The lipid-lowering effects of lomitapide are unaffected by adjunctive apheresis in patients with homozygous familial hypercholesterolaemia — A post-hoc analysis of a Phase 3, single-arm, open-label trial

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ABSTRACT

Objective: Lomitapide (a microsomal triglyceride transfer protein inhibitor) is an adjunctive treatment for homozygous familial hypercholesterolaemia (HoFH), a rare genetic condition characterised by elevated low-density lipoprotein-cholesterol (LDL-C), and premature, severe, accelerated atherosclerosis. Standard of care for HoFH includes lipid-lowering drugs and lipoprotein apheresis. We conducted a post-hoc analysis using data from a Phase 3 study to assess whether concomitant apheresis affected the lipid-lowering efficacy of lomitapide.

Methods: Existing lipid-lowering therapy, including apheresis, was to remain stable from Week −6 to Week 26. Lomitapide dose was escalated on the basis of individual safety/tolerability from 5 mg to 60 mg a day (maximum). The primary endpoint was mean percent change in LDL-C from baseline to Week 26 (efficacy phase), after which patients remained on lomitapide through Week 78 for safety assessment and further evaluation of efficacy. During this latter period, apheresis could be adjusted. We analysed the impact of apheresis on LDL-C reductions in patients receiving lomitapide.

Results: Of the 29 patients that entered the efficacy phase, 18 (62%) were receiving apheresis at baseline. Twenty-three patients (13 receiving apheresis) completed the Week 26 evaluation. Of the six patients who discontinued in the first 26 weeks, five were receiving apheresis. There were no significant differences in percent change from baseline of LDL-C at Week 26 in patients treated (−48%) and not treated (−55%) with apheresis (p = 0.545). Changes in Lp(a) levels were modest and not different between groups (p = 0.436).

Conclusion: The LDL-C lowering efficacy of lomitapide is unaffected by lipoprotein apheresis.

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1. Introduction

Homozygous familial hypercholesterolaemia (HoFH) is a rare genetic disease caused by mutations in genes affecting functionality of the low-density lipoprotein receptor (LDLR) [1].

HoFH is characterised by markedly elevated low-density lipoprotein-cholesterol (LDL-C) levels and premature, severe and accelerated atherosclerosis [1–3]. The need for aggressive lipid-lowering therapy for the treatment of FH is recognized by multiple guidelines worldwide [3–6]. Specific therapeutic targets for LDL-C lowering in HoFH are set by the European Atherosclerosis Society (EAS) at LDL-C <2.5 mmol/L for adults, or <1.8 mmol/L in adults with atherosclerotic cardiovascular disease [1]. In spite of treatment with traditional lipid-lowering therapies, including statins and ezetimibe, LDL-C in patients with HoFH typically remains above goal levels [7,8]. Therefore, the standard of care for HoFH includes lipoprotein apheresis (LA), where available, which transiently removes LDL-C from plasma during extracorporeal circulation with the aim of delaying the onset and progression of cardiovascular disease [3,9–12].

Although LA (a technique that selectively removes apolipoprotein B (apoB)-containing lipoproteins and spares negatively-charged molecules such as high-density lipoprotein-cholesterol [HDL-C] [13–16]) has largely supplanted non-selective therapeutic plasma exchange (TPE) [12,15,16], both are still used to treat HoFH. As a result of low catabolic rate and ongoing production of LDL, both LA and TPE methods lower LDL-C levels only transiently [17], and the procedure is generally repeated every 7–14 days, consistent with international clinical recommendations [3,18,19].

Although effective at lowering LDL-C, apheresis is not universally available due to a range of factors that include the need for specialisation and training, and costs associated with providing the treatment. Additionally, not all patients are suited to apheresis due to the frequency of treatments (at least bi-weekly), and the need to maintain vascular access. There is, therefore, a need for additional therapies in patients with HoFH.

