

Review proposal of TA393/TA394: alirocumab/evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

TA393 and TA394 were published in June 2016 and scheduled to be considered for review in 2019.

1. Proposal

The guidance should be transferred to the 'static guidance list'.

2. Rationale

Alirocumab (TA393) and evolocumab (TA394) were recommended in 2016 for people with primary non-familial hypercholesterolaemia, primary heterozygous-familial hypercholesterolaemia and mixed dyslipidaemia only if certain low-density cholesterol (LDL-C) concentration levels are met or if the person has a high risk of cardiovascular risk.

The recommendations were optimised because the cost-effectiveness estimates for both alirocumab and evolocumab for the whole population were above the range normally considered a cost-effective use of NHS resources.

In both appraisals a key uncertainty was the modelling of cardiovascular events because this was not an outcome recorded in the clinical trials. Instead a surrogate outcome, LDL-C concentration, was used to estimate the rate of cardiovascular events using data from clinical trials for statin therapies. Therefore, in TA393 and TA394, research recommendations were made because long term clinical effectiveness data for these technologies on reducing cardiovascular events was not available but that clinical trials were ongoing (ODYSSEY outcomes for alirocumab, FOURIER for evolocumab). The results from FOURIER have confirmed that evolocumab reduces LDL-C concentration as well as the risk of cardiovascular events¹. After adjusting for treatment duration, the cardiovascular outcomes results from FOURIER are consistent with those observed with statin therapies². The results from ODYSSEY have also demonstrated a significant reduction in cardiovascular events, with the best benefit found in the subgroup of patients with the highest serum level of LDL-C³. Therefore these trials are unlikely to change the recommendations in TA393 and TA394.

Sanofi (alirocumab) and Amgen (evolocumab) have not indicated any future changes to the commercial arrangements for these technologies. Alirocumab and evolocumab were selected by Accelerated Access Collaborative for rapid-uptake within the NHS because they are high-potential technologies.

Based on this information a review of the guidance would not provide value for the NHS.

3. Summary of new evidence and implications for review

The search strategies from the original Assessment reports were adapted for the Cochrane Library, Medline, Medline In-Process and Embase. References from 15th May 2015 (TA393) / 1st March 2015 (TA394) to 24th June 2019 were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed below. See Appendix C for further details of ongoing and unpublished studies.

Has there been any change to the price of the technologies since the guidance was published?

No.

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

No. There have been license extensions granted for both evolucumab and alirocumab to include 'adults with established atherosclerotic cardiovascular disease'. The extension for evolucumab was considered at topic selection (ID1131) but it was decided that an appraisal of this topic would not add value for the NHS.

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

The clinical trial data included in the original submissions for TA393 and TA394 included LDL-C concentration. This was used as a surrogate endpoint for cardiovascular outcomes because the trials were not statistically powered to measure differences in cardiovascular outcomes. The committee concluded that although it was reasonable to infer that evolucumab and alirocumab would reduce cardiovascular disease on the basis of the surrogate outcomes, the extent of the reduction was uncertain, particularly with low concentrations of LDL-C.

The FOURIER randomised controlled trial (n=27,564) included people with atherosclerotic cardiovascular disease and LDL-C levels of 1.8 mmol/L or more who were receiving statin therapy. It provided data on cardiovascular outcomes for evolucumab. Evolocumab lowered LDL-C levels by 59% from baseline levels compared with placebo, from a median of (2.4 mmol/L to 0.78 mmol/L). Compared with placebo evolucumab significantly reduced the risk of the primary endpoint (composite of cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina or coronary revascularization; hazard ratio, 0.85; 95% CI, 0.79 to 0.92). The results were consistent across key subgroups, including patients in the lowest quartile for baseline LDL cholesterol levels (1.9 mmol/L).

The ODYSSEY Outcomes randomised controlled trial (n=18,924) included people with acute coronary syndrome. It provided data on cardiovascular outcomes (median follow-up was 2.8 years). The primary end point was a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. Alirocumab significantly reduced the risk of the primary endpoint compared with placebo (hazard ratio, 0.85; 95% confidence interval [CI], 0.78 to 0.93). The absolute benefit of alirocumab with respect to the composite primary end point was greater among patients who had a baseline LDL cholesterol level of 2.6 mmol/L or more than among patients who had a lower baseline level.

Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?

Yes, see Appendix C. No implications anticipated.

Additional comments

ID1515 bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia has been scoped as part of Batch 65. A referral from the DHSC is yet to be received.

4. Equality issues

None.

Proposal paper sign off

Jasdeep Hayre – Associate Director, Technology Appraisals

19 July 2019

Contributors to this paper

Guidance Information Specialist: Tom Hudson

Technical Analyst: Luke Cowie

Associate Director: Jasdeep Hayre

Project Manager: Emily Richards

Appendix A – Information from existing guidance

1. Original remit

TA394: *“To appraise the clinical and cost effectiveness of evolocumab within its marketing authorisation for treating primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia”.*

TA393: *“To appraise the clinical and cost effectiveness of alirocumab within its marketing authorisation for treating primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia”.*

2. Current guidance

TA394:

1.1 Evolocumab is recommended as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia, only if:

- The dosage is 140 mg every 2 weeks.
- Low-density lipoprotein concentrations are persistently above the thresholds specified in table 1 despite maximal tolerated lipid-lowering therapy. That is, either the maximum dose has been reached, or further titration is limited by intolerance (as defined in NICE's guideline on [familial hypercholesterolaemia](#)).
- The company provides evolocumab with the discount agreed in the patient access scheme.

1.2 This guidance is not intended to affect the position of patients whose treatment with evolocumab was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

Table 1. Low-density lipoprotein cholesterol concentrations above which evolocumab is recommended

	Without CVD	With CVD	
		High risk of CVD ¹	Very high risk of CVD ²
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C concentration is persistently above 4.0 mmol/litre	Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre
Primary heterozygous-familial hypercholesterolaemia	Recommended only if LDL-C concentration is persistently above 5.0 mmol/litre	Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre	

¹ High risk of CVD is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; coronary heart disease; ischaemic stroke; peripheral arterial disease.

² Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).

Abbreviations: CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

TA393:

1.1 Alirocumab is recommended as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia, only if:

- Low-density lipoprotein concentrations are persistently above the thresholds specified in table 2 despite maximal tolerated lipid-lowering therapy. That is, either the maximum dose has been reached or further titration is limited by intolerance (as defined in NICE's guideline on [familial hypercholesterolaemia: identification and management](#)).
- The company provides alirocumab with the discount agreed in the patient access scheme.

1.2 This guidance is not intended to affect the position of patients whose treatment with alirocumab was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

Table 2. Low-density lipoprotein cholesterol concentrations above which alirocumab is recommended

	Without CVD	With CVD	
		High risk of CVD ¹	Very high risk of CVD ²
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C concentration is persistently above 4.0 mmol/l	Recommended only if LDL-C concentration is persistently above 3.5 mmol/l
Primary heterozygous-familial hypercholesterolaemia	Recommended only if LDL-C concentration is persistently above 5.0 mmol/l	Recommended only if LDL-C concentration is persistently above 3.5 mmol/l	

¹High risk of cardiovascular disease is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina requiring hospitalisation), coronary or other arterial revascularisation procedures, coronary heart disease, ischaemic stroke, peripheral arterial disease.

²Very high risk of cardiovascular disease is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).

Abbreviations: CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

3. Research recommendations from original guidance

TA394: *“The committee was aware that an ongoing randomised controlled trial, FOURIER, would test whether or not low-density lipoprotein cholesterol (LDL-C) is a viable surrogate for cardiovascular outcomes for evolocumab. The committee agreed that this trial would give useful data on the direct effect of evolocumab on cardiovascular disease”.*

TA393: *“The committee was aware that an ongoing randomised controlled trial exploring the occurrence of cardiovascular events of alirocumab compared with placebo are available is expected in 2018. The committee agreed that this trial would give useful data on the direct effect of alirocumab on cardiovascular disease”.*

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – ‘Yes/No’
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the Technology Appraisal process.	A review of the appraisal will be planned into the NICE’s work programme.	No
The decision to review the guidance should be deferred to a specific date or trail is available.	NICE will reconsider whether a review is necessary at the specified date.	No
The guidance should be incorporated into an on-going clinical guideline.	<p>The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review.</p> <p>This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.</p>	No
The guidance should be updated in an on-going clinical guideline ¹ .	<p>Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn.</p> <p>Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).</p>	No

¹ Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the [guide to the processes of technology appraisal](#).

