Single Technology Appraisal

Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 years and over [ID2704]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

1. **Comments on the stakeholder engagement from** Ultragenyx

2. **Consultee and commentator comments on the stakeholder engagement** from:
   a. HEART UK
   b. Chiesi
   c. NHS England data on lomitapide dose

3. **Comments on the stakeholder engagement from experts:**
   a. Jaimini Cegla, Consultant in Metabolic Medicine – clinical expert, nominated by HEART UK

4. **External Assessment Group response to stakeholder engagement comments**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

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Stakeholder engagement response form

As a stakeholder you have been invited to comment on key uncertainties around the maintenance dose of lomitapide in NHS clinical practice, the number of lomitapide capsules per adult and the effectiveness of lower doses of lomitapide than used in the economic modelling for this appraisal.

Important information

This engagement is being conducted because there is some uncertainty about the dose of lomitapide, the comparator for evinacumab in adults, used in the cost effectiveness analysis of evinacumab. For the economic modelling, the dose of lomitapide was based on a median dose of 40 mg/day lomitapide, using 2.2 capsules of lomitapide calculated as an average number of capsules weighted by the proportion receiving lomitapide in the study of Cuchel et al. 2013. NICE received information prior to final guidance publication that the dose of lomitapide used in the economic modelling was higher than the lomitapide dose used in clinical practice in the UK. This potentially overestimates the costs of lomitapide and raises uncertainty about the cost effectiveness of evinacumab.

Because the dose and number of capsules of lomitapide have an impact on the cost effectiveness of evinacumab, these issues need to be explored in more depth by the appraisal committee. In February 2024, NICE asked NHS England to provide real world data on the dose of lomitapide for treating homozygous familial hypercholesterolaemia. Data from 18 adults from 5 NHS trusts indicated that the average dose of lomitapide is 16.9 mg/day, which suggests that the dose of lomitapide is lower than 40 mg/day. Please consider this information when providing your response.

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NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Ultragenyx
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Ultragenyx are the sponsor of the STA submission and the manufacturer of evinacumab.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	None

Key issues for engagement

All: Please use the table below to respond to the key issues for engagement.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Dose of lomitapide per adult used in NHS clinical practice for the treatment of homozygous familial hypercholesterolaemia. Please provide information on the maintenance dose of lomitapide per adult used in NHS practice. (The Summary of Product Characteristics for lomitapide indicates that the dose is up titrated starting from 5mg daily to 10 mg and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, and to the maximum recommended dose of 60 mg daily,	No	We are unaware of any published evidence, or colloquial evidence (hospital audits, unpublished registries, other grey literature) (1) regarding the use of lomitapide in the NHS England in any context. We also note this question refers to the “maintenance dose” of lomitapide. However, as alluded to in the SmPC (2), the dosing of lomitapide needs to be kept dynamic and flexible depending on response to treatment and for reasons of tolerability. Smooth titration to target, including down titration following tolerance issues or, for instance, raised liver function tests (LFTs), should involve all doses between 5 mg and 60 mg being made available on a clinical basis according to patient need.

based on acceptable safety and tolerability.)		
Number of lomitapide capsules per adult used in NHS clinical practice	No	The number of lomitapide capsules per adult used in NHS clinical practice is clearly and directly related to the dose specified in question 1. Thus, optimal clinical use of lomitapide will invariably involve combinations of capsules based on individual clinical need in order to maximise therapeutic benefit, whilst remaining on the acceptable side of tolerability. These data are not typically reported in studies of the drug.
Request for published or unpublished data on the efficacy of lower doses of lomitapide (for example, 20mg daily) in terms of: • changes in low density lipoprotein cholesterol (LDL-C) • discontinuation rates • need for LDL apheresis.	No	As part of the submission process for ID2704, Ultragenyx has carried out a full systematic literature review (SLR) of the evidence base for lomitapide globally. These studies are described in Appendix D1 (page 37 to 69). This response briefly describes the evidence identified in the SLR (since updated) and the company's opinion of its suitability for use in the CEM. **Observational studies** Most of the published evidence for lomitapide are derived from observational studies, with two (relatively) large retrospective registries providing the most patient data. A condition of regulatory approval for lomitapide was the establishment of a registry with the primary aim of safety monitoring (3). This

		registry, *the Lomitapide Observational Worldwide Evaluation Registry* (LOWER) now has 5-year data published (4). The most recent publication summarised data from the cohort inception on March 1, 2014, to the reporting cut-off of February 28, 2019. A total of 292 patients who were prescribed lomitapide were identified (4). The LOWER registry did collect some efficacy and limited dosing data, reporting reductions in LDL-C of up to 46.8% at a median dose of lomitapide of 23.78 mg/day (capsule usage not reported). Nevertheless, the response was highly variable, and there was substantial evidence from wider datasets, including patients who ceased taking the drug, that much of the effect was not due to the drug itself. The other registry of note on lomitapide is the Pan-European registry by D'Erasmo et al. (2021) (5). This was a multicentre, retrospective, observational study including lipid centres treating HoFH patients with lomitapide in Europe with the aim to confirm the effectiveness and safety of lomitapide. In total, data from 75 patients were reported receiving a median dose of 20 mg/day (capsule usage not reported), achieving reductions in LDL-C of up to -60% (nadir).

		We have identified four other studies investigating the efficacy of lomitapide. D'Erasmo has also reported two other observational studies on the drug; a registry set in Italy (6) and a comparison of cohorts receiving lomitapide in Italy or LDL apheresis in France (7). However, it is unclear whether these studies were in unique patients not already included in the Pan-European study, and their methodology and reporting limitations make interpretation particularly difficult. Two case series have also reported on lomitapide (8, 9). It is not possible to accurately estimate capsule usage from the dosage of lomitapide reported in the observational studies, and it is not possible to relate these to drug efficacy. LDL apheresis discontinuation rates were reported narratively in some studies but were inadequate to provide quantitative evidence. Observational studies, especially when retrospective and non-comparative such as the LOWER (4) and Pan-European (5) registries, are near the lowest rank in the evidence-based medicine (EBM) hierarchy of evidence (10). Retrospective studies are especially prone to bias in patient selection, data collection, data imputation and analyses, and the influence of both known and unidentified confounders (11). In the case of LOWER and the Pan-European registry, there are specific and serious issues on how these studies selected and followed up patients and

		accounted for patient attrition (which was exceptionally high in both studies). The studies made no attempt to control for known confounders, such as disentangling the requirement for patients to be on a strict low-fat diet, from the effect of the drug itself. It is also not possible to obtain usable, generalisable information from the case series published, which are generally considered to be in the lowest place in the EBM hierarchy of study quality (10). There may be similar issues with evidence generated from the Stakeholder Responses, with the additional limitation in that these have not been published or peer reviewed. **Experimental evidence** There is a paucity of good-quality experimental evidence for lomitapide. We identified only two studies that had an experimental design; these were the proof-of-concept study by Cuchel *et al.* (2007) (12), and the pivotal trial by Cuchel *et al.* (2013) (13). The first of these studies was a dose escalation study performed in six patients with HoFH which was used to establish the dose range of the drug in clinical practice. This study provides clear evidence for lomitapide having a dose-response relationship with LDL-C lowering. Whilst data from this study can be clearly used to link lomitapide dose with efficacy, interpretation requires caution

		owing to the methodology of the study, the small sample size, and assumptions made about the linearity of response. The pivotal trial by Cuchel *et al.* (2013) (13) was critiqued extensively by the company in the submission Document B (Section B.2.9.3, pages 89 to 93). This prospective single-armed study reported that lomitapide was associated with a reduction in LDL-C of -40.1% (14) using intention to treat analysis, or -50% at a median dose of 40 mg using per protocol analysis (13). This trial also informed an extension study where longer-term data were made available and analysed at up to 294 weeks (over 5 years) of follow up (15). The authors reported in this study that "the median lomitapide dose remained mostly consistent at 40 mg (range, 20 to 60 mg) from week 36 in the pivotal study to week 282 in the extension trial". Additionally, data from the pivotal trial was used to assess the impact of lomitapide on LDL apheresis (16), to perform a more detailed analysis of 6 patients from the cohort (17), and provide an analysis of lipid target attainment and impact on major cardiovascular adverse events (MACE) (18). Thus, this study is the most comprehensive and exhaustively analysed of any on lomitapide. **Conclusion**

