Journal of Clinical Lipidology (2016) 10, 273–282

Journal of Clinical Lipidology

LOWER, a registry of lomitapide-treated patients with homozygous familial hypercholesterolemia: Rationale and design

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KEYWORDS:
Homozygous familial hypercholesterolemia;
Lomitapide;
Registry;
Safety;
Effectiveness;
Cardiovascular imaging;
Pregnancy

BACKGROUND: Lomitapide is an orally active selective inhibitor of microsomal triglyceride transfer protein approved as adjunctive therapy for homozygous familial hypercholesterolemia (HoFH). The Lomitapide Observational Worldwide Evaluation Registry (LOWER) is a global, long-term, prospective, observational treatment registry established as a regulatory requirement.

OBJECTIVES: LOWER will evaluate the long-term safety and effectiveness of lomitapide in clinical practice. The objectives include evaluation of the occurrence of events of special interest and assessment of the long-term effectiveness of lomitapide in maintaining reduced serum lipid levels.

METHODS: LOWER is a noninterventional study open to eligible lomitapide-treated patients. At least 300 patients will be enrolled and followed for at least 10 years. Data will be collected in conjunction with usual care visits and analyzed annually. LOWER includes a cardiovascular imaging substudy; an independent pregnancy exposure registry is also open.

RESULTS: Events of special interest include hepatic abnormalities, gastrointestinal events, certain gastrointestinal tumors, major adverse cardiovascular events, and events associated with coagulopathy. Data will be collected on demographics, diagnosis, patient history, lomitapide dosing, concomitant treatment, lipid profile, and other laboratory results.

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Submitted April 1, 2015. Accepted for publication November 22, 2015.

http://dx.doi.org/10.1016/j.jacl.2015.11.011

CONCLUSION: LOWER will assess the long-term safety, efficacy, and patterns of use of lomitapide, increase understanding of the benefit-to-risk profile, and add to knowledge of HoFH.

Introduction

Lomitapide is currently approved in the EU, United States, Canada, Mexico, and Taiwan for the treatment of homozygous familial hypercholesterolemia (HoFH) as an adjunct to a low-fat diet and other lipid-lowering treatments, including apheresis. The US Food and Drug Administration (FDA), the European Commission, Health Canada, and the Taiwan FDA required Aegerion Pharmaceuticals to establish a registry of lomitapide-treated patients as a condition of being able to introduce lomitapide for treatment of patients in each of these countries. Aegerion Pharmaceuticals subsequently initiated the Lomitapide Observational Worldwide Evaluation Registry (LOWER) to collect information on the safety and effectiveness outcomes of patients treated with lomitapide.

Here, we present the background to HoFH and lomitapide and describe the rationale, aims, and methods of LOWER, which opened for patient recruitment in March 2014.

Background

HoFH is a rare hereditary disorder of lipoprotein metabolism characterized by exceptionally high levels of low-density lipoprotein cholesterol (LDL-C). Clinical manifestations may vary but often include markedly premature coronary artery disease, supravalvular aortic stenosis due to aortic root atheroma, and cutaneous manifestations such as tendon xanthomata.[1–4] Although there are no universally accepted clinical diagnostic criteria for HoFH, an untreated serum LDL-C of >13 mmol/L (500 mg/dL), or an on-treatment LDL-C of more 8 mmol/L (300 mg/dL) together with the appearance of cutaneous xanthomata before the age of 10 years, have often been used to diagnose HoFH clinically. As molecular diagnostic techniques have advanced, genotyping of patients with severe hypercholesterolemia has become an integral part of clinical practice in many settings. This has led to the realization that the spectrum of clinical severity in HoFH is much wider than initially thought and that the clinical criteria often fail to identify patients with milder phenotypes.

Although the HoFH phenotype may result from mutations in multiple genes, low-density lipoprotein receptor (LDL-R) dysfunction is the final common pathophysiological pathway leading to LDL-C elevation in patients with HoFH and LDL-R mutations are by far the most common genetic causes of HoFH.[3] Patients with HoFH secondary to LDL-R mutations inherit a mutated allele from each parent, resulting in severe functional impairment of the LDL-R pathway.[5–7] Residual LDL-R activity may vary considerably between mutations. Patients with HoFH can be classified as receptor negative or receptor defective (<2% or 2%–25% of residual activity, respectively) based on LDL uptake studies in cultured fibroblasts, although receptor function is nowadays often inferred after the identification of specific mutations.[4,8–10]

