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Clinical evidence review of lomitapide for treating homozygous familial hypercholesterolaemia in adults

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About this clinical evidence review

Clinical evidence reviews provide a summary of the best available evidence for a single technology within a licensed indication for which the responsible commissioner is NHS England. The clinical evidence review supports NHS England in producing clinical policies but is **not NICE guidance or advice**.

Summary

Homozygous familial hypercholesterolaemia (HoFH) is an inherited genetic condition that causes exceptionally high cholesterol levels (including low density lipoprotein cholesterol [LDL-C]) in the blood from birth. It results in premature life-threatening major cardiac events such as heart attack, heart valve disease, stroke, the need for major cardiac surgery, and premature cardiac death.

Lomitapide (Lojuxta, Amryt Pharma) received a marketing authorisation from the European Medicines Agency in July 2013 for use as an adjunct to a low-fat diet and other lipid-lowering medicines with or without lipoprotein apheresis in adults with homozygous familial hypercholesterolaemia.

Evidence review

This evidence review considers lomitapide for the treatment of HoFH in adults. The key effectiveness outcome considered was a reduction in LDL-C. Safety outcomes including adverse events were also considered. The evidence review was undertaken in line with NHS England's methods for undertaking clinical evidence reviews.

A literature search was undertaken, which identified 34 references (see appendix 2 for search strategy). The company also provided a submission of evidence. After applying the inclusion and exclusion criteria, a total of 8 references were included for the clinical evidence review.

Results

The main evidence of the effect of lomitapide comes from a phase 3, single-arm, open-label study, Cuchel et al. 2013 (NCT00730236) that included 29 adults with HoFH. A long-term, uncontrolled, follow-on study of Cuchel et al. 2013 reported by Blom et al. 2017 (n=19) was also included. Another smaller (n=9) phase 3, single-arm, open-label study was included, Harada-Shiba et al. 2017, conducted only in a Japanese population. Other included studies were: 2 single-arm, open-label studies of adults with HoFH:

(Cuchel et al. 2007, a phase 2 dose-escalation [proof of concept], n=6, and Yahya et al. 2016, n=4 patients), and; 3 uncontrolled retrospective studies with small sample sizes (4 to 15 patients) (D'Erasmo et al. 2017, Roeters van Lennep et al. 2015 and Stefanutti et al. 2016).The key outcome reported in all studies was change in LDL-C from baseline to follow-up.

Effectiveness

The main evidence (Cuchel et al. 2013) found that there was a statistically significant reduction of 50% in LDL-C when lomitapide (at maximum tolerated dose) was added to a patient's current fixed lipid lowering treatment after 26 weeks, decreasing mean LDL-C level from 8.7 mmol/L to 4.3 mmol/L. This finding was supported by 2 other studies.

Safety and tolerability

Based on the safety data from the included studies and the summary of product characteristics (SPC) for lomitapide, gastrointestinal-related adverse events (such as diarrhoea, nausea, dyspepsia and vomiting) were the most commonly reported. Most of the adverse events reported were of mild to moderate intensity according to Cuchel et al. 2013. For severe gastrointestinal events, the SPC states that these occur mostly at the start of treatment and are considered manageable for most patients by temporary treatment discontinuation or temporary down titration of the dose. Elevated aminotransferase levels of more than 3 or 5 times the upper limit of normal (ULN) were also very commonly reported. The SPC states that liver aminotransferase abnormalities was the most serious adverse event. Cuchel et al. 2013 reported 34.5% (10/29) of patients had an increase in their aminotransferase levels that were either 3 or 5 times the upper limit of normal. The adverse events were managed by dose reduction or temporarily stopping treatment with lomitapide. Persistent gastrointestinal-related adverse events and continued elevated aminotransferase levels of 3 or 5 times the ULN were reported as reasons for discontinuing treatment with lomitapide.

The studies reported in the evidence review suggest that there is an increased risk of hepatic fat accumulation whilst on treatment with lomitapide. In the

study by Cuchel et al. 2013, 20 patients experienced an increase in mean hepatic fat from 1% at baseline to 8.6% at week 26, and was maintained at 8.3% at week 78. The European public assessment report [EPAR] for lomitapide states that fat accumulation in the liver is a natural consequence of the mechanism of action of lomitapide.

Evidence gaps

People with HoFH have a high risk of cardiovascular disease. The included studies did not report any cardiovascular events as an outcome, however the EPAR for lomitapide states that reduction in LDL-C is considered an important surrogate endpoint with potential benefits in terms of cardiovascular outcome.

The included studies were conducted in Dutch, American, Spanish, Italian and Japanese populations and there was no data from a UK population.

All included studies were open-label, non-comparative trials. The rarity of HoFH limits the number of potential people for clinical trials.

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Abbreviations

Term	Definition
ApoB	Apolipoprotein B
ALT	Alanine transaminase
ASP	Aspartate transaminase
BAS	Bile acid sequestrant
FH	Familial hypercholesterolaemia
HoFH	Homozygous familial hypercholesterolaemia
HeFH	Heterozygous familial hypercholesterolaemia
LDL-C	Low density lipoprotein cholesterol
LDLR	Low density lipoprotein receptor
Non-HDL-C	Non-high density lipoprotein cholesterol
PSCK-9	proprotein convertase subtilisin/kexin type 9
ULN	Upper level of normal
VLDL	Very low density lipoprotein

Medical definitions

Term	Definition
Atherogenic	Causing increases in fatty deposits in the arteries
Atherosclerosis	The thickening and hardening of artery walls, which can cause partial or total blockages in the arteries
Cholesterol	A type of fat known as a lipid that is carried in the blood. It is produced by the liver and can also be found in some foods. It is essential for several processes in the body but too much causes atherosclerosis, increasing the risk of cardiovascular events.
Hepatic fibrosis	This occurs when persistent inflammation causes scar tissue around the liver and nearby blood vessels, but the liver is still able to function normally
Hepatic steatosis	This occurs when there is an accumulation of fat in the liver (also known as 'fatty liver')
High density lipoprotein (HDL) cholesterol	Also known as 'good' cholesterol because it absorbs cholesterol and transports it to the liver where it is removed from the body.
Lipoprotein	A protein in the body that carries cholesterol in the blood, to and from cells.
Lipoprotein apheresis (lipoprotein apheresis)	This involves using a machine to filter the blood and remove low density lipoprotein cholesterol (and other atherogenic lipoproteins).
Low density lipoprotein (LDL) cholesterol	Also known as 'bad' cholesterol because it has a tendency to deposit in the arteries. This causes plaque build-up which can thicken and block the artery, causing cardiovascular problems. LDL cholesterol makes up the majority of cholesterol in the body.
Microsomal triglyceride transfer protein	A protein that releases atherogenic lipoproteins into the blood stream or absorbs them from the intestine
Non-HDL cholesterol	This is the sum of all 'bad' cholesterol, including LDL cholesterol. It is calculated by subtracting HDL cholesterol from total cholesterol.
Steatohepatitis	This occurs when the liver becomes inflamed

Introduction

Focus of review

In some individuals, a high cholesterol concentration in the blood is caused by an inherited genetic defect known as familial hypercholesterolaemia (FH). Raised cholesterol concentrations in the blood are present from birth and lead to early development of atherosclerosis and coronary heart disease. The disease is transmitted from generation to generation in such a way that siblings and children of a person with FH have a 50% risk of having FH.

FH is caused by mutations in 1 or more genes responsible for cholesterol production and removal; people with homozygous familial hypercholesterolaemia (HoFH) have 2 defective copies of these genes. Symptoms of HoFH appear in childhood and it is associated with premature life-threatening major cardiac events such as heart attack, heart valve disease, stroke, and premature cardiac death. The term HoFH includes pure or simple HoFH, autosomal recessive hypercholesterolaemia (ARH), compound heterozygous familial hypercholesterolaemia and double heterozygous familial hypercholesterolaemia.

See table 1 for the population, intervention, comparator and outcomes summary.

Table 1: Decision problem

	Final scope issued by NICE
Population	Adults with homozygous familial hypercholesterolaemia

Intervention	Lomitapide (Lojuxta) as an adjunct to other lipid lowering drugs with or without low density lipoprotein (LDL) apheresis
Comparator(s)	Lipoprotein apheresis combined with maximum tolerated statin, ezetimibe and a bile acid sequestrant, with or without evolocumab Maximum tolerated statin, ezetimibe and a bile acid sequestrant, with or without evolocumab Liver transplant, with or without heart transplant
Outcomes	Change in plasma lipid and lipoprotein levels, including LDL cholesterol, non-HDL cholesterol, and apolipoprotein B Change in amount of aminotransferase enzymes in the blood Change in fat levels in the liver Change in bilirubin Cardiovascular events Mortality

The focus of this review is on lomitapide as an adjunct to a low-fat diet and other lipid lowering medicines, with or without low density lipoprotein (LDL) apheresis for treating adults with HoFH.

Epidemiology

The prevalence of HoFH is estimated to be 1 per 1 million population in the UK (France et al, 2016), although this may be an underestimate because of phenotypic variation (France et al. 2016). Based on actual patient numbers being treated in major apheresis centres, it is estimated that the prevalence of HoFH may be 1 in 670,000 adults in England. Applying these prevalence rates to the England population aged 18 and over (approximately 43 million, ONS 2016), there are between 43 to 64 adults patients in England with HoFH. Based on prevalence rates and life expectancy, is it estimated there will be around 1 new case of HoFH every year.

It is not expected that all of patients with HoFH would be eligible for treatment with lomitapide. Lomitapide is given as an adjunct to other lipid lowering therapies, with or without lipoprotein apheresis. Patients would therefore use several other treatments until their disease was no longer controlled on those treatments, before adding lomitapide. In addition, it is a requirement in the marketing authorisation for lomitapide that patients must have no more than

20% of their diet from fat before and during treatment (to minimise the risk of more severe gastrointestinal adverse events), and some patients may have difficulty adhering to this.

Additionally, the summary of product characteristics (SPC) for lomitapide states that genetic confirmation of HoFH should be obtained whenever possible. In the Cuchel et al. 2013 study, diagnostic criteria for HoFH were based on either genetic criteria (documented mutation(s) in both alleles of the LDL receptor or of other genes known to affect LDL receptor function), or clinical criteria (history of untreated total cholesterol greater than 13 mmol/L and triglycerides less than 3.4 mmol/L and both parents with history of untreated cholesterol greater than 6.5 mmol/L). In England, HEART UK's (France et al. 2016) diagnostic criteria for HoFH similarly includes genetic criteria (the presence of 2 disease causing alleles affecting introns and exons of the LDLR (low density lipoprotein receptor), APOB (apolipoprotein B), PCSK-9 (proprotein convertase subtilisin/kexin type 9) and LDLRAP1 (low density lipoprotein receptor adapter protein 1) gene loci, or clinical criteria (having an LDL-C level of more than 13 mmol/L in an untreated adult with clinically obvious tendon or cutaneous xanthoma). It states genetic diagnosis supplementary to clinical assessment is preferred. It also includes another diagnostic criterion, where there is qualifying cholesterol level and both parents with genetically confirmed HeFH. Similar diagnostic criteria is stated in the European Atherosclerosis Society (EAS) consensus guidelines on diagnosis and management of HoFH.

The genetic background determines LDLR activity, response to pharmacotherapy and the severity of disease. The presence of mutations affecting APOB and LDLRAP1 have a more favourable prognosis than those affecting LDLR or PCSK-9. About three quarters of patients are receptor defective (residual LDLR activity [2 to 25%] and the rest are receptor negative (LDLR activity less 2%) (France et al. 2016).

Product overview

Mode of action

Established cholesterol lowering drugs act mainly by up-regulating LDLR activity. Lomitapide works independently of the LDLR pathway and is the first inhibitor of a protein in the body known as microsomal triglyceride transfer protein. This is involved in assembling fatty substances such as cholesterol and triglyceride into larger particles called lipoproteins, which are then released into the blood stream. By blocking this protein, lomitapide decreases the level of fats released into the blood, thereby helping to reduce the level of cholesterol in people with HoFH (European Medicines Agency: lomitapide). The European public assessment report [EPAR] states that lomitapide represents a new class of drugs with a mechanism of action that differs from those of other classes of lipid lowering medicines.

Regulatory status

Lomitapide received a marketing authorisation from the European Medicines Agency in July 2013 for use as an adjunct to a low-fat diet and other lipid-lowering medicines with or without lipoprotein apheresis in adults with HoFH.

The summary of product characteristics (SPC) also states that genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinaemia and secondary causes of hypercholesterolaemia (for example nephrotic syndrome or hypothyroidism) must be excluded (SPC: lomitapide).

Dosing information

The starting dose of lomitapide is 5 mg daily. If tolerated, this is increased after 2 weeks to 10 mg daily then, at minimum 4-week intervals, to 20 mg, 40 mg and up to a maximum of 60 mg daily. Lomitapide is taken once daily at least 2 hours after the evening meal (SPC: lomitapide).

The SPC states that patients should follow a diet supplying less than 20% of energy from fat before starting treatment with lomitapide and should continue

this diet during treatment. In addition, patients should take daily dietary supplements that provide 400 IU vitamin E and approximately 200 mg linoleic acid, 110 mg eicosapentaenoic acid (EPA), 210 mg alpha linolenic acid (ALA) and 80 mg docosahexaenoic acid (DHA) daily during treatment with lomitapide.

See the SPC for further details of the dosing recommendations.