		Ultragenyx used data from the pivotal trial by Cuchel *et al*. (2013) as it was the only study that reported data comparable to the ELIPSE randomised controlled trial (RCT) on evinacumab (19). This was done by using change from baseline data from the Cuchel study and the intervention arm of ELIPSE in a Matched-Adjusted Indirect Comparison (MAIC), described fully in Section B.2.9 (pages 83 to 95). The observational studies identified cannot be used for this purpose as they did not adequately report dosage or capsule usage and they cannot be used to reliably link dose with efficacy. Therefore, they cannot be used in the MAIC and by extension, they cannot be used to inform the CEM. Consequently, our conclusions are that if observational data is to be used to inform the economics aspect of the decision problem, an alternate form of analysis will be required, such as cost-minimisation analysis.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to stakeholder engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

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Insert key issue description (e.g. lomitapide dose/lomitapide capsule number per adult/lomitapide effectiveness)	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the stakeholder engagement	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue description (e.g. lomitapide dose/capsule number/lomitapide effectiveness)	N/A	N/A	N/A
Company's base case following stakeholder engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues for engagement.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Dose of lomitapide per adult used in NHS clinical practice for the treatment of homozygous familial hypercholesterolaemia. Please provide information on the maintenance dose of lomitapide per adult used in NHS practice. (The Summary of Product Characteristics for lomitapide indicates that the dose is up titrated starting from 5mg daily to 10 mg and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, and to the maximum recommended dose	Yes/No	As we represent HCPs treating HoFH patients, we have gathered a consensus view on this position from the key centres, which are as follows: Imperial College Healthcare NHS Trust Bristol Royal Infirmary University Hospitals Birmingham Royal Brompton & Harefield Hospitals Manchester Royal Infirmary • We are deeply concerned about the delay in publication of the Appraisal as it is delaying the treatment of our patients • Regarding lomitapide, all patients in the UK are on 1 or 2 capsules – individual centres will submit a breakdown of doses and number of tablets • A lomitapide capsule costs the same irrespective of whether it's 5mg, 10mg or 20mg. Therefore the original economic modelling based on 2.2 capsules more or less reflects actual clinical practice of 1-2 (actually 1.7) capsules daily. Further cost negotiations may lower the final price slightly towards the cost of 1.7 rather than 2.2 capsules.

of 60 mg daily, based on acceptable safety and tolerability.)		• The efficacy of lomitapide on LDL-c is not necessarily dose-dependent (eg 1 patient on 30mg with 30% LDL-c reduction and one on 10 mg with 60% reduction). • The efficacy of lomitapide in our experience is between 30-70% which is very much in line with the published real world data • There is a real unmet need which, as clinicians caring for patients, makes us deeply concerned about this delay to the publication of the final guidance. Both Evinacumab and lomitapide are effective at enabling patients to achieve target LDL-c (a more relevant goal of treatment than % reduction in LDL-c). However many of our patients do not tolerate lomitapide at all and remain on apheresis with its incumbent burden of treatment or are incompletely adherent and therefore sub-optimally treated on lomitapide. In comparison with lomitapide, evinacumab has a favourable side effect profile, does not require dietary restrictions and the mode of delivery will almost guarantee adherence. • We strongly encourage NICE to engage with Ultragenyx and come up with a solution on cost-effectiveness to avoid further delay As well as the above, we would also point out that Evinacumab we hope will be available for those aged 12 and above, whereas lomitapide is from age 18. Delaying this treatment further is putting many patients at extremely high risk and at a disadvantage as they are unable to access a suitable treatment. Patients have told us they feel robbed with not being given access to this treatment, HoFH is a severe condition and patients would also urge NICE not to delay any further.
Number of lomitapide capsules per adult used in NHS clinical practice	Yes/No	See above
Request for published or unpublished data on the efficacy of lower doses of	Yes/No	See above

lomitapide (for example, 20mg daily) in terms of: • changes in low density lipoprotein cholesterol (LDL-C) • discontinuation rates • need for LDL apheresis.		

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engagement (or revised base case)			

Sensitivity analyses around revised base case
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Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Chiesi Limited Chiesi Farmaceutici S.p.A. acquired Amryt Pharmaceuticals DAC and, as such, has assumed responsibility for Lojuxta® (lomitapide). However, the marketing authorisation holder for this product will remain as Amryt Pharmaceuticals DAC for the time being.
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**N/A**

Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	

Key issues for engagement

All: Please use the table below to respond to the key issues for engagement.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Dose of lomitapide per adult used in NHS clinical practice for the treatment of homozygous familial hypercholesterolaemia. Please provide information on the maintenance dose of lomitapide per adult used in NHS practice.	Yes	[redacted]The dosing schedule for lomitapide stated in the Summary of Product Characteristics is the schedule used the Cuchel et al., (2013) study. In this study, patients were 'force' titrated upwards until they reached the maximum tolerated dose. The study reports that lomitapide was initiated at a starting dose of 5 mg/day for the first two weeks and then escalated to 10, 20, 40, and 60 mg/day at 4- week intervals or until an individually determined maximum dose was achieved based on safety and tolerability. In the real-world, HCPs titrate up based on efficacy, so a lower dose than the dose reported in the Cuchel et al., (2013) study and the Summary of Product Characteristics is generally used. Use of the method where HCPs titrate up based on efficacy, rather than 'force' titrating patients upwards until they reached the maximum tolerated dose was utilised in the

(The Summary of Product Characteristics for lomitapide indicates that the dose is up titrated starting from 5mg daily to 10 mg and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, and to the maximum recommended dose of 60 mg daily, based on acceptable safety and tolerability.)		D'Erasmo et al., (2022) study. Results found that after a median of 19 months (interquartile range 11-41 months) of treatment with a mean dosage of 20 mg/day of lomitapide in 75 patients, low-density lipoprotein cholesterol (LDL-C) decreased by 60%: • Baseline median (IQR) LDL-C: 280.5 mg/dL (191.8-405.0 mg/dL) • Median (IQR) LDL-C after 19 months: 121.6 mg/dL (61.0-190.5 mg/dL) At the last visit, 32.0% of patients achieved LDL-C levels of <100 mg/dL and 18.7% of patients achieved LDL-C levels of <70 mg/dL. At baseline, 38 patients with HoFH were receiving LDL apheresis (LA), but after initiation of lomitapide 71% of these patients discontinued LA. The commercial in confidence data on current patient doses in England along with the D'Erasmo et al., (2022) study demonstrates the increased effectiveness of lomitapide in the real-world setting and at lower doses than in the clinical trial setting (Cuchel et al., 2013). In addition, these lower doses appear to be associated with reduced gastrointestinal adverse events (AEs) compared to the phase 3 trial reported in Cuchel et al., (2013).
Number of lomitapide capsules per adult used in NHS clinical practice	Yes	[redacted]
Request for published or unpublished data on the efficacy of lower doses of lomitapide	Yes	In this section we present 11 studies that investigate lomitapide in the real-world clinical setting. Studies are presented by the date of their publication and the data presented focuses on LDL-C changes, discontinuation rates, and need for LDL apheresis. **1.** [redacted]

