. JAMA 2014 [48]
Study type and design	Phase 3, 12-week, randomized, double-blind, placebo- and ezetimibe-controlled trial. The trial is now completed.
Sample size (n)	1899
Main inclusion and exclusion criteria	Inclusion criteria: • Male or female ≥ 18 to ≤ 80 years of age • Subjects not taking a statin must have fasting LDL-C of at least 150 mg/dL (4.0 mmol/L) • Subjects already on a non-intensive statin must have fasting LDL-C at screening ≥ 100 mg/dL (2.6 mmol/L) • Subjects already on a intensive statin must have fasting LDL-C at screening ≥ 80 mg/dL (2.1 mmol/L)

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Trial name: LAPLACE-2	NCT number: NCT01763866
	• Fasting triglycerides ≤ 400 mg/dL (4.5 mmol/L) Exclusion criteria: • Statin intolerance • NYHA III or IV heart failure • Uncontrolled hypertension • Uncontrolled cardiac arrhythmia • Type 1 diabetes, poorly controlled type 2 diabetes • Uncontrolled hypothyroidism or hyperthyroidism
Intervention	Evolocumab 140 mg Q2W or 420 mg QM (n=1117)
Comparators	Ezetimibe 10 mg /day (n=221) Placebo Q2W or QM (n=558)
Follow-up time	12-week treatment period and 2-week follow-up period.
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary outcomes: • Percent change in LDL-C from baseline to week 12 Secondary outcomes: • Absolute change in LDL-C from baseline to week 12 • All AEs, SAEs, withdrawal from the study due to AEs, and cardiovascular events **Other endpoints:** The following endpoints were included in the study but results are not included in this application: • Coprimary endpoint of percentage change in plasma LDL cholesterol from baseline to the mean of weeks 10 and 12 • Secondary endpoints: mean at weeks 10 and 12 for the change from baseline in LDL-C level, and the percent change from baseline in additional lipid parameters • Proportion of patients achieving LDL-C levels less than 70mg/dL
Method of analysis	Intention-to-treat analysis. Between group differences in lipid parameters were calculated using a repeated measures linear mixed effects model ,which included stratification factor(s) (study entry statin intensity and simvastatin contraindicated concomitant medication group for patients randomized to simvastatin), treatment, visit, and treatment by visit terms.
Subgroup analyses	Subgroup analyses were conducted according to various demographics and baseline characteristics [48]. The analyses are not included in this application.

Trial name: LAPLACE-TIMI57	NCT number: NCT01380730
Objective	To evaluate the effect of 12 weeks of subcutaneous evolocumab (AMG 145) administered Q2W or Q4W, compared with placebo, on percent change from baseline in LDL-C when used in addition to a statin in adults with hypercholesterolemia.
Publications – title, author, journal, year	Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study. Giugliano et al. Lancet 2012 [49]
Study type and design	Phase 2, double-blind, placebo-controlled, dose-ranging trial. The trial is now completed.
Sample size (n)	315
Main inclusion and exclusion criteria	Inclusion criteria: • Male or female ≥ 18 to ≤ 80 years of age • On an approved statin, with or without ezetimibe, with stable dose(s) for at least 4 weeks • Fasting LDL-C ≥ 85 mg/dL • Fasting triglycerides ≤ 400 mg/dL Exclusion criteria: • MI, UA, percutaneous coronary intervention, coronary artery bypass graft or stroke within 3 months prior to randomization • Type 1 diabetes; newly diagnosed or poorly controlled type 2 diabetes (HbA1c > 8.5%) • Uncontrolled hypertension • NYHA III or IV heart failure, or known left ventricular ejection fraction < 30% • Uncontrolled cardiac arrhythmia
Intervention	Evolocumab 140mg Q2W (n=78)
Comparator	Placebo Q2W (n=78)
Follow-up time	12-week trial with 12 weeks of follow-up.
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary outcomes: • Percent change in LDL-C from baseline to week 12 Secondary outcomes: • Absolute change in LDL-C from baseline to week 12 • All AEs, SAEs, withdrawal from the study for any reason, withdrawal from the study due to AEs, cardiovascular events, and all-cause mortality **Other endpoints:** The following secondary endpoints were included in the study but results are not included in this application: • Percentage changes from baseline to week 12 in concentrations of non-HDL-C and apo-B, and ratios of total cholesterol to HDL-C and apo-B to apo-A1 concentrations

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Trial name: LAPLACE-TIMI57	NCT number: NCT01380730
	• Absolute and percentage changes in the above parameters from baseline at each scheduled visit • Proportion of patients at 12 weeks achieving the target concentrations of LDL-C (<1·8 mmol/L), non-HDL-C (<2·6 mmol/L), and apo-B (<0·8 g/L)
Method of analysis	Modified intention-to-treat analysis. Analyses used an ANCOVA model with covariates for treatment group and the stratification factors. All efficacy endpoints were analysed with LOCF imputation.
Subgroup analyses	Subgroup analyses of the primary endpoint were conducted according to various demographics and baseline characteristics, statin/LLT use, and baseline lipids [49]. The analyses are not included in this application.

Trial name: GAUSS-2	NCT number: NCT01763905
Objective	To evaluate the effect of 12 weeks of subcutaneous evolocumab Q2W and QM, compared with ezetimibe, on percent change from baseline in LDL-C in hypercholesterolemic adults unable to tolerate an effective dose of a statin (HMG-CoA (5-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors).
Publications – title, author, journal, year	Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. Stroes et al. J Am Coll Cardiol 2014 [50]
Study type and design	Phase 3, double-blind, placebo- and ezetimibe-controlled trial. The trial is now completed.
Sample size (n)	307
Main inclusion and exclusion criteria	Inclusion criteria: • Male or female ≥ 18 to ≤ 80 years of age • Not on a statin or on a low dose statin with stable dose for at least 4 weeks • History of intolerance to at least 2 statins • Subject not at LDL-C goal • Lipid lowering therapy has been stable prior to enrolment for at least 4 weeks. • Fasting triglycerides ≤ 400 mg/dL Exclusion criteria: • NYHA III or IV heart failure • Uncontrolled cardiac arrhythmia • Uncontrolled hypertension • Type 1 diabetes, poorly controlled type 2 diabetes • Uncontrolled hypothyroidism or hyperthyroidism
Intervention	Evolocumab 140mg Q2W (n=103)
Comparator	Ezetimibe 10 mg/day (n=51)
Follow-up time	12-week treatment period.
Is the study used in the health economic model?	No

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Trial name: GAUSS-2	NCT number: NCT01763905
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary outcomes: • Percent change in LDL-C from baseline to week 12 Secondary outcomes: • Absolute change in LDL-C from baseline to week 12 • All AEs, SAEs, withdrawal from the study due to AEs, and all-cause mortality **Other endpoints:** The following endpoints were included in the study but results are not included in this application: • Coprimary endpoint of percentage change in plasma LDL cholesterol from baseline to the mean of weeks 10 and 12 • Secondary endpoints: Percent of patients with LDL-C <70 mg/dL • Percent change from baseline in non-HDL-C, apo-B, total cholesterol/HDL-C ratio, apo-B/apo-A-I ratio, Lp(a), triglycerides, HDL-C, and VLDL-C
Method of analysis	Intention to treat analysis. The primary and secondary endpoints were analysed using a linear mixed-effects model with repeated measures, with parameters to account for missing data. Multiplicity adjustment was based on a combination of sequential testing, the Hochberg procedure and fallback procedure to control the overall significance level for all primary and secondary endpoints.
Subgroup analyses	None

Trial name: GAUSS-4	NCT number: NCT02634580
Objective	The primary objective of the study was to evaluate the effect of 12 weeks of subcutaneous evolocumab compared with ezetimibe, on percent change from baseline in LDL-C in hypercholesterolemic adults unable to tolerate an effective dose of a statin.
Publications – title, author, journal, year	Evolocumab vs. ezetimibe in statin-intolerant hyperlipidaemic Japanese patients: Phase 3 GAUSS-4 trial. Koba et al. J Atheroscler Thromb 2020 [51]
Study type and design	Phase 3, double-blind, parallel-group trial. The trial is now completed.
Sample size (n)	61
Main inclusion and exclusion criteria	Inclusion Criteria: • Male or female ≥ 20 to ≤ 80 years of age • Japanese by self-identification • Not on a statin or on a low dose statin with stable dose for at least 4 weeks. • Subject not at LDL-C goal • History of statin intolerance to at least 2 statins • Lipid lowering therapy has been stable prior to screening for at least 4 weeks • Fasting triglycerides ≤ 400 mg/dL

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Trial name: GAUSS-4	NCT number: NCT02634580
	Exclusion Criteria: • NYHA III or IV heart failure • Uncontrolled cardiac arrhythmia • Uncontrolled hypertension • Type 1 diabetes • Poorly controlled type 2 diabetes • Uncontrolled hypothyroidism or hyperthyroidism
Intervention	Evolocumab 420mg QM + daily placebo (n=21) Evolocumab 140mg Q2W + daily placebo (n=19)
Comparators	Ezetimibe 10mg + placebo QM (n=11) Ezetimibe 10mg + placebo Q2W (n=10)
Follow-up time	12-week double-blind treatment period and 9-month open-label extension period.
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary outcomes: • Percent change in LDL-C from baseline to week 12 Secondary outcomes: • Absolute change in LDL-C from baseline to week 12 • All AEs, SAEs, withdrawal from the study for any reason, withdrawal from the study due to AEs, cardiovascular events, and all-cause mortality **Other endpoints:** The following endpoints were included in the study but results are not included in this application: • Coprimary endpoint of percentage change in plasma LDL cholesterol from baseline to the mean of weeks 10 and 12 • Secondary endpoints at weeks 10 and 12: Achievement of LDL-C < 70 mg/dL (1.8 mmol/L), and the percent change from baseline in total cholesterol, apo-B and non-HDL-C • Percent change from baseline in Lp(a), triglycerides, and HDL-C
Method of analysis	Intention to treat analysis. For the co-primary efficacy endpoints, a repeated-measure linear-effect model was used to compare the efficacies of evolocumab (Q2W and Q4W groups were pooled) and ezetimibe (pooled). The model included terms of treatment group, stratification factor of screening LDL-C level, scheduled visit, and the interaction of treatment group with scheduled visit.
Subgroup analyses	Subgroup analyses of the primary endpoint were conducted according to various demographics and baseline characteristics, statin/LLT use, and baseline lipids [51]. The analyses are not included in this application.

Abbreviations: ACS, acute coronary syndrome; AE, adverse event; ANCOVA, analysis of covariance; apo-B; apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CV, cardiovascular; HbA1c, glycosylated haemoglobin A1c; HDL, high density lipoprotein; HeFH, heterozygous familial hypercholesterolaemia; ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol; LLT, lipid-lowering therapy; Lp(a), lipoprotein(a); LOCF, last observation carried forward; LS, least-squares; MI, myocardial infarction; non-FH, non-familial hypercholesterolemia;

NYHA, New York Heart Association; PCSK9, proprotein convertase subtilisin/kexin type 9; QM, once monthly; Q2W, every two weeks; Q4W, every four weeks; SAE, serious adverse event: UA, unstable angina; VLDL-C , very low density lipoprotein-cholesterol.

Inclisiran studies	
Trial name: ORION-9	**NCT number: NCT03397121**
Objective	To evaluate the effect of inclisiran treatment on LDL-C in subjects with HeFH
Publications – title, author, journal, year	Inclisiran for the treatment of heterozygous familial hypercholesterolaemia. Raal FJ, et al. N Engl J Med 2020; 382(16):1520-1530 [52]
Study type and design	ORION-9 was a phase 3 double-blind, randomised, placebo-controlled trial conducted in 8 countries at 46 sites, including 6 sites in Denmark. In total, 482 adults with HeFH were randomly assigned in a 1:1 ratio to receive subcutaneous injections of inclisiran sodium (at a dose of 300 mg) or matching placebo on days 1, 90, 270, and 450. The trial is now completed.
Sample size (n)	482
Main inclusion and exclusion criteria	Inclusion criteria: • Male or female participants ≥18 years of age. • History of HeFH with a diagnosis of HeFH by genetic testing; and/or a documented history of untreated LDL-C of >190 mg/dL, and a family history of familial hypercholesterolaemia, elevated cholesterol or early heart disease that may indicate familial hypercholesterolaemia. • Serum LDL-C ≥2.6 mmol/L (≥100 mg/dL) at screening. • Fasting triglyceride <4.52 mmol/L (<400 mg/dL) at screening. • Participants on statins should be receiving a maximally tolerated dose. • Participants not receiving statins must have documented evidence of intolerance to all doses of at least 2 different statins. • Participants on lipid-lowering therapies (such as a statin and/or ezetimibe) should be on a stable dose for ≥30 days before screening with no planned medication or dose change during study participation. Exclusion criteria: • NYHA class IV heart failure. • Uncontrolled cardiac arrhythmia • Uncontrolled severe hypertension • Active liver disease • Females who are pregnant or nursing, or who are of childbearing potential and unwilling to use at least 2 methods of highly effective contraception (failure rate less than 1% per year) (combined oral contraceptives, barrier methods, approved contraceptive implant, long-term injectable contraception, or intrauterine device) for the entire duration of the study. Exemptions from this criterion: o Women >2 years postmenopausal (defined as 1 year or longer since last menstrual period) AND more than 55 years of age. o Postmenopausal women (as defined above) and less than 55 years of age with a negative pregnancy test within 24 hours of randomisation. o Women who are surgically sterilised at least 3 months prior to enrolment. • Males who are unwilling to use an acceptable method of birth control during the entire study period (condom with spermicide). • Treatment with other investigational products or devices within 30 days or 5 half-lives of the screening visit, whichever is longer. • Treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9.

Intervention	A total of 242 subjects received inclisiran sodium 300 mg as a subcutaneous injection (1.5 mL) on day 1, day 90 then every 6 months (days 270 and 450).
Comparator	A total of 240 subjects received matching placebo as a subcutaneous injection (1.5 mL) on day 1, day 90 then every 6 months (days 270 and 450).
Follow-up time	Of the subjects in the intention-to-treat population, 235 subjects (91.7%) in the inclisiran group and 231 (96.3%) in the placebo group completed the trial activities through day 540.
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary outcomes: • Percent change in LDL-C from baseline to day 510. Secondary outcomes: • Absolute change in LDL-C from baseline to day 510 • All AEs, SAEs, withdrawal from the study for any reason, withdrawal from the study due to AEs, cardiovascular events, and all-cause mortality **Other endpoints:** The following endpoints were included in the study but results are not included in this application: • Time-adjusted percent change in LDL-C from baseline between day 90 and day 540 (second primary outcome) • Time-adjusted absolute change in LDL-C from baseline between day 90 and day 540 (secondary endpoint) • Percent change in PCSK9, total cholesterol, apo-B and non–HDL cholesterol from baseline to day 510 • Prespecified exploratory outcomes: the proportion of subjects who met the lipid targets for their level of cardiovascular risk and the treatment response according to the underlying genotype of familial hypercholesterolaemia
Method of analysis	Intention-to-treat analysis. The percent change in LDL-C from baseline to day 510 was analysed using an ANCOVA model applied to each of the 100 multiply imputed datasets. The model included a fixed effect for treatment and baseline LDL-C as a covariate. Analysis of the secondary outcome absolute change in LDL-C from baseline to day 510 was performed only after the analyses of the two primary end points were completed and the null hypotheses were rejected.
Subgroup analyses	A prespecified subgroup analysis was made of the percent change from baseline in the LDL-C level according to genotype (the presence or absence of a monogenic familial hypercholesterolaemia variant) and according to the presence or absence of variants in *LDLR*, *APOB*, and *PCSK9*. Mean differences in treatment effects between these subgroups were determined.

Trial name: ORION-10	**NCT number: NCT03399370**
Objective	To evaluate the effect of 300 mg of inclisiran in subjects with ASCVD and elevated LDL-C

Trial name: ORION-10	NCT number: NCT03399370
Publications – title, author, journal, year	Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. Ray KK, et al. N Engl J Med 2020; 382(16):1507-1519 [9]
Study type and design	ORION-10 was a phase 3 double-blind, randomised, placebo-controlled trial conducted at several sites in the USA. In total, 1561 adults with ASCVD were randomly assigned in a 1:1 ratio to receive subcutaneous injections of inclisiran sodium (at a dose of 300 mg) or matching placebo on days 1, 90, 270, and 450. The trial is now completed.
Sample size (n)	1,561
Main inclusion and exclusion criteria	Inclusion criteria: • Male or female participants ≥18 years of age. • History of ASCVD (coronary heart disease, cardiovascular disease, or peripheral arterial disease. • Serum LDL-C ≥1.8 mmol/L (≥70 mg/dL) at screening. • Fasting triglyceride <4.52 mmol/L (<400 mg/dL) at screening. • Participants on statins should be receiving a maximally tolerated dose. • Participants not receiving statins must have documented evidence of intolerance to all doses of at least 2 different statins. • Participants on lipid-lowering therapies (such as a statin and/or ezetimibe) should be on a stable dose for ≥30 days before screening with no planned medication or dose change during study participation. Exclusion criteria: • NYHA class IV heart failure. • Uncontrolled cardiac arrhythmia • Uncontrolled severe hypertension • Active liver disease • Females who are pregnant or nursing, or who are of childbearing potential and unwilling to use at least 2 methods of highly effective contraception (failure rate less than 1% per year) (combined oral contraceptives, barrier methods, approved contraceptive implant, long-term injectable contraception, or intrauterine device) for the entire duration of the study. Exemptions from this criterion: o Women >2 years postmenopausal (defined as 1 year or longer since last menstrual period) and more than 55 years of age. o Postmenopausal women (as defined above) and less than 55 years of age with a negative pregnancy test within 24 hours of randomisation. o Women who are surgically sterilised at least 3 months prior to enrolment. • Males who are unwilling to use an acceptable method of birth control during the entire study period (condom with spermicide). • Treatment with other investigational products or devices within 30 days or 5 half-lives of the screening visit, whichever is longer. • Treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9.
Intervention	A total of 781 subjects received inclisiran sodium 300 mg as a subcutaneous injection (1.5 mL) on day 1, day 90 then every 6 months (days 270 and 450).
Comparators	A total of 780 subjects received matching placebo as a subcutaneous injection (1.5 mL) on day 1, day 90 then every 6 months (days 270 and 450).

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Trial name: ORION-10	NCT number: NCT03399370
Follow-up time	Of the subjects in the intention-to-treat population, 89% in the inclisiran group and 87% in the placebo group completed the trial activities through day 540.
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** <u>Primary outcomes:</u> • Percent change in LDL-C from baseline to day 510. <u>Secondary outcomes</u>: • Absolute change in LDL-C from baseline to day 510 • All AEs, SAEs, withdrawal from the study for any reason, withdrawal from the study due to AEs, cardiovascular events, and all-cause mortality **Other endpoints:** The following endpoints were included in the study but results are not included in this application: • Time-adjusted percent change in LDL-C from baseline between day 90 and day 540 (second primary outcome) • Time-adjusted absolute change in LDL-C from baseline between day 90 and day 540 (secondary endpoint) • Percent change in PCSK9, total cholesterol, apo-B and non–HDL cholesterol from baseline to day 510 • Prespecified exploratory outcomes: the incidence of specific cardiovascular MedDRA terms, including those classified within cardiac death, and any signs or symptoms of cardiac arrest, nonfatal myocardial infarction, or stroke
Method of analysis	Intention-to-treat analysis. The percent change in LDL-C from baseline to day 510 was analysed using an ANCOVA model applied to each of the 100 multiply imputed datasets. The model included a fixed effect for treatment and baseline LDL-C as a covariate. Analysis of the secondary outcome absolute change in LDL-C from baseline to day 510 was performed only after the analyses of the two primary end points were completed and the null hypotheses were rejected.
Subgroup analyses	A prespecified subgroup analysis was made of the percent change from baseline in the LDL-C level according to specific baseline characteristics: sex, age group, body mass index category, race, statin treatment at baseline, intensity of statin treatment, presence of metabolic disease (diabetes, metabolic syndrome or neither), or renal function. Mean differences in treatment effects between these subgroups were determined.

Trial name: ORION-11	NCT number: NCT03400800
Objective	To evaluate the effect of 300 mg of inclisiran in subjects with ASCVD or an ASCVD risk equivalent and elevated LDL-C
Publications – title, author, journal, year	Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. Ray KK, et al. N Engl J Med 2020; 382(16):1507-1519 [9]

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Trial name: ORION-11	NCT number: NCT03400800
Study type and design	ORION-11 was a phase 3 double-blind, randomised, placebo-controlled trial conducted at several sites in Europe and South Africa. In total, 1617 adults with ASCVD or an ASCVD risk equivalent were randomly assigned in a 1:1 ratio to receive subcutaneous injections of inclisiran sodium (at a dose of 300 mg) or matching placebo on days 1, 90, 270, and 450. The trial is now completed.
Sample size (n)	1,617

Main inclusion and exclusion criteria	Inclusion criteria:
	• Male or female participants ≥18 years of age.
	• History of ASCVD (coronary heart disease, cardiovascular disease, or peripheral arterial disease.
	• Serum LDL-C ≥1.8 mmol/L (≥70 mg/dL) at screening.
	• Fasting triglyceride <4.52 mmol/L (<400 mg/dL) at screening.
	• Calculated glomerular filtration rate >30 mL/min by estimated glomerular filtration rate (eGFR) using standardised clinical methodology.
	• Participants on statins should be receiving a maximally tolerated dose.
	• Participants not receiving statins must have documented evidence of intolerance to all doses of at least 2 different statins.
	• Participants on lipid-lowering therapies (such as a statin and/or ezetimibe) should be on a stable dose for ≥30 days before screening with no planned medication or dose change during study participation.
	• Subjects were willing and able to give informed consent before initiation of any study-related procedures and willing to comply with all required study procedures.
	
	Exclusion criteria:
	• NYHA class IV heart failure.
	• Uncontrolled cardiac arrhythmia
	• Uncontrolled severe hypertension
	• Active liver disease
	• Females who are pregnant or nursing, or who are of childbearing potential and unwilling to use at least 2 methods of highly effective contraception (failure rate less than 1% per year) (combined oral contraceptives, barrier methods, approved contraceptive implant, long-term injectable contraception, or intrauterine device) for the entire duration of the study. Exemptions from this criterion:
	  ○ Women >2 years postmenopausal (defined as 1 year or longer since last menstrual period) and more than 55 years of age.
	  ○ Postmenopausal women (as defined above) and less than 55 years of age with a negative pregnancy test within 24 hours of randomisation.
	  ○ Women who are surgically sterilised at least 3 months prior to enrolment.
	• Males who are unwilling to use an acceptable method of birth control during the entire study period (condom with spermicide).
	• Treatment with other investigational products or devices within 30 days or 5 half-lives of the screening visit, whichever is longer.
	• Treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9.

Intervention	A total of 810 subjects received inclisiran sodium 300 mg as a subcutaneous injection (1.5 mL) on day 1, day 90 then every 6 months (days 270 and 450).
Comparators	A total of 807 subjects received matching placebo as a subcutaneous injection (1.5 mL) on day 1, day 90 then every 6 months (days 270 and 450).

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Trial name: ORION-11	NCT number: NCT03400800
Follow-up time	Of the subjects in the intention-to-treat population, 95% in both the inclisiran group and the placebo group completed the trial activities through day 540.
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary outcomes: • Percent change in LDL-C from baseline to day 510. Secondary outcomes: • Absolute change in LDL-C from baseline to day 510 • All AEs, SAEs, withdrawal from the study for any reason, withdrawal from the study due to AEs, cardiovascular events, and all-cause mortality **Other endpoints:** The following endpoints were included in the study but results are not included in this application: • Time-adjusted percent change in LDL-C from baseline between day 90 and day 540 (second primary outcome) • Time-adjusted absolute change in LDL-C from baseline between day 90 and day 540 (secondary endpoint) • Percent change in PCSK9, total cholesterol, apo-B and non–HDL cholesterol from baseline to day 510 • Prespecified exploratory outcomes: the incidence of specific cardiovascular MedDRA terms, including those classified within cardiac death, and any signs or symptoms of cardiac arrest, nonfatal myocardial infarction, or stroke
Method of analysis	Intention-to-treat analysis. The percent change in LDL-C from baseline to day 510 was analysed using an ANCOVA model applied to each of the 100 multiply imputed datasets. The model included a fixed effect for treatment and baseline LDL-C as a covariate. Analysis of the secondary outcome absolute change in LDL-C from baseline to day 510 was performed only after the analyses of the two primary end points were completed and the null hypotheses were rejected.
Subgroup analyses	A prespecified subgroup analysis was made of the percent change from baseline in the LDL-C level according to specific baseline characteristics: sex, age group, body mass index category, race, statin treatment at baseline, intensity of statin treatment, presence of metabolic disease (diabetes, metabolic syndrome or neither), or renal function. Mean differences in treatment effects between these subgroups were determined.