Epidemiology of homozygous familial hypercholesterolemia

Historically, the prevalence of HoFH has been reported as 1 case per million.[2,4] However, emerging studies suggest that the prevalence of HeFH, and consequently HoFH, may be higher than previously thought. Recent literature suggests an estimated prevalence of HeFH of ~1 case in 200[2] and of deleterious *LDLR* mutations in 0.45% of a control population and 1.9% of individuals with early-onset myocardial infarction or coronary artery disease.[11] Extrapolating from these data, the prevalence of HoFH is estimated to be ~6 cases per million. Analysis of a Dutch database of molecularly defined HoFH suggested a prevalence of ~1 case per 160,000–300,000.[3] Prevalence data are, however, continuing to evolve, and these calculations could be underestimates or overestimates of the prevalence in the general patient population. Information on the prevalence of FH in non-European populations is generally limited, and conclusions about the possible worldwide prevalence remain speculative. However, as a result of founder effects, the prevalence of HeFH and HoFH is higher in certain populations such as the Afrikaners in South Africa, Christian Lebanese, and French Canadians.[4]

Untreated LDL-C levels in homozygous familial hypercholesterolemia

The range of untreated and treated LDL-C levels in HoFH is wide (Fig. 1). In two recent clinical trials of novel therapies for HoFH, the LDL-C levels at study entry in conventionally treated patients ranged from a mean of 8.7 ± 2.9 mmol/L (336 ± 112 mg/dL) to 11.4 ± 3.6 mmol/L (441 ± 139 mg/dL).[12,13] Not all patients with HoFH have extreme LDL-C elevations. In a study from the Netherlands, only 50% of patients with molecularly defined HoFH met the clinical criterion of untreated LDL-C >13 mmol/L (500 mg/dL), with some

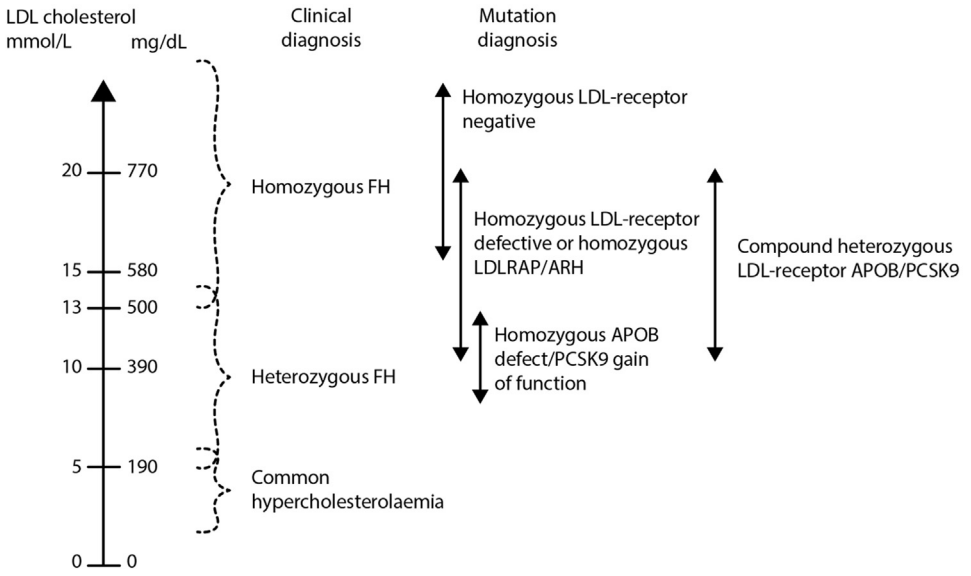

Figure 1 Reported LDL-C levels for clinical and genetic diagnoses of FH. Reproduced from Cuchel et al, *European Heart Journal* 2014[4] under a Creative Commons license (http://creativecommons.org/licenses/by-nc/4.0/legalcode).

patients presenting with untreated LDL-C levels as low as 4.4 mmol/L (170 mg/dL).[3]

Improved molecular diagnosis has led to the understanding that a conventional diagnosis of HoFH encompasses a wide range of underlying mutations,[3,14,15] with different effects on LDL-C levels, and highlights the need for caution in interpreting historical LDL-C values.[16] Furthermore, some patients with clinical FH (10%–40%) lack an identified disease-causing mutation.[2]

Although a genetic diagnosis is highly desirable, the phenotype of severe hypercholesterolemia can be identified clinically, allowing for timely initiation of treatment.[7] In 33 patients with severe FH (19 with HoFH), LDL-C levels were more predictive of carotid intima-media thickness than were the results of genetic screening.[17] The time-integrated exposure of the vasculature to LDL-C (cholesterol-year score) is thus the major determinant of atherosclerotic vascular damage and ultimately cardiovascular events.[18] Because LDL-C is frequently high in patients with HoFH, their cholesterol-year scores follow very steep trajectories, emphasizing the importance of early diagnosis and aggressive treatment.