(for example, 20mg daily) in terms of: • changes in low density lipoprotein cholesterol (LDL-C) • discontinuation rates • need for LDL apheresis.		[redacted]**All-case surveillance study by Harada-Shiba et al. (2024) - Real-world safety and efficacy of lomitapide in homozygous familial hypercholesterolemia: interim report of special-use survey in Japan** This study evaluated the safety and efficacy of lomitapide in real-world clinical practice in Japan. In the interim analysis presented in this article, 39 patients (aged 15-65 years) with HoFH received a median dose of lomitapide of 9.8 mg/day across 42 months. • **LDL-C Changes**: In the 39 patients with HoFH who received lomitapide, the mean (SD) LDL-C level decreased from 225.9 (172.0) mg/dl to 159.4 (93.0) mg/dl at 12 months and further decreased to 122.1 (66.7) mg/dl at 42 months. These results illustrate the long-term efficacy of lomitapide in substantially lowering LDL-C levels. • **Discontinuation rates**: There were 74 drug-related AEs reported in 24 (61.5%) of the 39 patients included in the safety analysis. Drug-related AEs lead to the lomitapide dose being reduced in 15 patients (38.5%), withdrawn temporarily for 4 patients (10.3%), and discontinued in 1 patient (2.6%). This suggests that there was a focus on adjusting doses to manage AEs rather than outright discontinuing patients from treatment.

		• **Need for LDL Apheresis**: Among patients who had been receiving treatment other than pharmacotherapy prior to starting lomitapide, lipoprotein apheresis was being performed in 26 patients (66.7%). At the start of lomitapide treatment, 25 patients were undergoing lipoprotein apheresis. Once treatment with lomitapide had started, the apheresis interval remained unchanged in 21 patients, 1 patient withdrew from apheresis, 1 patient had a longer interval between apheresis, and 2 patients had shorter intervals. One patient started lipoprotein apheresis after lomitapide administration, but the interval was subsequently prolonged compared with the time of initiation. **2. Retrospective cohort study by Suppressa et al. (2023): Long-term effectiveness and safety of lomitapide: Real-world experience from Italy in patients with homozygous familial hypercholesterolemia** In this study, the aim was to evaluate the long-term effectiveness and safety of lomitapide in patients with HoFH. There were 13 patients with HoFH from two centres in Italy assessed for LDL-C changes, changes in doses of concomitant lipid-lowering therapies, AEs, and cardiovascular events. Patients in the study received lomitapide for up to 6.5 years for a median of 44 months and the median lomitapide dose received was 20 mg/day. • **LDL-C changes**: During the period that patients received lomitapide treatment, LDL-C decreased by 69% from a mean (SD) of 311.1 (149.8) mg/dL at baseline to 96.5 (51.7) mg/dL at last follow-up. In 5 patients (38%), LDL-C levels of <100 mg/dL were achieved at last visit and all of these patients had LDL-C levels of <70 mg/dL. • **Discontinuation rates**: There were 2 patients who discontinued lomitapide treatment due to GIAEs and 1 patient temporarily interrupted their lomitapide treatment due to diarrhoea.

		• **Need for apheresis**: At baseline, there were 2 patients receiving apheresis and both of these patients discontinued their apheresis after receiving lomitapide. **3. Case reports by Vogt (2023): Lomitapide but not evolocumab reduces LDL-cholesterol to goal in homozygous familial hypercholesterolemia – 2 case reports** This study assessed 2 patients with HoFH and compared treating these patients with lomitapide and evolocumab. Both patients had HoFH and established atherosclerotic cardiovascular disease (ASCVD) and were undergoing regular lipoprotein-apheresis. Lomitapide was administered with Rosuvastatin 40 mg and Ezetimibe 10 mg in a clinical setting and after this, both patients were switched to biweekly Evolocumab 420 mg. • **LDL-C changes**: In patient 1, baseline LDL-C was 252 mg/dL and this decreased to 68 mg/dL (minimum 46mg/dL) while the patient was receiving a lomitapide dose of 20 mg/day. LDL-C levels increased to 176 mg/dL when the patient was switched from lomitapide to Evolocumab due to reimbursement issues. Reimbursement for lomitapide allowed the patient to back-switch to lomitapide and when this was done, the LDL-C goal was achieved (52mg/dL, range 28-68). In patient 2, LDL-C levels reduced from 236 mg/dL to 71 mg/dL when the patient was receiving lomitapide at a dose of 30 mg/day. This reduction occurred despite their apheresis-frequency being reduced. When the patient was switched to Evolocumab (reimbursement issues), LDL-C levels rose to 214 mg/dL. • **Discontinuation rates**: Discontinuation of lomitapide in these two patients was caused by reimbursement issues. The study reports that both patients were fully adherent to diet instructions and no safety concerns arose. • **Needs for LDL apheresis**: While patient 1 was receiving lomitapide, they achieve their LDL-C level goals and lipoprotein apheresis was discontinued. In patient 2, the

		frequency of apheresis was reduced but no details on the scale of this reduction was provided. **4. Case series by Kayikcioglu et al. (2023): Case report: Therapy adherence, MTTP variants, and course of atheroma in two patients with HoFH on low-dose, long-term lomitapide therapy** This study aimed to present the possibility of preventing the progression of atherosclerotic burden with effective and safe LDL-C reduction in patients with HoFH on low-dose lomitapide therapy and emphasise the role of treatment adherence in therapy success. There were 2 adult (≥18 years) patients with HoFH included and assessed. • **LDL-C Changes**: In two adult patients with HoFH, low-dose long-term lomitapide therapy (5-20 mg/day) resulted in substantial LDL-C reductions. Patient 1 received 20 mg/day and reported a 49% reduction in LDL-C at the end of 6 months. Baseline LDL-C levels were 248 mg/dl for the first patient and, after the 1st year of lomitapide treatment, pre- and post-apheresis session levels of LDL-C were 132 mg/dl and 54 mg/dl, respectively. In patient 2, investigators observed an additional 27% reduction in LDL-C for a 5 mg daily dose of lomitapide at the end of 1 month, and this reduction increased to 49% at the end of 6 months while the patient was receiving a dose of 20 mg/day. Furthermore, in patient 2, baseline LDL-C levels were 562 mg/dl and after 1 year, pre- and post-apheresis session levels of LDL-C were 256 mg/dl and 133 mg/dl, respectively. • **Discontinuation Rates**: Patient 1 was treated for 8 years and continued treated with no increase in serum liver enzyme levels, weight loss, liver steatosis, and no change in hepatic fibro scans. Neither patient discontinued treatment permanently; however, patient 2 stopped treatment for 3 years and then resumed and continued treatment for almost 5 years, at last follow-up.

