

# Lomitapide: a review of its clinical use, efficacy, and tolerability

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**Abstract:** Lomitapide is an inhibitor of MTP, an enzyme located in the endoplasmic reticulum of hepatocytes and enterocytes. This enzyme is responsible for the synthesis of very low-density lipoproteins in the liver and chylomicrons in the intestine. Lomitapide has been approved by the US Food and Drug Administration, European Medicines Agency, and other regulatory agencies for the treatment of hypercholesterolemia in adult patients with homozygous familial hypercholesterolemia. Clinical trials have shown that lomitapide reduces low-density-lipoprotein cholesterol levels by around 40% in homozygous familial hypercholesterolemia patients on treatment with statins with or without low-density-lipoprotein apheresis, with an acceptable safety and tolerance profile. The most common adverse events are gastrointestinal symptoms that decrease in frequency with long-term treatment, and the increase in liver fat remains stable. This review analyzes the clinical use, efficacy, and tolerability of lomitapide.

**Keywords:** lomitapide, homozygous familial hypercholesterolemia, safety, efficacy, cardiovascular disease

## Core evidence clinical impact summary for lomitapide

| Outcome measure                  | Evidence   | Implications  |
|----------------------------------|--|---|
| <b>Disease-oriented evidence</b> |  |   |
| LDL-C reduction in homozygous FH | Phase II and III, single-arm studies in HoFH ≥18 years old; real-world clinical experience (registries); clinical cases using lomitapide (dose up-titrated from 5 to 60 mg/day or to maximum tolerated every 4 weeks) in monotherapy (Phase II) or with statins with or without LDL-apheresis (Phase III and registries) | Dose-dependent LDL-C reductions between 25-51%; also, triglycerides were reduced by 35-65%. In Phase III trials, reduction was maintained after 26 weeks and in long-term extension studies. During the trial, 74% patients achieved an LDL-C level below 100 mg/dL at least once during the efficacy phase.<br><br>In those adult patients on LDL-apheresis, it is probable that one in three will reduce the frequency of the apheresis or even discontinue it. |

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(Continued).

| Outcome measure                  | Evidence   | Implications   |
|----------------------------------|--|--|
| <b>Patient-oriented evidence</b> |  |  |
| Tolerability and safety          | Phase II and III, single-arm studies in HoFH $\geq 18$ years old; real-world clinical experience (registries); clinical cases using lomitapide (dose up-titrated from 5 to 60 mg/day or to maximum tolerated every 4 weeks) in monotherapy (Phase II) or with statins with or without LDL-apheresis (Phase III and registries) | All studies have demonstrated that gastrointestinal symptoms are the most frequent adverse events and are related to the dose, transient and related to a bad adherence to a low-fat diet. Due to its mechanism of action, variable liver fat accumulation and an increase in transaminases occurs with lomitapide and return to baseline levels after 4 weeks of discontinuation of the drug. In the extension trials, the frequency of adverse events diminished compared to pivotal trials.                 |
| Net Benefit                      |  | HoFH is a rare and severe disorder causing death and cardiovascular disease since childhood. These patients have few therapeutic options like LDL-apheresis (not available in all countries) or liver transplantation. Although there are some adverse events, few patients discontinued medication due to them, and LDL-C reduction is important depending of the dose. The up-titration every 4 weeks or more and a good adherence to a low-fat diet can improve the tolerability and maximize the efficacy. |
| Economic evidence                |  | Lomitapide is an expensive medication, and there are no cost-effective studies.  |

## Introduction

Homozygous familial hypercholesterolemia (HoFH) is a rare and severe genetic disease, characterized by severe hypercholesterolemia and very premature atherosclerotic cardiovascular disease (ASCVD).<sup>1,2</sup> In >90% of cases, it is caused by mutations in both alleles of *LDLR* gene, and less frequently in other genes like *APOB*, *PCSK9*, and *LDLRAP1*.<sup>1,2</sup> The estimated prevalence varies from one in 160,000 to 1,000,000 in the general population.<sup>1,3,4</sup> Higher prevalence has been observed in certain populations with a founder genetic effect.<sup>5</sup> Clinically,

it is characterized by extremely high total and low-density-lipoprotein cholesterol (LDL-C) plasma levels, in general total cholesterol >500 mg/dL, cutaneous xanthomas, atheromatosis of the aortic valve and supraaortic region of the aortic root, and atherosclerotic coronary artery disease since early childhood.<sup>1,2,6,7</sup> The severity of the disorder depends mainly on the residual activity of *LDLR*. There are patients with null mutations that do not express *LDLR* activity (<2%), considered receptor-negative, and there are others that express some activity (2%–25%) that are considered receptor-defective.<sup>1,2</sup>

