Use of Microsomal Triglyceride Transfer Protein Inhibitors in Patients With Homozygous Familial Hypercholesterolemia: Translating Clinical Trial Experience Into Clinical Practice

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Homozygous familial hypercholesterolemia (HoFH) is associated with severe hypercholesterolemia and premature cardiovascular morbidity and mortality. The most frequent cause of HoFH is loss of function mutations in the gene for the low-density lipoprotein receptor, resulting in reduced clearance of low-density lipoprotein (LDL) cholesterol from the circulation. Patients with HoFH have attenuated responsiveness to lipid-lowering therapies such as statins, cholesterol absorption inhibition, and bile acid binding resins because of impaired LDL receptor expression. Lomitapide is a novel microsomal triglyceride transfer protein inhibitor that does not depend on the ability to upregulate LDL receptors on the surface of hepatocytes. Lomitapide reduces production of apolipoprotein B-containing lipoproteins, significantly reduces serum levels of LDL cholesterol, and is approved for use in patients with HoFH in the United States and the European Union.

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KEY WORDS

Atherosclerosis • Homozygous familial hypercholesterolemia • Lomitapide • Low-density lipoprotein cholesterol • Microsomal triglyceride transfer protein • Very low-density lipoprotein cholesterol

Homozygous familial hypercholesterolemia (HoFH) is a congenital disorder associated with severe hypercholesterolemia (untreated total cholesterol usually > 500 mg/dL), cutaneous and tendinous xanthomas, and premature coronary artery disease, often resulting in death in the second or third decade of life in the absence of treatment.[1] Most cases are caused by a large number of loss-of-function mutations in both alleles of the low-density lipoprotein (LDL) receptor gene, although in some cases a similar phenotype may result from mutations in other genes, such as proprotein convertase subtilisin/kexin type 9 (*PCSK9*), apolipoprotein B (*APOB*), or LDL receptor adaptor protein-1 (*LDLRAP1*, genetic defect in the condition autosomal recessive hypercholesterolemia).[1] Patients with HoFH have reduced responsiveness to standard lipid-lowering medications, including statins, that depend (to a significant degree) on the upregulation of functional hepatic LDL receptors for their lipid-lowering effect. The most effective treatment of HoFH is weekly or biweekly LDL apheresis to mechanically filter out LDL cholesterol; this treatment slows the progression of atherosclerotic disease.[1] Liver transplantation is another option, but this approach has serious logistic limitations and complications associated with the need for immunosuppressive therapy and is generally a treatment of last resort. In the past year, two novel pharmacologic approaches have been approved by the US Food and Drug Administration (FDA) to reduce hypercholesterolemia in patients with HoFH. One approach is the development of antisense technology to inhibit ApoB synthesis; the other targets microsomal triglyceride transfer protein (MTP) to inhibit synthesis of very low-density lipoprotein (VLDL) particles, the precursors for LDL biosynthesis in plasma.[2,3]

In the past year, two novel pharmacologic approaches have been approved by the US Food and Drug Administration to reduce hypercholesterolemia in patients with HoFH. One approach is the development of antisense technology to inhibit ApoB synthesis; the other targets microsomal triglyceride transfer protein to inhibit synthesis of very low-density lipoprotein particles, the precursors for LDL biosynthesis in plasma.

Microsomal Triglyceride Transfer Protein

MTP catalyzes the transfer of cholesterol esters, triglycerides, and phospholipids between membranes and from membranes to apolipoprotein B (ApoB).[4–6] It localizes to the luminal aspect of the endoplasmic reticulum (ER), where it lipidates ApoB48 in jejunal enterocytes and ApoB100 in hepatocytes, leading to the formation and secretion of chylomicrons and VLDLs, respectively.[7] MTP forms a functional heterodimer with protein disulfide isomerase (PDI).[8] PDI does not play a catalytic role in lipoprotein biogenesis[9]; instead, it functions as a chaperone for MTP in the ER. Association of MTP with the PDI moiety is achieved by noncovalent interactions and is necessary for its solubility, lipid transfer activity, and retention in the ER.[4,10] Loss-of-function genetic polymorphisms in MTP are etiologic for abetalipoproteinemia (Bassen-Kornzweig syndrome),[11–13] an autosomal recessive disorder characterized by an absence of circulating ApoB-containing lipoproteins, steatorrhea, enteric and hepatic steatosis, impaired absorption of fat-soluble vitamins (A, D, E, K), erythrocyte acanthocytosis, neuropathy, ataxia, and retinitis pigmentosa.