		• **Need for LDL Apheresis**: Patient 1 declined to be weaned off apheresis but had their apheresis frequency reduced to every 2 months and patient 2 reduced apheresis from monthly to every 2-3 months. **5. Retrospective observational study by D'Erasmo et al. (2022) - Efficacy and safety of lomitapide in homozygous familial hypercholesterolaemia: the pan-European retrospective observational study** This study evaluated the medium-term effectiveness and safety of lomitapide in a large cohort of patients with HoFH in Europe. The cohort included 75 patients (≥18 years) with HoFH, all treated with lomitapide in a real-world clinical setting followed for a median duration of 19 months. • **LDL-C Changes**: The study found that, in the 75 patients treated with lomitapide (at 24 months, median dose: 20 mg/day; mean dose 20.3 mg/day), there was a substantial reduction in LDL-C levels. After a median of 19 months (interquartile range [IQR] 11–41 months) with a mean lomitapide dose of 20 mg, LDL-C decreased by 60%, from baseline. Consistent with these results, the average LDL-C reduction over 5 years was 64.7% (IQR 52.2–79.9) with an absolute reduction of 168 mg/dL from baselines values (mean daily dose of lomitapide of 33.7 [SD: 15.9] mg/day). There was also data from four patients showing that lomitapide could sustain LDL-C reduction up to 9 years. At the last visit, 32.0% of patients achieved LDL-C levels of <100 mg/dL and 18.7% achieved LDL-C levels of <70 mg/dL. These results demonstrated the LDL-C-lowering effect of lomitapide in a real-world setting. • **Discontinuation Rates**: A total of 13.3% of patients (10 patients) permanently stopped lomitapide treatment. Reasons for discontinuation were reported for 6 patients: one for colon cancer, four for physicians' decision (side effects/enrolment in clinical trials with other drugs) and one patient moved to a country where lomitapide

		was not reimbursed. This indicates a relatively high tolerance and acceptance of lomitapide treatment among the studied population. • **Need for LDL Apheresis**: At baseline, 38 HoFH patients were receiving LDL apheresis, but after treatment with lomitapide, LDL apheresis was stopped in 13 patients at nadir and stopped in 14 further patients at last follow-up (P McNemar < 0.001). Therefore, 27 out of 38 patients (71%) receiving LDL apheresis, stopped treatment. • **Safety and Tolerability**: The study also focused on the safety profile of lomitapide, noting that GIAEs remained stable or decreased over time. GIAEs occurred in 40% of patients and liver transaminases increased (3–5 x upper limits of normal) in 13% of patients. Diarrhoea (32.2%) and nausea (22.6%) were the most common GIAEs within the first three months of therapy but showed a tendency to decrease over time. Between 10-13% of patients experienced an elevation of liver function tests (LFTs), mostly between 3 and 5 times the upper limit of normal (ULN). Among patients with liver ultrasound evaluation (n = 45), a modest increase in hepatic steatosis was noted during treatment; however, liver stiffness measured by elastography in 30 of these patients remained within the normal range. Only 3 patients showed a marked increase in liver stiffness (>10 times ULN), with 2 patients permanently stopping the treatment and one restarting without further safety concerns. Among patients with HoFH exposed to lomitapide for at least 2 years, the MACE incident rate was 7.4 per 1000 person-years in the 2 years after treatment with lomitapide as compared to 21.2 per 1000 person-years before treatment with lomitapide. Although GIAEs were common, the authors of the study noted that liver safety in patients was reassuring and there was no sign of and increased risk of liver fibrosis. **6. Retrospective case series by Aljenedil et al. (2020): Lomitapide for treatment of homozygous familial hypercholesterolemia: The Québec Experience**

		This study assessed the experience of using lomitapide as an adjunctive treatment for patients with a diagnosis of HoFH in Quebec. A total of 12 adult (≥18 years) patients with HoFH were included and all received lomitapide doses ranging from 5-20 mg/day. All patients were on a statin, ezetimibe 10mg/day, and 5 patients were receiving apheresis. • **LDL-C Changes**: Lomitapide treatment resulted in a 38% mean reduction in LDL-C levels (intention-to-treat basis). • **Discontinuation Rates**: Gastrointestinal side effects led to treatment discontinuation in 3 out of 12 patients and, in the remaining 9 patients, there were 6 patients that required downward drug titration because of gastrointestinal side effects (n=5) and elevated liver enzymes (n=1). Eventually 2 of the 6 patients also discontinued treatment. These results emphasise the need for monitoring, treatment regimen adjustment based on tolerability, and the need to adhere to a low-fat diet with dietician support. • **Need for LDL Apheresis**: The use of lomitapide did not modify the frequency of LDL apheresis during the study follow-up (range: 4-124 months; median: 27 months). **7. Cohort study by Kolovou et al. (2019): Microsomal triglyceride transfer protein inhibitor (lomitapide) efficacy in the treatment of patients with homozygous familial hypercholesterolaemia** This study evaluated the efficacy and safety of lomitapide in patients with HoFH undergoing lipoprotein apheresis who have not achieved their recommended LDL-C treatment goals. There were 12 patients (aged 8-62 years old) with HoFH treated with lomitapide (average dose of 21.4 +/-10.5 mg/day) and followed-up for 3–24 months. • **LDL-C Changes**: In 12 patients undergoing lomitapide treatment alongside lipid-lowering therapies (LLT), LDL-C levels were reduced further by 56.8% (P = 0.005) compared to LLT alone and reduced by 54% (P = 0.031) compared to LLT in

		combination with lipoprotein apheresis (time-averaged level). These results demonstrate the efficacy that lomitapide has in lowering LDL-C when added to other LLTs, including statins, ezetimibe, colesevelam and apheresis (n=9), administered every 7-15 days • **Discontinuation Rates**: The study focused on efficacy and did not provide specific details on discontinuation rates. • **Need for LDL Apheresis**: After lomitapide administration to the 9 patients on LLT and apheresis, 78% (7 out of 9 patients) stopped apheresis and 22% (2 out of 9 patients) remained on apheresis treatment with reduced frequency (once a month). **8. Case study by Real et al. (2018): Management of Homozygous Familial Hypercholesterolaemia in Two Brothers** This study examined two 'real-world' cases of lomitapide use in brothers (≥18 years) with HoFH and considered the factors that led to initiation and adaptation of therapy. • **LDL-C Changes**: The two brothers were given escalating doses of oral lomitapide which enabled substantial LDL-C reduction. Patient 1 had an LDL-C of 747mg/dL at diagnosis. Their mean interval LDL-C levels remained at 128 mg/dL with biweekly apheresis, statins and ezetimibe. On 10 mg lomitapide, LDL-C decreased to 40 mg/dL and apheresis was stopped. Patient 2 had and LDL-C level of 829 mg/dL at diagnosis and pre-apheresis LDL-C levels were 196 mg/dL with biweekly apheresis, statins and ezetimibe. He was treated with rosuvastatin 40 mg plus ezetimibe 10 mg and added lomitapide 5 mg/day. Lomitapide was up-titrated to 40 mg/day but then decreased back down to 20mg/day due to the patient experiencing headache. Their LDL-C levels were reported to reduce by 43% to a level of 112 mg/dL (<100 mg/dL interval mean). • **Discontinuation Rates**: Neither patient, discontinued lomitapide, but dose adjustment was necessary for one patient due to headache and their dose was reduced from 40 mg/day to 20 mg/day.