Guidelines and treatment

Numerous dyslipidemia and FH guidelines have been published.[1,2,4,6,19–26] Guidelines specific to HoFH are summarized in Table 1. In the recently published European Atherosclerosis Society guidelines for HoFH, it is noted that the target of LDL-C <1.8 mmol/L (<70 mg/dL) in adults with clinical atherosclerotic cardiovascular disease is ambitious, thus careful evaluation of the benefit vs risk of therapeutic options is needed.[4]

Intensive lipid-lowering therapy is indicated in all patients with HoFH. High doses of potent statins such as rosuvastatin or atorvastatin together with ezetimibe form the basis of therapy, whereas the other cholesterol-lowering medications such as bile acid sequestrants and niacin are used occasionally.[1,2,6,19,20,26] Cautious addition of a fibrate may be considered in patients with elevated triglycerides and low levels of high-density lipoprotein cholesterol.[4,26]

Most patients with HoFH are not able to reach treatment targets despite intensive conventional pharmacologic therapy as they have high baseline lipid levels and often respond suboptimally to therapy. In particular, statins have limited effectiveness because their mode of action involves up-regulation of LDL-R on the cell membrane[28] and hence is dependent on the presence of residual LDL-R function.

Many patients treated with conventional lipid-lowering medications require lipoprotein apheresis to lower LDL-C levels further. Apheresis improves cardiovascular outcomes compared with historical control data[29,30] but, even with the combination of apheresis and statins, many patients still do not achieve sufficient lowering of LDL-C and their disease continues to progress.[31] Liver transplantation is another therapeutic option but is limited by a shortage of donor organs and the risks of immunosuppression.[32]

This unmet need for more effective medical therapy for HoFH[4,7,33,34] led to the exploration of novel approaches that could potentially provide significant additional LDL-C reduction. Lomitapide is an inhibitor of microsomal triglyceride transfer protein (MTP), whereas mipomersen is an antisense oligonucleotide that inhibits apoB100 synthesis. PCSK9 inhibitors upregulate LDL-R function and are only effective in receptor-defective patients.[35]

Lomitapide

Lomitapide is a first-in-class oral MTP inhibitor approved for the treatment of HoFH (as an adjunct to a low-fat diet and other lipid-lowering treatment, including apheresis).[36] It is

Table 1 Therapeutic targets in homozygous familial hypercholesterolemia-specific guidelines

Guideline	Recommendations for HoFH
European Atherosclerosis Society Consensus Panel (specific to HoFH)[2,4]	Adults: <2.5 mmol/L (<100 mg/dL) Adults with clinical atherosclerotic cardiovascular or coronary heart disease or diabetes: <1.8 mmol/L (<70 mg/dL) Children: <3.5 mmol/L (<135 mg/dL)
Integrated guidance from the International FH Foundation[26]	LDL-C to be reduced as much as possible
National Lipid Association (USA)[1]	≥50% reduction in LDL-C LDL-C <2.5 mmol/L (<100 mg/dL) in those at higher risk
National Institute for Clinical Excellence Clinical Guideline 71 (UK)[27]	Patients with HoFH should be referred to a specialist center and be seen by a cardiologist for evaluation of coronary heart disease

FH, familial hypercholesterolemia; HoFH, homozygous FH; LDL-C, low-density lipoprotein cholesterol.

classed as an orphan drug in the United States and was approved by the US FDA in December 2012 as Juxtapid® and by the European Commission in July 2013 as Lojuxta®.[37–39]

Lomitapide binds to and inhibits MTP, which is present in the lumen of the endoplasmic reticulum and thereby prevents the assembly of apoB-containing lipoproteins in enterocytes and hepatocytes. The inhibition of hepatic very low density lipoproteins synthesis lowers circulating LDL-C levels (Fig. 2).[34] The effects of lomitapide are independent of LDL-R, as lomitapide works by inhibiting lipoprotein production rather than by increasing clearance. This is a key consideration in a disease characterized by defective or absent LDL-R function.

