Common Drug Review
Clinical Review Report

July 2015

Drug	lomitapide (Juxtapid) (oral capsules)
Indication	As an adjunct to a low-fat diet and other lipid-lowering drugs, with or without LDL apheresis, to reduce low-density lipoprotein cholesterol (LDL-C) in adult patients with homozygous familial hypercholesterolemia (HoFH).

Listing request	As per indication, plus:
	• Due to its benefit-risk profile, the prescribing of Juxtapid should be limited to physicians experienced in the diagnosis and treatment of familial hypercholesterolemia.
	
	The manufacturer proposes the following criteria be considered when assessing eligibility for Juxtapid in the treatment of HoFH:
	Typical clinical and lab criteria would include:
	• Untreated LDL-C > 10.3 mmol/L (400 mg/dL)
	OR:
	• Treated LDL-C > 5.2 mmol/L (200 mg/dL) with one or both of the following:
	  ○ Cutaneous or tendinous xanthomas (past or present); or
	  ○ Clinically evident premature CV disease and, when family history is available, evidence of FH in both parents
	OR:
	• DNA confirmation of 2 mutant alleles in genes for the LDL receptor, apo B, PCSK-9 or ARH.

Manufacturer	Aegerion Pharmaceuticals, Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in cardiology who provided input on the conduct of the review and the interpretation of findings.

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ABBREVIATIONS

ALT	alanine aminotransferase
apo A1	apolipoprotein A1
apo B	apolipoprotein B
AST	aspartate aminotransferase
CI	confidence interval
FH	familial hypercholesterolemia
HDL-C	high-density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolemia
HoFH	homozygous familial hypercholesterolemia
ITT	intention-to-treat
LDL-C	low-density lipoprotein cholesterol
LOCF	last observation carried forward
non-HDL-C	non-high-density lipoprotein cholesterol
SAE	serious adverse event
SD	standard deviation
ULN	upper limit of normal
VLDL-C	very-low-density lipoprotein cholesterol
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Familial hypercholesterolemia (FH) is a common genetic disorder of lipid metabolism affecting between 14 and 34 million people worldwide.[1] FH is characterized by markedly elevated plasma levels of low-density lipoprotein cholesterol (LDL-C), the chronic exposure to which leads to an increased susceptibility to premature coronary artery disease and cardiac death,[1-6] sometimes before the age of 10 in the most severe presentation of the disease.[3] Patients with untreated FH have a 20-fold increased risk, irrespective of the underlying genetic mutation, of developing premature coronary artery disease compared with people without FH.[3] FH is subdivided into heterozygous (HeFH) or homozygous (HoFH) disease.[1,3,6,7] HoFH is the more severe and rare form of FH. Historically, the prevalence of HoFH is estimated at 1 in 1,000,000;[1,2] however, more recent data have suggested a prevalence of 1 in 300,000 to 1 in 160,000.[2] In certain subpopulations of the world (e.g., French Canadians), prevalence estimates may be higher because of the founder effect.[1,8]

To date, there has been no evidence to suggest that identifying the causal mutations in FH improves clinical outcomes compared with treatment provided in the absence of genotyping;[9] thus, the diagnosis of FH is clinical and is based on LDL-C concentration, hallmark physical findings (e.g., xanthomas), presence of early cardiovascular disease, and family history.[1,6,7] There are currently no Canadian-specific guidelines or diagnostic criteria for diagnosing FH;[6] lowering LDL-C is the therapeutic strategy based on evidence accumulated from treating hypercholesterolemia in the general population.[6] There is some disagreement among guideline groups[1,6,10] regarding the intensity of LDL-C lowering treatment, however: Some recommend a ≥ 50% reduction from baseline,[6,10] while others target less than 2.5 mmol/L[1] or less than 1.8 mmol/L[1] or 2.0 mmol/L[6] depending on the presence of cardiovascular disease.

Maximally titrated, high-potency statin treatment is the cornerstone of therapy for FH.[1,6,8] However, statin monotherapy is often insufficiently effective in FH,[10] especially in HoFH;[3] hence, additional therapy with ezetimibe or bile acid-binding resins (or both) is recommended, as well as niacin and fibric acid derivatives.[1,6,8,10] Apheresis is recommended when LDL-C remains elevated despite maximal pharmacotherapy;[6,8] however, access to apheresis treatment centres may be limited.[10]

Lomitapide is a microsomal transfer protein inhibitor that prevents the transfer of triglyceride onto apolipoprotein (apo) B-100 in the liver and apo B-48 in the intestine to reduce circulating levels of LDL-C.[11] Lomitapide is initiated at a dose of 5 mg orally once daily and increased to 10 mg daily after two weeks. The dose is subsequently increased at four-week intervals to 20 mg and then 40 mg, up to a maximum of 60 mg daily according to safety and tolerability. [12] Lomitapide is indicated as an adjunct treatment to a low-fat diet and other lipid-lowering drugs, with or without LDL apheresis, to reduce LDL-C in adult patients with HoFH.[12] Reimbursement is being sought by the manufacturer in accordance with this indication along with several criteria that include eligibility based on LDL levels and genetic confirmation of LDL receptor mutation status.

The objective of this review is to evaluate the beneficial and harmful effects of lomitapide added to other lipid-lowering therapy in patients with HoFH.

Results and Interpretation

Included Studies

The evidence for this review was drawn from one phase III (UP1002/AEGR-733-005), multinational, open-label, single-arm, uncontrolled study, which included 29 adults with HoFH. The primary efficacy outcome was the per cent change in LDL-C from baseline to week 26. The change in non-LDL-C was also measured. The study was divided into two phases: a 26-week efficacy phase, during which the maximally tolerated dose of study drug was established; and a 52-week safety phase, during which the maximally tolerated dose established from the efficacy phase was continued at the same dose until week 78. All patients received lomitapide in combination with their background lipid-lowering therapy. Background lipid-lowering therapy was fixed during the efficacy phase and modifiable during the safety phase. Apheresis treatments were used in 62.1% of patients and were not permitted to vary during the 26-week efficacy phase. Of the 29 patients studied, 5 (17.2%) were recruited from Canadian sites. Upon completion of the pivotal study (UP1002/AEGR-733-005), 19 (82.6%) patients entered AEGR-733-012, an open-label extension study, which was similar in design to the safety phase of the pivotal study.

Efficacy

A statistically significant reduction in LDL-C was observed after 26 weeks of lomitapide treatment (−40.1% versus baseline; 95% confidence interval [CI], –51.9% to –28.2%). A similar, statistically significant reduction in non-high-density lipoprotein cholesterol (non-HDL-C) was observed after 26 weeks of treatment. Of the 13 patients who were receiving apheresis treatments at the beginning of the 52-week safety phase, 3 (23.1%) stopped apheresis treatment and 3 (23.1%) lengthened the interval between apheresis treatments through week 78. In the open-label extension study, reduction in both LDL-C (–45.5%) and non-HDL-C (–47.1%) persisted in 17 patients who completed 126 weeks of treatment.

The major limitations with this study were the following: First, the magnitude of the treatment effect is unclear, because there was no comparator arm and background lipid-lowering treatments (including apheresis) may have been altered at the start of the trial. Second, the trial failed to address the outcomes that were most important to patients, namely, preventing cardiovascular complications and improving quality of life.

Harms

Diarrhea, nausea, and vomiting were the most commonly reported adverse events; however, during the efficacy phase, diarrhea and nausea were reported at more than double the frequency of the safety phase (79.3% and 62.1% versus 34.8% and 30.4%), suggesting that patients who did not tolerate lomitapide well during the first 26 weeks of the study may not have completed the subsequent 52 weeks of the safety phase. During the efficacy phase only, three patients (10.3%) experienced serious adverse events, and four patients (13.8%) withdrew from the study because of non-serious adverse events. No deaths were reported through 78 weeks of treatment.

Markers of hepatotoxicity, including liver transaminases and hepatic fat, were examined separately as harms of interest. Elevations in alanine aminotransferase (19.3 U/L and 15.0 U/L) and hepatic fat (7.3% and 6.9%) were observed after 26 weeks and 78 weeks from baseline, and small subsets of patients experienced elevations in alanine aminotransferase of greater than or equal to three times the upper limit of normal (ULN) (n = 10) and greater than or equal to five times ULN (n = 4). There is uncertainty regarding the meaningfulness of the hepatic fat accumulation observed during the pivotal study, which is a consequence of this drug's mechanism of action.[13]

Patient input for this submission indicated that patients believed that adverse effects from lomitapide would not be worse than those experienced from current therapy; however, evidence from this review suggests that this expectation may be unfounded. To this point, the safety profile of lomitapide observed in the open-label extension study appears similar to that observed in the pivotal study (UP1002/AEGR-733-005) in terms of tolerability and the types of adverse events being reported.

Conclusions

In one multinational, open-label, single-arm, uncontrolled study (UP1002/AEGR-733-005), which included 29 adults with HoFH, lomitapide was associated with a 40% reduction from baseline in LDL-C after 26 weeks. However, the true efficacy of lomitapide is uncertain due to the absence of a comparator arm from the study. Furthermore, outcomes were limited to changes in lipoprotein concentrations, whereas mortality, morbidity (particularly cardiovascular events), and quality of life were not assessed. Lomitapide treatment was associated with gastrointestinal adverse events such as diarrhea, nausea, vomiting, dyspepsia, and constipation. Lomitapide is associated with elevations in transaminases and hepatic fat, but the clinical meaningfulness of these findings is currently unknown.

TABLE 1: SUMMARY OF RESULTS

Outcome		UP 1002/AEGR-733-005	
		Efficacy Phase (n = 29) Weeks 0 to 26	Safety Phase (n = 23) Weeks 26 to 78
Efficacy			
Change From baseline in LDL-C,[a] mean (SD)			
Baseline (mg/dL)		336.4 (113.5)	—
Week 26 (mg/dL)		189.6 (104.2)	—
Absolute change: baseline to week 26		–146.9 (127.1)	—
Per cent change (%)		–40.1 (31.3)	—
95% CI (%)		–51.9 to –28.2	
P value		< 0.001	—
Change From baseline in Non-HDL-C, mean (SD)			
Baseline (mg/dL)		385.8 (131.6)	—
Week 26 (mg/dL)		217.1 (112.7)	—
Absolute change: baseline to week 26		–168.7 (141.4)	—
Per cent change (%)		–40.0 (29.7)	—
95% CI (%)		–51.3 to –28.8	
P value		< 0.001	—
Change from baseline in apheresis treatments,[b,c] mean (SD)			
Baseline	Patients, n (%)	18 (100)	—
	Number of treatments	1.4 (0.9)	—
Week 26	Patients, n (%)	13 (72.2)	—
	Number of treatments	2.0 (0.9)	—
Week 78	Patients, n (%)	—	11 (61.1)
	Number of treatments	—	5.0 (2.3)
Harms			
AEs			
Patients, n (%)		27 (93.1)	21 (91.3)
SAEs			
Patients, n (%)		3 (10.3)	0

Outcome	UP 1002/AEGR-733-005	
	Efficacy Phase (n = 29) Weeks 0 to 26	Safety Phase (n = 23) Weeks 26 to 78
WDAEs		
Patients, n (%)	4 (13.8)	0
Deaths		
n (%)	0	0
Notable Harms		
Change from baseline to week 26, 78; mean (SD)	**Observed Change, Weeks 0 to 26**	**Observed Change, Weeks 26 to 78**
ALT (U/L)	19.3 (31.5)	15.0 (29.1)
AST (U/L)	6.8 (17.8)	8.9 (20.2)
Alkaline phosphatase (U/L)	–6.6 (31.0)	–15.8 (24.3)
Total bilirubin (mg/dL)	0.0 (0.4)	0.1 (0.3)
Hepatic fat (%) (NMRS)	7.3 (6.8)	6.9 (5.0)

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NMRS = nuclear magnetic resonance spectroscopy; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.

[a] Intention-to-treat set was used for lipoprotein analyses.

[b] A total of 18 (62.1%) patients were receiving apheresis at baseline.

[c] Safety set was used for apheresis and safety analyses.

Note: To convert to SI units, multiply by 0.0259 for LDL-C and non-HDL-C, and by 17.1 for total bilirubin.[14]

Source: UP1002/AEGR-733-005 Clinical Study Report.[15]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Familial hypercholesterolemia (FH) is a common genetic disorder of lipid metabolism affecting between 14 and 34 million people worldwide.[1] FH is characterized by markedly elevated plasma levels of low-density lipoprotein cholesterol (LDL-C), the chronic exposure to which leads to an increased susceptibility to premature coronary artery disease and cardiac death,[1-6] sometimes before the age of 10 in the most severe presentation of the disease.[3] Patients with untreated FH have a 20-fold increased risk, irrespective of the underlying genetic mutation, of developing premature coronary artery disease compared with people without FH.[3] FH is subdivided into heterozygous (HeFH) or homozygous (HoFH) disease,[1,3,6,7] with HoFH being the more severe and rare form with a prevalence of 1 in 1,000,000;[1,2,16] however, more recent data suggest a prevalence of 1 in 300,000 to 1 in 160,000,[2] which may be partly explained by founder effects in certain subpopulations of the world (e.g., French Canadians).[1,8] As described in the Pharmacoeconomic Report, according to the manufacturer there are 27 patients with HoFH in Canada.

To date, there has been no evidence to suggest that identifying the causal mutations in FH leads to different clinical outcomes than treatment provided in the absence of genotyping;[9] moreover, in some patients, a confirmatory molecular diagnosis may prove elusive, since not all patients with a clinical diagnosis of FH will have that diagnosis confirmed by molecular data.[9] Thus, the diagnosis of FH has been and remains a clinical one, supported by several diagnostic criteria developed by different countries, the most common among these being the Dutch Lipid Clinic Network (Table 10) criteria and the UK Simon Broome Registry criteria.[1,6,7] There are currently no Canadian-specific guidelines or diagnostic criteria for diagnosing FH.[6]

1.2 Standards of Therapy

Although evidence from randomized controlled trials supporting LDL-C as the primary treatment target in FH is lacking, lowering LDL-C is nonetheless the therapeutic strategy based on the body of evidence accumulated from the general population.[6] According to the European Atherosclerosis Society,[1] adult patients with FH should be treated to an LDL-C target of less than 2.5 mmol/L (or less than 1.8 mmol/L in the case of comorbid coronary heart disease or diabetes); it is acknowledged, however, that in patients with HoFH, these aggressive targets may not be achievable with current lipid-lowering treatments.[1] In North America, the US National Lipid Association's Expert Panel on Familial Hypercholesterolemia[10] and the Canadian Cardiovascular Society[6] both recommend a ≥ 50% reduction in LDL-C from baseline, and the Canadian Cardiovascular Society alternatively recommends reducing LDL-C to less than 2.0 mmol/L when comorbid cardiovascular disease exists.