Abbreviations: ACS, acute coronary syndrome; AE, adverse event; ANCOVA, analysis of covariance; apo-B; apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CV, cardiovascular; HbA1c, glycosylated haemoglobin A1c; HDL, high density lipoprotein; HeFH, heterozygous familial hypercholesterolaemia; ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol; LLT, lipid-lowering therapy; Lp(a), lipoprotein(a); LOCF, last observation carried forward; LS, least-squares; MI, myocardial infarction; non-FH, non-familial hypercholesterolemia; NYHA, New York Heart Association; PCSK9, proprotein convertase subtilisin/kexin type 9; QM, once monthly; Q2W, every two weeks; Q4W, every four weeks; SAE, serious adverse event: UA, unstable angina; VLDL-C , very low density lipoprotein-cholesterol.

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Baseline characterisics for the HeFH population

Table 40 Baseline Characteristics by Study for Patient with HeFH on MTD statin

Reference and NCT number	Treatment group, N	Sex N (%) male	Age (y) Mean (SD)	BMI (kg/m²) Mean (SD)	HeFH N (%)	ASCVD N (%)	CHD N (%)	PAD N (%)	ACS N (%)	ASCVD risk equivalent N (%)	Background statins N (%)	Background statin high dose N (%)	Background ezetimibe N (%)	Statin intolerant N (%)	LDL-C mmol/L Mean (SD)
Alirocumab studies															
NCT01266876 Stein, 2012[34]	ALI 150mg Q2W N= 16	13 (81)	56.3 (10.2)	30.7 (5.1)	16 (100)	4 (25)	NR	NR	NR	NR	16 (100)	NR	11 (69)	0 (0)	3.8 (0.8)
	Placebo N= 15	9 (60)	51.9 (9.6)	29.4 (4.9)	15 (100)	7 (47)	NR	NR	NR	NR	15 (100)	NR	11 (73)	0 (0)	3.9 (0.9)
Odyssey Long Term[7] NCT01507831 Robinson, 2015[37]	ALI 150mg Q2W N= 1553	983 (63.3)	60.4 (10.4)	30.2 (5.7)	276 (17.8)	NR	1055 (67.9)	NR	NR	639 (41.1)	1552 (>99.9)	727 (46.8)	216 (13.9)	NA	3.2 (1.1)[1,a]
	Placebo N= 788	474 (60.2)	60.6 (10.4)	30.5 (5.5)	139 (17.6)	NR	552 (70.1)	NR	NR	323 (41.0)[2]	787 (99.9)	368 (46.7)	118 (15)	NA	3.2 (1.1)[1,a]
Odyssey High FH NCT01617655 Ginsberg, 2016[35]	ALI 150mg Q2W N= 72	35 (48.6)	49.8 (14.2)	28.8 (5.2)	72 (100)	NR	31 (43.1)	NR	NR	13 (18.1)	72 (100)	53 (73.6)	14 (19.4)	NA	5.1 (1.5)[1,a]
	Placebo N= 35	22 (62.9)	52.1 (11.2)	28.9 (4.2)	35 (100)	NR	22 (62.9)	NR	NR	5 (14.3)[2]	35 (100)	25 (71.4)	12 (34.3)	NA	5.2 (1.1)[1,a]
Odyssey FH I NCT01623115 Kastelein, 2015[36]	ALI 75mg Q2W N= 323	180 (55.7)	52.1 (12.9)	29.0 (4.6)	323 (100)	NR	147 (45.5)	NR	NR	54 (16.7)[2]	323 (100)	267 (82.7)	181 (56.0)	NA	3.7 (0.1)[3,a]
	Placebo N= 163	94 (57.7)	51.7 (12.3)	30.0 (5.4)	163 (100)	NR	78 (47.9)	NR	NR	25 (15.3)[2]	163 (100)	139 (85.3)	97 (59.5)	NA	3.7 (0.1)[3,a]

Reference and NCT number	Treatment group, N	Sex N (%) male	Age (y) Mean (SD)	BMI (kg/m²) Mean (SD)	HeFH N (%)	ASCVD N (%)	CHD N (%)	PAD N (%)	ACS N (%)	ASCVD risk equivalent N (%)	Background statins N (%)	Background statin high dose N (%)	Background ezetimibe N (%)	Statin intolerant N (%)	LDL-C mmol/L Mean (SD)
Odyssey FH II	ALI 75mg Q2W N=167	86 (51.5)	53.2 (12.9)	28.6 (4.6)	167 (100)	NR	58 (34.7)	NR	NR	15 (9.0)[2]	167 (100)	145 (86.8)	112 (67.1)	NA	3.5 (0.1)[3,a]
NCT01709500 Kastelein, 2015[36]	Placebo N=82	45 (54.9)	53.2 (12.5)	27.7 (4.7)	82 (100)	NR	31 (37.8)	NR	NR	4 (4.9)[2]	82 (100)	75 (91.5)	53 (64.6)	NA	3.5 (0.1)[3,a]
Evolocumab studies															
RUTHERFORD-2	EVO 140mg Q2W N= 110	66 (60)	52.6 (12.3)	NR	111 (100)	38 (35)[4]	NR	NR	NR	NR	111 (100)	NR	68 (61.3)	0 (0)[5]	4.2 (1.3)[a]
NCT01763918 Raal, 2015[37]	Placebo Q2W N= 54	29 (54)	51.1 (14.2)	NR	55 (100)	16 (30)[4]	NR	NR	NR	NR	55 (100)	NR	33 (60.0)	0 (0)[5]	3.9 (0.9)[a]
Inclisiran studies															
ORION-9	Inclisiran N=242	112 (46.3)	54.4 (12.48)	29.0 (5.68)	242 (100)	59 (24.4)	53 (21.9)	3 (1.23)	NR	183 (75.6)	219 (90.5)	185 (76.4)	135 (55.8)	22 (9.1)	3.9 (1.3)[6,b]
NCT03397121 Raal, 2020[52]	Placebo N=240	115 (47.9)	55.0 (11.81)	28.8 (5.09)	240 (100)	73 (30.4)	70 (29.1)	1 (0.41)	NR	167 (69.6)	217 (90.4)	171 (71.2)	120 (50.0)	22 (9.2)	4.0 (1.5)[6,b]

Unless otherwise stated, values are mean (SD), or % of ITT population.

[1]Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.02586. Conversion factor was not reported in the publication.
[2]Reported as coronary heart disease risk equivalent.
[3]LS mean (SE).
[4]Reported as coronary artery disease.
[5]Assumption based on trial design/ inclusion criteria, but not reported explicitly.
[6]Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.02586, as requested in the publication.
[7]Baseline characteristics are reported for the full population.

LDL-C analysis method:
a Calculated
b Reflexive

ALI, alirocumab; ACS, acute coronary syndrome; ASCVD: atherosclerotic cardiovascular disease; ATORV, atorvastatin; BMI, body mass index; CHD, coronary heart disease; EVO, evolocumab; EZE, ezetimibe; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low density lipoprotein cholesterol; LS mean, least squares mean; MI, myocardial infarction; non-HS, non-haemorrhagic stroke; NR, not reported; PAD, peripheral artery disease; Q2W, every two weeks; Q4W, every four weeks; QM, every month, SD, standard deviation; SE, standard error.

Comparability of patients across studies for patients with HeFH

Five studies with alirocumab, one with evolocumab and one with inclisiran were included in the analysis. The mean age ranged from 49-60 years, proportion with ASCVD or CHD ranged from 21-70%, proportion of patients on ezetimibe ranged from 15-73% and mean baseline LDL-C ranged from 3.3 to 4.4 mmol/L, except for ODYSSEY High FH, where the mean baseline LDL-C was 5.1 to 5.2 mmol/L. The impact of the differences in background ezetimibe and statin treatment, as well as cardiac risk and severity (including baseline LDL-C) is discussed in Section 7.1.1.1. ODYSSEY HIGH [35] was identified as an outlier among trials of patients with HeFH, given the inclusion criteria (LDL-C ≥4.14 mmol/L) and observed mean baseline LDL-C (5.1-5.2 mmol/L) which were higher than in comparator trials. ODYSSEY HIGH FH is excluded in a sensitivity analysis in the NMA report, see Appendix L – NMA report.

Comparability of the study populations with Danish patients with HeFH eligible for treatment

The Danish patient population for HeFH patients has been described by the Danish Medicines Council [32]:

- The average age for primary HeFH is 35 year and secondary prevention is 50 year.
- 60% of the HeFH population is men.
- It is expected that 50% will have a LDL-C ≥ 3,5 mmol/L.
- 20% of the 2.500 diagnosed FH patients are primary prevention and 80% secondary prevention (ASCVD population).
- It is expected that all patients will be treated with high intensive statin and ezetimibe.

In the studies included in this application, the average age ranges from 49 to 60 years, and LDL-C at baseline ranges from 3.2 to 5.2 mmol/L, the proportion of patients with ASCVD or CHD ranged from 21 to 70% (slightly fewer than in the Danish population). 15 to 73% were treated with ezetimibe which is considerably fewer than what is expected in the Danish population, however, subgroup data for percent change in LDL-C presented by two of the included trials did not suggest background/baseline ezetimibe use to be a treatment-effect modifier (see Table 8). Even if it seems that more patients in the trials are in primary prophylaxis (i.e. more than 20% without ASCVD or CHD), the results are considered transferable to Danish clinical practice.

Baseline characterisics for the ASCVD and risk equivalent populations

Table 41 Baseline Characteristics by Study for Patient with ASCVD and risk equivalent on MTD statin

Reference and NCT number	Treatment group, N	Sex N (%) male	Age (y) Mean (SD)	BMI (kg/m²) Mean (SD)	HeFH N (%)	ASCVD N (%)	CHD N (%)	PAD N (%)	ACS N (%)	ASCVD risk equivalent N (%)	Background statins N (%)	Background statin high dose N (%)	Background ezetimibe N (%)	Statin intolerant N (%)	LDL-C mmol/L Mean (SD)
Alirocumab studies															
Odyssey Outcomes	ALI 75mg Q2W N= 9462	7072 (74.7)	58.5 (9.3)	28.5 (4.9)	NR	NR	NR	373 (3.9)	9462 (100)	NR	NR	8380 (88.6)	269 (2.8)	NA	2.4 (0.8)[1,a]
NCT01663402 Schwartz, 2018[18]	Placebo N= 9462	7090 (74.9)	58.6 (9.4)	28.5 (4.8)	NR	NR	NR	386 (4.1)	9462 (100)	NR	NR	8431 (89.1)	285 (3.0)	NA	2.4 (0.8)[1,a]
Odyssey Long Term	ALI 150mg Q2W N= 1553	983 (63.3)	60.4 (10.4)	30.2 (5.7)	276 (17.8)	NR	1055 (67.9)	NR	NR	639 (41.1)	1552 (>99.9)	727 (46.8)	216 (13.9)	NA	3.2 (1.1)[3,b]
NCT01507831 Robinson, 2015[37]	Placebo N= 788	474 (60.2)	60.6 (10.4)	30.5 (5.5)	139 (17.6)	NR	552 (70.1)	NR	NR	323 (41.0)[2]	787 (99.9)	368 (46.7)	118 (15)	NA	3.2 (1.1)[3,b]
Odyssey Choice I	ALI 75mg Q2W N= 78	51 (65.4)	60.7 (9.1)	30.1 (4.9)	6 (7.7)	NR	NR	NR	NR	NR	78 (100)	NR	9 (11.5)	NA	3.0 (0.9)[b]
NCT01926782 Roth, 2016[38]	Placebo N= 157	101 (64.3)	61.6 (9.7)	30.9 (6.2)	12 (7.6)	NR	NR	NR	NR	NR	157 (100)	NR	22 (14.0)	NA	2.9 (1.0)[b]
NCT01288443	ALI 150mg Q2W N= 31	10 (32.3)	59.9 (11.1)	28.2 (4.3)	NR	2 (6.5)[4]	NR	3 (9.7)	NR	NR	31 (100)	NR	NR	NR	3.2 (0.7)[3,b]
McKenney, 2012[39]	Placebo N= 31	16 (51.6)	53.3 (8.5)	27.9 (4.8)	NR	2 (6.5)[4]	NR	0 (0)	NR	NR	31 (100)	NR	NR	NR	3.4 (0.7)[3,b]
Odyssey Combo I	ALI 75mg Q2W N= 209	131 (62.7)	63.0 (9.5)	32.62 (6.30)	NR	NR	164 (78.5)	NR	NR	85 (40.7)[2]	208 (99.5)	129 (61.7)	15 (7.2)	NA	2.6 (0.8)[3,b]

Reference and NCT number	Treatment group, N	Sex N (%) male	Age (y) Mean (SD)	BMI (kg/m²) Mean (SD)	HeFH N (%)	ASCVD N (%)	CHD N (%)	PAD N (%)	ACS N (%)	ASCVD risk equivalent N (%)	Background statins N (%)	Background statin high dose N (%)	Background ezetimibe N (%)	Statin intolerant N (%)	LDL-C mmol/L Mean (SD)
NCT01644175 Kereiakes, 2015[40]	Placebo N= 107	77 (72.0)	63.0 (8.8)	32.03 (7.07)	NR	NR	83 (77.6)	NR	NR	51 (47.7)	107 (100.0)	69 (64.5)	11 (10.3)	NA	2.7 (0.9)[3,b]
Odyssey KT	ALI 75mg Q2W N= 97	83 (85.6)	61.2 (10.4)	26.3 (4.0)	NR	NR	96 (99.0)	NR	NR	21 (21.6)	97 (100)	71 (73.2)	14 (14.4)	NA	2.5 (0.7)[3,b]
NCT02289963 Koh, 2018[41]	Placebo N= 102	81 (79.4)	60.1 (9.1)	26.6 (3.8)	NR	NR	95 (93.1)	NR	NR	26 (25.5)	102 (100)	73 (71.6)	12 (11.8)	NA	2.6 (0.7)[3,b]
Odyssey Combo II	ALI 75mg Q2W N= 479	360 (75.2)	61.7 (9.4)	30.0 (5.4)	NR	461 (96.2)	437 (91.2)	24 (5.0)	NR	151 (31.5)[2]	478 (99.8)	320[4] (66 8)	NR	NA	2.8 (0.9)[b]
NCT01644188 Cannon, 2015 [42]	Placebo N= 241	170 (70.5)	61.3 (9.2)	30.3 (5.1)	NR	224 (92.9)	212 (88.0)	11 (4.6)	NR	72 (29.9)	241 (100)	160 (66.4)[4]	NR	NA	2.7 (0.9)[b]
Odyssey East	ALI 75mg Q2W N= 407	315 (77.4)	58.8 (10.7)	25.6 (3.7)	0 (0)	NR	398 (97.8)	NR	NR	51 (12.5)	NR	277 (68.1)	NR	NR	2.9 (1.3)[b]
NCT02715726 Han, 2020[43]	EZE N= 208	146 (70.2)	58.3 (11.2)	25.2 (3.0)	0 (0)	NR	202 (97.1)	NR	NR	25 (12.0)	NR	142 (68.3)	NR	NR	2.9 (1.3)[b]
Evolocumab studies															
Fourier NCT01764633 Sabatine, 2017[19]	EVO 420mg or 140mg Q2W Q4W N= 13784	10,397 (75.4)	62.5 (9.1)	NR	NR	13784 (100)[5]	NR	1858 (13.5)	MI: 11145 (80.9) non-HS: 2686 (19.5)	NR	13,784 (100)	9,585 (69.5)	726 (5.3)	NR	2.4 (2.1-2.8)[1,6,c]
	Placebo N= 13780	10,398 (75.5)	62.5 (8.9)	NR	NR	13780 (100)[5]	NR	1784 (12.9)	MI: 11206 (81.3) non-HS: 2651 (19.2)	NR	13,780 (100)	9518 (69.1)	714 (5.2)	NR	2.4 (2.1-2.8)[1,6,c]
LAPLACE-2 NCT01763866 Robinson, 2014[48]	EVO 140mg Q2W or 420mg QM[7] N= 1117	625 (56.0)	59.6 (9.9)	NR	NR	226 (23.8)[4]	NR	124 (11.1)[8]	NR	NR	NR	NR	NR	NR	2.8 (1.1)[9,a]

Reference and NCT number	Treatment group, N	Sex N (%) male	Age (y) Mean (SD)	BMI (kg/m²) Mean (SD)	HeFH N (%)	ASCVD N (%)	CHD N (%)	PAD N (%)	ACS N (%)	ASCVD risk equivalent N (%)	Background statins N (%)	Background statin high dose N (%)	Background ezetimibe N (%)	Statin intolerant N (%)	LDL-C mmol/L Mean (SD)
	EZE[7] N= 221	112 (50.7)	60.8 (9.3)	NR	NR	38 (17.2)[4]	NR	19 (8.6)[8]	NR	NR	NR	NR	NR	NR	2.8 (1.0)[9,a]
	Placebo[7] N= 558	291 (52.2)	59.9 (10.2)	NR	NR	123 (22.0)[4]	NR	55 (9.9)[8]	NR	NR	NR	NR	NR	NR	2.8 (1.0)[9,a]
LAPLACE-TIMI57 NCT01380730 Giugliano, 2012[49]	EVO 140mg Q2W N= 78	33 (42)	63.5 (56.0-69.0)[6]	29.4 (26.8-34.3)[6]	NR	31 (40)	NR	9 (12)	19 (24)[10]	NR	78 (100)	25 (32)	7 (9)	NR	3.1 (0.6)[d]
	Placebo Q2W N= 78	36 (46)	61.0 (55.0-67.0)[6]	30.1 (26.7-33.9)[6]	NR	22 (28)	NR	8 (10)	11 (14)[10]	NR	78 (100)	19 (24)	7 (9)	NR	3.2 (0.7)[d]
Inclisiran studies															
ORION-10 NCT03399370 Ray, 2020[9]	Inclisiran N=781	535 (68.5)	66.4 (8.9)	31.5 (6.25)	8 (1.0)	781 (100)	703 (90.0)	90 (11.5)	6 (0.8)	0 (0)	701 (89.8)	525 (67.2)	80 (10.2)	171 (21.9)	2.7 (1.0)[1,a]
	Placebo N=780	548 (70.3)	65.7 (8.9)	31.8 (6.44)	12 (1.5)	780 (100)	719 (92.2)	84 (10.8)	5 (0.6)	0 (0)	692 (88.7)	537 (68.8)	74 (9.5)	173 (22.2)	2.7 (1.0)[1,a]
ORION -11 NCT03400800 Ray, 2020[9]	Inclisiran N=810	579 (71.5)	64.8 (8.3)	29.7 (4.79)	14 (1.7)	712 (87.9)	614 (75.8)	75 (9.3)	1 (0.1)	98 (12.1)	766 (94.6)	640 (79.0)	52 (6.3)	95 (11.7)	2.8 (1.1)[1,a]
	Placebo N=807	581 (72.0)	64.8 (8.7)	30.2 (5.15)	14 (1.7)	702 (87.0)	623 (77.2)	72 (8.9)	4 (0.5)	105 (13.0)	766 (94.9)	631 (78.2)	62 (7.7)	90 (11.2)	2.7 (0.9)[1,a]

Unless otherwise stated, values are mean (SD), or % of ITT population.

[1]Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.02586, as requested in the publication.

[2]Reported as coronary heart disease risk equivalent.

[3]Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.02586. Conversion factor was not reported in the publication.

[4]Reported as coronary artery disease.

[5]Assumption based on trial design/ inclusion criteria, but not reported explicitly.

[6]Values represent median (IQR).

[7]Combined treatment arms reported here.

[8]Reported as peripheral artery disease and cerebrovascular disease.

[9]Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.0259, as requested in the publication.

[10]Reported as myocardial infarction.

LDL-C analysis method:
a Reflexive

b Calculated
c Not reported
d Measured

ALI, alirocumab; ACS, acute coronary syndrome; ASCVD: atherosclerotic cardiovascular disease; ATORV, atorvastatin; BMI, body mass index; CHD, coronary heart disease; EVO, evolocumab; EZE, ezetimibe; LDL-C, low density lipoprotein cholesterol; LS mean, least squares mean; MI, myocardial infarction; non-HS, non-haemorrhagic stroke; NR, not reported; PAD, peripheral artery disease; Q2W, every two weeks; Q4W, every four weeks; QM, every month, SD, standard deviation; SE, standard error.

Table 42 Baseline Characteristics by Study for Patient with ASCVD and risk equivalent intolerant to statin

Reference and NCT number	Treatment group, N	Sex N (%) male	Age (y) Mean (SD)	BMI (kg/m²) Mean (SD)	HeFH N (%)	ASCVD N (%)	CHD N (%)	PAD N (%)	ACS N (%)	ASCVD risk equivalent N (%)	Background statins N (%)	Background statin high dose N (%)	Background ezetimibe N (%)	Statin intolerant N (%)	LDL-C mmol/L Mean (SD)
Alirocumab studies															
Odyssey Choice II NCT02023879 Stroes, 2016[44]	ALI 75mg Q2W N= 116	69 (59.5)	62.5 (9.9)	29.4 (5.6)	15 (12.9)	NR	57 (49.1)	NR	NR	NR	0 (0)	NR	70 (60.3)	NR[1]	4.0 (1.2)[2,a]
	Placebo N= 58	31 (53.4)	63.1 (10.7)	28.5 (4.6)	5 (8.6)	NR	27 (46.6)	NR	NR	NR	0 (0)	NR	35 (60.3)	NR	4.1 (1.2)[2,a]
Odyssey Nippon NCT02584504 Teramoto, 2019[45]	ALI 150mg Q2W N= 53	33 (62.3)	63.6 (10.4)	26.4 (4.7)	13 (24.5)	NR	NR	0 (0)	6 (11.3)	NR	18 (34.0)	0 (0)	14 (26.4)	NR	3.9 (0.8)[2,a]
	Placebo N= 56	37 (66.1)	64.6 (10)	25.6 (4.0)	14 (25.0)	NR	NR	1 (1.8)	6 (10.7)	NR	19 (33.9)	0 (0)	11 (19.6)	NR	3.9 (0.8)[2,a]
Odyssey Alternative NCT01709513 Moriarty, 2015[46]	ALI 75mg Q2W N= 126	70 (55.6)	64.1 (9.0)	29.6 (6.6)	NR	NR	64 (50.8)	1 (0.8)	NR	NR	NR	NR	NR	126 (100)	4.9 (1.9)[3,a]
	EZE N= 125	67 (53.6)	62.8 (10.1)	28.4 (4.9)	NR	NR	54 (43.2)	2 (1.6)	NR	NR	NR	NR	NR	124 (100)	5.0 (1.8)[3,a]
	ATORV N= 63	35 (55.6)	63.4 (8.9)	29.7 (5.4)	NR	NR	28 (44.4)	3 (4.8)	NR	NR	NR	NR	NR	63 (100)	4.8 (1.5)[3,a]

Reference and NCT number	Treatment group, N	Sex N (%) male	Age (y) Mean (SD)	BMI (kg/m²) Mean (SD)	HeFH N (%)	ASCVD N (%)	CHD N (%)	PAD N (%)	ACS N (%)	ASCVD risk equivalent N (%)	Background statins N (%)	Background statin high dose N (%)	Background ezetimibe N (%)	Statin intolerant N (%)	LDL-C mmol/L Mean (SD)
Evolocumab studies															
GAUSS-2	EVO 140mg Q2W N= 103	57 (55)	61 (10)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	103 (100)	5.0 (1.5)[2,b]
NCT01763905 Stroes, 2014[50]	EZE N= 51	24 (47)	62 (10)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	51 (100)	5.0 (1.7)[2,b]
GAUSS-4	EVO 140mg Q2W or 420mg Q4W[1] N= 40	19 (47.5)	65.8 (9.8)	NR	NR	NR	NR	10 (25)[4]	NR	NR	8 (20.0)	NR	NR	40 (100)	5.0 (1.4)[5,c]
NCT02634580 Koba, 2020[51]	EZE[1] N= 21	11 (52.4)	61.8 (11.9)	NR	NR	NR	NR	1 (4.8)[4]	NR	NR	6 (28.6)	NR	NR	21 (100)	4.7 (1.5)[5,c]
Inclisiran studies															
ORION -10[6]	Inclisiran N=781	535 (68.5)	66.4 (8.9)	31.5 (6.25)	8 (1.0)	781 (100)	703 (90.0)	90 (11.5)	6 (0.8)	0 (0)	701 (89.8)	525 (67.2)	80 (10.2)	171 (21.9)	2.7 (1.0)[3,c]
NCT03399370 Ray, 2020[9]	Placebo N=780	548 (70.3)	65.7 (8.9)	31.8 (6.44)	12 (1.5)	780 (100)	719 (92.2)	84 (10.8)	5 (0.6)	0 (0)	692 (88.7)	537 (68.8)	74 (9.5)	173 (22.2)	2.7 (1.0)[3,c]
ORION -11[6]	Inclisiran N=810	579 (71.5)	64.8 (8.3)	29.7 (4.79)	14 (1.7)	712 (87.9)	614 (75.8)	75 (9.3)	1 (0.1)	98 (12.1)	766 (94.6)	640 (79.0)	52 (6.3)	95 (11.7)	2.8 (1.1)[3,c]
NCT03400800 Ray, 2020[9]	Placebo N=807	581 (72.0)	64.8 (8.7)	30.2 (5.15)	14 (1.7)	702 (87.0)	623 (77.2)	72 (8.9)	4 (0.5)	105 (13.0)	766 (94.9)	631 (78.2)	62 (7.7)	90 (11.2)	2.7 (0.9)[3,c]

Unless otherwise stated, values are mean (SD), or % of ITT population.