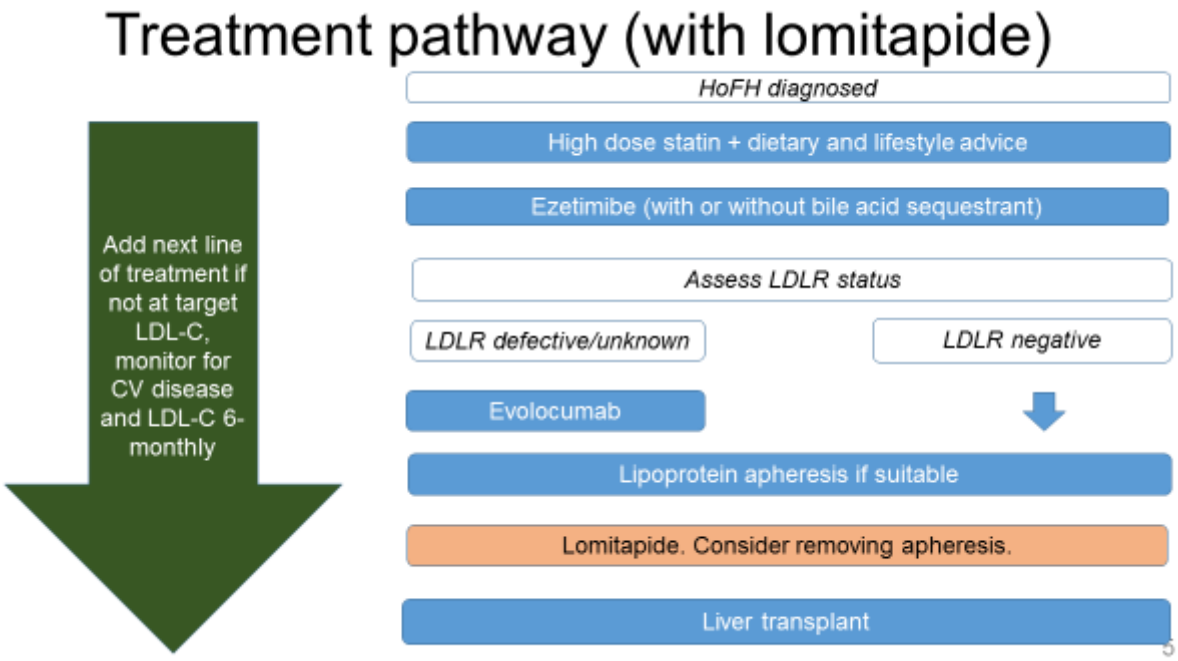
Treatment pathway and current practice

The NICE guideline on the identification and management of familial hypercholesterolaemia, recommends statins as initial treatment for all adults with familial hypercholesterolaemia (FH) in addition to dietary and lifestyle advice. Prescribing of medicines for adults with HoFH should be undertaken within a specialist centre, where other treatments may include ezetimibe, a bile acid sequestrant (resin) and a fibrate. In clinical practice, lipoprotein apheresis would be added if the disease was not controlled by these medicines. The PCSK-9 inhibitor, evolocumab, also has a licence for treating HoFH in combination with other lipid lowering therapies. France et al. 2016 states that evolocumab would only be given to patients who have HoFH that is either LDLR defective or unknown because receptor negative patients do not respond to PSCK-9 inhibitors (although if testing was not possible, this treatment may be tried first). If disease progression occurs despite treatment with lipid lowering medication and lipoprotein apheresis, liver transplantation would be considered. Specific therapeutic targets for lowering LDL-C in HoFH are set by HEART UK and the European Atherosclerosis Society (EAS) at LDL-C of less than 2.5 mmol/L (100 mg/dL) for adults, or less than 1.8 mmol/L (70 mg/dL) in adults with clinical atherosclerotic cardiovascular disease.

The combination of current medicines and lipoprotein apheresis is often unable to reduce LDL-C to recommended target levels in many people with HoFH (Ito, 2015). This means patients still have high LDL-C levels and are at continued risk of atherosclerotic disease progression and the likely resultant

life-threatening cardiac events (for example heart attack, stroke, major cardiac surgery, and premature cardiac death).

Figure 1 Pathway of care for for adults with homozygous FH in England (with lomitapide)



Abbreviations: HoFH; homozygous familial hypercholesterolaemia; LDL-C, low density lipid cholesterol; LDLR, low density lipid receptor; PCSK9; proprotein convertase subtilisin/kexin type 9;

Innovation and unmet need

Lomitapide represents a new class of drugs with a mechanism of action that differs from those of other classes of lipid-lowering medicines (European public assessment report [EPAR] for lomitapide).

Established cholesterol lowering drugs act mainly by improving the activity of low density lipoprotein receptors (LDLR, which take cholesterol from the blood). Lomitapide works in a different way to established cholesterol lowering drugs because it works independently of the LDLR pathway, by blocking the action of a protein that releases LDL-C into the blood stream.

Lomitapide may be an option before a liver transplant is considered. However, there is a shortage of organs, and the procedure is rarely carried out for people with HoFH because their need for a liver transplant is not prioritised above that of a patient with hepatic failure.

Equality issues

No relevant equality concerns were identified or raised.

Evidence base

Identification of studies

A literature search was done, which identified 331 references (see appendix 1 for search strategy). These references were screened using their titles and abstracts and 34 full text references were obtained.

The company submission identified 2 unique references to published studies and 1 additional reference (that was identified in the literature search but was excluded based on being an abstract) for which the company provided a manuscript of the study in its submission.

A total of 37 full text references were assessed for relevance. Full text inclusion and exclusion criteria were applied to the identified studies and 8 studies were included in the clinical evidence review.

Please note, the European public assessment report (EPAR) for lomitapide and the clinical trial.gov website were also used to supplement the published data from the pivotal study (Cuchel et al, 2013).

See appendix 2 for inclusion criteria and a list of studies excluded at full text with reasons.

Clinical evidence

Overview of included studies

The main evidence for the clinical effectiveness of lomitapide comes from a phase 3, single-arm, open-label study, Cuchel et al. 2013 (NCT00730236) that included 29 adults with HoFH. A long-term, uncontrolled, follow-on study of Cuchel et al. 2013 reported by Blom et al. 2017 (n=19) provides evidence for up to 246 weeks of treatment. A smaller (n=9) phase 3, single-arm, open-label study Harada-Shiba et al. 2017, conducted only in a Japanese population, provides further evidence. Other included studies were, 2 single-arm, open-label studies that enrolled adults with HoFH: (Cuchel et al. 2007, a phase 2 dose-escalation [proof of concept] that included 6 patients, and Yahya et al. 2016 included 4 patients) and 3 uncontrolled retrospective studies with small sample sizes (4 to 15 patients) (D'Erasmo et al. 2017, Roeters van Lennep et al. 2015 and Stefanutti et al. 2016).

The European Public Assessment Report (EPAR) for lomitapide included data from 6 phase 2 studies and 1 phase 3 study, including Cuchel et al. 2013, which the EPAR describes as the main study for the proposed indication in HoFH.

A summary of the characteristics of the included studies is shown in table 2. The more detailed evidence tables can be found in appendix 3.

Table 2 Summary of included studies

Study	Population	Intervention and comparison	Primary outcome
Cuchel et al. 2013 Phase 3, single-arm, open-label study (NCT00730236)	29 adults (mean age 30.7 years) with HoFH on lipid lowering treatment	Lomitapide initiated at starting dose of 5 mg/day titrated to a maximum of 60 mg/day if tolerated No comparator	Percentage change in LDL C level from baseline to week 26 Efficacy phase was 26 weeks followed by 52-week safety phase
Blom et al. 2017 Phase 3, long term, single-arm, open-label, follow	19 adults (mean age 30.4 years) with HoFH on lipid lowering treatment	Maximum tolerated dose of lomitapide (up to 60 mg/day) No comparator	Percentage change in LDL-C level from baseline to week 126 (78 weeks of the pivotal study plus

on study of NCT00730236	including plasmapheresis or lipoprotein apheresis		48 weeks of the extension study) and week 246
Harada Shiba et al. 2017 Phase 3, single-arm, open-label study	9 Japanese adults (aged 33 to 75 years) with HoFH receiving lipid lowering treatment	Lomitapide started 5 mg/day increased to maximum tolerated dose (60 mg/day) No comparator	Mean percentage change from baseline to week 26 in LDL-C levels at maximum tolerated dose of lomitapide Efficacy phase was 26 weeks followed by 30 weeks of the safety phase.
Cuchel et al. 2007 Phase 2 single-arm, open-label study	6 adults with HoFH (aged 18 to 40 years). No other lipid lowering treatment allowed until study completion	Lomitapide administered at 4 doses (0.03, 0.1, 0.3, and 1.0 mg/kg per day) No comparator	No specific primary outcome but included percentage change in LDL-C level from baseline to follow-up Follow-up 28 days after last dose of study drug
Yahya et al. 2016 Single-arm, open-label study	4 adults with HoFH (aged 20 to 62 years) receiving lipid lowering treatment	Lomitapide (dose range 10 to 30 mg daily) No comparator	No specific primary outcome but included change in LDL C level from baseline to follow-up Length of follow-up not specified, however treatment duration varied between 9 and 36.5 weeks
D'Erasmo et al. 2017 Retrospective observational study	15 adults (mean age 37.7 years) with HoFH on standard lipid lowering treatment	Lomitapide daily No comparator	No specific primary outcome but included percentage change in LDL-C level from baseline to follow-up Mean follow-up 32.3 months
Roeters van Lennep et al. 2015 Case series (appears to be retrospective)	4 adults with HoFH (age range 20 to 62 years) receiving lipid lowering treatment	Lomitapide administered according to prescribed protocol (dose range 5 mg to 60 mg daily) No comparator	No specific primary outcome but included percentage change in LDL-C levels from baseline to follow-up Follow-up varied between 20 and 50 weeks
Stefanutti et al.	7 adults (aged	Lomitapide (dose	No specific primary

2016 Case series (appears to be retrospective)	23 to 32 years) with HoFH receiving lipoprotein apheresis and ezetimibe only	range 5 mg to 60 mg daily) No comparator	outcome but included percentage change in LDL-C levels from baseline to follow-up Follow-up varied between 12 and 50 weeks
Abbreviations HoFH, homozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol;			

Key outcomes

The key outcomes identified in the scope are discussed below for effectiveness and safety. Table 3 below provides a grade of evidence summary of key outcomes (see appendix 5 for the details of grading evidence using the National Service Framework Long-term conditions tool [NSF-LTC]). The more detailed evidence tables and results for each study can be found in appendices 3 and 4.

Effectiveness

The primary outcome measure to assess clinical effectiveness of lomitapide in the majority of studies was the percentage change in LDL-C levels from baseline to follow-up. All the studies reporting this outcome measure included adults with HoFH (with or without cardiovascular disease) using other lipid lowering treatments, including lipoprotein apheresis. The maximum tolerated dose of lomitapide was used which varied across the studies.

The main phase 3, single-arm, open-label study, Cuchel et al. 2013 (n=29) reported a statistically significant reduction of 50% (95%CI −62% to −39%, p<0.0001) in LDL-C levels after 26 weeks with lomitapide (median dose 40 mg/day), decreasing mean LDL-C level from 8.7 mmol/L to 4.3 mmol/L. After 78 weeks (at study completion), Cuchel et al. 2013 found the reduction in LDL-C levels from baseline was 38% (95%CI −52% to −24%, p=0.0001). A follow-up study of Cuchel et al. 2013 was reported by Blom et al. 2017 (n=19). The reduction in LDL-C levels was reported to be 45.5% (95%CI −61.6% to −29.4%, p<0.0001) 126 weeks after starting lomitapide, decreasing mean

LDL-C level from 365mg/dL (~9.3 mmol/L) to 189mg/dL (~4.9 mmol/L). Furthermore, from baseline to week 246, Blom et al. 2017 reported that a total of 14 patients taking lomitapide had LDL-C levels less than 100 mg/dL (~2.5 mmol/L) and 11 patients had LDL-C levels less than 70 mg/dL (~1.8 mmol/L) on at least 1 occasion (no statistical analysis reported).

Similarly, the phase 3, single-arm, open-label study, Harada-Shiba et al. 2017 (n=9) found a statistically significant reduction of 42% (95%CI −56% to −28%, p<0.0001) in LDL-C levels at 26 weeks (mean dose of lomitapide 21.9 mg/day). The observational study, D'Erasmo et al. 2017 (n=15) found that treatment with lomitapide (mean dose 19 mg/day) reduced LDL-C levels by 68.2% (p<0.05; duration of treatment 8 to 86 months).

Secondary outcomes used to assess the efficacy of lomitapide included the change in non-high density lipoprotein cholesterol (non-HDL-C; the sum of all 'bad' cholesterol, including LDL cholesterol) and apolipoprotein B (ApoB; an important protein for 3 of the 4 main types of lipoprotein, including LDL) levels from baseline to follow-up.

Cuchel et al. 2013 found a statistically significant reduction of 50% in non-HDL-C levels with lomitapide at week 26. Similar statistically significant reductions in non-HDL-C levels were found in the studies reported by D'Erasmo et al. 2017 (8 to 86 months treatment) and Harada-Shiba et al. 2017 (at 26 weeks of treatment); 67.8% and 50% respectively.

Cuchel et al. 2013 and Harada-Shiba et al. 2017 both found a statistically significant reduction of 49% in ApoB levels after 26 weeks of lomitapide treatment.

Although not reported as an outcome measure in the majority of studies, the addition of lomitapide to existing lipid lowering treatments resulted in a decreased frequency of lipoprotein apheresis or stopping lipoprotein apheresis in some of the patients with HoFH (Cuchel et al. 2013, D'Erasmo et al. 2017, Harada-Shiba et al. 2017, Roeters van Lennep et al. 2015, Stefanutti et al. 2016). This may benefit patients because it is needed about once every

2 weeks (France et al. 2016) and can be invasive, time consuming, and impact quality of life of patients (Bruckert 2014). The SPC states that the clinical benefit of reductions in background lipid lowering therapy, including lipoprotein apheresis, is not certain.

The studies assessing the effect of lomitapide on LDL-C, non-HDL-C and ApoB levels included between 4 to 29 patients with HoFH, and the key primary efficacy outcome, percentage change in LDL-C levels, was carried out over a short-term time period (26 weeks). Extended follow-up of the key primary efficacy outcome was reported up to 56 weeks (Harada-Shiba et al. 2016), 78 weeks (Cuchel et al. 2013) and up to 246 weeks (Blom et al. 2017) which showed lomitapide maintained the reduction in LDL-C levels over a longer period of time. The studies were of an open label and uncontrolled nature, which has the potential to introduce bias. In addition, these studies did not adjust for confounding factors (such as treatment with other lipid-lowering interventions including lipoprotein apheresis) which may have influenced the results. There were no UK patients included in any of the studies therefore it is unclear if the results would be generalisable to NHS practice.

The EPAR for lomitapide states that "although the long-term effect of lipid reduction of lomitapide on cardiovascular events was not investigated, reduction in LDL-C is considered an important surrogate endpoint with potential benefits in terms of cardiovascular outcome". Studies assessing the long-term cardiovascular outcomes and survival suggests that maximum lipid lowering treatment (including lipoprotein apheresis) ensures long-term reduction in the cholesterol burden and risk of cardiovascular complications and improves survival (Bruckert et al. 2017 and Thompson et al. 2017):

- Thompson et al. 2017 (n=133) did a retrospective survey of lipid levels and clinical outcomes for people with HoFH treated with a combination of lipid lowering treatments between 1990 and 2014 in South Africa and the UK. It found that the risk of death of people with the highest levels of serum cholesterol (>15.1 mmol/L) (which is 90% LDL-C in people with HoFH), was 11.5 times higher than those with the lowest levels of

serum cholesterol (<8.1mmol/L). And the risk of death for those with cholesterol levels 8.1 to 15.1mmol/L was 3.6 times higher than those with the lowest levels (<8.1mmol/L). Both of these results were statistically significant (p<0.001). The study also found statistically significant results for cardiovascular specific death and major adverse cardiac events.