While management of FH includes lifestyle modification (e.g., low-fat and low-cholesterol diet; regular physical activity; weight, blood pressure, and diabetes control; smoking cessation), pharmacologic treatment with a backbone of maximally titrated high-potency statins is the cornerstone of therapy in FH.[1,6,8] Statin monotherapy is often insufficiently effective in FH,[10] especially in HoFH where LDL receptors may be completely absent or defective (i.e., with 2% to 30% activity);[3] hence, combination therapy is usually required.[1,6,8] The Canadian, US, and European organizations[1,6,10] all recommend second-line therapy with ezetimibe or bile acid-binding resins (or both), and the US National Lipid Association[10] includes niacin and fibric acid derivatives as additional treatment options. Only the European Atherosclerosis Society explicitly outlines a preferred sequence of second-line treatment, in which ezetimibe is tried before bile acid-binding resins.[1] In patients with HoFH whose LDL-C remains

greater than or equal to 7.8 mmol/L (or non-high-density lipoprotein [HDL] greater than or equal to 8.5 mmol/L) despite six months of maximally tolerated drug therapy, the US association recommends add-on LDL apheresis treatment.[8] Similarly, the Canadian society[6] recommends extracorporeal plasma exchange or LDL apheresis if LDL-C remains greater than 8.5 mmol/L despite maximal pharmacotherapy. Therapeutic options for FH are presented comparatively in Table 2 and Appendix 6: Summary of Plasma Exchange and Low-Density lipoprotein Apheresis.

Achieving LDL-C control in HoFH is difficult with current pharmacotherapies owing to absent or insufficiently functioning LDL receptors in these patients coupled with tolerability issues from some drugs; moreover, access to apheresis treatment centres, particularly those performing LDL apheresis, may be limited.[10] Hence, patients remain insufficiently protected against cardiovascular complications arising from chronic exposure to high levels of plasma LDL-C — a concern articulated by patients submitting input for this review (see Appendix 1: Patient Input Summary).

1.3 Drug

Lomitapide is a first-in-class drug from the microsomal transfer protein inhibitor class of drugs, which works by inhibiting the transfer of triglyceride onto apolipoprotein (apo) B-100 in the liver and apo B-48 in the intestine to form very-low-density lipoproteins (VLDL-C) and chylomicrons, respectively.[11] By inhibiting VLDL-C assembly in the liver, circulating levels of LDL-C are reduced.[11] Lomitapide is initiated at a dose of 5 mg orally once daily and is increased to 10 mg daily after two weeks. The dose is subsequently increased at four-week intervals to 20 mg and then 40 mg, up to a maximum of 60 mg daily according to safety and tolerability. The recommended administration is with a glass of water, without food, two hours after the evening meal.[12] Lomitapide has a Health Canada indication as an adjunct treatment to a low-fat diet and other lipid-lowering drugs, with or without LDL apheresis, to reduce LDL-C in adult patients with HoFH.[12] Reimbursement is being sought by the manufacturer in accordance with this indication along with the proposed additional listing criteria in the box below.

Indication under review
As an adjunct to a low-fat diet and other lipid-lowering drugs, with or without LDL apheresis, to reduce low-density lipoprotein cholesterol (LDL-C) in adult patients with homozygous familial hypercholesterolemia (HoFH).
Listing criteria requested by sponsor

As per indication, plus:
• Due to its benefit-risk profile, the prescribing of Juxtapid should be limited to physicians experienced in the diagnosis and treatment of familial hypercholesterolemia
The manufacturer proposes the following criteria be considered when assessing eligibility for Juxtapid in the treatment of HoFH:
Typical clinical and lab criteria would include:
• Untreated LDL-C > 10.3 mmol/L (400 mg/dL)
OR:
• Treated LDL-C > 5.2 mmol/L (200 mg/dL) with one or both of the following:
  ○ Cutaneous or tendinous xanthomas (past or present); or
  ○ Clinically evident premature CV disease and, when family history is available, evidence of FH in both parents
OR:
• DNA confirmation of 2 mutant alleles in genes for the LDL receptor, apo B, PCSK-9 or ARH.

TABLE 2: KEY CHARACTERISTICS OF THERAPIES USED IN FAMILIAL HYPERCHOLESTEROLEMIA

	Microsomal Triglyceride Transfer Protein Inhibitors	HMG-CoA Reductase Inhibitors ("Statins")	Cholesterol Absorption Inhibitors	Bile Acid Sequestrants ("Resins")	Niacin (Nicotinic Acid) Derivatives	Fibrates	Apheresis[a]
Available Drugs Within Class[17]	Lomitapide[12]	Atorvastatin; fluvastatin; lovastatin; pravastatin; rosuvastatin; simvastatin	Ezetimibe	Cholestyramine; colesevelam; colestipol	Niacin (immediate-release; extended-release)	Bezafibrate; fenofibrate (plain; microcoated; micronized; nanocrystals); gemfibrozil	Available procedures: LDL apheresis, plasma exchange[18]
Mechanism of Action	Inhibits the transfer of TG onto apo B-100 in the liver and apo B-48 in the intestine to form VLDL-C and chylomicrons, respectively; the hepatic inhibition of VLDL-C assembly reduces circulating levels of LDL-C.[11]	Competitively inhibits HMG-CoA reductase, resulting in reduced cholesterol biosynthesis and increased clearance of LDL-C secondary to upregulated LDL receptors.[19]	Inhibits intestinal absorption of cholesterol, resulting in LDL receptor upregulation.[16, 19]	Prevents intestinal reabsorption of bile acids resulting in increased fecal excretion of LDL-C-bound bile acids and consequent LDL receptor upregulation.[16]	Reduces the availability of FFA substrate for hepatic VLDL-C assembly and impairs the conversion of VLDL-C to LDL-C.[19]	Activates the alpha subunit of the PPAR-alpha receptor, thereby increasing LPL activity, VLDL catabolism, and plasma TG clearance.[19] May increase LDL-C slightly if baseline TG elevated.[19]	*LDL apheresis*: Selectively removes apo B–containing particles (i.e., LDL-C, VLDL-C, Lp[a]) from the blood through a system of extracorporeal precipitation.[10,20] *Plasma exchange*: Non-selective procedure in which plasma is isolated from blood, discarded, and replaced with a substitution fluid; both the substitution fluid and residual cellular components from the blood are then returned to the patient.[18]

	Microsomal Triglyceride Transfer Protein Inhibitors	HMG-CoA Reductase Inhibitors ("Statins")	Cholesterol Absorption Inhibitors	Bile Acid Sequestrants ("Resins")	Niacin (Nicotinic Acid) Derivatives	Fibrates	Apheresis[a]
Indication[b]	*Indicated in HoFH:* As an adjunct to a low-fat diet and other lipid-lowering drugs, with or without LDL apheresis, to reduce LDL-C in adult patients.[12]	*Indicated in HoFH: Atorvastatin:* As an adjunct to treatments such as LDL apheresis, or as monotherapy if such treatments are not available.[21] *Rosuvastatin*: Either alone or as an adjunct to diet and other lipid-lowering treatments such as apheresis.[22] *Simvastatin*: As an adjunct to diet in primary hypercholesterolemia (type IIa);[c] limited data available in HoFH.[23] *Not indicated in HoFH:* *Fluvastatin, lovastatin, pravastatin*: as an adjunct to diet in hypercholesterolemia (type IIa),[c] when diet and other non-pharmacologic measures are inadequate.[24]	*Indicated in HoFH:* In combination with a statin; as an adjunct to treatments such as LDL apheresis or if such treatments are not possible.[25]	*Not indicated in HoFH* *Colesevelam*: In primary hyper-cholesterolemia (Type IIa)[c] as an adjunct to diet and lifestyle changes when statin therapy alone is inadequate *or* when statin therapies are not tolerated.[26]	*Not indicated in HoFH* *Niacin* (extended-release): In primary hyper-cholesterolemia (Type IIa)[c] as an adjunct to therapeutic lifestyle changes.[27]	*Not indicated in HoFH* *Bezafibrate, fenofibrate, gemfibrozil*: In primary hyper-cholesterolemia (Type IIa)[c] as an adjunct to diet and other therapeutic measures.[28-30]	*LDL apheresis:* Two systems have been granted licensure from Health Canada: HELP[18] and DSL LA-15.[31] *Plasma exchange*: NA.
Route of Administration	Oral	Oral	Oral	Oral	Oral	Oral	IV
Recommended Dose	5 mg to 60 mg daily at 4-week intervals.[12]	*Atorvastatin*: 10 mg to 80 mg daily.[24] *Fluvastatin*: 20 mg to 80 mg daily.[24] *Lovastatin*: 20 mg to 80 mg daily.[24] *Pravastatin*: 10 mg to 40 mg daily.[24] *Rosuvastatin*: 5 mg to 40 mg daily.[24] *Simvastatin*: 10 mg to 80 mg daily.[24]	*Ezetimibe*: 10 mg daily.[25]	*Cholestyramine*: 4 g three to four times daily.[32] *Colesevelam*: 1,875 mg twice daily or 3,750 mg daily.[26] *Colestipol* (tablets): 2 g to 16 g once daily or in divided doses.[33]	*Niacin/niacinamide*: Immediate-release: 1.5 g to 2 g daily;[27] Extended-release: 500 mg to2,000 mg daily.[27]	*Bezofibrate*: 400 mg daily.[28] *Fenofibrate*: 145 mg daily.[29] *Gemfibrozil*: 600 mg twice daily.[30]	*LDL apheresis or plasma exchange*: Treatment sessions usually every 1 to 2 weeks for 2 to 3 hours at a time.[18]

	Microsomal Triglyceride Transfer Protein Inhibitors	HMG-CoA Reductase Inhibitors ("Statins")	Cholesterol Absorption Inhibitors	Bile Acid Sequestrants ("Resins")	Niacin (Nicotinic Acid) Derivatives	Fibrates	Apheresis[a]
Serious Side Effects and Safety Issues	Contraindicated in active liver disease, moderate to severe liver impairment, or unexplained, persistently abnormal LFTs; known, significant, chronic bowel disease; with moderate to strong CYP 3A4 inhibitors.[12] Warnings and precautions: Risk of treatment-emergent hepatotoxicity (i.e., hepatic steatosis, elevated transaminases).[12]	Contraindicated in active liver disease or unexplained, persistently abnormal transaminases.[24] Warnings and precautions: Elevated transaminases; myalgia; small risk of type 2 diabetes with high-dose, high-potency statins.[24]	Contraindicated in active liver disease or unexplained, persistently elevated transaminases.[25] Warnings and precautions: Myalgia, elevated transaminases.[25]	Contraindicated in complete bowel[26] or biliary obstruction.[26,32] Warnings and precautions: May worsen pre-existing constipation; can impair absorption of fat-soluble vitamins such as vitamin K, which can affect coagulation.[26,32]	Contraindicated in active liver disease, peptic ulcer disease, hyperuricemia with history of gouty arthritis or uncontrolled hyperglycemia, and severe hypotension.[27] Warnings and precautions: Modest, transient hyperglycemia; hyperuricemia; persistent, unexplained elevations in transaminases.[27]	Contraindicated in hepatic insufficiency, pre-existing gallbladder disease, severe renal dysfunction, chronic or acute pancreatitis.[29] Warnings and precautions: Combination with statins increases risk of myopathy with possibility of acute renal failure; abnormal liver function tests; risk of cholelithiasis; mild decreases in Hgb, Hct, and WBC may occur.[29]	*LDL apheresis*: Uncommon: marked hypotension, hemorrhagic events, anaphylaxis with concomitant ACEI treatment.[34] *Plasma exchange*: Risk of infection.[18]

ACEI = angiotensin-converting enzyme inhibitor; apo = apolipoprotein; CYP = cytochrome; DSL LA-15 = dextran sulphate Liposorber LA-15; FFA = free fatty acid; Hct = hematocrit; HELP = heparin-induced extracorporeal lipoprotein precipitation; Hgb = hemoglobin; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; LFT = liver function test; Lp(a) = lipoprotein (a); NA = not applicable; TG = triglyceride; VLDL-C = very-low-density lipoprotein cholesterol; WBC = white blood cell.

[a] Refer to Appendix 6: Summary of Plasma Exchange and Low-Density lipoprotein Apheresis for further details of this therapeutic modality.

[b] Health Canada indication.

[c] Primary hypercholesterolemia type IIa is synonymous with familial hypercholesterolemia.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of lomitapide added to other lipid-lowering therapy in patients with HoFH.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Other studies were selected for inclusion based on the criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Patients with a confirmed diagnosis of HoFH **Subgroups** • Age • Apheresis co-treatment: yes/no • Baseline LDL-C • Presence of CVD at baseline • Baseline LDL-R status: negative or defective
Intervention	Lomitapide added to current lipid-lowering therapy[a]
Comparators	Standard of care[b]

Outcomes	**Key efficacy outcomes**
	• Mortality
	• Morbidity
	  • CV events
	  • hospitalizations
	  • minimally invasive CV interventions (e.g., PCI)
	• Lipoprotein profile
	  • LDL-C
	  • non-HDL-C
	• Frequency of LDL apheresis or plasma exchange
	• Quality of life
	
	Harms outcomes
	AEs, SAEs, WDAEs, mortality
	Notable harms: markers of hepatotoxicity

Study Design	Published and unpublished RCTs, DB versus open-label

AE = adverse events; CV = cardiovascular; CVD = cardiovascular disease; DB = double blind; HDL-C = high-density lipoprotein cholesterol; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SAE = serious adverse events; WDAE = withdrawal due to adverse event.

[a] Includes other lipid-lowering drugs with or without LDL apheresis.

[b] Defined as various combinations of statins, bile acid sequestrants, ezetimibe, niacin, fibrates, LDL apheresis, or plasma exchange.

Supplemental Issues

1. Comparison of LDL apheresis and plasma exchange
2. Summary of open-label extension study (NCT00943306)

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with In-Process records and daily updates through Ovid, Embase (1974–) through Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Juxtapid (lomitapide).

No methodological filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on November 17, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on March 18, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of CADTH's Grey Matters (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) checklist: Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases (Free), and Internet Search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information about unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in Appendix 3: Excluded Studies.

