Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study

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Summary

Background Patients with homozygous familial hypercholesterolaemia respond inadequately to existing drugs. We aimed to assess the efficacy and safety of the microsomal triglyceride transfer protein inhibitor lomitapide in adults with this disease.

Methods We did a single-arm, open-label, phase 3 study of lomitapide for treatment of patients with homozygous familial hypercholesterolemia. Current lipid lowering therapy was maintained from 6 weeks before baseline through to at least week 26. Lomitapide dose was escalated on the basis of safety and tolerability from 5 mg to a maximum of 60 mg a day. The primary endpoint was mean percent change in levels of LDL cholesterol from baseline to week 26, after which patients remained on lomitapide through to week 78 for safety assessment. Percent change from baseline to week 26 was assessed with a mixed linear model.

Findings 29 men and women with homozygous familial hypercholesterolaemia, aged 18 years or older, were recruited from 11 centres in four countries (USA, Canada, South Africa, and Italy). 23 of 29 enrolled patients completed both the efficacy phase (26 weeks) and the full study (78 weeks). The median dose of lomitapide was 40 mg a day. LDL cholesterol was reduced by 50% (95% CI –62 to –39) from baseline (mean 8·7 mmol/L [SD 2·9]) to week 26 (4·3 mmol/L [2·5]; p<0·0001). Levels of LDL cholesterol were lower than 2·6 mmol/L in eight patients at 26 weeks. Concentrations of LDL cholesterol remained reduced by 44% (95% CI –57 to –31; p<0·0001) at week 56 and 38% (–52 to –24; p<0·0001) at week 78. Gastrointestinal symptoms were the most common adverse event. Four patients had aminotransaminase levels of more than five times the upper limit of normal, which resolved after dose reduction or temporary interruption of lomitapide. No patient permanently discontinued treatment because of liver abnormalities.

Interpretation Our study suggests that treatment with lomitapide could be a valuable drug in the management of homozygous familial hypercholesterolaemia.

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Introduction

Homozygous familial hypercholesterolaemia is a life-threatening disease most commonly caused by loss-of-function mutations in both alleles of the LDL receptor gene. Mutations in other genes, including *APOB*, *PCSK9*, and autosomal recessive hypercholesterolaemia *LDLRAP1*, which alter the function of the LDL receptor or its ligand ApoB, could also contribute to such a phenotype. As a consequence of impaired LDL-receptor function, untreated total plasma cholesterol levels are typically greater than 13 mmol/L, resulting in premature and progressive atherosclerosis often leading to cardiovascular disease before age 20 years and death before age 30 years.[1–3] Early initiation of aggressive treatment for these patients is, therefore, essential.[4]

Patients with homozygous familial hypercholesterolaemia respond inadequately to conventional drug therapies,[2,5–7] which generally reduce LDL cholesterol through upregulation of hepatic LDL receptors. Therefore, the current standard of care for familial hypercholesterolaemia includes LDL apheresis, which transiently reduces LDL cholesterol by more than 50%[8,9] and can delay the onset and progression of atherosclerosis.[7–9] However, even with the combined use of available drug therapies and apheresis, these patients still have substantially elevated levels of LDL cholesterol and persistently high risk of cardiovascular disease.[10] Liver transplantation has also been done in patients with this disease.[11,12] In recent years, alternative therapeutic approaches have been developed that target either ApoB synthesis[13] or the production of VLDL, the precursor of LDL.[14]

Lomitapide (Aegerion Pharmaceuticals, Cambridge, MA, USA) is an inhibitor of the microsomal triglyceride transport protein (MTP), a key protein in the assembly and secretion of ApoB-containing lipoproteins in the liver and intestine.[15] The drug substantially reduced levels of LDL cholesterol in the Watanabe Heritable Hyperlipidaemic rabbit, an animal model of homozygous familial hypercholesterolaemia.[16] We have shown that lomitapide given orally for 16 weeks as monotherapy was effective in reducing LDL cholesterol levels in six patients with homozygous familial hypercholesterolaemia and that its efficacy was mediated by a reduction in LDL production.[14] To assess the long-term safety and efficacy of lomitapide when added to currently available lipid-lowering drug therapy with or without apheresis (standard of care), we assessed adult patients with homozygous familial hypercholesterolaemia over a 78 week treatment period. Safety assessments included an analysis of the effects of chronic MTP inhibition on the liver.

Methods

Study design and patients

In our phase 3, open-label study, patients were recruited from 11 centres in four countries (USA, Canada, South Africa, and Italy). Diagnostic criteria for homozygous familial hypercholesterolaemia were based either on clinical criteria (history of untreated total cholesterol >13 mmol/L and triglycerides <3·4 mmol/L and both parents with history of untreated total cholesterol >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. Exclusion criteria included: major surgery in the previous 3 months, congestive heart failure, history of liver disease or transaminases greater than twice the upper limit of normal (ULN), serum creatinine >221 μmol/L, recent malignancy, alcohol or drug abuse, known bowel disease or malabsorption, or chronic lung disease.

Patients were screened for eligibility 12 weeks before the first dose of lomitapide. Screening procedures included medical and drug history, review of current lipid-lowering therapies, physical examination, vital signs, 12-lead electrocardiograph (ECG), fasting lipid panel, safety laboratory assessments, and dietary counselling. All 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. At the end of the run-in phase, patients entered a 26-week efficacy phase, during which they received lomitapide in addition to their current lipid-lowering therapy. Lomitapide was initiated at a starting dose of 5 mg a day for the first 2 weeks and then escalated to 10, 20, 40, 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. Patients remained at their maximum dose through to the end of the 26-week efficacy phase. A fasting lipid and safety panel, including liver function tests, was obtained at baseline, before each dose escalation, and then every 4 weeks through to week 26 (primary endpoint).

After completion of the efficacy phase, patients continued to receive lomitapide and entered a 52-week safety phase (weeks 26–78) during which concomitant lipid-lowering therapies, including LDL apheresis, could be modified at the investigators discretion. Assessments during this phase were done every 5 weeks to 10 weeks and at the end of treatment. Total treatment duration was 78 weeks. 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.