		• **Need for LDL Apheresis**: Notably, one brother was able to discontinue LDL apheresis while receiving a dose of 10mg/day of lomitapide, demonstrating lomitapide's potential in reducing LDL-C to target levels without the need for apheresis. **9. Retrospective cohort study by D'Erasmo et al. (2017): Efficacy of Lomitapide in the Treatment of Familial Homozygous Hypercholesterolemia: Results of a Real-World Clinical Experience in Italy.** This study aimed to evaluate the benefits of lomitapide in patients with HoFH treated with the usual clinical care. There were 15 patients (>18 years) with HoFH from across Italy included and all received lomitapide in addition to lipid lowering therapy for at least 6 months (mean follow-up: 32.3 [SD: 29.7] months). • **LDL-C Changes**: In the 15 patients included in this study, treatment with an average dose of 19 mg/day of lomitapide reduced mean LDL-C levels by 68.2% ± 24.8%, with 60% of patients achieving LDL-C levels of <100 mg/dL and 46.6% achieving LDL-C levels of <70 mg/dL at last visit. • **Discontinuation Rates and Safety**: The study reported that 53.3% of patients reported at least one episode of diarrhoea, but no severe liver issues or discontinuations due to AEs were reported. A subset of patients was evaluated by liver ultrasound and fibroscan (n = 5) or nuclear magnetic resonance with spectroscopy (MRS) (n = 1), and results showed no evidence of liver damage. • **Need for LDL Apheresis**: During the follow-up (mean duration: 32.3 [SD: 29.7] months) 80% of patients receiving LDL apheresis were able to stop due to marked LDL-C reduction. **10. Case series by Van Lennep et al. (2015) - Treating homozygous familial hypercholesterolemia in a real-world setting: Experiences with lomitapide.**

		This study reviewed four individual real-world patients with HoFH who received lomitapide with the aim of illustrating how these patients responded to therapy and to demonstrate how side effects were managed in the clinical practice setting. There were 4 patients (≥18 years) with HoFH included and varying doses of lomitapide were received by patients.
		
		• **LDL-C Changes**: All patients experienced clinically meaningful reductions in LDL-C levels (35%-73% reductions) after receiving treatment with lomitapide. The reductions in LDL-C levels in patients were as follows:
		  ○ Patient 1 achieved an 83% reduction while receiving a stepwise escalated dose of lomitapide up to 30mg/day over 8 months (dose started at 5 mg/day).
		  ○ Patient 2 achieved a 46% reduction while receiving a dose of 5mg/day
		  ○ Patient 3 achieved a 35% reduction while receiving a dose of 10mg/day
		  ○ Patient 4 achieved a reduction of 73% while receiving a dose of 20mg/day
		• **Discontinuation Rates**: Three of the patients experienced GIAEs but were managed with appropriate dietary control. One patient discontinued lomitapide due to an increase in LFT > 5 x ULN which resolved after temporarily stopping lomitapide but recurred on re-challenge and so lomitapide was permanently discontinued.
		• **Need for LDL Apheresis**: Only patient 4 was on apheresis at baseline and remained on apheresis.
		
		Overall Summary
		
		This collection of real-world evidence, made up of case reports and observational studies, provides valuable insights into the use of lomitapide in the treatment of patients with HoFH. Across various global populations and clinical settings, lomitapide's effectiveness, safety, and impact on treatment protocols (including the need for LDL apheresis) at lower doses than in the clinical trial setting is demonstrated. Here, a summary of the key findings and trends from the real-world studies that are described above is presented.

		Efficacy in Lowering LDL-C Lomitapide demonstrated an ability to lower LDL-C levels in patients with HoFH in real-world clinical practice at a range of doses. The average reductions of LDL-C in patients treated with lomitapide across the cohort studies ranged from approximately 38% to 68% when added to available lipid lowering therapies (statins, ezetimibe, evolocumab and apheresis). In some cases, patients achieved target LDL-C levels for the first time and individual patient data from case studies showed patients achieving even greater levels of LDL-C reduction than in the cohort studies. However, data from individual patients or case studies is potentially subject to more uncertainty and bias. Despite this, the data from the real-world studies strongly suggest that lomitapide has a potent lipid-lowering effect when administered at lower doses then in the clinical study reported in Cuchel et al., (2013). **Discontinuation Rates and Side Effects** The rates at which patients discontinued lomitapide treatment due to AEs was relatively low across the studies and this suggests that lomitapide is generally well tolerated among patients in the real-world setting and at lower doses then those reported in Cuchel et al., (2013). Gastrointestinal side effects were the most common reason for lowering doses or discontinuing lomitapide. Well-established management strategies such as dose adjustments and dietary modifications showed some evidence of mitigating AEs therefore allowing patients to continue treatment and to benefit from the LDL-C lowering capabilities of lomitapide. **Impact on the Need for LDL Apheresis** Nine studies reported the proportion of patients who were on LDL apheresis and of these studies, 6 reported that the rate of discontinuation from LDL apheresis was ≥50% among

		patients treated with lomitapide. These results further emphasise the potential effect that lomitapide has in reducing the burden and cost associated with regular apheresis sessions. **Real-World Application and Long-Term Efficacy** The real-world experiences described in the studies highlights the ability of lomitapide treatment to help patients with HoFH achieve sustained LDL-C reduction over time. In some cases, LDL-C reductions led to a reduced need for costly and burdensome LDL-C apheresis. The effectiveness of lomitapide reported in real-world clinical practice was often achieved with substantially lower doses than those used in clinical trials and recommended in the Summary of Product Characteristics. This suggests that personalised treatment plans could optimise the long-term benefits of lomitapide while minimising any potential AEs and reducing medication costs for the NHS. **Conclusion** The results reported across the case reports and observational studies summarised in this section suggest that lomitapide is a highly effective option for managing HoFH when administered at lower doses than the dose used for the economic evaluation of evinacumab in the draft guidance. Lomitapide has been reported to consistently reduce LDL-C levels in patients with HoFH in real-world clinical practice when added to other lipid lowering therapies, including statins, ezetimibe, evolocumab and apheresis. There was also evidence to suggest that, in many cases, patients treated with lomitapide were able to reduce or completely stop LDL apheresis. The safety profile of lomitapide, characterised by manageable side effects and relatively low discontinuation rates, further supports the case that it is a valuable option for lipid-lowering in patients with HoFH. Finally, the NHS patient data collected on lomitapide shows that in the real-world setting, patients are managed on lomitapide doses substantially lower than the dose quoted in the evinacumab company submission and economic model.

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		Vogt A. Lomitapide but not evolocumab reduces LDL-cholesterol to goal in homozygous familial hypercholesterolemia – 2 case reports. Atherosclerosis. Abstract. 2023;379(1):S122. DOI:https://doi.org/10.1016/j.atherosclerosis.2023.06.427.