Options	Consequence	Selected – ‘Yes/No’
<p>The guidance should be transferred to the ‘static guidance list’.</p>	<p>The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider.</p>	<p>Yes</p>
<p>The guidance should be withdrawn</p>	<p>The guidance is no longer relevant, and an update of the existing recommendations would not add value to the NHS.</p> <p>The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.</p>	<p>No</p>

Appendix C – Other relevant information

Relevant Institute work

Published

Cardiovascular disease: risk assessment and reduction, including lipid modification (2014 updated 2016) NICE guideline CG181

Familial hypercholesterolaemia: identification and management (2008 updated 2017) NICE guideline CG71

Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (2016) NICE technology appraisal guidance 385

Cardiovascular risk assessment and lipid modification (2015) NICE quality standard 100

Familial hypercholesterolaemia (2013 updated 2017) NICE quality standard 41

Cardiovascular disease prevention (2017) NICE pathway

Familial hypercholesterolaemia (2017) NICE pathway

In progress

Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia. NICE Technology Appraisal. Publication expected: TBC.

Details of changes to the marketing authorisation for the technology

Marketing authorisation and price considered in original appraisal

TA394 (Evolocumab):

“Adults with primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin, or a statin plus 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 cannot tolerate or cannot be given statins”.*

The list price for evolocumab at the time of the original TA was £170.10 for a 140-mg prefilled pen or syringe (excluding VAT; MIMS, March–May 2016). The company agreed a patient access scheme, based around a simple discount, with the Department of Health. The level of the discount is commercial in confidence.

TA393 (Alirocumab):

“Adults with primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

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

The list price for alirocumab at the time of the original TA was £168 for a 75 mg or 150 mg single-use prefilled pen (excluding VAT; MIMS, January 2016).

The company agreed a patient access scheme, based around a simple discount, with the Department of Health. The level of the discount is commercial in confidence.

Marketing authorisation (for this appraisal) and current price

TA394 (Evolocumab):

In May 2018 the marketing authorisation for evolocumab was extended to cover...

...reduction of cardiovascular risk by lowering LDL-C levels, in adults with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease), as an adjunct to correction of other risk factors:

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

This is in addition to the indication considered in NICE TA394

A marketing authorisation was also granted for a 420 mg solution for injection formulation in 2017. No pricing information was found for this formulation.

The list price for the formulation mentioned in the original appraisal remains unchanged. [BNF online, accessed 12th June 2019]

TA393 (Alirocumab):

In March 2019 a license extension was granted, this covers;

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

- in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or,

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

Alirocumab is in phase III as an adjunctive therapy for homozygous familial hypercholesterolaemia (hoFH) in children aged 8-17 years.

The list price for the formulation mentioned in the original appraisal remains unchanged. [C+D data online, accessed 12th June 2019]