Lomitapide is a small-molecule microsomal triglyceride transfer protein (MTP) inhibitor and is approved in several countries worldwide as an adjunct to other lipid-lowering therapies, with or without apheresis, in adult patients with HoFH [20]. The safety and efficacy of lomitapide was evaluated in a Phase 3 study (NCT00730236), which included patients receiving apheresis. Lomitapide and apheresis work via different modes of action, therefore it is reasonable to suggest that their effects may be independent. A post-hoc analysis using data from this study was conducted to ascertain if concomitant apheresis affected the lipid-lowering efficacy of lomitapide.

2. Methods

2.1. Study design and treatment

The study design, patient population and results have been described previously [21] and summarized in the supplemental material.

Apheresis was provided either via LA or TPE. Techniques and schedules employed by the study investigators reflected local clinical practice, individual patient requirements and physician choices [21]. Mean volume of blood or plasma processed and plasma substituted (for patients treated with TPE) were calculated according to apheresis technique and local clinical practice. Gender, haematocrit, body mass index and pre-treatment LDL-C were used to determine the appropriate plasma or blood volume to be processed. During extracorporeal procedures,

heparin was preferred over acid-citrate dextrose as an anticoagulant.

Fasting lipid profiles were obtained with recognition that apheresis treatment causes a sharp drop in LDL-C, followed by a rebound phase. Therefore, in patients undergoing apheresis, and according to the protocol, it was important that lipid parameters were evaluated at a time that was as close as possible to, and before the scheduled apheresis treatment. Once established, this time point was to be maintained relative to the previous apheresis session, so that pre-apheresis lipid assessments were always performed at the same point on the LDL rebound curve. Per protocol, post-apheresis samples were not routinely obtained; therefore, time-averaged (mean interval) values for lipid parameters [17] were not calculable.

During the 6-week run-in phase, a stable-frequency apheresis regimen (e.g., apheresis every 7–14 days, with some flexibility for individualisation) was established and was to be maintained during the 26-week efficacy phase. If the visit schedule was inconsistent with a patient's apheresis schedule, then the investigator was to request a protocol deviation. If a patient was unable to come for an apheresis treatment per his/her usual regimen, apheresis was to be rescheduled as soon as possible. If apheresis was missed at the time of a study visit, then blood samples were taken before apheresis treatment and as close as possible to the apheresis regimen established during the run-in phase, or as altered during the safety phase. At Week −2 and Week 0 (baseline), Week 18, and Week 26 (primary efficacy time point), fasting lipids were drawn just prior to the apheresis treatment and apheresis must have occurred ±1 day from the regimen established during the run-in phase. Following the efficacy phase, patients entered a 52-week safety phase during which statins and other lipid-lowering therapies (including frequency of apheresis) could be adjusted on a case-by-case basis at the physician and patient's discretion based on established protocol criteria.

2.2. Statistical analysis

The post-hoc analysis presented here was conducted using data collected during the period of the Phase 3 study (baseline to Week 26) that assessed efficacy with no changes to background therapy allowed. An analysis using a mixed-model repeated-measures analysis, accounting for multiple observations per subject, was conducted to assess potential differences in percent change from baseline to Week 26 in lipid parameters for subjects who did and who did not receive apheresis. The model included treatment with apheresis (yes, no), baseline lipid level, and categorical study week as fixed parameters and a study week-by-apheresis interaction. A t-test was applied to assess the differences in least square means for percent change from baseline to Week 26 between the two subgroups. Fisher's Exact test was used to evaluate the significance of differences between attainment of LDL-C thresholds observed in patients receiving apheresis versus those not. Wilcoxon rank sum exact test was used to assess change in hepatic fat at Week 26 from baseline comparing subjects on apheresis versus no apheresis. Spearman rank correlation was used to assess the relationship between percent change in hepatic fat and the change from baseline in LDL-C at Week 26 independent of apheresis. The intent-to-treat population was used for the analysis, and missing values were not imputed.