If patients had confirmed alanine transaminase (ALT) or aspartate transaminase (AST) elevations between 5·0 and 9·9 times the ULN, or >100 U/L but <200 U/L above the baseline value, the dose of lomitapide was reduced to the previously tolerated dose level, with the possibility to re-escalate once transaminase elevations were resolved. Adverse events were coded with MedDRA (version 11.0). These events were judged by the investigators as: not related, unlikely, possibly, probably, or definitely related to study drug, and were reviewed regularly by an independent data and safety monitoring board. The study was approved by each institution's review board or ethics committee and all patients provided written, informed consent.

Procedures

Blood was drawn at baseline and at each visit following a 12 h fast. Routine testing included a standard metabolic panel, a complete blood count, urinalysis, and measurement of fat soluble vitamins and fatty acids. All testing was done at a US Centers for Disease Control and Prevention standardised lipid central laboratory (PPD, Highland Heights, KY, USA and Brussels, Belgium) or referred to a partnering laboratory for the measurement of vitamin K and essential fatty acids. In patients undergoing apheresis, samples for the fasting lipid profile were obtained shortly before the scheduled apheresis treatment. The timing of treatments (eg, every 14 days) and study blood sampling was maintained throughout the study so that lipid assessments would be done at the same point on the LDL cholesterol rebound curve. Lipid and lipoprotein analyses were done with serum. Total cholesterol, directly measured LDL cholesterol and HDL cholesterol, and triglycerides were measured enzymatically. Non-HDL cholesterol and VLDL cholesterol were calculated. ApoA-I and ApoB were measured by immunonephelometry.

Hepatic lipid content was assessed by nuclear magnetic resonance spectroscopy (NMRS) studies at baseline and at 6-month intervals. All quantitative measurements were done by a single external radiologist who was masked to patients' clinical status and results of liver function tests. NMRS was not done in three patients who had contraindications to MRI. In these patients a CT

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scan or ultrasound was done at the discretion of the local physician or if recommended by the data and safety monitoring board.

Statistical analysis

The sample size calculation was based on an assumption of a 25% change from baseline in LDL cholesterol at week 26 with a 30% SD and 15% dropout rate. Using an alpha of 0·05 with 90% power, 20 patients were needed. The statistical analyses were done with SAS software (version 9.1). Continuous variables were summarised by descriptive statistics (sample size, mean, SD, median, minimum and maximum). Categorical variables were summarised by frequency (N) and percentages (%). Baseline values of lipid parameters were the average of two measurements taken 2 weeks apart (after 4 weeks and 6 weeks of entering the run-in phase). The primary efficacy endpoint measure was the percent change from baseline in concentration of LDL cholesterol at the maximum tolerated dose after 26 weeks of treatment. Prespecified secondary endpoints included percent changes in other lipid parameters, long-term safety, and changes in hepatic-fat content. All patients who received at least one dose of the study drug were in the assessment of the primary and secondary endpoints (intention-to-treat analysis) up to the end of the efficacy phase (week 26). Significance of the percent changes in LDL cholesterol from baseline to 26 weeks was assessed with a mixed linear model, which assumes a missing-at-random mechanism. An additional secondary statistical analysis was done imputing missing data with the last-observation-carried-forward method, because this was the statistical approach described in the original statistical analysis plan. Further secondary efficacy and safety analyses were done during the safety phase (weeks 26–78); an on-sample *t* test was used to assess percent change from baseline at week 56 and week 78. Correlations were assessed with Spearman's rank-correlation. Statistical significance was defined as p≤0·05.

This study is registered with ClinicalTrials.gov (NCT00730236).

Role of the funding source

The sponsor of the study had no role in study design, data collection, primary data analysis, data interpretation, or initial writing of the report, but was invited to comment on the written report. The corresponding author had full access to all the data in the study and had final responsibility for the final content of the report and the decision to submit for publication.

Results

Of the 32 patients with homozygous familial hypercholesterolaemia who were screened for eligibility, 31 entered the run-in period and 29 men and women were enrolled in the efficacy phase. All patients were 18 years or older and met diagnostic criteria. 23 of 29 enrolled patients completed both the efficacy phase (26 weeks) and the full study (78 weeks; appendix). Six patients discontinued the study during the efficacy phase (the first 4 days after enrolment and the last at week 22): four patients discontinued because of adverse events (three were gastrointestinal events and one was headache); one was withdrawn for non-compliance with the protocol; and one withdrew consent for personal reasons.

The baseline characteristics of the patients enrolled in the study are shown in the appendix. Briefly, all 29 patients were either homozygotes or compound heterozygotes for mutations in the *LDLR* gene or genes affecting LDL-receptor functionality. 27 patients were treated with statins, primarily rosuvastatin or

	Baseline (n=29)	Week 26 (n=23)			Week 56 (n=23)			Week 78 (n=23)		
		Concentrations	Change from baseline (%)	p value†	Concentrations	Change from baseline (%)	p value‡	Concentrations	Change from baseline (%)	p value‡
Total cholesterol, mmol/L	11·1 (3·5)	6·1 (2·9)	−46% (−56 to −35)	<0·0001	7·1 (3·7)	−39% (−51 to −27)	<0·0001	7·3 (3·9)	−35% (−48 to −22)	<0·0001
LDL cholesterol, mmol/L	8·7 (2·9)	4·3 (2·5)	−50% (−62 to −39)	<0·0001	5·1 (3·2)	−44% (−57 to −31)	<0·0001	5·4 (3·4)	−38% (−52 to −24)	0·0001
VLDL cholesterol, mmol/L	0·5 (0·3)	0·3 (0·3)	−45% (−61 to −29)	<0·0001	0·4 (0·4)	−28% (−48 to −10)	0·0185	0·4 (0·4)	−31% (−54 to −7)	0·0389
Non-HDL cholesterol, mmol/L	10·0 (3·4)	5·1 (2·8)	−50% (−61 to −39)	<0·0001	5·9 (3·6)	−44% (−57 to −31)	<0·0001	6·2 (3·8)	−39% (−53 to −25)	<0·0001
Triglycerides, mmol/L	1·0 (0·4 to 2·9)	0·5 (0·1 to 1·7)	−45% (−61 to −29)	<0·0001	0·7 (0·2 to 2·9)	−29% (−47 to −11)	0·0157	0·7 (0·2 to 4·1)	−31% (−54 to −8)	0·0368
ApoB, g/L	2·6 (0·8)	1·3 (0·7)	−49% (−60 to −38)	<0·0001	1·5 (0·8)	−45% (−57 to −33)	<0·0001	1·5 (0·9)	−43% (−56 to −29)	<0·0001
Lipoprotein (a), μmol/L	2·4 (0·6 to 2·1)	1·7 (0·3 to 7·1)	−15% (−30 to 0·9)	0·0003	2·0 (0·5 to 8·6)	−19% (−31 to −8)	0·0111	2·6 (0·6 to 7·0)	−1% (−17 to 6)	0·5827
HDL cholesterol, mmol/L	1·1 (0·3)	1·0 (0·4)	−12% (−20 to −4)	0·0001	1·2 (0·4)	1% (−13 to 15)	0·954	1·1 (0·3)	−5% (−13 to 3)	0·1396
ApoA-I, g/L	1·2 (0·3)	1·0 (0·2)	−14% (−17 to −4)	0·0003	1·1 (0·3)	1% (−11 to 13)	0·568	1·1 (0·3)	−4% (−10 to 3)	0·1155