Registered and unpublished trials

Trial name and registration number	Details
Evolocumab	
<p>A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate the Impact of Evolocumab on Major Cardiovascular Events in Patients at High Cardiovascular Risk Without Prior Myocardial Infarction or Stroke</p> <p>NCT03872401; VESALIUS-CV; 20170625; 2018-004565-14</p>	<p>n = 13000</p> <p>Estimated completion date: May 2024</p> <p>Currently recruiting</p>
<p>A Multicenter, Open-label, Single-arm, Extension Study to Assess Long-term Safety of Evolocumab Therapy in Patients With Clinically Evident Cardiovascular Disease</p> <p>NCT02867813; FOURIER OLE; 20130295; 2015-004780-36</p>	<p>Extension study to FOURIER trial</p> <p>n = 5037</p> <p>Estimated completion date: September 2021</p> <p>Status: active, not recruiting</p>
<p>A Multicenter, Open-label, Single-arm, Extension Study to Assess Long-term Safety of Evolocumab Therapy in Subjects With Clinically Evident Cardiovascular Disease in Selected European Countries</p> <p>NCT03080935; 20160250; 2016-004066-26; FOURIER OLE</p>	<p>Extension study to FOURIER trial</p> <p>n = 1600</p> <p>Active, not recruiting</p> <p>Estimated completion date: December 2022</p>
<p>A Multicenter, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Evolocumab</p> <p>NCT02304484; 20140128; 2014-001524-30</p>	<p>Extension study for people who have completed the GLAGOV trial</p> <p>n = 770</p> <p>Completed, March 2018</p> <p>Results available at clinicaltrials.gov</p>
<p>A Randomized Trial of Evolocumab on Saphenous Vein Graft Patency Following Coronary Artery Bypass Surgery</p> <p>NEWTON-CABG</p>	<p>Trial of graft occlusion and (cardiovascular) mortality at two years</p> <p>n = 766</p> <p>Currently recruiting</p> <p>Estimated completion date: December 2023</p>

Trial name and registration number	Details
<p>A Double Blind, Randomized, Placebo Controlled, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy on LDL-C of Evolocumab (AMG 145) in Subjects With HIV and With Hyperlipidemia and/or Mixed Dyslipidemia</p> <p>NCT02833844; 20130286; 2015-004735-12</p>	<p>n = 467</p> <p>Active, not recruiting</p> <p>Estimated completion date: July 2019 (primary outcome); January 2020 (overall)</p>
<p>A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety and Efficacy of Evolocumab (AMG 145) in Addition to Optimal Stable Background Statin Therapy in Chinese Subjects With Primary Hypercholesterolemia and Mixed Dyslipidemia</p> <p>NCT03433755; 20150172</p>	<p>n = 450</p> <p>Currently recruiting</p> <p>Estimated completion date: October 2020</p>
<p>A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of Evolocumab (AMG 145) on LDL-C in Combination With Statin Therapy in Japanese Subjects With High Cardiovascular Risk and With Hyperlipidemia or Mixed Dyslipidemia</p> <p>NCT01953328; AMG145; 20120122</p>	<p>n = 409</p> <p>Completed, June 2014</p> <p>Results available at clinicaltrials.gov</p>
<p>EVOlocumab for Early Reduction of LDL-cholesterol Levels in Patients With Acute Coronary Syndromes (EVOPACS) - A Randomized, Double-blind, Placebo-controlled Multicenter Study</p> <p>NCT03287609; EVOPACS; 2017-01753</p>	<p>n = 308</p> <p>Active, recruiting</p> <p>Estimated completion date: May 2019 (primary outcome); September 2019 (overall)</p>
<p>High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study</p> <p>NCT03570697; 20160184; 2017-003236-37; HUYGENS</p>	<p>Randomised, placebo-controlled trial</p> <p>n = 150</p> <p>Currently recruiting</p> <p>Estimated completion date: June 2021</p>