Lomitapide dose in NHS

Data on lomitapide dose for treatment of homozygous familial hypercholesterolaemia was sourced from 5 NHS Trusts:

- Manchester University NHS Foundation Trust ;
- University Hospitals Bristol and Weston NHS Foundation Trust;
- Guy's and St Thomas NHS Foundation Trust;
- Nottingham University Hospitals NHS Trust;
- Imperial College Healthcare NHS Trust

The above trusts gave permission to share the data in the tables below with the NICE committee, NICE technical team, the external assessment group and all the registered stakeholders for the evaluation of evinacumab for homozygous familial hypercholesterolaemia [ID2704]. This will enable further exploratory analysis on the dose of lomitapide. Permission was granted to include this data in committee papers on the NICE website.

Lomitapide dose daily	**5 mg**	**10 mg**	**15 mg**	**20 mg**	**25 mg**	**30 mg**	**40 mg**	**60 mg**
Number adults - email 1	2	2	1	4	0	0	0	0
Number adults- email 2	0	0	1	1	0	1	0	0
Number adults- email 3	1	1	1	0	1	2	0	0
TOTALS (N=18)	3	3	3	5	1	3	0	0
Proportion (%)	16.7	16.7	16.7	27.8	5.6	16.7	0.0	0.0
average dose=16.94 mg								

SUMMARY TABLE

Lomitapide dose daily	**5 mg**	**10 mg**	**15 mg**	**20 mg**	**25 mg**	**30 mg**	**40 mg**	**60 mg**
Number of patients	3	3	3	5	1	3	0	0
Proportion (%)	16.7	16.7	16.7	27.8	5.6	16.7	0.0	0.0

10 April 2024

Dear NICE Team, please find below data on the dosage of lomitapide that is used at Imperial College Healthcare NHS Trust:

Patient #	Dosage (mg)	# Capsules	Average capsules
1	30	2	
2	25	2	
3	30	2	
4	10	1	
5	5	1	
6	Currently abroad	0	
7	15	2	

The efficacy of LDL-c lowering has been between 30 and 70%

Kind regards

Dr Jaimini Cegla FRCP FRCPath PhD

Clinical Lead for Lipids and Cardiovascular Risk Service

Imperial College Healthcare NHS Trust

BMJ TAG

Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 years and over [ID2704]

EAG response to stakeholder feedback

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1 Introduction

The National Institute for Health and Care Excellence (NICE) undertook stakeholder engagement due to concerns around the dose of lomitapide (the comparator for evinacumab in adults used in the cost effectiveness analysis of evinacumab), in the economic modelling potentially being higher than that used in UK clinical practice. The dose of lomitapide used in the economic model was calculated using data from the study by Cuchel *et al.* 2013[1] and was based on a median dose of 40 mg/day of lomitapide. However, prior to the publication of final guidance for evinacumab, NICE received information to suggest that the dose of lomitapide used in clinical practice is lower than 40mg/day.

In February 2024, NICE requested prescribing data for lomitapide from NHS England to provide real world data on the dose of lomitapide used in UK clinical practice for the treatment of homozygous familial hypercholesterolaemia (HoFH). The average dose of lomitapide was calculated to be 16.9 mg/day using data from NHS England which comprised 18 adults from 5 NHS trusts; these data therefore suggest that the dose of lomitapide used in clinical practice is lower than 40 mg/day.

In response to the stakeholder engagement, responses were received from Chiesi (the marketing company for lomitapide) and HEART UK, along with NHS prescribing data for lomitapide from NHS England and also from an NHS trust that is already included in the data from NHS England.

This report contains the External Assessment Group (EAG) critique of the responses to stakeholder engagement and updated EAG cost-effectiveness analyses. It should be noted that some of the data provided in the response by Chiesi was marked as commercial-in-confidence, and the EAG critique of these data is provided in a confidential appendix.

2 Clinical effectiveness

2.1 Dose of lomitapide per adult used in NHS clinical practice for the treatment of homozygous familial hypercholesterolaemia

Chiesi reported that the dosing schedule for lomitapide stated in the Summary of Product Characteristics was used in the Cuchel *et al*. 2013[1] study, and that patients were 'force' titrated upwards in the study until they reached the maximum tolerated dose of lomitapide. Chiesi also reported that any titration in real-world clinical practice would be based on efficacy, and thus a lower dose than reported in the Cuchel *et al*. 2013 study would generally be used.

As discussed in Section 1, data from NHS England for 18 adults with HoFH from 5 NHS trusts suggests an average dose of lomitapide of 16.9 mg/day (range: 5mg/day to 30mg/day) in NHS clinical practice. The data from NHS England therefore suggest that the dose of lomitapide used in NHS clinical practice is lower than the 2.2 capsules dose used in the cost-effectiveness analysis originally provided in the company submission for evinacumab and used in the EAG analyses.

2.2 Number of lomitapide capsules per adult used in NHS clinical practice

Based on the lomitapide prescribing data provided by NHS England, the EAG estimates that the mean number of lomitapide capsules used is 1.4/day (Section 3). The EAG notes that HEART UK reported a slightly higher mean number of lomitapide capsules of 1.7/day in their response, but they also reported that "*all patients in the UK are on 1 or 2 capsules*".

2.3 Request for published or unpublished data on the efficacy of lower doses of lomitapide (for example, 20mg daily) in terms of changes in low density lipoprotein cholesterol (LDL-C), discontinuation rates and need for LDL apheresis.

The response from Chiesi contained a summary of 11 studies investigating lomitapide in the real-world clinical setting, although only 10 of these can be discussed in this report due to confidentiality:

1. case reports of 2 patients by Vogt *et al.* 2023;[2]
2. case study of two brothers by Real *et al.* 2018;[3]
3. case series of 2 patients by Kayikcioglu *et al.*2023;[4]
4. case series of 4 patients by Roeters van Lennep *et al.* 2015;[5]
5. retrospective case series of 12 patients from Canada by Aljenedil *et al.* 2020;[6]

6. cohort study of 12 patients (location not reported but authors all associated with institutions in Greece) by Kolovou *et al.* 2020;[7]
7. retrospective cohort study of 13 patients in Italy by Suppressa *et al.* 2023;[8]
8. retrospective cohort study of 13 patients in Italy by D'Erasmo *et al.* 2017;[9]
9. interim analysis of 39 patients enrolled in an all-case surveillance study in Japan by Harada-Shiba *et al.* 2024;[10] and
10. retrospective observational study of 75 patients in Europe by D'Erasmo *et al.* 2022[11].

The EAG notes that 8 of the studies[2-9] comprised of 13 or fewer patients and neither of the 2 remaining studies[10-12] were exclusively conducted in the UK. The EAG provides a short narrative overview of the two studies containing >13 patients[10, 11] below but does not discuss the smaller studies due to concerns around the reliability of the evidence from case reports and case series, and concerns around the generalisability of the small non-UK cohort studies. The EAG also notes that the two studies with >13 patients reported by Chiesi were identified and included in the appendices of the evinacumab company submission[10, 11] but due to methodological limitations they were deemed less suitable than the Cuchel *et al.* 2013 study for informing the efficacy of lomitapide in the company submission. The EAG also notes that the appendices of the company submission included a summary of a prospective cohort study of 187 patients from the USA, Europe, Canada, Argentina and Taiwan from the Lomitapide Observational Worldwide Evaluation Registry (LOWER) which is potentially of relevance for the efficacy of a lower dose of lomitapide and therefore the EAG also discusses this study below.[13]

The study by Harada-Shiba *et al.* 2024[10] is reported as an interim report of a survey of 39 patients from Japan with a median dose of lomitapide of 9.8 mg/day across 42 months and a mean dose of lomitapide beyond 24 months follow-up of between 14 mg and 16 mg, although there was only a small number of cases at these later timepoints. Limited detail on the methods was reported for the study but it provides results for change in LDL-C, lomitapide discontinuation rates and LDL apheresis usage. The EAG notes that the mean percentage change in LDL-C level from baseline varied from -12.1% in patients followed for 3 months, to -41.2% in patients with 42 months follow-up. However, the EAG also notes that in the discussion of the paper it is reported that, "*the median dose of lomitapide in Japanese phase III trials was 20 mg/day compared with 40 mg/day in overseas phase III trials suggesting that the effective dose in Japanese patients may be lower than in overseas studies*". The EAG thus recommends caution in drawing conclusions for UK patients from these data.