Data are mean (SD), median (range) for triglycerides and lipoprotein (a) at baseline, weeks 26, 56, and 78, or mean (95% CI) for percent change. †p values from mixed model. ‡p values from one-sample *t* test.

Table: **Lipid and lipoprotein concentrations at baseline and weeks 26, 56, and 78 (end of study)**

atorvastatin, 22 with ezetimibe (all in combination with a statin), three with niacin, one with a fibrate, and one with a bile acid sequestrant. 18 patients regularly underwent apheresis with a frequency that ranged from weekly to every 6 weeks. Despite aggressive lipid lowering treatment, total cholesterol, LDL cholesterol, and ApoB were substantially elevated at baseline (table).

Compliance with study drug dosing, defined as more than 80% of capsules taken, was 28 (93%) during the efficacy phase and 22 (95%) during the safety phase. Of the six patients who discontinued lomitapide treatment, two were receiving 5 mg, two were receiving 10 mg, one was receiving 20 mg, and one was receiving 40 mg. Among the 23 patients who completed the study, the maximum dose was 5 mg in one patient; 20 mg in five; 40 mg in six, and 60 mg in 11 at the end of the efficacy phase. The dose distribution remained similar at week 78.

Mean levels of LDL cholesterol remained stable during the run-in phase, as shown by a mean percent change from screening in LDL cholesterol of –1·20% (95% CI –15·66 to 13·18) at week 0. Mean percent changes in LDL cholesterol during the efficacy phase are shown in figure 1. Mean LDL cholesterol significantly decreased by 50% from baseline to the end of the efficacy phase (week 26; table). Percent changes from baseline for key secondary endpoints (total cholesterol, ApoB, and triglycerides) were consistent with those for LDL cholesterol at week 26 (table). Analysis done with the last observation carried forward gave similar results.

Overall, 19 of 23 patients with data at week 26 had decreased concentrations of LDL cholesterol of more than 25% with 12 having more than a 50% reduction. Eight patients had LDL cholesterol levels lower than 2·6 mmol/L at week 26, with one having levels lower than 1·8 mmol/L. On the basis of LDL cholesterol response, three patients permanently discontinued LDL apheresis and three permanently increased the time interval between apheresis treatments at some point during the safety phase (weeks 26–78). Lomitapide significantly reduced LDL cholesterol at week 78, despite changes in concomitant lipid lowering therapy or any adjustment in lomitapide dose (table). Similar efficacy results were reported for total cholesterol, ApoB, and triglycerides (table). Lipoprotein (a) levels were significantly reduced from baseline at week 26 and 56, but were not significantly different at week 78 (table).

Concentrations of HDL cholesterol were significantly reduced at week 26, and mirrored the reduction in the levels of ApoA-I (table). HDL cholesterol and ApoA-I returned to levels similar to those at baseline by week 78 (table).

A summary of adverse events reported during the efficacy and safety phase is shown in the appendix. Most patients had at least one adverse event during both the efficacy (27 of 29 patients) and safety (21 of 23) phases. Most adverse events were assessed as mild to moderate in intensity. The most commonly reported events during treatment with lomitapide were gastrointestinal in nature (27 patients during the efficacy phase, and 17 during the safety phase). The three patients who discontinued the study because of gastrointestinal disorders permanently stopped lomitapide by week 12 (appendix). No patients died during the study. Three (10%) of 29 patients had serious adverse events: one had acute coronary syndrome and angina pectoris and lower respiratory tract infection, one had elective hysterectomy for menorrhagia, and one had chest pain. All serious adverse events were assessed as

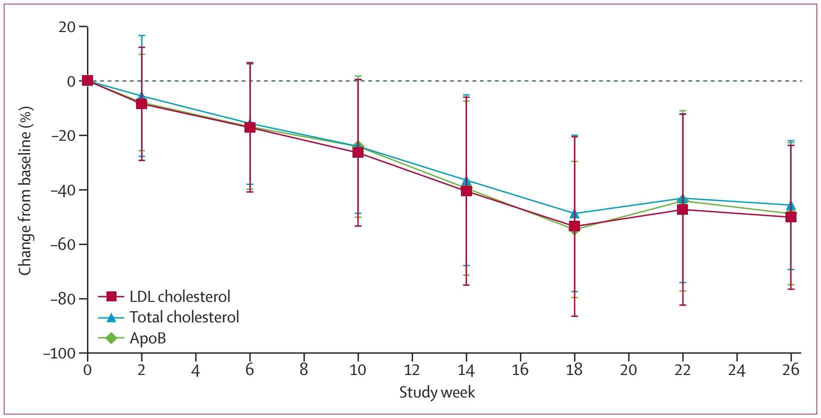

Figure 1: **Mean percent changes in LDL cholesterol, total cholesterol, and ApoB levels from baseline to week 26 (end of efficacy phase)**
Data available at each time point are expressed as mean (SD).