- In a retrospective single-centre study, Bruckert et al. 2017 evaluated the association of cardiovascular complications with changes in cholesterol over time (up to 38 years) in 53 people with HoFH, as well as total cholesterol burden. It found that cumulative total cholesterol was highly associated with the incidence of an adverse clinical event. A 100 mmol/L increase in cumulative total cholesterol (an average exposure of 10 mmol/L per 10 years or 20 mmol/L per 5 years) was associated with a doubling of the risk of a cardiovascular event.

Results from a South African modelling study (Leipold et al. 2017) which took hazard ratios from a treated HoFH population model suggested that if a person with HoFH was prescribed lomitapide in addition to standard of care from 18 years of age, the median increase in life expectancy compared with not taking lomitapide was 11.2 years, with a median 5.6-year delay in time to first cardiovascular event. These data are based on an estimate of a 38% lowering in LDL-C levels with lomitapide. NICE has not validated any methods used to generate these estimates and the estimates are not actual data, therefore results from this modelling study need to be interpreted with caution.

Safety and tolerability

The safety and tolerability outcomes in the included studies were adverse events, treatment discontinuation, elevated serum aminotransferase (a marker commonly associated with liver disease) and change in hepatic fat levels.

There were no treatment related deaths reported in majority of the included studies. Adverse events described as the "most serious" in the SPC for lomitapide were liver aminotransferase abnormalities (and the frequency of

increases in these levels were reported as “very common” in the SPC). Raised aminotransferase levels in the blood suggest that the liver may not be functioning as it should do because of an adverse effect on it, and is associated with liver disease. Elevations in serum aminotransferases (alanine transaminase [ALT], aspartate transaminase [AST] or both) of 3 or 5 times the ULN were reported in the majority of studies. These occurred in 34.5% (10/29), 21.1% (4/19) and 33.3% (3/9) of patients in Cuchel et al. 2013, Blom et al. 2017 and Harada-Shiba et al. 2017 respectively. D’Erasmo et al. 2017 reported that 1 out of the 10 patients that had elevated serum aminotransferase levels had a rise in ALT of 3 times ULN. Treatment discontinuation due to elevated serum aminotransferases has been reported in 3 studies (n=1 in each study, Blom et al. 2017, Harada-Shiba et al. 2017 and Roeters van Lennep et al. 2015). Results from the studies suggest that these elevations are transient and can be reversible with both reductions in the dose and short-term withdrawal of lomitapide.

The studies reported in the evidence review suggest that there is an increased risk of hepatic fat accumulation whilst on treatment with lomitapide (some fat in the liver is normal, but when there is too much this can lead to health problems, including cirrhosis and liver failure). The SPC notes that hepatic steatosis (fatty liver) was recorded in a study for lomitapide as hepatic fat >5.56%, and the frequency of hepatic steatosis was reported in the SPC as “common”. In the study by Cuchel et al. 2013, patients experienced an increase in mean hepatic fat from 1% at baseline to 8.6% at week 26, and was maintained at 8.3% at week 78. In the extension study by Blom et al. 2017, patients experienced an increase in the median hepatic fat from 0.7% at baseline to 10.2% at week 246 of the study. Harada-Shiba et al. 2017 found that mean hepatic fat increased from 3.2% at baseline to 15.6% at week 26, and to 12.7% at week 56 of the study. D’Erasmo et al. 2017 reported that 2 patients experienced fatty liver with lomitapide treatment (one of these patient’s had fatty liver at baseline). The EPAR for lomitapide states that association of lomitapide treatment with liver fat accumulation was observed, however data are limited.

The SPC states that the adverse effect of lomitapide on the liver is related to the pharmacodynamic effect of lomitapide and the potential long-term development of hepatotoxic effects, such as fibrosis, cannot currently be assessed, due to limited data. It also states enzyme levels, fat fraction or other imaging markers are not a reliable predictor of hepatotoxic effects.

There are several special warnings and precautions for use in the SPC for lomitapide. The SPC includes warnings on liver abnormalities and liver monitoring, monitoring of liver function tests, dose modification based on elevated hepatic aminotransferases, hepatic steatosis and risk of progressive liver disease, monitoring for evidence of progressive liver disease, concomitant use of statins, CYP3A4 inhibitors and inducers and reduced absorption of fat soluble vitamins and serum fatty acids.

The most commonly reported adverse events during lomitapide treatment were gastrointestinal-related. The pivotal phase 3, single arm, open label study, Cuchel et al. 2013 reported that gastrointestinal-related adverse events (commonly diarrhoea, nausea, dyspepsia and vomiting) occurred in 93.1% (27/29) of the patients during the study. Most adverse events were reported to be mild or moderate, although 3 patients permanently discontinued treatment with lomitapide because of gastrointestinal-related adverse events. Severe adverse events were reported to be unrelated to lomitapide. Harada-Shiba et al. 2017 (a phase 3, single arm, open label study) found that all patients experienced at least one treatment-emergent adverse event, with 88.9% (8/9) reporting gastrointestinal-related events. One patient experienced a severe adverse event, which was reported to be diarrhoea. Adverse events were lessened by reducing the dose or temporarily withholding lomitapide during the efficacy phase, and less treatment-emergent adverse events were reported in the safety phase (75%, 6/8). This suggests that as the study progressed, adverse events became less frequent. The observational study, D'Erasmo et al. 2017 found that 53.3% (8/15) of patients taking lomitapide reported diarrhoea, of which 4 patients reported it as persistent. Nausea and vomiting was reported by 20% (3/15) of patients, of which 2 patients reported

it as persistent. Persistent abdominal pain was reported by 2 patients. All the gastrointestinal-related adverse events were reported to be mild. No severe adverse events were reported in the study. Smaller studies included in this evidence review suggest that having a low fat diet may influence the gastrointestinal tolerability of lomitapide. The EPAR for lomitapide states that the occurrence of gastrointestinal adverse events is a drawback of lomitapide treatment, but this may be partly ameliorated by using a dose escalation scheme as recommended in the SPC. The EPAR states “severe gastrointestinal adverse events that occur mostly at the start of treatment, are considered manageable for most patients by temporary treatment discontinuation or temporary down titration of the dose”.

In the main study, Cuchel et al. 2013 with 29 patients followed up to 78 weeks after starting lomitapide, 4 patients out of 29 discontinued treatment with lomitapide due to an adverse event (gastrointestinal related in 3). In the study by Blom et al. 2017, 3 patients discontinued treatment with lomitapide because of relocation, raised aminotransferases and sudden cardiac death (the company reported that that the cardiac death was not treatment related, and that discontinuation due to raised transaminases was in a patient who failed to comply with alcohol recommendations). Harada Shiba et al. 2017 followed patients up to 56 weeks after starting lomitapide and found that 1 patient out of 9 discontinued treatment with lomitapide because of raised aminotransferases.

Results for the safety and tolerability of lomitapide are based on studies that included less than 30 patients with HoFH, and long-term effects are unknown. There were no UK patients included in any of the studies therefore it is unclear if the results would be generalisable to NHS practice

Evidence gaps

The evidence for this review is based on a phase 3 single-arm open-label study (Cuchel et al. 2013, n=29) that was also reported in the EPAR. The results of this study are supported by other uncontrolled studies with less than

20 patients with HoFH. Most of the studies that demonstrated the efficacy of lomitapide for reducing LDL-C levels in adults with HoFH were short-term and of an open label and uncontrolled nature with no comparators. Although long-term follow-up efficacy data up to 246 weeks are available for 1 study (in Blom et al, the long-term extension of Cuchel et al), most studies and primary outcomes were over a short term period, with no study including more than 30 patients. Therefore more data are needed to evaluate the long-term effectiveness of lomitapide in maintaining control of serum lipid levels in clinical practice.

There were a limited number of people with HoFH treated with lomitapide up to 246 weeks in the study by Blom et al. 2017 (n=19) that briefly reported adverse events associated with long-term use. Further safety information is needed to evaluate the longer-term effect of lomitapide on the liver and gastrointestinal system.

People with HoFH have a high risk of cardiovascular disease. The included studies did not report any cardiovascular events as an outcome, however the EPAR for lomitapide states that reduction in LDL-C is considered an important surrogate endpoint with potential benefits in terms of cardiovascular outcome.

The included studies were conducted in Dutch, American, Spanish, Italian and Japanese populations and there were no data from a UK population, therefore the generalisability to NHS practice is uncertain.

Long-term safety and efficacy of lomitapide in patients with HoFH is being studied in the Lomitapide Observational Worldwide Evaluation Registry (LOWER) study (NCT02135705). This a long-term study (target follow-up of 10 years) in patients taking lomitapide to provide further data on its safety and effectiveness, including its side effects on the liver, stomach, gut, and cardiovascular system (to assess the progression of atherosclerosis). The study will also provide data on pregnancies in women taking the medicine, and on healthcare professionals' compliance with the recommendations to screen and monitor patients before and during treatment. Three-year data

from the LOWER study are due to be published in May 2018 (personal communication with the company, Amryt Pharma)

Table 3 Grade of evidence for key outcomes

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
Percentage change in low-density lipoprotein cholesterol (LDL-C) level	Blom et al. 2017	4/10	Directly applicable	B	LDL-C is known as 'bad' cholesterol because it has a tendency to deposit in the arteries, which can lead to major cardiovascular events. Target LDL-C levels to prevent events are <2.5 mmol/L for adults or <1.8 mmol/L for adults who already have cardiovascular disease. The main study, Cuchel et al. 2013 (n=29) of patients with HoFH receiving fixed lipid lowering treatments including LDL apheresis and a low fat diet reported a 50% (95%CI −62% to −39%, p<0.0001) reduction from baseline in LDL-C levels after 26 weeks of treatment with lomitapide. This reduction was maintained in Blom et al. 2017 (a long term follow up of Cuchel et al. 2013), which reported a 45.5% (95% CI −61.6% to −29.4%, p<0.001) reduction from baseline in LDL-C after 126 weeks of treatment. These results were supported by several smaller studies (see appendix 4). Although average LDL-C levels after 26 weeks in Cuchel et al. 2013 (4.3 mmol/L) did not meet preventative targets (see above), results suggest a patient with HoFH taking other lipid lowering therapies can expect lomitapide to lower LDL-C levels after 26 weeks of treatment. In the main study, patients had a reduction of 50%, and there was a 95% probability that the true reduction was within the range of 39 to 62%. Results suggest that this reduction may continue into the longer term, although more data would be needed to confirm this. Results should be interpreted with caution as they are based on open-label, single-arm studies. This means that studies cannot compare the treatment with any other standard treatment (which means there is no direct evidence that lomitapide is any better or worse than other treatments for this outcome). They also cannot be blinded or randomised, which can lead to biases, influencing
	Cuchel et al. 2007	5/10	Directly applicable		
	Cuchel et al. 2013	6/10	Directly applicable		
	D'Erasmo et al. 2017	5/10	Directly applicable		
	Harada-Shiba et al. 2017	6/10	Directly applicable		
	Roeters van Lennep et al. 2015	2/10	Directly applicable		
	Stefanutti et al. 2016	3/10	Directly applicable		
	Yahya et al. 2016	3/10	Directly applicable		

					results and the true effect of treatment. Studies also did not adjust for confounding factors which may also have influenced results (such as treatment with other lipid lowering interventions including lipoprotein apheresis).
Percentage change in non-high density lipoprotein cholesterol (non-HDL-C) level	Cuchel et al.2013	6/10	Directly applicable	B	Non-HDL-C is the total of all 'bad' cholesterol in the body that causes heart disease, including LDL-C. It is calculated by subtracting HDL-C (also known as 'good' cholesterol) from total cholesterol. The main study, Cuchel et al. 2013 (n=29) patients with HoFH receiving fixed lipid lowering treatments including LDL apheresis and a low fat diet reported a -50% (95%CI −61% to−39%, p<0.0001) reduction in non-HDL-C levels from baseline after 26 weeks of treatment with lomitapide. Results suggest that patients with HoFH taking other lipid lowering therapies can expect lomitapide to lower non-HDL-C levels after 26 weeks of treatment. In the main study (Cuchel et al. 2013), patients had a reduction of 50%, and there was a 95% probability that the true value was contained within the range of 39% to 61%. Results should be interpreted with caution as they are based on open-label, single-arm studies. This means that studies cannot compare the treatment with any other standard treatment (which means there is no direct evidence that lomitapide is any better or worse than other treatments for this outcome). They also cannot be blinded or randomised, which can lead to biases, influencing results and the true effect of treatment. Studies also did not adjust for confounding factors which may also have influenced results (such as treatment with other lipid lowering interventions including lipoprotein apheresis).
	D'Erasmo et al.2017	5/10	Directly applicable		
	Harada-Shiba et al.2017	6/10	Directly applicable		
Percentage change in ApoB level	Cuchel et al. 2013	6/10	Directly applicable	B	Apolipoprotein B (ApoB) is a type of protein that binds to lipids ('fats') to form lipoproteins and has a number of functions such as transporting lipids (such as LDL-C) around the body. High levels are thought to be related to heart disease. The main study, Cuchel et al. 2013 with 29 patients with HoFH receiving fixed lipid lowering treatments including lipoprotein apheresis and a low fat diet reported a 49% −49% (95%CI −60% to −38%, p<0.0001) reduction in ApoB levels from baseline after 26 weeks of treatment with lomitapide. Results suggest that a patient with HoFH taking other lipid lowering therapies
	Harada-Shiba et al. 2017	6/10	Directly applicable		
	Yahya 2016	3/10	Directly applicable		

					can expect lomitapide to lower ApoB levels. The reduction in the main study (Cuchel et al. 2013) was 49%, and there is a 95% probability that the true reduction was contained within the range of 38% and 60%. These results should be interpreted with caution as they are based on open-label, single arm studies. Results should be interpreted with caution as they are based on open-label, single-arm studies. This means that studies cannot compare the treatment with any other standard treatment (which means there is no direct evidence that lomitapide is any better or worse than other treatments for this outcome). They also cannot be blinded or randomised, which can lead to biases, influencing results and the true effect of treatment. Studies also did not adjust for confounding factors which may also have influenced results (such as treatment with other lipid lowering interventions including lipoprotein apheresis).
Adverse events	Blom et al. 2017	4/10	Directly applicable	B	This outcome looks at how many people had adverse events while they were taking treatment. Please also see treatment discontinuation, and change in levels of aminotransferase (the SPC states that liver aminotransferase abnormalities was the most serious adverse event) and hepatic fat, for more discussion of adverse events. There were no treatment related deaths reported. The main study Cuchel et al. 2013 with 29 patents followed up for up to 78 weeks after starting lomitapide found 93.1% of patients reported at least 1 adverse event, most were gastrointestinal-related. These included diarrhoea, nausea, vomiting, and dyspepsia. Similar gastrointestinal-related adverse events were reported in other studies. The summary of product characteristics also states that increases in aminotransferase (an outcome that can be associated with liver disease) and hepatic steatosis (an outcome that can be associated with cirrhosis and liver failure) were very commonly and commonly reported respectively. The EPAR states that lomitapide has a considerable impact on liver function tests. For more detail on these outcomes please see below. Weight loss was also very commonly reported.
	Cuchel et al. 2007	5/10	Directly applicable		
	Cuchel et al. 2013	6/10	Directly applicable		
	D'Erasmo et al. 2017	5/10	Directly applicable		