A post-hoc estimation of statistical power based on the number of subjects receiving/not receiving apheresis (n = 18 versus 11) revealed that this sample size would have 80% power to detect a 32% difference in percent change in LDL-C from baseline between apheresis groups.

3. Results

3.1. Patients

Overall patient characteristics and results have been presented previously [21].

Of the 29 patients who entered the efficacy phase, 18 (62%) were receiving either LA or TPE at baseline (Table 1). Baseline characteristics were well matched between patients who received apheresis and those who did not. Twenty-three patients (13 receiving apheresis) completed the Week 26 evaluation (Fig. 1).

Six patients discontinued during the efficacy phase (five due to adverse events [AEs] [four gastrointestinal [GI] AEs], one headache, and one patient withdrew consent). Five of the six patients that discontinued were receiving apheresis (four withdrew due to AEs: one due to headache, and three due to GI AEs) (Fig. 1).

The apheresis technique used was region dependent. All South African and Canadian patients and one US patient received TPE (n = 7). All Italian and the remaining US patients received LA (n = 11).

Thirteen patients received apheresis once every two weeks. A further four patients received weekly apheresis. In the US, Canadian and South African centres the predominant schedule was once every two weeks. In the Italian centres, two patients received apheresis every week, one patient was treated once every two weeks, and one patient once every 6 weeks.

3.2. Lomitapide efficacy in patients receiving and not receiving apheresis during the efficacy phase

The efficacy of lomitapide in the overall population has been reported [21]. By the end of the efficacy phase (Week 26), during which apheresis schedules were to remain consistent, lomitapide was associated with a similar mean percent reduction in LDL-C from baseline irrespective of whether patients received apheresis or not (ITT population; Table 2). According to a mixed model repeated measures, overall percent reductions in LDL-C from baseline were −51.0% in all patients, −48.0% in those on apheresis and −55.1% in those not on apheresis (p = 0.545). Similarly, percent reductions in non-HDL-C (−48.3% versus −54.2%; p = 0.613), total cholesterol (−43.8% versus −49.8%; p = 0.575) and apoB (−47.9% versus −53.2%; p = 0.625) were not significantly different between those on apheresis and those not (Table 2). Lipoprotein(a) [Lp(a)] levels did not change markedly over the course of the study, and percent reductions were not significantly different between the two groups (−12.8% versus −23.1%; p = 0.436), although baseline levels were lower in the apheresis group than in the non-apheresis group (2.3 μmol/L versus 3.5 μmol/L) (Table 2). Triglycerides and Lp(a) were also assessed using non-parametric methods and mixed model methods on the log results given the distribution of these parameters. These analyses chiefly confirmed there was no

significant difference between those on apheresis and those not.

The sample size of the study was not sufficient to enable statistical significance to be declared on the difference in percent reduction in LDL-C from baseline between apheresis groups.

3.3. Attainment of LDL-C threshold and apheresis reductions

Despite intensive lipid-lowering management, mean LDL-C levels at baseline were 8.4 mmol/L for patients receiving apheresis and 9.2 mmol/L for those not receiving apheresis (Table 1) prior to lomitapide treatment. No subject had reached targets recommended in guidelines set by the recent European Atherosclerosis Society consensus statement [1]. We analysed attainment of LDL-C below recommended thresholds over the course of the study and ascertained if differences between subjects receiving apheresis or not existed. When considering all subjects enrolled (n = 29), about a quarter of subjects reached LDL-C levels <2.5 mmol/L at Week 26, with no significant differences in attainment of LDL-C thresholds observed between those receiving apheresis and those not (Table 3, p = 0.4327 and p = 1.000 for thresholds of 2.5 mmol/L and 1.8 mmol/L, respectively). When analysis was conducted on data collected during the entire 78 week-long trial, about half (55%) the subjects attained an LDL-C level of <2.5 mmol/L and about a third (34%) subjects attained an LDL-C level <1.8 mmol/L at least once. Two of the patients who discontinued the study (one receiving, one not receiving apheresis) achieved an LDL-C level <2.5 mmol/L prior to discontinuation.