Patients with null mutations usually have higher LDL-C levels, do not respond to conventional lipid-lowering treatments (LLTs) and have poorer prognosis than those patients that are LDLR-defective.<sup>7</sup> However, high variability in the phenotype of HoFH, especially related to age of diagnosis and LDL-C levels, has been described in different homozygous cohorts worldwide.<sup>1,2</sup> In general, if these patients are not treated, life expectancy is <30 years of age.<sup>1</sup>

Due to the very high cholesterol exposure since birth and thus higher ASCVD risk, patients with HoFH must be treated from the second year of life with statins and ezetimibe, and most will require invasive procedures like LDL apheresis or (in exceptional cases) a liver transplant.<sup>2</sup> Currently, new drugs like lomitapide and evolocumab precipitate significantly lower cholesterol levels and thus reduce the necessity for more invasive procedures.<sup>1,2</sup>

## Lomitapide approval by regulatory agencies

Lomitapide (Juxtapid, Aegerion Pharmaceuticals [US]; Lojuxta, Amryt Pharma [UK]) received the status of orphan drug for the treatment of HoFH in 2007 and was approved by the US Food and Drug Administration (FDA) in 2012, “under exceptional circumstances” by the European Medicines Agency (EMA) in 2013, and by other international agencies in Japan and key Latin America markets to treat adult patients with HoFH, associated with a low-fat diet and other lipid-lowering medications or treatment (LDL apheresis is included in the FDA approval).<sup>11,12</sup> For the EMA, the patient's disease should be confirmed by genetic testing whenever possible.

Lack of evidence of long-term lomitapide treatment in cardiovascular morbidity and mortality reduction was considered a limitation by the FDA and EMA at the time of approval, and needs to be confirmed in further studies. On the other hand, due to the increased risk of hepatotoxicity and considering the unknown long-term effect, regulatory agencies recommended that patients receiving lomitapide be closely monitored and managed. For this reason, in 2012 the FDA also approved lomitapide risk-evaluation and -mitigation strategies to mitigate the risk of hepatotoxicity with the participation of health-care providers, patients, and pharmacies.

## Mechanism of action

Lomitapide is a small molecule that binds directly to and inhibits MTP in the endoplasmic reticulum of hepatocytes

and enterocytes. This enzyme plays a key role in the early stages of very low-density lipoprotein (VLDL) and chylomicron assembly, most likely by transferring triglycerides to nascent ApoB as it enters the lumen of the endoplasmic reticulum, controlling the number of ApoB-containing lipoprotein particles secreted to the bloodstream.<sup>13</sup> Analysis of the rare recessive genetic disorder abetalipoproteinemia, produced by mutations in the *MTP* gene located in chromosome 4q22–24, has suggested that inhibition of MTP could be a new target to reduce plasma-lipid levels. Clinically, abetalipoproteinemia is characterized by the absence of ApoB and ApoB-containing lipoproteins in plasma associated with systemic manifestations. These patients have very low plasma levels of cholesterol and triglycerides and undetectable levels of ApoB and LDL.<sup>14</sup>

By inhibiting MTP in hepatocytes and enterocytes, lomitapide reduces plasma levels of all ApoB-containing lipoproteins, including VLDL, LDL and chylomicrons. Its mechanism of action also explains some adverse events.<sup>15</sup> Liver steatosis can be explained by the intracellular increase in triglycerides associated with impaired assembly and secretion of ApoB-containing lipoprotein. In addition, studies in mice have shown that chemical inhibition of MTP decreases cholesterol ester synthesis and increases free-cholesterol levels in hepatic and intestinal cells. It has been suggested that this accumulation of free cholesterol in the endoplasmic reticulum produces oxidative stress and increases some gene transcriptions, producing an increase in plasma transaminases.<sup>15</sup> On the other hand, the effect of lomitapide on the gastrointestinal tract is suspected to be driven by the increase of intracellular triglycerides in the enterocytes, reduction in chylomicron formation, and reduction in dietary fat absorption, causing steatorrhea and gastrointestinal symptoms.<sup>16</sup>

## Metabolism of lomitapide

Lomitapide is metabolized in the liver through CYP3A4 to metabolites M1 and M3, which do not show MTP-inhibitory activity. More than 50% of the dose is excreted in the urine and 33%–35% in the feces of healthy volunteers. In patients with mild–moderate hepatic impairment, systemic exposure to a single oral dose of 60 mg was 47% higher compared to healthy volunteers. Similar data were obtained in patients with end-stage renal disease treated with hemodialysis.<sup>17</sup>

Due to its metabolism, lomitapide interacts with many other drugs, and dosage adjustment is necessary in these cases. There are strong interactions with clarithromycin,

nefazodone, itraconazole, ketoconazole, and some protease inhibitors, and moderate interaction with erythromycin, fluconazole, verapamil, and grapefruit juice. These strong and moderate CYP3A4 inhibitors are contraindicated with lomitapide. If a weak inhibitor like oral contraceptives or atorvastatin is required, the maximum dose of lomitapide should not be >30 mg per day.