	Harada-Shiba et al. 2017	6/10	Directly applicable		The results suggests that the adverse events most likely to be experienced by patients taking lomitapide are gastrointestinal-related. Patients may also experience increases in hepatic fat or aminotransferase, markers which can lead to more serious problems with the liver. For patients, these adverse events may, as in the study, be lessened by reducing the dose or temporarily withholding lomitapide. Results should be interpreted with caution as they are based on single arm studies. It means that they cannot randomise patients (which can lead to biases, influencing results and hiding the true adverse effects of treatment) or compare the treatment with any other standard treatment (which means it is not possible to determine what proportion of side effects are attributable to lomitapide treatment and what proportion are likely to be a direct consequence of the disease or other lipid lowering treatment the patients were on. Similarly, there is no direct evidence that lomitapide is more or less safe than other treatments).
	Roeters van Lennep.et al. 2015	2/10	Directly applicable		
	Stefanutti et al. 2016	3/10	Directly applicable		
Treatment discontinuation	Cuchel et al. 2013	6/10	Directly applicable	B	This outcome considered how many people had to stop taking lomitapide during the study. In the main study, Cuchel et al. 2013 with 29 patients followed up to 78 weeks after starting lomitapide, 4 patients out of 29 discontinued treatment with lomitapide due to an adverse event, which was gastrointestinal-related in 3 patients. In the study by Blom et al. 2017, 3 patients discontinued treatment with lomitapide because of relocation, raised aminotransferases and sudden cardiac death (the company reported that that the cardiac death was not
	D'Erasmo et al. 2017	5/10	Directly applicable		
	Harada-Shiba et al. 2017	6/10	Directly applicable		

	Roeters van Lennep et al. 2015	2/10	Directly applicable		treatment related, and that discontinuation due to raised transaminases was in a patient who failed to comply with alcohol recommendations). Harada-Shiba et al. 2017 followed patients up to 56 weeks after starting lomitapide and found that 1 patient out of 9 discontinued treatment with lomitapide because of raised aminotransferases. The results suggest that adverse events related to gastrointestinal system and raised aminotransferases may limit treatment with lomitapide, but the elevations may be temporary and possibly reversible with both reductions in the dose and short term withdrawal of lomitapide Results should be interpreted with caution as they are based on single arm studies. It means that they cannot randomise patients (which can lead to biases, influencing results and hiding the true adverse effects of treatment) or compare the treatment with any other standard treatment (which means it is not possible to determine what proportion of side effects are attributable to lomitapide treatment and what proportion are likely to be a direct consequence of the disease or other lipid lowering treatment the patients were on. Similarly, there is no direct evidence that lomitapide is more or less safe than other treatments).
Change in aminotransferase levels	Blom et al. 2017	4/10	Directly applicable	B	This outcome considered how many people had raised serum aminotransferases whilst on lomitapide. Raised aminotransferase levels in the blood suggest that the liver may not be functioning as it should do because of an adverse effect on it and is associated with liver disease. The SPC states that liver aminotransferase abnormalities was the most serious adverse event. The main study, Cuchel et al. 2013 with 29 patients followed up to 78 weeks after starting lomitapide found 10 patients experienced raised serum aminotransferase levels, of which 4 patients had an increase in a type of aminotransferase enzyme called alanine transaminase (ALT) that was 5 times the upper level of the normal range it should be in. A similar rise in aminotransferase levels were reported by other smaller studies. The EPAR states that lomitapide has a considerable impact on liver function tests, particularly on serum aminotransferases which is thought to be related to the
	Cuchel et al. 2007	5/10	Directly applicable		
	Cuchel et al. 2013	6/10	Directly applicable		
	D'Erasmo et al. 2017	5/10	Directly applicable		

	Harada-Shiba et al. 2017	6/10	Directly applicable		way lomitapide works to lower LDL-C in the body. Results suggest that lomitapide has an impact on the liver causing a rise in serum aminotransferase levels which were found to decrease when the dose of lomitapide was reduced or when it was stopped. Patients have their liver function tests monitored regularly (required by the SPC). Results should be interpreted with caution as they are based on single arm studies. It means that they cannot randomise patients (which can lead to biases, influencing results and hiding the true adverse effects of treatment) or compare the treatment with any other standard treatment (which means it is not possible to determine what proportion of side effects are attributable to lomitapide treatment and what proportion are likely to be a direct consequence of the disease or other lipid lowering treatment the patients were on. Similarly, there is no direct evidence that lomitapide is more or less safe than other treatments).
	Roeters van Lennep et al. 2015	2/10	Directly applicable		
Change in hepatic fat level	Blom 2017	4/10	Directly applicable	B	A healthy liver should contain little or no fat. The EPAR states that a build-up of fat in the liver is a natural consequence of the mechanism of action of lomitapide. This can progress to cirrhosis (a serious condition where normal liver tissue is replaced by scar tissue) and liver failure. The EPAR notes that hepatic steatosis (fatty liver) was recorded as fat in the liver more than 5.56%.This outcome considered how many people had changes to their hepatic (in the liver) fat levels whilst on lomitapide. The main study, Cuchel et al. 2013 with 29 patients followed up to 78 weeks after starting lomitapide assessed hepatic fat using nuclear magnetic resonance spectroscopy (if contraindicated, computerised tomography or ultrasound was used). In 20 patients there was an increase in mean hepatic fat from 1% before treatment to 8.6% after 26 weeks of treatment and 8.3% after 78 weeks of treatment. Similar increases in hepatic fat were found in other studies. In the extension of Cuchel et al. 2013, hepatic fat levels were 10.2% (95%CI 8.3% to 14.7%) at week 246 (n=11) (Blom et al. 2017).
	Cuchel 2007	5/10	Directly applicable		
	Cuchel 2013	6/10	Directly applicable		
	D'Erasmo 2017	5/10	Directly applicable		
	Harada-Shiba 2017	6/10	Directly applicable		

	Roeters van Lennep. 2015	2/10	Directly applicable		Results suggest that there is a risk of an increase in hepatic fat when taking lomitapide which is thought to be related to the way in which lomitapide works. The EPAR suggests that the increase in hepatic fat seen with lomitapide treatment can be reversed when it is stopped. The EPAR states that the impact of these findings remains unclear because of limited patient numbers and duration of exposure. Results should be interpreted with caution as they are based on single arm studies. It means that they cannot randomise patients (which can lead to biases, influencing results and hiding the true adverse effects of treatment) or compare the treatment with any other standard treatment (which means it is not possible to determine what proportion of side effects are attributable to lomitapide treatment and what proportion are likely to be a direct consequence of the disease or other lipid lowering treatment the patients were on. Similarly, there is no direct evidence that lomitapide is more or less safe than other treatments).
	Stefanutti 2016	3/10	Directly applicable		

Relevance to guidelines and NHS England policies

NICE have issued the following guidance related to familial hypercholesterolaemia:

- Familial hypercholesterolaemia: identification and management (2006, updated 2017) NICE guideline 71
- Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (2016) NICE technology appraisal guidance 385
- Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (2016) NICE technology appraisal guidance 393
- Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (2016) NICE technology appraisal guidance 394

References

Blom D J, Averna M R, Meagher E A, et al. (2017) Long-Term Efficacy and Safety of the Microsomal Triglyceride Transfer Protein Inhibitor Lomitapide in Patients With Homozygous Familial Hypercholesterolaemia. Circulation 136, 332-335

Bruckert E, Kalmykova O, Bittar R et al. (2017) Long-term outcome in 53 patients with homozygous familial hypercholesterolaemia in a single centre in France. Atherosclerosis 257, 130-137

Cuchel, M., Bruckert, E., Ginsberg, H. et al. (2014). Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. European Heart Journal, 35(32), 2146-2157

Cuchel M, Blom DJ, Averna MR et al (2013) Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet 381, 40-6

Cuchel M, Bloedon LT, Szapary PO et al. (2007) Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolaemia. New England Journal of Medicine 356, 148-56

D'Erasmo L, Cefalu A B, Noto D, et al. (2017) Efficacy of Lomitapide in the Treatment of Familial Homozygous Hypercholesterolaemia: Results of a Real-World Clinical Experience in Italy. Advances in Therapy 34, 1200-1210

France M, Rees A, Datta D et al. (2016) HEART UK statement on the management of homozygous familial hypercholesterolaemia in the United Kingdom. Atherosclerosis, 255 128-139

Ito M and Watts G (2015) Challenges in the Diagnosis and Treatment of Homozygous Familial Hypercholesterolemia. Drugs. 75 (15) 1715-1724

Harada-Shiba M et al. (2017) Efficacy and Safety of Lomitapide in Japanese Patients with Homozygous Familial Hypercholesterolaemia. Journal of Atherosclerosis & Thrombosis 24, 402-411

Roeters van Lennep RJ, Averna M, and Alonso R (2015) Treating homozygous familial hypercholesterolaemia in a real-world setting: Experiences with lomitapide. Journal of Clinical Lipidology 9, 607-17

Stefanutti C, Morozzi C, Di Giacomo, et al. (2016) Management of homozygous familial hypercholesterolaemia in real-world clinical practice: A report of 7 Italian patients treated in Rome with lomitapide and lipoprotein apheresis. Journal of Clinical Lipidology 10, 782-9

Thompson GR., Dirk J et al. (2017) Survival in homozygous familial hypercholesterolaemia is determined by the on-treatment level of serum cholesterol, European Heart Journal, ehx317

Yahya R, Favari E, Calabresi L, Verhoeven A J et al. (2016) Lomitapide affects HDL composition and function. Atherosclerosis 251, 15-18

Appendix 1 Search strategy

Database: Ovid MEDLINE
Platform: Ovid
Version: 1946 – July wk 3 2017
Search date: 01/08/2017
Number of results retrieved: 86
Search strategy:
Database: Ovid MEDLINE(R) <1946 to July Week 3 2017>
Search Strategy:
---
1 (lomitapide or lojuxta or juxtapid or AEGR-733 or AEGR 733 or BMS-201038 or BMS 201038).tw. (109)
2 Hypercholesterolaemia/ (24940)
3 (Hypercholesterol* or hypercholester*).tw. (30289)
4 (cholesterol adj4 (elevat* or high* or raise*)).tw. (49754)
5 (buerger gruetz syndrome or buerger grutz syndrome).tw. (0)
6 hyperbetalipopoprotein*.tw. (0)
7 (Gout adj lipoid).tw. (0)
8 harbitz mueller syndrome.tw. (0)
9 (hyper adj4 lipoprotein*).tw. (154)
10 ldl receptor disorder.tw. (1)
11 (mckusick 14430 or mckusick 1440).tw. (0)
12 (tendinous adj xantho*).tw. (106)
13 (tendon adj xanthogranulomatosis).tw. (0)
14 or/2-13 (83823)
15 1 and 14 (92)
16 animals/ not humans/ (4409697)
17 15 not 16 (92)
18 limit 17 to english language (86)

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 2013 to Daily Update
Platform: Ovid
Version: see above
Search date: 01/08/2017
Number of results retrieved:107
Search strategy
Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 2013 to Daily Update
Search Strategy:
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1 (lomitapide or lojuxta or juxtapid or AEGR-733 or AEGR 733 or BMS-201038 or BMS 201038).tw. (129)
2 Hypercholesterolaemia/ (3459)
3 (Hypercholesterol* or hypercholester*).tw. (7637)
4 (cholesterol adj4 (elevat* or high* or raise*)).tw. (15855)
5 (buerger gruetz syndrome or buerger grutz syndrome).tw. (0)
6 hyperbetalipopoprotein*.tw. (0)
7 (Gout adj lipoid).tw. (0)
8 harbitz mueller syndrome.tw. (0)
9 (hyper adj4 lipoprotein*).tw. (32)

10 ldl receptor disorder.tw. (0)
11 (mckusick 14430 or mckusick 1440).tw. (0)
12 (tendinous adj xantho*).tw. (19)
13 (tendon adj xanthogranulomatosis).tw. (0)
14 or/2-13 (23206)
15 1 and 14 (113)
16 animals/ not humans/ (563588)
17 15 not 16 (113)
18 limit 17 to english language (107)

Database: Embase
Platform: Ovid
Version: 1974 to 2017 wk 31
Search date: 01/08/2017
Number of results retrieved: 348
Search strategy:

Database: Embase <1974 to 2017 Week 31>
Search Strategy:
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1 lomitapide/ (399)
2 (lomitapide or lojuxta or juxtapid or AEGR-733 or AEGR 733 or BMS-201038 or BMS 201038).tw. (293)
3 1 or 2 (471)
4 Familial hypercholesterolaemia/ (7386)
5 (Hypercholesterol* or hypercholester*).tw. (43331)
6 (cholesterol adj4 (elevat* or high* or raise*)).tw. (68609)
7 (buerger gruetz syndrome or buerger grutz syndrome).tw. (0)
8 hyperbetalipopoprotein*.tw. (0)
9 (Gout adj lipoid).tw. (0)
10 harbitz mueller syndrome.tw. (0)
11 (hyper adj4 lipoprotein*).tw. (194)
12 ldl receptor disorder.tw. (1)
13 (mckusick 14430 or mckusick 1440).tw. (0)
14 (tendinous adj xantho*).tw. (141)
15 (tendon adj xanthogranulomatosis).tw. (0)
16 or/4-15 (105718)
17 3 and 16 (356)
18 nonhuman/ not human/ (4027223)
19 17 not 18 (356)
20 limit 19 to english language (348)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED
Platform: Wiley
Version:
CDSR –8 of 12, August 2017
DARE – 2 of 4, April 2015 (legacy database)
CENTRAL – 7 of 12, July 2017
HTA – 4 of 4, October 2016
NHS EED – 2 of 4, April 2015 (legacy database)
Search date:

Number of results retrieved: CDSR –0; DARE 0 ; CENTRAL 13 ; HTA 3 ; NHS EED 0
.
Search strategy:
Search Name:
Date Run: 01/08/17 13:16:39.3
Description:

ID	Search	Hits
#1	lomitapide or lojuxta or juxta pid or AEGR-733 or AEGR 733 or BMS-201038 or BMS 201038:ti,ab,kw (Word variations have been searched)	16

Appendix 2 Study selection

The search strategy presented in Appendix 1 yielded 335 studies. After removing duplicates 331 records were screened on title, abstract and full text articles in EPPI Reviewer according to the inclusion and exclusion criteria in table 4.