In a single-arm, open-label, Phase III study of patients with HoFH, in which lomitapide was added to existing lipid-lowering therapy (which could include apheresis), LDL-C was reduced significantly by lomitapide.[13] The starting dose of lomitapide was 5 mg/day for the first 2 weeks, with dose escalation at 4-week intervals to a maximum dose of 60 mg; in the study, the median dose was 40 mg/day. Using a mixed linear model, which assumes a missing-at-random mechanism, the mean LDL-C level in the intent-to-treat population was reduced from 8.7 mmol/L (336 mg/dL) at baseline to 4.3 mmol/L (166 mg/dL) and in the 23 patients completing 26 weeks of treatment, a 50% decrease was also seen ($P < .0001$).[13] LDL-C levels were reduced by 40% when response was evaluated using the last observation carried forward statistical method for patients who discontinued prematurely. All 23 patients completing the first 26 weeks of treatment remained on lomitapide for a further

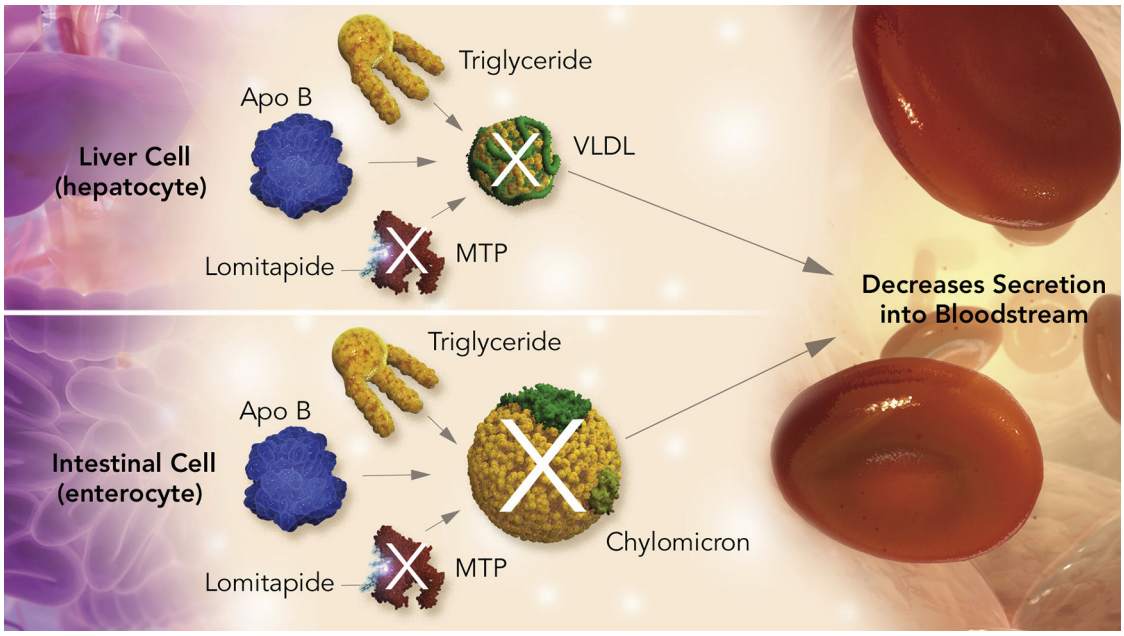

Figure 2 Mode of action of lomitapide. Apo B, apolipoprotein B; MTP, microsomal triglyceride transfer protein; VLDL, very low density lipoprotein.

year, and the mean LDL-C level after 78 weeks was 5.4 mmol/L (209 mg/dL). During this further year of treatment, the patient's physician could alter lipid-lowering therapy, including reducing or discontinuing apheresis, but the lomitapide dose remained constant.

Gastrointestinal (GI) symptoms were the most common adverse effects and were more frequent during the dose escalation phase, with a decrease in incidence and severity later on in the study. Aminotransaminase levels ≥5 times the upper limit of normal were observed in four patients but resolved with dose reduction or temporary interruption. No patients discontinued treatment owing to hepatic adverse events. The side effects of lomitapide are clinically manageable provided patients follow a low-fat diet (<20% of energy derived from dietary fat), receive support and encouragement from their treating physician, and close attention is paid to avoiding drug–drug interactions and to hepatic monitoring.

Consistent with its mechanism of action, lomitapide increases hepatic fat with or without concomitant increases in transaminases. Hepatic steatosis is a risk factor for progressive liver disease, including steatohepatitis and potentially cirrhosis. The long-term consequences of hepatic steatosis associated with lomitapide treatment are unknown. The prescribing information in the United States includes a boxed warning, owing to the risk of hepatotoxicity.[40] Risk minimization strategies include regulation and restriction of prescriptions, as well as prescriber education. The EMA recommends screening for steatohepatitis/fibrosis at baseline and annually thereafter, using imaging and biomarker evaluations. Prescribers need to be able to identify the target population correctly and be aware of monitoring recommendations, pregnancy contraindication, and the need for contraception. Patients and prescribers are provided with educational material before commencing lomitapide and are required to complete a REMs program in the United States.