The biogenesis of ApoB-containing lipoproteins is a highly regulated process. Within the ER, MTP catalyzes the bulk transfer of triglyceride into the ER lumen and is also responsible for lipidating ApoB.[14] As ApoB messenger RNA is translated into protein, MTP binds to the nascent ApoB and transfers cholesterol esters, phospholipids, and triglycerides to it.[5,15] Lipidation allows for appropriate three-dimensional folding of ApoB, renders it competent for secretion,[16] and induces the progressive core expansion and formation of lipoproteins.[17] If lipidation is impaired, ApoB is targeted for proteosomal degradation with no net accumulation within the cell and no induction of ER stress (a state that can induce cellular apoptosis) within hepatocytes.[18]

Therapeutic Inhibition of MTP

VLDLs are the biochemical precursors to such atherogenic lipoproteins as intermediate-density lipoproteins and LDL. Given that abetalipoproteinemia is associated with the absence of ApoB lipoproteins in serum, it is reasonable to assume that MTP might be an appropriate therapeutic target for lowering levels of atherogenic lipoproteins by using systemically available molecules to inhibit its activity (Figure 1).

A number of MTP inhibitors have been tested in cultured hepatocytes and animal models to ascertain their efficacy for impacting serum levels of ApoB-containing lipoproteins. BMS200150 potently inhibits secretion of ApoB from Hep G2 cells (a human hepatocyte cell line used to study lipoprotein production and secretion) in culture.[19] When administered orally to rodents, CP-346086

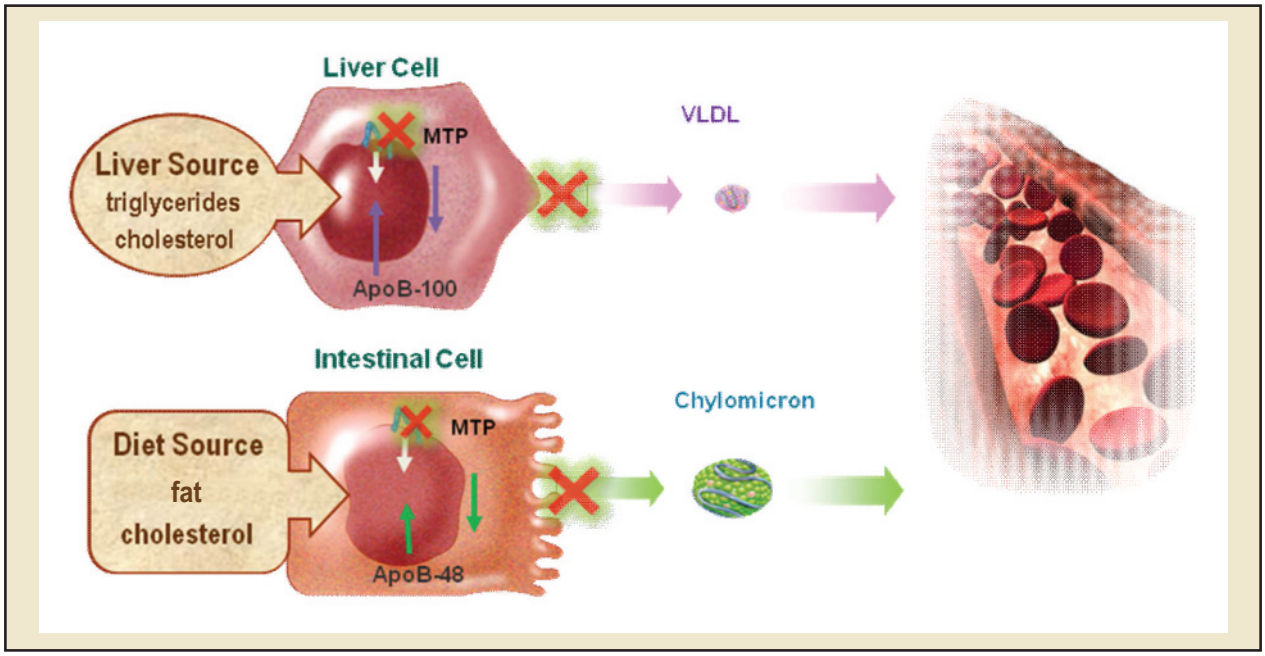


Figure 1. Lomitapide mechanism of action. Microsomal transfer protein (MTP) facilitates the assembly of very low-density lipoprotein (VLDL) and chylomicrons by combining triglycerides with apolipoprotein B (ApoB). The MTP inhibitor lomitapide blocks the production of VLDL (the precursor of LDL) in the liver and reduces the formation of chylomicrons in the intestinal cells. Consequently, lomitapide reduces the secretion of VLDL, which lowers LDL without requiring the upregulation of hepatic LDL receptors that is necessary for the LDL cholesterol reduction associated with statins, ezetimibe, or bile acid-binding drugs. The mechanism of action of lomitapide also results in a modest increase in hepatic fat and a decrease in fat absorption, which results in the side effects associated with this class of drugs. Reproduced with permission from Aegerion Pharmaceuticals, Inc. © 2013.