3. RESULTS

3.1 Findings From the Literature

One study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in Appendix 3: Excluded Studies.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

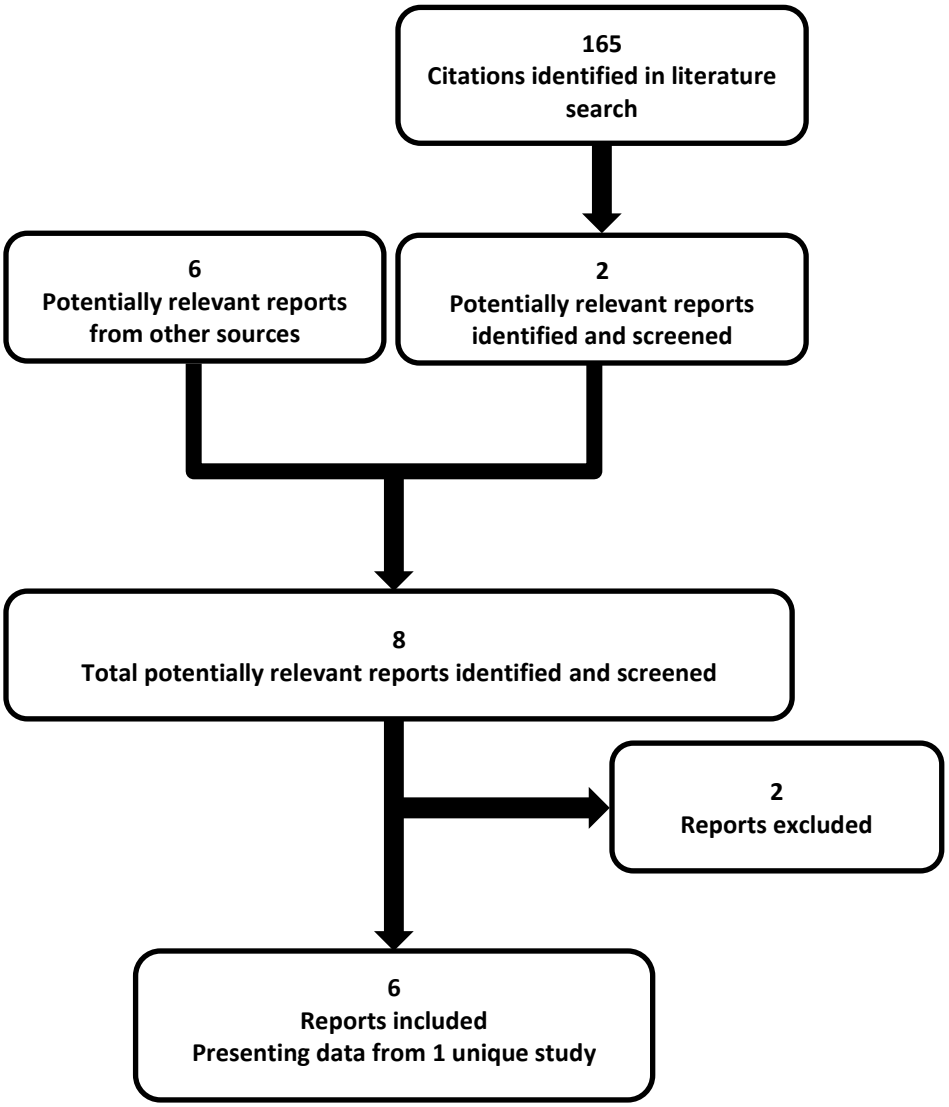


TABLE 4: DETAILS OF INCLUDED STUDY

		UP 1002/AEGR-733-005
DESIGNS AND POPULATIONS	**Study Design**	Open-label, single-arm, multi-centre
	Locations	11 study centres in 4 countries: Canada (2 sites), US (2 sites), South Africa (3 sites), Italy (4 sites)
	Entered Efficacy Phase (N)	29

	Inclusion Criteria	• Males and females (non-pregnant) ≥ 18 years of age
		• Diagnosis of functional HoFH by ≥ 1 of the following clinical criteria:
		  ○ documented functional mutation in both LDLR alleles or alleles known to affect LDLR functionality
		  ○ skin fibroblast LDLR activity < 20% normal
		  ○ untreated TC > 500 mg/dL (> 13.0 mmol/L) and TG < 300 mg/dL (< 7.8 mmol/L) **and** both parents with documented untreated TC > 250 mg/dL (> 6.5 mmol/L)
		• Stable concurrent lipid-lowering medication for ≥ 6 weeks before the baseline visit and through week 26
		• Body weight ≥ 40 kg and < 136 kg

	Exclusion Criteria[a]	• Uncontrolled hypertension (treated: SBP > 180 mm hg, DBP > 95 mm hg) • History of chronic renal insufficiency (SCr > 2.5 mg/dL [> 221 µmol/L]) • History of cirrhosis or abnormal LFTs at screening (AST or ALT > 2 × ULN or total bilirubin of > 1.5 mg/dL (25.7 µmol/L); chronic hepatitis B or C; documented diagnosis of certain liver diseases[b] • Any major surgery < 3 months before screening visit • Cardiac insufficiency (NYHA Class III or IV) • Known significant GI bowel disease or malabsorption • Documented diagnosis of certain pulmonary conditions[c]
DRUGS	**Intervention**	Lomitapide: initially 5 mg orally once daily for 2 weeks, then escalated every 4 weeks until 60 mg/day or maximum tolerated dose achieved
	Comparators	None
DURATION	**Phase**	
	Run-in	–6 weeks to 0 weeks
	Efficacy phase	26 weeks (week 0 to week 26)
	Safety phase	52 weeks (week 26 to week 78)
OUTCOMES	**Primary End Point**	• % change from baseline in LDL-C levels at 26 weeks

	Other End Points	**Secondary**
		• Mean % change from baseline to week 26 in:
		  ○ total cholesterol
		  ○ apo B
		  ○ triglycerides
		  ○ non-HDL-C
		  – VLDL-C
		  – Lp(a)

		UP 1002/AEGR-733-005
NOTES	**Publications**	Cuchel et al. 2013[35]

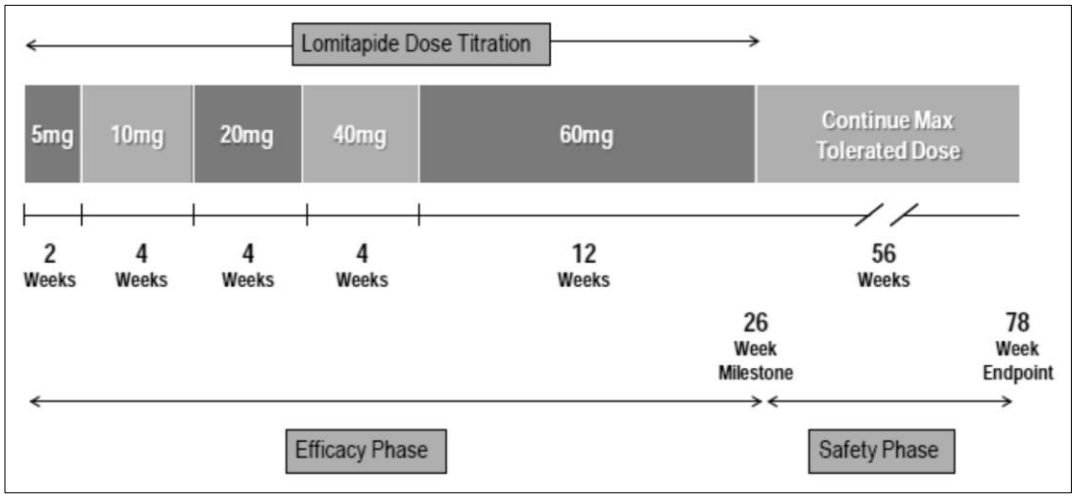
ALT = alanine aminotransferase; AST = aspartate aminotransferase; apo = apolipoprotein; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; HoFH = homozygous familial hypercholesterolemia; GI = gastrointestinal; LDL-C = low-density lipoprotein cholesterol; LDLR = LDL receptor; LFT = liver function test; Lp(a) = lipoprotein (a); NYHA = New York Heart Association; SBP = systolic blood pressure; SCr = serum creatinine; TC = total cholesterol; TG = triglycerides; ULN = upper limit of normal; VLDL-C = very-low-density lipoprotein.
[a] To convert to SI units, multiply by 0.0259 for LDL-C and non-HDL-C, 0.0113 for triglycerides, and 88.4 for serum creatinine.[14]
[b] Non-alcoholic steatohepatitis, alcoholic liver disease, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, Wilson disease, hemochromatosis, alpha-antitrypsin deficiency.
[c] Asthma, chronic obstructive pulmonary disease, or idiopathic pulmonary fibrosis.
Note: Four additional reports were included.[12,36-38]
Source: UP1002/AEGR-733-005 Clinical Study Report.[15]

3.2 Included Studies

3.2.1 Description of Studies

UP1002/AEGR-733-005 was a multinational (four-country), open-label, single-arm study of 29 patients. The study was divided into a 26-week efficacy phase followed by a 52-week safety phase for a total observation period of 78 weeks (Figure 2). Of the 29 patients studied, 12 (41.4%) were from North America, including 5 (17.2%) patients from Canada. The primary objective of the study was to evaluate the efficacy and safety of lomitapide in combination with other lipid-lowering pharmacotherapy in patients with HoFH. All patients received the study drug. During the efficacy phase, lomitapide was administered according to a forced titration protocol starting with 5 mg orally once daily followed by an increase to 10 mg daily after two weeks. The dose was subsequently increased at four-week intervals to 20 mg and then 40 mg, up to a maximum of 60 mg daily according to safety and tolerability. The maximally tolerated dose of lomitapide achieved during the efficacy phase was maintained throughout the safety phase according to safety and tolerability, with no further dose escalation permitted. Concomitant oral lipid-lowering therapies were permitted during the 78 weeks of the study; doses were fixed from at least six weeks before baseline through the efficacy phase but modifiable during the safety phase. Similarly, apheresis treatments — plasma exchange or LDL apheresis — were permitted throughout the duration of the study; treatment frequency was fixed from at least six weeks before baseline through the efficacy phase but modifiable during the safety phase. Because of the fat malabsorption induced by lomitapide's mechanism of action, all patients were also prescribed a low-fat diet (total fat < 20% of daily energy), vitamin E, and a fatty acid supplement.

FIGURE 2: SCHEMATIC OF STUDY DESIGN



Source: UP1002/AEGR-733-005 Clinical Study Report.[15]

3.2.2 Populations

a) Inclusion and Exclusion Criteria

UP1002/AEGR-733-005 enrolled patients ≥ 18 years of age with a diagnosis of HoFH based on documented functional mutations affecting the LDL receptor pathway, markedly reduced LDL receptor activity (< 20% of normal), or an untreated total cholesterol > 13.0 mmol/L in combination with documented hypercholesterolemia (untreated total cholesterol greater than 6.5 mmol/L) in both parents. In addition, eligible patients had to be on stable concomitant lipid-lowering therapy (including apheresis) as of at least six weeks before baseline through the 26-week efficacy phase. Patients were excluded if there was any history of liver disease or abnormal liver function tests at screening, chronic renal insufficiency, significant gastrointestinal disease or malabsorption, pulmonary disease, heart failure, non-skin malignancy, or excess alcohol consumption.

b) Baseline Characteristics

Of the 29 patients studied, 5 (17.2%) were recruited from Canadian sites. Overall, patients enrolled in the study were young adults with a mean age of 30.7 years and a pre-obese or overweight body mass index of 25.8 kg/m^2. Males (55.2%) slightly outnumbered females, and the majority of patients were Caucasian (86.2%). Mean total cholesterol at baseline was 11.1 mmol/L while mean LDL-C was 8.7 mmol/L. The clinical expert consulted by CDR indicated that the baseline aggregate lipid profile was consistent with the lipid profile of patients with FH. Also expected in this high-risk population was the high prevalence (93.1%) of comorbid cardiovascular disease reported at baseline. Accordingly, statin (93.1%) and ezetimibe (75.9%) therapy were commonly prescribed lipid-lowering therapies, while apheresis treatments were used in 62.1% of patients. Among patients receiving apheresis at baseline, 55.6% reported receiving LDL apheresis. No information was provided on smoking status. While no aggregate data were provided on diabetes status, a review of the individual patient narrative summaries revealed one documented case of comorbid type 2 diabetes (Table 5).

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

Characteristic	UP1002/AEGR-733-005 (n = 29)	
Age (years)		
Mean (SD)	30.7 (10.6)	
Median (range)	30.0 (18.0, 55.0)	
Sex, n (%)		
Female	13 (44.8)	
Race, n (%)		
Caucasian	25 (86.2)	
Asian	2 (6.9)	
African-American	1 (3.4)	
Other	1 (3.4)	
Region, n (%)		
Canada	5 (17.2)	
Italy	6 (20.7)	
South Africa	11 (37.9)	
United States	7 (24.1)	
Skin fibroblast LDLR activity		
< 20% of normal	7 (24.1)	
Weight (kg)		
Mean (SD)	73.5 (18.1)	
Body mass index (kg/m^2)		
Mean (SD)	25.8 (5.4)	
Lipoprotein	**Conventional units (mg/dL)**	**SI units[a]**
TC	429.7 (135.1)	11.1 (3.5) mmol/L
LDL-C	336.4 (113.5)	8.7 (2.9) mmol/L
HDL-C	43.9 (10.7)	1.1 (0.3) mmol/L
TG	103.2 (48.0)	1.2 (0.5) mmol/L
Non-HDL-C	385.8 (131.6)	10.0 (3.4) mmol/L
VLDL-C	20.6 (9.6)	0.5 (0.2) mmol/L
TC/HDL-C[b]	9.8 (12.6)	
Apo B	259.4 (79.7)	2.6 (0.8) g/L
Apo A1	114.7 (27.7)	1.1 (0.3) g/L
Lp(a)[c]	77.9 (64.4)	2.8 (2.3) µmol/L
Relevant medical history		
History of cardiovascular disease, n (%):	27 (93.1)	
Coronary artery bypass	10 (34.5)	
Angina pectoris	8 (27.6)	
Coronary artery disease	7 (24.1)	
Aortic valve replacement	3 (10.3)	
Supraventricular aortic stenosis	3 (10.3)	
Aortic stenosis	2 (6.9)	
Diabetes, n (%)	1 (3.4)[d]	
Hypertension, n (%)	6 (20.7)	

Characteristic	UP1002/AEGR-733-005 (n = 29)
Smoking, n (%)	Not reported
Concomitant lipid-lowering drug therapies	
Statin, n (%):	27 (93.1)
Rosuvastatin	13 (44.8)
Atorvastatin	9 (31.0)
Simvastatin	5 (17.2)
Ezetimibe, n (%)	22 (75.9)
Niacin, n (%)	3 (10.3)
Bile acid sequestrant, n (%)	1 (3.4)
Fibrate, n (%)	1 (3.4)
Concomitant apheresis	
Receiving apheresis at baseline, n (%)	18 (62.1)
Type of apheresis, n (%):	
LDL apheresis	10 (55.6)
Plasmapheresis	6 (33.3)
Type not reported	2 (11.1)

ACVD = atherosclerotic cardiovascular disease; Apo = apolipoprotein A1; HDL-C = high-density lipoprotein cholesterol; HoFH = homozygous hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; LDLR = LDL receptor; Lp(a) = lipoprotein (a); SD = standard deviation; SI = international system of units; TC = total cholesterol; TG = triglycerides; VLDL-C = very-low-density lipoprotein cholesterol.

[a] Conversion factors for SI units: Multiply by 0.0259 for cholesterol, 0.0113 for triglycerides, 0.01 for apo B and apo A1, and 0.0357 for Lp(a).[14]

[b] Calculated by the CADTH Common Drug Review.

[c] Lp(a) reported in nmol/L (conventional units).

[d] Diabetes not reported in aggregate; data derived from individual patient narrative summaries.

Source: UP1002/AEGR-733-005 Clinical Study Report.[15]

3.2.3 Interventions

All patients received lomitapide according to a forced-dose titration schedule with stopping rules in case of signs of hepatoxicity. The dosage was initiated at 5 mg daily for two weeks and then increased to 10 mg daily for four weeks, followed by 20 mg, 40 mg, and 60 mg daily at four-week intervals unless stopping rules applied. Rarely, patients who met additional safety and efficacy criteria could have had their dose increased to 80 mg daily. (Note that the maximum recommended dose approved by Health Canada was 60 mg daily.) Background lipid-lowering therapies, which included various combinations of oral medications and apheresis, were continued during the study, but the dosing was fixed during the 26-week efficacy phase. During the ensuing safety phase (weeks 26 to 78), the maximally tolerated dose of lomitapide was maintained throughout the 52-week observation period unless a dose reduction was indicated for safety or tolerability reasons; no further dose escalations were permitted. In the event of a dose reduction, however, rechallenge was permitted, but not beyond the maximally tolerated dose established during the efficacy phase. Background therapies, by comparison, were able to be modified during the safety phase at the discretion of the investigator.

3.2.4 Outcomes

The primary efficacy outcome in UP1002/AEGR-733-005 was the per cent change from baseline in LDL-C levels at 26 weeks. Secondary efficacy outcomes included the mean per cent change from baseline to week 26 in total cholesterol, apo B, triglycerides, non-HDL-C, VLDL-C, and lipoprotein (a). Changes in HDL-C, apo A1, and high-sensitivity c-reactive protein were examined only in an exploratory (tertiary)

manner. Harms outcomes included changes in laboratory tests; hepatic fat; pulmonary function tests; and physical, electrocardiogram, and vital statistics findings. Table 6 presents a comparison of the outcomes studied in UP1002/AEGR-733-005 with those identified in the review protocol.