[1]Combined treatment arms reported here.

[2]Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.02586. Conversion factor was not reported in the publication.

[3]Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.02586, as requested in the publication.

[4]Reported as cardiovascular disease or peripheral artery disease.

[5]Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.0259, as requested in the publication.

[6]Baseline characteristics are reported for the full population.

LDL-C analysis method:
a Calculated
b Not reported

c Reflexive

ALI, alirocumab; ACS, acute coronary syndrome; ASCVD: atherosclerotic cardiovascular disease; ATORV, atorvastatin; BMI, body mass index; CHD, coronary heart disease; EVO, evolocumab; EZE, ezetimibe; LDL-C, low density lipoprotein cholesterol; LS mean, least squares mean; MI, myocardial infarction; non-HS, non-haemorrhagic stroke; NR, not reported; PAD, peripheral artery disease; Q2W, every two weeks; Q4W, every four weeks; QM, every month, SD, standard deviation; SE, standard error.

Comparability of patients across studies for patients with ASCVD and risk equivalent

For patients with ASCVD and risk equivalents on MTD statin eight studies with alirocumab, three with evolocumab and two with inclisiran were included in the analysis. For patients with ASCVD and risk equivalent intolerant to statin three studies with alirocumab, two with evolocumab and two with inclisiran were included in the analysis. The mean age ranged from 53 to 66 years, proportion with ASCVD ranged from 23 to 100% (where reported), for patients on MTD statin 46 to 89% were on high intensive statin (where reported), proportion of patients on ezetimibe ranged from 2 to 15% for patients on MTD and from 19 to 60% for patients intolerant to statin (where reported). Mean baseline LDL-C ranged from 3.9 to 4.9 mmol/L for patients on MTD statin, and from 2.7 to 5 mmol/L for patients intolerant to statin. The impact of the differences in background ezetimibe and statin treatment, as well as cardiac risk and severity (including baseline LDL-C) is discussed in Section 7.1.1.1. ODYSSEY OUTCOMES [18] was deemed an outlier amongst trials of ASCVD patients receiving MTD statin. In this trial, the median time since a recent acute coronary event was 2.6 months which, based on clinical expert feedback, may result in highly variable LDL-C values at baseline due to plaque rupture, and subsequently unreliable results. ODYSSEY OUTCOMES is excluded in a sensitivity analysis in the NMA report, see Appendix L – NMA report.

Comparability of the study populations with Danish patients with ASCVD and risk equivalent eligible for treatment

The Danish patient population for ASCVD patients has been described by the Danish Medicines Council (ref: Omkostningseffektiviteten af PCSK9 hæmmere):

- The average age for ASCVD patients is 60 year.
- 60% of the ASCVD population is men.
- It is expected that 25% of the population will have a LDL ≥ 2,6 mmol/L (acute coronary syndrome, polyvascular disease and ischemic stroke).
- It is expected that all patients will be treated with high intensive statin and ezetimibe.

In the studies included in this application, the average age ranged from 53 to 66 years, and LDL-C at baseline ranged from 3.9 to 4.9 mmol/L for patients on MTD statin, and from 2.7 to 5 mmol/L for patients intolerant to statin, these would be patients eligible for treatment with PCSK9 inhibitors [59]. The proportion of patients with ASCVD ranged from 23 to 100%. for patients on MTD statin 46 to 89% were on high intensive statin (where reported). Proportion of patients treated with ezetimibe was generally low, however, subgroup data for percent change in LDL-C presented by two of the included trials did not suggest background/baseline ezetimibe use to be a treatment-effect modifier (see Table 8). In general, the results are considered transferable to Danish clinical practice.

Appendix D Efficacy and safety results per study

Outcome measures

Table 43 Definition, validity and clinical relevance of included outcome measuresDefinition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
LDL-C	**Percent Change from baseline in LDL-C (mmol/L) at 24 Weeks** **Absolute change from baseline in LDL-C (mmol/L) at 24 Weeks** If measures of LDL-C were reported in units mg/dL, they were converted to mmol/L by multiplying by a factor of 0.02586, which is conversion rate reported in FOURIER ([19] and the highest number of decimal places found in the literature.	The method of LDL-C assessment was reported in all studies. Six studies, including the phase III ORION studies, used reflexive testing (i.e., if LDL-C was less than 40 mg/dL or if triglycerides were above 400 mg/dL, LDL-C was measured by ultracentrifugation), 15 studies reported calculated LDL-C, and one study trials measured LDL-C directly. The method was not described for two studies. Based on common application of the Friedewald formula, including ORION-10 and ORION-11 trials, this method of reporting LDL-C was prioritised in the case that studies reported multiple methods. For the purposes of the NMA, it was assumed that differences in the method of LDL-C assessment would not modify the observed relative effects Appendix L – NMA report.	The association between LDL-C levels and ASCVD risk in individuals with hypercholesterolemia (including familial and non-familial disease) has been investigated in published studies. In particular, a meta-analysis of over 200 prospective cohort studies, Mendelian randomization studies (i.e. observational studies that compare outcomes according to the presence of specific mutations), and randomized interventional trials including more than 2 million participants with over 20 million person-years of follow-up and over 150,000 cardiovascular (CV) events demonstrated a dose-dependent log-linear association between the magnitude of exposure to LDL-C and the risk of ASCVD, and an increase in effect with increasing duration of exposure [1]. Interventional studies of lipid-lowering agents have consistently shown that reductions in LDL-C levels reduce ASCVD morbidity and mortality. This has been demonstrated in individual studies (studies of statins, non-statins, and most recently PCSK9 inhibitors), as well as in meta-analyses of statin trials [18, 19, 31, 53, 54]. Minimal clinically important difference: It is not possible in published literature to define the minimum reduction in LDL-C that gives a clinical significant change on cardiovascular outcomes. There are several factors besides LDL lowering that influence the total risk of cardiovascular outcomes. Besides that, the population is a heterogenic group with different risk factors, baseline LDL-C and LDL-C targets [24]. For instance for secondary prevention the high risk groups should according to guideline aim for a 50% decrease of LDL-C [20]. In primary prevention even smaller changes in LDL-C might be clinically significant if the time with the reduction and treatment is long enough, as both the concentration of LDL-C as well as time of exposure are defining the total plaque burden [2].

Outcome measure	Definition	Validity	Clinical relevance
Serious Adverse Events (SAE)	Proportion of patients with ≥1 SAE during the study period		Generally used safety outcome Data from studies with a duration of at least one year are included in an indirect comparison.
Adverse events (AE)	Proportion of patients with ≥1 AE during the study period		Generally used safety outcome Data from studies with a duration of at least one year are included in an indirect comparison.
Withdrawal any reason	Proportion of patients that discontinue during the study period		Generally used safety outcome Data from studies with a duration of at least 24 weeks are included in the NMA.
Withdrawal due to AE	Proportion of patients that discontinue due to an AE/SAE during the study period		Generally used safety outcome Data from studies with a duration of at least 24 weeks are included in the NMA.

Results per study

Trials reported outcomes as least squares (LS) mean and mean. The LS mean was utilised when reported, and mean was considered appropriate when not reported, to align with the approach used in the ORION trials.

HeFH population

Table 44 HeFH populations. Results per study

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* value		
Alirocumab studies														
NCT01266876 mITT population	% change from baseline in LDL-C	Calculated	12 weeks	ALI 150mg Q2W	16	-67.9 (19.4)	-57.25	-71.0; -43.5	<0.0001	NA	NA	NA	See also Appendix M – Statistical methods. For analysis of the primary efficacy variable, the percent change from baseline in calculated LDL-C at week 12 or LOCF was analysed in the mITT population using an analysis of covariance (ANCOVA) model with treatment group and randomisation strata of ezemitimibe use as fixed effects, and the corresponding baseline value as covariate. Throughout the ANCOVA model, we compared every group of REGN727 with placebo using appropriate contrasts and the 95% CIs of the difference versus placebo. To address the multiple comparisons of the four	Table 2, Stein, 2012 [34]
				Placebo	15	-10.65 (19.5)								
	Absolute change from baseline in LDL-C	Calculated	12 weeks	ALI 150mg Q2W	16	-2.7 (0.8)[a]	-2.20	-2.8; -1.6	<0.0001	NA	NA	NA		Table 2, Stein, 2012 [34]
				Placebo	15	-0.5 (0.8)[a]								

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* value		
													treatment groups compared with placebo for the primary efficacy endpoint analysis, a hierarchical testing procedure was we applied ensure strong control of the overall type-1 error rate at the two-sided 0·05 significance level. Continuous secondary efficacy variables were analysed in the mITT population using the same ANCOVA model as for the primary endpoint.	
Odyssey Long term Subgroup (NCT01507831) HeFH subgroup	% change from baseline in LDL-C	Calculated	24 weeks	ALI 150 mg Q2W	271	-56.3 (31.3)	-63.3 (2.9)[1]	-69.0; -57.6	0.6038	NA	NA	NA	See also Appendix M – Statistical methods. The assessment of continuous secondary efficacy end points was similar to the assessment of the primary efficacy end point: The intention-to-treat analysis that was used for the evaluation of the primary end point included all LDL cholesterol values that were collected, regardless of whether they were obtained while the patient was receiving the study drug or after the study drug was discontinued, up to week 24. We accounted for missing data by using a mixed-effects model for repeated measures. Patients who discontinued the study drug prematurely were	Figure S2, Robinson, 2015 [37]
				Placebo	145	7.0 (28.9)								

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* value		
													asked to return for further clinic visits and assessments until the scheduled final visit.	
	Absolute change from baseline in LDL-C	Calculated	24 weeks	ALI 150 mg Q2W	271	NR	NR	NR	NR	NA	NA	NA	NA	Robinson, 2015 [37]
				Placebo	145	NR								
Odyssey HIGH FH (NCT01617655) ITT population	% change from baseline in LDL-C	Calculated	24 weeks	ALI 150 mg Q2W	71	-45.7 (29.5)	-39.1 (6.0)[1]	-51.1;-27.1	<0.0001	NA	NA	NA	The primary efficacy endpoint was analysed in the ITT population, defined as all randomized patients with at least one calculated LDL-C value at baseline and at least one available calculated LDL-C value within one of the analysis windows up to week 24. A mixed effect model with repeated measures approach to account for missing data was used to provide least-squares (LS) means estimates within each treatment arm and for the comparison between treatment arms for the primary and continuous secondary efficacy endpoints with a hierarchical procedure used to control type I error and handle multiple secondary endpoint analyses.	Table 2, Ginsberg, 2016 [35]
				Placebo	35	-6.6 (29.0)								
	Absolute change from baseline in LDL-C	Calculated	24 weeks	ALI 150 mg Q2W	71	-2.3 (1.5)[a]	-1.9 (0.3)[2]	-2.5;-1.3	<0.0001	NA	NA	NA		Table 2, Ginsberg, 2016 [35]
				Placebo	35	-0.4 (1.5)[a]								

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* value		
Odyssey FH I (NCT01623115) ITT population	% change from baseline in LDL-C	Calculated	24 weeks	ALI 75 mg Q2W-150 mg Q2W	322	-48.8 (28.7)	-57.9 (2.7)[1]	-63.3;-52.6	<0.0001	NA	NA	NA	The ITT analysis included all randomized patients with an LDL-C measurement available at baseline and at least one of the post-randomization time points between Weeks 4 and 24, regardless of treatment adherence. The primary efficacy analysis was conducted using a mixed effects model with repeated measures (MMRM). The least-squares mean difference between alirocumab and placebo in percentage change in LDL-C from baseline to week 24 was calculated from the model, using all LDL-C values regardless of adherence to treatment.	Table 2, Kastelein, 2015 [36]
				Placebo	163	9.1 (28.1)								
	Absolute change from baseline in LDL-C	Calculated	24 weeks	ALI 75 mg Q2W-150 mg Q2W	322	NR	NR	NR	NR	NA	NA	NA	NA	Kastelein, 2015 [36]
				Placebo	163	NR								
Odyssey FH II (NCT01709500) ITT population	% change from baseline in LDL-C	Calculated	24 weeks	ALI 75 mg Q2W-150 mg Q2W	166	-48.7 (24.5)	-51.4 (3.4)[1]	-58.1;-44.8	<0.0001	NA	NA	NA	The ITT analysis included all randomized patients with an LDL-C measurement available at baseline and at least one of the post-randomization time points between Weeks 4 and 24, regardless of treatment adherence. The primary efficacy analysis was conducted using a mixed effects model with repeated measures (MMRM). The least-squares mean difference between alirocumab and placebo in	Table 2, Kastelein, 2015 [36]
				Placebo	81	2.8 (25.2)								

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* value		
													percentage change in LDL-C from baseline to week 24 was calculated from the model, using all LDL-C values regardless of adherence to treatment.	
	Absolute change from baseline in LDL-C	Calculated	24 weeks	ALI 75 mg Q2W-150 mg Q2W	166	NR	NR	NR	NR	NA	NA	NA	NA	Kastelein, 2015 [36]
				Placebo	81	NR								
Evolocumab studies														
RUTHERFORD-2 (NCT01763918)	% change from baseline in LDL-C	Calculated	12 weeks	EVO 140 mg Q2W	110	-61.3 (18.5)	-59.2[3]	-65.1;-53.4	<0.0001	NA	NA	NA	All analyses included data from any patient who received at least one dose of the study drug, and patients were analysed within the dosing frequency group to which they were randomly assigned (i.e., every 2 weeks vs monthly). The coprimary and co-secondary continuous efficacy endpoints were analysed within each dosing frequency group using a repeated measures linear model, with terms for treatment group, stratification factor, scheduled visit, and the interaction of treatment and scheduled visit. There was no imputation of any missing data. The covariate analyses were run using a	Table 2, Raal, 2015 [47]
				Placebo	54	-2.0 (18.4)								
	Absolute change from baseline in LDL-C	Calculated	12 weeks	EVO 140 mg Q2W	110	-2.6 (0.8)[a]	-2.4[3]	-2.7;-2.1	<0.0001	NA	NA	NA		Table 2, Raal, 2015 [47]
				Placebo	54	-0.2 (0.7)[a]								

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* value		
													similar repeated measures model but included the covariates of interest, one at a time, as a fixed effect.	
Inclisiran studies														
ORION-9 (NCT03397121) ITT population	% change from baseline in LDL-C	Reflexive	150	Inclisiran 284 mg	242	-45.5 (24.2)	-50.50	-54.8; -46.2	<0.0001	NA	NA	NA	See also Appendix M – Statistical methods. Intention-to-treat analysis. The percent change in LDL-C from baseline to day 510 was analysed using an ANCOVA model applied to each of the 100 multiply imputed datasets. The model included a fixed effect for treatment and baseline LDL-C as a covariate. Analysis of the secondary outcome absolute change in LDL-C from baseline to day 510 was performed only after the analyses of the two primary end points were completed and the null hypotheses were rejected.	Novartis, data on file.
				Placebo	240	5.0 (24.5)								
			510	Inclisiran 284 mg	231	-39.7 (-43.7;-35.7)[4]	-47.9	-53.5;-42.3	<0.001	NA	NA	NA		Raal, 2020 [52]
				Placebo	229	8.2 (4.3;12.2)[4]								
	Absolute change from baseline in LDL-C	Reflexive	150	Inclisiran 284 mg	242	-1.8 (1.0)[b]	-1.90	-2.1; -1.7	<0.0001	NA	NA	NA		Novartis, data on file.
				Placebo	240	0.1 (1.0)[b]								
			510	Inclisiran 284 mg	231	-1.5 (-1.7;-1.4)[4]	1.8	-2.0;-1.6	<0.001	NA	NA	NA		Raal, 2020 [52]

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* value		
				Placebo	229	0.3 (0.1;0.4) [4]								

Grey fields mark calculated values. ALI, alirocumab; CI, confidence interval; EVO, evolocumab; EZE, ezetimibe; ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol; LSM, least squares mean; mITT, modified intention-to-treat; NA, not applicable; NR, not reported; SE, standard error.

[1] LSM (SE)

[2] Mean (SE)

[3] LSM (CI 95%)

[4] (CI 95%)

[a] Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.02586. Conversion factor was not reported in the publication.

ASCVD and risk equivalent populations on MTD statin

Table 45 ASCVD and risk equivalent populations on MTD statin. Results per study

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* value		
Alirocumab studies														
Odyssey Outcomes (NCT01663402) ITT population	% change from baseline in LDL-C	Reflexive	4 months	ALI 75 mg Q2W SC- 150 mg Q2W	8,602	-55.8 (27.8)	NR	NR	NR	NA	NA	NA	NA	Clinicaltrials.gov Schwartz, 2018 [18]
				Placebo	8,750	4.4 (28.1)								
	Absolute change from baseline in LDL-C	Reflexive	4 months	ALI 75 mg Q2W SC- 150 mg Q2W	8,602	NR	NR	NR	NR	NA	NA	NA	NA	Clinicaltrials.gov Schwartz, 2018 [18]
				Placebo	8,750	NR								

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* value		
Odyssey Long Term (NCT01507831) ITT population	% change from baseline in LDL-C	Calculated	24 weeks	ALI 150 mg Q2W	1,530	-61 (27.4)	-61.9 (1.3)[1]	-64.3;-59.4	<0.001	NA	NA	NA	The intention-to-treat analysis that was used for the evaluation of the primary end point included all LDL cholesterol values that were collected, regardless of whether they were obtained while the patient was receiving the study drug or after the study drug was discontinued, up to week 24. Missing data were accounted for by using a mixed-effects model for repeated measures. The assessment of continuous secondary efficacy end points was similar to the assessment of the primary efficacy end point.	Table 2, Robinson, 2015 [37]
				Placebo	780	0.8 (27.9)								
	Absolute change from baseline in LDL-C	Calculated	24 weeks	ALI 150 mg Q2W	1,530	-1.9 (0.9)[a]	-1,80	-1.9; -1.7	<0.0001	NA	NA	NA	See Appendix M – Statistical methods..	Table 2, Robinson, 2015 [37]
				Placebo	780	-0.1 (0.9)[a]								
Odyssey Choice I (NCT01926782) ITT population	% change from baseline in LDL-C	Calculated	24 weeks	ALI 75 mg Q2W	76	–51.6 (28.8)	-51.5[1]	4.0[1]	<0.0001	NA	NA	NA	The primary efficacy analysis included all randomized patients with an LDL-C measurement available at baseline and at least one of the post-randomization time points between Weeks 4 and 24, regardless of treatment adherence (ITT population), and was analysed using a mixed-effects model with repeated measures, with parameters to account for missing data. Key secondary endpoints were analysed as for the primary endpoint.	Supplement Table 4, Roth, 2016 [38]
				Placebo	156	–0.1 (28.7)								

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* value		
	Absolute change from baseline in LDL-C	Calculated	24 weeks	ALI 75 mg Q2W	76	NR	NR	NR	NR	NA	NA	NA	NA	Roth, 2016 [38]
				Placebo	156	NR								
NTC01288443 mITT population	% change from baseline in LDL-C	Calculated	12 weeks	ALI 150mg Q2W	29	–72.4 (17.2)	-67.30	-76.0; -58.6	<0.0001	NA	NA	NA	See also Appendix M – Statistical methods. The primary efficacy endpoint was analyzed in the modified intent-to-treat (mITT) population, defined as all randomized patients with an evaluable primary endpoint, using an analysis of covariance model with treatment group and randomization strata of atorvastatin dose as fixed effects, and baseline LDL-C as covariate. The last observation carried forward method was applied to impute missing week 12 LDL-C on-treatment values. Each SAR236553 treatment group was compared with placebo using appropriate contrasts. Ninety-five percent confidence intervals of the difference versus placebo were not adjusted for multiple comparisons. Secondary efficacy endpoints were analyzed in the mITT population using the same analysis of covariance model, with treatment group and randomization strata of atorvastatin dose as fixed effect, and corresponding baseline value as covariate.	Table 2, McKenney, 2012 [39]
				Placebo	31	–5.1 (17.3)								

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* value		
	Absolute change from baseline in LDL-C	Calculated	12 weeks	ALI 150mg Q2W	29	NR	NR	NR	NR	NA	NA	NA	NA	McKenney, 2012 [39]
				Placebo	31	NR								

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* value		
Odyssey Combo I (NCT01644175) ITT population	% change from baseline in LDL-C	Calculated	24 weeks	ALI 75 mg Q2W SC- 150 mg Q2W	205	–48.2 (27.8)	-45.9[2]	-52.5;-39.3	<0.0001	NA	NA	NA	The primary end point was assessed in the ITT population, which included all randomized patients regardless of treatment adherence with ≥1 available LDL-C value both at baseline and at one of the planned time points between weeks 4 and 24. A mixed effect model with repeated measures was used to account for missing data. All available postbaseline data from week 4 to week 52 were used regardless of status on or off treatment. The model included fixed categorical effects of treatment group, randomization strata, time point, treatment-by-time point interaction, and strata-by-time point interaction as well as the continuous fixed covariates of baseline LDL-C value and baseline value-by time point interaction. This model provided baseline adjusted least squares means estimates at week 24 for both treatment groups with their corresponding 95% CIs. The difference between these estimates will be provided with their corresponding 95% CI and P values. Secondary end points were analysed with the same methodology as for the primary end point.	Table II, Kereiakes, 2015 [40]
				Placebo	106	–2.3 (28.1)								
	Absolute change from	Calculated	24 weeks	ALI 75 mg Q2W SC- 150 mg Q2W	205	–1.3 (0.9)[b]	-1.20	-1.4; -1.0	<0.0001	NA	NA	NA	See Appendix M – Statistical methods..	Supplementary table II,

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* val ue		
	baseline in LDL-C			Placebo	106	–0.1 (0.8)[b]								Kereiakes, 2015 [40]
Odyssey KT (NCT02289963) ITT population	% change from baseline in LDL-C	Calculated	24 weeks	ALI 75 mg Q2W SC- 150 mg Q2W	97	–57.1 (29.6)	-63.4 (4.2)[1]	-71.6;-55.2	<0.00 01	NA	NA	NA	The primary efficacy analysis included a mixed effect model with repeated measures, with parameters to account for missing data. The mixed effect model with repeated measures included fixed categorical effects of treatment group (alirocumab vs placebo), time point, randomization strata, treatment-by-time point interaction, and strata-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction. Alirocumab was compared with placebo using appropriate contrasts, and the 95% confidence interval of the difference was provided. Continuous secondary endpoints with a normal distribution were analysed as for the primary endpoint.	Table 2, Koh, 2018 [41]
				Placebo	102	6.3 (29.3)								
	Absolute change from baseline in LDL-C	Calculated	24 weeks	ALI 75 mg Q2W SC- 150 mg Q2W	97	–1.4 (0.8)[b]	-1.6 (0.1)[1]	-1.8;-1.3	<0.00 01	NA	NA	NA		Table 2, Koh, 2018 [41]
				Placebo	102	0.1 (0.8)[b]								
	% change from baseline in LDL-C	Calculated	24 weeks	ALI 75 mg Q2W SC- 150 mg Q2W	467	–50.6 (30.3)	-29.8 (2.3)[1]	-34.4;-25.3	<0.00 01	NA	NA	NA	The primary endpoint was analysed using a mixed effect model with a repeated measures (MMRM)approach to account for missing data. All available post-baseline data at planned time-	Table 2, Cannon, 2015 [42]

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* val ue		
Odyssey Combo II (NCT01644188) ITT population				EZE	240	–20.7 (29.4)							points from Week 4 to 52 regardless of status on- or off-treatment were used in the MMRM for the ITT analysis, with the model used to provide least-squares (LS) mean estimates and comparison between treatment arms of LDL-C reductions at week 24. The models included fixed categorical effects of treatment group, randomization strata, time-point, treatment-by-time-point interaction, and strata-by-time-point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline value-by-time-point interaction. Secondary endpoints comprising continuous variables with a normal distribution were analysed using the MMRM model.	
	Absolute change from baseline in LDL-C			ALI 75 mg Q2W SC- 150 mg Q2W	467	–1.5 (0.7)[a]	- 0.80	-0.9; -0.7	<0.00 01	NA	NA	NA	See Appendix M – Statistical methods..	Figure 3, Cannon, 2015 [42]
				EZE	240	–0.7 (0.8)[a]								
Odyssey EAST (NCT02715726) ITT population	% change from baseline in LDL-C	Calculated	24 weeks	ALI 75 mg Q2W SC/ 150 mg Q2W	403	–56.0 (30.1)	-35.6 (2.5) [1]	-40.6;-30.7	<0.00 01	NA	NA	NA	The primary efficacy endpoint was analysed in the ITT population using a mixed-effect model with repeated measures approach to handle missing data. All postbaseline data available	Table 2, Han, 2020 [43]

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* val ue		
				EZE	208	−20.3 (28.8)							within the week 4 to week 24 analysis window were used (on-treatment and off-treatment through week 24). The model included the fixed categorical effects of treatment group (alirocumab vs ezetimibe), time point, randomization strata, treatment-by-time point interaction, and strata-by time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction. Alirocumab was compared to ezetimibe using appropriate contrasts, and the 95% confidence interval of the difference was provided. Continuous secondary endpoints anticipated to have a normal distribution were analysed using the same mixed-effect model with repeated-measures model as for the primary endpoint with the continuous fixed covariates of corresponding baseline value and baseline value-by-time point interaction.	