Although the studies conducted to date have demonstrated that lomitapide has a risk–benefit profile that is acceptable for regulatory approval, further information from "real-life" clinical practice is required. This information, to be collected in the form of a registry, will help to establish the long-term safety profile of lomitapide, characterize its effectiveness and patterns of use in actual practice, and assess implementation of risk minimization interventions.

Lomitapide registry: LOWER

Establishment of a registry of lomitapide-treated patients is a regulatory requirement from the US FDA, the EMA, Health Canada, and the Taiwan FDA. Aegerion Pharmaceuticals has shown its commitment to meeting this requirement by establishing LOWER (ClinicalTrials.gov Identifier: NCT02135705). Specifically in Europe, lomitapide was approved under exceptional circumstances and, in accordance with Article 14(8) of Regulation No 726/2004, Aegerion Pharmaceuticals is required to conduct the following measures:

- To set up a long-term prospective observational study to systematically collect information on the safety and effectiveness outcomes of patients treated with lomitapide
- To evaluate the occurrence and outcomes of pregnancy in women of reproductive potential treated with lomitapide

LOWER will provide data on the long-term safety and effectiveness of lomitapide in clinical practice and yield the opportunity to learn more about HoFH in patients taking lomitapide, including patient demographic and risk characteristics, treatment approaches, and outcomes in accordance to the agreed requirements of the risk management plan. Owing to the rarity of HoFH, it was not feasible to study the potential effects of lowering LDL-C with lomitapide on the incidence of cardiovascular outcomes such as myocardial infarction, stroke, and death from cardiovascular causes in the pivotal trial; however, these endpoints will be collected in LOWER.

Cardiovascular imaging substudy: CAPTURE

Magnetic resonance imaging (MRI) studies in patients with established coronary and carotid atheroma have demonstrated that LDL-C reduction with statin therapy reduces atheroma burden significantly.[41–43] High spatial-resolution MRI is a robust and reproducible noninvasive technique that can be used serially to evaluate changes in atherosclerosis in vivo over time. It can measure carotid artery wall thickness accurately and has greater clinical utility than carotid intima-media thickness measurements by ultrasound.[44,45] MRI has been used in clinical trials to evaluate atherosclerotic plaque burden.[46] Carotid MRI can examine the full extent of the common internal and external carotid arteries in a single session using multiple image contrasts. This allows not only measurements of atherosclerotic plaque burden but also determination of plaque composition. Several studies have shown that atherosclerotic plaque components, such as the presence of a large lipid-rich necrotic core or intra-plaque hemorrhage, are characteristics of high-risk/vulnerable lesions that are susceptible to rupture. Finally, using dynamic contrast-enhanced MRI can provide information on increased plaque microvasculature and permeability; also hallmarks of high-risk or vulnerable lesions.

The CAPTURE (Effects of Lomitapide on Carotid and Aortic Atherosclerosis in Patients Treated with Lomitapide in Usual Care) study, a substudy of LOWER, will investigate the effects of lomitapide on the regression and/or stabilization of atheroma in the carotid artery and aorta.

CAPTURE will examine the hypothesis that LDL-C reduction with lomitapide results in regression and/or stabilization of atheroma in the carotid artery and aorta. Such an effect, if demonstrated, would provide meaningful

clinical data based on an "intermediate outcome" and establish a biologically plausible link between LDL-C reduction and expectation of a reduction in the incidence of major cardiovascular events (MACE) in this patient population. Serial vascular imaging findings in lomitapide-treated patients will be described; because CAPTURE is a sub-study of the observational LOWER registry, non-lomitapide-treated HoFH patients will not be enrolled, and there is no comparator control group.

Pregnancy exposure registry

Lomitapide has a pregnancy classification of X and is contraindicated for use during pregnancy because of the risk of fetal harm based on findings of teratogenicity in animal studies. Females of reproductive potential should have a negative pregnancy test before starting lomitapide and should use effective contraception during therapy with lomitapide.

A separate registry, the Global Lomitapide Pregnancy Exposure Registry (PER), will study the effects of lomitapide on pregnancy outcomes in women exposed to lomitapide during pregnancy and will aim to evaluate, using root-cause analysis, whether risk minimization strategies were followed. This PER, which is independent of LOWER, will seek to identify pregnancies occurring in women exposed to lomitapide during the 30 days before the last menstrual period before a positive pregnancy test or during pregnancy. Women who conceive while taking lomitapide will be encouraged to enroll in this separate registry if LOWER is active in their country.