TABLE 6: EFFICACY AND SAFETY OUTCOMES IN UP1002/AEGR-733-005 VERSUS CDR SYSTEMATIC REVIEW PROTOCOL

UP1002/AEGR-733-005[15]	CDR Systematic Review Protocol
Efficacy	
Primary: • LDL-C: per cent change from baseline after 26 weeks	**Key:** • Mortality • Morbidity (i.e., CV events, hospitalizations, and minimally invasive CV interventions)

Secondary:
• Per cent change in lipid parameters from baseline after 26 weeks:
  • TC
  • apo B
  • TGs
  • non-HDL-C
  • VLDL-C
  • Lp(a)
	• Lipoprotein profile (i.e., LDL-C, non-HDL-C)
	• Frequency of LDL apheresis or plasma exchange
	• Quality of life

Exploratory: • HDL-C • apo A1 • hsCRP	
Safety	

• AEs
• Changes in:
  • laboratory tests
  • hepatic fat, liver biopsy results
  • PFTs
  • PE and ECG findings, vital signs
	• AEs
	• SAEs
	• WDAEs
	• Notable harms: markers of hepatotoxicity

AE = adverse event; apo = apolipoprotein A1; CDR = CADTH Common Drug Review; CV = cardiovascular; ECG = electrocardiogram; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity c-reactive protein; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); PE = physical exam; PFT = pulmonary function test; SAE = serious adverse event; TC = total cholesterol; TG = triglyceride; WDAE = withdrawal due to adverse event; VLDL-C = very-low-density lipoprotein cholesterol.

3.2.5 Statistical Analysis

The sample size was determined based on observing a 25% change in the primary efficacy end point (LDL-C) after 26 weeks, assuming a standard deviation (SD) of 30% and a dropout of 15%. With 90% power at a two-sided significance level of 5%, it was determined that 20 patients would be needed; for assessments of safety, up to five additional patients would be needed.

Descriptive statistics were used to summarize the data. The mean, SD, median, minimum, and maximum were presented for continuous variables, while discrete variables summarized data using frequency and percentage. All statistical tests were conducted at an overall significance level of 0.05.

a) Efficacy Phase: Week 0 to 26

Primary Efficacy Outcome

Testing of the null hypothesis of no change in the primary efficacy outcome — per cent change in LDL-C from baseline to week 26 — was performed using a paired t-test (or Wilcoxon signed rank test for non-normal data). Testing was also carried out for each visit. There was no adjustment for multiple comparisons. Last observation carried forward (LOCF) was employed for patients who discontinued before week 26. A sensitivity analysis using a baseline minus area-under-the-curve approach was conducted to test the robustness of the results obtained by the LOCF method. Responder analyses examined the proportion of patients who experienced 15% and 25% reductions in LDL-C from baseline to week 26 or LOCF. A clinical benefit analysis was also performed, which examined patients who achieved ≥ 15% reduction in LDL-C from baseline and who did not experience clinical worsening in liver function tests that led to treatment discontinuation.

Secondary Efficacy Outcomes

The same analytical methods as were employed for the primary efficacy outcome were used for secondary outcomes — total cholesterol, apo B, triglycerides, non-HDL-C, VLDL-C, and lipoprotein (a). Key secondary outcomes — total cholesterol, apo B, and triglycerides — were specifically tested sequentially in the order presented, each at an overall significance level of 0.05. Statistical significance could be declared only if the prior outcome was statistically significant. The remaining three secondary outcomes — non-HDL-C, VLDL-C, and lipoprotein (a) — were subsequently tested separately, in a similar sequential manner. Exploratory outcomes (HDL-C and apo A1) were analyzed similarly to the primary efficacy outcome, and high-sensitivity c-reactive protein was analyzed using Wilcoxon signed rank test.

Subgroup Analyses

Pre-specified subgroup analyses were conducted on the mean per cent change and mean absolute change in LDL-C to examine possible treatment by subgroup interactions; these subgroups included maximum tolerated dose (efficacy phase), use of apheresis (efficacy phase), study drug dose adjustment (i.e., reduction, no reduction) after week 26 (safety phase), and changes in background lipid-lowering therapy after week 26 (safety phase).

Safety Analyses

Safety parameter data were collected during both the efficacy and safety phases of the study. The manufacturer conducted safety analyses on the incidence, severity grade, and relationship to study drug of all treatment-emergent adverse events reported during the trial. Changes from baseline in clinical laboratory results, vital signs, electrocardiogram findings, hepatic fat, pulmonary function tests, and gastrointestinal symptoms were also included among the safety reporting.

b) Analysis Populations

The primary analysis set for performing efficacy analyses in UP1002/AEGR-733-005 was the intention-to-treat (ITT) set, defined by the manufacturer as all patients who entered the efficacy phase, received at least one dose of treatment, and had a baseline and post-baseline LDL-C value. It should be noted that a true ITT set would consist of all patients who entered the efficacy phase regardless of treatment received or data contributed; thus, the ITT set in UP1002/AEGR-733-005 must be viewed as a modified ITT set. The safety analysis set was defined as all patients who received at least one dose of treatment.

3.3 Patient Disposition

In UP1002/AEGR-733-005, a total of 32 patients were screened and 31 deemed eligible for the run-in. Twenty-nine patients completed the run-in and entered the 26-week efficacy phase; two patients discontinued from the run-in phase having withdrawn consent. Of the 29 patients, 23 (79.3%) completed the efficacy phase; of the six patients who discontinued, three (10.3%) withdrew consent, two (6.9%) experienced an adverse event, and one (3.4%) was described as non-compliant or lacking in cooperation. Of the 23 patients who entered the 52-week safety phase, all 23 completed to week 78. Follow-up data are therefore complete for 79.3% of patients (Table 7).

TABLE 7: PATIENT DISPOSITION

	UP 1002/AEGR-733-005
Screened, N	32
Entered run-in phase, N (%)	31 (96.9)
Discontinued run-in phase, N (%)	2 (6.5)
Entered 26-week efficacy phase, N	29
Discontinued efficacy phase, N (%)	6 (20.7)
Withdrew consent	3 (10.3)[a]
Adverse event	2 (6.9)
Non-compliance or lack of cooperation	1 (3.4)
Entered 52-week safety phase, N	23
Discontinued safety phase, N (%)	0
ITT, N	29 (100.0)
Safety, N	29 (100.0)

ITT = intention-to-treat analysis set.
[a] Two of the three patients who withdrew consent as the reason for premature discontinuation from the study also experienced adverse events that led to treatment discontinuation.
Source: UP1002/AEGR-733-005 Clinical Study Report.[15]

3.4 Exposure to Study Treatments

3.4.1 Lomitapide

The mean exposure to lomitapide during the efficacy phase was 159.6 (SD 50.9) days, which corresponded to an average daily dose of 25.7 (SD 11.9) mg daily. The maximum tolerated dose of lomitapide during the efficacy phase was less than 60 mg daily for two-thirds of patients, with 10%, 7%, 21%, and 24% tolerating a maximum of 5 mg, 10 mg, 20 mg, and 40 mg daily, respectively. The highest mean dose achieved during the efficacy phase was 44.6 mg at week 26 and 40.9 mg at week 46 during the safety phase (Figure 5). Dose reductions or interruptions were recorded for eight (27.6%) patients during the efficacy phase beginning at the 20 mg dosing threshold (one patient [3.4%]). The highest frequency (four patients [13.8%]) of dose reductions or interruptions occurred at the 60 mg dose. During the safety phase, in which patients completing the efficacy phase entered on their maximum tolerated dose of lomitapide, dose reductions or interruptions were recorded in 8 (34.8%) of 23 patients. As in the efficacy phase, these dose reductions or interruptions began at the 20 mg dosing threshold (one patient [4.3%]) and were most frequent (four patients [17.4%]) at the 60 mg dose. Mean treatment compliance with lomitapide was reported as > 90% during both the efficacy (93%) and safety (95%) phases.

3.4.2 Concomitant Lipid-Lowering Therapies

a) Statin Co-therapy

A total of 27 (93.1%) patients reported taking statin therapy at baseline, namely rosuvastatin (44.8%), atorvastatin (31.0%), or simvastatin (17.2%). During the efficacy phase, statin doses (unspecified by drug) ranged from 10.0 mg (1 patient [3.7%]) to 160.0 mg (1 patient [3.7%]), with most taking 40.0 mg (15 patients [55.6%]) or 80.0 mg (8 patients [29.6%]) daily. During the efficacy phase, modification (i.e., dose reduction, interruption, discontinuation, or rechallenge) of statin dose occurred in four (14.8%) patients; these were considered protocol deviations and often occurred in association with adverse events. No patients changed statin type during the study.

b) Apheresis Co-therapy

Of the 18 patients who received apheresis during the efficacy phase, 11 (61.1%) either missed an apheresis treatment or modified (i.e., prolonged or shortened) the time between treatment sessions by at least two days. At baseline, the median number of apheresis treatments received was 1.0 per four-week period. During the efficacy phase, it was 1.0 per two-week period at week 2, and 2.0 per four-week period from weeks 6 through 26. During the safety phase, the median number of apheresis treatments was 5.0 per 10-week period at week 36, 4.0 per 10-week period from weeks 46 through 66, and 5.0 per 12-week period at week 78 (Figure 4).

3.5 Critical Appraisal

3.5.1 Internal Validity

The assessment of the comparative efficacy of lomitapide was complicated by the non-comparative study design.

Twenty-nine patients entered the 26-week efficacy phase after completing the run-in. Of these 29 patients, six (20.7%) prematurely discontinued from the efficacy phase: three patients withdrew consent, two experienced an adverse event, and one was described as non-compliant or uncooperative. Sample size determination was based on a projected loss of 15% compared with the > 20% loss experienced during the study. Although statistical significance was still achieved on the primary efficacy outcome, there is some concern about tolerability since these premature discontinuations were related to adverse events. Patients may have qualified for enrolment into the study by having an untreated total cholesterol > 13.0 mmol/L and triglycerides less than 7.8 mmol/. There was no “on-treatment” LDL-C eligibility criterion, which is somewhat surprising given that most if not all patients would be expected to be receiving lipid-lowering treatment before study enrolment. Hence, it is unclear to what extent background lipid-lowering treatments (including apheresis) may have been modified (e.g., existing therapies stopped or doses changed, new therapies started) before study entry. For example, the clinical study report indicates that apheresis treatment schedules were determined during the run-in phase.

Although the duration of the study was long enough to observe a change in lipoproteins from baseline, it was too short to observe any hard clinical end points such as development of cardiovascular complications. Such outcomes were considered important to patients submitting input for this drug review (see Appendix 1: Patient Input Summary).

3.5.2 External Validity

As described in the second paragraph under Internal Validity, investigators were permitted to reduce, at their discretion, background lipid-lowering therapy in patients who achieved LDL-C < 100 mg/dL (2.6 mmol/L). Since no further dose escalations in lomitapide dosing were permitted during the safety phase, reducing background therapy would be expected to allow LDL-C to rise. As such, the clinical

expert consulted by CDR confirmed that in the absence of mitigating tolerability or safety issues, this de-escalation of background therapy was not reflective of clinical practice. Clinicians consider these patients to be at very high risk for cardiovascular complications and death, and so the clinical management of these patients tends to be aggressive.

The relative LDL-C-lowering potency of statin therapy varies by drug within the statin class: Rosuvastatin is about twice as potent as atorvastatin, which is about twice as potent as simvastatin.[39] Guidelines recommend using maximally potent statin dosing in adult patients with FH, which corresponds to atorvastatin 80 mg daily or rosuvastatin 40 mg daily; simvastatin is not recommended.[1] At baseline, background statin therapy was reported in 27 (93.1%) patients and was maximally potent in 19 of 27 (70.4%) patients: 11 of 13 (84.6%) rosuvastatin users, 8 of 9 (88.9%) atorvastatin users, and 0 of 5 (0%) simvastatin users. It is unclear how statin dosing changed during the course of the study, as dosing, though reported, was not specified by drug. If background statin therapy was not optimized before the efficacy phase, then the observed lipid-lowering efficacy of lomitapide may have been greater than what it would have been in the setting of optimized background statin therapy.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol (Section 2.2, Table 3) are reported in this section. See Appendix 4: Detailed Outcome Data for detailed efficacy data.

3.6.1 Mortality

No deaths were reported during the study. Mortality was not studied as an efficacy outcome.

3.6.2 Morbidity

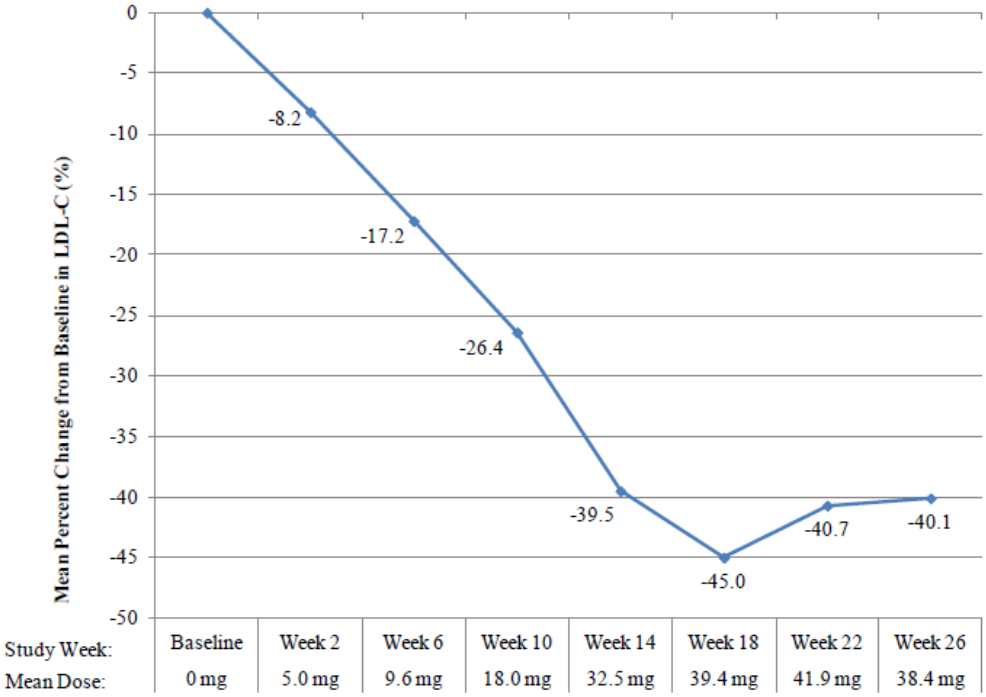
Morbidity (related to cardiovascular events) was not studied in UP1002/AEGR-733-005.

3.6.3 Lipoprotein Profile

After 26 weeks, a statistically significant reduction in LDL-C was observed from baseline (–40.1%; 95% confidence interval [CI], –51.9% to –28.2%) (Table 8). Statistically significant incremental reductions in LDL-C were observed at each visit, reached a nadir of –45.0% at week 18, and then began to drift slightly upward to –40.7% at week 22 (Table 11) (Figure 3).

After 26 weeks, a statistically significant reduction in non-HDL-C was observed from baseline (–40.0%; 95% CI, –51.3% to –28.8%) (Table 8: Key Efficacy Outcomes). As with LDL-C, statistically significant incremental reductions in non-HDL-C were noted at each visit (except week 2), reached a nadir of –52.7% at week 18, and then began to drift slightly upward to –46.7% at week 22 (Table 13). Changes in other lipoprotein parameters are presented for completeness in Table 12.