During the safety phase, when concomitant lipid-lowering therapies could be modified at the discretion of the individual prescriber and patient, the apheresis regimen of six of the 13 patients (46%) receiving apheresis at the end of the efficacy phase underwent a change that was maintained until the end of the study. Three patients stopped apheresis (Fig. 2A—C) and a further three patients decreased the frequency of apheresis treatments (Fig. 2D—F) [21]. In general, LDL-C levels were maintained following either a reduction in the frequency or discontinuation of apheresis (Fig. 2A—F). Similar results were observed with apoB levels (data not shown).

3.4. Safety

Adverse event (AE) reporting in the study was for lomitapide associations only. Therefore, only limited comment can be made on the side-effect profile of apheresis in this setting. No side effects resulting in failure to return for an apheresis session were recorded.

For lomitapide, the full safety and tolerability data from the Phase 3 study have been reported previously [21]. Briefly, four patients (three receiving apheresis) had confirmed elevations in aminotransferases between 5 and 10× upper limit upper limit of normal that resolved with dose reduction or interruption of study drug. The most commonly reported AEs were gastrointestinal (GI)-related, predominantly assessed as mild-to-moderate in intensity. There was no difference between the incidence of GI- and non-GI-related disorders for patients receiving apheresis and those not receiving apheresis; however, five of the six discontinuations in the study were for patients receiving apheresis.

Withdrawals were due to AEs in four of the five patients receiving apheresis who discontinued the study (Fig. 2). These four patients were receiving a range of daily doses of lomitapide (5, 10 and 40 mg). The number of withdrawals was too low for meaningful comparisons to be made.

Mean hepatic fat in 21 patients with evaluable nuclear magnetic resonance spectroscopy scans from both treatment groups combined was 1.0% (range, 0—3.8) at baseline, and 8.3% (0.8—33.6) at Week 26. Percent change in hepatic fat was negatively associated

Table 1
Baseline characteristics of patients.

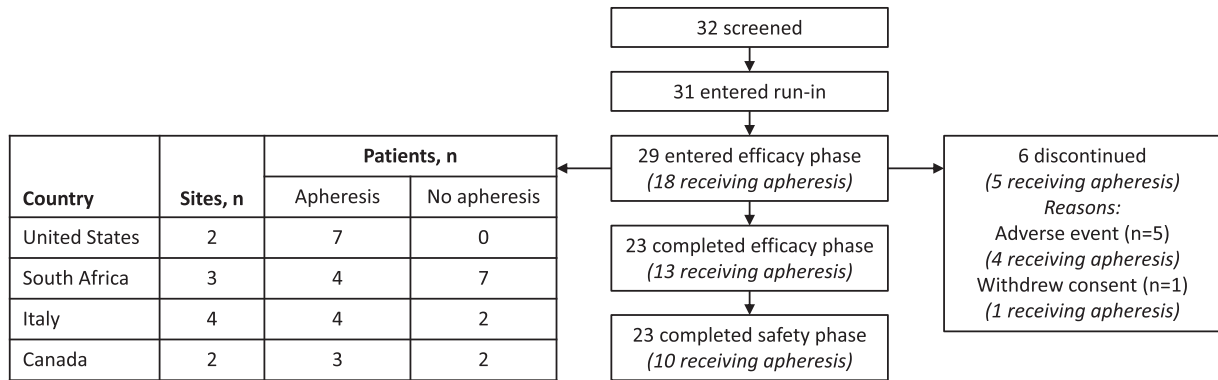| Parameter	Overall (n = 29)	Apheresis (n = 18)	No apheresis (n = 11)	p-value[a]
Age (years), mean ± SD	31 ± 11	31 ± 10	30 ± 12	0.890
Male, n (%)	16 (55%)	11 (61%)	5 (46%)	0.429
BMI (kg/m^2), mean ± SD	25.8 ± 5.4	25.0 ± 3.0	27.3 ± 8.0	0.280
Statin therapy, n (%)	27 (93%)	16 (88.9%)	11 (100%)	0.286
Ezetimibe plus statin, n (%)	22 (69%)	14 (67%)	8 (73%)	0.070
LDL-C (mmol/L), mean ± SD	8.7 ± 3.0	8.4 ± 2.8	9.2 ± 3.2	0.509
LDL-C (mg/dL), mean ± SD	336 ± 114	325 ± 108	355 ± 125	0.509