inhibits MTP and intestinal and hepatic triglyceride secretion; LDL cholesterol, VLDL cholesterol, and total cholesterol were also significantly reduced in serum. However, both intestinal and hepatic fat content were increased if the CP-346086 was administered with meals. If dosed apart from meals, only hepatic fat content increased. After 2 weeks of treatment, total cholesterol, triglycerides, and LDL cholesterol were reduced by 47%, 75%, and 72%, respectively.[16] In Watanabe-heritable hyperlipidemic rabbits[20] (a model for human homozygous familial hypercholesterolemia), lomitapide (BMS201038) significantly reduced ApoB and the formation of atherogenic plaque relative to control animals. The same effect was seen with implitapide in ApoE knockout mice.[21] The latter studies established proof of concept that in animal models characterized by dyslipidemia and marked elevation in risk for atherosclerotic disease, MTP inhibition reduced atherogenesis and plaque burden. However, clinical development for broad use of almost all of the compounds designed to inhibit MTP was discontinued because of increased risk for hepatic steatosis and adverse gastrointestinal side effects.

As described, HoFH is a rare autosomal codominant disorder most often caused by mutations in both alleles of the *LDLR* gene. This results in the inability to express functional LDL receptors and, in turn, to reduced hepatic uptake and clearance of LDL cholesterol.[22,23] HoFH can arise from homozygous loss of function or compound heterozygous loss of function polymorphisms (approximately 1600 of which are known) in the *LDLR* gene. The incidence of HoFH is thought to be approximately one per million in the United States; however, given the array of mutations that can affect the function of the LDL receptor, this incidence likely underestimates the true prevalence of HoFH. Patients with HoFH have lifelong severe elevations in LDL cholesterol because of an inability to clear this lipoprotein from serum; untreated LDL cholesterol levels are wide ranging, but generally vary from 300 to 1000 mg/dL. Patients with HoFH have a severely heightened risk for developing premature coronary artery disease and its sequelae, including myocardial infarction and death, often in the second or third decade of life, although acute coronary syndromes can occur as early as the first decade of life depending on the severity of dyslipidemia. Apheresis is an effective treatment for HoFH, but is time consuming and must be performed at 2-week intervals. Lipid-lowering drugs such as statins, ezetimibe, and bile acid–binding resins induce LDL cholesterol reduction in part by increasing the surface expression of LDL receptors on hepatocytes. Because patients with HoFH do not express functional LDL receptors, their responsiveness to these classes of drugs is significantly attenuated and it is extremely challenging to induce significant LDL cholesterol reductions.[24]

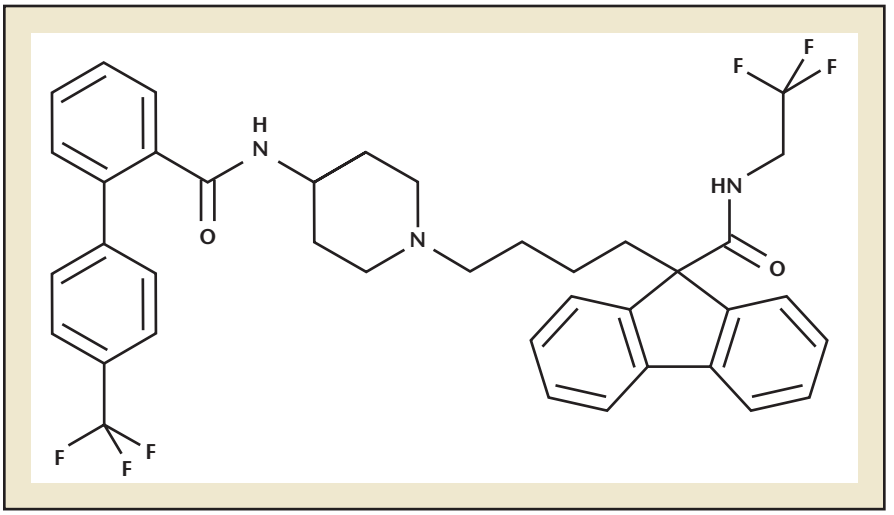


Figure 2. Chemical structure of lomitapide.