Because lomitapide is an inhibitor of CYP3A4, it could be expected that drugs that are substrates for the same CYP may increase their plasma levels. This is an important issue in HoFH patients who need a high-dose statin, and other cardiovascular drugs, such as warfarin and calcium-channel blockers, among others. It has been shown that lomitapide increases systemic exposure to simvastatin, and the maximum dose of this statin should not exceed 40 mg/day in combination with lomitapide. On the other hand, minimal and nonclinically relevant interactions have been observed with rosuvastatin, ezetimibe, and fenofibrate, and no dose adjustments were required.<sup>18</sup> In addition, lomitapide also inhibits Pgp, and it would be necessary to reduce doses of such Pgp substrates as colchicine, digoxin, among others.

## Clinical efficacy and tolerability

The lipid-lowering efficacy of lomitapide has been demonstrated in healthy volunteers, patients with HoFH, and with moderate hypercholesterolemia in non-HoFH patients.<sup>9,19–21</sup> Considering that the approved indication for lomitapide is HoFH, only clinical trials and clinical cases reported with this disorder are discussed herein (Table 1). Trials in HoFH have been conducted in adults aged ≥18 years, designed as single-arm with dose-escalation protocol to minimize or reduce the frequency of gastrointestinal adverse effects.

## Phase II proof-of-concept trial (NCT01556906)

In a Phase II proof-of-concept trial,<sup>19</sup> six patients with diagnosed HoFH (five with molecular confirmation, and one with phenotype and LDLR-activity studies) aged 18–40 years were treated with lomitapide at four different doses (0.03, 0.1, 0.3, and 1 mg/kg body weight per day) that were titrated every 4 weeks. All LLTs, including LDL apheresis, had been discontinued at least 4 weeks before initiation of treatment. Due to lomitapide's mechanism of action, patients were advised to follow a diet with fat content <10% of total caloric intake. After 4 weeks at

doses of 0.3 and 1 mg/kg/day, LDL-C levels were reduced by 25% and 51% and triglycerides by 34% and 65%, respectively. Lipoprotein kinetic studies performed in three subjects showed a 70% reduction in the rate of production of ApoB, confirming the mechanism of action of lomitapide, regardless of a lack of functional LDL receptors. No effect on high-density lipoprotein, ApoA, and lipoprotein were observed. Although all patients tolerated the highest dose, the most frequent adverse events were gastrointestinal symptoms, especially increased stool frequency, that were transient, dose-related, and explained mostly by low adherence to diet. No patient withdrew treatment due to an adverse event. Increased transaminases were observed in four patients, and one patient required downtitration of the dose, showing a reduction in transaminase levels. High variability in liver-fat accumulation was observed among patients, ranging from <10% to >30%. Transaminase and hepatic fat levels returned to baseline levels 4 weeks after discontinuation of the drug in all patients except one, in whom normalization occurred after 3 months.

## Pivotal Phase III trial (NCT00730236)

The long-term safety and efficacy of lomitapide in HoFH were demonstrated in a multicenter, 78-week, single-arm, open-label Phase III study on 29 molecularly confirmed adult patients (age 18–59 years, mean age 30.7 years).<sup>9</sup> The primary efficacy end point was percentage change from baseline in plasma LDL-C levels at the maximum-tolerated dose of lomitapide after 26 weeks of treatment. Secondary end points were changes in other lipid parameters, safety measures, and changes in hepatic fat content. A total of 28 patients had homozygotes or compound heterozygotes, and one patient had autosomal-recessive hypercholesterolemia. Patients were advised to follow a low-fat diet (<20% total calories) and other LLTs, including LDL apheresis, were maintained during the first 26 weeks (efficacy phase). In this phase, lomitapide was escalated from 5 mg/day to 60 mg/day or the maximum-tolerated dose every 4 weeks. After the efficacy phase, patients continued to receive lomitapide for another 52 weeks (safety phase), keeping constant the dose of lomitapide, but other lipid-lowering therapies could be modified according to physician criteria.

In sum, 23 patients completed both phases. Six patients discontinued the treatment in the efficacy phase, due to