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* value		
	Absolute change from baseline in LDL-C			ALI 75 mg Q2W SC/ 150 mg Q2W	403	–1.6 (0.8)[b]	-1.00	-1.1; -0.9	<0.0001	NA	NA	NA	See Appendix M – Statistical methods..	Figure 2, Han, 2020 [43]
				EZE	208	–0.6 (0.8)[b]								
Evolocumab studies														
FOURIER (NCT01764633) ITT population	% change from baseline in LDL-C	NR	24 weeks	EVO 140 mg Q2W or 420 mg QM	12,964	–62 (24.1)	61	60.4; 61.6	<0.001	NA	NA	NA	See also Appendix M – Statistical methods. Efficacy analyses were conducted on an intention to-treat basis. No imputation was performed for missing data on clinical outcomes.	Supplementary figure S2 and Figure 1, Sabatine, 2017 [19]
				Placebo	12,954	–1.0 (28.0)								
	Absolute change from baseline in LDL-C			EVO 140 mg Q2W or 420 mg QM	12,964	–1.8 (0.9)[a]	1.5[a]	1.5; 1.5	<0.0001	NA	NA	NA		Supplementary figure S2 and Figure 1, Sabatine, 2017 [19]
				Placebo	12,954	–0.3 (0.8)[a]								
LAPLACE-2 (NCT01763866)	% change from	Reflexive	12 weeks	EVO 140 mg Q2W	555[4]	–61.7 (27.0)[4]	-71.00	-74.8; -67.2	<0.0001	NA	NA	NA	See Appendix M – Statistical methods..	Robinson, 2014 [48]

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* val ue		
population	baseline in LDL-C			or 420 mg QM										
				EZE 10 mg	112[4]	–18.3 (27.0)[4]	-27.60	-33.5; -21.7	<0.00 01	NA	NA	NA	See Appendix M – Statistical methods..	
				Placebo	281[4]	9.3 (26.0)[4]								
	Absolute change from baseline in LDL-C			EVO 140 mg Q2W or 420 mg QM	555[4]	–1.8 (1.0)[4,c]	-2.00	-2.1; -1.9	<0.00 01	NA	NA	NA	See Appendix M – Statistical methods..	Robinson, 2014 [48]
				EZE 10 mg	112[4]	–0.5 (0.9)[4,c]	-0,70	-0.9; -0.5	<0.00 01	NA	NA	NA	See Appendix M – Statistical methods..	
				Placebo	281[4]	0.2 (0.9)[4,c]								

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* value		
LAPLACE-TIMI57 (NCT01380730) mITT population	% change from baseline in LDL-C	Measured	12 weeks	EVO 140 mg Q2W	78	−63.34 (21.2)	-66.1 (2.7)[1]	-71.5;-60.7	<0.0001	NA	NA	NA	See also Appendix M – Statistical methods. The analyses of efficacy and safety were done for all randomly assigned patients who were given at least one dose of study drug (modified intention to treat). Analyses of the primary and secondary efficacy endpoints were done with an ANCOVA model with covariates for treatment group and the stratification factors—screening LDL concentration (<3·4 mmol/L vs ≥3·4 mmol/L) and baseline use of ezetimibe (yes vs no). All efficacy endpoints were analysed with last observation carried forward (LOCF) imputation.	Clinialtrials.gov, Table 2, Giugliano, 2012 [49]
				Placebo	78	2.76 (21.1)								
	Absolute change from baseline in LDL-C			EVO 140 mg Q2W	78	−2.1 (0.8)[b]	-2.0 (0,1)[1]	-2.2;-1.8	<0.0001	NA	NA	NA		Clinicaltrials.gov, Table 2, Giugliano, 2012 [49]
				Placebo	78	−0.0 (0.8)[b]								
Inclisiran studies														
ORION-10 (NCT03399370) ITT population	% change from baseline in LDL-C	Reflexive	150	Inclisiran 284 mg	781	−59.5 (26.4)	-60.40	-63.0; -57.8	<0.0001	NA	NA	NA	See also Appendix M – Statistical methods. Intention-to-treat analysis. The percent change in LDL-C from baseline to day 510 was analysed using an ANCOVA model applied to each of the 100 multiply imputed datasets. The model included a fixed effect for treatment and baseline LDL-C as a covariate. Analysis of the secondary outcome absolute change in LDL-C from baseline to day 510 was performed only after the analyses of the two primary end points were completed and the null hypotheses were rejected.	Novartis, data on file.
				Placebo	780	0.9 (26.4)								
			510	Inclisiran 284 mg	691	-51.3[5]	-52.3	-55.7;-48.8	<0.001	NA	NA	NA		Ray, 2020 [9]
				Placebo	666	1.0[5]								
	Absolute change	Reflexive	150	Inclisiran 284 mg	781	−1.6 (0.7)[a]	-1.60	NR	<0.0001	NA	NA	NA		Novartis, data on file.

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* value		
	from baseline in LDL-C			Placebo	780	–0.0 (0.7)[a]								
			510	Inclisiran 284 mg	691	-1.5[5]	-1.5	-1.48;-1.32	<0.001	NA	NA	NA		Ray, 2020 [9]
				Placebo	666	-0.1[5]								
ORION-11 (NCT03400800) ITT population	% change from baseline in LDL-C	Reflexive	150	Inclisiran 284 mg	810	–45.9 (47.9)	-54.20	-58.9; -49.5	<0.0001	NA	NA	NA	See also Appendix M – Statistical methods. Intention-to-treat analysis. The percent change in LDL-C from baseline to day 510 was analysed using an ANCOVA model applied to each of the 100 multiply imputed datasets. The model included a fixed effect for treatment and baseline LDL-C as a covariate. Analysis of the secondary outcome absolute change in LDL-C from baseline to day 510 was performed only after the analyses of the two primary end points were completed and the null hypotheses were rejected.	Novartis, data on file.
				Placebo	807	8.3 (47.8)								
			510	Inclisiran 284 mg	724	-45.8[5]	-49.9	-53.1;-46.6	<0.001	NA	NA	NA		Ray, 2020 [9]
				Placebo	739	4.0[5]								
	Absolute change from baseline in LDL-C	Reflexive	150	Inclisiran 284 mg	810	–1.3 (1.2)[a]	-1.40	-1.5; -1.3	<0.0001	NA	NA	NA		Novartis, data on file.
				Placebo	807	0.1 (1.3)[a]								
			510	Inclisiran 284 mg	724	-1.3[5]	-1,3	-1.42;-1.26	<0.001	NA	NA	NA		Ray, 2020 [9]

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* val ue		
				Placebo	739	0.0[5]								

Grey fields mark calculated values.. ALI, alirocumab; CI, confidence interval; EVO, evolocumab; EZE, ezetimibe; ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol; LSM, least squares mean; mITT, modified intention-to-treat; NA, not applicable; NR, not reported; SE, standard error.

[1] LSM (SE)

[2] Estimated mean (95% CI) change from baseline (%)

[3] CI was not reported.

[4] To assure that LAPLACE-2 was given its proper weight in analyses, before analysis, we mathematically combined each group (i.e., the placebo arms, the ezetimibe 10 mg arms, and the evolocumab 140 mg arm) to calculate a group mean and group SD for each. The pooled mean was n-weighted mean across all arms within group. For the pooled SD, the following formula was used, and modified as necessary by number of arms with data; it accounts for individual arm variation and variation in the means across arms (where, for instance, σ_1^2 is the within-group variance for group 1, μ_1 is the mean for group 1, μ is the estimate of the global mean, and σ is the estimate of the global SD). σ=√((n_1 σ_1^2+n_2 σ_2^2+n_1 (μ_1-μ)^2+n_2 (μ_2-μ)^2)/(n_1+n_2))

[5] LSM, SE was not reported.

[a] Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.02586, as requested in the publication.

[b] Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.02586. Conversion factor was not reported in the publication.

[c] Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.0259, as requested in the publication.

ASCVD and risk equivalent populations intolerant to statin

Table 46 ASCVD and risk equivalent populations intolerant to statin. Results per study

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* value		
Alirocumab studies														
Odyssey Choice II (NCT02023879) ITT population	% change from baseline in LDL-C	Calculated	24 weeks	ALI 75 mg Q2W	115	–53.5 (17.2)	-58.2 (2.8)	-63.7; -52.7	<0.0001	NA	NA	NA	See also Appendix M – Statistical methods. The primary efficacy analysis was conducted in the ITT population, which included all randomized patients with an evaluable primary endpoint. Analysis utilized a mixed-effect model with repeated measures to account for missing data as used in previous alirocumab studies. Secondary lipid endpoints were analyzed as for the primary endpoint.	Table 2, Stroes, 2016 [44]
				Placebo	57	4.7 (17.4)								
	Absolute change from baseline in LDL-C	Calculated	24 weeks	ALI 75 mg Q2W	115	-2.1 (0.7)[a]	-2.20	-2.4; -2.0	<0.0001	NA	NA	NA		Table 2, Stroes, 2016 [44]
				Placebo	57	0.1 (0.7)[a]								
Odyssey NIPPON (NCT02584504) ITT population	% change from baseline in LDL-C	Calculated	12 weeks	ALI 150 mg Q2W	53	–70.1 (16.7)	-65.8 (3.1)[1]	-72.9;-58.7	<0.0001	NA	NA	NA	The primary efficacy endpoint was analyzed in the ITT population using a mixed-effect model with repeated measures (MMRM) approach. The model included the fixed categorical effects of treatment group, time point, stratification factor of statin, treatment-by-time-point interaction and statin-by-time-point interaction, and the	Table 2, Teramoto, 2019 [45]
				Placebo	56	–4.3 (16.5)								

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* value		
													continuous fixed covariates of baseline calculated LDL-C value, and baseline value- by-time-point interaction. Continuous secondary endpoints with a normal distribution were analyzed using the MMRM model.	
	Absolute change from baseline in LDL-C	Calculated	12 weeks	ALI 150 mg Q2W	53	-2.6 (0.7)[a]	-2.50	-2.8; -2.2	<0.0001	NA	NA	NA	See Appendix M – Statistical methods..	Figure 1, Teramoto, 2019 [45]
				Placebo	56	-0.1 (0.8)[a]								
Odyssey ALTERNATIVE (NCT01709513) ITT population	% change from baseline in LDL-C	Calculated	24 weeks	ALI 75 mg Q2W SC-150 mg Q2W	126	–45.0 (24.7)	-30.4 (3.1)[1]	-36.6;-24.2	<0.0001	NA	NA	NA	The ITT analysis used for evaluation of the primary end point included all calculated LDL-C values, irrespective of treatment adherence, up to week 24. Missing data were accounted for using a mixed-effect model with repeated measures approach. The consistency of the treatment effect for the primary end point was assessed across prespecified subgroups. A P value of #.05 was considered to be statistically significant.	Table 2, Moriarty, 2015 [46]
				EZE	122	–14.6 (24.3)								
	Absolute change from baseline in LDL-C	Calculated	24 weeks	ALI 75 mg Q2W SC-150 mg Q2W	126	-2.6 (0.7)[b]	-1.60	-1.8; -1.4	<0.0001	NA	NA	NA	See Appendix M – Statistical methods..	Figure 3 Moriarty, 2015 [46]

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* value		
				EZE	122	-1.0 (0.9)[b]								
Evolocumab studies														
GAUSS-2 (NCT01763905)	% change from baseline in LDL-C	NR	12 weeks	EVO 140 mg Q2W	103	−56.1 (19.4)	-38.1[2]	-43.7;-32.4	<0.001	NA	NA	NA	Efficacy and safety analysis included all randomized patients who received at least one dose of the study drug. The co-primary and co-secondary efficacy endpoints were analysed using a repeated measures linear effects model for each dose frequency with no imputation of missing data. Multiplicity adjustment was based on a combination of sequential testing, the Hochberg procedure (Hochberg. Biometrika 1988;75:800-2), and fallback procedure to control the overall significance level for all primary and secondary endpoints. Covariate analysis was conducted using a similar repeated measures model but included the covariates of interest, one at a time, as a fixed effect.	Table 2, Stroes, 2014 [50]
				EZE 10 mg daily	51	−18.1 (18.2)								
	Absolute change from baseline in LDL-C	NR	12 weeks	EVO 140 mg Q2W	103	-2.7 (1.1)[a]	-1.8[2]	-2.1;-1.5	<0.001	NA	NA	NA		Table 2, Stroes, 2014 [50]
				EZE 10 mg daily	51	-0.9 (1.0)[a]								
GAUSS-4 (NCT02634580)	% change from baseline in LDL-C	Reflexive	12 weeks	EVO 140 mg Q2W/420 QM	40	−59.5 (17.1)	-40.1[2]	-48.7;-31.6	<0.0001	NA	NA	NA	The primary analysis of the 12-week double blind period was conducted using the full analysis set (all randomized patients who received at least one dose	Table 2, Koba, 2020 [51]

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* value		
				EZE 10 mg daily	21	−19.0 (13.7)							of the study drug). For the co-primary efficacy endpoints, a repeated-measure linear-effect model was used to compare the efficacies of evolocumab (Q2W and Q4W groups were pooled) and ezetimibe (pooled). The model included terms of treatment group, stratification factor of screening LDL-C level, scheduled visit, and the interaction of treatment group with scheduled visit. Missing values were not imputed when the repeated-measure linear-effect model is used because missing data can be handled using the behaviour of the observed data. For the co-secondary endpoints, the statistical model and testing were similar to the primary analysis of the co-primary endpoints. Multiplicity adjustment was performed for the co-primary and co-secondary endpoints in the primary analysis via sequential testing and by using Hochberg and fallback procedures to preserve the family-wise type 1 error rate at 0.05.	

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* value		
	Absolute change from baseline in LDL-C	Reflexive	12 weeks	EVO 140 mg Q2W/420 QM	40	-2.9 (0.8)[b]	-2.00	-2.4; -1.6	<0.0001	NA	NA	NA	See Appendix M – Statistical methods..	Clinicaltrials.gov Koba, 2020 [51]
				EZE 10 mg daily	21	-0.9 (0.8)[b]								
Inclisiran studies														
ORION-10 Subgroup (NCT03399370) No statins at baseline subgroup	% change from baseline in LDL-C	Reflexive	150	Inclisiran 284 mg	115	–55.0 (29.0)	-60.10	-67.6; -52.6	<0.0001	NA	NA	NA	See Appendix M – Statistical methods..	Novartis, data on file.
				Placebo	117	5.1 (29.3)								
			510	Inclisiran 284 mg	80[4]	NR	-54.8[4]	-62.0;-47.6[4]	<0.0001	NA	NA	NA	See also Appendix M – Statistical methods. The difference in the percentage change from baseline between inclisiran and placebo was analysed for each subgroup with the use of a mixed-effects model for repeated measures. The model used observed case data and thus all data available on a patient, who could have data at day 510 missing but have data at earlier time points.	Figure 3, Ray, 2020 [9]
				Placebo	88[4]	NR								

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* value		
	Absolute change from baseline in LDL-C	Reflexive	150	Inclisiran 284 mg	115	-1.9 (0.8)[b]	-1.90	-2.1; -1.7	<0.0001	NA	NA	NA	See Appendix M – Statistical methods..	Novartis, data on file.
				Placebo	117	0.0 (0.8)[b]								
			510	Inclisiran 284 mg	80	NR	NR	NR	NR	NA	NA	NA	NA	Figure 3, Ray, 2020 [9]
				Placebo	88	NR								
ORION-11 Subgroup (NCT03400800) No statins at baseline subgroup	% change from baseline in LDL-C	Reflexive	150	Inclisiran 284 mg	53	–45.4 (20.6)	-42.70	-50.6; -34.8	<0.0001	NA	NA	NA	See Appendix M – Statistical methods..	Novartis, data on file.
				Placebo	53	–2.7 (20.8)								
			510	Inclisiran 284 mg	44[4]	NR	-41.6[4]	-51.1;-32.1[4]	<0.0001	NA	NA	NA	See also Appendix M – Statistical methods. The difference in the percentage change from baseline between inclisiran and placebo was analysed for each subgroup with the use of a mixed-effects model for repeated measures. The model used observed case data and thus all data available on a patient, who could have data at day 510 missing but have data at earlier time points.	Figure 4, Ray, 2020 [9]
				Placebo	41[4]	NR								

Study ID	Outcome	LDL-C analysis type	Assess-ment day	Study arm	N	Mean (SD)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
							Difference	95% CI	*P* value	Diffe-rence	95% CI	*P* value		
	Absolute change from baseline in LDL-C	Reflexive	150	Inclisiran 284 mg	53	-1.7 (0.7)[b]	-1.50	-1.8; -1.2	<0.0001	NA	NA	NA	See Appendix M – Statistical methods..	Novartis, data on file.
				Placebo	53	-0.2 (0.7)[b]								
			510	Inclisiran 284 mg	44	NR	NR	NR	NR	NA	NA	NA	NA	Figure 4, Ray, 2020 [9]
				Placebo	41	NR								

Grey fields mark calculated values. ALI, alirocumab; CI, confidence interval; EVO, evolocumab; EZE, ezetimibe; ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol; LSM, least squares mean; mITT, modified intention-to-treat; NA, not applicable; NR, not reported; SE, standard error.

[1] LSM (SE)

[2] LSM (95% CI)

[3] Mean (SE)

[4] Values reported for the sub-group with no statin treatment at baseline.

[a] Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.02586. Conversion factor was not reported in the publication.

[b] Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.02586, as requested in the publication.

[c] Values are reported in mg/dL in the publication and converted to mmol/L for reporting in this table by multiplying by 0.0259, as requested in the publication.

Appendix E Safety data for intervention and comparators

This appendix contains the following information on safety data:

- Included safety outcomes by study (Table 47 to Table 49)
- AE and SAEs by study (Table 47 to Table 49)
- Cardiovascular events by study (Table 50 to Table 55)
- Extract from the Summary of Product Characteristics (Table 56)

Included safety outcomes

Table 47 HeFH population. Safety results

Study ID	Intervention	Analysis set	N	Timepoint of assessment	Any grade AEs N (%)	Serious AEs N (%)	Discontinuation due to AE N (%)	Discontinuation any reason N (%)	All-cause mortality N (%)
Alirocumab studies									
NCT01266876 Stein, 2012 [34]	Alirocumab 150mg Q2W	Safety	16	20 weeks	12 (75)	0	0	NR	0
	Placebo		15	20 weeks	9 (60)	1 (6.6)	0	2 (13.3)	0
Odyssey Long term Subgroup[a] (NCT01507831) Robinson, 2015 [37]	Alirocumab 150mg Q2W	Safety	1550	78 weeks	1255 (81.0)	290 (18.7)	111 (7.2)[b]	437 (28.1*)	8 (0.5)
	Placebo		788	78 weeks	650 (82.5)	154 (19.5)	46 (5.8)[b]	193 (24.5*)	10 (1.3)

Study ID	Intervention	Analysis set	N	Timepoint of assessment	Any grade AEs N (%)	Serious AEs N (%)	Discontinuation due to AE N (%)	Discontinuation any reason N (%)	All-cause mortality N (%)
Odyssey HIGH FH (NCT01617655) Ginsberg, 2016 [35]	Alirocumab 150mg Q2W	ITT	72	78 weeks	51 (70.8)	10 (13.9)	3 (4.2)	29 (40.3*)	0
	Placebo		35	78 weeks	28 (80)	4 (11.4)	2 (5.7)	9 (25.7*)	0
Odyssey FH I (NCT01623115) Kastelein, 2015 [36]	Alirocumab 75mg Q2W	Safety	322	78 weeks	263 (81.7)	44 (13.7)	11 (3.4)	76 (23.6)	6 (1.9)
	Placebo		163	78 weeks	129 (79.1)	22 (13.5)	10 (6.1)	33 (20.3)	0
Odyssey FH II (NCT01709500) Kastelein, 2015 [36]	Alirocumab 75mg Q2W	Safety	167	78 weeks	125 (74.9)	15 (9)	6 (3.6)	17 (10.2)	0
	Placebo		81	78 weeks	66 (81.5)	8 (9.9)	1 (1.2)	10 (12.4)	0
Evolocumab studies									
RUTHERFORD-2 (NCT01763918) Raal, 2015 [47]	Evolocumab 140mg Q2W	ITT	110	12 weeks	61 (55)	3 (3)	0	NR	0
	Placebo Q2W		55	12 weeks	23 (43)	2 (4)	0	NR	0

Study ID	Intervention	Analysis set	N	Timepoint of assessment	Any grade AEs N (%)	Serious AEs N (%)	Discontinuation due to AE N (%)	Discontinuation any reason N (%)	All-cause mortality N (%)
Inclisiran studies									
ORION-9 (NCT03397121) Raal, 2020 [52].	Inclisiran 284mg	Safety	241	540 days	185 (76.8)	18 (7.5)	3 (1.2)	7* (2.9*)	1 (0.4)
	Placebo		240	540 days	172 (71.7)	33 (13.8)	0	10* (4.2*)	1 (0.4)

Abbreviations: AE, adverse event; ITT, intention-to-treat; N, number; NR, not reported; Q2W, once every two weeks.
[a] Data are reported for the full population.
[b] values reported in the table from the publication but do not match those reported in the text (113 and 47 for the alirocumab and placebo arms respectively).
* Calculated data

Table 48 ASCVD and risk equivalent populations on MTD statin. Safety results

Study ID	Intervention	Analysis set	N	Timepoint of assessment	Any grade AEs N (%)	Serious AEs N (%)	Discontinuation due to AE N (%)	Discontinuation any reason N (%)	All-cause mortality N (%)
Alirocumab studies									
Odyssey Outcomes (NCT01663402) Schwartz, 2018 [18]	Alirocumab 75mg Q2W	Treated	9451	**2.8 years (median)**	7165 (75.8)	2202 (23.3)	343 (3.6)	1343 (14.2)	334 (3.5)
	Placebo		9443	**2.8 years (median)**	7282 (77.1)	2350 (24.9)	324 (3.4)	1496 (15.8)	392 (4.1)
Odyssey Long Term (NCT01507831) Robinson, 2015 [37]	Alirocumab 150mg Q2W	Safety	1550	**78 weeks**	1255 (81.0)	290 (18.7)	111 (7.2)[a]	437 (28.1*)	8 (0.5)
	Placebo		788	**78 weeks**	650 (82.5)	154 (19.5)	46 (5.8)[a]	193 (24.5*)	10 (1.3)
Odyssey Choice I (NCT01926782) Roth, 2016 [38]	Alirocumab 75mg Q2W	Safety	78	**48 weeks**	55 (70.5)	9 (11.5)	4 (5.1)	13* (16.7*)	NR
	Placebo		157	**48 weeks**	115 (73.2)	23 (14.6)	13 (8.3)	28* (17.8*)	NR
NTC01288443 McKenney, 2012 [39]	Alirocumab 150mg Q2W	Safety	31	**12 weeks**	19 (16.3)	0	1 (3.2)	4 (12.9*)	NR
	Placebo		31	**12 weeks**	14 (45.2)	1 (3.2)	0	0	NR