Only one patient (2.6%) was reported to discontinue treatment with lomitapide during the Harada-Shiba *et al.* 2024 study but it is also noted that the current analysis is from an interim report. With regards to the need for LDL apheresis, 25 patients were on LDL apheresis at the start of lomitapide and of these, one patient withdrew from LDL apheresis, one patient had a longer interval between apheresis, and two patients had shorter intervals. In addition, one patient started LDL apheresis after lomitapide administration, but the interval was subsequently prolonged compared with the time of initiation.

The publication for the LOWER study contains five-year data and reported that the global median dose of lomitapide used in the study was 10 mg/day. Lomitapide was associated with a 33.9% (standard deviation [SD] 27.6) mean reduction in low-density lipoprotein cholesterol (LDL-C) at 6 months and a 25.3% (SD 6 38.7) reduction at month 48, although the EAG notes that these results include data from patients who have discontinued treatment with lomitapide but remained in follow-up in the registry. The EAG considers the number of patients discontinuing treatment with lomitapide in the LOWER study to be high, with 54.6% of patients discontinuing treatment and 23.8% of patients discontinuing treatment but remaining in follow-up in the registry. The EAG also notes that only 60.3% of patients with ongoing follow-up in the registry are still on lomitapide and therefore considers the reliability of the efficacy data for lomitapide to be questionable. Data are reported for the cohort of patients who remain on lomitapide and are still being followed-up in the registry: the mean percentage reduction in LDL-C is greater for this cohort at all timepoints compared with the full analysis set population. For example, at 6 months for the patients remaining in follow-up and on lomitapide, percentage reduction in LDL-C from baseline was 45.3% compared with 33.9% for the full analysis set population (all patients with patients with at least 1 postbaseline visit). No data were reported on the need for LDL apheresis in patients on lomitapide.

The retrospective observational study by D'Erasmo *et al*. 2022[11] included 75 patients with a median dose of lomitapide of 20 mg/day and a mean dose of 20.3 mg/day. A total of 4 patients were recruited from the UK and the country with the highest patient enrolment was Italy (n=34). The publication only reported data for median change in LDL-C and not mean change: after a median of 19 months (interquartile range [IQR] 11–41 months), there was a 60% median reduction in LDL-C from baseline. The median change in LDL-C from baseline to 6 months was approximately 35%.

D'Erasmo *et al*. 2022 reported that a total of 13.3% of patients (10 patients) permanently stopped lomitapide treatment. The reasons for discontinuation were colon cancer (n=1), physicians' decision

(side effects/enrolment in clinical trials with other drugs [n=4]), patient moved to a country where lomitapide was not reimbursed (n=1) and not reported (n=4). In terms of LDL apheresis, 38 HoFH patients were receiving LDL apheresis at baseline, but after treatment with lomitapide, LDL apheresis was stopped in 27 out of the 38 patients (71%).

The EAG notes that HEART UK reported that the efficacy of lomitapide on LDL-C is not necessarily dose-dependent (e.g. one patient is on 30mg with a 30% LDL-C reduction and another patient is on 10 mg with 60% reduction). In addition, HEART UK reported that the efficacy of lomitapide in their experience is between 30-70% and that they considered it to align with the published real-world data, although no references to published studies were provided in their response.

The EAG has concerns about the reliability and generalisability of the evidence from the 10 observational studies reporting data on lomitapide presented by Chiesi and the data from the LOWER study. In particular, the EAG notes that the methodology for some of the studies is poorly reported and that the studies are likely to be at risk of bias. For those studies where the study design is reported, many are retrospective and four contain less than five patients. The EAG also notes that there is heterogeneity across the studies and that the mean and median doses of lomitapide used in the studies varies (e.g. mean dose of 13.0 mg/day in the LOWER study and mean dose of 20.7mg/day in D'Erasmo *et al*. 2022).

2.4 Conclusions of the clinical effectiveness evidence

The EAG considers the data from NHS England, Chiesi and HEART UK confirm that the dose of lomitapide used in NHS clinical practice is likely to be lower than the dose in the Cuchel *et al*. 2013 study, and that the number of capsules per day is likely to be lower than the 2.2 lomitapide capsules used in the company's cost-effectiveness analysis for evinacumab.

The EAG does not consider any of the 10 lomitapide studies reported by Chiesi or the LOWER study to be suitable for inclusion in an indirect treatment comparison with evinacumab from the ELIPSE study. The EAG also recommends caution in drawing conclusions of the efficacy of the higher dose of lomitapide used in Cuchel *et al.* 2013 versus the efficacy of lomitapide in the 11 observational studies reported in Section 2.3 due to differences in study design, outcome reporting and heterogeneity in the patient populations. For example, the EAG notes that the D'Erasmo *et al.* 2022 study reports only median percentage change in LDL-C values whereas Cuchel *et al.* 2013 reports mean percentage change. Also, the mean age in the LOWER registry is much higher than in Cuchel *et*

al. 2013 (51.4 years versus 30.7 years, respectively) and the baseline LDL-C is lower than in Cuchel *et al.* 2013 (237.1mg/dL versus 336.4mg/dL, respectively).

Despite the limitations in the clinical efficacy data, the EAG considers that the studies of lomitapide provide evidence to suggest that lomitapide is associated with a reduction of LDL-C in adults with HoFH. However, the EAG does not consider there to be robust data to inform a reliable estimate of the reduction in LDL-C with lomitapide in patients with HoFH in NHS clinical practice nor to enable a robust comparison of evinacumab versus lomitapide for the likely dose of lomitapide used in NHS clinical practice.

3 Cost effectiveness

Confidential patient access scheme (cPAS) discounts are available for the comparator lomitapide and evolocumab. These discounts are included in the confidential appendix.

Table 1. Previous EAG base case

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Evinacumab	[redacted]	[redacted]	-	-	-
Lomitapide	6,280,861	10.45	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

3.1 Dose of lomitapide per adult per day assumed in the economic model

As described in Section 1, the daily dose of lomitapide in the model was informed using Cuchel *et al.* 2013, [1] which aimed to evaluate the efficacy of lomitapide. Patients in the study were treated with the equivalent of 2.2 capsules when calculated as the average number of capsules weighted by the proportion of patients receiving lomitapide. Lomitapide is currently provided packs of 5mg, 10mg and 20mg capsules with the cost of all packs and therefore capsules being equal.