Methods

Objectives of LOWER

The objectives of LOWER are:

- To evaluate the occurrence of the following in patients treated with lomitapide:
  - Hepatic events
  - GI events
  - Small bowel, hepatic, colorectal, and pancreatic tumors
  - Events associated with coagulopathy
  - MACE
  - Death, including cause of death
- To report pregnancies and evaluate the outcomes of pregnancy in females of reproductive potential treated with lomitapide. Patients who become pregnant will be asked to enroll into the PER
- To evaluate the long-term effectiveness of lomitapide in reducing LDL-C levels
- To assess whether lomitapide prescribers are following the recommended screening and monitoring recommendations aimed at risk minimization

Design

LOWER is a voluntary, long-term, prospective, multicenter, uncontrolled, noninterventional study of adult patients with HoFH treated with lomitapide as part of their physician-directed disease management. There are no protocol-mandated procedures or tests, and all patients receive usual care. Patient registration will be accomplished by the treating physicians with the consent of the lomitapide-treated patients. All health care professionals treating adult patients with lomitapide in countries where LOWER is being conducted are eligible to participate and to include patients in the registry. Regions include, but are not limited to, North America, Europe, Latin America, and Asia.

The criteria for patient inclusion are broad so that the HoFH population included in LOWER should be representative of that seen in clinical practice. All adult patients ($\geq$18 years) who initiate lomitapide treatment at the time of registry enrollment or within the previous 15 months are eligible.

Data collection will reflect the information generated as part of the usual care of patients with HoFH. The data will be entered into a secure online database by participating sites. Information to be collected and summarized includes patient demographics, medical history and detailed information regarding the diagnosis of HoFH, previous and current medications and therapies, the results of diagnostic and laboratory tests, findings on physical examination, and all adverse events. The data to be collected are included in the Supplementary Appendix.

Clinical events

The events of special interest to be evaluated in LOWER have been defined based on data from the clinical program or events considered to be of particular interest in the HoFH population and are defined in Table 2. Events of special interest will be considered as serious and reported to the FDA and relevant EU Competent Authorities, as appropriate.

Other effectiveness endpoints include the reduction in LDL-C from baseline, absolute and percentage change from baseline in other lipoprotein parameters, and changes in concomitant medications or apheresis treatments. Data will also be collected for demographic and diagnostic information, family and medical history, medications, dietary supplements and apheresis schedule, weight and body mass index, lomitapide dosing, hepatic, GI and cardiovascular procedures and diagnostic tests, lipid profile, hepatic safety monitoring according to country-specific labeling, pregnancy testing, creatine kinase, and international normalized ratio.

Follow-up

Patients who have continued treatment with lomitapide will be followed per protocol for 10 years. The minimum exposure of patients who remain on lomitapide and who do

Table 2 Events of special interest in LOWER

Events of special interest	Rationale
Hepatic abnormalities • Elevations of hepatic transaminases resulting in discontinuation of lomitapide • Elevations of hepatic transaminases >3 × ULN that persist despite dose reduction or interruption • Elevations of hepatic transaminases ≥5 × ULN • Symptomatic liver injury • Abnormalities identified during hepatology evaluations • Events that trigger other hepatic evaluation or testing	Elevations of aminotransferase levels (not associated with increases in bilirubin or alkaline phosphatase) were observed in clinical trials of lomitapide As a consequence of the mode of action, an increase in hepatic triglyceride accumulation occurs in some patients. The clinical relevance of this finding over the long term is unknown
GI events of special interest • Events leading to permanent treatment discontinuation or hospitalization or triggering additional investigations	As a consequence of the mode of action, GI side effects can occur with the use of lomitapide. Controlling dietary fat intake to <20% energy from fat is recommended to reduce GI-related side effects
Tumors of the small bowel, liver, colon, rectum, or pancreas	An increased incidence of tumors of the liver and small bowel was observed (at doses above the human exposure level at a dose of 60 mg) in a dietary exposure study in mice; although lomitapide was not mutagenic or genotoxic in preclinical studies. The mechanism involved and the relevance for clinical use are unknown
Events associated with coagulopathy, including • Abnormal bleeding • Cerebral hemorrhage • GI bleeding	Some patients with HoFH receive long-term anticoagulant therapy. As a result of a drug–drug interaction between lomitapide and warfarin, the international normalized ratio may increase in these patients and should be monitored regularly
MACE • Myocardial infarction • Hospitalizations for stable and unstable angina • Stroke • Transient ischemic attacks • Cardiovascular deaths	Patients with HoFH are predisposed to premature atherosclerosis and the effects of lomitapide on cardiovascular outcomes is of interest
All-cause mortality	
Pregnancy • Frequency of intended or unintended pregnancies	Lomitapide is contraindicated during pregnancy because lomitapide was found to be teratogenic in rats and ferrets. Women who become pregnant will be encouraged to enroll in the separate PER in which they will be followed for pregnancy outcomes