Study ID	Intervention	Analysis set	N	Timepoint of assessment	Any grade AEs N (%)	Serious AEs N (%)	Discontinuation due to AE N (%)	Discontinuation any reason N (%)	All-cause mortality N (%)
Odyssey Combo I (NCT01644175) Kereiakes, 2015 [40]	Alirocumab 75mg Q2W	Safety	207	62 weeks	157 (75.8)	26 (12.6)	13 (6.3)	51 (24.6*)	1 (0.5)
	Placebo		107	62 weeks	81 (75.7)	14 (13.1)	8 (7.5)	32 (29.9*)	1 (0.9)
Odyssey KT (NCT02289963) Koh, 2018 [41]	Alirocumab 75mg Q2W	ITT	97	24 weeks	57 (58.8)	17 (17.5)	2 (2.1)	10 (10.3)	1 (1)
	Placebo		102	24 weeks	63 (61.8)	10 (9.8)	1 (1)	5 (4.9)	0
Odyssey Combo II (NCT01644188) Cannon, 2015 [42]	Alirocumab 75mg Q2W	Safety	479	104 weeks	391 (81.6)	124 (25.9)	44 (9.2)	71 (14.8*)	6 (1.3)
	Ezetimibe 10mg		241	104 weeks	198 (82.2)	60 (24.9)	19 (7.9)	35 (14.5*)	6 (2.5)
Odyssey EAST (NCT02715726) Han, 2020 [43]	Alirocumab 75mg Q2W	Safety	406	34 weeks	278 (68.5)	41 (10.1)	6 (1.5)	NR	2 (0.49)
	Ezetimibe 10mg		206	34 weeks	130 (63.1)	23 (11.2)	3 (1.5)	NR	3 (1.46)
Evolocumab studies									
FOURIER (NCT01764633) Sabatine, 2017 [19]	Evolocumab 140mg Q2W/ 420mg QM	Treated	13769	Median 2.2 years	10664 (77.4)	3410 (24.8)	226 (1.6)	1682 (12)	444 (3.2)
	Placebo		13756	Median 2.2 years	10644 (77.4)	3404 (24.7)	201 (1.5)	1746 (13)	426 (3.1)
LAPLACE-2 (NCT01763866)	Evolocumab 140mg Q2W/ 420mg QM	Randomised	1117	12 weeks	406 (36.3)	23 (2.1)	21 (1.9)	NR	NR

Study ID	Intervention	Analysis set	N	Timepoint of assessment	Any grade AEs N (%)	Serious AEs N (%)	Discontinuation due to AE N (%)	Discontinuation any reason N (%)	All-cause mortality N (%)
Robinson, 2014 [48]	Ezetimibe 10mg		221	12 weeks	89 (40.3)	2 (0.9)	4 (1.8)	NR	NR
	Placebo		558	12 weeks	219 (39.2)	13 (2.3)	12 (2.2)	NR	NR
LAPLACE-TIMI57 (NCT01380730)	Evolocumab 140mg Q2W		78	12 weeks	43 (55)	4 (5)	2 (3)	2 (2.6*)	1 (1)
Giugliano, 2012 [49]	Placebo Q2W		78	12 weeks	33 (42)	4 (5)	0	0	0
Inclisiran studies									
ORION-10 (NCT03399370)	Inclisiran 284mg	Safety	781	540 days	574 (73.5)	175 (22.4)	19 (2.4)	60* (7.7*)	12 (1.5)
Ray, 2020 [9].	Placebo		778	540 days	582 (74.8)	205 (26.3)	17 (2.2)	85*	11 (1.4)
ORION-11 (NCT03400800)	Inclisiran 284mg	Safety	811	540 days	671 (82.7)	181 (22.3)	23 (2.8)	N=810 38 (4.7)	14 (1.7)
Ray, 2020 [9].	Placebo		804	540 days	655 (81.5)	181 (22.5)	18 (2.2)	N=807 37 (4.6)	15 (1.9)

Abbreviations: AE, adverse event; ITT, intention-to-treat; N, number; NR, not reported; Q2W, once every two weeks; QM, once monthly.
a values reported in the table from the publication but do not match those reported in the text (113 and 47 for the alirocumab and placebo arms respectively)

* Calculated data

Table 49 ASCVD and risk equivalent populations intolerant to statin. Safety results

Study ID	Intervention	Analysis set	N	Timepoint of assessment	Any grade AEs N (%)	Serious AEs N (%)	Discontinuation due to AE N (%)	Discontinuation any reason N (%)	All-cause mortality N (%)
Alirocumab studies									
Odyssey Choice II (NCT02023879) Stroes, 2016 [44]	Alirocumab 75mg Q2W	Safety	115	34 weeks	84 (73)	6 (5.2)	2 (1.7)	8* (6.9*)	0
	Placebo		58	34 weeks	37 (63.8)	4 (6.9)	2 (3.4)	6* (10.3*)	0
Odyssey NIPPON (NCT02584504) Teramoto, 2019 [45]	Alirocumab 150mg Q2W	ITT	53	12 weeks	25 (47.2)	2 (3.8)	1 (1.9)	3 (5.7*)	1 (1.9)
	Placebo		56	12 weeks	26 (46.4)	1 (1.8)	0	1 (1.8*)	0
Odyssey ALTERNATIVE (NCT01709513) Moriarty, 2015 [46]	Alirocumab 75mg Q2W	ITT	126	24 weeks	104 (82.5)	12 (9.5)	23 (18.3)	30 (23.8*)	NR
	Ezetimibe 10mg		124	24 weeks	100 (80.6)	10 (8.1)	31 (25)	42 (33.9*)	NR
Evolocumab studies									
GAUSS-2 (NCT01763905) Stroes, 2014 [50]	Evolocumab 140mg Q2W	**NR**	103	14 weeks	63 (61)	5 (5)	6 (6)	NR	0
	Placebo Q2W + Ezetimibe 10mg		51	14 weeks	35 (69)	1 (2)	4 (8)	NR	0
GAUSS-4 (NCT02634580)	Evolocumab 140mg Q2W/ 420mg QM	Treated	40	12 weeks	23 (57.5)	0	2 (5)	3 (7.5*)	0

Study ID	Intervention	Analysis set	N	Timepoint of assessment	Any grade AEs N (%)	Serious AEs N (%)	Discontinuation due to AE N (%)	Discontinuation any reason N (%)	All-cause mortality N (%)
Koba, 2020 [51]	Placebo Q2W/ QM + ezetimibe 10mg		21	12 weeks	13 (61.9)	2 (9.5)	0	1 (4.8*)	0
Inclisiran studies									
ORION-10 Subgroup[a] (NCT03399370) Ray, 2020 [9].	Inclisiran 284mg	Safety	781	540 days	574 (73.5)	175 (22.4)	19 (2.4)	60* (7.7*)	12 (1.5)
	Placebo		778	540 days	582 (74.8)	205 (26.3)	17 (2.2)	85*	11 (1.4)
ORION-11 Subgroup[a] (NCT03400800) Ray, 2020 [9].	Inclisiran 284mg	Safety	811	540 days	671 (82.7)	181 (22.3)	23 (2.8)	N=810 38 (4.7)	14 (1.7)
	Placebo		804	540 days	655 (81.5)	181 (22.5)	18 (2.2)	N=807 37 (4.6)	15 (1.9)

Abbreviations: AE, adverse event; ITT, intention-to-treat; N, number; NR, not reported; Q2W, once every two weeks; QM, once monthly.
[a] Data are reported for the full population.

* Calculated data

AE and SAEs by study

Table 50 HeFH populations. SAEs and AEs per study

Study ID	Outcome	Assess-ment day	Study arm	N	Mean % (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
						Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Alirocumab studies													
NCT01266876 Safety population	SAE, proportion	12 weeks	ALI 150mg Q2W	16	0.0 (0.0;18.8)	-6.21	-26.81;15.23	-	0.472	0.047;4.744	0.5239	See Appendix M – Statistical methods.	Stein, 2012 [34]
			Placebo	15	6.7 (0.0;19.3)								
	AE, proportion	12 weeks	ALI 150mg Q2W	16	75.0 (53.8;96.2)	15.00	-17.83;44.63	-	1.250	0.758;2.062	0.3824	See Appendix M – Statistical methods.	Table 4, Stein, 2012 [34]
			Placebo	15	60.0 (35.2;84.8)								
Odyssey Long term Subgroup (NCT01507831) HeFH subgroup[1]	SAE, proportion	78 weeks	ALI 150 mg Q2W	1550	18.7 (16.8; 20.7)	-0.83	-4.25;2.51	-	0.957	0.803;1.141	0.6266	See Appendix M – Statistical methods.	Table 3, Robinson, 2015 [37]
			Placebo	788	19.5 (16.8; 22.3)								

Study ID	Outcome	Assess-ment day	Study arm	N	Mean % (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
						Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	AE, proportion	78 weeks	ALI 150 mg Q2W	1550	81.0 (79.0; 82.9)	-1.52	-4.77;1.82	-	0.982	0.943;1.022	0.3649	See Appendix M – Statistical methods.	Table 3, Robinson, 2015 [37]
			Placebo	788	82.5 (79.8; 85.1)								
Odyssey HIGH FH (NCT01617655) ITT population	SAE, proportion	78 weeks	ALI 150 mg Q2W	72	13.9 (5.9;21.9)	2.46	- 12.32;15.03	-	1.215	0.410;3.603	0.7251	See Appendix M – Statistical methods.	Table 3, Ginsberg, 2016 [35]
			Placebo	35	11.4 (0.9;22.0)								
	AE, proportion	78 weeks	ALI 150 mg Q2W	72	70.8 (60.3;81.3)	-9.17	-24.97;8.76	-	0.885	0.709;1.106	0.2832	See Appendix M – Statistical methods..	Table 3, Ginsberg, 2016 [35]
			Placebo	35	80.0 (66.7; 93.3)								
Odyssey FH I (NCT01623115) Safety population	SAE, proportion	78 weeks	ALI 75 mg Q2W-150 mg Q2W	322	13.7 (9.9;17.4)	0.17	-6.54;6.44	-	1.012	0.629;1.629	0.9594	See Appendix M – Statistical methods.	Table 3, Kastelein, 2015 [36]
			Placebo	163	13.5 (8.3;18.7)								

Study ID	Outcome	Assess-ment day	Study arm	N	Mean % (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
						Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	AE, proportion	78 weeks	ALI 75 mg Q2W-150 mg Q2W	322	81.7 (77.5;85.9)	2.54	-4.84;10.23	-	1.032	0.939;1.134	0.5120	See Appendix M – Statistical methods.	Table 3, Kastelein, 2015 [36]
			Placebo	163	79.1 (72.9;85.4)								
Odyssey FH II (NCT01709500) Safety population	SAE, proportion	78 weeks	ALI 75 mg Q2W-150 mg Q2W	167	9.0 (4.6;13.3)	-0.89	-9.39;6.64	-	0.909	0.402;2.057	0.8196	See Appendix M – Statistical methods.	Table 3, Kastelein, 2015 [36]
			Placebo	81	9.9 (3.4;16.4)								
	AE, proportion	78 weeks	ALI 75 mg Q2W-150 mg Q2W	167	74.9 (68.3;81.4)	-6.63	-16.90;4.56	-	0.919	0.802;1.052	0.2213	See Appendix M – Statistical methods..	Table 3, Kastelein, 2015 [36]
			Placebo	81	81,5 (73.0;89.9)								

Study ID	Outcome	Assess-ment day	Study arm	N	Mean % (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
						Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Evolocumab studies													
RUTHERFORD-2 (NCT01763918) ITT population	SAE, proportion	12 weeks	EVO 140 mg Q2W	110	2.7 (0.0; 5.8)	-0.91	-8.43;5.05	-	0.750	0.129;4.358	0.7486	See Appendix M – Statistical methods.	Table 3, Raal, 2015 [47]
			Placebo	55	3.6 (0.0;8.6)								
	AE, proportion	12 weeks	EVO 140 mg Q2W	110	55.5 (46.2;64.7)	13.64	-2.53;29.03	-	1.326	0.931;1.889	0.1180	See Appendix M – Statistical methods.	Table 3, Raal, 2015 [47]
			Placebo	55	41.8 (28.8;54.9)								
Inclisiran studies													
ORION-9 (NCT03397121) Safety population	SAE, proportion	540 days	Inclisiran 284 mg	241	7.5 (4.1;10.8)	-6.28	-11.76;-0.70	-	0.543	0.315;0.938	0.0284	See Appendix M – Statistical methods.	Table 3, Raal, 2020 [52]
			Placebo	240	13.8 (9.4;18.1)								
	AE, proportion	540 days	Inclisiran 284 mg	241	76.8 (71.4;82.1)	5.10	-2.74;12.85	-	1.071	0.964;1.190	0.2023	See Appendix M – Statistical methods.	Table 3, Raal, 2020 [52]
			Placebo	240	71.7 (66.0;77.4)								

Grey fields mark calculated values. ALI, alirocumab; CI, confidence interval; EVO, evolocumab; EZE, ezetimibe; ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol; LSM, least squares mean; mITT, modified intention-to-treat; NA, not applicable; NR, not reported; SE, standard error. [1] SAEs and AEs are reported for the full population.

Table 51 ASCVD and risk equivalent populations on MTD statin. SAEs and AEs per study

Study ID	Outcome	Assess-ment day	Study arm	N	Mean % (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
						Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Alirocumab studies													
Odyssey Outcomes (NCT01663402) Treated population	SAE, proportion	2.8 years (median)	ALI 75 mg Q2W SC-150 mg Q2W	9451	23.3 (22.4;24.2)	-1.59	-2.81;-0.37	-	0.936	0.890;0.985	0.0108	See Appendix M – Statistical methods.	Table 3, Schwartz, 2018 [18]
			Placebo	9443	24.9 (24.0;25.8)								
	AE, proportion	2.8 years (median)	ALI 75 mg Q2W SC-150 mg Q2W	9451	75.8 (74.9;76.7)	-1.30	-2.51;-0.09	-	0.983	0.968;0.999	0.0348	See Appendix M – Statistical methods.	Table 3, Schwartz, 2018 [18]
			Placebo	9443	77.1 (76.3;78.0)								

Study ID	Outcome	Assess-ment day	Study arm	N	Mean % (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
						Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Odyssey Long Term (NCT01507831) Safety population	SAE, proportion	78 weeks	ALI 150 mg Q2W	1550	18.7 (16.8;20.7)	-0.83	-4.25;2.51	-	0.957	0.803;1.141	0.6266	See Appendix M – Statistical methods.	Table 3, Robinson, 2015 [37]
			Placebo	788	19.5 (16.8;22.3)								
	AE, proportion	78 weeks	ALI 150 mg Q2W	1550	81.0 (79.0;82.9)	-1.52	-4.77;1.82	-	0.982	0.943;1.022	0.3649	See Appendix M – Statistical methods.	Table 3, Robinson, 2015 [37]
			Placebo	788	82.5 (79.8; 85.1)								
Odyssey Choice I (NCT01926782) Safety population	SAE, proportion	48 weeks	ALI 75 mg Q2W	78	11.5 (4.4;18.6)	-3.11	-11.73;6.54	-	0.788	0.383;1.620	0.5165	See Appendix M – Statistical methods.	Table 2, Roth, 2016 [38]
			Placebo	157	14.6 (9.1;20.2)								

Study ID	Outcome	Assess-ment day	Study arm	N	Mean % (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
						Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	AE, proportion	48 weeks	ALI 75 mg Q2W	78	70.5 (60.4;80.6)	-2.74	-15.14;9.23	-	0.963	0.811;1.143	0.6642	See Appendix M – Statistical methods.	Table 2, Roth, 2016 [38]
			Placebo	157	73.2 (66.3;80.2)								
NTC01288443 Safety population	SAE, proportion	12 weeks	ALI 150mg Q2W	31	0,0 (0.0;9.7)	-3.03	-14.90;9.19	-	0.500	0.048;5.250	0.5634	See Appendix M – Statistical methods.	Table 3, McKenney, 2012 [39]
			Placebo	31	3,2 (0.0; 9.4)								
	AE, proportion	12 weeks	ALI 150mg Q2W	31	61.3 (44.1;78.4)	16.13	-8.65;38.95	-	1.357	0.841;2.189	0.2108	See Appendix M – Statistical methods.	Table 3, McKenney, 2012 [39]
			Placebo	31	45.2 (27.6;62.7)								

Study ID	Outcome	Assess-ment day	Study arm	N	Mean % (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
						Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Odyssey Combo I (NCT01644175) Safety population	SAE, proportion	62 weeks	ALI 75 mg Q2W SC-150 mg Q2W	207	12.6 (8.0;17.1)	-0.52	-8.75;7.06	-	0.960	0.524;1.760	0.8949	See Appendix M – Statistical methods.	Table III, Kereiakes, 2015 [40]
			Placebo	107	13.1 (6.7;19.5)								
	AE, proportion	62 weeks	ALI 75 mg Q2W SC-150 mg Q2W	207	75.8 (70.0;81.7)	0.14	-9.61;10.35	-	1.002	0.878;1.143	0.9774	See Appendix M – Statistical methods.	Table III, Kereiakes, 2015 [40]
			Placebo	107	75.7 (67.6;83.8)								
Odyssey KT (NCT02289963) ITT population	SAE, proportion	NR	ALI 75 mg Q2W SC-150 mg Q2W	97	17.5 (10.0;25.1)	7.72	-2.02;17.23	-	1.788	0.862;3.709	0.1188	See Appendix M – Statistical methods.	Table 3, Koh, 2018 [41]
			Placebo	102	9.8 (4.0;15.6)								
	AE, proportion	NR	ALI 75 mg Q2W SC-150 mg Q2W	97	58.8 (49.0;68.6)	-3.00	-16.43;10.52	-	0.951	0.759;1.193	0.6658	See Appendix M – Statistical methods..	Table 3, Koh, 2018 [41]

Study ID	Outcome	Assess-ment day	Study arm	N	Mean % (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
						Difference	95% CI	*P* value	Difference	95% CI	*P* value		
			Placebo	102	61.8 (52.3;71.2)								
Odyssey Combo II (NCT01644188) Safety population	SAE, proportion	104 weeks	ALI 75 mg Q2W SC-150 mg Q2W	479	25.9 (22.0;29.8)	0.99	-5.83;7.60	-	1.040	0.797;1.357	0.7741	See Appendix M – Statistical methods.	Table 3, Cannon, 2015 [42]
			EZE	241	24.9 (19.4;30.4)								
	AE, proportion	104 weeks	ALI 75 mg Q2W SC-150 mg Q2W	479	81,6 (78.2;85.1)	-0.53	-6.35;5.56	-	0.994	0.924;1.068	0.8614	See Appendix M – Statistical methods.	Table 3, Cannon, 2015 [42]
			EZE	241	82.2 (77.3;87.0)								
Odyssey EAST (NCT02715726) Safety population	SAE, proportion	34 weeks	ALI 75 mg Q2W SC/ 150 mg Q2W	406	10.1 (7.2;13.0)	-1.07	-6.49;4.00	-	0.904	0.558;1.465	0.6833	See Appendix M – Statistical methods.	Table 3, Han, 2020 [43]
			EZE	206	11.2 (6.9;15.5)								

Study ID	Outcome	Assess-ment day	Study arm	N	Mean % (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
						Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	AE, proportion	34 weeks	ALI 75 mg Q2W SC/ 150 mg Q2W	406	68.5 (64.0;73.0)	5.37	-2.56;13.37	-	1.085	0.959;1.228	0.1953	See Appendix M – Statistical methods.	Table 3, Han, 2020 [43]
			EZE	206	63.1 (56.5;69.7)								
Evolocumab studies													
FOURIER (NCT01764633) Treated population	SAE, proportion	2.2 years (median)	EVO 140 mg Q2W or 420 mg QM	13769	24.8 (24.0;25.5)	0,02	-1.00;1.04	-	1.001	0.960;1.043	0.9690	See Appendix M – Statistical methods.	Table 3, Sabatine, 2017 [19]
			Placebo	13756	24.7 (24.0;25.5)								
	AE, proportion	2.2 years (median)	EVO 140 mg Q2W or 420 mg QM	13769	77.4 (76.8;78.1)	0.07	-0.92;1.06	-	1.001	0.988;1.014	0.8861	See Appendix M – Statistical methods..	Table 3, Sabatine, 2017 [19]
			Placebo	13756	77.4 (76.7;78.1)								
LAPLACE-2 (NCT01763866)	SAE, proportion	12 weeks	EVO 140 mg Q2W or 420 mg QM	1117	2.1 (1.2;2.9)	-0.27	-1.90;1.19	-	0.884	0.451;1.731	0.7189	See Appendix M – Statistical methods.	Table 5, Robinson, 2014 [48]

Study ID	Outcome	Assess-ment day	Study arm	N	Mean % (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
						Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Randomised population[1]			EZE 10 mg	221	0,9 (0.0; 2.2)	-1.42	-3.14;0.83		0.388	0.088;1.707	0.2106		
			Placebo	558	2.3 (1.1;3.6)								
	AE, proportion	12 weeks	EVO 140 mg Q2W or 420 mg QM	1117	36.3 (33.5;39.2)	-2.90	-7.84;2.02	-	0.926	0.814;1.054	0.2440	See Appendix M – Statistical methods.	Table 5, Robinson, 2014 [48]
			EZE 10 mg	221	40.3 (33.8;46.7)	1.02	-6.53;8.68		1.026	0.848;1.242	0.7914		
			Placebo	558	39.2 (35.2;43.3)								
LAPLACE-TIMI57 (NCT01380730)	SAE, proportion	12 weeks	EVO 140 mg Q2W	78	5.1 (0.2;10.0)	0.00	-7.50;7.50	-	1.000	0.259;3.857	1.0000	See Appendix M – Statistical methods.	Table 3, Giugliano, 2012 [49]
			Placebo	78	5.1 (0.2;10.0)								
	AE, proportion	12 weeks	EVO 140 mg Q2W	78	55.1 (44.1;66.2)	12.82	-2.87;27.87	-	1.303	0.939;1.808	0.1131	See Appendix M – Statistical methods.	Table 3, Giugliano, 2012 [49]
			Placebo	78	42.3 (31.3;53.3)								
Inclisiran studies													

Study ID	Outcome	Assess-ment day	Study arm	N	Mean % (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
						Difference	95% CI	*P* value	Difference	95% CI	*P* value		
ORION-10 (NCT03399370) Safety population	SAE, proportion	540 days	Inclisiran 284 mg	781	22.4 (19.5;25.3)	-3.94	-8.19;0.32	-	0.850	0.713;1.014	0.0704	See Appendix M – Statistical methods.	Table 2, Ray, 2020 [9]
			Placebo	778	26.3 (23.3;29.4)								
	AE, proportion	540 days	Inclisiran 284 mg	781	73.5 (70.4;76.6)	-1.31	-5.65;3.04	-	0.982	0.927;1.042	0.5542	See Appendix M – Statistical methods.	Table 2, Ray, 2020 [9]
			Placebo	778	74.8 (71.8;77.9)								
ORION-11 (NCT03400800) Safety population	SAE, proportion	540 days	Inclisiran 284 mg	811	22.3 (19.5;25.2)	-0.19	-4.26;3.87	-	0.991	0.827;1.189	0.9254	See Appendix M – Statistical methods.	Table 2, Ray, 2020 [9]
			Placebo	804	22.5 (19.6;25.4)								
	AE, proportion	540 days	Inclisiran 284 mg	811	82.7 (80.1;85.3)	1.27	-2.47;5.01	-	1.016	0.970;1.063	0.5058	See Appendix M – Statistical methods.	Table 2, Ray, 2020 [9]
			Placebo	804	81.5 (78.8;84.2)								

Grey fields mark calculated values. ALI, alirocumab; CI, confidence interval; EVO, evolocumab; EZE, ezetimibe; ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol; LSM, least squares mean; mITT, modified intention-to-treat; NA, not applicable; NR, not reported; SE, standard error.