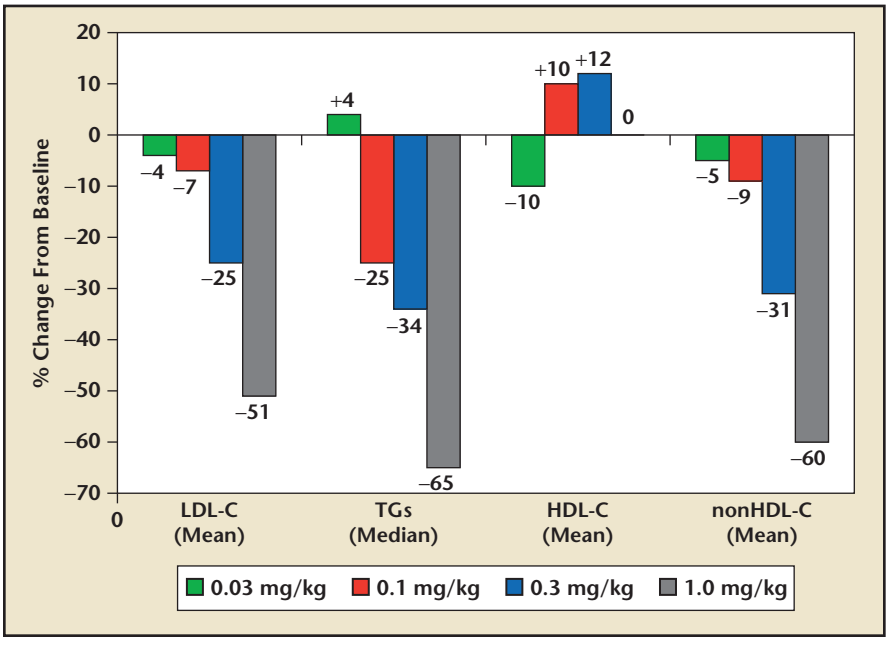
Lomitapide

Inhibition of MTP provides a novel strategy for reducing serum levels of ApoB lipoproteins in patients with HoFH. The efficacy of an MTP inhibitor does not depend on capacity for stimulating an upregulation in the expression of hepatocyte LDL receptors. Lomitapide (Juxtapid® [US]/Lojuxta® [EU]; AEGR-733, formerly BMS-201038; Aegerion Pharmaceuticals, Cambridge, MA) is currently the only MTP inhibitor approved by the FDA and European Commission for use as a lipid-lowering agent in patients with HoFH. The chemical structure of lomitapide is shown in Figure 2. It is an orally administered systemic agent with an absolute bioavailability of 7% and a terminal half-life of 39.7 hours. Lomitapide does not induce cytochrome P450 (CYP) 1A2, CYP3A4, or CYP2B6, and depends on CYP3A4 for metabolism. Its use is contraindicated in combination with moderate and strong inhibitors of CYP3A4. According to the US prescribing information, the dose of lomitapide should not exceed 30 mg when used in combination with weak/mild CYP3A4 inhibitors, such as amiodarone, fluoxetine, or ticagrelor.[25]

The early clinical development of lomitapide focused on developing the drug as a monotherapy for broad use to treat patients with hypercholesterolemia. The fixed-dose regimens, at doses ranging from 25 mg/d to 100 mg/d were associated with dose-limiting adverse events, primarily gastrointestinal events and aminotransferase elevations that led to a high rate of treatment discontinuations. The development of lomitapide in the general hypercholesterolemia patient population was halted and subsequent development focused specifically on HoFH patients.

A small, proof-of-concept, open-label study of lomitapide was completed in six subjects with HoFH who were treated for 4 months (Figure 3).[3] This study demonstrated that lomitapide monotherapy was effective in reducing LDL cholesterol levels. The mean LDL cholesterol level was 614 mg/dL at baseline. After 4 weeks at the 1.0-mg/kg dose, the mean level was reduced to 303 mg/dL, a 50.9% reduction from the baseline level ($P < .001$). Gastrointestinal adverse events were the most commonly reported. Adverse events were mild to moderate in intensity and included increased stool frequency, nausea, vomiting, heartburn, stomach pain and distress, and transaminase elevation. Variable elevations in transaminases were observed and appeared to be dose dependent. There were no increases in bilirubin or alkaline phosphatase.