Table 4 Inclusion and exclusion criteria for titles, abstracts and full text articles

Screening criteria	Inclusion	Exclusion
Population	Homozygous familial hypercholesterolaemia, including compound heterozygous hypercholesterolaemia	Heterozygous hypercholesterolaemia (except compound heterozygous hypercholesterolaemia)
Intervention	Lomitapide alone or in combination with other treatments	Any intervention without lomitapide
Comparator	Any	None
Outcomes	Any	None
Other		Abstracts Non-English language Duplicates Case reports of 1 or 2 participants Opinion pieces Commentaries

		Full text paper not available Editorials Epidemiological studies Burden of disease studies

Table 5 Studies excluded based on full text

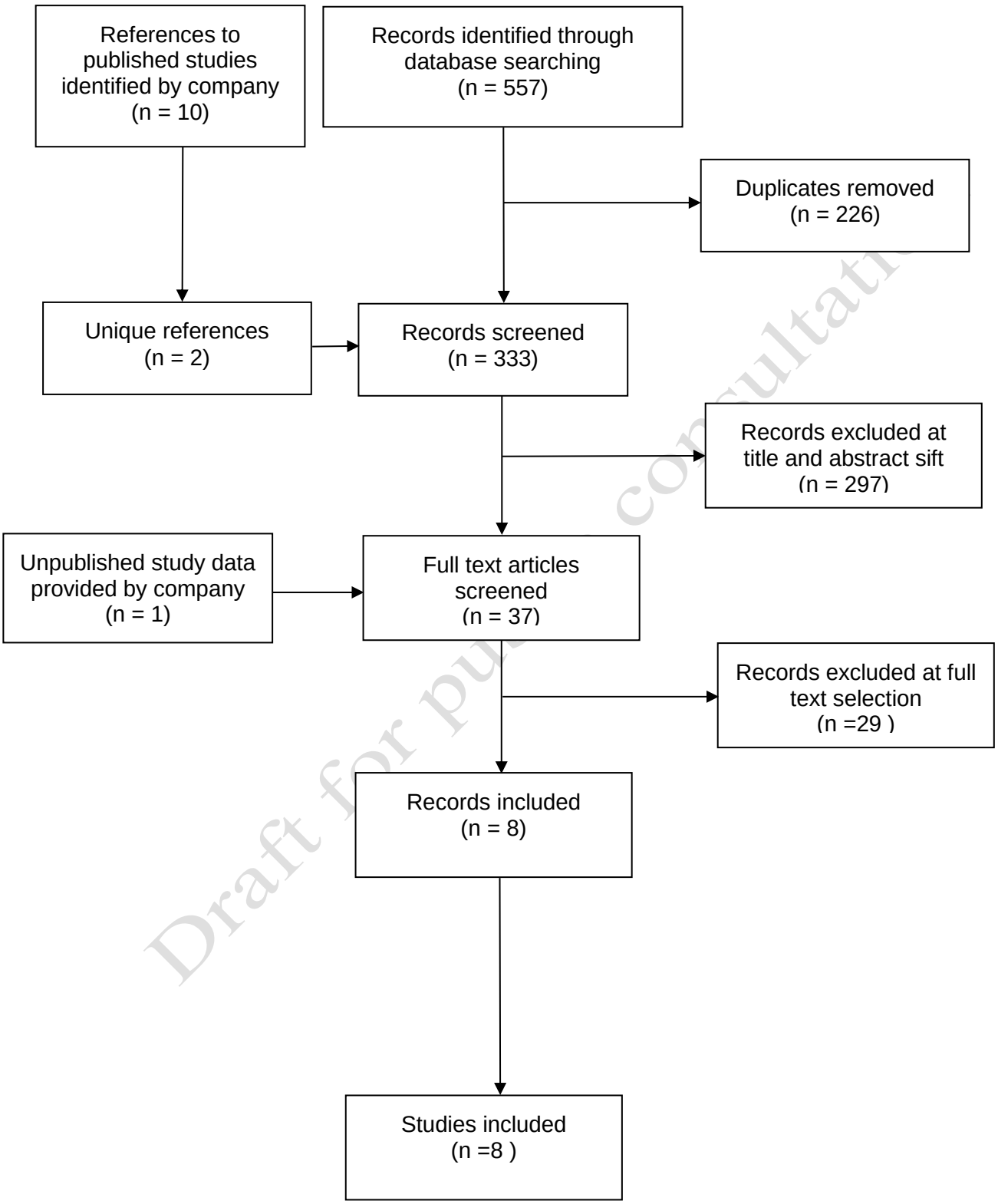
Study reference	Reason for exclusion
Averna M, Cuchel M, Meagher E et al. (2012) A phase 3 study of lomitapide, a microsomal triglyceride transfer protein (MTP) inhibitor, in patients with homozygous familial hypercholesterolaemia (HoFH). Perfusion, vol 25, issue 5, p 174	Full paper unavailable
Averna M, Cuchel M, Meagher E et al. (2012) A phase 3 study of lomitapide, a microsomal triglyceride transfer protein (MTP) inhibitor, in patients with homozygous familial hypercholesterolaemia (HoFH). Perfusion, vol 25, issue 5, p 175	Abstract only
Averna M, Cefalu A B, Stefanutti C, Di Giacomo , S , Sirtori C R, and Vigna G (2016) Individual analysis of patients with HoFH participating in a phase 3 trial with lomitapide: The Italian cohort. Nutrition Metabolism & Cardiovascular Diseases 26, 36-44	Original phase 3 open label study already included in the review
Blom D, Averna M, Meagher E et al. (2015) Abstract 12450: Long-Term Efficacy and Safety of Lomitapide for the Treatment of Homozygous Familial Hypercholesterolaemia: Results of the Phase 3 Extension Trial. Circulation, vol 132, p A12450	Abstract
Blom D, Kastelein JJ, Larrey D et al. (2015) Abstract 10818: Lomitapide Observational Worldwide Evaluation Registry (LOWER): One-Year Data. Circulation, vol 132, p A10818	Abstract
Bruckert E, Kalmykova O, Bittar R et al. (2017) Long-term outcome in 53 patients with homozygous familial hypercholesterolaemia in a single centre in France. Atherosclerosis 257, 130-137	Exclude based on intervention not including lomitapide
Cuchel M (2012) A phase 3 study of the Microsomal Triglyceride Transfer protein (MTP) inhibitor lomitapide in patients with homozygous familial hypercholesterolaemia. European Heart Journal 33, 951	Abstract

Cuchel M, Blom DJ, Averna MR et a. (2013) Abstract 16516: Sustained LDL-C Lowering and Stable Hepatic Fat Levels in Patients With Homozygous Familial Hypercholesterolaemia Treated With the Microsomal Triglyceride Transfer Protein Inhibitor, Lomitapide: Results of an Ongoing Long-Term Extension Study. Circulation, vol 128, p A16516	Abstract
Cuchel M, Meagher E A, Shah P K, Bloedon L A. T, and Rader D J (2013) Apheresis treatment did not impact the efficacy of lomitapide in patients with homozygous familial hypercholesterolaemia: Results from the pivotal phase. Journal of Clinical Lipidology 7 (3), 286-287	Abstract
Cuchel M, Meagher EA, Shah PK et al. (2013). Management of aminotransferase elevations observed in a phase 3 study of patients with homozygous familial hypercholesterolaemia treated with lomitapide. Journal of Clinical Lipidology, vol 7, issue 3, p 263-264	Abstract
Cuchel M, Meagher EA, Toit Theron H et al. (2012) Abstract 17396: Apheresis Treatment does not Affect the Lipid-Lowering Efficacy of Lomitapide, a Microsomal Triglyceride Transfer Protein Inhibitor, in Patients with Homozygous Familial Hypercholesterolaemia. Circulation, vol 126, p A17396	Abstract
Cuchel M, Meagher E, Marais AD et al. (2010) L5 PHASE 3 study of microsomal triglyceride transfer protein inhibitor (MTP-I) lomitapide in subjects with homozygous familial hypercholesterolaemia (hOFH): 56-week results. Atherosclerosis supplements, vol 11, issue 2, p14	Abstract
Davidson M, Littlejohn T, Rodstein S et al. (2009) Efficacy, safety and tolerability of the MTP inhibitor AEGR-733 combined with atorvastatin. Atherosclerosis supplements, vol 10, issue 2, p e781	Abstract
Dunbar R, Bloedon L, Duffy D et al. (2009) Impact of high doses of the MTP-inhibitor, AEGR-733, on the single dose pharmacokinetics of atorvastatin and rosuvastain. Atherosclerosis supplements, vol 10, issue 2, p e780	Abstract
Dunbar R, Bloedon L, Gadi R et al. (2009) Impact of the MTP-inhibitor AEGR-733 on the single-dose pharmacokinetics of extended-release niacin. Atherosclerosis Supplement, vol 10, issue 2, p e782	Abstract
Harada-Shiba M, Yoshida M, Ikewakei K et al. (2015) Abstract 12468: Efficacy and Safety of Lomitapide in Japanese Patients With Homozygous Familial Hypercholesterolaemia on Concurrent Lipid-Lowering Therapy. Circulation, vol 132, p A12468	Abstract
Kolovou G, Vasiliadis I, Gontoras N et al. (2015) Microsomal transfer protein inhibitors, new approach	Review article reporting 2 cases with no outcome

for treatment of familial hypercholesterolaemia, review of the literature, original findings, and clinical significance. Cardiovascular Therapeutics, vol 33, p71-78	measures
Kolovou G D, Kolovou V, Papadopoulou A, and Watts G F (2016) MTP Gene Variants and Response to Lomitapide in Patients with Homozygous Familial Hypercholesterolaemia. Journal of Atherosclerosis & Thrombosis 23, 878-83	Exclude based on study question not being relevant
Leipold R, Raal F, Ishak J, et al. (2016) Potential efficacy of lomitapide, a MTP (microsomal triglyceride transfer protein) inhibitor, on survival in homozygous familial hypercholesterolaemia (HOFH): Results of an event modelling analysis. Value in Health 19 (7), A373-A374	Abstract
Leipold R, Raal F, Ishak J, et al. (2016) Potential efficacy of lomitapide, a MTP (microsomal triglyceride transfer protein) inhibitor, on survival in homozygous familial hypercholesterolaemia (HOFH): Results of an event modelling analysis. (manuscript provided by the company)	Exclude based on study type
Liu X, Men P, Wang Y, Zhai S, Zhao Z, and Liu G (2017) Efficacy and Safety of Lomitapide in Hypercholesterolaemia. American Journal of Cardiovascular Drugs 17, 299-309	Exclude based on population. Relevant individual studies extracted and included
Rader DJ (2012) A phase 3 study of the microsomal triglyceride transfer protein (MTP) inhibitor lomitapide in patients with homozygous familial hypercholesterolaemia. Journal of clinical lipidology, vol 6, issue 3, p282-283	Abstract
Sahebkar A and Watts G F (2013) New LDL-cholesterol lowering therapies: pharmacology, clinical trials, and relevance to acute coronary syndromes. Clinical Therapeutics 35, 1082-98	Review article
Samaha F, McKenney J, Bloedon L T, Sasiela W J, and Rader D J (2008) Inhibition of microsomal triglyceride transfer protein alone or with ezetimibe in patients with moderate hypercholesterolaemia. Nature Clinical Practice Cardiovascular Medicine 5, 497-505	Exclude based on population including all adults with hypercholesterolaemia
Stefanutti C, Blom D J, Averna M R, Meagher E A, Theron Hd, Marais A D, Hegele R A, Sirtori C R, Shah P K, Gaudet D, Vigna G B, Sachais B S, Di Giacomo , S , du Plessis, A M, Bloedon L T, Balser J, Rader D J, Cuchel M, Phase 3 Ho, and F H Lomitapide Study Investigators (2015) The lipid-lowering effects of lomitapide are unaffected by adjunctive apheresis in patients with homozygous familial hypercholesterolaemia - a post-hoc analysis of a Phase 3, single-arm, open-label trial. Atherosclerosis 240, 408-14	Exclude based on outcomes

Taubel J, Sumeray M, Lorch U, and McLean A (2016) Pharmacokinetics and Pharmacodynamics of Lomitapide in Japanese Subjects. Journal of Atherosclerosis & Thrombosis 23, 606-20	Exclude based on population
Toth P, Case D, Joshi P et al. (2015) Impact of lomitapide and lomitapide/ezetimibe combination therapy on low-density lipoprotein subfractions and risk marker ratios. Atherosclerosis 241, e203-e204	Abstract
Tuteja S, Duffy D, Dunbar R L, Movva R, Gadi R, Bloedon L T, and Cuchel M (2014) Pharmacokinetic interactions of the microsomal triglyceride transfer protein inhibitor, lomitapide, with drugs commonly used in the management of hypercholesterolaemia.	Exclude based on study type being pharmacokinetic-pharmacodynamic with no relevant outcomes
Zimetti F, Favari E, Adorni M P, Ronda N, Bernini F, Cefalu A B, Averna M, Yahya R, Bos S, Verhoeven A, Sijbrands E, Roeters Van Lennep, J, and Mulder M (2015) Lomitapide treatment highly affects lipoprotein profile and HDL functionality in patients with familial hypercholesterolaemia. Atherosclerosis 241 (1), e112	Abstract

Figure 1 Flow chart of included studies



Appendix 3 Evidence tables

Table 6 Blom et al 2017

Study reference	Blom D J, Averna M R, Meagher E A, et al. (2017) Long-Term Efficacy and Safety of the Microsomal Triglyceride Transfer Protein Inhibitor Lomitapide in Patients With Homozygous Familial Hypercholesterolaemia. Circulation 136, 332-335
Unique identifier	NCT00943306
Study type (and NSF-LTC study code)	Phase 3, long term, single-arm open-label, follow on study of NCT00730236 (Cuchel et al.2013) (P1 Primary research using quantitative approaches)
Aim of the study	To provide additional long-term efficacy and safety data (including an exploratory analysis of the potential metabolic consequences of hepatic fat accumulation)
Study dates	September 2009 to December 2014
Setting	Centres in US, Canada, Italy and South Africa
Number of participants	19
Population	Adults (mean age 30.4 years, 10 male and 9 female) with homozygous familial hypercholesterolaemia (HoFH) on maximum tolerated dose of lomitapide in combination with lipid lowering therapy (including lipoprotein apheresis) which could be modified
Inclusion criteria	Adults with HoFH who completed the pivotal study NCT00730236
Exclusion criteria	Patients with HoFH who met any of the stopping rules for study discontinuation at the final visit of NCT00730236 study
Intervention(s)	Maximum tolerated dose of lomitapide (up to 80 mg/day) in addition to existing lipid lowering therapy including plasmapheresis or lipid apheresis
Comparator(s)	None
Length of follow-up	78 weeks of pivotal study (NCT00730236) and 48 weeks extension phase
Outcomes	Primary outcome: Percentage change in low density lipoprotein cholesterol (LDL-C) after 48 weeks of the extension study
	Secondary outcomes: • Percentage change in lipid parameters • Percentage change in hepatic fat
	Safety outcomes: • Adverse events
Source of funding	Aegerion Pharmaceuticals

NSF-LTC

Criteria	Score	Narrative description of study quality
1. Are the research questions/aims and design clearly stated?	1/2	Aim is described and appropriate but design not clearly stated
2. Is the research design appropriate for the aims and objectives of the research?	1/2	Clear and appropriate for the type of study. However, the design is itself is prone to bias and the sample size is small.
3. Are the methods clearly described?	1/2	Methods not fully described and population characteristics unclear, however it is prospective follow up from the main phase 3 trial. Open-label extension studies can be prone to bias. Changes to lipid lowering therapy was allowed which increases confounding. Small sample size.
4. Are the data adequate to support the authors' interpretations / conclusions?	0/2	Limitations in study methods reduce the confidence in the data, and thus the conclusions
5. Are the results generalisable?	1/2	There were no details on the patient characteristics in the study. Therefore there is uncertainty in the generalisability
Total	4/10	
Applicability *	Directly applicable	The intervention and the indication are directly relevant to the decision problem.