FIGURE 3: MEAN PER CENT CHANGE FROM BASELINE IN LDL-C LEVELS BY VISIT DURING THE 26-WEEK EFFICACY PHASE (LOCF, ITT)



ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; LOCF = last observation carried forward.
Source: UP1002/AEGR-733-005 Clinical Study Report.[15]

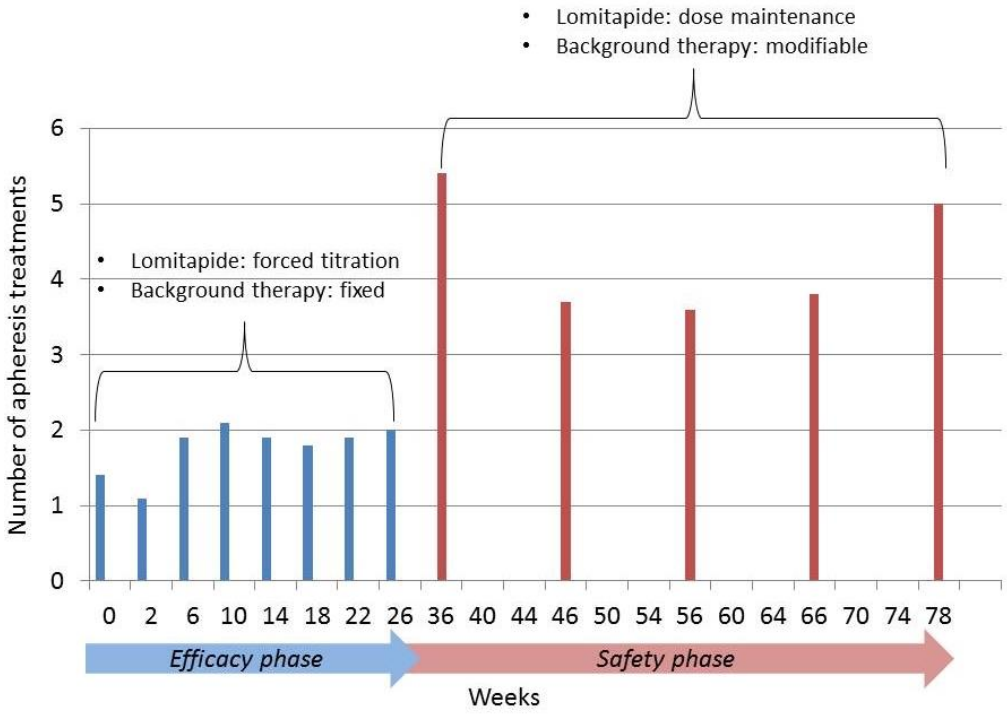
a) Subgroup Analysis by Apheresis Treatment Status

The manufacturer conducted several pre-specified subgroup analyses of the primary outcome; however, only one coincided with the subgroups of interest identified in the CDR systematic review protocol: apheresis co-treatment (yes/no). No statistically significant differences were noted in the per cent reduction of LDL-C observed regardless of apheresis treatment status (Table 14).

3.6.4 Apheresis

Frequency of apheresis treatment was identified as a key efficacy outcome in the CDR systematic review protocol, but was not modifiable by design during the 26-week efficacy phase of the study; thus, few insights can be drawn from these data. At baseline, apheresis treatment was reported in 18 patients, which corresponded to a mean of 1.4 treatments per four-week period; however, at week 26, apheresis treatment was only reported for 13 patients, corresponding to a mean of 2.0 treatments per four-week period (Table 8). Thirteen patients receiving apheresis treatments entered the safety phase. During the safety phase — when background lipid-lowering therapies, including apheresis, could be modified at the investigator's discretion — the mean number of apheresis treatments was 5.4 per 10-week period at week 36 and 5.0 per 12-week period at week 78 (Figure 4). Of the 13 patients who entered the safety phase, who were also receiving apheresis, 3 (23.1%) were able to completely stop apheresis treatment and 3 (23.1%) were able to lengthen the interval between apheresis treatments through week 78.

FIGURE 4: MEAN NUMBER OF APHERESIS TREATMENTS RECEIVED BY VISIT (SAFETY SET)



Source: UP1002/AEGR-733-005 Clinical Study Report.[15]

3.6.5 Quality of Life

Quality of life was not studied as an efficacy outcome in UP1002/AEGR-733-005.

TABLE 8: KEY EFFICACY OUTCOMES[a]

Observed LDL-C	Efficacy Phase Weeks 0 to 26
N (%)	29 (100)
Baseline (mg/dL)	336.4 (113.5)
Week 26 (mg/dL)	189.6 (104.2)
Absolute change: baseline to week 26	–146.9 (127.1)
Per cent change (%)	–40.1 (31.3)
95% CI (%)	–51.9 to –28.2
P value	< 0.001
Observed non-HDL-C	
N (%)	29 (100)
Baseline (mg/dL)	385.8 (131.6)
Week 26 (mg/dL)	217.1 (112.7)
Absolute change: baseline to week 26	–168.7 (141.4)
Per cent change (%)	–40.0 (29.7)
95% CI (%)	–51.3 to –28.8
P value	< 0.001

Observed LDL-C		Efficacy Phase Weeks 0 to 26
Apheresis[b]		
Baseline	Patients, n (%)	18 (100)
	Number of treatments	1.4 (0.9)
Week 26	Patients, n (%)	13 (72.2)
	Number of treatments	2.0 (0.9)
Week 78[c]	Patients, n (%)	11 (61.1)
	Number of treatments	5.0 (2.3)

CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.
[a] Intention-to-treat set was used for lipoprotein analyses; safety set was used for apheresis analyses.
[b] A total of 18 (62.1%) patients were receiving apheresis at baseline.
[c] Safety phase: weeks 26 to 52.
Source: UP1002/AEGR-733-005 Clinical Study Report.[15]

3.7 Harms

Only those harms identified in the review protocol (Section 2.2, Table 3) are reported in this section. See Appendix 4: Detailed Outcome Data for detailed harms data.

3.7.1 Adverse Events

The overall frequency of adverse events was comparable during the 26-week efficacy phase and 52-week safety phase (93.1% versus 91.3%). Diarrhea, nausea, and vomiting were the most commonly occurring adverse events for both phases, though the frequencies were higher during the efficacy phase (79.3%, 62.1%, and 27.6%) than during the safety phase (34.8%, 30.4%, and 21.7%). Dyspepsia, constipation, nasopharyngitis, and chest pain were also frequently encountered in both phases, but also more prevalent during the efficacy phase (24.1%, 20.7%, 17.2%, and 13.8%) than during the safety phase (17.4%, 13.0%, 13.0%, and 13.0%). (Table 9).

3.7.2 Serious Adverse Events

Serious adverse events (SAEs) occurred in three (10.3%) patients during the efficacy phase while no SAEs were reported during the safety phase. During the efficacy phase, one patient experienced three SAEs (i.e., acute coronary syndrome, angina pectoris, and lower respiratory tract infection). Arteriosclerosis and menorrhagia were reported separately in two other patients (Table 9).

3.7.3 Withdrawal Due to Adverse Events

Withdrawal due to adverse events (WDAEs) were reported in four (13.8%) patients during the efficacy phase. Separate reports of headache, diarrhea, and gastroenteritis led to the withdrawal of three patients, and one patient experienced three adverse events, namely, abdominal pain, diarrhea, and nausea. All of these WDAEs occurred during the efficacy phase; no WDAEs were reported during the safety phase (Table 9).

3.7.4 Notable Harms

Markers of hepatotoxicity were identified as harms of interest and are presented in Table 15. During the efficacy phase, alanine aminotransferase (ALT) increased from a mean of 30.2 (SD 23.8) U/L at baseline to 49.5 (SD 36.7) U/L at week 26, corresponding to an observed change of 19.3 (SD 31.5) U/L. The observed increase in ALT (mean 15.0 [SD 29.1] U/L) was similar when examined over 78 weeks during the safety phase. By comparison, aspartate aminotransferase (AST) rose only slightly by 6.8 (SD 17.8) U/L and 8.9 (SD 20.2) U/L after 26 weeks and 78 weeks, respectively, while alkaline phosphatase

decreased during both periods. Total bilirubin remained virtually unchanged throughout the study. Hepatic fat, however, increased by 7.3% and 6.9% after 26 weeks and 78 weeks, respectively.

During the 78 weeks of the study, 10 (34.5%) patients experienced elevations in ALT from baseline that exceeded three times ULN. Of these 10 patients, 6 (20.7%) also experienced concurrent elevations in AST from baseline that exceeded three times ULN. For 9 (90%) of these 10 patients, the increase in ALT above three times ULN was initially detected during the efficacy phase, and persisted into the safety phase for 3 (30.0%) patients; for 1 of the 10 patients, the elevated ALT was noted during the safety phase. Elevations in ALT in excess of five times ULN were noted in four (13.8%) patients during the efficacy phase only; of these four patients, one (3.4%) experienced a transient elevation in ALT ≥ 10 × ULN. There did not appear to be a clear relationship between transaminase elevations and lomitapide dose, as elevations were seen at both the low (10 mg) and high (60 mg) end of the dosing spectrum. No post-baseline liver biopsies were performed as a result of concerns of liver toxicity. No patient was discontinued from the study because of worsening liver function tests.

TABLE 9: HARMS

	UP1002/AEGR-733-005	
AEs	**Efficacy Phase Weeks 0 to 26 (n = 29)**	**Safety Phase Weeks 26 to 78 (n = 23)**
Patients with ≥ 1 AEs, N (%)	27 (93.1)	21 (91.3)
Most common AEs (≥ 10%):		
Diarrhea	23 (79.3)	8 (34.8)
Nausea	18 (62.1)	7 (30.4)
Vomiting	8 (27.6)	5 (21.7)
Abdominal pain	8 (27.6)	1 (4.3)
Dyspepsia	7 (24.1)	4 (17.4)
Constipation	6 (20.7)	3 (13.0)
Abdominal distension	6 (20.7)	2 (8.7)
Flatulence	6 (20.7)	2 (8.7)
Abdominal discomfort	6 (20.7)	0
Weight decreased	6 (20.7)	1 (4.3)
Abdominal pain upper	5 (17.2)	2 (8.7)
ALT increased	5 (17.2)	1 (4.3)
Nasopharyngitis	5 (17.2)	3 (13.0)
Chest pain	4 (13.8)	3 (13.0)
Gastroenteritis	4 (13.8)	0
Angina pectoris	3 (10.3)	0
Defecation urgency	3 (10.3)	0
Dizziness	3 (10.3)	2 (8.7)
Gastroesophageal reflux disease	3 (10.3)	0
Nasal congestion	3 (10.3)	0
Pharyngolaryngeal pain	3 (10.3)	1 (4.3)
Rectal tenesmus	3 (10.3)	1 (4.3)
Fatigue	2 (6.9)	3 (13.0)
Influenza	2 (6.9)	4 (17.4)

	UP1002/AEGR-733-005	
AEs	**Efficacy Phase Weeks 0 to 26 (n = 29)**	**Safety Phase Weeks 26 to 78 (n = 23)**
SAEs		
Patients with ≥ 1 SAEs, N (%)	3 (10.3)	0
Any SAEs:		
Acute coronary syndrome[a]	1	0
Angina pectoris[a]	1	0
Arteriosclerosis	1	0
Lower respiratory tract infection[a]	1	0
Menorrhagia	1	0
WDAEs		
WDAEs, N (%)	4 (13.8)	0
Diarrhea[b]	2	0
Abdominal pain[b]	1	0
Gastroenteritis	1	0
Headache	1	0
Nausea[b]	1	0
Deaths		
Number of deaths, N (%)	0	0
Notable harms		
Change from baseline to week 26, 78 Mean (SD)	**Observed change weeks 0 to 26**	**Observed change weeks 26 to 78**
ALT (U/L)	19.3 (31.5)	15.0 (29.1)
AST (U/L)	6.8 (17.8)	8.9 (20.2)
Alkaline phosphatase (U/L)	–6.6 (31.0)	–15.8 (24.3)
Total bilirubin (mg/dL)	0.0 (0.4)	0.1 (0.3)
Hepatic fat (%) (NMRS)	7.3 (6.8)	6.9 (5.0)

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; NMRS = nuclear magnetic resonance spectroscopy; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] One patient experienced three SAEs.
[b] One patient experienced three WDAEs.
Source: UP1002/AEGR-733-005 Clinical Study Report.[15]

4. DISCUSSION

4.1 Summary of Available Evidence

The evidence for this review was drawn from one phase III (UP1002/AEGR-733-005) multinational, open-label, single-arm, uncontrolled study, which included 29 patients aged ≥ 18 years with a diagnosis of HoFH. The study was divided into two phases: a 26-week efficacy phase, during which the maximally tolerated dose of study drug was established through a forced-dose titration protocol, and a 52-week safety phase, during which the maximally tolerated dose established from the efficacy phase was continued at the same dose until week 78. All patients received lomitapide in combination with background lipid-lowering therapy.

4.2 Interpretation of Results

4.2.1 Efficacy

The primary efficacy outcome in UP1002/AEGR-733-005 was the per cent change from baseline in LDL-C levels at 26 weeks. By comparison, the CDR systematic review protocol considered mortality and morbidity (i.e., cardiovascular events, hospitalizations, and minimally invasive cardiovascular interventions) to be key efficacy outcomes, followed by lipoprotein profile (i.e., LDL-C, non-HDL-C), frequency of apheresis treatments, and quality of life. Mortality, morbidity, and quality of life were not studied in UP1002/AEGR-733-005. The duration of the study was insufficient to assess morbidity and mortality. It is not clear why quality of life was not studied, especially since this was a key outcome — along with preventing cardiovascular complications — identified by patients submitting input for this drug review.

A major limitation with this study was the uncertainty around the magnitude of the treatment effect. While a statistically significant reduction in LDL-C was observed after 26 weeks of lomitapide treatment (–40.1%; 95% CI, –51.9% to –28.2%), the lack of a comparator arm limits the interpretation of the magnitude of the treatment effect observed. The same limitation applies to any other outcomes studied, including non-HDL-C, which achieved a similarly statistically significant reduction after 26 weeks of treatment. In addition, it should be noted the approximate 40% reduction in LDL-C observed during the efficacy phase of the pivotal study (26 weeks) failed to achieve the threshold of a ≥ 50% reduction from baseline as recommended by North American guideline groups.[6,10] Similarly, at the end of the efficacy phase of the pivotal study (78 weeks), the mean LDL-C concentration was 4.9 mmol/L, which was substantially higher than the target concentration of less than 2.5 mmol/L that is recommended by European guidelines.[1]

In addition to changes in lipoproteins (i.e., LDL-C and non-HDL-C), changes in apheresis treatment frequency were of interest to the CDR systematic review protocol. However, any interpretation of the apheresis treatment frequency data available from the included study is severely limited by the study design, which did not permit apheresis treatments to vary during the 26-week efficacy phase. Furthermore, due to the small number of people receiving apheresis treatments in the study, it is difficult to draw any meaningful conclusions from these data. Despite a desire by patients to see a reduction in the frequency of their apheresis treatments (see Appendix 1: Patient Input Summary), according to the clinical expert consulted by CDR, it is unlikely that physicians would choose to withdraw apheresis from the treatment plan; rather, lomitapide would most likely be added to existing treatments, including apheresis. Moreover, some experts suggest that achieving VLDL-C levels through LDL apheresis may confer additional anti-inflammatory, rheological, or antioxidant benefits.[4]

In the patient input received for this submission (see Appendix 1: Patient Input Summary), patients described the physical and psychological tolls of living with HoFH. In addition to the physical and emotional challenges they face, patients underlined the disruption to their daily activities from having to attend hospital and clinic visits (e.g., for apheresis) or from having to undergo surgeries for cardiovascular complications. Patients receiving apheresis treatments described a reduced quality of life, citing significant fatigue experienced after a treatment session and how their life "revolves around the appointments." Current drug therapies were perceived to be inadequately protective against cardiovascular complications. Expectations about lomitapide treatment centered around a hope that the drug would reduce LDL-C levels enough to enable a reduction in the frequency of apheresis sessions. Quality of life and cardiovascular complications were not assessed as outcomes in the study despite being articulated as key outcomes by patients submitting input for this drug review. Data on apheresis treatment frequency were limited to descriptive summaries.