Figure 3. Lomitapide effectively reduced low-density lipoprotein cholesterol (LDL-C) and triglycerides (TGs) in patients with homozygous familial hypercholesterolemia (HoFH) in a phase 2 proof-of-concept (POC) study. The figure shows the mean percentage change from baseline in LDL-C, TGs (median), high-density lipoprotein cholesterol (HDL-C), and nonHDL-C at the end of each 4-week dose period. Adapted from Cuchel M et al.[3]



In addition to liver enzyme elevations, increases in hepatic fat as measured by magnetic resonance imaging (MRI) were also observed and were highly variable from patient to patient. These increases also appeared to be dose dependent and returned to baseline within the 4-week washout period, except in a single patient who returned to baseline after 14 weeks after being removed from therapy. No patients withdrew from the study for any reason due to an adverse event. This was the first lomitapide trial to:

- Use a stepwise dose escalation with weight-based dosing. Lomitapide (monotherapy) treatment commenced at a low dose (0.03 mg/kg) and patients were escalated to higher doses every 4 weeks (0.1 mg/kg, 0.3 mg/kg, and 1.0 mg/kg, respectively);
- Include a requirement that patients follow a rigorous low-fat diet (both the dose-escalation regimen and the low-fat diet were implemented in an attempt to improve gastrointestinal tolerability);
- Suspend all lipid-lowering treatments, including drugs and apheresis, within 4 weeks prior to the start of study drug treatment—patients remained off these therapies until after the 4-week posttreatment follow-up assessment;
- Demonstrate a substantially improved tolerability profile when lomitapide was administered at a low starting dose with subsequent stepwise dose escalation and subjects consumed, on average, 16.7% energy from fat (range, < 10% to ~ 30%).

Following the small, phase 2 proof-of-concept study, lomitapide was subsequently tested in a single-arm open-label, phase 3 protocol in a larger cohort of HoFH patients. Based on the results of this study, the FDA approved lomitapide for HoFH patients in December 2012; it was approved by the European Commission in July 2013.[26]

Phase 3 Study Design

In this study, 29 patients with phenotypic and/or genotypic features of HoFH from 11 centers located in the United States, Canada, South Africa, and Italy were followed for 78 weeks. Prior to entry into the trial, patients were screened for eligibility and entered into a 6-week run-in phase during which standard lipid-lowering therapy was stabilized (including LDL apheresis), and a low-fat diet along with daily dietary supplementation of vitamin E and essential fatty acids was initiated. Following the run-in phase, patients entered the efficacy phase in which each initiated lomitapide therapy in addition to stable background lipid-lowering therapy for 26 weeks. Dosing of lomitapide was escalated at fixed doses. Treatment with lomitapide was started at the low 5-mg/d dose and, at predefined intervals, the dose was increased incrementally from 10 mg/d, to 20 mg/d, to 40 mg/d, to a maximum of 60 mg/d based on tolerability and safety. After completion of the 26-week efficacy phase, patients continued lomitapide therapy for an additional 52 weeks. Background lipid-lowering therapies remained unchanged during the efficacy phase and could be altered during the 52-week safety phase. A separate, long-term treatment phase was offered to those eligible patients who completed the 78 weeks of trial therapy. Patients had clinical and laboratory assessments at baseline and during treatment. Hepatic lipid content was assessed by nuclear magnetic resonance spectroscopy except in those patients with a contraindication to MRI; in those patients computed tomography or ultrasound was available.[26]

Phase 3 Results

A total of 32 patients with HoFH were screened for participation; 31 entered the run-in phase, 29 entered the (26-week) efficacy phase, and 23 completed the full 78-week study. Six patients withdrew during the efficacy phase, four due to gastrointestinal side effects. Lomitapide produced significant and sustained reductions in total cholesterol, LDL cholesterol, VLDL cholesterol, non-HDL cholesterol, triglycerides, and ApoB (Table 1, Figure 4). Small but significant reductions in lipoprotein(a), HDL, and ApoA-1 observed at 26 weeks were not sustained at 78 weeks. Because of large reductions in LDL cholesterol, three patients were able to discontinue LDL apheresis and three additional patients were able to reduce the frequency of apheresis.[26]

Tolerability and Side Effects

Compliance with study drug (> 80% of capsules taken) was 93% during the 26-week efficacy phase and 95% during the safety phase. There were no deaths in the study. Adverse events attributable to the drug were mostly gastrointestinal intolerance. Hepatic fat increased from baseline (Table 2): 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. The long-term implications of this finding remain uncertain. Hepatic transaminase elevation of three

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TABLE 1

Effect of Lomitapide on Lipid Variables in a Phase 3 Trial

	Baseline (n = 29)	Change at wk 26 (%) (n = 23)	*P* Value	Change at wk 56 (%) (n = 23)	*P* Value	Change at wk 78 (%) (n = 23)	*P* Value
Total cholesterol (mg/dL)	429	−46	< .0001	−39	< .0001	−35	< .0001
LDL cholesterol (mg/dL)	336	−50	< .0001	−44	< .0001	−38	.0001
HDL cholesterol (mg/dL)	42	−12	.0001	1	.9	−5	.13
VLDL cholesterol (mg/dL)	19	−45	< .0001	−28	.01	−31	.03
TG (mg/dL)	88	−45	< .0001	−29	.01	−31	.03
Non-HDL cholesterol (mg/dL)	386	−50	< .0001	−44	< .0001	−39	< .0001
ApoB (g/L)	2.6	−49	< .0001	−45	< .0001	−43	< .0001
ApoA (g/L)	1.2	−14	.0003	1	.56	−4	.11
Lp(a) (μM/L)	2.4	−15	.0003	−19	.01	−1	.58