**Table 1** Main Phase II and Phase III trials with lomitapide in homozygous familial hypercholesterolemia patients

|                           | Dose   | Duration  | Mean (mg/day)                                     | Number of participants (completers) | Mean baseline LDL-C (mg/dL)   | LDL-C reduction, % (SD)  | Gastrointestinal adverse events (n)   | Increase in transaminases (number of patients)                                       | Hepatic fat  |
|---------------------------|--|---|---|-------------------------------------|---|--|---|--|--|
| Phase II proof-of-concept | 0.03 mg/kg<br>0.3 mg/kg<br>0.1 mg/kg<br>1 mg/kg        | 4 weeks<br>4 weeks<br>4 weeks<br>4 weeks                      | All patients achieved max dose                    | 6 (6)                               | 614   | 3.7 (8.3)<br>7.1 (20.1)<br>24.7 (5.3)<br>50.9 (9.3)                    | Five of six, mild and transient   | 4  | 4/6 (<10% to >30%)   |
| Pivotal Phase III         | 5 mg/day, uptitrated every 4 weeks to MTD or 60 mg/day | Efficacy phase 26 weeks, then a safety phase for 52 weeks     | 40 mg   | 29 (23)                             | 337   | Efficacy phase: 40 ITT<br>50 completers<br>Safety phase: 38 completers | 27 of 29 in efficacy phase and 17 of 23 in safety phase; three patients discontinued medication in efficacy phase | Ten patients had ALT, AST, or both >3xULN; four with ALT >5xULN; one with AST >5xULN | Mean content increased from 1% to 8.6% at week 26 and 8.3% at week 78 (data available in 20 patients)      |
| Extension trial           | MTD from the pivotal trial                             | 126 weeks up to 286 weeks from baseline                       | 40 mg   | 19 (17) from pivotal trial          | 356   | 45.5 at week 126   |   | Four with ALT or AST >5xULN  | Mean content increased from 0.6% to 7.7% at week 126 and 10.2% at week 246 (data available in 17 patients) |
| Phase III, Japan          | 5 mg/day, uptitrated every 4 weeks to MTD or 60 mg/day | Efficacy phase 26 weeks, then a safety phase for 30 weeks     | 22 mg in efficacy phase and 18 mg in safety phase | 9 (8)                               | 199   | Efficacy phase: 42%<br>Safety phase: 38%                               | Eight of nine; no patient discontinued medication   | Three patients had ALT and AST >3xULN; one had ALT >5xULN and discontinued treatment | Mean content increased from 3.2% to 15.6% at week 126 and 12.7% at week 56                                 |
| Extension trial           | MTD from the previous trial                            | 119 weeks from baseline (60 weeks from end of previous trial) | 22 mg   | Five of eight from previous trial   | Baseline value calculated as derived from end of efficacy and safety phases | 35.6% from derived baseline to week 60                                 | Three of five; no discontinuation   | Four of five with increase in ALT or AST <3xULN                                      | Not measured   |

**Abbreviations:** MTD, maximum tolerated dose; LDL-C, low-density-lipoprotein cholesterol; ULN, upper limit of normal; ITT, intention to treat.

gastrointestinal symptoms (three), headache (one), withdrawal of consent (one), and bad treatment compliance (1). A total of 27 patients were receiving atorvastatin or rosuvastatin with or without ezetimibe, and 18 cases were on LDL apheresis. The primary efficacy outcome was a mean 40% reduction in LDL-C levels in the intention-to-treat analysis ( $n=29$ ) and 50% in those that completed the efficacy phase ( $n=23$ ) compared to baseline levels. This reduction was maintained at week 78 (38%,  $P=0.0001$ ). More than 50% of patients achieved a reduction in LDL-C levels  $\geq 50\%$  and LDL-C levels  $<100$  mg/dL at least once during the study. All ApoB-containing lipoproteins and triglycerides were significantly reduced. A post hoc analysis in those patients receiving LDL apheresis (18 of 29) showed no effect of the procedure in percentage reduction obtained with lomitapide compared with those patients not on apheresis.<sup>22</sup>

### Extension trial (NCT00943306)

All patients who completed the 78-week pivotal trial were invited to continue with lomitapide at the maximum-tolerated dose until transition to commercial or compassionate use of the drug.<sup>23</sup> Nineteen patients were enrolled in this trial, 17 completed 126 weeks, and 14 completed 246 weeks of follow-up. The median dose of lomitapide during the extension trial was similar to that in the pivotal trial (40 mg per day). Mean reduction in LDL-C levels was 45.5% at week 126, and stayed constant during all the extension trial. During the extension, 14 (74%) patients achieved LDL-C levels  $<100$  mg/dL. Gastrointestinal symptoms (diarrhea, nausea, vomiting) were the most common adverse events reported in the extension trial; however, they were less frequent than in the pivotal trial (42% and 84.2%, respectively).

### Phase III trial in Japan

Harada-Shiba et al conducted a trial in Japan in nine adults aged 33–75 years with molecularly defined HoFH, with a similar design to the multicenter Phase III trial.<sup>21</sup> First, a pretreatment phase to stabilize diet ( $<20\%$  fat and supplementation with vitamins and  $\omega_3$ ) and LLT, including apheresis, then a 26-week efficacy phase with dose escalation of lomitapide, and finally a safety phase for an additional 30 weeks, where other LLTs could be modified. Patients started with lomitapide 5 mg/day and escalated until the maximum-tolerated dose or up to 60 mg/day. All patients except two were receiving atorvastatin or rosuvastatin with or without ezetimibe or resins, and six were on LDL apheresis. Mean LDL-C at baseline was 199 mg/dL (121–331 mg/dL). Eight patients completed the efficacy

phase and continued to the safety phase. One patient discontinued treatment due to persistent elevation of AST and ALT. Mean lomitapide dose was 22 mg per day at the end of the efficacy phase and 18 mg per day in the safety phase. A significant 42% mean reduction in LDL-C levels was observed at week 26, five patients reached a reduction in LDL-C  $\geq 50\%$ , and six patients achieved LDL-C  $<100$  mg/dL at least once during the efficacy phase. Significant reductions in LDL-C levels were observed in all patients with or without apheresis (10%–65%).