[a] Apheresis versus no apheresis.

Fig. 1. Patient disposition.

Table 2
Percent change from baseline in lipid and lipoprotein levels at Week 26 in patients with and without apheresis treatment using Mixed Model Repeated Measures.[a]

Parameter	Overall (n = 29)		Apheresis (n = 18)		No apheresis (n = 11)		p-value[b]
	Baseline (range)	% Change	Baseline (range)	% Change	Baseline (range)	% Change	
TC, mmol/L	11.1 (4.9—18.7)	−46.3	10.7 (4.9—16.4)	−43.8	11.8 (6.3—18.7)	−49.8	0.575
LDL-C, mmol/L	8.7 (3.9—14.6)	−51.0	8.4 (3.9—12.9)	−48.0	9.2 (4.3—14.6)	−55.1	0.545
Non-HDL, mmol/L	10.0 (4.1—17.1)	−50.7	9.6 (4.1—15.4)	−48.3	10.7 (5.0—17.1)	−54.2	0.613
TG, mmol/L	2.7 (0.8—6.5)	−43.3	2.8 (0.8—6.5)	−45.2	2.5 (1.3—4.6)	−41.2	0.777
ApoB, g/L	2.6 (1.2—4.3)	−50.1	2.5 (1.2—3.6)	−47.9	2.8 (1.4—4.3)	−53.2	0.625
HDL-C, mmol/L	1.1 (0.7—1.8)	−11.3	1.1 (0.9—1.7)	−10.3	1.1 (0.7—1.8)	−12.4	0.760
ApoA-I, g/L	1.1 (0.6—1.9)	−10.6	1.2 (0.8—1.6)	−11.3	1.1 (0.6—1.9)	−9.2	0.730
Lp(a), μmol/L	2.8 (0.6—12.1)	−17.2	2.3 (0.7—4.7)	−12.8	3.5 (0.6—12.1)	−23.1	0.436

[a] Mixed model includes treatment with apheresis (yes/no), baseline lipid level, and categorical study week as fixed parameters and a study week-by-apheresis interaction.
[b] Apheresis versus no apheresis.

Table 3
LDL-C treatment goal attainment in the overall population and in subjects with and without apheresis treatment over the course of the trial (efficacy plus safety phases).

LDL-C, mmol/L (mg/dL)	Overall (n = 29)		Apheresis (n = 18)		No apheresis (n = 11)	
	<2.5 (<100)	<1.8 (<70)	<2.5 (<100)	<1.8 (<70)	<2.5 (<100)	<1.8 (<70)
At Week 26, n (%)	8 (28%)	1 (3%)	4 (22%)	1 (6%)	4 (36%)	0
At any time, n (%)	16 (55%)	9 (31%)	8 (44%)	5 (28%)	8 (73%)	4 (36%)

with change in LDL-C at Week 26 independent of apheresis (p = 0.754 for apheresis versus non-apheresis; Spearman rank correlation for change from baseline between LDL-C and hepatic fat = −0.4207, p = 0.05). Similar to the recorded GI AEs, there was no difference in the hepatic fat content at Week 26 between patients receiving apheresis and those not receiving apheresis. Mean hepatic fat data at Week 26 are presented in Table 4.