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Table 52 ASCVD and risk equivalent populations intolerant to statin. SAEs and AEs per study

Study ID	Outcome	Assess-ment day	Study arm	N	Mean % (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
						Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Alirocumab studies													
Odyssey Choice II (NCT02023879) Safety population	SAE, proportion	34 weeks	ALI 75 mg Q2W	115	5.2 (1.2; 9.3)	-1.68	-10.56;5.86	-	0.757	0.222;2.576	0.6553	See Appendix M – Statistical methods.	Table 3, Stroes, 2016 [44]
			Placebo	58	6.9 (0.4;13.4)								
	AE, proportion	34 weeks	ALI 75 mg Q2W	115	73.0 (64.9;81.2)	9.25	-5.31;23.94	-	1.145	0.916;1.432	0.2349	See Appendix M – Statistical methods.	Table 3, Stroes, 2016 [44]
			Placebo	58	63.8 (51.4;76.2)								
Odyssey NIPPON (NCT02584504) ITT population	SAE, proportion	12 weeks	ALI 150 mg Q2W	53	3.8 (0.0; 8.9)	1.99	-5.61;9.63	-	2.113	0.197;22.626	0.5362	See Appendix M – Statistical methods.	Table 3, Teramoto, 2019 [45]
			Placebo	56	1.8 (0.0; 5.3)								

Study ID	Outcome	Assess-ment day	Study arm	N	Mean % (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
						Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	AE, proportion	12 weeks	ALI 150 mg Q2W	53	47.2 (33.7;60.6)	0.74	-17.69;19.13	-	1.016	0.681;1.516	0.9382	See Appendix M – Statistical methods.	Table 3, Teramoto, 2019 [45]
			Placebo	56	46.4 (33.4;59.5)								
Odyssey ALTERNATIVE (NCT01709513) ITT population	SAE, proportion	24 weeks	ALI 75 mg Q2W SC-150 mg Q2W	126	9.5 (4.4;14.6)	1.46	-5.76;8.61	-	1.181	0.530;2.633	0.6843	See Appendix M – Statistical methods.	Table 3, Moriarty, 2015 [46]
			EZE	124	8.1 (3.3;12.9)								
	AE, proportion	24 weeks	ALI 75 mg Q2W SC-150 mg Q2W	126	82.5 (75.9;89.2)	1.89	-7.76;11.50	-	1.023	0.910;1.151	0.6993	See Appendix M – Statistical methods.	Table 3, Moriarty, 2015 [46]
			EZE	124	80.6 (73.7;87.6)								

Study ID	Outcome	Assess-ment day	Study arm	N	Mean % (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
						Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Evolocumab studies													
GAUSS-2 (NCT01763905)	SAE, proportion	14 weeks	EVO 140 mg Q2W	103	4.9 (0.7; 9.0)	2.89	-4.84;8.73	-	2.476	0.297;20.639	0.4021	See Appendix M – Statistical methods.	Table 3, Stroes, 2014 [50]
			EZE 10 mg daily	51	2.0 (0.0; 5.8)								
	AE, proportion	14 weeks	EVO 140 mg Q2W	103	61.2 (51.8;70.6)	-7.46	-22.62;8.68	-	0.891	0.700;1.134	0.3493	See Appendix M – Statistical methods.	Table 3, Stroes, 2014 [50]
			EZE 10 mg daily	51	68.6 (55.9;81.4)								
GAUSS-4 (NCT02634580) Treated population	SAE, proportion	12 weeks	EVO 140 mg Q2W/420 QM	40	0.0 (0.0; 7.5)	-10.66	-27.09;4.18	-	0.183	0.020;1.656	0.1306	See Appendix M – Statistical methods.	Table 3, Koba, 2020 [51]
			EZE 10 mg daily	21	9.5 (0.0; 22.1)								

Study ID	Outcome	Assess-ment day	Study arm	N	Mean % (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
						Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	AE, proportion	12 weeks	EVO 140 mg Q2W/420 QM	40	57.5 (42.2;72.8)	-4.40	-28.66;21 21	-	0.929	0.605;1.426	0.7356	See Appendix M – Statistical methods.	Table 3, Koba, 2020 [51]
			EZE 10 mg daily	21	61.9 (41.1;82.7)								
Inclisiran studies													
ORION-10 Subgroup (NCT03399370)	SAE, proportion	540 days	Inclisiran 284 mg	781	22.4 (19.5;25.3)	-3.94	-8.19;0.32	-	0.850	0.713;1.014	0.0704	See Appendix M – Statistical methods.	Table 2, Ray, 2020 [9]
No statins at baseline subgroup[1]			Placebo	778	26.3 (23.3;29.4)								
	AE, proportion	540 days	Inclisiran 284 mg	781	73.5 (70.4;76.6)	-1.31	-5.65;3.04	-	0.982	0.927;1.042	0.5542	See Appendix M – Statistical methods.	Table 2, Ray, 2020 [9]
			Placebo	778	74.8 (71.8;77.9)								
ORION-11 Subgroup (NCT03400800)	SAE, proportion	540 days	Inclisiran 284 mg	811	22.3 (19.5;25.2)	-0.19	-4.26;3.87	-	0.991	0.827;1.189	0.9254	See Appendix M – Statistical methods.	Table 2, Ray, 2020 [9]

Study ID	Outcome	Assess-ment day	Study arm	N	Mean % (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
						Difference	95% CI	*P* value	Difference	95% CI	*P* value		
No statins at baseline subgroup[1]			Placebo	804	22.5 (19.6;25.4)								
	AE, proportion	540 days	Inclisiran 284 mg	811	82.7 (80.1;85.3)	1.27	-2.47;5.01	-	1.016	0.970;1.063	0.5058	See Appendix M – Statistical methods.	Table 2, Ray, 2020 [9]
			Placebo	804	81.5 (78.8;84.2)								

Grey fields mark calculated values. ALI, alirocumab; CI, confidence interval; EVO, evolocumab; EZE, ezetimibe; ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol; LSM, least squares mean; mITT, modified intention-to-treat; NA, not applicable; NR, not reported; SE, standard error.

[1] SAEs and AEs are reported for the full population.

Cardiovascular events by study

Table 53 HeFH population. Cardiovascular adverse events

Study ID	Intervention	Analysis set	Definition	Timepoint of assessment	N	Experienced MACE N (%)	CV deaths N (%)	Experienced resuscitated cardiac events, N (%)	Experienced non-fatal MI N (%)	Experienced stroke N (%)	Required revascularisation procedure, N (%)
Alirocumab studies											
NCT01266876 Stein, 2012 [34]	Alirocumab 150mg Q2W		Outcome not reported	20 weeks	NR	NR	NR	NR	NR	NR	NR
	Placebo				NR	NR	NR	NR	NR	NR	NR
Odyssey Long term Subgroup[a] (NCT01507831) Robinson, 2015 [37]	Alirocumab 150mg Q2W	Safety	Cardiovascular adverse events	78 weeks	1550	27 (1.7)	4 (0.3)	NR	14 (0.9)	9 (0.6)	48 (3.1)
	Placebo				788	26 (3.3)	7 (0.9)	NR	18 (2.3)	2 (0.3)	24 (3.0)
Odyssey HIGH FH (NCT01617655) Ginsberg, 2016 [35]	Alirocumab 150mg Q2W	Safety	NR	78 weeks	72	NR	0	NR	4 (5.6)	0	5 (6.9)
	Placebo				35	NR	0	NR	0	0	0
Odyssey FH I (NCT01623115)	Alirocumab 75mg Q2W	Safety	Positively adjudicated	78 weeks	322	8 (2.5)	3 (0.9)	NR	1 (0.3)	1 (0.3)	2 (0.6)

Study ID	Intervention	Analysis set	Definition	Timepoint of assessment	N	Experienced MACE N (%)	CV deaths N (%)	Experienced resuscitated cardiac events, N (%)	Experienced non-fatal MI N (%)	Experienced stroke N (%)	Required revascularisation procedure, N (%)
Kastelein, 2015 [36]	Placebo		cardiovascular events		163	3 (1.8)	0	NR	1 (0.6)	0	2 (1.2)
Odyssey FH II (NCT01709500)	Alirocumab 75mg Q2W	Safety	Positively adjudicated cardiovascular events	78 weeks	167	2 (1.2)	0	NR	0	0	2 (1.2)
Kastelein, 2015 [36]	Placebo				81	1 (1.2)	0	NR	1 (1.2)	0	1 (1.2)
Evolocumab studies											
RUTHERFORD-2 (NCT01763918)	Evolocumab 140mg Q2W		Outcome not reported	12 weeks	NR	NR	NR	NR	NR	NR	NR
Raal, 2015 [47]	Placebo Q2W				NR	NR	NR	NR	NR	NR	NR
Inclisiran studies											
ORION-9 (NCT03397121)	Inclisiran 284mg	Safety	Other cardiovascular adverse events (non-adjudicated)	540 days	240	10 (4.1)	1 (0.4)	NR	3 (1.2)	0	NR
Raal, 2020 [52].	Placebo				241	10 (4.2)	0	NR	1 (0.4)	0	NR

Abbreviations: MACE, major adverse cardiovascular events; MI, myocardial infarction; N, number; NR, not reported; Q2W, once every two weeks.
[a] Data are reported for the full population.
* calculated value

Table 54 ASCVD and risk equivalent populations on MTD statin. Cardiovascular adverse events.

Study ID	Intervention	Analysis set	Definition	Timepoint of assessment	N	Experienced MACE N (%)	CV deaths N (%)	Experienced resuscitated cardiac events, N (%)	Experienced non-fatal MI, N (%)	Experienced stroke, N (%)	Required revascularisation procedure, N (%)
Alirocumab studies											
Odyssey Outcomes (NCT01663402) Schwartz, 2018 [18]	Alirocumab 75mg Q2W	ITT	Composite endpoint of cardiovascular events	**2.8 years (median)**	9462	793 (8.4)	240 (2.5)	NR	626 (6.6)	111 (1.2)	731 (7.7)
	Placebo				9462	899 (9.5)	271 (2.9)	NR	722 (7.6)	152 (1.6)	828 (8.8)
Odyssey Long Term (NCT01507831) Robinson, 2015 [37]	Alirocumab 150mg Q2W	Safety	Cardiovascular adverse events	**78 weeks**	1550	27 (1.7)	4 (0.3)	NR	14 (0.9)	9 (0.6)	48 (3.1)
	Placebo				788	26 (3.3)	7 (0.9)	NR	18 (2.3)	2 (0.3)	24 (3.0)
Odyssey Choice I (NCT01926782) Roth, 2016 [38]	Alirocumab 75mg Q2W	Safety	Adjudicated cardiovascular events[a]	**48 weeks**	78	1 (1.3)	NR	NR	NR	NR	NR
	Placebo				157	2 (1.3)	NR	NR	NR	NR	NR
NTC01288443 McKenney, 2012 [39]	Alirocumab 150mg Q2W		Outcome not reported	**12 weeks**	NR	NR	NR	NR	NR	NR	NR
	Placebo				NR	NR	NR	NR	NR	NR	NR

Study ID	Intervention	Analysis set	Definition	Timepoint of assessment	N	Experienced MACE N (%)	CV deaths N (%)	Experienced resuscitated cardiac events, N (%)	Experienced non-fatal MI, N (%)	Experienced stroke, N (%)	Required revascularisation procedure, N (%)
Odyssey Combo I (NCT01644175) Kereiakes, 2015 [40]	Alirocumab 75mg Q2W	Safety	Adjudicated treatment emergent cardiovascular events	62 weeks	207	NR	1* (0.5)	NR	1* (0.5)	2* (1.0)	3 (1.4)
	Placebo				107	NR	1* (0.9)	NR	1* (0.9)	0	1 (0.9)
Odyssey KT (NCT02289963) Koh, 2018 [41]	Alirocumab 75mg Q2W	Safety	Positively adjudicated cardiovascular events	24 weeks	97	NR	NR	NR	0	0	3 (3.1)
	Placebo				102	NR	NR	NR	1* (1.0)	1* (1.0)	4 (3.9)
Odyssey Combo II **(NCT01644188)** Cannon, 2015 [42]	Alirocumab 75mg Q2W	Safety	Adverse events	104 weeks	479	23 (4.8)	4* (0.8)	NR	16* (3.3)	2* (0.4)	21 (4.4)
	Ezetimibe 10mg QD				241	8 (3.3)	2* (0.8)	NR	5* (2.1)	1* (0.4)	7 (2.9)
Odyssey EAST (NCT02715726) Han, 2020 [43]	Alirocumab 75mg Q2W	NR	Positively adjudicated cardiovascular events	34 weeks	406	NR	NR	NR	7 (1.7)	1 (0.2)	8 (2.0)
	Ezetimibe 10mg QD				206	NR	NR	NR	6 (2.9)	2 (1.0)	3 (1.5)
Evolocumab studies											

Study ID	Intervention	Analysis set	Definition	Timepoint of assessment	N	Experienced MACE N (%)	CV deaths N (%)	Experienced resuscitated cardiac events, N (%)	Experienced non-fatal MI, N (%)	Experienced stroke, N (%)	Required revascularisation procedure, N (%)
FOURIER (NCT01764633) Sabatine, 2017 [19]	Evolocumab 420mg QM or 140mg Q2W	Treated	Cardiovascular event	Median 2.2 years	13784	1344 (9.8)[b]	251 (1.8)	NR	468 (3.4)	213* (1.5*)[c]	759 (5.5)
	Placebo				13780	1563 (11.3)	240 (1.7)	NR	639 (4.6)	265* (1.9*)[c]	965 (7.0)
LAPLACE-2 (NCT01763866) Robinson, 2014 [48]	Evolocumab 420mg QM or 140mg Q2W	Treated	Positively adjudicated cardiovascular events[a]	12 weeks	1117	5 (0.4)	NR	NR	NR	NR	NR
	Ezetimibe 10mg QD				221	2 (0.9)	NR	NR	NR	NR	NR
	Placebo QM or Q2W				558	3 (0.4)	NR	NR	NR	NR	NR
LAPLACE-TIMI57 (NCT01380730) Giugliano, 2012 [49]	Evolocumab 140mg Q2W	mITT	Clinical cardiovascular events	12 weeks	78	0	0	NR	0	NR	0
	Placebo Q2W				78	0	0	NR	0	NR	0

Study ID	Intervention	Analysis set	Definition	Timepoint of assessment	N	Experienced MACE N (%)	CV deaths N (%)	Experienced resuscitated cardiac events, N (%)	Experienced non-fatal MI, N (%)	Experienced stroke, N (%)	Required revascularisation procedure, N (%)
Inclisiran studies											
ORION-10 (NCT03399370) Ray, 2020 [9].	Inclisiran 284mg	Safety	Cardiovascular adverse events	540 days	781	58 (7.4)	7 (0.9)	NR	20 (2.6)	11 (1.4)	NR
	Placebo				778	79 (10.2)	5 (0.6)	NR	18 (2.3)	7 (0.9)	NR
ORION-11 (NCT03400800) Ray, 2020 [9].	Inclisiran 284mg	Safety	Cardiovascular adverse events	540 days	811	63 (7.8)	9 (1.1)	NR	10 (1.2)	2 (0.2)	NR
	Placebo				804	83 (10.3)	10 (1.2)	NR	22 (2.7)	8 (1.0)	NR

Abbreviations: MACE, major adverse cardiovascular events; MI, myocardial infarction; mITT, modified intention-to-treat; N, number; NR, not reported; Q2W, once every two weeks; QD, once daily; QM, once monthly.
a reported as part of adverse events
b primary endpoint including; CV death, MI, stroke, hospitalisation for unstable angina or coronary revascularisation. Data also reported for secondary endpoint; CV death, MI or stroke.
c calculated from stroke categories; haemorrhagic, non-haemorrhagic or unknown.
* calculated value

Table 55 ASCVD and risk equivalent populations intolerant to statin. Cardiovascular adverse events.

Study ID	Intervention	Analysis set	Definition	Timepoint of assessment	N	Experienced MACE N (%)	CV deaths N (%)	Experienced resuscitated cardiac events, N (%)	Experienced non-fatal MI N (%)	Experienced stroke N (%)	Required revascularisation procedure N (%)
Alirocumab studies											
Odyssey Choice II (NCT02023879)	Alirocumab 75mg Q2W	NR	Positively adjudicated cardiovascular events	34 weeks	115	NR	NR	NR	1 (0.9)	NR	1 (0.9)
Stroes, 2016 [44]	Placebo				58	NR	NR	NR	0	NR	0
Odyssey NIPPON (NCT02584504)	Alirocumab 150mg Q2W	NR	NR	12 weeks	53	NR	NR	NR	NR	NR	0
Teramoto, 2019 [45]	Placebo				56	NR	NR	NR	NR	NR	1 (1.8)
Odyssey ALTERNATIVE (NCT01709513)	Alirocumab 75mg Q2W	ITT	Positively adjudicated	24 weeks	126	NR	NR	NR	1 (0.8)	NR	NR
Moriarty, 2015 [46]	Ezetimibe 10mg				122	NR	NR	NR	0	NR	NR
Evolocumab studies											
GAUSS-2 (NCT01763905)	Evolocumab 140mg Q2W			14 weeks	NR	NR	NR	NR	NR	NR	NR

Study ID	Intervention	Analysis set	Definition	Timepoint of assessment	N	Experienced MACE N (%)	CV deaths N (%)	Experienced resuscitated cardiac events, N (%)	Experienced non-fatal MI N (%)	Experienced stroke N (%)	Required revascularisation procedure N (%)
Stroes, 2014 [50]	Placebo Q2W + Ezetimibe 10mg		Outcome not reported		NR	NR	NR	NR	NR	NR	NR
GAUSS-4 (NCT02634580) Koba, 2020 [51]	Evolocumab 140mg Q2W	NR	NR	12 weeks	19	NR	0	NR	0	NR	NR
	Evolocumab 420mg QM				21	NR	0	NR	0	NR	NR
	Ezetimibe 10mg QD + placebo Q2W				10	NR	0	NR	0	NR	NR
	Ezetimibe 10mg QD + placebo QM				11	NR	0	NR	0	NR	NR

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Study ID	Intervention	Analysis set	Definition	Timepoint of assessment	N	Experienced MACE N (%)	CV deaths N (%)	Experienced resuscitated cardiac events, N (%)	Experienced non-fatal MI N (%)	Experienced stroke N (%)	Required revascularisation procedure N (%)
Inclisiran studies											
ORION-10 Subgroup[a] (NCT03399370) Ray, 2020 [9].	Inclisiran 284mg	Safety	Cardiovascular adverse events	540 days	781	58 (7.4)	7 (0.9)	NR	20 (2.6)	11 (1.4)	NR
	Placebo				778	79 (10.2)	5 (0.6)	NR	18 (2.3)	7 (0.9)	NR
ORION-11 Subgroup[a] (NCT03400800) Ray, 2020 [9].	Inclisiran 284mg	Safety	Cardiovascular adverse events	540 days	811	63 (7.8)	9 (1.1)	NR	10 (1.2)	2 (0.2)	NR
	Placebo				804	83 (10.3)	10 (1.2)	NR	22 (2.7)	8 (1.0)	NR

Abbreviations: ITT, intention to treat; MACE, major adverse cardiovascular events; MI, myocardial infarction; N, number; NR, not reported; Q2W, once every two weeks; QM, once monthly.
[a] Data are reported for the full population.
* calculated value

Extract from the Summary of Product Characteristics

Table 56 Extract from the Summary of Product Characteristics

	Alirocumab	Evolocumab	Inclisiran
Posology, specical populations	**Elderly** No dose adjustment is needed for elderly patients. **Hepatic impairment** No dose adjustment is needed for patients with *mild* or *moderate* hepatic impairment. No data are available in patients with severe hepatic impairment (see section 5.2). **Renal impairment** No dose adjustment is needed for patients with *mild* or *moderate* renal impairment. Limited data are available in patients with severe renal impairment (see section 5.2).	**Elderly patients (age ≥ 65 years)** No dose adjustment is necessary in elderly patients. **Patients with hepatic impairment** No dose adjustment is necessary in patients with *mild* hepatic impairment, see section 4.4 for patients with moderate and severe hepatic impairment. **Patients with renal impairment** No dose adjustment is necessary in patients with renal impairment (see section 5.2).	**Elderly (age ≥65 years)** No dose adjustment is necessary in elderly patients. **Hepatic impairment** No dose adjustments are necessary for patients with *mild* (Child-Pugh class A) or *moderate* (Child-Pugh class B) hepatic impairment. No data are available in patients with severe hepatic impairment (Child-Pugh class C) (see section 5.2). Inclisiran should be used with caution in patients with severe hepatic impairment. **Renal impairment** No dose adjustments are necessary for patients with *mild*, *moderate* or *severe* renal impairment or patients with end-stage renal disease (see section 5.2). There is limited experience with inclisiran in patients with severe renal impairment. Inclisiran should be used with caution in these patients. See section 4.4 for precautions to take in case of haemodialysis.
Contraindications	Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.	Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.	Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

	Alirocumab	Evolocumab	Inclisiran
Special warnings and precautions for use	**Traceability** In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. **Allergic reactions** General allergic reactions, including pruritus, as well as rare and sometimes serious allergic reactions such as hypersensitivity, nummular eczema, urticaria, and hypersensitivity vasculitis have been reported in clinical studies. Angioedema has been reported in the postmarketing setting (see section 4.8). If signs or symptoms of serious allergic reactions occur, treatment with alirocumab must be discontinued and appropriate symptomatic treatment initiated (see section 4.3). **Renal impairment** In clinical studies, there was limited representation of patients with severe renal impairment (defined as eGFR < 30 ml/min/1.73 m2) (see section 5.2). Alirocumab should be used with caution in patients with severe renal impairment. **Hepatic impairment** Patients with severe hepatic impairment (Child-Pugh C) have not been studied (see section 5.2). Alirocumab should be used with caution in patients with severe hepatic impairment.	**Traceability** In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. **Hepatic impairment** In patients with moderate hepatic impairment, a reduction in total evolocumab exposure was observed that may lead to a reduced effect on LDL-C reduction. Therefore, close monitoring may be warranted in these patients. Patients with severe hepatic impairment (Child-Pugh class C) have not been studied (see section 5.2). Evolocumab should be used with caution in patients with severe hepatic impairment. **Dry natural rubber** Repatha 140 mg solution for injection in pre-filled syringe The needle cover of the glass pre-filled syringe is made from dry natural rubber (a derivative of latex), which may cause severe allergic reactions. Repatha 140 mg solution for injection in pre-filled pen The needle cover of the pre-filled pen is made from dry natural rubber (a derivative of latex), which may cause severe allergic reactions. **Sodium content** This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially 'sodium-free'.	**Haemodialysis** The effect of haemodialysis on inclisiran pharmacokinetics has not been studied. Considering that inclisiran is eliminated renally, haemodialysis should not be performed for at least 72 hours after inclisiran dosing. **Sodium content** This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

	Alirocumab	Evolocumab	Inclisiran
Interaction with other medicinal products and other forms of interaction	**Effects of alirocumab on other medicinal products** Since alirocumab is a biological medicinal product, no pharmacokinetic effects of alirocumab on other medicinal products and no effect on cytochrome P450 enzymes are anticipated. **Effects of other medicinal products on alirocumab** Statins and other lipid-modifying therapy are known to increase production of PCSK9, the protein targeted by alirocumab. This leads to the increased target-mediated clearance and reduced systemic exposure of alirocumab. Compared to alirocumab monotherapy, the exposure to alirocumab is about 40%, 15%, and 35% lower when used concomitantly with statins, ezetimibe, and fenofibrate, respectively. However, reduction of LDL-C is maintained during the dosing interval when alirocumab is administered every two weeks.	No interaction studies have been performed. The pharmacokinetic interaction between statins and evolocumab was evaluated in the clinical trials. An approximately 20% increase in the clearance of evolocumab was observed in patients coadministered statins. This increased clearance is in part mediated by statins increasing the concentration of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) which did not adversely impact the pharmacodynamic effect of evolocumab on lipids. No statin dose adjustments are necessary when used in combination with evolocumab. No studies on pharmacokinetic and pharmacodynamics interaction between evolocumab and lipidlowering medicinal products other than statins and ezetimibe have been conducted.	Inclisiran is not a substrate for common drug transporters and, although in vitro studies were not conducted, it is not anticipated to be a substrate for cytochrome P450. Inclisiran is not an inhibitor or inducer of cytochrome P450 enzymes or common drug transporters. Therefore, inclisiran is not expected to have clinically significant interactions with other medicinal products. Based on the limited data available, clinically meaningful interactions with atorvastatin, rosuvastatin or other statins are not expected.