Results were consistent with those obtained in the pivotal Phase III trial, although there were differences in age of patients, molecular characteristics, baseline LDL-C levels, and median lomitapide dose among both studies. Mean reduction from baseline remained significant at week 56 (37.5%). As in the pivotal trial, some patients treated with LDL apheresis were able to increase the interval between procedures. Gastrointestinal symptoms were the most common adverse events, reported by eight patients, and were well managed with reduction or temporary interruption of the dose. Another two patients had increased ALT levels that improved with lomitapide dose reduction. As expected, there was an increase in hepatic fat content from 3.2% at baseline to 15.6% at the end of the efficacy phase, with stabilization at 12.7% at the end of the safety phase. At 4 weeks after discontinuation of lomitapide, fat content in all patients had returned to baseline values.

### Extension trial (AEGR-733-301)

Five of eight patients that finished the 56-week Phase III trial continued taking the maximum-tolerated dose of lomitapide until the drug was approved, commercially available in Japan, or until the medication was discontinued.<sup>24</sup> Mean lomitapide exposure was 442 days. All patients continued with their concomitant LLT during this period, and were advised to adhere to a low-fat diet with daily intake of vitamins and fatty-acid supplements. The primary efficacy end point in this trial was change in LDL-C during the extension period from a derived baseline LDL-C. This baseline value was calculated from average LDL-C level at 26 weeks (end of the efficacy period of the former Phase III trial) and the value at extension-study start (end of the 56-week Phase III study). A mean 35.6% LDL-C reduction from baseline value was observed at week 60 of follow-up. Variability in LDL-C reduction was not correlated with the dose of lomitapide. Four patients had an LDL-C reduction  $>25\%$

and two patients achieved LDL-C <100 mg/dL during the study. Triglyceride levels were significantly reduced by 55%. Safety and tolerability of lomitapide treatment were acceptable and in accordance with the previous trial.

## Real-world clinical experience LOWER registry (NCT02135705)

The FDA, EMA, and other regulatory agencies required the establishment of a lomitapide-treated patient registry. Aegerion Pharmaceuticals initiated in 2014 the prospective, noninterventional, multicenter, observational cohort LOWER study.<sup>25</sup> The main objectives were to evaluate the long-term efficacy and safety of lomitapide in HoFH adult patients in clinical practice and to evaluate the occurrence of events of special interest, such as hepatic abnormalities, gastrointestinal events, cancer, events associated with coagulation, major adverse cardiovascular events (MACEs), all-cause mortality, and pregnancy. A substudy of LOWER will be the CAPTURE study, which will investigate the effects of lomitapide on the regression and/or stabilization of atheroma in the carotid artery and aorta.

The first report was presented at ACC 2018 (data not published), and included 163 patients enrolled between March 2014 and March 2017.<sup>26</sup> Of these, 121 continued in the study and 59 continued with the medication. Lomitapide dose ranged from 5 mg every other day to 40 mg per day. Mean LDL-C change at month 36 was 40.5% in the full-set analysis (n=147 of 163 patients) and 47.2% considering only the 59 patients that continued on lomitapide, and 68% of patients reached LDL-C <100 mg/dL and 42% LDL-C <70 mg/dL at least once after initiating treatment. Safety data (adverse events and ESI) from the 3 years of LOWER were consistent with those reported in the phase III trial, and no new safety signals were identified. The 3-years analysis of the LOWER registry confirmed the sustained risk–benefit profile described in the pivotal Phase III trial.

## Italy real-world clinical experience

Clinical experience with lomitapide in Italy was evaluated retrospectively in 15 adults with HoFH (mean age 38 years, ten with mutations in *LDLR* and five autosomal recessive hypercholesterolemia) treated with the drug for ≥6 months together with maximal-tolerated LLTs, including LDL apheresis in ten subjects.<sup>27</sup> Mean lomitapide dose was 19 mg per day, and 80% were taking 10 mg per day or more. Mean LDL-C reduction in the last visit was 68% compared to baseline values, and 60% of patients reached

LDL-C <100 mg/dL and 47% LDL-C <70 mg/dL. Other lipid parameters like triglycerides and non-HDL-C were also significantly reduced. During the mean 3-year follow-up, eight of ten patients discontinued LDL apheresis. No significant differences were observed in percentage reduction of LDL-C or genotype. Regarding safety, none of the patients discontinued medication due to adverse events and none developed persistent elevation of transaminases >5× upper limit of normal (ULN). All gastrointestinal symptoms were considered mild by physicians.