Trial name and registration number	Details
<p>Double-blind, Randomized, Multicenter, Placebo-Controlled Study to Characterize the Efficacy, Safety, and Tolerability of 24 Weeks of Evolocumab for LDL-C Reduction in Pediatric Subjects 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia</p> <p>NCT02392559; HAUSER-RCT; 20120123; 2014-002277-11</p>	<p>n = 159</p> <p>Active, not recruiting</p> <p>Estimated completion date: November 2019</p> <p>Single arm follow-up study due to complete in June 2021</p>
<p>EVOLVD: Cholesterol Lowering With EVOLocumab to Prevent Cardiac Allograft Vasculopathy in De-novo Heart Transplant Recipients</p> <p>NCT03734211; EVOLVD; 2017-005097-19</p>	<p>Randomised, placebo-controlled trial</p> <p>n = 130</p> <p>Not yet recruiting</p> <p>Estimated completion date: October 2021 (primary outcome); December 2021 (overall)</p>
<p>EXpanded Combination of Evolocumab Plus Empagliflozin on Diabetes: EXCEED-BHS3 Trial</p> <p>NCT03932721; EXCEED-BHS3</p>	<p>Randomised trial of evolocumab as add-on to antidiabetic therapy</p> <p>n = 110</p> <p>Currently recruiting</p> <p>Estimated completion date: June 2020 (primary outcome); October 2020 (overall)</p>
<p>Impact of the PCSK9 Inhibitor Evolocumab on the Pharmacodynamic Effects of Clopidogrel in Patients With Atherosclerotic Cardiovascular Disease and High On-Treatment Platelet Reactivity</p> <p>NCT03096288; IIS AMG001</p>	<p>Randomised, placebo-controlled trial</p> <p>n = 90</p> <p>Status given as “currently recruiting”</p> <p>Estimated completion date: June 2019 (primary outcome); September 2019 (overall)</p>
<p>Randomized, Double-blind, Placebo Controlled, Parallel-group, Prospective Clinical Study to Analyse the Effect of Evolocumab on Vascular Function</p> <p>NCT03626831; EVO; CRC2017EVO</p>	<p>n = 65</p> <p>Not yet recruiting</p> <p>Estimated completion date: December 2019 (primary outcome); August 2020 (overall)</p>

Trial name and registration number	Details
<p>A Double-blind, Randomized, Multicenter Study to Evaluate the Safety and Efficacy of Evolocumab, Compared With Ezetimibe, in Hypercholesterolemic Japanese Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor Due to Muscle Related Side Effects</p> <p>NCT02634580; GAUSS-4; 20140234</p>	<p>n = 61</p> <p>Completed, May 2018</p> <p>Results available at clinicaltrials.gov</p>
<p>Effect of Evolocumab on Carotid Plaque Composition in Asymptomatic Carotid Artery Stenosis</p> <p>NCT03931161; EVOCAR-1</p>	<p>Randomised, placebo-controlled trial</p> <p>n = 60</p> <p>Not yet recruiting</p> <p>Estimated completion date: April 2023</p>
<p>The Effects of Evolocumab on Endothelial and Inflammatory Biocellular Markers in Patients With Myocardial Microvascular Dysfunction</p> <p>NCT03829046; GCO 18-1412; 20167719</p>	<p>Randomised, controlled trial of evolocumab vs. placebo</p> <p>n = 40</p> <p>Not yet recruiting</p> <p>Estimated completion date: October 2020</p>
<p>A Randomized, Actively Controlled, Open-label, Multicenter Study of Efficacy and Safety of Evolocumab Compared With Low Density Lipoprotein Cholesterol (LDL-C) Apheresis, Followed by Single-Arm Evolocumab Administration in Subjects Receiving LDL-C Apheresis Prior to Study Enrollment</p> <p>NCT02585895; 20140316 2015-001343-37</p>	<p>n = 39</p> <p>Completed, January 2017</p> <p>Results available at clinicaltrials.gov</p>
<p>A Multicenter, Randomized, Double-blind, Placebo-controlled, Crossover Trial to Evaluate the Effects of Evolocumab Added to Standard Lipid-lowering Therapy on Fasting and Post Fat Load Lipids in Patients With Familial Dysbetalipoproteinemia</p> <p>NCT03811223; EVOLVE-FD; UMCU-VASC-CO-002</p>	<p>n = 30</p> <p>Not yet recruiting</p> <p>Estimated completion date: January 2021 (primary outcome); March 2021 (overall)</p>