Data are mean, median for TGs, at baseline, weeks 26, 56, and 78, or mean (95% CI) for percentage change.
P values at week 26 are from the mixed model and *P* values at week 56 and 78 are from one-sample *t* test.
Significance from baseline to week 26 (primary endpoint) was assessed with a mixed linear model which assumes a missing at random mechanism. All patients who received at least one dose of the study drug were in the assessment of the primary and secondary endpoints (intent-to-treat) up to the end of the efficacy phase (week 26).
ApoA, apolipoprotein A; ApoB, apolipoprotein B; HDL, high-density lipoprotein; Lp(a), lipoprotein(a); LDL, low-density lipoprotein; TG, triglycerides; VLDL, very low-density lipoprotein.
Adapted from Cuchel M et al.[26]

times the upper limit of normal were noted in 10 patients (in association with increased alcohol intake in three patients), were not accompanied by elevation in bilirubin or alkaline phosphatase or impaired hepatic synthetic function, and were managed by temporary cessation or dose reduction. There was no discontinuation of treatment due to these findings.

Lomitapide is an effective LDL-lowering agent for patients with HoFH who do not respond adequately to existing therapies. Dosing with lomitapide was associated with frequent hepatic and gastrointestinal side effects, both of which were likely due to the mechanism of action of the drug. It has been demonstrated that the initiation of very low doses with gradual titration of the dose in

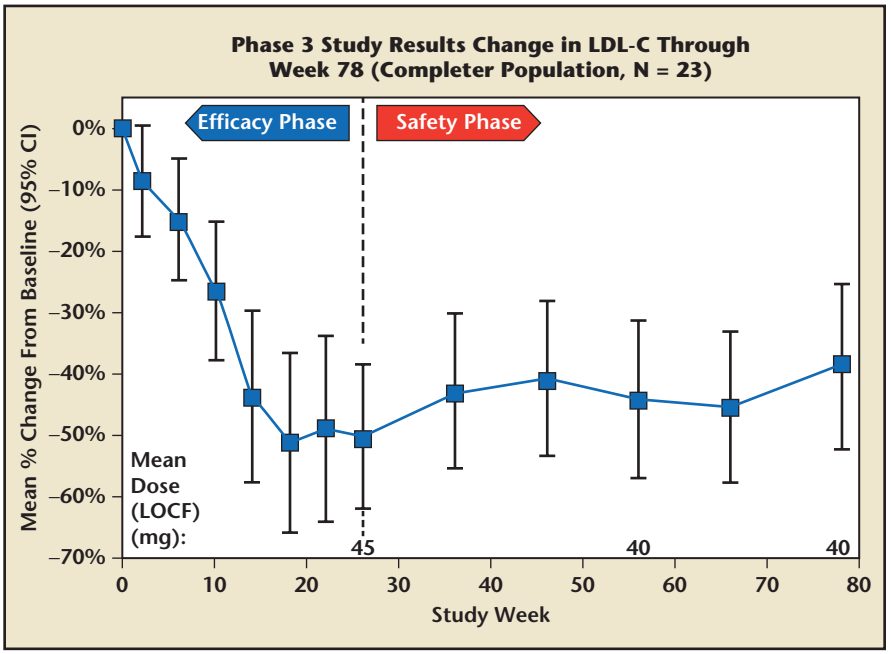

Figure 4. Mean percentage change in LDL-C (95% CI) through week 78 of treatment for the phase 3 HoFH study. Results are presented for the 23 patients who completed the efficacy phase through week 26 and entered the safety phase; all of these patients completed the study. As shown, persistence of the lipid-lowering effect was observed through week 78 of treatment. The patients' background lipid-lowering therapy could be modified during the safety phase. CI, confidence interval; HoFH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LOCF, last observation carried forward. Data from Juxtapid [package insert][25] and Cuchel M et al.[26]

TABLE 2

Effect of Lomitapide on Percentage Hepatic Fat Content Measured by Magnetic Resonance Spectroscopy in a Phase 3 Study

Baseline (n = 20)	Week 26 (n = 20)	Week 56 (n = 20)	Week 78 (n = 20)
1.0% (0-5.0%)	8.6% (0-33.6%)	5.8% (0-16.5%)	8.3% (0-19%)