4. Discussion

Treatment with lomitapide significantly lowered LDL-C in patients with HoFH receiving maximal standard lipid-lowering therapy [21]. The current post-hoc analysis showed that the LDL-C-reducing efficacy of lomitapide is independent of whether or not patients received apheresis in this study. The percent reduction in LDL-C level in either group (apheresis or no apheresis) and the number of patients who reached EAS treatment goals of LDL-C <1.8 mmol/L and <2.5 mmol/L [1] during the trial were similar among patients who received apheresis versus those who did not, and were consistent with those observed in the overall population [21]. Individual profiles of the patients who discontinued apheresis after Week 26 do not appear to indicate any clinically meaningful changes in LDL-C levels after stopping the procedure [21].

These findings support the hypothesis that the efficacy of lomitapide is unaltered by the application of apheresis and that the combination of the two therapeutic approaches provides additional lipid-lowering benefit to patients on apheresis. Some patients were able to adjust their apheresis schedules while receiving lomitapide. This could form the basis of an expanded multimodal approach to lipid lowering whereby the relative doses of lomitapide, statins and apheresis could be modulated to suit individual patient responses, tolerances and lifestyle requirements. A multimodal approach of this type may be particularly relevant in HoFH, in which different mutation profiles confer different levels of key receptor and peptide function in lipoprotein catabolism.

To date, lomitapide is the only drug among the new generation of lipid-lowering agents to have been tested in clinical settings that include apheresis, and to be approved for combination therapy in patients with HoFH. Mipomersen is also approved in the United States as an adjunctive lipid-lowering therapy for HoFH. However, the Phase 3 trial for mipomersen did not include patients receiving apheresis, and the product label specifically states that mipomersen use is not recommended in patients undergoing LA [22,23]. PCSK9 inhibitors are currently in Phase 3 development as lipid lowering therapies, and have been tested in patients with HoFH. Results for the PCSK9 inhibitor evolocumab indicate that this approach is effective in at least some patients with HoFH, depending upon their level of receptor activity [24]. Interestingly,
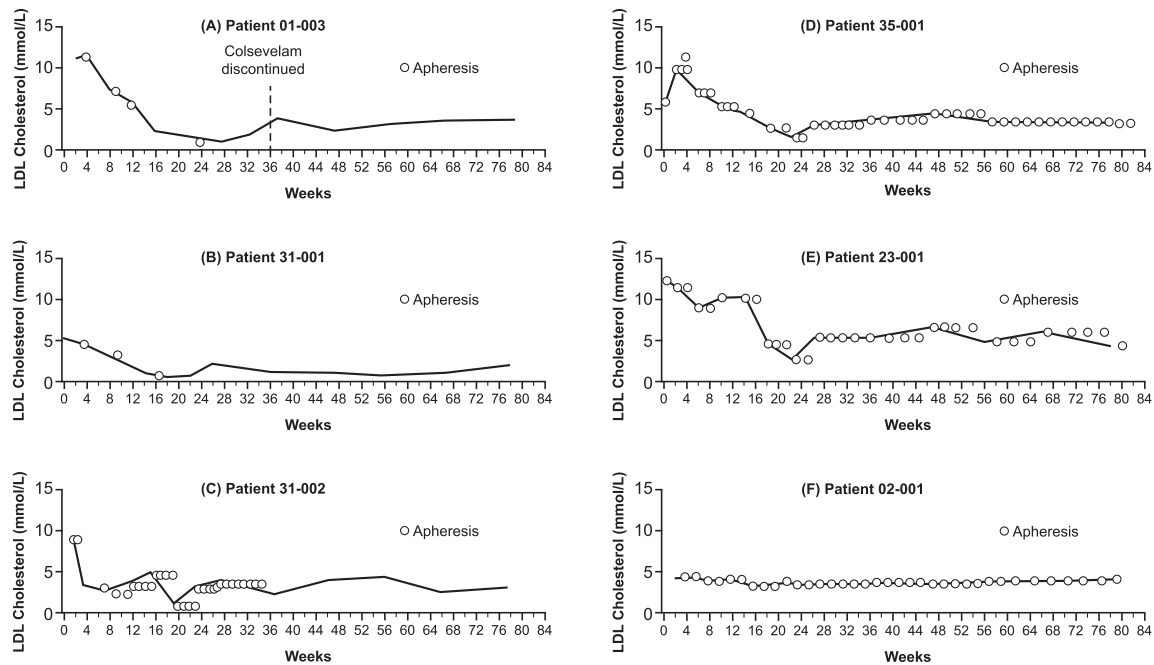
Fig. 2. Individual LDL-C profiles for patients who discontinued apheresis (A—C) or extended apheresis intervals (D—F) during the safety phase of the trial. Lipid parameters were evaluated at a time that was as close as possible to, and before, the scheduled apheresis treatment. Once established, this time point for lipid assessment blood draws was maintained, relative to the previous apheresis visit, so that lipid assessments were always performed at the same point on the LDL rebound curve.