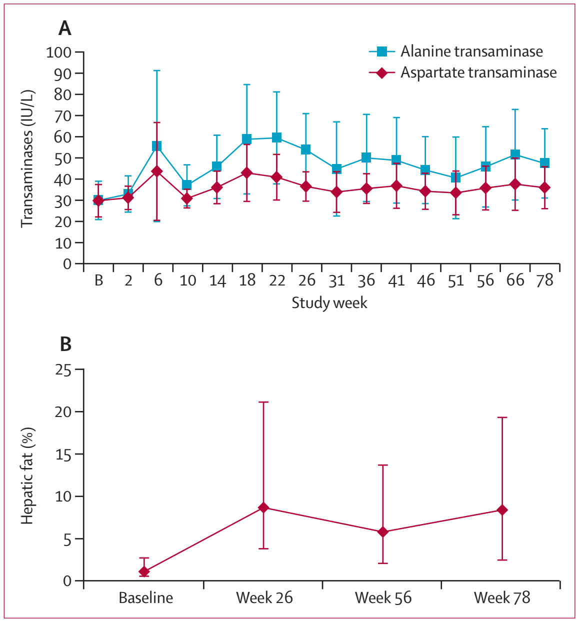

Figure 2: **Alanine transaminase and aspartate transaminase levels and percentage of hepatic fat in the liver**
Data are mean, 95% CI. Laboratory reference ranges for alanine transaminase levels were 10–40 U/L in men and 10–33 U/L in women; reference ranges for aspartate transaminase levels were 10–43 U/L in men and 10–36 U/L in women (A). Percentage of fat in the liver, as measured by nuclear magnetic resonance spectroscopy at baseline and 26, 56, and 78 weeks of lomitapide treatment (n=20; B).

Panel: Research in context

Systematic review

We searched PubMed for intervention studies of homozygous familial hypercholesterolaemia between January, 1980, and August, 2012. Patients with this rare disease have untreated cholesterol levels greater than 13 mmol/L. Drug-based treatments were scarcely effective until the introduction of HMG-CoA reductase inhibitors (statins). Patients with homozygous familial hypercholesterolaemia have an inadequate response to existing lipid-lowering drug therapies such as statins and ezetimibe[7,17–19] and remain at very high risk for cardiovascular events and mortality. Treatment at high doses of atorvastatin and rosuvastatin results in about 27% reduction in LDL cholesterol.[19] Addition of ezetimibe to statin treatment can result in an additional 20% reduction in LDLcholesterol.[7] Apheresis treatment can acutely lower LDL cholesterol levels by 70–80% and result in a time-average reduction by 40–50% when done regularly.[20] A phase 3, randomised study assessing the efficacy of an anti-ApoB antisense oligonucleotide, mipomersen, showed a reduction in LDL cholesterol of about 25% in patients with homozygous familial hypercholesterolaemia treated with maximum-tolerated lipid-lowering drug therapy.[13]

Interpretation

Our study expands the results obtained in a previous phase 2 study.[14] We report that lomitapide, when given in addition to currently available lipid-lowering therapy, results in an additional 50% reduction in LDL cholesterol, potentially bringing these high-risk patients closer to target levels. The limitations due to the single-arm, open-label design and the safety considerations of potential dose-related transaminase elevations, and liver-fat accumulation are counterbalanced and outweighed by the significant LDL cholesterol-lowering effects of lomitapide in this severe disorder of unmet medical need. Our study suggests that treatment with lomitapide could be a valuable drug in the management of homozygous familial hypercholesterolaemia.

unrelated or unlikely related to study treatment. No serious adverse events were reported between weeks 26 and 78.

Ten patients had elevated levels of ALT, AST, or both of more than three times the ULN at least once during the study (figure 2). Four of these patients had ALT increases more than five times the ULN and one patient had a similar elevation in AST; these elevations occurred at lomitapide doses of 10 mg, 20 mg, 40 mg, and 60 mg. No patient discontinued treatment permanently because of elevations in liver-function-test parameters and all elevations were managed either by dose reduction or temporary interruption of lomitapide as per protocol. Of note, three of four patients with elevations of more than five times the ULN in liver-function-test parameters reported consuming quantities of alcohol higher than those allowed per protocol. No patient had elevations in bilirubin or alkaline phosphatase levels.

Hepatic fat was measured non-invasively with NMRS. Mean hepatic fat in the 20 patients with evaluable NMRS scans was 1·0% (range 0–5·0) at baseline, 8·6% (0–33·6) at week 26, 5·8% (0–16·5%) at week 56, and 8·3% (0–19·0%) at week 78 (figure 2). Percent change in hepatic fat was negatively associated with change in LDL cholesterol. This association was significant at week 26 (r=–0·50, 95% CI –0·76 to –0·09; p=0·0161) and week 56 (r=–0·55, –0·79 to –0·15; p=0·0083), but was not significant at week 78 (r=–0·21, –0·59 to 0·25; p=0·3618).

Discussion

Our open-label study shows that lomitapide, administered concurrently with background lipid-lowering therapies including LDL apheresis, significantly reduced LDL cholesterol in patients with homozygous familial hypercholesterolaemia. This reduction is similar to that reported during lomitapide monotherapy in patients with the disorder,[14] and shows that lomitapide had similar efficacy when added to existing concomitant treatment (panel).

While studies of cardiovascular outcome are not feasible in view of the rarity of homozygous familial hypercholesterolaemia, retrospective studies show that even a modest reduction in LDL cholesterol, either by pharmacological intervention or LDL apheresis, results in apparent improvement in morbidity and mortality.[6,8,9,21] Furthermore, observational studies clearly show that patients with homozygous familial hypercholesterolaemia and some LDL-receptor function (receptor-defective) have lower levels of LDL cholesterol and better prognosis than those with no LDL-receptor function (receptor-negative).[4] Thus, although we are unable to provide direct evidence, the magnitude of LDL cholesterol reduction with lomitapide would be expected to reduce cardiovascular risk and improve survival.

Reduction of LDL cholesterol levels was somewhat attenuated at the end of the study. This effect could be explained by the changes during the safety phase that were made in apheresis treatment or in concomitant lipid lowering therapy in some of the better responders, as well as reductions in lomitapide dose in some of the patients that had elevated liver enzymes or gastrointestinal tolerability issues.