Data are mean and range as measured by nuclear magnetic resonance spectroscopy in the 20 patients in whom it was evaluable.
Adapted from Cuchel M et al.[26]

conjunction with a low-fat diet resulted in improved tolerability and liver safety.[26] Hepatic steatosis is a recognized effect of the mechanism of action of MTP inhibition, but longer-term studies demonstrated that hepatic fat increased initially but eventually plateaued at a level that is considered clinically acceptable without evidence of steatohepatitis.[26] This issue, however, remains a concern. Periodic monitoring of liver enzymes is required, but the clinical data support the safety of down-titration of the dose or short-term discontinuation of the drug if liver enzymes are elevated greater than three times the upper limit of normal. Once the liver enzymes have returned to baseline or stabilized, the dose can be titrated higher if necessary, with improved LDL cholesterol reduction and adequate safety. Therefore, adaptation of the liver to the steatosis probably occurs that allows the drug to be used chronically. The long-term health consequences of mild-to-moderate hepatic steatosis are uncertain and therefore continued monitoring for potential safety issues is important.

Integrating Lomitapide Into Clinical Practice

Lomitapide is an MTP inhibitor that results in substantial reductions in VLDL, LDL, and ApoB.[27] With this broad reduction in the spectrum of atherogenic particles, either alone or in addition to a statin, lomitapide might be predicted to reduce the risk for cardiovascular events (myocardial infarction, stroke, and cardiovascular death) in patients with HoFH; however, no outcomes data are currently available. A significant reduction in LDL cholesterol is seen even in patients with no detectable functional LDL receptors.[3]

Maximally Medically Treated HoFH Patients

Patients with HoFH are treated with a variety of conventional lipid-lowering medications. Use of statins in patients with HoFH has a lesser impact on the reduction in LDL cholesterol given polymorphisms in both alleles of the LDL receptor. In a study of patients with LDL cholesterol > 160 mg/dL but without confirmed HoFH, Jones and colleagues[28] demonstrated that atorvastatin, 40 mg/d, induced a 51% reduction in LDL cholesterol. By comparison, Marais and colleagues[29] studied the effect of either rosuvastatin, 80 mg/d, or atorvastatin, 80 mg/d, in patients with confirmed HoFH and found that the maximal LDL cholesterol reduction overall was 21%. Of note, increasing atorvastatin to 120 or 160 mg/d resulted in no further reduction in LDL cholesterol.[30] Adding ezetimibe, 10 mg/d, to maximally titrated statins in this population can result in an additional 20.5% reduction in LDL cholesterol.[31] Thus, in the published literature to date, conventional medical therapy can result in an approximately 20% to 30% reduction in LDL cholesterol, but that level of LDL cholesterol reduction is generally still well above conventional treatment targets for patients at high risk for coronary artery disease. In this population, the addition of lomitapide could be expected to further reduce LDL cholesterol, and may provide the opportunity to reach established LDL cholesterol treatment goals of < 100 mg/dL or < 70 mg/dL.[26]

Because anywhere from one to three lipid-lowering drugs are being used in patients with HoFH, the probability of adverse effects, including elevations of liver transaminases more than three times the upper limit of normal, is somewhat increased. Clinicians must measure aspartate aminotransferase and alanine aminotransferase results prior to initiating lomitapide therapy (at a minimum of once monthly during the first year of therapy and prior to any increase in dose, and at a minimum of once every 3 months after the first year of therapy and prior to any increase in dose).[7] In the case of multidrug-associated liver toxicity, all potentially offending drugs should be stopped until liver function tests return to baseline and other causes of liver disease, such as alcohol, metabolic syndrome, and viral hepatitis, are ruled out.

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Statin- and Multidrug-Intolerant HoFH Patients

Population-based studies indicate that approximately 10% of the general population develop intolerance to statin medications, primarily due to myalgia and, to a lesser extent, arthralgia and gastrointestinal, neurologic, or immunologic adverse effects.[32,33]

Recent studies have found that one of the final common pathways for the clearance of statins, the organic anion-transporting polypeptide OATP1B1 in the hepatocyte, has a loss of function polymorphism in approximately 15% of the population.[34] In the setting of statin intolerance, a variety of strategies have been suggested, including a drug holiday, reduction in dose, reduction in frequency, or the use of nonstatin alternatives.[35] All of these approaches result in lesser reductions in LDL cholesterol than the maximal dose of a statin drug.