Table 4
Hepatic fat levels at baseline and Week 26 in the overall population of lomitapide-treated patients and those treated with and without apheresis (efficacy plus safety phases).

Parameter (%)	Overall (N = 21)		Apheresis (n = 12)		No apheresis (n = 9)	
	Value	% Change	Value	% Change	Value	% Change
Baseline						
Mean (SD)	1.0 (1.0)	–	1.4 (1.1)	–	0.6 (0.5)	–
Median (25%, 75% IQR)	0.7 (0.4, 1.1)	–	1.0 (0.4, 2.2)	–	0.7 (0.2, 0.7)	–
Min—Max	0.0—3.8	–	0.4—3.8	–	0.0—1.7	–
Week 26						
Mean (SD)	8.3 (7.5)	7.3 (6.8)	9.1 (9.2)	7.7 (8.3)	7.3 (4.7)	6.8 (4.4)
Median (25%, 75% IQR)	6.6 (3.8, 11.9)	5.7 (2.7, 11.0)	6.9 (3.4, 12.2)	5.7 (2.0, 11.2)	6.0 (4.8, 9.5)	5.7 (4.3, 9.3)
Min—Max	0.8—33.6	0.4—29.9	0.8—33.6	0.4—29.9	1.6—16.3	0.9—14.5
p-value[a]	–	–	–	–	–	0.754

IQR, interquartile range.
[a] Descriptive p-value based on Wilcoxon rank sum exact test for change in hepatic fat at Week 26 from baseline comparing subjects on apheresis versus no apheresis.

LA has been shown to reduce plasma PSCK9 levels [25], which may increase the apparent efficacy of PCSK9 inhibitors in combination with apheresis. The ongoing phase 2/3 TAUSSIG study of evolocumab in severe familial hypercholesterolaemia (FH) (n = 5) included two patients receiving apheresis, but analysis by apheresis is not available and the sample size is extremely small [26]. Thus, the efficacy of these drugs in presence of apheresis remains to be determined.

MTP inhibitors are known to affect hepatic secretion of apoB-containing lipoproteins and lomitapide has been shown to decrease the production of LDL-apoB in patients with HoFH [27]. It is therefore probable that lomitapide favourably affects the rebound curve of LDL and other apoB-containing lipoproteins characteristic of apheresis by limiting the secretion of these lipoproteins. Data from a recently published case report supports this possibility [28]. Based on how the drug is metabolised and its low systemic availability [29], it is unlikely that apheresis affects lomitapide levels; however, this question was not directly assessed in the Phase 3 study. Of the six patients in the study who stopped or altered their apheresis schedule, no apparent rebound of LDL-C or

apoB levels was observed over the 78-week study period. Additional data in more patients would be needed to confirm these findings.