We noted a significant decrease in lipoprotein (a) levels at week 26, that persisted up to week 56. The mechanism underlying this effect is not known, but a similar finding has been reported with other drugs affecting the secretion of ApoB-containing lipoproteins by the liver.[13] The reason for loss of significance in lipoprotein (a) reduction at week 78 is not clear. Lipoprotein (a) levels are substantially affected by apheresis treatment,[22,23] thus changes in apheresis treatment that were allowed during the safety phase could have confounded the effect on lipoprotein (a). Further studies are needed to test this hypothesis and clarify these findings.

HDL cholesterol and ApoA-I levels were transiently decreased during the efficacy phase, a finding reported in previous studies with lomitapide.[14,24] The mechanism(s) underlying these changes are not known and further studies will be necessary to explain this effect. Possible reasons might include the low-fat diet or the inhibitory effects of lomitapide on dietary fat absorption; the reduced secretion of triglyceride-rich lipoproteins, which carry ApoA-I, from the gut or liver, as a direct consequence of MTP inhibition; or a reduction in ApoA-I production. The decrease in levels of HDL cholesterol occurred during the titration period, when the dose was gradually increased, and subsequently returned to levels approaching those at baseline once the dose was stabilised, suggesting the existence of a compensatory mechanism. The clinical implications of this temporary reduction in levels of HDL cholesterol are unknown.

Our study was the first long-term study of any MTP inhibitor in human beings, and safety and tolerability were carefully assessed. Lomitapide, initiated at a low dose and escalated to an individualised maximum dose in the presence of a low-fat diet, was generally well tolerated. All three discontinuations due to gastrointestinal events occurred during the titration phase. The incidence and the number of patients who experienced gastrointestinal events improved during the safety phase suggesting that patients become more tolerant or learnt to control their diet better, similar to patients with abetalipoproteinaemia.[15] Indeed, of the 23 patients who completed the efficacy phase, all 23 remained on lomitapide for another 12 months and completed the entire protocol. Investigators and patients were aware of the lomitapide dose and the lipid response because of the open-label design of the study, therefore, we cannot exclude the possibility that this factor influenced the reporting and assessment of adverse events.

Accumulation of liver fat is intrinsically linked to the mechanism of action of MTP inhibitors, and has been the basis of concerns regarding the clinical use of this class of agents. The 18-month duration of this study afforded the first opportunity to assess the effect of chronic MTP inhibition on liver safety and liver fat. While ALT levels more than three times the ULN were seen in ten of 29 patients, these changes were generally transient or resolved with dose reduction and were not associated with elevated bilirubin or alkaline phosphatase or evidence of impaired synthetic function.

As expected, mean hepatic fat increased from 1·0% to 8·6% at week 26, but no further increase was reported for the remainder of the study. Since the clinical significance and long-term implications of the increase in hepatic fat as a result of lomitapide therapy is not clearly understood, rigorous and standardised long-term monitoring will be necessary.

Our study has several limitations that need to be taken into account when interpreting the results. The study was a non-randomised, open-label study. Since homozygous familial hypercholesterolaemia is a rare disease, our intent was to expose the maximum number of patients to treatment for the duration of the study so that safety (especially the potential liver adverse events) could be assessed fully. Furthermore, in view of the striking changes in LDL cholesterol and ApoB that were reported in the phase 2 study[14] we expected to be able to easily discern the effect of lomitapide treatment from the potential effects of any variables that might confound the interpretation, such as regression to the mean. We acknowledge that the absence of a control group could bias the interpretation of the efficacy data, however, we minimised this possibility with the introduction of a run-in period to stabilise low-fat diet and concomitant lipid lowering treatments and assess any effect of these factors, as well as establishing the baseline for lipid-related data as the average of two measurements taken 2 weeks apart at the end of the run-in period. The inclusion of patients receiving apheresis treatment could have also potentially introduced a confounder for the assessment of LDL-cholesterol lowering. However, in view of the well-defined rules that were followed if apheresis treatment was present, we do not believe that the primary endpoint results were confounded by the presence of such treatment. Finally, patients enrolled in this study were representative of the adult patients with homozygous familial hypercholesterolaemia followed in the usual clinical setting and the results obtained can be generalised and applied globally to different health-care environments.

In summary, lomitapide, added to a low-fat diet and ongoing lipid-lowering treatment, substantially and stably reduced the levels of LDL cholesterol and ApoB in adult patients with homozygous familial hypercholesterolaemia and maintained these effects over 18 months. While most patients had at least one reported gastrointestinal-related adverse effect and three of 29 patients withdrew due to gastrointestinal-related symptoms early in the study, the overall frequency of these side-effects diminished over time. The mean percent hepatic fat that increased at 6 months remained stable thereafter. Overall, this study suggests that the benefit–risk ratio of lomitapide in patients with homozygous familial hypercholesterolaemia, who are at high risk of cardiovascular events and death at a young age, could be favourable.

Contributors

MC, DJR, and LTB designed the study in collaboration with the investigators. MC, EAM, HdTT, DJB, ADM, RAH, MRA, PKS, DG, CRS, GBV, and AMEDP were site investigators who recruited patients and gathered data. KJP supervised the statistical analysis. MC, EAM, DJB, ADM, RAH, CRS, GBV, and DJR interpreted the data. MC and DJR wrote the report. All authors critically reviewed and approved the report.

Phase 3 HoFH Lomitapide Study investigators

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Conflicts of interest

MC received research grant, speaker honoraria, and travel support for attending scientific meetings from Aegerion Pharmaceuticals. DJB received support for attending scientific meetings and speaking honoraria from Aegerion. CRS owns equity in Aegerion Pharmaceuticals. WJS was an employee at Aegerion Pharmaceuticals and owns equity in the company. LTB is an employee and owns equity in Aegerion Pharmaceuticals. DJR is an inventor on a patent related to lomitapide, serves as the chair of the scientific advisory board for Aegerion Pharmaceuticals, and owns equity in the company. CRS and

DJR were excluded from the day-to-day conduct of the study and were not involved in the care and management of study patients. None of the authors were paid by Aegerion Pharmaceuticals or any other agency to write this Article. All other authors declare no conflicts of interest.