Trial name and registration number	Details
Impact of LDL-cholesterol Lowering on Platelet Activation NCT03331666; AAAR1041	Evolocumab vs. placebo n = 22 Not yet recruiting Estimated completion date: February 2020 (primary outcome); June 2020 (overall)
Alirocumab	
A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of Praluent on Neurocognitive Function in Patients With Heterozygous Familial Hypercholesterolemia or With Non-Familial Hypercholesterolemia at High and Very High Cardiovascular Risk NCT02957682; R727-CL-1532; 2016-003189-16	n = 2176 Estimated completion date: March 2020 (primary outcome); May 2020 (overall) Status: active, not recruiting
Long Term Safety Study of PRALUENT in Patients With Heterozygous Familial Hypercholesterolemia or With Non-Familial Hypercholesterolemia at High and Very High Cardiovascular Risk and Previously Enrolled in the Neurocognitive Function Trial NCT03694197; R727-CL-1609; 2018-002810-11	Single arm study for participants from prior RCT study NCT02957682 n = 1600 Enrolling by invitation. Estimated completion date: November 2023
A Multi-country, Multicenter, Single-arm, Open-label Study to Document the Safety, Tolerability and Effect of Alirocumab on Atherogenic Lipoproteins in High Cardio-vascular Risk Patients With Severe Hypercholesterolemia Not Adequately Controlled With Conventional Lipid-modifying Therapies NCT02476006; LPS14245; 2015-000620-28; U1111-1163-0984; ODYSSEY APPRISE	n = 998 Completed, April 2019

Trial name and registration number	Details
<p>A Randomized, Double-blind, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Ezetimibe in Asia in High Cardiovascular Risk Patients With Hypercholesterolemia Not Adequately Controlled With Their Statin Therapy</p> <p>NCT02715726; ODYSSEY EAST; EFC13889; U1111-1150-8859</p>	<p>n = 615</p> <p>Completed, August 2018</p>
<p>Effects of the PCSK9 Antibody AliroCuMab on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction: A Serial, Multivessel, Intravascular Ultrasound, Near-Infrared Spectroscopy And Optical Coherence Tomography Imaging Study</p> <p>NCT03067844; PACMAN-AMI; 2016-01382</p>	<p>Randomised controlled trial</p> <p>n = 220</p> <p>Currently recruiting</p> <p>Estimated completion date: December 2019 (primary outcome); March 2021 (overall)</p>
<p>A Randomized, Open-label, Blinded Intravascular Ultrasound Analysis, Parallel Group, Multicenter Study to Evaluate the Effect of Praluent® (Alirocumab) on Coronary Atheroma Volume in Japanese Patients Hospitalized for Acute Coronary Syndrome With Hypercholesterolemia Not Adequately Controlled With Statin</p> <p>NCT02984982; ODYSSEY J-IVUS; ALIROL08069; U1111-1184-8764</p>	<p>n = 208</p> <p>Completed, July 2018</p>
<p>A Randomized, Double-Blind, Placebo-Controlled Study Followed by an Open Label Treatment Period to Evaluate the Efficacy and Safety of Alirocumab in Children and Adolescents With Heterozygous Familial Hypercholesterolemia</p> <p>NCT03510884; EFC14643; 2017-001903-60; U1111-1193-0721</p>	<p>n = 150</p> <p>Currently recruiting</p> <p>Estimated completion date: February 2022</p>
<p>Effect of PCSK9 Inhibition on Cardiovascular Risk in Treated HIV Infection (EPIC-HIV Study)</p> <p>NCT03207945; EPIC-HIV; 17-22800</p>	<p>Randomised, controlled trial of alirocumab vs. placebo</p> <p>n = 140</p> <p>Currently recruiting</p> <p>Estimated completion date: November 2021</p>