## Clinical case reports

Few cases of HoFH patients treated with lomitapide have been published in the last few years. Alonso et al reported the first case in Spain treated with lomitapide. A 42-year-old woman molecularly defined as heterozygous compound hypercholesterolemia, with severe hypercholesterolemia and aortic valve replacement at age 29 years.<sup>28</sup> LDL-C was 277 mg/dL under treatment with rosuvastatin 40 mg, ezetimibe 10 mg, and colesvelam 2.5 g per day. Lomitapide was uptitrated from 5 mg to 20 mg per day in 6 months, and a 54% additional reduction in LDL-C, 66% in triglycerides, and 31% in lipoprotein(a) were observed in this period. Gastrointestinal symptoms were mild, occurred in the first few days after initiation of the drug, and were related to fat intake. Also, an increase in AST and ALT <2×ULN was observed with the dose of 20 mg that did not require lomitapide dose modification.

Raper et al reported the case of a 49-year-old HoFH female with premature ASCVD treated with lomitapide over maximum-tolerated LLT and LDL apheresis for 5 years.<sup>29</sup> The patient was part of the Phase II trial; therefore, she stopped all LLTs before initiation with lomitapide. Baseline LDL-C was 637 mg/dL, and at the end of the higher-dose phase (1 mg/kg/day) her LDL-C was 301 mg/dL. Then she entered the pivotal Phase III trial, and high-dose rosuvastatin plus ezetimibe, colesvelam, and monthly LDL apheresis were stabilized before restarting lomitapide. She remained at the highest dose (60 mg per day) and enrolled in the extension study until lomitapide was approved by the FDA. She stayed on drug therapy >5 years. At the end of Phase III, she had achieved LDL-C of 28 mg/dL (93% reduction from baseline), and LDL apheresis was discontinued. In the extension trial, with lomitapide 60 mg, the patient had LDL-C levels <10 mg/dL. Lomitapide was then downtitrated to 40 mg/dL, and after a rebound in LDL-C levels, lomitapide dose was uptitrated again to 60 mg, achieving LDL-C levels around 50 mg/dL

(−87% from baseline). Transient increase in transaminases was observed during the follow-up, probably related to other transitory medication. Hepatic fat content remained stable at <7% and related to lower LDL-C levels.

Kolovou et al<sup>30</sup> evaluated the lipid-lowering efficacy of lomitapide according to variants in the *MTP* gene in four HoFH patients (two with molecular confirmation) treated with high-intensity statins and LDL apheresis. Lomitapide was added, starting at 5 mg and going up to 40 mg per day. Two patients had LDL-C reductions >50% and were considered hyperresponders (both treated with lomitapide 10 mg), and the other two patients (treated with 30 and 40 mg per day) had reductions <50% and considered hyporesponders. Six *MTP* variants were found, and shared only by the two hyperresponders and not the hyporesponders. These results suggest that some variants in *MTP*, the target of lomitapide, may explain the variability in response to medication in HoFH patients.

van Lennep et al reported four molecularly defined HoFH cases (two from the Netherlands, one from Italy, and the previously described one from Spain) treated with lomitapide according to prescription protocol.<sup>31</sup> One patient from the Netherlands stopped lomitapide due to an increase in AST and ALT levels >5×ULN, and normal levels were achieved 4 weeks after discontinuation. Observed LDL-C reductions were 35%–83%. The patient from Italy was also treated with LDL-apheresis, and although a reduction of 73% in LDL-C was obtained with the inclusion of lomitapide, he decided to continue the procedure with larger intervals between apheresis. Gastrointestinal symptoms were observed in three patients during lomitapide treatment. One patient required reduction in lomitapide dose and adjustment in diet to manage these symptoms, and in the others changes in the dose were not necessary.

Real et al reported two HoFH brothers (47 and 46 years old) with very premature ASCVD treated with lomitapide over maximum combined LLT and LDL apheresis.<sup>32</sup> In the first patient, LDL-C remained close to 130 mg/dL in the interapheresis period. Lomitapide was used at 5 and 10 mg per day, obtaining LDL-C of 25–70 mg/dL. No increase in transaminases or alteration in FibroScan results was observed. The second brother had an LDL-C of 152 mg/dL in the interapheresis period. He was treated with lomitapide up to 40 mg per day; however, due to headache, this was reduced to 20 mg. At this dose, LDL-C of 86 mg/dL was obtained in the interapheresis period. No elevation in transaminases was

observed, and FibroScan results were normal. Recently, Thompson et al reported four cases from a cohort of 133 patients with HoFH treated with lomitapide >1 year in addition to other LLTs, and had an average 46% reduction in cholesterol levels.<sup>33</sup>

Although lomitapide has not been approved for children with HoFH, the first case of compassionate use of the drug in a 7-year-old child for 4 years was recently published. Indications in low-fat diet, vitamin, and  $\omega_3$  supplementation and precautions in the up-titration of lomitapide were similar to those used in adults. On top of atorvastatin (up to 60 mg a day) and ezetimibe, lomitapide 20 mg achieved a 37% reduction in LDL-C. No increase in transaminases or liver steatosis were observed in the long term.<sup>34</sup>