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SUPPLEMENTARY MATERIAL

Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolemia: a single-arm, open-label, phase 3 study

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Subjects' baseline characteristics

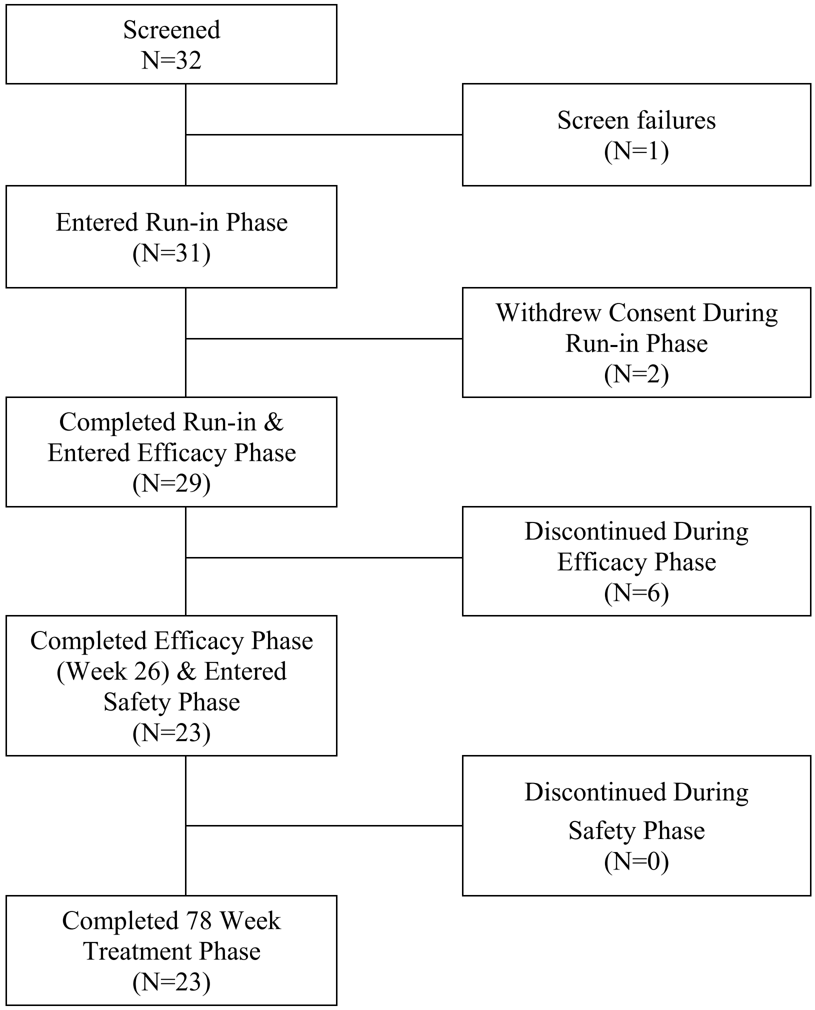
Recruitment was open from December 2007 to March 2010. Screening visit was performed in 32 potential study subjects; one subject was excluded from participating, because of elevated transaminases, and two subjects did not complete the run-in period for personal reasons (Supplemental Figure 1). Of the 29 subjects enrolled, 7 subjects were recruited in the two sites in the USA, 5 in the two sites in Canada, 11 in the three sites in South Africa and 6 in the four sites in Italy. All eligible subjects were counseled by a trained nutritionist/dietitian on how to follow a diet supplying <20% energy from fat while consuming adequate calories to maintain weight and were provided with daily dietary supplementation of vitamin E and essential fatty acids, starting at the initiation of the run-in period and continuing throughout the study.

The demographic and clinical characteristics of the study subjects are provided in Supplemental Table 1. The majority of the enrolled subjects met the clinical criteria for HoFH and qualified for the trial on that basis. However, full molecular characterization of the genetic mutation(s) responsible for the HoFH phenotype was available for all 29 subjects. Twenty-eight subjects were either true homozygotes or compound heterozygotes for mutations in the *LDLR* gene and one was homozygous for an ARH (*LDLRAP1*) gene mutation. Mean age of enrolled subjects was approximately 31 years, with a range between 18 and 55 years. Subjects entered the trial with evidence of significant cardiovascular morbidity despite maximal lipid-lowering therapy. Ten (35%) of the 29 patients had undergone CABG surgery prior to study entry; five of these patients were ≤ 21 years of age, including three patients under the age of 8 at the time of open-heart surgery. Three patients had undergone multiple CABG procedures. Coronary angioplasty was performed in 3 patients (10%), including one patient who required three procedures at the ages of 20, 21 and 22 years. Aortic valve replacement had been performed in three patients (10%), and mitral valve replacement or repair in three patients (10%). Cerebrovascular disease was also evident, with three patients (10%) having suffered a transient ischemic attack, and one patient (3%) having undergone carotid endarterectomy. Arterial stenosis, including the aortic, carotid, and coronary arteries, was reported in eight patients (28%).

Supplemental Table 1- Baseline characteristics of study subjects (n=29)

Age, years	30·7 ± 10·6
Gender, n	
Male	16 (55·2%)
Female	13 (44·8%)
Race, n	
Caucasian	25 (86·2%)
Asian	2 (6·9%)
African American	1 (3·4%)
Other	1 (3·4%)
Genetic diagnosis, n	29 (100%)
Cadiovascular disease, n	27
Valvular disease	21
CAD	21
BMI, kg/m^2	25·8 ± 5·43
Lipid-Lowering drugs, n (%)	
Statins	27 (93·1%)
Ezetimibe	22 (75·9%)
Bile acid sequestrants	1 (3·4%)
Nicotinic Acid	3 (10·3%)
Fibrates	1 (3·4%)
LDL/Plasma Apheresis	18 (62·1%)

Supplemental Figure 1: Subjects disposition



Changes in apheresis treatment

Eighteen subjects received plasma or LDL apheresis when recruited in the study. Treatment intervals ranged between 7 and 42 days and were required to be stable during the run-in period and the efficacy phase. Per protocol apheresis treatment could be modified during the safety phase at the discretion of the investigator. During this phase six subjects modified their apheresis treatment. Three subjects stopped apheresis permanently after having reached LDL-C <4·0 mmol/L: two of them (one previously receiving apheresis every 28 days and one every 42) at week 26 and one (previously receiving weekly treatment) at week 36. Three other subjects permanently changed the interval between apheresis sections, one of them increasing it from weekly to biweekly and two from every 14 to every 21days.