As discussed in Section 2.1, stakeholder feedback from HEART UK stated that the mean dose of lomitapide across 18 adults from 5 NHS trusts (Imperial College Healthcare NHS Trust, Bristol Royal Infirmary, University Hospitals Birmingham, Royal Brompton & Harefield Hospitals and Manchester Royal Infirmary) was 16.9 mg/day, provided in a mean of 1.7 capsules. Compared to the modelling assumptions, these values are lower than the 2.2 capsules previously assumed. The clinician feedback from HEART UK also suggested that the efficacy of lomitapide was not dose dependent, with the treatment effect stated to be between a 30-70% LDL-C reduction. This opinion is broadly comparable to the 53.4% LDL-C reduction assumed in the EAG base case, associated with the previously assumed dose and capsules from Cuchel *et al.* 2013.

NHS England also provided data on the lomitapide doses from 18 patients across five different NHS trusts (Manchester University NHS Foundation Trust, University Hospitals Bristol and Weston NHS Foundation Trust, Guy's and St Thomas NHS Foundation Trust, Nottingham University Hospitals NHS Trust and Imperial College Healthcare NHS Trust). The EAG notes that Imperial College Healthcare NHS Trust also contributed to the feedback provided from HEART UK, with additional patient overlap being possible between the stakeholder feedbacks given the NHS trusts contributing to each and their geographical locations.

Across the 18 patients in the NHS England dataset, the EAG calculated the mean dose of lomitapide per patient to be 16.9 mg/day, with a mean of 1.4 capsules per person per day when using the assumed number of capsules required for each dose as presented in Table 2. The EAG notes that the mean dose of lomitapide was the same in both the HEART UK and NHS England datasets (16.9mg/day) but the mean number of capsules differed (1.7 and 1.4 capsules, respectively). No data or opinion was provided by NHS England regarding the treatment effectiveness of lomitapide.

Table 2. EAG assumed number of capsules required per dose of lomitapide.

	Number of capsules required per dose of lomitapide					
Dose	5mg	10mg	15mg	20mg	25mg	30mg
Capsules required	1	1	2	1	2	2

Note: lomitapide is currently supplied in capsules of 5mg, 10mg and 20mg.

The EAG therefore considers that the previously assumed number of capsules per patient per day in the economic model is an overestimate compared to the HEART UK and NHS England stakeholder feedback. From the 2.2 capsules previously assumed, 1.7 capsules may better reflect current clinical practice given this value was reported directly from the HEART UK stakeholder feedback and does not include assumptions made around the number of capsules required based on the lomitapide dose.

3.2 Scenario analysis

The EAG has conducted multiple scenarios using the stakeholder feedback responses (Table 3). While one and two lomitapide capsules per day have been explored the EAG considers 1.7 capsules/day to be the most relevant given its direct reporting from HEART UK. A capsule per administration threshold analysis was also conducted to identify at what number of lomitapide capsules resulted in an ICER of £20,000 or £30,000.

Critically, while robust real-world evidence from stakeholders has been used to inform the dosing of lomitapide, as discussed in Section 2.4, no robust evidence for the lomitapide treatment effect estimates have been provided at a lower dose. As such, scenarios around the number of capsules of lomitapide (scenarios 1 to 4) are uncertain as no change in the treatment effectiveness of lomitapide is assumed following the change in the number of capsules.

As a means of assessing the uncertainty around the treatment effect when assuming a lower dose of lomitapide, the EAG conducted a treatment effectiveness threshold analysing using an ICER threshold of £20,000 and £30,000 (scenario 5). Finally, a scenario assuming that the treatment effect

of lomitapide is equal to that of evinacumab (47.1% LDL-C reduction) at the lower dose (1.7 capsules) was explored (scenario 6).

Table 3. Lomitapide dose and treatment effectiveness scenario analysis

#	Scenario	ICER (£/QALY) / cost difference (ICER quadrant)	£20,000 ICER threshold (ICER quadrant)	£30,000 ICER threshold (ICER quadrant)	Net health benefit (£30,000 WTP threshold)
0	Previous EAG base case	[redacted]	-	-	[redacted]
1	1.7 lomitapide capsules per administration	[redacted]	-	-	[redacted]
2	2 lomitapide capsules per administration	[redacted]	-	-	[redacted]
3	1 lomitapide capsules per administration	Evinacumab dominated	-	-	[redacted]
4	Lomitapide capsule threshold analysis	-	1.052 capsules (SW ICER)	1.053 capsules (SW ICER)	-
5	Scenario 1 & lomitapide efficacy threshold analysis	-	-	-	-
6	Scenario 1 & assuming lomitapide efficacy is equal to evinacumab (47.1% LDL-C reduction)	Evinacumab cost saving ([redacted])	-	-	-

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein concentration; N/A, not applicable; QALY, quality adjusted life year; SW, south-west.

As presented, when one lomitapide capsule per administration is assumed, evinacumab is dominated. However, if more than 1.05 capsules are assumed, evinacumab is less costly and less effective, resulting in an ICER in the south-west (SW) quadrant of the cost-effectiveness plane.

The EAG notes that when no change in the treatment effectiveness of lomitapide is assumed the incremental difference in QALYs is [redacted], when instead the lowest lomitapide treatment effectiveness threshold from the HEART UK stakeholder feedback (30% LDL-C reduction) is assumed, the incremental QALYs increase to [redacted]. As such, due to the low incremental difference in QALYs and high incremental difference in costs, independent of the efficacy of lomitapide assumed it was not possible to achieve an ICER of £20,000 or £30,000 when conducting the lomitapide efficacy threshold analysis. Instead, the nature of the ICER changes from evinacumab being less effective and cost saving when assuming no change in lomitapide treatment efficacy with a lower dose (a south-west quadrant ICER of [redacted]/QALY when using the MAIC treatment effect [53.4% LDL-C reduction]), to evinacumab being more effective and cost saving when using a lower lomitapide

treatment effect (south-east quadrant ICER of [redacted]/QALY when assuming the lower treatment effect estimate from HEART UK [-30% LDL-C reduction]).

3.3 EAG preferred assumptions

Given the feedback from HEART UK and NHS England, the EAG considers that 1.7 capsules of lomitapide per day should be assumed in the model in contrast to the previously assumed 2.2 capsules. Therefore, given that the incremental difference in QALYs is [redacted], and that the incremental difference in costs is [redacted] when assuming 1.7 mean capsules of lomitapide, the EAG considers that the main driver of cost-effectiveness is cost based. Thus, when QALYs are considered to be the same, lomitapide is [redacted] more costly than evinacumab. These assumptions inform the EAG's updated base case, presented in Table 4.

Table 4. EAG updated base case

Interventions	Total Costs (£)	Incremental costs (£)
Evinacumab	[redacted]	-
Lomitapide	4,860,409	[redacted]

3.4 Conclusions on the health economic evidence

The EAG considers the dose and number of capsules of lomitapide suggested by HEART UK to be a better reflection of clinical practice compared to that previously assumed in the model, informed using Cuchel *et al.* 2013. [1] Due to the limitations in the studies provided by Chiesi in their stakeholder feedback no robust evidence for the lomitapide treatment effect estimates have been provided at the lower lomitapide dose. As such, the EAG has conducted multiple scenario analysis around the dosing and efficacy of lomitapide the results of which highlight that independent of the efficacy of lomitapide at the lower dose the cost differences is the primary driver of cost effectiveness. Thus, when the QALY benefit for evinacumab and lomitapide are considered equal, evinacumab is cost saving.

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