Table 7 Cuchel et al 2007

Study reference	Cuchel M, Bloedon LT, Szapary PO et al. (2007) Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolaemia. New England Journal of Medicine 356, 148-56
Unique identifier	Not specified in the paper
Study type (and NSF-LTC study code)	Phase 2 single-arm open-label study (P1 Primary research using quantitative approaches)
Aim of the	To evaluate the safety, tolerability, and efficacy of lomitapide

study	(BMS-201038) for the treatment of patients with homozygous familial hypercholesterolaemia (HoFH).
Study dates	Not clearly stated in the paper, total study was 16 weeks
Setting	General clinical research centre in Pennsylvania, US
Number of participants	6
Population	Adults with HoFH (3 males and 3 females aged between 18 and 40 years). Two of the patients had significant cardiovascular disease (both had undergone prosthetic-valve replacement and were receiving anticoagulation therapy). All lipid lowering treatments, including apheresis, were suspended at least 4 weeks before the baseline visit and continued to be suspended until the study was completed. No other drug treatment was suspended.
Inclusion criteria	Patients with HoFH
Exclusion criteria	Exclusion criteria were major surgery in the previous 3 months, congestive heart failure, history of liver disease or aminotransferase levels of more than 3 times the upper limit of the normal range, a serum creatinine level of more than 2.5 mg/dL (221 micromol/L), cancer within the past 5 years, or history of alcohol abuse or drug abuse.
Intervention(s)	Lomitapide (BMS-201038) was administered at 4 different doses (0.03, 0.1, 0.3, and 1.0 mg/kg of body weight per day), to each patient for 4 weeks, and returned for a final visit after a 4-week drug washout period. The patients were advised to consume a diet containing less than 10% of energy from total dietary fat while consuming adequate calories to maintain weight or promote growth. All patients received a standard multivitamin that supplied 100% of the reference dietary intake for all vitamins and minerals.
Comparator(s)	None
Length of follow-up	The patients returned to the research centre at days 7, 14, and 28 after the start of a new dose, and 28 days after the last dose of the study drug
Outcomes	• Percentage change in low density lipoprotein cholesterol (LDL-C) • Percentage change in apolipoprotein B, apolipoprotein A-1 • Percentage change in high density lipoprotein cholesterol (HDLC) • Percentage change in triglycerides (TG)
	Safety outcomes: • Adverse events
Source of funding	Supported by a Distinguished Clinical Scientist Award from the Doris Duke Charitable Foundation (to one of the authors) and grants (K12-RR017625 and M01-RR00040) from the National

	Centre for Research Resources.

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	1/2	Both the aim and the type of research design are clearly stated in the study, however the design of the study has not been adequately described.
2. Is the research design appropriate for the aims and objectives of the research?	1/2	The study was a phase 2 dose escalation study and appears to be appropriate to assess the main objectives of the study. However, the open-label nature of the study makes it prone to biases and confounding. Also the study has a small sample size.
3. Are the methods clearly described?	1/2	Some details of methods provided. However, the type of study is prone to biases and confounding. Also the sample size is small.
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	Limitations in the study methods reduce the confidence in the data, and thus the conclusions.
5. Are the results generalisable?	1/2	Too limited details available to be certain if generalisable. Population and indication appear generalizable.
Total	5/10	
Applicability *	Directly applicable	The intervention and the indication are directly relevant to the decision problem

Table 8 Cuchel et al. 2013

Study reference	Cuchel M, Blom DJ, Averna MR et al (2013) Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet 381, 40-6

Unique identifier	NCT00730236
Study type (and NSF-LTC study code)	Phase 3 single-arm open-label study (P1 Primary research using quantitative approaches)
Aim of the study	To assess the efficacy and safety of the microsomal triglyceride transfer protein inhibitor lomitapide in adults with homozygous familial hypercholesterolaemia (HoFH) disease.
Study dates	December 2007 to October 2011
Setting	11 centres across USA, Canada, South Africa, and Italy
Number of participants	29
Population	Adult patients with HoFH. This included patients with homozygotes or compound heterozygotes for mutations in the LDLR gene or genes affecting LDL-receptor functionality. The mean age was 30 years old with 86% of the patients of white origin. Ninety-three percent of the patients had cardiovascular disease. Ninety-three percent of the patients were treated with statins, primarily rosuvastatin or atorvastatin and 76% with ezetimibe (all in combination with a statin). Sixty-two percent of the patients regularly underwent apheresis with a frequency that ranged from weekly to every 6 weeks. During the run-in phase (before the efficacy phase) dietary vitamin E and fatty acids were taken as dietary supplements as part of a low fat diet. During the efficacy phase (week 0 to 26) there was no dose modification of concomitant lipid lowering treatment. Lipid lowering treatment could be modified in the safety phase (week 26 to 78.
Inclusion criteria	Adults with HoFH based either on clinical criteria (history of untreated total cholesterol of greater than 13 mmol/L and triglycerides of less than 3·4 mmol/L and both parents with history of untreated total cholesterol of greater than 6·5 mmol/L) or on documented mutation(s) in both alleles of the LDL receptor or of other genes known to affect LDL receptor function. Enrolled patients were required to enter a minimum 6-week run-in phase during which concomitant lipid-lowering therapies, including apheresis, the daily dietary supplementation of vitamin E, and essential fatty acids were initiated, and the required low-fat diet was stabilised.
Exclusion criteria	Patients who had: major surgery in the previous 3 months, congestive heart failure, history of liver disease or aminotransferase greater than twice the upper limit of normal, serum creatinine greater than 221 micromol/L, recent malignancy, alcohol or drug abuse, known bowel disease or malabsorption, or chronic lung disease.
Intervention(s)	Lomitapide was initiated at a starting dose of 5 mg a day for the first 2 weeks and then escalated to 10 mg, 20 mg, 40 mg, and 60 mg a day at 4-week intervals or until an individually determined maximum dose was achieved on the basis of safety and

	tolerability.
Comparator(s)	Not applicable
Length of follow-up	The full study was 78 weeks this included 26 weeks of the efficacy phase followed by 52 weeks of the safety phase. Eligible patients completing the treatment phase were offered the option to enter a separate long-term study, in which they continued to receive lomitapide. Patients who did not enter the long-term study discontinued lomitapide at week 78 and returned for a final follow-up visit at week 84 (6-weeks after the end of the safety phase).
Outcomes	Primary outcome: • Percentage change from baseline in concentration of low density lipid cholesterol (LDL-C) at the maximum tolerated dose after 26 weeks of treatment.
	Secondary outcomes: • Percentage changes in other lipid parameters
	Safety outcomes: • Treatment emergent events • Changes in hepatic-fat content
Source of funding	FDA office of the orphan product development, Aegerion Pharmaceuticals.

NSF-LTC

Criteria	Score	Narrative description of study quality
1. Are the research questions/aims and design clearly stated?	2/2	Clear and appropriate
2. Is the research design appropriate for the aims and objectives of the research?	1/2	Open-label nature of the study with no comparator.
3. Are the methods clearly described?	1/2	Methods well described in manuscript. Powered adequately as number of participants included was greater than 20 as calculated in the study. However, limitations in study methods, such as some potential for bias given the study type with no control group, and confounding (due to changes in lipid-lowering therapy and apheresis frequency).

4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	The data supports the author's conclusions. However, there are a number limitations of the methods used in the study. These had been adequately addressed by the author in their interpretation
5. Are the results generalisable?	1/2	The participants enrolled in this study were representative of the adults with HoFH taking the usual lipid-lowering therapy and/or apheresis. As the study enrolled non-UK adults with HoFH, the results may not be fully generalisable.
Total	6/10	
Applicability *	Directly applicable	The intervention and indication are directly relevant to the decision problem

Table 9 D'Erasmo et al 2017

Study reference	D'Erasmo L, Cefalu A B, Noto D, et al. (2017) Efficacy of Lomitapide in the Treatment of Familial Homozygous Hypercholesterolaemia: Results of a Real-World Clinical Experience in Italy. Advances in Therapy 34, 1200-1210
Unique identifier	Not specified in the paper
Study type (and NSF-LTC study code)	Retrospective observational study (P1 Primary research using quantitative approaches)
Aim of the study	To evaluate the benefits of lomitapide in adults with homozygous familial hypercholesterolaemia (HoFH) followed with usual clinical care
Study dates	Not clearly stated in the paper
Setting	Lipid clinics across Italy
Number of participants	15
Population	Adults (mean age 37.7±13.5 years, 9 females and 6 males) with HoFH. 14 of the adults were Italian and 1 was from Jordan. 13 patients had a history of coronary heart disease and 6 patients reported evidence of aortic valve stenosis. All of the patients were receiving standard lipid lowering treatment with a statin and/or ezetimibe and 10 patients were also on

	lipoprotein apheresis (LA). 4 of the patients included in this study were previously enrolled in the phase 3 study NCT00730236.
Inclusion criteria	Adults with HoFH who have been on lomitapide treatment for at least 6 months
Exclusion criteria	Not specified
Intervention(s)	Lomitapide daily in addition to lipid lowering treatment
Comparator(s)	None
Length of follow-up	Mean follow-up was 32.3±29.7 months
Outcomes	• Percentage change in low density lipoprotein cholesterol (LDL-C) • Percentage change in total cholesterol (TC) • Percentage change in high density lipoprotein cholesterol (HDLC) • Percentage change in triglycerides (TG) • Percentage change in non-HDLC
	Safety outcomes: • Adverse events
Source of funding	No sponsorship was received to fund and write up this study

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**

1. Are the research questions/aims and design clearly stated?	1/2	Clear and appropriate for an observational study
2. Is the research design appropriate for the aims and objectives of the research?	1/2	Retrospective study with no comparator
3. Are the methods clearly described?	1/2	Methods are described in the paper. However there are some limitations due the type of study being retrospective and observational making it prone to biases and confounding. Also there was a small sample size with no power calculations.
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	Limitations in the study methods reduce the confidence in the data, and thus the conclusions. Authors do acknowledge study limitations in their conclusions
5. Are the results generalisable?	1/2	This was a retrospective study for adults who were already on lomitapide treatment in addition to lipid lowering treatment.
Total	5/10	
Applicability *	Directly applicable	The intervention and indication are relevant to the decision problem

Table 10 Harada-Shiba et al 2017

Study reference	Harada-Shiba M et al. (2017) Efficacy and Safety of Lomitapide in Japanese Patients with Homozygous Familial Hypercholesterolaemia. Journal of Atherosclerosis & Thrombosis 24, 402-411
Unique identifier	Not specified in the paper
Study type (and NSF-LTC study code)	Phase 3 single-arm open label study (P1 Primary research using quantitative approaches)
Aim of the study	The primary aim of this study was to evaluate the efficacy of lomitapide in reducing low density lipoprotein cholesterol (LDL-C) in combination with other lipid lowering treatments in Japanese adults with homozygous familial hypercholesterolaemia (HoFH)
Study dates	Not clearly stated in the paper

Setting	Six centres in Japan
Number of participants	9
Population	Japanese adults (aged between 33 to 75 years, 4 female and 5 males) with HoFH. All patients had documented low density lipoprotein receptor (LDLR) defects consistent with a diagnosis of HoFH. All patients were on concomitant lipid lowering treatment (combination of statin, ezetimibe and bile acid sequestrant), including 6 on lipoprotein apheresis. No other information on medical history provided. During the lomitapide dose escalation period (efficacy phase), lipid lowering treatment doses remained fixed. During the lomitapide dose maintenance period (safety phase), lipid lowering treatment could be adjusted. During the run-in phase (before the efficacy phase) dietary vitamin E and fatty acids were taken as dietary supplements as part of a low fat diet.
Inclusion criteria	Japanese men and women 18 years or older with functional HoFH. Diagnosis of HoFH had to be based on 1 or more criteria as specified in the study protocol.
Exclusion criteria	People with uncontrolled hypertension, history of chronic renal insufficiency, or significant liver disease were excluded from enrolment in the study. Patients who required use of potentially hepatotoxic medications, especially those that could induce microvesicular or macrovesicular steatosis, were also excluded. In addition, patients who required use of strong or moderate CYP3A4 inhibitors or simvastatin at a dose of more than 10 mg daily, and patients who were unable to limit their alcohol consumption to no more than 1 alcoholic drink per day were excluded.
Intervention(s)	During the efficacy phase, oral lomitapide was initiated at 5 mg/day and escalated to each patient's maximum tolerated dose (up to a maximum of 60 mg/day) in addition to existing lipid lowering treatments.
Comparator(s)	None
Length of follow-up	Efficacy phase was 26 weeks and the safety phase was 30 weeks.
Outcomes	Primary outcome: • Mean percentage change from baseline to Week 26 in directly measured LDL-C at the maximum tolerated dose of lomitapide
	Secondary outcomes: • Mean percentage change in other lipid parameters: total cholesterol (TC); non-high-density lipoprotein cholesterol (non-HDLC); very low density lipoprotein cholesterol (VLDL-C);triglycerides; apolipoprotein B; lipoprotein(a); high density lipoprotein cholesterol (HDLC); and apolipoprotein A-1.
	Safety outcomes: • Treatment-emergent adverse events

	• Liver function tests • Laboratory parameters, electrocardiogram results, vital signs, physical examinations, and weight. • Hepatic fat percentage
Source of funding	Aegerion Pharmaceuticals

NSF-LTC

Criteria	Score	Narrative description of study quality
1. Are the research questions/aims and design clearly stated?	2/2	Clear and appropriate
2. Is the research design appropriate for the aims and objectives of the research?	1/2	Clear and appropriate for type of study, however open-label with no comparator.
3. Are the methods clearly described?	1/2	Methods well described in manuscript. However, limitations in study methods, such as some potential for bias given the study type with no control group, and confounding. Sample size is small with no power calculation.
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	The data partially supports the author's conclusions. However, there are a number limitations of the methods used in the study. These had not been adequately addressed by the author in their interpretation
5. Are the results generalisable?	1/2	The study includes adults with HoFH taking the usual lipid-lowering therapy and/or apheresis. However, the study was carried out in Japanese adults with HoFH and so the results are only partially generalisable.