Trial name and registration number	Details
<p>Effect of Alirocumab on Saphenous Vein Graft Atherosclerosis: The Alirocumab for Stopping Atherosclerosis Progression in Saphenous Vein Grafts (ASAP-SVG) Pilot Trial</p> <p>NCT03542110; ASAP-SVG; ASAP-SVG, QR#32711/1</p>	<p>Randomised, placebo-controlled trial</p> <p>n = 138</p> <p>Enrolling by invitation</p> <p>Estimated completion date: February 2021 (primary outcome); March 2021 (overall)</p>
<p>A RaNdomized Double-blInd Placebo ConTrolled Study Characterizing The Effects of PCSK9 Inhibition On Arterial Wall Inflammation in Patients With Elevated Lp(a) (ANITSCHKOW)</p> <p>NCT02729025; ANITSCHKOW; 20130293; 2015-003731-35</p>	<p>n = 129</p> <p>Completed, April 2019</p> <p>Results available at clinicaltrials.gov</p>
<p>A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Alirocumab in Patients With Homozygous Familial Hypercholesterolemia</p> <p>NCT03156621; ODYSSEY HoFH; R727-CL-1628 2017-000351-95</p>	<p>n = 74</p> <p>Currently recruiting</p> <p>Estimated completion date: September 2019 (primary outcome); February 2020 (overall)</p>
<p>INvestigating the Lowest Threshold of Vascular bENefits From LDL Cholesterol Lowering With a PCSK9 mAb InhibiTor (Alirocumab) in Patients With Stable Cardiovascular Disease</p> <p>NCT03355027; INTENSITY-HIGH</p>	<p>Randomised, controlled trial of alirocumab vs. ezetimibe</p> <p>n = 60</p> <p>Status given as “currently recruiting”</p> <p>Estimated completion date: March 2019 (primary outcome); May 2019 (overall)</p>
<p>A Double Blind, Randomized Trial of Alirocumab and Plaque Regression in Peripheral Arterial Disease</p> <p>NCT02959047; 19404</p>	<p>Alirocumab vs. placebo</p> <p>n = 54</p> <p>Currently recruiting</p> <p>Estimated completion date: July 2020 (primary outcome); July 2021 (overall)</p>
<p>Arterial wall inflammation measured with 18F-FDG PET/CT in patients with statin intolerance before and after treatment with a PCSK-9 inhibitor</p> <p>2016-004794-41; Vista</p>	<p>Alirocumab vs. placebo</p> <p>n = 50</p> <p>Estimated completion date: not stated</p>

Trial name and registration number	Details
Effect of Alirocumab(Proprotein Convertase Subtilisin/Kexin type9 Inhibitor) and Rosuvastatin or Rosuvastatin Alone on Lipid Core Plaques in Coronary Artery Disease Evaluated by Near-infrared Spectroscopy Intravascular Ultrasound NCT03529253; ANTARES; 290068	n = 30 Currently recruiting Estimated completion date: September 2020
The Efficacy of Alirocumab for Thin-cap fibroatheroma in Patients With Coronary Artery Disease Estimated by Optical Coherence Tomography: Single Center, Randomized, Open-label, Trial NCT03552432; ALTAIR; KobeU-290017	Placebo-controlled trial n = 24 Currently recruiting Estimated completion date: September 2020 (primary outcome); September 2021 (overall)
Effect of Alirocumab on Postprandial Hyperlipemia in Patients With Type 2 Diabetes : a Randomized, Double-blind, Placebo-controlled, Cross-over Trial NCT03344692; EUTERPE; RC16-0406	n = 24 Currently recruiting Estimated completion date: June 2020
Alirocumab in Patients With Acute Myocardial Infarction: A Randomized Controlled Double-Blinded Study NCT02938949; HM20008008	Placebo-controlled trial n = 20 Completed
Effect of PCSK9-Antibody (Alirocumab) on Dyslipidemia Secondary to Nephrotic Syndrome NCT03004001; VA16-029	Placebo-controlled trial n = 20 Recruitment status unknown Estimated completion date: December 2018
Modulation of postprandial lipemia, inflammation, and vascular function by PCSK9 inhibition in diabetes 2016-003253-15; 58836; PLEIADES-pcsk9	Alirocumab vs. placebo n = 20 Estimated completion date not stated

References

- 1 Sabatine MS et al (2017) Evolocumab and clinical outcomes in patients with cardiovascular disease. The New England Journal of Medicine 376 (1713-1722)
- 2 Landmesser, U et al (2017) 2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia. European Heart Journal. <https://doi.org/10.1093/eurheartj/ehx549>
- 3 Turgeon, RD et al (2018). Cardiovascular Efficacy and Safety of PCSK9 Inhibitors: Systematic Review and Meta-analysis Including the ODYSSEY OUTCOMES Trial. Canadian Journal of Cardiology, 34(12), 1600-1605.