GI, gastrointestinal; HoFH, homozygous familial hypercholesterolemia; MACE, major adverse cardiovascular events; PER, pregnancy exposure registry.

not withdraw from the study is 10 years. The registry will include a minimum of 3000 patient exposure years. The study is expected to end in non-EU countries when a total of at least 300 enrolled patients have been followed for 10 years. It will remain open indefinitely in the EU.

Statistical considerations

The incidence of serious adverse events and events of special interest will be documented using two-sided 95% confidence intervals. Analyses will be performed using SAS version 8.2 or higher. Data will be analyzed annually. Subsets of patients who have been exposed to lomitapide will be compared and incidence rates of events of special interest tabulated. Long-term serum lipid levels in a clinical practice setting will be evaluated. Prescribing patterns of practitioners in a real-world setting will be described.

Organization and oversight

A Steering Committee (SC), including clinicians and scientists with expertise in HoFH, hepatology, cardiology, epidemiology, and biostatistics, will provide subject matter expertise for the program. The members of the SC are responsible for reviewing data from the registry over time, comparing these data with the product information, and making recommendations to Aegerion Pharmaceuticals about the conduct of the study. An independent Endpoint Adjudication Committee will review and validate events of special interest.

CAPTURE cardiovascular substudy

The objectives of CAPTURE are listed in Table 3. The primary objective is to assess changes in atheroma burden,

Table 3 Objectives of CAPTURE (Effects of Lomitapide on Carotid and Aortic Atherosclerosis in Patients Treated with Lomitapide in Usual Care), the cardiovascular substudy of LOWER

Primary objective:
- To assess the changes in atheroma burden as reflected by average carotid vessel wall area on MRI scanning after 2 years of treatment with lomitapide compared with baseline

Secondary objectives:
- To assess the changes in atheroma burden as reflected by changes in average aortic vessel wall area, average aortic, and carotid vessel lumen area, total vessel area, wall thickness, normalized wall index, and standard deviation of wall thickness on MRI after 2 years of lomitapide treatment compared with baseline
- To assess the changes in atheroma burden as reflected by changes in average aortic and carotid vessel wall area, lumen area, total vessel area, wall thickness, normalized wall index, and standard deviation of wall thickness after 1 year and 5 years of lomitapide treatment compared with baseline
- To assess changes in LDL-C and other lipoproteins at 1, 2, and 5 years of lomitapide treatment compared with baseline and the correlation of these laboratory evaluations with the change from baseline in MRI parameters of carotid and aortic atheroma

Exploratory analyses
- To evaluate major plaque compositional features including the necrotic lipid area, fibrous cap thickness, and calcium area. These plaque composition analyses will be performed at imaging time points if sufficient data exist with respect to both the size and frequency of the plaques
- To assess changes in markers of inflammatory and cardiovascular processes at 1, 2, and 5 years of lomitapide treatment compared with baseline and to correlate these changes with the change from baseline in MRI parameters of carotid and aortic atheroma

LDL-C, low-density lipoprotein cholesterol; MRI, magnetic resonance imaging.

as reflected by the change in average carotid vessel wall area on MRI scanning after 2 years of lomitapide treatment. The sub-study will be conducted at regional sites in countries in the EU, USA, and Canada. To minimize selection bias, consecutive patients enrolled in LOWER who meet the relevant eligibility criteria will be invited to participate in the sub-study. A total of 57 patients will be enrolled in the substudy, to provide 40 evaluable subjects. These individuals will undergo MRI of the carotid artery and aorta at baseline and after 1, 2, and 5 years of lomitapide treatment. An interim analysis, to determine if an increase in sample size is warranted, will be performed when 2-year MRI assessments are available for 20 evaluable patients.

Discussion

LOWER will provide comprehensive real-world data on the clinical use of lomitapide as a treatment for HoFH. The clinical studies already conducted have documented the short-term risk–benefit profile of lomitapide and provided the basis for regulatory approval. LOWER will complement and expand these data by providing long-term safety data and generating information on use in everyday clinical practice.