Total	6/10	
Applicability	Directly applicable	The intervention and indication are directly relevant to the decision problem

Table 11 Roeters van Lennep et al 2015

Study reference	Roeters van Lennep RJ, Averna M, and Alonso R (2015) Treating homozygous familial hypercholesterolaemia in a real-world setting: Experiences with lomitapide. Journal of Clinical Lipidology 9, 607-17
Unique identifier	Not specified in study paper
Study type (and NSF-LTC study code)	Case series (appears to be retrospective) (P1 Primary research using quantitative approaches)
Aim of the study	To review 4 individual real world patients with homozygous familial hypercholesterolaemia (HoFH) who received lomitapide to illustrate how these patients responded to therapy and to demonstrate how side-effects were managed in the clinical practice setting
Study dates	2014 to 2015
Setting	Clinical practice setting in Netherlands, Spain and Italy
Number of participants	4
Population	Adults with HoFH, 3 females and 1 male. 2 adults were compound heterozygote and 2 were homozygotes. Patient 1 (age 20 years) was maintained on a statin and a bile acid sequestrant. No other medical history reported. Patient 2 (age 62 years) was diagnosed later in life with HoFH in 2014 which was treated with a statin. Medical history included percutaneous coronary intervention (4 stents implanted) and type 2 diabetes. Evidence of moderate hepatic stenosis was also reported. Patient 3 (age 42 years) was treated with a number of different lipid lowering therapies including statins, ezetimibe and bile acid sequestrants. Medical history included coronary bypass and aortic valve replacement. Evidence of hepatic stenosis was reported. Patient 4 (age 36 years) was on lipid apheresis and lipid lowering treatments such as a statin and ezetimibe. Medical history included coronary bypass grafts (twice) and mechanical aortic valve replacement 3 (patients 1,3 and 4) of the 4 patients carried on with lipid lowering treatment whilst on lomitapide Low density lipoprotein cholesterol levels (LDL-C) of the patients ranged between 7.3 mmol/L and 14.11 mmol/L whist on conventional treatment.

Inclusion criteria	Not applicable
Exclusion criteria	Not applicable
Intervention(s)	Lomitapide administered according to prescribed protocol (dose range from 5 mg to 60 mg)
Comparator(s)	None
Length of follow-up	This varied between 20 and 50 weeks
Outcomes	• Percentage change in LDL-C • Percentage change in total cholesterol (TC) • Percentage change in high-density lipoprotein cholesterol (HDLC) • Percentage change in triglycerides (TG)
	Safety outcomes: • Adverse events
Source of funding	Publication of the paper was sponsored by Aegerion Pharmaceuticals

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**

1. Are the research questions/aims and design clearly stated?	1/2	The research aim is stated however, the design of the study was not reported
2. Is the research design appropriate for the aims and objectives of the research?	0/2	There were no details on the study design to assess for appropriateness.
3. Are the methods clearly described?	0/2	No details of the methods as a whole, but methods used for each case in the study briefly described. The type of study is prone to biases and confounding. Small sample size to make inferences from.
4. Are the data adequate to support the authors' interpretations / conclusions?	0/2	Limitations in the study methods reduce the confidence in the data and thus the conclusions
5. Are the results generalisable?	1/2	Too limited details available to be certain if generalisable but population and indication appear generalisable
Total	2/10	
Applicability *	Directly applicable	The intervention and the indication are directly relevant to the decision problem

Table 12 Stefanutti et al 2016

Study reference	Stefanutti C, Morozzi C, Di Giacomo S et al. (2016) Management of homozygous familial hypercholesterolaemia in real-world clinical practice: A report of 7 Italian patients treated in Rome with lomitapide and lipoprotein apheresis. Journal of Clinical Lipidology 10, 782-9
Unique identifier	Not specified in study paper
Study type (and NSF-LTC study code)	Case series (appears to be retrospective) (P1 Primary research using quantitative approaches)
Aim of the study	To examine the efficacy and safety of lomitapide in 7 H homozygous familial hypercholesterolaemia (HoFH) patients treated with lipoprotein apheresis (LA)
Study dates	Start dates and follow-up varied for each patient
Setting	Clinical practice setting in Italy

Number of participants	7
Population	Adults with genetically determined HoFH receiving LA. 5 patients were receiving LA biweekly and 2 were receiving LA weekly. 2 males and 6 females aged between 23 and 32 years. 4 patients had slight aortic valve disease, 2 patients had moderate aortic valve disease and 1 adult had coronary artery disease with previous bypass and aortic and mitral valves replaced. Prior to treatment with lomitapide, statins were stopped in those patients who were taking them however ezetimibe was still continued. No sign of accumulation of fat in the liver was seen at baseline (prior to lomitapide treatment) in any of the adults included in this case series
Inclusion criteria	Not applicable
Exclusion criteria	Not applicable
Intervention(s)	Lomitapide administered according to the product label and vitamins given accordingly (dose range from 5 mg to 60 mg)
Comparator(s)	None
Length of follow-up	Varied between 12 and 50 weeks
Outcomes	• Percentage change in low density lipoprotein cholesterol (LDL-C) • Percentage change in total cholesterol (TC) • Percentage change in non-high-density lipoprotein cholesterol (non-HDLC) • Percentage change in frequency of LA • Rebound of LDL-C, TC and non-HDLC levels post-LA
	Safety outcomes: • Adverse events
Source of funding	The states that the editorial support was funded by Aegerion

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**

1. Are the research questions/aims and design clearly stated?	1/2	Design not clearly stated
2. Is the research design appropriate for the aims and objectives of the research?	1/2	Due to the rarity of the disease the research design although not clearly stated is appropriate as the aim was to 'examine' the efficacy and safety of lomitapide in a real world setting
3. Are the methods clearly described?	0/2	Limited details of methods. The type of study is prone to biases and confounding not being taken into account. No sample size calculations as small population included
4. Are the data adequate to support the authors' interpretations / conclusions?	0/2	Limitations in the study methods reduce the confidence in the data and thus the conclusions
5. Are the results generalisable?	1/2	The study population, intervention and outcomes match the decision problem, however due to the limitations in the methodology there is uncertainty in the generalisability of these results
Total	3/10	
Applicability *	Directly applicable	The intervention and the indication are directly relevant to the decision problem

Table 13 Yahya et al 2016

Study reference	Yahya R, Favari E, Calabresi L, Verhoeven A J et al. (2016) Lomitapide affects HDL composition and function. Atherosclerosis 251, 15-18
Unique identifier	Not specified in study paper
Study type (and NSF-LTC study code)	Single-arm open-label study (P1 Primary research using quantitative approaches)
Aim of the study	To determine the effect of lomitapide treatment on the capacity of high density lipoprotein (HDL) to promote cholesterol efflux from macrophages in 4 homozygous familial hypercholesterolaemia (HoFH) patients

Study dates	Not clearly stated in the paper
Setting	Medical centre in the Netherlands and a university hospital in Italy
Number of participants	4
Population	Adults with HoFH (ages 20, 29, 36 and 62 years). Three of the patients had a history of cardiovascular disease. All 4 patients were receiving treatments with either a combination of a statin and ezetimibe, statin and bile acid sequestrant, or a fibrate and bile acid sequestrant, One patient was receiving lipoprotein apheresis (LA) treatment every 1 or 2 weeks.
Inclusion criteria	Not specified in the paper
Exclusion criteria	Not specified in the paper
Intervention(s)	Lomitapide treatment according to a prescribed protocol (not specified in the paper but linked to Roeters van Lennep et al 2015 reference – dose range 5 mg to 60 mg)
Comparator(s)	None
Length of follow-up	Length of follow-up not specified, however treatment duration varied between 9 and 36.5 weeks.
Outcomes	• Percentage change in low density lipoprotein cholesterol (LDL-C) • Percentage change in apolipoprotein B, apolipoprotein A-1 • Percentage change in HDLC • Percentage change in triglycerides (TG)
Source of funding	None stated. Authors of the paper have received grants or personal fees from Aegerion Pharmaceuticals outside of the submitted work.

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**

1. Are the research questions/aims and design clearly stated?	1/2	The research aim is stated however the design of the study is not clear
2. Is the research design appropriate for the aims and objectives of the research?	0/2	There were no details on the study design to assess for appropriateness.
3. Are the methods clearly described?	1/2	No details of the methods as a whole, but methods used for each outcome described. The type of study is prone to biases and confounding. Small sample size to make inferences from.
4. Are the data adequate to support the authors' interpretations / conclusions?	0/2	Limitations in the study methods reduce the confidence in the data and thus the conclusions
5. Are the results generalisable?	½	Too limited details available to be certain if generalisable but population and indication appear generalisable
Total	3/10	
Applicability *	Directly applicable	The intervention and the indication are directly relevant to the decision problem

Appendix 4 Results tables

Table 14 Blom et al. 2017

	Lomitapide once daily[a] in addition to lipid lowering treatment		
	Baseline	**At week 126[b]**	**Analysis**
N	**19**	**17**	
Primary outcomes			
LDL-C levels	356±127 mg/dL	189±120 mg/dL	Mean percentage change in LDL-C from baseline to week 48 −45.5% (95% CI −61.6% to−29.4%, p<0.001)[c]
Safety outcomes			
Number of patients discontinuing treatment	3 patients discontinued treatment with lomitapide earlier on in the follow-up study because of relocation, raised aminotransferases and sudden cardiac death. It was not clear in the study if the latter 2 reasons for discontinuation were treatment-related.		
Elevated serum aminotransferase x 5 ULN	n/a	21.1% (4/19)[d]	n/a
Median change in hepatic fat	0.7% (95%CI 0.5% to 1.1%) (n=18)	7.7% (95%CI 5.7% to 14.6%) (n=13)[e]	Already reported
Adverse events	• Incidence of drug-related adverse events was 42.1% in the extension trial[f] • Common adverse events reported were gastrointestinal, including diarrhoea, nausea, dyspepsia and vomiting • Major cardiovascular events occurred in 2 patients (sudden cardiac death and coronary artery bypass graft)		

Abbreviations

CI, confidence interval; LDL-C, low density lipid cholesterol; ULN, upper level of normal;

[a] Median lomitapide dose remained mostly consistent at 40 mg (range 20 mg to 60 mg) from week 36 in the phase 3 study NCT00730236 (Cuchel et al. 2013) to week 282 (the extension study extended beyond 48 weeks) in the extension trial. Median treatment duration with lomitapide across both trials was 5.1 years (range 2.1 to 5.7 years)

[b] 78 week pivotal plus 48 weeks extension phase

[c] From baseline to week 246, a total of 14 patients achieved levels less than 100 mg/dL and 11 patients achieved LDL-C levels less than 70 mg/dL on at least 1 occasion

[d] Increases in 5 x ULN were typically associated with concomitant use of cytochrome P450 inhibitors or excess alcohol use and managed by discontinuing offending medicines, reducing lomitapide dose or withholding lomitapide temporarily

and re-introducing lomitapide [e] At week 246 (n=11) this increased to 10.2% (95%CI 8.3% to 14.7%) [f] Compared with 84.2% in the pivotal study by Cuchel et al. 2013

Table 15 Cuchel et al. 2007

	Lomitapide once daily[a]		
	Baseline	**After 4 weeks of treatment[b]**	**Analysis**
N	**6**	**6**	
Selected key outcomes			
LDL-C levels (mean)	614 mg/dL	At mean dose 20.1 mg: 465 mg/dL	Mean change in LDL-C levels from baseline to after 4 weeks of treatment −24.7% (p<0.001)
		At mean dose 67 mg: 303 mg/dL	Mean change in LDL-C levels from baseline to after 4 weeks of treatment −50.9% (p<0.001)
ApoB levels (mean)	310 mg/dL	At mean dose 20.1 mg: 262 mg/dL	Mean change in ApoB levels from baseline to after 4 weeks of treatment −14% (p=0.08)
		At mean dose 67 mg: 136 mg/dL	Mean change in ApoB levels from baseline to after 4 weeks of treatment −55.6% (p<0.001)
Triglycerides level (mean)	283 mg/dL	At mean dose 20.1 mg: 165 mg/dL	Mean change in TG levels from baseline to after 4 weeks of treatment −34.1% (p=0.02)
		At mean dose 67 mg: 88 mg/dL	Mean change in TG levels from baseline to after 4 weeks of treatment −65.2% (p<0.001)
Safety outcomes			
Elevated serum aminotransferase[c]	• Elevated liver aminotransferase levels were reported in 4 of the 6 patients. The elevation in aminotransferase levels was dose-dependent in 2 patients and for the other 2 patients there was a substantial increase which resulted in 1 of them		

	having the dose of 0.3 mg/kg reduced
Change in hepatic fat[c]	• There was a substantial increase in hepatic fat in 4 patients in response to treatment with lomitapide (BMS-201038) (reported to be between 18% and 24% for 2 patients and greater than 30% for the other 2 patients).
Adverse events	• Adverse events judged to be possibly or probably drug-related included primarily gastrointestinal adverse events (increased stool frequency, nausea, vomiting, heartburn, stomach pain). Of these, the most commonly reported gastrointestinal adverse events was increased stool frequency • Episodes of increased stool frequency were often temporally related to ingestion of a high-fat meal. • 1 serious adverse event (reaction to a suture which led to hospitalisation) was reported which was thought to be unrelated to the study drug.
Abbreviations ApoB, Apolipoprotein B; LDL-C, low density lipoprotein cholesterol; TG, triglycerides;	
[a] Dose escalation ranged from 0.03 mg/kg to 1 mg/kg, total duration of treatment was 4 weeks for each dose. The results shown in this table are for doses of 0.3 mg/kg and 1 mg/kg for which the percentage reduction in mean values for the specified outcome is calculated. See paper for results for other doses. [b] Patients in this study received 4 different doses (2 of which are reported in this table) each for 4 weeks and returned for a final visit after a 4-week drug wash out period [c] Aminotransferase and hepatic fat levels returned to baseline levels 4 weeks after the therapy was ceased in all the patients except in 1 patient, in whom they did not return to the normal range until 14 weeks after cessation of therapy.	