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	Alirocumab	Evolocumab	Inclisiran
Undesirable effects	The most common adverse reactions, at recommended doses, are local injection site reactions (6.1%), upper respiratory tract signs and symptoms (2.0%), and pruritus (1.1%). Most common adverse reactions leading to treatment discontinuation in patients treated with alirocumab were local injection site reactions. **Common** (≥1/100 to <1/10): • Upper respiratory tract signs and symptoms • Pruritus • Injection site reactions **Rare** (≥1/10,000 to <1/1,000): • Hypersensitivity, hypersensitivity vasculitis • Urticaria, eczema nummular **Not known:** • Angioedema • Flu-like illness	The most commonly reported adverse reactions at the recommended doses are nasopharyngitis (7.4%), upper respiratory tract infection (4.6%), back pain (4.4%), arthralgia (3.9%), influenza (3.2%), and injection site reactions (2.2%). The safety profile in the homozygous familial hypercholesterolaemia population was consistent with that demonstrated in the primary hypercholesterolaemia and mixed dyslipidaemia population. **Common** (≥ 1/100 to < 1/10): • Influenza • Nasopharyngitis • Upper respiratory tract infection • Hypersensitivity • Rash • Nausea • Back pain Arthralgia • Injection site reactions **Uncommon** (≥ 1/1,000 to < 1/100): • Urticaria • Influenza-like illness **Rare** (≥ 1/10,000 to < 1/1,000): • Angioedema	The only adverse reactions associated with inclisiran were adverse reactions at the injection site (8.2%). **Common** (≥1/100 to <1/10): Adverse reactions at the injection site

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	Alirocumab	Evolocumab	Inclisiran
Undesirable effects (cont.)	**Immunogenicity/ Anti-drug-antibodies (ADA)** In the ODYSSEY OUTCOMES trial, 5.5% of patients treated with alirocumab 75 mg and/or 150 mg every 2 weeks (Q2W) had anti-drug antibodies (ADA) detected after initiating treatment compared with 1.6% of patients treated with placebo, most of these were transient responses. Persistent ADA responses were observed in 0.7% of patients treated with alirocumab and 0.4% of patients treated with placebo. Neutralising antibody (NAb) responses were observed in 0.5% of patients treated with alirocumab and in <0.1% of patients treated with placebo. Anti-drug antibody responses, including NAb, were low titer and did not appear to have a clinically meaningful impact on the efficacy or safety of alirocumab, except for a higher rate of injection site reactions in patients with treatment emergent ADA compared to patients who were ADA negative (7.5% vs 3.6%). The long-term consequences of continuing alirocumab treatment in the presence of ADA are unknown. In a pool of ten placebo-controlled and active-controlled trials of patients treated with alirocumab 75 mg and/or 150 mg Q2W as well as in a separate clinical study of patients treated with alirocumab 75 mg Q2W or 300 mg every 4 weeks (including some patients with dose adjustment to 150 mg Q2W), the incidence of detecting ADA and NAb was similar to the results from the ODYSSEY OUTCOMES trial described above.	**Immunogenicity** In clinical studies, 0.3% of patients (48 out of 17,992 patients) treated with at least one dose of evolocumab tested positive for binding antibody development. The patients whose sera tested positive for binding antibodies were further evaluated for neutralising antibodies and none of the patients tested positive for neutralising antibodies. The presence of anti-evolocumab binding antibodies did not impact the pharmacokinetic profile, clinical response, or safety of evolocumab.	**Immunogenicity** In the pivotal studies 1,830 patients were tested for anti-drug antibodies. Confirmed positivity was detected in 1.8% (33/1,830) of patients prior to dosing and in 4.9% (90/1,830) of patients during the 18 months of treatment with inclisiran. No clinically significant differences in the clinical efficacy, safety or pharmacodynamic profiles of inclisiran were observed in the patients who tested positive for anti-inclisiran antibodies. **Laboratory values** In the phase III clinical studies, there were more frequent elevations of serum hepatic transaminases between >1x the upper limit of normal (ULN) and ≤3x ULN in patients on inclisiran (ALT: 19.7% and AST: 17.2%) than in patients on placebo (ALT: 13.6% and AST: 11.1%). These elevations did not progress to exceed the clinically relevant threshold of 3x ULN, were asymptomatic and were not associated with adverse reactions or other evidence of liver dysfunction.

Appendix F Comparative analysis of efficacy and safety

Most outcomes are compared by a network meta-analysis (NMA), however AEs and SAEs were not included in the NMA, and therefore an indirect comparion a.m. Bucher has been applied.

Network Meta Analysis

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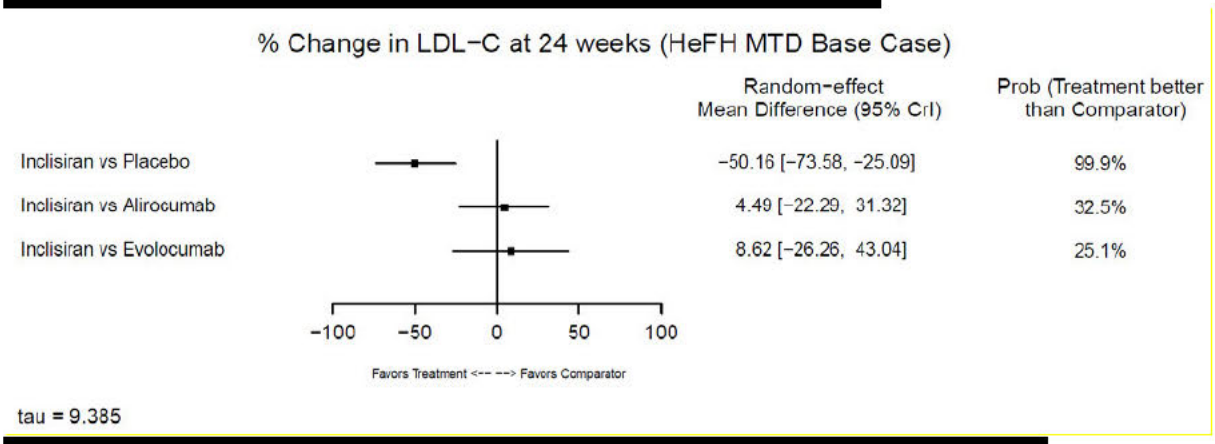

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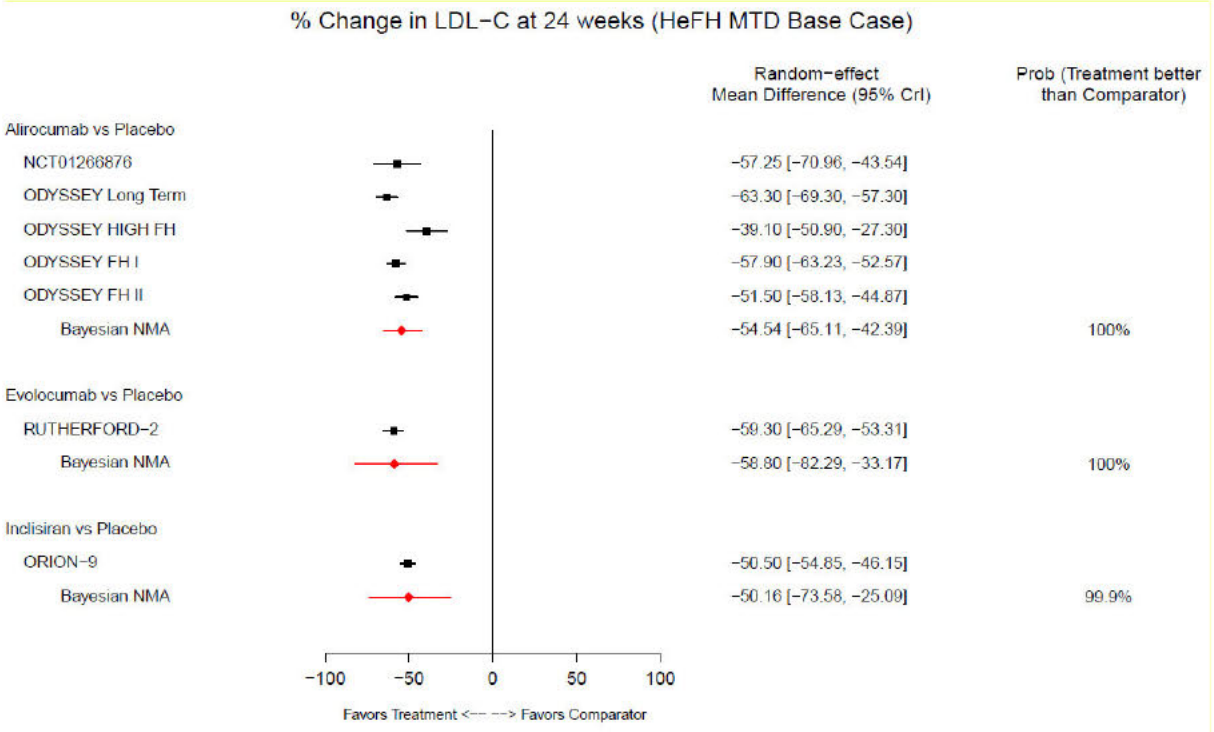

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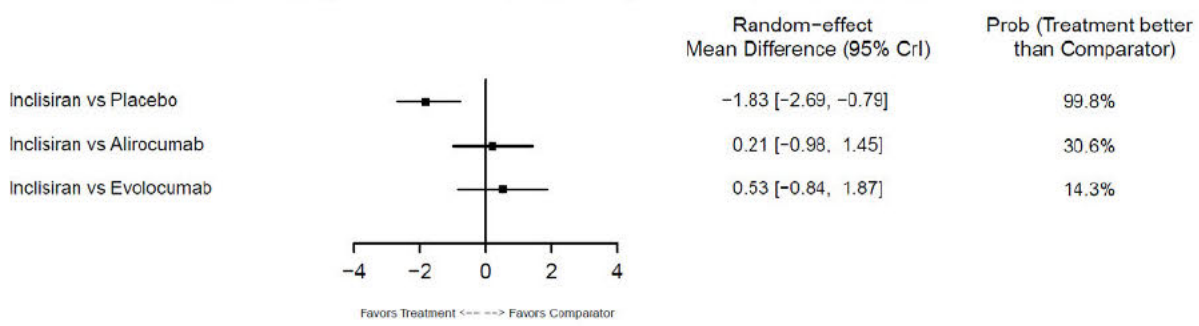
Absolute Change in LDL-C at 24 weeks (HeFH MTD Base Case) in mmol/L



tau = 12.510

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Red = Bayesian NMA results

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AEs and SAEs

Table 57 Indirect comparisons of studies comparing inclisiran to alirocumab for patients with HeFH

Indirect comparisons of studies comparing inclisiran to alirocumab for patients with HeFH									
Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference (%-points)	CI	*P* value	Difference	CI	*P* value		
Proportion of patients with an AE	Odyssey FH I, Odyssey FH II, Odyssey HIGH FH, ORION-9	6.610	-3.110;16.329	NA	1.091	0.960;1.241	0.18222	See Appendix M – Statistical methods.	No
Proportion of patients with an SAE	Odyssey FH I, Odyssey FH II, Odyssey HIGH FH, ORION-9	-6.356	-13.544;0.832	NA	0.537	0.275;1.047	0.0680	See Appendix M – Statistical methods.	No

AE, adverse event, CI, confidence interval; NA, not applicable; SAE, serious adverse event

Figure 28 HeFH population. Differences in AEs – alirocumab versus placebo.

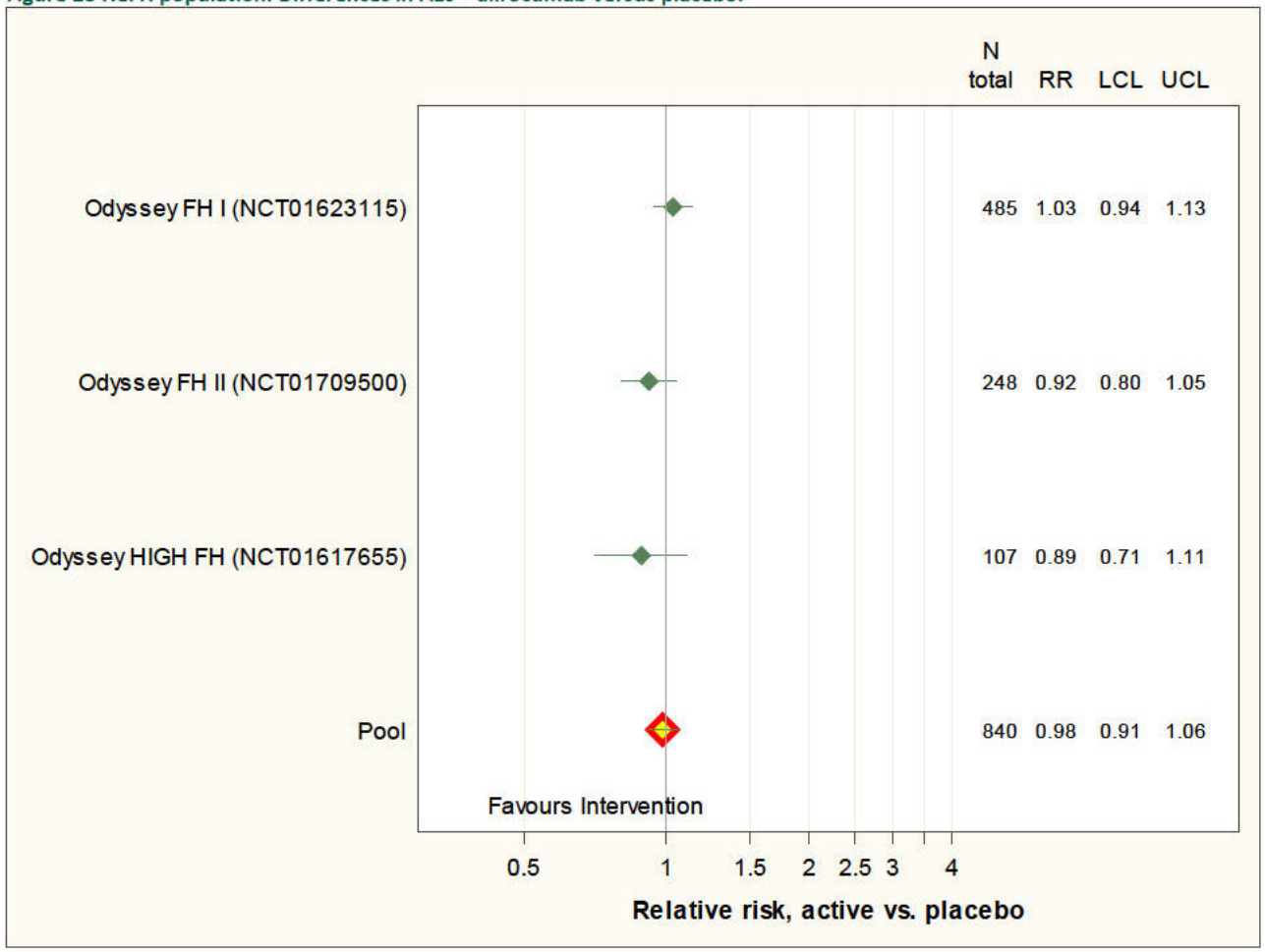
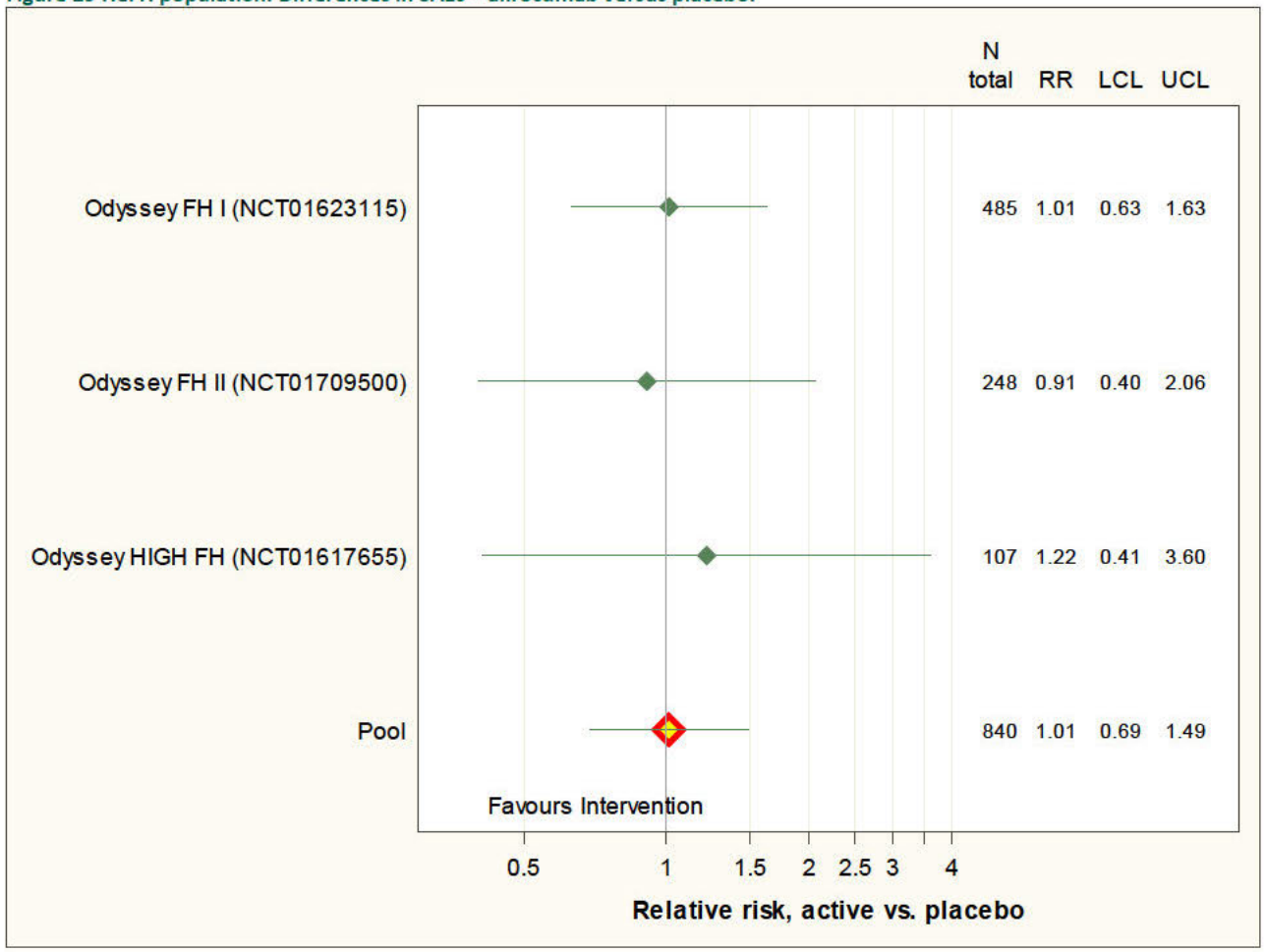


Figure 29 HeFH population. Differences in SAEs – alirocumab versus placebo.



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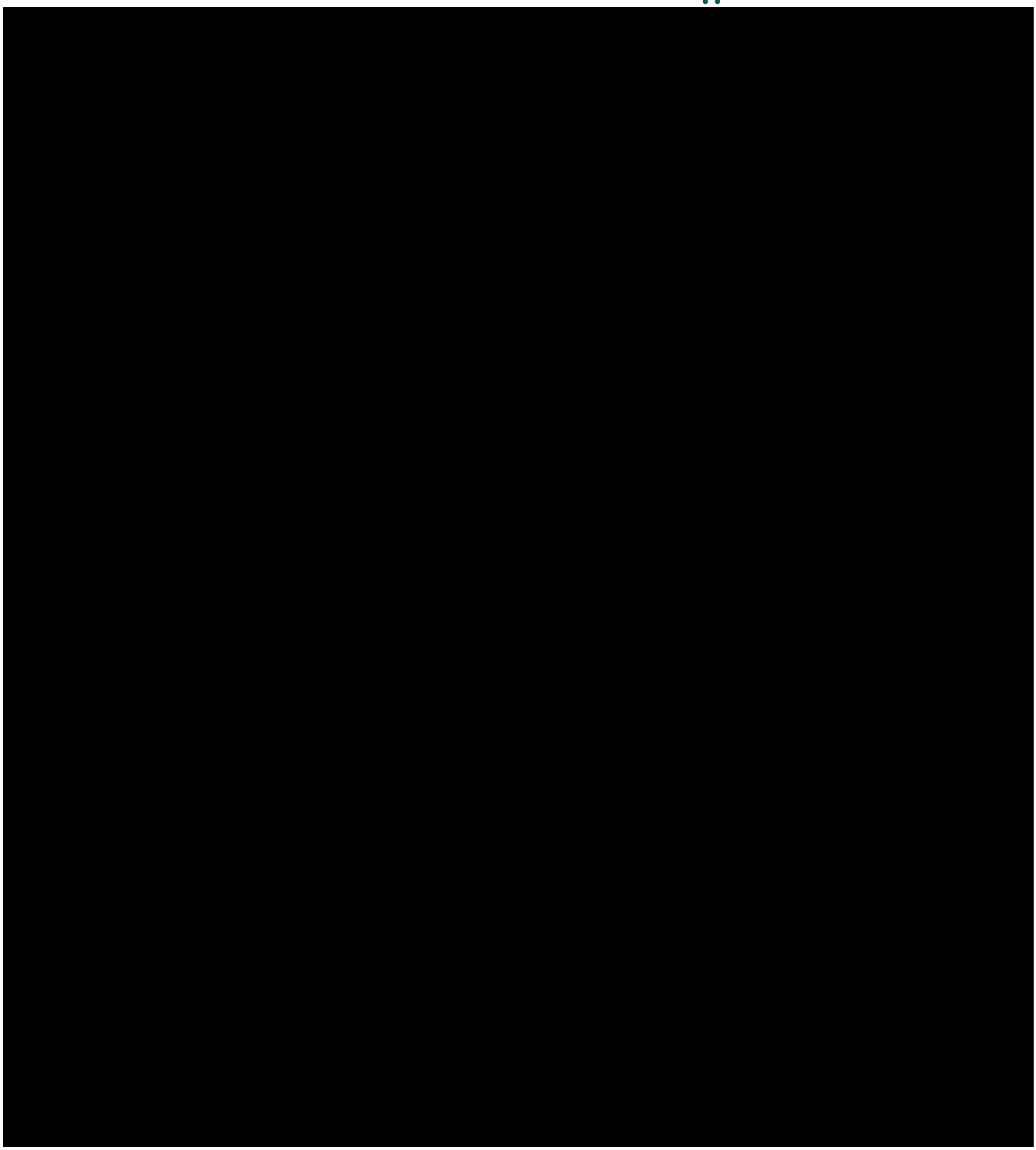

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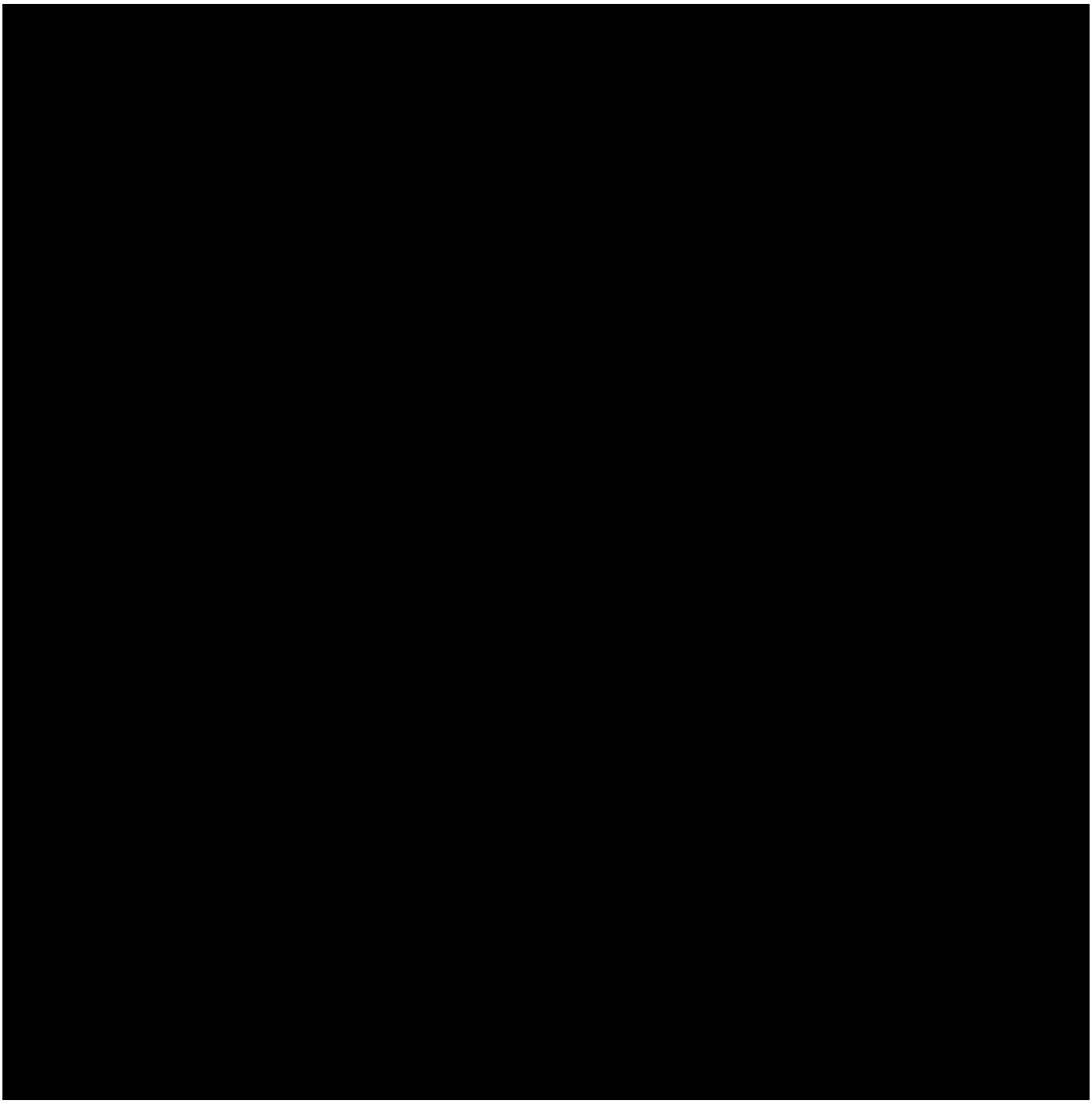

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AEs and SAEs

Table 58 Indirect comparisons of studies comparing inclisiran to alirocumab for patients with ASCVD and risk equivalent

Indirect comparisons of studies comparing inclisiran to alirocumab for patients with ASCVD and risk equivalent									
Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference (%-points)	CI	*P* value	Difference	CI	*P* value		
Proportion of patients with an AE	Odyssey Combo I, Odyssey Long Term, Odyssey Outcomes, ORION-10, ORION-11	1.482	-1.569;4.533	NA	1.020	0.981;1.061	0.3128	See Appendix M – Statistical methods.	No
Proportion of patients with an SAE	Odyssey Combo I, Odyssey Long Term, Odyssey Outcomes, ORION-10, ORION-11	-0.503	-3.656;2.650	NA	0.976	0.853;1.118	0.7294	See Appendix M – Statistical methods.	No

AE, adverse event, CI, confidence interval; NA, not applicable; SAE, serious adverse event

Table 59 Indirect comparisons of studies comparing inclisiran to evolocumab for patients with ASCVD and risk equivalent

Indirect comparisons of studies comparing inclisiran to evolocumab for patients with ASCVD and risk equivalent									
Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference (%-points)	CI	*P* value	Difference	CI	*P* value		
AE, proportion	Fourier, ORION-10, ORION-11	0.100	-2.902;3.101	NA	1.002	0.965 ; 1.041	0.916	See Appendix M – Statistical methods.	No
SAE, proportion	Fourier, ORION-10, ORION-11	-2.003	-5.116;1.110	NA	0.915	0.801 ; 1.045	0.190	See Appendix M – Statistical methods.	No

AE, adverse event, CI, confidence interval; NA, not applicable; SAE, serious adverse event

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Figure 42 ASCVD and risk equivalent population. Differences in AEs – alirocumab versus placebo.