Safety and Tolerability

No clinically meaningful changes were observed in hematology, renal function, electrolytes, serum protein or urinalysis parameters. Median CRP at baseline was 2·0 mg/L (range 0·2, 50·6 mg/L). Median CRP change compared to baseline at week 26 was -0·2 mg/L (-16·0, 33·2 mg/L, p=0.4123), -0·5 mg/L at week 56 (-15·5, 1·2 mg/L, p=0.0070) and -0·7 mg/L at week 78 (-17·2, 5·3 mg/L, p=0·0246). No clinically meaningful changes were observed in fat soluble vitamins (supplemental table 2) or essential fatty acids (supplemental table 3). This includes also the subject that underwent elective hysterectomy for menorrhagia: this subject had a known long-standing history of menorrhagia and was scheduled to have an elective hysterectomy. Her lipid-soluble vitamins levels, including vitamin K, did not indicate a deficient state. As expected mean levels of vitamin E decreased in parallel with LDL-C, however, levels remained within the normal range; the ratio of vitamin E/total lipids did not reach <1.0 in any subject at any time during treatment with lomitapide. All five patients receiving warfarin concomitantly with lomitapide required warfarin dose modification during treatment based on changes in international normalized ratio (INR). No clinically meaningful changes over time occurred for vital signs or electrocardiograms. Weight decreased at week 26 by a mean of 3·4 kg (-4·7%) and at week 78 by a mean of 2·3 kg (-3·1%) from baseline. None of the subjects had a body mass index (BMI) < 18·5 kg/m^2 at any time during the study.

Four of the six subjects that did not complete the efficacy phase discontinued because of AEs: one subject discontinued because of headache while at 40 mg. This AE was deemed unlikely related by the investigator. One subject presented with gastrointestinal AEs while taking lomitapide 5 mg, was diagnosed with gastroenteritis and was never able to escalate the dose: the subject discontinued the study by week 5. Finally, two other subjects developed diarrhea (accompanied by nausea and abdominal pain in one subject) and discontinued lomitapide by week 10 and 12, respectively while at 10 mg dose. Of note, all of these subjects reported dietary fat intake outside of the recommended range. Supplemental table 4 list the treatment emergent adverse events reported in 10% or more of the subjects.

Supplemental Table 2 - Fat Soluble Vitamins at Baseline, Week 26 and Week 78

	Baseline (n=29)	**Week 26 (n=23)**	**% Change**	**Week 78 (n=23)**	**% Change**
Vitamin E (mg/dL)	2·9±1·1	1·6±0·6	-39·9±24·7	1·7±0·8	-35·3±30·8
Vitamin E/Total Lipids	5·9±2·4	6·0±2·1	20·2±53·1	5·2±1·4	4·7±39·0
Retinol (µg/dL)	44·8±16·9	53·3±18·5	11·3±23·0	53·5±13·5	15·2±27·8
25 hydroxy vitamin D (ng/mL)	17·5±11·2	26·4±13·0	65·7±65·1	31·9±18·5	103·5±106·5
Uncarboxylated osteocalcin (ng/mL)	6·7±3·1	7·6±3·2	10·4±39·8	7·7± 2·9	15·6±42·0

Absolute values are mean ± SD; percent change ± SD. Uncarboxylated osteocalcin is a marker for vitamin K. Reference ranges (M=male;F=Female): Retinol: M 38-93, F: 32-80 µg/dL; Vitamin D, 25OH: 7-54 ng/mL; Vitamin E: M: 0·5-1·62; F: 0·5-1·73 mg/dL;

Supplemental Table 3 – Essential fatty acids at Baseline, Week 26 and Week 78

	Baseline (n=29)	Week 26 (n=23)	% Change	Week 78 (n=23)	% Change
Linoleic acid	4023·6±1059·2	3095·6± 1023·6	-22·0±26·3	3764·8±1326·6	-5·1±37·43
Arachidonic acid	2148·1±502·9	1136·1±365·7	-48·6±20·4	1278·3±673·8	-41·1±31·1
Alpha linolenic acid	74·2±51·0	38·3±29·0	-42·3±43·7	64·7±61·53	54·3±403·1
Eicosanoid acid	209·8±128·0	74·9±35·9	-58·0±24·2	107·3±95·2	-41·3±65·5
DHA acid	348·2±155·8	218·2±75·0	-36·0±38·5	251·8±178·6	-31·1±43·0

Absolute values are mean ± SD; percent change ± SD. All fatty acids are μmol/L.
Reference ranges: Alpha linolenic acid: 50-130; Arachidonic acid: 520-1490; DHA acid: 30-250; Eicosanoid acid: 14-100; Linoleic acid: 2270-3850.

Supplemental Table 4: Treatment-emergent adverse events (TEAE) reported in 10% or more of all Subjects during the study