Table 16 Cuchel et al 2013

	Lomitapide once daily[a] in addition to lipid lowering treatment[b]		
	Baseline	**Week 26**	**Analysis**
N	**29**	**23[c]**	
Primary outcome			
LDL-C levels (mean)	8.7 mmol/L	4.3 mmol/L	Mean percentage change in LDL-C from baseline to week 26 −50% (95%CI−62% to −39%) (p<0.0001)[d]
Key secondary outcomes			
Non-HDLC levels (mean)	10 mmol/L	5.1 mmol/L	Mean percentage change in non-HDLC from baseline

			to week 26 −50% (95%CI −61% to −39%) (p<0.0001)
ApoB levels (mean)	2.6 mmol/L	1.3 mmol/L	Mean percentage change in ApoB from baseline to week 26 −49% (95%CI −60% to −38%) (p<0.0001)
Triglycerides level (median)	1 mmol/L	0.5 mmol/L	Median percentage change in TG from baseline to week 26 −45% (95%CI −61% to −29%) (p<0.0001)
Safety outcomes[e]			
Mean change in hepatic fat[f] (n=20)	1% (range 0 to 5%)	8.6% (0 to 33.6%),	Already reported in the table
Elevated serum aminotransferase[g]	• More than 3 x ULN of ALT, AST or both, n=10 • More than 5 x ULN of ALT, n=4[h] (of the 10 patients reported with more than 3 x ULN aminotransferase)		
Number of patients with at least 1 adverse event	27 (93.1%)[i]		
Number of patients discontinuing treatment	6[j]		
Abbreviations ApoB, apolipoprotein B; CI, confidence interval; LDL-C; low density lipoprotein cholesterol; non-HDLC, non-high density lipoprotein cholesterol; TG, triglycerides; ULN, upper level of normal			
[a] Lomitapide was initiated at a starting dose of 5 mg a day for the first 2 weeks and then escalated to 10 mg, 20 mg, 40 mg, and 60 mg a day at 4-week intervals or until an individually determined maximum dose was achieved on the basis of safety and tolerability. Median dose was reported to be 40 mg/day [b] Lipid lowering treatment was fixed during the efficacy phase (week 0 to 26) and was allowed to be adjusted during the safety phase (week 26 to 78) [c] Out of the 29 patients included in the study, 23 patients completed the efficacy phase and the full study. [d] At 78 weeks, (end of study) mean percentage change in LDL-C level was −38% (−52% to −24%, p=0.0001) from baseline [e] n=29 safety population [f] At week 56, hepatic fat was reported to be 5.8% (0 to 16.5%) and at week 78, 8.3% (0 to 19%). Percentage change in hepatic fat was reported to be negatively			

associated with change in LDL-C with a significant association at week 26 (r=−0.50, 95%CI −0.76 to −0.09, p=0.0161) and week 56 (r=−0.55, 95%CI −0.79 to −0.15, p=0.0083) but not at week 78.

[g] Elevations occurred at lomitapide doses of 10 mg, 20 mg, 40 mg, and 60 mg. Elevations were managed either by dose reduction or temporary interruption of lomitapide as per protocol

[h] 3 of these patients reported consuming quantities of alcohol higher than those allowed per protocol.

[i] The most commonly reported adverse event was gastrointestinal (93.1%) of which diarrhoea (79.3%) and nausea (65.5%) were most reported. The percentage of adverse events related to infections and infestations and investigations (such as decrease in weight and increase in aminotransferase) were 58.8% and 51.7% respectively.

[j] 4 patients discontinued because of adverse events (3 were gastrointestinal events and one was headache); 1 patient was withdrawn for non-compliance with the protocol; and 1 patient withdrew consent for personal reasons.

Table 17 D'Erasmo et al. 2017

	Lomitapide once daily[a] in addition to lipid lowering treatment		
	Baseline	**Follow-up[b]**	**Analysis**
N	**15**	**15**	
Selected key outcomes			
LDL-C levels (mean±SD)	426 mg/dL ±204 mg/dL	Nadir[c] 81.9 mg/dL ±56 mg/dL	Mean percentage change 76.5% ±16.7% (p<0.05)
		Last results 113.7 mg/dL ±86.8 mg/dL	Mean percentage change 68.2% ±24.8% (p<0.05)
Non-HDLC levels (mean±SD)	447,7 mg/dL ±204.1 mg/dL	Nadir[c] 90.9 mg/dL ±58.6 mg/dL	Mean percentage 75.3%±16.9% (p<0.05)
		Last results 123.3 mg/dL ±87 mg/dL	Mean percentage 67.8%±23.8% (p<0.05)
Triglycerides level (mean±SD)	106.8 mg/dL ±36 mg/dL	Nadir[c] 43.7 mg/dL ±24.3 mg/dL	Mean percentage 54.8%±23.1% (p<0.05)
		Last results 50 mg/dL ±20.7 mg/dL	Mean percentage 52.8%±20.5% (p<0.05)
Safety outcomes			
Gastrointestinal	• Diarrhoea, 53.3% (n=8) of which 26.6% (n=3) were reported		

adverse events[d]	as persistent Nausea and vomiting, 20% (n=4) of which 13.3% (n=2) reported as persistent • Abdominal pain, 13.3% (n=2) all of which reported as persistent
Elevated aminotransferase[e]	2 patients with AST 1 x ULN 8 patients with ALT 1 x ULN and 1 patient with 3 x ULN
Other	• At follow-up 8 patients out of the 10 that were receiving LA permanently discontinued LA treatment. • At follow-up 9 patients oral lipid lowering treatment remained unchanged, 3 patients had stopped oral lipid lowering treatment and 1 patients had oral lipid lowering treatment added (a statin and ezetimibe) • No drop outs • At baseline only 1 patient out of 5 had liver steatosis, however at follow-up 2 patients had fatty liver
Abbreviations ALT, alanine transaminase; AST, aspartate transaminase; LA, lipid apheresis;; LDL-C, low density lipoprotein cholesterol; non-HDLC, non-high density lipoprotein cholesterol; SD, standard deviation; TG, triglycerides; ULN, upper level of normal,	
[a] Mean dose was 19±13.3 mg/day (range 5 mg to 60 mg/day) [b] Mean duration of treatment was 32.3±29.7 months (range 8 to 86 months). [c] Nadir refers to the maximum LDL-C reduction [d] Data are reported as percentages of at least one episode of gastro-intestinal side effects. Side-effects is defined as persistent when observed in more than 2 consecutive blood controls. [e] Data are reported for last visit results at follow up after lomitapide treatment	

Table 18 Harada-Shiba et al. 2017

	Lomitapide once daily in addition to lipid lowering treatment[a]		
	Baseline	**Week 26**	**Analysis**
N	**9**	**9[b]**	
Primary outcome			
LDL-C levels (mean)	199 mg/dL	118 mg/dL	Mean percentage change from baseline to week 26 −42% (95%CI −56% to −28%) (p=0.0001)[c]
Key secondary outcomes			
Non-HDLC levels (mean)	228 mg/dL	140 mg/dL	Mean percentage change from baseline to week 26 −40% (95%CI −53% to −28%) (p<0.0001)
ApoB levels (mean)	148 mg/dL	85 mg/dL	Mean percentage change from baseline to week 26 −45% (95%CI −59% to −32%) (p<0.0001)
Triglycerides level (median)	104 mg/dL	57 mg/dL	Median percentage change from baseline to week 26 −46% (95%CI −54% to −21%) (p<0.0001)
Safety outcomes			
	Efficacy phase (week 0 to 26) n=9	Safety phase (week 26 to 56) n=8	
Total treatment-emergent adverse events, n	9[d]	7[e]	
Adverse events leading to discontinuation, n	1[f]	0	
Dose held or reduced due to an adverse event, n	8	3	
Mean change in hepatic fat (range)	Increased from 3.2% (0,1% to 15.7%) at baseline to 15.6% (2.1% to 38.8%[g]) at week 26 (n=9)	12.7% (3.6% to 40,2%) at week 56 (n=8)	
Elevated serum aminotransferase[h]	• More than 3 x ULN of ALT, AST or both, n=3 • More than 5 x ULN of ALT, n=1 (of the 3 reported above)		

Abbreviations ALT, alanine transaminase; ApoB, apolipoprotein B; AST, aspartate transaminase; CI, confidence interval; LDL-C; low density lipoprotein cholesterol; non-HDLC, non-high density lipoprotein cholesterol; ULN, upper level of normal
[a] During the efficacy phase (week 0 to 26) the mean dose of lomitapide was 21.9 mg/day whilst on fixed doses of lipid lowering treatment(s). Maximum tolerated daily doses were 5 mg (n=1), 10 mg (n=1), 40 mg (n=1) and 20 mg (n=5). During the safety phase (week 27 to 56), lomitapide was maintained at maximum tolerated dose (mean dose 18.1 mg/day) and lipid lowering treatment could be adjusted. [b] 8 patients completed the efficacy phase of the study, 1 patient discontinued at week 22 with the last observation carried forward. All 9 patients were included in the safety analysis [c] At 56 weeks, (end of study) mean percentage change in LDL-C level was −38% (−58% to −17%, p=0.003) from baseline [d]All adverse events were drug-related. This included 3 patients with severe adverse events of abnormal LFTs (n=2) and diarrhoea (n=1) [e] 6 patients had drug-related adverse events and 1 patient had a serious adverse event which was chest pain. [f] Reason for discontinuation was elevated aminotransferase [g] Last observation carried forward [h] In 2 of these patients, transaminase elevations were effectively managed by reduction in the lomitapide dose or temporary dose interruption with both patients completing

Table 19 Roeters van Lennep et al. 2015

	Lomitapide once daily in addition to lipid lowering treatment[a]		
	Baseline	**Follow-up[b]**	**Analysis**
N	**4**	**4**	
Selected key outcomes			
LDL-C levels (range)	7.3 mmol/L to 14.11 mmol/L	2.86 mmol/L to 6.58 mmol/L	Percentage change from baseline to follow-up (range) −36.4% to −79.7%
Total cholesterol levels (range)	9 mmol/L to 17.30 mmol/L	4 mmol/L to 8.2 mmol/L	Percentage change from baseline to follow-up (range) −32.6% to −76.8%
Triglycerides level (range)	0.7 mmol/L to 3.08 mmol/L	0.28 mmol/L to 2 mmol/L	Percentage change from baseline to follow-up (range) −28.6% to −84.7
Safety outcomes			
Adverse events	3 patients reported gastrointestinal-related adverse events. This included nausea, diarrhoea, loss of appetite and stomach discomfort. These were reported to settle with dietary advice and/or dose reduction		
Elevated serum aminotransferase	2 patients experienced elevated transaminase levels which were managed by dose reduction or temporarily withholding lomitapide.		
Adverse events leading to discontinuation	1[c] patient who had elevated aminotransferase had the lomitapide treatment stopped permanently		
Changes in hepatic fat	Hepatic steatosis was documented in 2 patients before treatment with lomitapide. One of these patients discontinued treatment and the other patient did not report any additional complications		
Other information			
1 patient was on LA and the addition of lomitapide extended the treatment interval of LA			
Abbreviations ALT, alanine transaminase; LA, lipid apheresis; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; ULN, upper level of normal,			
[a] Doses ranged between 5 mg and 30 mg daily [b] Duration of treatment ranged between 20 weeks to 50 weeks [c] Lomitapide treatment was stopped in week 38 due to increase in ALT levels (greater than 3 x ULN).			

Table 20 Stefanutti et al. 2016

	Lomitapide[a] once daily in addition to ezetimibe		
	Baseline	**Follow-up[b]**	**Analysis**
N[c]	**7**	**7**	
Selected key outcomes			
LDL-C nadir levels[d] (range)	Not reported	49 mg/dL to 150 mg/dl	Percentage change from baseline to follow-up (range) −5% to −83%
Safety outcomes			
Adverse events	4 patients reported gastrointestinal-related adverse events. These were reported to settle with dietary advice and/or dose reduction		
Elevated serum aminotransferase	3 patients experienced a transient rise in transaminase levels (less than 3 x ULN) which were managed by temporarily withholding lomitapide in 1 patient.		
Changes in hepatic fat	No clinically relevant accumulation of hepatic fat reported in any patient		
Other information			
2 of the 7 patients on LA reported to reduce LA from weekly to biweekly (after 4 months and 10 months of lomitapide)			
Abbreviations LA, lipid apheresis; LDL-C, low density lipoprotein cholesterol; ULN, upper level of normal			
[a] After titration, lomitapide doses ranged from 10 mg to 30 mg daily for 5 of the patients, 1 patient received 60 mg/day and the other received 5 mg/day. Lomitapide was administered in addition to ezetimibe (statins were stopped) [b] Follow-up varied between 12 and 50 weeks [c] 1 patient with HoFH in this study had enrolled in the phase 3 study of lomitapide (Cuchel et al. 2013) [d] Time-averaged LDL-C levels (change from baseline LDL-C and nadir [lowest recorded] LDL-C level) reported in the study			

Table 21 Yahya et al. 2016

	Lomitapide once daily[a] in addition to lipid lowering treatment
N	**4**
Selected key outcomes	
Percentage change in LDL-C from baseline to follow-up[b] (range)	−34% to −89%
Percentage change in ApoB from baseline to follow-up[b] (range)	−24% to −89%
Percentage change in triglycerides from baseline to follow-up[b] (range)	−78% to −30%
Safety outcomes	
Adverse events	All patients had some gastrointestinal symptoms during lomitapide treatment which were minimised by a low fat diet.
Elevated aminotransferase	
Treatment discontinuations	2 patients[b]
Abbreviations ApoB, Apolipoprotein B; LDL-C, low density lipoprotein cholesterol; ULN, upper level of normal	
[a] Dose ranged from 5 mg to 30 mg [b] Duration of treatment ranged between 9 to 36.5 weeks. [b] Lomitapide treatment was stopped in 1 patient because of non-adherence. In another patient lomitapide was stopped because of persistent liver enzyme elevations that were 5 xULN which returned to normal after discontinuing treatment.	

Appendix 5 Grading of the evidence base

Each study is assigned one of the following codes

NSF-LTC Categories of research design

Primary research based evidence
P1 Primary research using quantitative approaches
P2 Primary research using qualitative approaches
P3 Primary research using mixed approaches (quantitative and qualitative)
Secondary research based evidence
S1 Meta-analysis of existing data analysis
S2 Secondary analysis of existing data
Review based evidence
R1 Systematic reviews of existing research

For each key outcome, studies were grouped and the following criteria were applied to achieve an overall grade of evidence by outcome.

Grade	**Criteria**
Grade A	More than 1 study of at least 7/10 quality and at least 1 study directly applicable
Grade B	One study of at least 7/10 which is directly applicable OR More than one study of a least 7/10 which are indirectly applicable OR More than one study 4-6/10 and at least one is directly applicable OR One study 4-6/10 which is directly applicable and one study of least 7/10 which is indirectly applicable
Grade C	One study of 4-6/10 and directly applicable OR Studies 2-3/10 quality OR Studies of indirect applicability and no more than one study is 7/10 quality

Applicability should be classified as:

- Direct studies that focus on people with the indication and characteristics of interest
- Indirect studies based on evidence extrapolated from populations with other conditions and characteristics