Upon completion of the UP1002/AEGR-733-005 (pivotal) study, 19 patients were invited to participate in AEGR-733-012, an open-label extension study (Appendix 5: Summary of Open-Label Extension Study (AEGR-733-012)). Statistically significant reductions for both LDL-C (–45.5%) and non-HDL-C (–47.1%) were observed in the 17 patients who completed week 126. These changes were similar in magnitude to the reductions observed at week 78 (–50.8% and –51.0%, respectively) of the pivotal study and were slightly larger than the reductions observed at week 26 (–40.1% and –40.0%, respectively) of the pivotal study. Since LDL-C and non-HDL-C levels during the efficacy phase of the pivotal study tended to drift upward before week 26, it is possible that the sustained, and even slightly greater, per cent reductions observed at week 78 and 126 were a consequence of modifying background lipid-lowering therapies, since lomitapide dosing was not modifiable outside of tolerability and safety concerns. Nonetheless, the reduction in LDL-C observed at the end of the 26-week efficacy phase appeared to be sustained through the 52-week safety phase and through an additional 48 weeks of follow-up during the open-label extension study among those with complete data. As noted above, the non-comparative study design precludes any definitive assessment of the true magnitude of the treatment effect, even though the reduction in LDL-C was sustained.

4.2.2 Harms

As would be expected, based on the mechanism of action of lomitapide, gastrointestinal adverse events were common, with diarrhea, nausea, and vomiting representing the most commonly reported adverse events for both phases; however, during the efficacy phase, diarrhea and nausea were reported at more than double the frequency of the safety phase (79.3% and 62.1% versus 34.8% and 30.4%) suggesting that patients who did not tolerate lomitapide well during the first 26 weeks of the study may not have completed the subsequent 52 weeks of the safety phase. Dyspepsia, constipation, nasopharyngitis, and chest pain were also prevalent. During the efficacy phase only, three patients (10.3%) experienced SAEs, which were cardiovascular, infectious, and gynecological in nature. Four patients (13.8%) withdrew from the study because of non-SAEs; these were mostly gastrointestinal in nature. As described in the Critical Appraisal, the > 20% dropout that occurred during the efficacy phase may signify tolerability issues with this drug and explain the lower prevalence of adverse events recorded during the safety phase. No deaths were reported during the 78 weeks of the study.

Markers of hepatotoxicity, including liver transaminases and hepatic fat, were examined separately as harms of interest. Elevations in ALT (19.3 U/L and 15.0 U/L) and hepatic fat (7.3% and 6.9%) were observed after 26 weeks and 78 weeks from baseline, and small subsets of patients experienced elevations in ALT of greater than or equal to three times ULN (n = 10) and greater than or equal to five times ULN (n = 4). However, no patient was discontinued from the study because of worsening liver

function tests. To this point, the safety profile of lomitapide observed in the open-label extension study appears similar to that observed in the pivotal study (UP1002/AEGR-733-005) in terms of tolerability and the types of adverse events being reported; no new safety signals have been identified from these data. That is not to say that there is a lack of concern about the potential long-term safety of the drug, in particular the risk of liver toxicity. In fact, this was a major source of concern highlighted by the US Food and Drug Administration.[13] There is currently clinical uncertainty regarding the meaningfulness of the hepatic fat accumulation observed during the pivotal study, which is a consequence of this drug's mechanism of action.[13] There was some concern expressed that patients with HoFH treated with lomitapide could be trading off early cardiovascular disease for downstream liver disease.[13] In its approval letter to the manufacturer, the Food and Drug Administration requested further post-marketing studies, which included an examination of the potential for liver toxicity from chronic exposure to lomitapide.[38]

Patient input for this submission (see Appendix 1: Patient Input Summary) did not elaborate upon the types of adverse events patients were willing to tolerate from lomitapide therapy, only that patients believed that adverse effects from lomitapide would not be any worse than those experienced from current therapy; however, evidence from this review suggests that this expectation may be unfounded.

5. CONCLUSIONS

In one multinational, open-label, single-arm, uncontrolled study (UP1002/AEGR-733-005), which included 29 adults with HoFH, lomitapide was associated with a 40% reduction from baseline in LDL-C after 26 weeks. However, the true efficacy of lomitapide is uncertain due to the absence of a comparator arm from the study. Furthermore, outcomes were limited to changes in lipoprotein concentrations, and mortality, morbidity (particularly cardiovascular events), and quality of life were not assessed. Lomitapide treatment was associated with gastrointestinal adverse events such as diarrhea, nausea, vomiting, dyspepsia, and constipation. Lomitapide is associated with elevations in transaminases and hepatic fat, but the clinical meaningfulness of these findings is currently unknown.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH Common Drug Review staff based on the input provided by patient groups. It has not been systematically reviewed.

1. Brief Description of Patient Group Supplying Input

One patient group representing people with familial hypercholesterolemia (FH) provided input.

The FH Canada Patient Network is a not-for-profit organization that was established in August 2014. The purpose of the network is to raise awareness of FH, to provide education and a venue for advocacy and support, and to promote screening, diagnosis, and improved access to treatment and care for patients with FH. The Consumer Advocare Network has provided organizational and administrative support to the network at no cost. The FH Canada Patient Network has received no funding from pharmaceutical manufacturers to date and declared no conflicts of interest in compiling their submission.

2. Condition and Current Therapy-Related Information

This information was collected through interviews and survey responses from patients in FH clinics, the Juxtapid patient assistance program, and patients with Juxtapid experience through the monitored access programs in the United States. Responses from six patients who used Juxtapid and from six who did not use it were included in this submission.

FH has a significant impact on a patient's day-to-day life. The condition has physical and psychological impacts including cardiovascular effects (atherosclerosis, stroke, atrial fibrillation, and heart attack), chest pain, fatty skin deposits, trouble walking in the winter (due to shortness of breath in cold temperatures), and a loss of sensation in the hands. Some patients have been living with the condition since infancy. Patients report having been in and out of hospitals and having undergone multiple surgeries, each of which is disruptive to attending school, work, or social activities. Patients are faced with physical symptoms and the psychological impact of living with a "ticking bomb." Additionally, due to its familial nature, patients and their families have already seen the devastating consequences of the disease and loss of loved ones. In the words of one patient, "Every year, the risk to my heart and my BP increases because there is no way to control my cholesterol levels. It feels like a time bomb in my body that can go off at any time."

While none of the respondents were caregivers, the patients noted the impact on their families of providing care.

Patients reported that they use multiple therapies to try to manage the condition, including low-fat diets, statins, other low-density lipoprotein cholesterol (LDL-C) reduction drugs, apheresis, and mipomersen (Kynamro). All patients were on low-fat diets and a statin. Although some patients noted that they were not as adherent as they should be to low-fat diets, about 50% thought it was "much" or "very much" effective in lowering cholesterol. No patients reported side effects associated with a low-fat diet. Only 12% of patients thought statins were effective, and 12% reported some or few side effects. A non-statin LDL-C reduction drug such as ezetimibe, niacin, cholestyramine, colestipol, or colesevelam was used by 75% of patients, with 88% of these patients indicating that it was either "a little effective" or "not at all effective" in lowering cholesterol. Reported side effects of the non-statin medications varied according to drug, with one-third of patients reporting side effects associated with niacin, 25% with ezetimibe and cholestyramine, and some or few adverse events with the others.

Seventy-five per cent of patients were on apheresis between once a week and once every three weeks. Eighty per cent of these patients believed that apheresis was effective in managing cholesterol, and 50% of patients indicated that it resulted in some to serious side effects. Apheresis resulted in a significant burden to patients, disrupting school, work, and social activities. Patients reported being very tired from the treatment, being reduced to a part-time instead of a full-time class schedule, and relying on family members to drive them to their appointments. One patient stated that their life "revolves around the appointments." Mipomersen (Kynamro) was used by one patient, but was reported as not effective.

Most patients reported that the currently available treatments are not reducing LDL levels enough to avoid cardiovascular complications. Some treatments improve cholesterol in the short term, but patients are not confident in their long-term effectiveness and therefore endure continued uncertainty about their health and potential future cardiovascular events.

3. Related Information About the Drug Being Reviewed

Patients who had no experience with the drug expected that it would lower cholesterol levels. Patients recognized that the drug might not reduce cholesterol levels completely, but expected that it would improve levels and would allow for fewer apheresis treatments. A reduction in the frequency of apheresis treatments would help reduce stress, improve quality of life, and increase the amount of time they had for work, school, family, and social activities.

Patients who had experience with lomitapide reported improved LDL levels, energy, and quality of life. They experienced mild side effects, but these side effects were reduced when a low-fat diet was maintained concurrently. The number of apheresis treatments required was reduced, and patients cited a beneficial short-term effect of the drug.

4. Additional Information

The patient group emphasized that LDL levels are not adequately controlled with the currently available treatments. Apheresis is a common treatment for patients, but even it does not maintain LDL levels sufficiently, and it is very disruptive to the patient and their family. A treatment that may reduce the number of required apheresis treatment sessions, even a fraction, would be very beneficial. Patients understood the potential side effects of the new drug but believed that the side effects could not be any worse than those experienced with existing therapies. Patients also understood that the drug might not work for everyone, but they thought that patients should be given the opportunity to try it and have it available for continued use if it was effective for them.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	November 17, 2014
Alerts:	Biweekly search updates until March 18, 2015
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings

MULTI-DATABASE STRATEGY	
#	**Searches**
1	(Juxtapid or lomitapide or AEGR 733 or AEGR733 or BMS 201038 or BMS201038 or X4S83CP54E or Lojuxta or 202914-84-9).ti,ot,ab,sh,hw,rn,nm. use pmez
2	*lomitapide/
3	(Juxtapid or lomitapide or AEGR 733 or AEGR733 or BMS 201038 or BMS201038 or X4S83CP54E or Lojuxta or 202914-84-9).ti,ab. use oemezd
4	1 or 2 or 3
5	4 not conference abstract.pt.
6	remove duplicates from 5

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	November 2014
Keywords:	Juxtapid (lomitapide)
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (Free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Cuchel M, Bloedon LT, Szapary PO, Kolansky DM, Wolfe ML, Sarkis A, et al. Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. N Engl J Med. 2007 Jan 11;356(2):148-56.[40]	Non-pivotal study
Abbreviated clinical study report: protocol AEGR-733-012. a phase III, long-term, open-label, follow on study of microsomal triglyceride transfer protein (MTP) inhibitor 'lomitapide' (AEGR-733) in patients with homozygous familial hypercholesterolemia [**CONFIDENTIAL** internal manufacturer's report]. Cambridge (MA): Aegerion Pharmaceuticals, Inc.; 2014 Mar 31.[41]	Extension study

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 10: DIAGNOSIS[a] OF FAMILIAL HYPERCHOLESTEROLEMIA: DUTCH LIPID CLINIC NETWORK CRITERIA[1]

Diagnostic Criteria	Points
Family history	
First-degree relative with either: • known premature[b] CHD *or* • LDL-C > 95th percentile by age and gender for country	1
First-degree relative with tendon xanthoma and/or corneal arcus *or* child(ren) < 18 years with LDL-C > 95th percentile by age and gender for country	2
Clinical history	
Presence of premature[a] CHD	2
Presence of premature[a] cerebral or peripheral vascular disease	1
Physical examination	
Tendon xanthoma	6
Corneal arcus if < 45 years of age	4
Biochemical results (LDL-C)	
• > 8.5 mmol/L (> 325 mg/dL)	8
• 6.5 mmol/L to 8.4 mmol/L (251 to 325 mg/dL)	5
• 5.0 mmol/L to 6.4 mmol/L (191 to 250 mg/dL)	3
• 4.0 mmol/L to 4.9 mmol/L (155 to 190 mg/dL)	1
Molecular genetic testing (DNA analysis)	
Causative mutation shown in the LDLR, apo B, or PCSK9 genes	8

apo = apolipoprotein; CHD = coronary heart disease; DNA = deoxyribonucleic acid; FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; LDLR = LDL low-density lipoprotein receptor; PCSK9 = proprotein convertase subtilisin/kexin type 9.
[a] Scoring: definite FH: > 8 points; probable FH: 6 to 8 points; possible FH: 3 to 5 points; unlikely FH: 0 to 2 points.
[b] Men: < 55 years; women: < 60 years.