MedDRA SOC Preferred Term	Dose of Lomitapide at the Time of Onset of the TEAE[1]						All Patients (N=29)
	5 mg (N=29)	10 mg (N=27)	20 mg (N=26)	40 mg (N=21)	60 mg (N=13)	80 mg[2] (N=1)	
Number of Subjects with at Least One Adverse Event, n (%)	18 (62·1)	20 (74·1)	19 (73·1)	18 (85·7)	12 (92·3)	1 (100·0)	27 (93·1)
Gastrointestinal Disorders	**9 (31·0)**	**18 (66·7)**	**12 (46·2)**	**14 (66·7)**	**10 (76·9)**	**1 (100·0)**	**27 (93·1)**
Diarrhoea	5 (17·2)	14 (51·9)	5 (19·2)	11 (52·4)	5 (38·5)	0 (0·0)	23 (79·3)
Nausea	4 (13·8)	6 (22·2)	6 (23·1)	8 (38·1)	5 (38·5)	0 (0·0)	19 (65·5)
Dyspepsia	2 (6·9)	1 (3·7)	2 (7·7)	5 (23·8)	2 (15·4)	0 (0·0)	11 (37·9)
Vomiting	0 (0·0)	3 (11·1)	3 (11·5)	4 (19·0)	2 (15·4)	1 (100·0)	10 (34·5)
Abdominal Pain	1 (3·4)	4 (14·8)	2 (7·7)	2 (9·5)	1 (7·7)	1 (100·0)	8 (27·6)
Abdominal Discomfort	1 (3·4)	0 (0·0)	1 (3·8)	3 (14·3)	1 (7·7)	0 (0·0)	6 (20·7)
Abdominal Distension	1 (3·4)	2 (7·4)	1 (3·8)	2 (9·5)	2 (15·4)	1 (100·0)	6 (20·7)
Constipation	0 (0·0)	3 (11·1)	1 (3·8)	0 (0·0)	4 (30·8)	1 (100·0)	6 (20·7)
Flatulence	1 (3·4)	4 (14·8)	0 (0·0)	0 (0·0)	2 (15·4)	1 (100·0)	6 (20·7)
Abdominal Pain Upper	0 (0·0)	2 (7·4)	2 (7·7)	1 (4·8)	1 (7·7)	0 (0·0)	5 (17·2)
Defaecation Urgency	0 (0·0)	0 (0·0)	0 (0·0)	2 (9·5)	0 (0·0)	1 (100·0)	3 (10·3)
Gastrooesophageal Reflux Disease	0 (0·0)	0 (0·0)	0 (0·0)	1 (4·8)	2 (15·4)	1 (100·0)	3 (10·3)
Rectal Tenesmus	0 (0·0)	0 (0·0)	1 (3·8)	1 (4·8)	1 (7·7)	1 (100·0)	3 (10·3)
Infections and Infestations	**3 (10·3)**	**1 (3·7)**	**7 (26·9)**	**5 (23·8)**	**7 (53·8)**	**0 (0·0)**	**17 (58·6)**
Influenza	1 (3·4)	0 (0·0)	3 (11·5)	2 (9·5)	0 (0·0)	0 (0·0)	6 (20·7)
Nasopharyngitis	0 (0·0)	0 (0·0)	3 (11·5)	1 (4·8)	3 (23·1)	0 (0·0)	5 (17·2)
Gastroenteritis	1 (3·4)	0 (0·0)	0 (0·0)	2 (9·5)	1 (7·7)	0 (0·0)	4 (13·8)
Investigations	**4 (13·8)**	**4 (14·8)**	**5 (19·2)**	**4 (19·0)**	**3 (23·1)**	**0 (0·0)**	**15 (51·7)**
Weight Decreased	1 (3·4)	2 (7·4)	1 (3·8)	3 (14·3)	0 (0·0)	0 (0·0)	7 (24·1)
Alanine Aminotransferase Increased	0 (0·0)	1 (3·7)	3 (11·5)	2 (9·5)	1 (7·7)	0 (0·0)	5 (17·2)
General Disorders and Administration Site Conditions	**0 (0·0)**	**3 (11·1)**	**5 (19·2)**	**3 (14·3)**	**3 (23·1)**	**0 (0·0)**	**12 (41·4)**
Chest Pain	0 (0·0)	2 (7·4)	3 (11·5)	1 (4·8)	1 (7·7)	0 (0·0)	7 (24·1)
Fatigue	0 (0·0)	1 (3·7)	2 (7·7)	0 (0·0)	2 (15·4)	0 (0·0)	5 (17·2)
Pyrexia	0 (0·0)	1 (3·7)	1 (3·8)	0 (0·0)	1 (7·7)	0 (0·0)	3 (10·3)

MEDDRA SOC PREFERRED TERM	DOSE OF LOMITAPIDE AT THE TIME OF ONSET OF THE TEAE[1]						ALL PATIENTS (N=29)
	5 MG (N=29)	10 MG (N=27)	20 MG (N=26)	40 MG (N=21)	60 MG (N=13)	80 MG[2] (N=1)	
Musculoskeletal and Connective Tissue Disorders	**2 (6·9)**	**3 (11·1)**	**3 (11·5)**	**1 (4·8)**	**4 (30·8)**	**0 (0·0)**	**10 (34·5)**
Back Pain	0 (0·0)	0 (0·0)	3 (11·5)	0 (0·0)	1 (7·7)	0 (0·0)	4 (13·8)
Cardiac Disorders	**1 (3·4)**	**0 (0·0)**	**3 (11·5)**	**1 (4·8)**	**1 (7·7)**	**0 (0·0)**	**7 (24·1)**
Angina Pectoris	1 (3·4)	0 (0·0)	1 (3·8)	1 (4·8)	0 (0·0)	0 (0·0)	3 (10·3)
Palpitations	0 (0·0)	0 (0·0)	2 (7·7)	0 (0·0)	1 (7·7)	0 (0·0)	3 (10·3)
Nervous System Disorders	**2 (6·9)**	**1 (3·7)**	**2 (7·7)**	**2 (9·5)**	**1 (7·7)**	**0 (0·0)**	**7 (24·1)**
Dizziness	1 (3·4)	0 (0·0)	1 (3·8)	1 (4·8)	1 (7·7)	0 (0·0)	3 (10·3)
Headache	0 (0·0)	0 (0·0)	2 (7·7)	1 (4·8)	0 (0·0)	0 (0·0)	3 (10·3)
Respiratory, Thoracic and Mediastinal Disorders	**3 (10·3)**	**1 (3·7)**	**4 (15·4)**	**1 (4·8)**	**1 (7·7)**	**0 (0·0)**	**7 (24·1)**
Pharyngolaryngeal Pain	1 (3·4)	0 (0·0)	2 (7·7)	0 (0·0)	1 (7·7)	0 (0·0)	4 (13·8)
Nasal Congestion	1 (3·4)	1 (3·7)	0 (0·0)	1 (4·8)	0 (0·0)	0 (0·0)	3 (10·3)

[1]Patients may be counted more than once across lomitapide dose levels as the TEAEs are tabulated by dose at onset and patients were escalated through the dose levels to achieve maximum tolerated dose. The All Patients column includes overall incidence with patients counted only once if they experienced the event.
[2] One subject was escalated against protocol specified rules to 80 mg for about 1 month.