> ***… statin-intolerant patients with HoFH are either untreated or very minimally managed with medical therapies, making them excellent candidates for lomitapide treatment.***

Thus, statin-intolerant patients with HoFH are either untreated or very minimally managed with medical therapies, making them excellent candidates for lomitapide treatment. In the clinical trials program, there were no increased risks of muscle or joint complaints with lomitapide.[26]

HoFH Patients Treated With Lipid Apheresis

Periodic lipid apheresis with a venovenous circuit plasma separator and cholesterol-binding resin columns is an established treatment for HoFH. This procedure takes > 3 hours and is done every 1 to 2 weeks. Each session induces an approximately 80% reduction in LDL cholesterol; however, there is a return to baseline by the next session. Lipid apheresis also lowers lipoprotein(a) effectively. In general, HoFH patients with LDL cholesterol > 300 mg/dL are considered candidates for lipid apheresis.[36] Approximately 400 patients in the United States receive lipid apheresis therapy and the totality of the evidence suggests: (1) apheresis is complementary to pharmacologic intervention; (2) apheresis is a treatment alternative to statins and other lipid-lowering medications in patients intolerant of these agents; and (3) lipid apheresis may attenuate the progression of atherosclerosis and reduce risk for major cardiovascular events in well-treated patients.[33]

Lomitapide was used in conjunction with lipid apheresis in 62% of cases in the phase 3 HoFH trial .[26,37] Of the 29 HoFH subjects enrolled, 18 were receiving apheresis and 11 were not; 23 patients (13 receiving apheresis) completed the week 26 evaluation. Based on the results of a post hoc analysis, the efficacy of lomitapide appeared to be independent of whether patients were or were not receiving apheresis. Baseline LDL cholesterol levels in patients on apheresis and patients not on apheresis were 326 ± 108 mg/dL versus 355 ± 125 mg/dL, respectively. LDL cholesterol levels were reduced by 48% in patients undergoing apheresis treatment versus 55% in subjects not on apheresis treatment ($P = .54$). No between-group differences were observed for ApoB total cholesterol or triglycerides.[38]

If significant LDL cholesterol reductions are achieved with lomitapide, then lipid apheresis may be less frequent or perhaps discontinued. Hence, for patients undergoing apheresis, the therapeutic option of lomitapide should be presented and the benefits and risks of therapy discussed.

Summary

1. Homozygous familial hypercholesterolemia is an autosomal dominant disorder associated with severe elevations in serum LDL cholesterol and severe, premature, multivessel coronary artery disease.
2. Microsomal triglyceride transfer protein catalyzes the transfer of lipids to ApoB in both jejunal enterocytes and hepatocytes.
3. In animal models, MTP inhibition is associated with reductions atherogenic lipoproteins in serum as well as reduced atherosclerotic plaque burden.
4. Lomitapide is a microsomal triglyceride transfer protein inhibitor approved by the FDA and European Commission for use in the management of hyperlipidemia in patients with HoFH.
5. Lomitapide therapy induces significant reductions in serum VLDL cholesterol, LDL cholesterol, triglycerides, and non-HDL cholesterol in humans.
6. The impact of lomitapide on risk for cardiovascular events in patients with HoFH remains to be determined.
7. Lomitapide carries a boxed warning and the prescription of lomitapide (Juxtapid®; Aegerion Pharmaceuticals, Inc., Cambridge, MA) is only available through the Juxtapid Risk Evaluation and Mitigation Strategy Program.
8. Lomitapide is indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis—where available—to

reduce LDL cholesterol, total cholesterol, ApoB, and non-HDL cholesterol in patients with HoFH.

9. The safety and effectiveness of lomitapide have not been established in patients with hypercholesterolemia who do not have HoFH or in patients aged < 18 years.
10. Patients treated with lomitapide require careful and frequent surveillance of hepatic transaminases and an awareness that hepatic fat content increases with the initial course of treatment.
11. Future trials and clinical experience will provide important information about long-term safety and efficacy.
12. Lomitapide constitutes an important new therapeutic approach to the management of HoFH. ■

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MAIN POINTS

- Homozygous familial hypercholesterolemia (HoFH) is an autosomal dominant disorder associated with severe elevations in serum low-density lipoprotein (LDL) cholesterol and severe, premature, multivessel coronary artery disease. Lomitapide is a microsomal triglyceride transfer protein inhibitor approved by the US Food and Drug Administration and European Commission for use in the management of hyperlipidemia in patients with HoFH.
- Lomitapide is indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis—where available—to reduce LDL cholesterol, total cholesterol, apolipoprotein B, and non–high-density lipoprotein cholesterol in patients with HoFH.
- Patients treated with lomitapide require careful and frequent surveillance of hepatic transaminases and an awareness that hepatic fat content increases with the initial course of treatment.

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