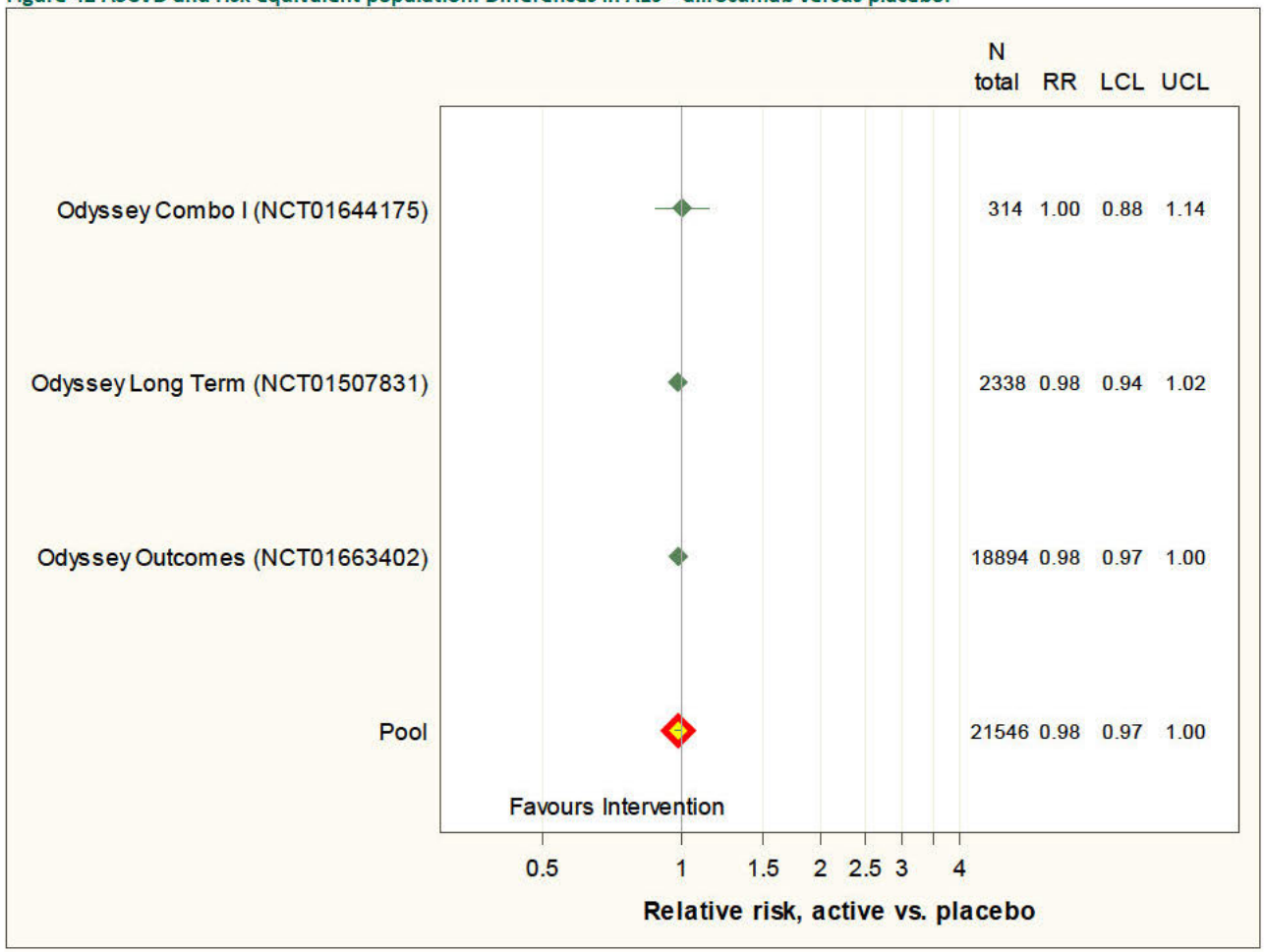

Figure 43 ASCVD and risk equivalent population. Differences in AEs – inclisran versus placebo.

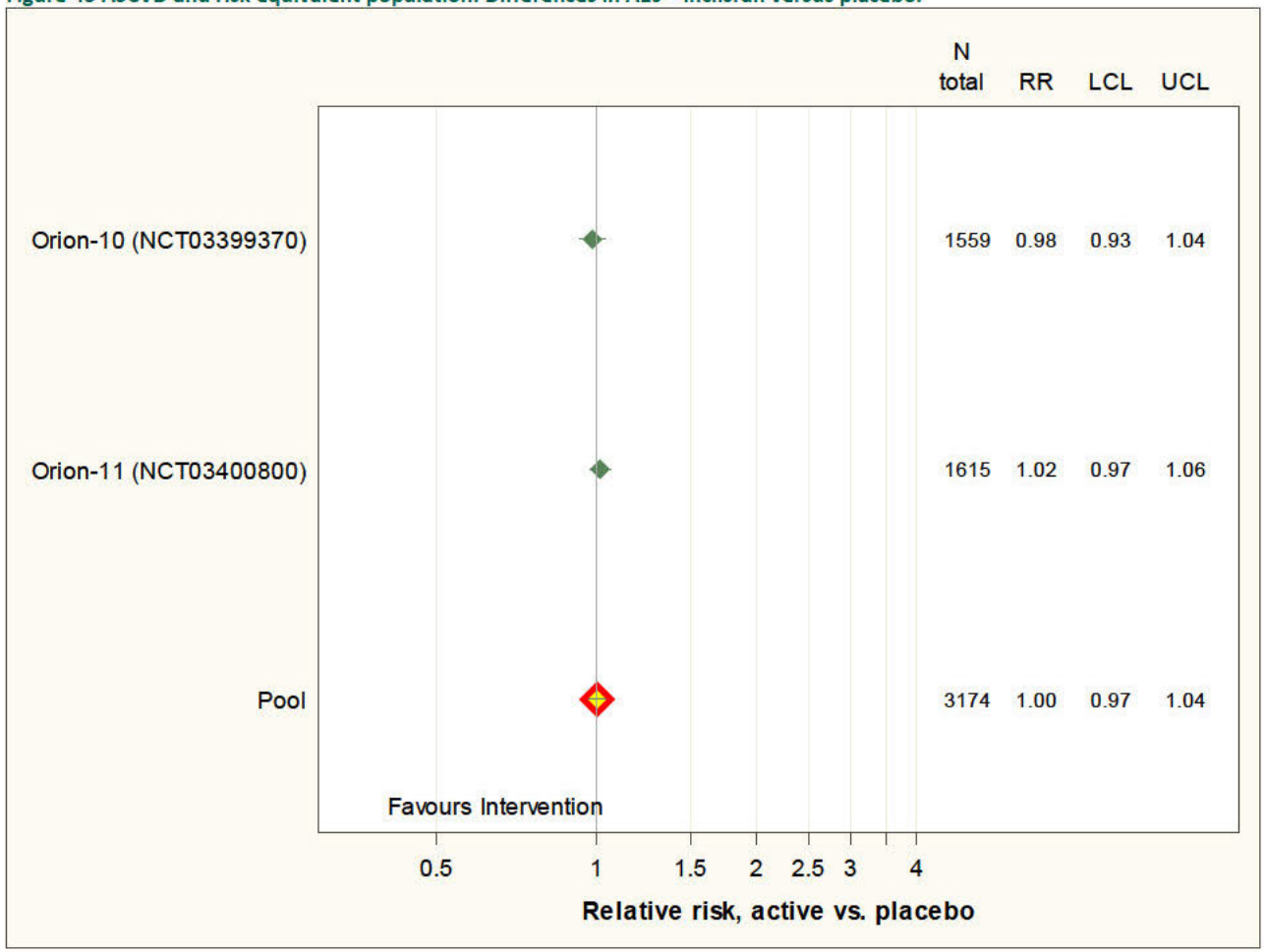

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Figure 44 ASCVD and risk equivalent population. Differences in SAEs – alirocumab versus placebo.

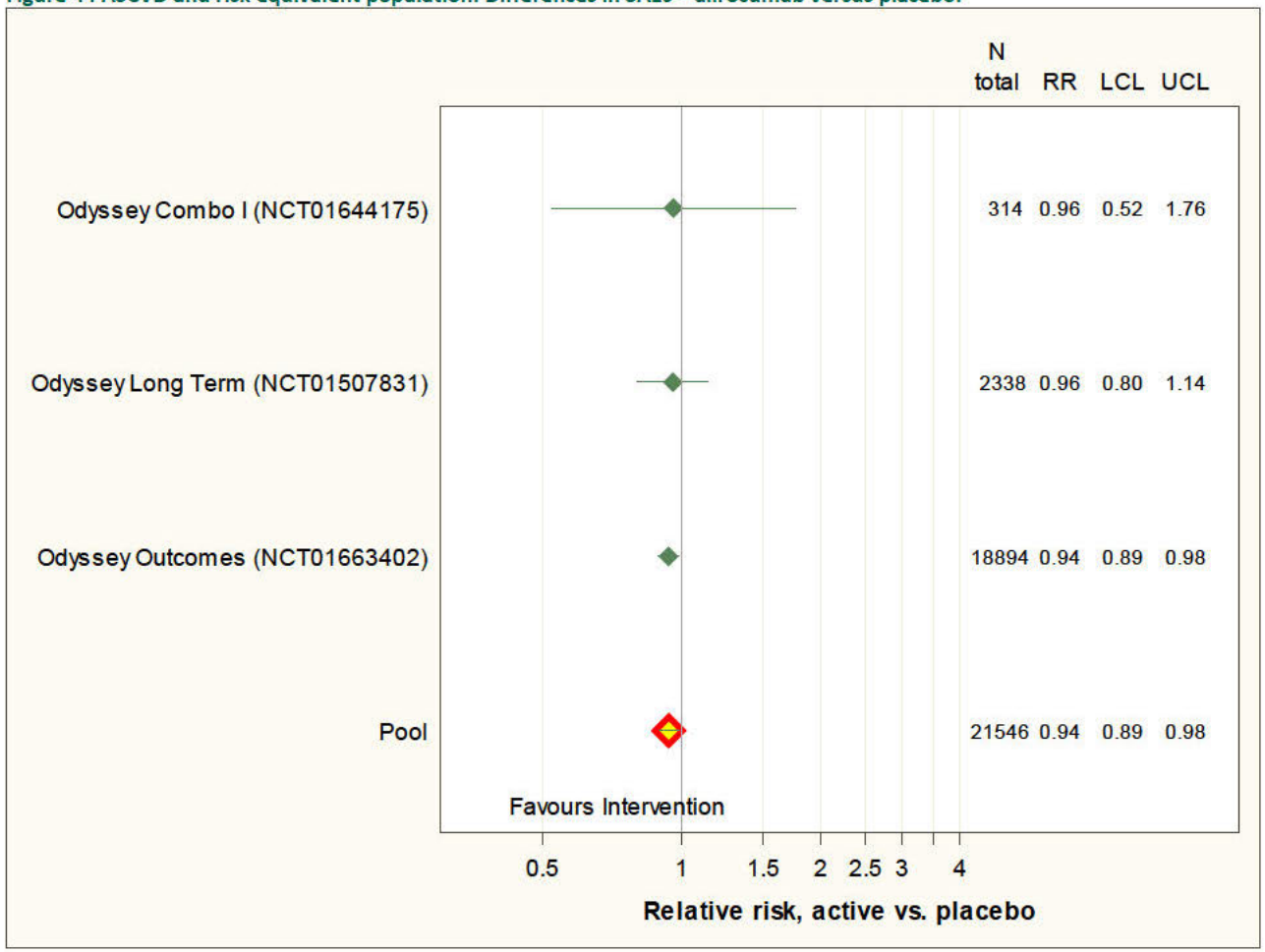

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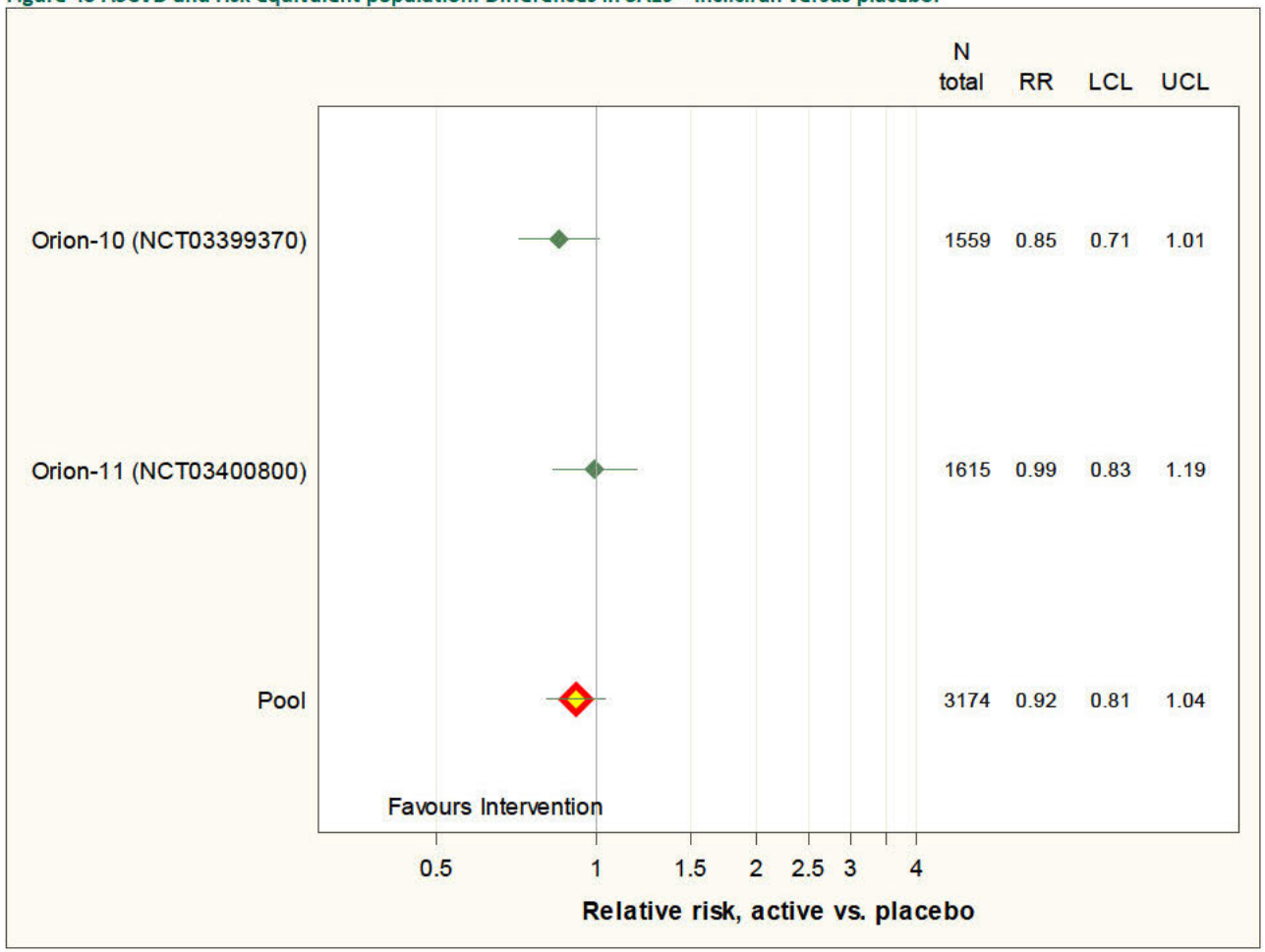
Figure 45 ASCVD and risk equivalent population. Differences in SAEs – incliciran versus placebo.



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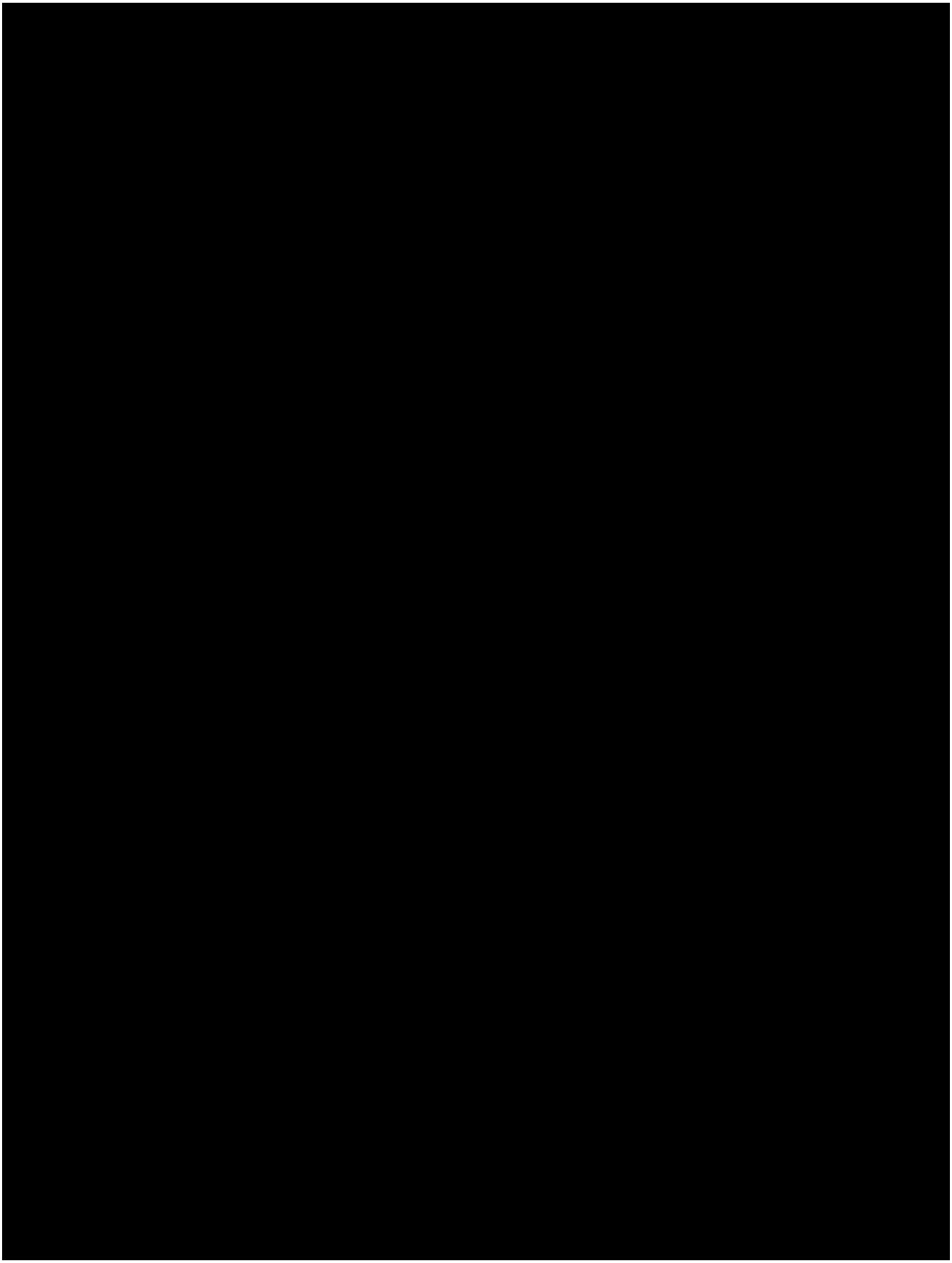

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Appendix G – Extrapolation

Not applicable. Please find the rationale in section 8.2.

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Appendix H – Literature search for HRQoL data

Not applicable. Please find the rationale in section 8.2.

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Appendix I Mapping of HRQoL data

Not applicable. Please find the rationale in section 8.2.

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Appendix J Probabilistic sensitivity analyses

Not applicable. Please find the rationale in section 8.2.

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Appendix K – EPAR inclisiran

The EPAR for inclisiran is available here and sent as a separate file.

leqvio-epar-public-assessment-report_e

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Appendix L – NMA report

The NMA report and the statistical analyssis plan are available here and sent as separate files:

[redacted]

EVM-29194_NMA Technical Report_21C

Appendix A_SAP.pdf

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Appendix M – Statistical methods

Statistical methods: inclisiran versus active comparators.

The endpoints considered were of two types:

- binary (fractions)
- continuous outcomes

There were four treatment arms involved (inclisiran, alirocumab, evolocumab and placebo).
Direct comparison was only possible for inclisiran versus placebo.
For the comparisons of versus either of the active arms, in selected patient subgroups and outcome,
the main approach was the same in every case.

For a given endpoint in the relevant selection of studies (considering outcome and subgroup of patients), the following steps were performed:

1) a meta-analysis of inclisiran versus placebo studies
2) a meta-analysis of active comparator versus placebo studies
3) a direct comparison of the meta-pools of inclisiran versus placebo and active comparator versus placebo

In general some simple pre-processing imputation was done on published data in cases where no doubt existed as to the relevant procedure: missing standard errors were derived from reported standard deviations and the number of patients, and missing proportions (and 95% CI') were derived from the number of events and patients. For fractions, a missing risk-ratio could then be derived in almost every case, including a confidence interval.

For the within study analyses of fractions, the incidences and 95% confidence intervals were found as exact Clopper-Pearson intervals, whereas risk differences were derived directly as Newcombe intervals, since the general principle of finding the absolute difference as $(RR - 1)*P_0$ where RR is the risk/effect ratio and P_0 is the normal comparator level in Danish setting for the given endpoint, could not be used in the present setup. It has not been possible for the applicant to establish the P_0 values.

Note that in some case one or two compared fractions were 0. In this case the procedure of Agresti and Caffo (2000), see above, was followed (the method of 4 ghosts in their terminology)[63].

The between study comparisons of inclisiran and active treatments were performed using Bucher's method. The calculations were based on the log-transformed scale for rates and fractions - and then transformed back to present estimates and confidence intervals as ratios.

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