## Lomitapide and cardiovascular outcomes

Due to the rarity and small number of homozygous patients and also ethical considerations, it is not feasible to perform a study to evaluate the effect of lomitapide on major cardiovascular outcomes. A modeling analysis of the potential effect of lomitapide on top of LLTs, including statins and ezetimibe with or without LDL apheresis, on MACEs and survival on HoFH patients has been published recently.<sup>35</sup> Considering a 38% reduction in LDL-C levels produced by lomitapide, a relative risk reduction of 23% in mortality and 15% in MACEs per mmol/L ( $\approx$ 40 mg/dL), LDL-C reduction was estimated. Moreover, an increase in median life expectancy of 11.2 years and a delay in time to first MACE by 5.7 years was predicted in patients if treatment started at 18 years of age.

A post hoc analysis from the efficacy phase of the pivotal Phase III trial and its extension was conducted to evaluate the number of patients that reach European Atherosclerosis Society goals, and compare ASCVD rates in patients receiving lomitapide with other HoFH cohorts receiving other medications (mipomersen or evolocumab).<sup>36–38</sup> Fifteen patients (51%) and eight patients (28%) had achieved LDL-C <100 mg/dL and 70 mg/dL at least once by week 26. Cases reaching LDL-C goals increased to 70% (16 of 23) <100 mg/dL and 30% (nine of 23) <70 mg/dL in patients who remained in the safety phase (week 78), and 53% (12 of 19) <100 mg/dL and 42% (eight of 19) <70 mg/dL in those who remained in the extension trial (week 126). Two MACEs were reported in the extension study, representing 1.7 events per 1,000 patient-months of lomitapide treatment (2%

annualized event rate).<sup>36</sup> The MACE rate in the mipomersen-treated cohort decreased from 21.7 to 9.5 events per 1,000 patient-months after initiation of the medication,<sup>37</sup> and the MACE rate in evolocumab-treated HoFH was 1.8 per 1,000 patient-months.<sup>38</sup> Considering differences in the demographic characteristics and design of the three cohorts, the results suggest that new lipid-lowering medication may reduce MACEs in HoFH patients by lowering LDL-C levels.

## Other potential clinical uses of lomitapide

As stated, the indication approved by the regulatory agencies for lomitapide is the treatment of patients with HoFH. However, due to its mechanism of action, VLDL and chylomicron levels are also significantly reduced; therefore, there is a potential role for treatment of severe hypertriglyceridemia, specially hyperchylomicronemia.<sup>39</sup> In December 2010 and March 2011, lomitapide received the status of orphan drug for hyperlipoproteinemia type I (familial chylomicronemia) in Europe and the US, respectively. In all the aforementioned HoFH trials and clinical reports, triglyceride reduction was a secondary end point, and a significant reduction of 25%–65% was observed.<sup>1,2</sup>

There has been only one case reported in the literature using lomitapide to treat a female patient with very severe hypertriglyceridemia (>2,000 mg/dL) due to familial chylomicronemia (confirmed homozygosity for a missense mutation in the *LPL* gene) and recurrent severe pancreatitis.<sup>40</sup> Until publication, she had been treated with lomitapide for 13 years. On lomitapide 20–40 mg per day, triglyceride levels were <1,000 mg/dL. During follow-up, the patient presented with three uncomplicated pancreatitis associated with temporary discontinuation of the drug or high fat intake. During the first 6 years of treatment, transaminases were in the normal range, and ultrasound showed fatty liver. After 5 years of treatment with lomitapide, liver biopsy showed marked macrovesicular steatosis without inflammation or fibrosis. Unfortunately, a progression to fibrosis was observed in the last liver biopsy, performed 13 years after initiation of lomitapide. It is not clear if the chronic use of lomitapide was the only cause of the progression to liver fibrosis, because no liver biopsy was performed before the initiation of treatment. Her liver had been exposed to much higher triglyceride

levels throughout life than occurs in HoFH patients, and it is known that in lipoprotein lipase deficiency, large triglycerides rich in lipoproteins are taken up by the reticuloendothelial system in the liver and bone marrow. Therefore, it is possible that an interaction between the genetic disorder and the medication through different mechanisms could explain the progression to fibrosis.