In addition, LOWER is expected to provide valuable information on the clinical and laboratory characteristics of HoFH. As it is a rare disease, there are few published studies on HoFH, and the natural history of the disease is poorly understood in the context of contemporary medical practice. Rare diseases, such as HoFH, are often underdiagnosed and inadequately treated, and the introduction of an effective new therapy may improve awareness and increase motivation for early diagnosis and treatment. In view of the need to expand and share relevant knowledge and experience of the management of HoFH, disease and drug registries have an important role to play.

As information about rare conditions is inherently limited and clinical trials are difficult to perform, registries can make a key contribution in generating longer term data that reflect real-world clinical practice. Several prospective registries have been implemented to study FH, including: the Simon Broome Familial Hyperlipidaemia Register in the UK, a long-term registry that has documented a reduction in mortality with statin therapy[47]; the CASCADE FH Registry,[48] a novel approach designed to address gaps in knowledge in FH screening, diagnosis, and treatment; the Australian and New Zealand Registry for Familial Hypercholesterolemia[49]; the Canadian FH registry[50]; and the Taiwan registry.[51]

To our knowledge, LOWER (together with the mipomersen registry required as a condition of FDA approval) is the first formal HoFH-specific registry. Unlike the registries already mentioned, LOWER is a drug-exposure registry rather than a disease registry. LOWER is expected to provide high-quality information on the clinical characteristics of patients with HoFH taking lomitapide and the impact of lomitapide on the natural history of the disease. A large number of cases will be included and information collected on baseline characteristics, including mutations, diagnostic criteria, previous therapies, and lipid profiles over time. It is anticipated that LOWER will provide robust data on the long-term safety and effectiveness of lomitapide in a patient population that is representative of usual clinical practice and much larger than the population included in the Phase III trial.

The registry will evaluate the use of lomitapide in conjunction with standard lipid-lowering therapies, including lipoprotein apheresis. LOWER will thus also provide an opportunity to assess the potential of lomitapide to allow a reduction in the frequency or cessation of apheresis while maintaining lipid control. The overall impact on cardiovascular morbidity and mortality will be recorded through evaluation of MACE.

LOWER will also document the effectiveness of the risk minimization strategies that have been implemented in facilitating the use of lomitapide, maximizing benefits for patients and managing risks appropriately.

The cardiovascular imaging substudy will provide data on the impact of LDL-C reduction with lomitapide on atherosclerosis. The separate PER will assess the effect of lomitapide exposure on the outcomes of pregnancy in women with HoFH, as well as extending the very limited information available on these patients.

Conclusions

LOWER will provide invaluable information on the treatment of this heterogeneous condition with lomitapide in routine clinical practice.

It is hoped that the infrastructure of the registry and the international cooperation involved in its implementation will also lead to significant improvements in the understanding and clinical management of HoFH.

The registry is now open, and all treating physicians are encouraged to enroll all eligible patients and thus contribute to this important initiative to improve patient outcomes.

Acknowledgment

Editorial support was provided by Christine Drewienkiewicz of Choice Healthcare Solutions and funded by Aegerion Pharmaceuticals. We thank the investigators and patients who make LOWER possible. A list of participating investigators is provided in Supplementary Appendix 3.

Participation in LOWER

For more information about participation in LOWER, visit http://www.juxtapid.com/juxtapid-registries, e-mail lower@aegerion.com or call 1-877-902-4099 (USA and Canada) or 00-800-000-10-20 (EU, Taiwan, and Latin American countries).

Financial disclosures

All authors have contributed by critical revision of the article and have approved the final version for submission. The authors report the following disclosures: Dirk J. Blom is an advisory board member for Aegerion Pharmaceuticals, Amgen, MSD, and Sanofi. Zahi A. Fayad has received research support from Aegerion Pharmaceuticals. John J.P. Kastelein is consultant to Aegerion, ISIS Pharma, AstraZeneca, Pfizer, Amgen, Regeneron, Sanofi, and Eli Lilly. Dominique Larrey, Lukas Makris, and Charles Schwamlein report no disclosures. LeAnne Bloeden is an employee and owns equity in Aegerion Pharmaceuticals. James Underberg is on the speaker's bureau for Genzyme, Merck, AstraZeneca, Amarin, Sanofi, and Kowa; is a consultant to Liposcience, Amgen, and Eli Lilly; is an advisory board member for Amgen, Aegerion Pharmaceuticals, Sanofi, Novartis, and AstraZeneca; and receives research funding from Aegerion Pharmaceuticals.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jacl.2015.11.011.

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