TABLE 11: MEAN (SD) CHANGES IN LDL-C BY VISIT FROM BASELINE TO WEEK 26 (ITT, LOCF)

Time Point	N	Observed Value (mg/dL) (mmol/L)[a]	Observed Change (mg/dL) (mmol/L)[a]	*P* Value[b]	Per Cent Change (%)	*P* Value[c]
Baseline	29	336.4 (113.5) 8.7 (2.9)	NA	NA	NA	NA
Week 2	29	305.4 (124.0) 7.9 (3.2)	–31.0 (75.9) –0.8 (2.0)	0.036	–8.2 (20.5)	0.041
Week 6	29	277.8 (124.9) 7.2 (3.2)	–58.6 (85.8) –1.5 (2.2)	< 0.001	–17.2 (23.7)	< 0.001
Week 10	29	247.6 (130.6) 6.4 (3.4)	–88.9 (103.1) –2.3 (2.7)	< 0.001	–26.4 (27.4)	< 0.001
Week 14	29	204.8 (132.3) 5.3 (3.4)	–131.7 (122.0) –3.4 (3.2)	< 0.001	–39.5 (34.7)	< 0.001
Week 18	29	180.8 (118.6) 4.7 (3.1)	–155.7 (126.9) –4.0 (3.3)	< 0.001	–45.0 (35.4)	< 0.001

Time Point	N	Observed Value (mg/dL) (mmol/L)[a]	Observed Change (mg/dL) (mmol/L)[a]	*P* Value[b]	Per Cent Change (%)	*P* Value[c]
Week 22	29	193.9 (127.4)	–142.6 (135.3)	< 0.001	–40.7 (36.7)	< 0.001
		5.0 (3.3)	–3.7 (3.5)			
Week 26	29	189.6 (104.2)	–146.9 (127.1)	< 0.001	–40.1 (31.3)	< 0.001
		4.9 (2.7)	–3.8 (3.3)			

ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; LOCF = last observation carried forward; NA = not applicable.
[a] Conversion to SI units: × 0.0259.[14]
[b] *P* value on the mean observed change from baseline based on paired t-test.
[c] *P* value on the mean per cent change from baseline based on paired t-test.
Source: UP1002/AEGR-733-005 Clinical Study Report.[15]

TABLE 12: CHANGE IN LIPOPROTEINS FROM BASELINE TO WEEK 26 OR LOCF (ITT, N = 29)

End Point	Time Point	Observed Value (mg/dL) (mmol/L)[a,b]	Observed Change (mg/dL) (mmol/L)[a,b]	Per Cent Change (%)	*P* Value[c]
Primary Efficacy End Point					
LDL-C	Baseline	336.4 (113.5)	NA	NA	NA
		8.7 (2.9)			
	Week 26	189.6 (104.2)	–146.9 (127.1)	–40.1 (31.3)	< 0.001
		4.9 (2.7)	–3.8 (3.3)		
Secondary Efficacy End Points					
Total cholesterol	Baseline	429.7 (135.1)	NA	NA	NA
		11.1 (3.5)			
	Week 26	258.1 (117.6)	–171.7 (146.4)	–36.4 (28.2)	< 0.001
		6.7 (3.0)	–4.4 (3.8)		
Apo B	Baseline	259.4 (79.7)	NA	NA	NA
		2.6 (0.8)			
	Week 26	148.1 (74.0)	–111.3 (96.8)	–39.4 (30.0)	< 0.001
		1.5 (0.7)	–1.1 (1.0)		
Triglycerides	Baseline	103.2 (48.0)	NA	NA	NA
		1.2 (0.5)			
	Week 26	63.7 (45.5)	–39.5 (53.0)	–29.0 (55.7)	0.009
		0.7 (0.5)	–0.4 (0.6)		
Non-HDL-C	Baseline	385.8 (131.6)	NA	NA	NA
		10.0 (3.4)			
	Week 26	217.1 (112.7)	–168.7 (141.4)	–40.0 (29.7)	< 0.001
		5.6 (2.9)	–4.4 (3.7)		
VLDL-C	Baseline	20.6 (9.6)	NA	NA	NA
		0.5 (0.2)			
	Week 26	12.7 (9.1)	–7.9 (10.6)	–28.6 (57.5)	0.012
		0.3 (0.2)	–0.2 (0.3)		
Lp(a)[b]	Baseline	77.9 (64.4)	NA	NA	NA
		0.08 (0.06)			
	Week 26	62.0 (41.4)	–15.9 (36.1)	–11.0 (34.0)	0.094
		0.06 (0.04)	–0.02 (0.04)		

End Point	Time Point	Observed Value (mg/dL) (mmol/L)[a,b]	Observed Change (mg/dL) (mmol/L)[a,b]	Per Cent Change (%)	*P* Value[c]
Tertiary (Exploratory) End Points					
HDL-C	Baseline	43.9 (10.7)	NA	NA	NA
		1.1 (0.3)			
	Week 26	41.0 (13.4)	–2.9 (8.7)	–6.9 (19.8)	0.072
		1.1 (0.3)	–0.08 (0.2)		
Apo A1	Baseline	114.7 (27.7)	NA	NA	NA
		1.1 (0.3)			
	Week 26	105.3 (22.5)	–9.4 (20.4)	–6.5 (16.1)	0.038
		1.1 (0.2)	–0.09 (0.2)		

Apo = apolipoprotein; HDL-C = high-density lipoprotein cholesterol; ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; LOCF = last observation carried forward; Lp(a) = lipoprotein (a); NA = not applicable; VLDL-C = very-low-density lipoprotein cholesterol.
[a] Conversion to SI units: for cholesterol, multiply by 0.0259; for triglycerides, multiply by 0.0113; for apolipoproteins, multiply by 0.01.[14]
[b] Lp(a) reported in nmol/L and converted to µmol/L (x 10^{-3}).[14]
[c] *P* value on the mean per cent change from baseline based on paired t-test.
Source: UP1002/AEGR-733-005 Clinical Study Report.[15]

TABLE 13: MEAN (SD) CHANGES IN NON-HDL-C BY VISIT FROM BASELINE TO WEEK 26 (ITT)

Time Point	N	Observed Value (mg/dL) (mmol/L)[a]	Change (mg/dL) (mmol/L)[c]	*P* Value[b]	Per Cent Change (%)	*P* Value[c]
Baseline	29	385.8 (131.6)	NA	NA	NA	NA
		10.0 (3.4)				
Week 2	29	355.1 (140.5)	–30.7 (94.9)	0.092	–6.0 (24.2)	0.19
		9.2 (3.6)	–0.8 (2.5)			
Week 6	29	316.7 (140.4)	–69.1 (102.8)	0.001	–17.2 (24.4)	< 0.001
		8.2 (3.6)	–1.8 (2.7)			
Week 10	27	281.0 (143.4)	–104.3 (120.4)	< 0.001	–26.1 (26.8)	< 0.001
		7.3 (3.7)	–2.7 (3.1)			
Week 14	27	230.4 (143.7)	–154.9 (142.1)	< 0.001	–39.5 (33.7)	< 0.001
		6.0 (3.7)	–4.0 (3.7)			
Week 18	23	188.9 (118.6)	–214.5 (138.1)	< 0.001	–52.7 (31.4)	< 0.001
		4.9 (3.1)	–5.6 (3.6)			
Week 22	24	210.2 (139.4)	–190.8 (150.6)	< 0.001	–46.7 (33.2)	< 0.001
		5.4 (3.6)	–4.9 (3.9)			
Week 26	23	196.1 (107.2)	–210.3 (128.4)	< 0.001	–49.7 (25.0)	< 0.001
		5.1 (2.8)	–5.4 (3.3)			

ITT = intention to treat; HDL-C = high-density lipoprotein cholesterol; NA = not applicable; SD = standard deviation.
[a] Conversion to SI units: × 0.0259.[14]
[b] *P* value on the mean observed change from baseline based on paired t-test.
[c] *P* value on the mean per cent change from baseline based on paired t-test.
Source: UP1002/AEGR-733-005 Clinical Study Report.[15]

TABLE 14: ESTIMATED DIFFERENCES[a] IN PER CENT CHANGE IN LIPID AND LIPOPROTEIN LEVELS FOR PATIENTS RECEIVING AND NOT RECEIVING APHERESIS FROM BASELINE TO WEEK 26 (ITT, N = 29)

Lipid Parameter	Apheresis Co-treatment, LSM (SD)		Estimated Difference (SD) (Apheresis vs. No Apheresis)	*P* Value[b]
	Yes (n = 18)	No (n = 11)		
LDL-C	–48.0 (7.5)	–55.1 (8.9)	7.1 (11.7)	0.5448
Total cholesterol	–43.8 (6.9)	–49.8 (8.2)	6.0 (10.7)	0.5753
Apo B	–47.9 (6.9)	–53.2 (8.2)	5.3 (10.8)	0.6246
Non-HDL-C	–48.3 (7.5)	–54.2 (8.9)	5.9 (11.7)	0.6132
Triglycerides	–45.2 (9.0)	–41.2 (10.6)	–4.0 (14.0)	0.7772
VLDL-C	–45.2 (9.1)	–41.3 (10.7)	–3.9 (14.0)	0.7820
HDL-C	–10.3 (4.6)	–12.4 (5.3)	2.2 (7.0)	0.7598
TC/HDL-C	–37.1 (6.6)	–43.2 (7.9)	6.1 (10.4)	0.5587
Apo A1	–11.3 (3.9)	–9.2 (4.5)	–2.1 (6.0)	0.7302
Lp(a)	–12.8 (8.6)	–23.1 (10.0)	10.3 (13.2)	0.4364

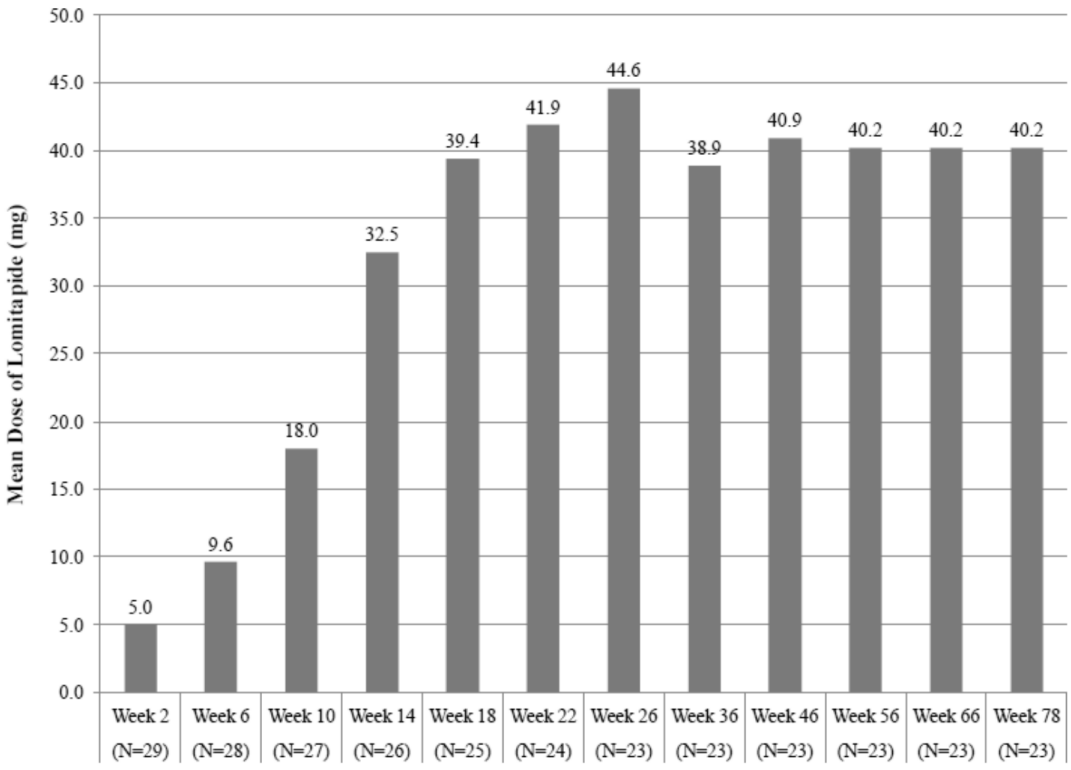
Apo = apolipoprotein; HDL-C = high-density lipoprotein cholesterol; ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; LOCF = last observation carried forward; Lp(a) = lipoprotein (a); LSM = least square mean; NA = not applicable; SD = standard deviation; TC = total cholesterol; VLDL-C = very-low-density lipoprotein cholesterol; vs. = versus.

[a] From a mixed-model repeated-measures analysis.

[b] *P* value based on t-test.

Source: UP1002/AEGR-733-005 Clinical Study Report.[15]

FIGURE 5: MEAN DOSE OF LOMITAPIDE (MG) BY STUDY WEEK DURING THE STUDY (SAFETY SET)



Source: UP1002/AEGR-733-005 Clinical Study Report.[15]

TABLE 15: NOTABLE HARMS: CHANGE IN LIVER FUNCTION TESTS AND PER CENT HEPATIC FAT FROM BASELINE TO WEEK 26 OR LOCF AND WEEK 78 (SAFETY SET)

Variable/ [Normal Range]/ Time Point	N	Observed Baseline Value Mean (SD)	Observed Value at Time Point Mean (SD)	Observed Change Mean (SD)
ALT (U/L) [M: 10–40; F: 10–33 U/L]				
Efficacy, week 26 or LOCF	29	30.2 (23.8)	49.5 (36.7)	19.3 (31.5)
Safety, week 78 or LOCF	23	29.8 (24.3)	44.8 (27.4)	15.0 (29.1)
AST (U/L) [M: 10–43; F: 10-36 U/L]				
Efficacy, week 26 or LOCF	29	30.0 (20.1)	36.8 (16.9)	6.8 (17.8)
Safety, week 78 or LOCF	23	26.3 (11.9)	35.2 (19.0)	8.9 (20.2)
Alkaline Phosphatase (U/L) [43–115 U/L]				
Efficacy, week 26 or LOCF	29	84.4 (32.5)	77.8 (42.9)	–6.6 (31.0)
Safety, week 78 or LOCF	23	86.1 (32.4)	70.3 (31.6)	–15.8 (24.3)
Total Bilirubin (mg/dL)[a] [0.1–1.1 mg/dL]				
Efficacy, week 26 or LOCF	29	0.8 (0.6)	0.7 (0.5)	0.0 (0.4)
Safety, week 78 or LOCF	23	0.6 (0.2)	0.7 (0.4)	0.1 (0.3)
Hepatic Fat (%) (NMRS) [NA]				
Efficacy, week 26	21[b]	0.9 (1.0)	9.0 (7.9)	7.3 (6.8)
Safety, week 78	20[b]	1.0 (1.0)	8.2 (5.2)	6.9 (5.0)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; LOCF = last observation carried forward; NMRS = nuclear magnetic resonance spectroscopy; SD = standard deviation.

[a] To convert to µmol/L, multiply by 17.1.[14]

[b] Ns presented are the number of patients with change from baseline values at weeks 26 and 78.

Source: UP1002/AEGR-733-005 Clinical Study Report.[15]

APPENDIX 5: SUMMARY OF OPEN-LABEL EXTENSION STUDY (AEGR-733-012)

Objectives

The objective of this section is to summarize the long-term, open-label extension study (733-012).[41] This study was an extension of pivotal study 733-005[15] and evaluated the efficacy and safety of lomitapide for patients with homozygous familial hypercholesterolemia (HoFH).

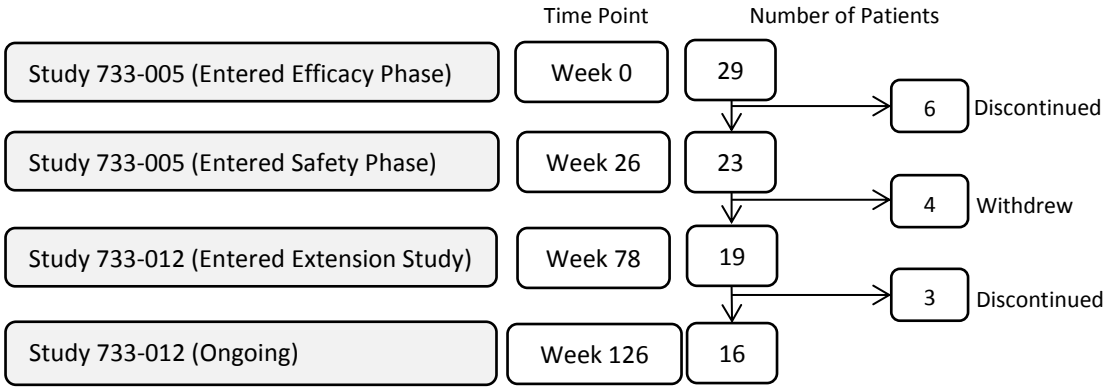
Summary

Study Methodology and Patient Disposition

Nineteen of the 23 patients who completed the 78-week pivotal study (733-005)[15] were enrolled in a long-term extension study (733-012).[41] Data were available up to December 31, 2012, at which point the study was ongoing and 16 patients were still receiving treatment. The anticipated completion date of the study was December 2014.

The safety analysis population consisted of all 19 patients, and the efficacy analysis population consisted of 17 patients who had completed a visit at week 126. Please see Figure 6: Patient Disposition Through Studies 733-005 and 733-012 for an illustration of patient disposition through studies 733-005 and 733-012.