Regarding lipoprotein(a), results were contradictory. In the pivotal Phase III trial, a significant 15% reduction was observed at the end of the efficacy phase; however, there were no differences compared to baseline values at the end of the safety phase.<sup>9</sup> In the Japanese Phase III trial, there were no differences in lipoprotein(a) levels at the end of the efficacy phase, but this was significant (–40%) at the end of the safety phase and near significant in the extension study.<sup>21</sup>

## Practical aspects in the clinical use of lomitapide

As stated, lomitapide has been approved for use only in HoFH patients ≥18 years old. Patients must comply with a low fat-diet to reduce gastrointestinal adverse events, the principal cause of discontinuation of the drug. Patients must continue with maximum-tolerated conventional lipid-lowering therapies, including intense-dose statins and ezetimibe with or without LDL apheresis. It is necessary to evaluate liver-function tests and liver imaging before initiation of lomitapide and then continue with liver-function analysis every time the dose of lomitapide is changed until the maximum-tolerated dose is achieved. HoFH patients usually require other cardiovascular medications, and precaution with some of them is important, due to interactions. Strong and moderate inhibitors of CYP3A4, including grapefruit juice, are contraindicated. Downtitration or temporary discontinuation of lomitapide are possible in cases of gastrointestinal adverse events or increased transaminase levels. In those adult patients on LDL apheresis, it is probable that one in three cases will reduce the frequency of the procedure or even stop it, according the results from the pivotal Phase III trial. It has been shown that apheresis does not affect the efficacy of the drug. In children with HoFH in whom lomitapide has not been approved, LDL apheresis, if available, is an important adjunctive treatment improving the prognosis of these cases. Long-term follow-up of HoFH patients receiving lomitapide is important to demonstrate efficacy,

**Table 2** Prescribing summary of lomitapide

|                           |   |
|---------------------------|---|
| Indications and cautions  | <ul style="list-style-type: none"> <li>• Adults (<math>\geq 18</math> years old) with homozygous familial hypercholesterolemia, if possible with molecular confirmation</li> <li>• Not indicated in heterozygous familial hypercholesterolemia patients or other hypercholesterolemic patients</li> <li>• Not indicated in children/adolescents <math>&lt; 18</math> years old (lack of evidence)</li> <li>• Use with caution in patients <math>&gt; 65</math> years old (limited evidence)</li> <li>• For patients with end-stage renal disease with dialysis, do not exceed 40 mg per day; not studied in end-stage renal disease not on dialysis</li> <li>• For patients with mild hepatic impairment, do not exceed 40 mg per day; contraindicated in more severe hepatic damage</li> </ul> |
| Dosage                    | <ul style="list-style-type: none"> <li>• Start with 5 mg once day and uptitrate gradually depending on safety and tolerability at least every 4 weeks.</li> <li>• Up to maximum tolerated dose or a maximum of 60 mg per day</li> <li>• Dose may be modified according to liver-function tests, tolerability, renal function, and concomitant medication</li> </ul>   |
| When?                     | <ul style="list-style-type: none"> <li>• At least 2 hours after evening meal (empty stomach)</li> </ul>   |
| Dietary advice            | <ul style="list-style-type: none"> <li>• Low-fat diet, <math>&lt; 20\%</math> of daily total energy from fat</li> <li>• Restriction of alcohol consumption (no more than 1 unit per day)</li> </ul>   |
| Supplementation           | <ul style="list-style-type: none"> <li>• Vitamin E (400 IU) + linoleic acid (200 mg), ALA (210 mg) + EPA (110 mg) + DHA (80 mg)</li> </ul>  |
| Monitoring liver function | <ul style="list-style-type: none"> <li>• Before initiation of treatment</li> <li>• Prior to each increase of dose</li> <li>• Refer to hepatologist if liver-function testing persists <math>&gt; 3 \times \text{ULN}</math>, or data suggest liver steatohepatitis or fibrosis</li> </ul>   |
| Hepatic imaging           | <ul style="list-style-type: none"> <li>• Screen for liver steatosis, steatohepatitis, and fibrosis at the beginning</li> </ul>  |
| Concomitant medication    | <ul style="list-style-type: none"> <li>• Moderate and strong CYP3A4 medications and grapefruit juice are contraindicated with lomitapide</li> <li>• For patients taking a mild CYP3A4 inhibitor before use of lomitapide, uptitrate the dose according to safety and tolerance</li> <li>• If patient requires a mild CYP3A4 inhibitor while taking lomitapide, downtitrate the dose and then uptitrate according to LDL-C reduction, safety and tolerance</li> </ul>  |

**Abbreviations:** ALA,  $\alpha$ -linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; ULN, upper limit of normal; LDL-C, low-density-lipoprotein cholesterol.

prevention of ASCVD, and that patients do not develop hepatic fibrosis or cirrhosis (Table 2).

## Disclosure

PM is the president of the Spanish Familial Hypercholesterolemia Foundation. RA is part of the scientific committee of the Spanish Familial Hypercholesterolemia Foundation, has received honorary fees as speaker and participated in advisory boards from Aegerion, Amgen, AstraZeneca, Abbott, Boehringer-Ingelheim, MSD, and Sanofi, and reports nonfinancial support from Tecnofarma and the European Atherosclerosis Society. AC has received honorary fees as speaker and participated in advisory boards from Abbott, Novo Nordisk, MSD, and Saval. The authors report no other conflicts of interest in this work.

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