FIGURE 6: PATIENT DISPOSITION THROUGH STUDIES 733-005 AND 733-012



Compared with the 29 patients included at baseline, the subset of patients (n = 19; 66%) who entered the extension study was similar in age (30.7 years versus 30.4 years), sex (47.4% female versus 44.8% female), and race (89.5% Caucasian versus 86.2% Caucasian). The mean weight of all 29 patients at baseline was slightly higher than the mean weight of patients included in the extension study (73.5 kg versus 69.5 kg). Patients were allowed to continue on lipid-lowering therapy (oral medications and apheresis) and were recommended to continue to follow the dietary guidelines outlined in study 733-005 (vitamin E supplements and fatty acids). Lomitapide dose modifications were allowed, but followed a predefined progression (starting at 5 mg and continuing up to 10 mg, 20 mg, 40 mg, 60 mg, and 80 mg as tolerated). Six patients (31.6%) were on apheresis at the start of the extension study (three were on LDL apheresis; three were on plasmapheresis), 13 (68.4%) patients were taking ezetimibe, and 16 patients (84.2%) were taking statins.

Patients were assessed every 12 weeks. The primary efficacy outcome was the per cent change in LDL-C at week 126 from baseline (i.e., week 0 in study 733-005), and secondary outcomes included total cholesterol, apolipoprotein (apo) B, triglycerides, non-high-density lipoprotein cholesterol (non-HDL-C), very-low-density lipoprotein cholesterol (VLDL-C), lipoprotein (a), HDL-C, and apo A assessed at each time point until week 126. Statistical analysis for efficacy outcomes was based on the percentage change from baseline (week 0) of the pivotal study to week 126. Safety outcomes included adverse events and laboratory measurements (including liver function tests and per cent hepatic fat). Additional assessments, including hepatic fat imaging, were conducted every 24 weeks.

Results

Efficacy outcomes are reported in Table 16. There was a statistically significant reduction in LDL-C levels from baseline (week 0 in study 733-005) to week 126 based on the percentage change in LDL-C (–5.5%). The observed values of LDL-C at week 126 were higher than those found at week 78 (the start of the extension study). For the secondary and tertiary end points, there was a statistically significant decrease in total cholesterol, apo B, triglycerides, non-HDL-C, VLDL-C, HDL-C, and apo A1 and a statistically significant increase in lipoprotein (a) from baseline to week 126.

TABLE 16: MEAN (SD) CHANGES IN PRIMARY, SECONDARY, AND TERTIARY EFFICACY END POINTS FROM BASELINE (WEEK 0) TO WEEK 126 (WEEK 126 COMPLETERS; N = 17)

End Point	Time Point	Observed Value (mg/dl)	Observed Change (mg/dl)	Per Cent Change (%)	*P* Value[a]
Primary Efficacy End Point					
LDL-C	Week 0[b]	355.6 (127.1)	NA	NA	NA
	Week 78[c]	162.1 (63.0)	–193.6 (111.1)	–50.8 (19.8)	NA
	Week 126	188.8 (120.3)	–166.8 (110.3)	–45.5 (31.4)	< 0.001
Secondary Efficacy End Points					
Total cholesterol	Week 0	456.8 (151.9)	NA	NA	NA
	Week 78	228.3 (72.3)	–228.5 (135.2)	–46.2 (18.8)	NA
	Week 126	252.9 (131.9)	–203.9 (126.3)	–43.2 (25.4)	< 0.001
Apo B	Week 0	278.2 (90.6)	NA	NA	NA
	Week 78	118.9 (46.5)	–159.3 (81.4)	–54.9 (17.0)	NA
	Week 126	125.3 (73.9)	–152.9 (82.4)	–53.6 (23.7)	< 0.001
Triglycerides	Week 0	109.7 (49.0)	NA	NA	NA
	Week 78	58.4 (43.4)	–51.3 (49.3)	–44.7 (33.9)	NA
	Week 126	65.9 (55.2)	–43.7 (50.5)	–37.5 (42.5)	0.005
Non-HDL-C	Week 0	412.0 (149.0)	NA	NA	NA
	Week 78	186.1 (69.4)	–225.9 (131.1)	–51.0 (19.3)	NA
	Week 126	211.5 (128.2)	–200.5 (124.4)	–47.1 (27.8)	< 0.001
VLDL-C	Week 0	21.9 (9.8)	NA	NA	NA
	Week 78	11.8 (8.7)	–10.1 (9.9)	–44.2 (34.4)	NA
	Week 126	13.2 (11.2)	–8.7 (10.4)	–36.8 (43.9)	0.006
Lp(a)[c]	Week 0	92.0 (76.2)	NA	NA	NA
	Week 78	86.6 (56.9)	–10.2 (51.3)	–4.9 (36.2)	NA
	Week 126	101.1 (69.0)	4.3 (36.0)	5.5 (43.6)	0.037
Tertiary Efficacy End Points					
HDL-C	Week 0	44.9 (11.1)	NA	NA	NA

End Point	Time Point	Observed Value (mg/dl)	Observed Change (mg/dl)	Per Cent Change (%)	*P* Value[a]
	Week 78	42.2 (12.0)	–2.6 (8.1)	–5.6 (20.2)	NA
	Week 126	41.4 (13.3)	–3.4 (8.2)	–8.3 (19.3)	0.010
Apo A1	Week 0	118.5 (30.3)	NA	NA	NA
	Week 78	111.5 (26.7)	–7.0 (18.5)	–4.4 (15.3)	NA
	Week 126	99.8 (24.6)	–18.7 (19.6)	–14.0 (17.7)	0.027

Apo = apolipoprotein; HDL-C = high-density lipoprotein cholesterol; ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; LOCF = last observation carried forward; Lp(a) = lipoprotein (a); NA = not applicable; VLDL-C = very-low-density lipoprotein cholesterol.
[a] *P* value based on the mean change from baseline to week 126 according to a mixed-model repeated-measures analysis.
[b] Week 0 data derived from a subset of patients (n = 17) in study 733-005 who continued into the long-term extension trial. Baseline datum for the full study population (n = 29) in study 733-005 was 336.4 mg/dL (SD 113.5)[15]
[c] Week 78 datum for the ITT population (n = 23) was 223.0 mg/dL (SD 135.4).[15]
Source: AEGR 733-012 Clinical Study Report.[41]

Harms outcomes are reported in Table 17. One death occurred, there was one withdrawal due to an adverse event, and 14 patients (73.7%) had at least one adverse event. The most common adverse events were diarrhea, nausea, influenza, angina pectoris, vomiting, gastroenteritis, and nasopharyngitis. From baseline to week 126, there was an increase in alanine aminotransferase (30.2 U/L versus 59.4 U/L), aspartate aminotransferase (26.9 U/L versus 47.4 U/L), and per cent hepatic fat (0.8% versus 10.2%).

TABLE 17: HARMS DATA (STUDY AEGR-733-012)

	AEGR-733-012[41]
	Extension Study Weeks 78 to 126 (N = 19)
Overall harms data	
Treatment duration, days (mean SD)	642.9 (290.4)
Average daily dose, mg/day (mean SD)	43.1 (15.9)
Patients with ≥ 1 AEs, N (%)	14 (73.7)
Severe AEs, N (%)	7 (36.8)
SAEs, N (%)	7 (36.8)
WDAEs, N (%)	1 (5.3)
Deaths due to AEs, N (%)	1 (5.3)
Adverse events, N (%)	
Diarrhea	7 (36.8)
Nausea	5 (26.3)
Vomiting	3 (15.8)
Abdominal pain	0 (0.0)
Dyspepsia	2 (10.5)
Constipation	0 (0.0)
Abdominal distension	2 (10.5)
Flatulence	1 (5.3)
Abdominal discomfort	0 (0.0)

	AEGR-733-012[41]
	Extension Study Weeks 78 to 126 (N = 19)
Weight decreased	1 (5.3)
Abdominal pain upper	0 (0.0)
ALT increased	2 (10.5)
Nasopharyngitis	3 (15.8)
Chest pain	1 (5.3)
Gastroenteritis	3 (15.8)
Angina pectoris	4 (21.1)
Defecation urgency	0 (0.0)
Dizziness	1 (5.3)
Gastroesophageal reflux disease	1 (5.3)
Nasal congestion	NR
Pharyngolaryngeal pain	NR
Rectal tenesmus	0 (0.0)
Fatigue	0 (0.0)
Influenza	5 (26.3)
SAEs, N (%)[a,b]	
Acute coronary syndrome	0 (0.0)
ALT increased	2 (10.5)
Angina pectoris	NR
Arteriosclerosis	NR
Lower respiratory tract infection	1 (5.3)
Menorrhagia	NR
WDAEs	
Investigator judgment	1 (5.3)
Notable harms — markers of hepatotoxicity	
ALT (U/L), mean (SD)	
Baseline (n = 19)	30.2 (25.9)
Week 78 (n = 19)	47.4 (28.9)
Week 126 (n = 17)	59.4 (47.1)
AST (U/L), mean (SD)	
Baseline (n = 19)	26.9 (12.8)
Week 78 (n = 19)	36.9 (19.8)
Week 126 (n = 17)	47.4 (50.3)
Alkaline phosphatase (U/L), mean (SD)	
Baseline (n = 19)	88.9 (34.8)
Week 78 (n = 19)	71.9 (34.4)
Week 126 (n = 17)	73.5 (23.7)
Total bilirubin (mg/dL), mean (SD)	

	AEGR-733-012[41]
	Extension Study Weeks 78 to 126 (N = 19)
Baseline (n = 19)	0.6 (0.2)
Week 78 (n = 19)	0.7 (0.4)
Week 126 (n = 17)	0.7 (0.3)
Hepatic fat (%) (NMRS), mean (SD)	
Baseline (n = 17)	0.8 (0.7)
Week 78 (n = 17)	7.9 (5.0)
Week 126 (n = 13)	10.2 (7.4)

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; NMRS = nuclear magnetic resonance spectroscopy; NR = not reported; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.
[a] Other severe adverse events occurring in 1 patient include dyspepsia, increased AST, coronary artery disease, facial palsy, gastroesophageal reflux disease, hypovolemic shock, influenza, international normalized ratio increased, rhabdomyolysis, and subdural hematoma.
[b] The manufacturer stated that one patient was incorrectly identified as being discontinued from treatment due to an SAE (hepatotoxicity). In errata, the manufacturer stated that it was not an SAE and that the treatment was interrupted, not discontinued.
Source: AEGR-733-012 Clinical Study Report.[41]

Critical Appraisal

The present study is limited by its small sample size (n = 19) and lack of control group. The absence of a control group makes it difficult to draw conclusions regarding the safety of lomitapide and with respect to the relative contributions of lomitapide and conventional lipid-lowering therapy (apheresis and statins) in reducing levels of LDL-C and other lipoproteins. Furthermore, the statistical analyses were conducted based on a comparison between baseline data (week 0 of the pivotal study) and week 126 data, so the maintenance of LDL-C reductions during the extension phase (week 78 and week 126) was limited to a descriptive interpretation.

Conclusion

During the course of 126 weeks, patients with HoFH experienced statistically significant reductions in levels of lipoprotein including LDL-C. The most common adverse events were gastrointestinal in nature. Due to the methodological limitations of this study, evidence for the long-term efficacy and safety of lomitapide is limited.

APPENDIX 6: SUMMARY OF PLASMA EXCHANGE AND LOW-DENSITY LIPOPROTEIN APHERESIS

Plasma exchange and low-density lipoprotein (LDL) apheresis are two extracorporeal blood filtration treatment options for patients with homozygous familial hypercholesterolemia (HoFH). The main difference between the two procedures is their specificity. Plasma exchange involves the separation of the patient's blood cells and plasma. The blood cells are retained and mixed with a replacement fluid to return to the patient, while the plasma is discarded. Consequently, this treatment removes nearly all plasma proteins, including high-density lipoprotein (HDL). Similar to plasma exchange, LDL apheresis involves the separation of the patient's blood and plasma; however, instead of the plasma being discarded, it passes through a precipitation filter for the selective removal of low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein (VLDL), and apo B–containing particles such as lipoprotein (a). Please refer to Table 18 for an overview of these two procedures.

Two LDL apheresis systems have been approved by Health Canada (the heparin-induced extracorporeal lipoprotein precipitation [HELP] system[18] and the dextran sulphate Liposorber LA-15 system[31]).
LDL apheresis is more efficacious than plasma exchange according to the per cent reduction in LDL-C levels (60% to 65% versus 50%, respectively). Because of its specificity, LDL apheresis is also better tolerated than is plasma exchange. The rate of adverse events is higher for plasma exchange than for LDL apheresis (12% versus 2% respectively).[18] The most commonly reported events for LDL apheresis include light-headedness, pain, hypotension, hypertension, bleeding, vomiting, allergic reactions, and shock.[42] For plasma exchange, susceptibility to infection is a concern,[18] and other reactions may include nausea, hypertension, hypotension, circumoral paresthesia, and hives.[18]

Plasma exchange is available more widely than LDL apheresis and is therefore used in more patients.[43] Plasma exchange is used in children who do not have a sufficiently large blood volume to allow for LDL apheresis.[43] Plasma exchange and LDL apheresis sessions both last two to three hours, require weekly or biweekly sessions, and are a lifelong commitment.[18] In 2007, Health Quality Ontario conducted a health technology assessment of LDL apheresis, based on the only system available at the time (HELP) compared with the existing plasma exchange technology, and found that LDL apheresis was approximately double the cost of using plasma exchange.[18] These figures are outlined in Table 18.

In summary, while LDL apheresis is more efficacious, offers the selective removal of lipoproteins, and is better tolerated by patients compared with plasma exchange, plasma exchange is available more widely and is less costly.

TABLE 18: COMPARISON OF LDL APHERESIS AND PLASMA EXCHANGE

	LDL Apheresis	Plasma Exchange
Specificity	Specific. Removes LDL-C, VLDL, and apo B–containing particles (e.g., Lp[a])[44]	Non-specific. Removes nearly all plasma proteins[18]
Efficacy	60% to 65% drop in LDL-C levels[42] Increases within 24 to 48 hours, returning to baseline levels within two weeks[42]	Approximately 50% reduction in LDL-C[18]
Session length, frequency and duration[18]	Two to three hours; weekly or biweekly; lifelong	
Category and grade of recommendation for use in treating HoFH[a]	Category I; Grade 1A (first-line therapy; strong recommendation, high-quality evidence)[45]	Category II; Grade 1C (second-line therapy for patients who are unable to undergo LDL apheresis; strong recommendation, low-quality to very-low-quality evidence)[45]
Availability	Two LDL apheresis units across Canada (Quebec and Edmonton)[18]	38 apheresis reporting centres[b] across Canada[46]
Side effects[18]	Adverse events: 2% of procedures	Adverse events: 12% of procedures
Cost (annually per patient) (C$ 2007)[18]	HELP system: • year 1: $39,467.92[c] • years 2+: $39,789.62[c]	System not specified: • year 1: $19,077.92[d] • years 2+: $19,385.62[d]

apo = apolipoprotein; HELP = heparin-induced lipoprotein precipitation; HoFH = homozygous familial hypercholesterolemia; LDL = low-density lipoprotein; VLDL = very-low-density lipoprotein.

[a] According to the American Society for Apheresis.

[b] Apheresis reporting centres include centres performing plasma exchange and other apheresis procedures.

[c] Includes equipment costs, dialysis equipment, equipment disposables, additional supplies, maintenance, medical fees, and personnel fees (does not account for genetic testing), and based on biweekly sessions for 13 patients requiring treatment (Ontario-based estimate of prevalence by Health Quality Ontario).[18]

[d] Includes equipment, fluid replacement, additional supplies, maintenance, medical fees, and personnel fees, and based on biweekly sessions for 13 patients requiring treatment (Ontario-based estimate of prevalence by Health Quality Ontario).[18]

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