In this post-hoc analysis, Lp(a) levels did not change significantly for either of the apheresis groups. This is not a surprising finding given that patient numbers are small, and the Lp(a) levels are higher in the non-apheresis group. This latter finding is expected because apheresis removes apoB-containing lipoproteins from blood. This post-hoc analysis was not powered for significance. However, it is intriguing to observe that Lp(a) levels at baseline are approximately 50% higher in the non-apheresis group than those in the apheresis group, and mean reductions in Lp(a) over the course of the study were twice that in the non-apheresis group compared to the apheresis group. A larger sample size may provide data on which firm conclusions can be made about the relative abilities of lomitapide and lomitapide/apheresis combination therapy to control the rebound dynamics of Lp(a).

As compared to the modest effect of lomitapide in lowering Lp(a), both apheresis and mipomersen reduce circulating levels of Lp(a) more substantially [30,31]. This activity may confer an

additional cardioprotective effect, as elevated Lp(a) is an independent risk factor for CVD in FH [32]. The effect of Lp(a) reduction on long-term patient outcomes in FH remains to be determined; nevertheless, the differential effects of lomitapide, mipomersen, apheresis or novel targeted therapeutic approaches on Lp(a) levels [32] underscore the need to consider multimodal therapies in HoFH according to individual patient needs.

Safety data for lomitapide, including hepatic fat and GI tolerability, did not appear to differ between patients on apheresis compared with those who were not. The low number of patients in the analysis makes it difficult to make conclusions about the relative GI tolerability of lomitapide in combination with apheresis *versus* lomitapide alone. Of the six patients who discontinued the study, five were receiving apheresis, including three who discontinued because of GI AEs. This highlights the need to individualise therapy in HoFH patients, and for physicians and patients to be prepared to adjust the relative doses of apheresis and lomitapide to enable patients to remain on maximally effective combination regimens.

We recognize that this analysis has some limitations. Firstly, in the study protocol, the apheresis schedule was not fixed. As such, apheresis treatment was individualised on a per-patient basis, also taking into account physician experience. Therefore, not all patients received an optimal apheresis treatment schedule (in particular, one patient received apheresis once every 6 weeks). Secondly, the analysis by apheresis treatment was post hoc, and not pre-specified in the original protocol. As such, the study was not powered to detect small differences in response to treatment between apheresis treatment groups. Additionally, the small number of trial participants did not allow us to explore possible differences in response according to apheresis technique, which was not standardized and was undertaken according to site-specific protocols. Further, and in contrast to the TESLA trial of evolocumab in HoFH [24], a sub-analysis by receptor functionality was not possible based on study design that allowed for a maximum tolerated dose to be individually determined. However, due to the mode of action of lomitapide as an inhibitor of MTP, we would not expect LDL-receptor functionality to significantly affect efficacy, in contrast to the situation with statins and other agents that rely on functioning LDL-receptor. Finally, because analysis by apheresis was not defined a priori, AE data were collected and formally analysed only in relation to lomitapide, not apheresis.

Further data are required on the association between the effects of lomitapide and in particular LA (rather than TPE). Specific data from more controlled settings with only selectively chosen apheresis techniques would be most valuable. Importantly, given the significant add-on effect of lomitapide, it would be interesting to investigate whether it is possible to modulate the volume of blood/ plasma processed and to adjust the frequency of apheresis with the aim of making substantial, positive qualitative changes for patients who are candidates for lifelong therapy while not losing any potential beneficial effects of decreased LDL-C. Although the possibility to conduct larger clinical trials is hindered by the relative rarity of HoFH, it would be valuable to examine the relative clinical performance of lomitapide with and without standardized apheresis protocols, and to determine overall healthcare costs associated with the delivery of lomitapide and apheresis monotherapies, where data are currently lacking.

In conclusion, lomitapide, added to a low-fat diet and ongoing standard lipid-lowering treatment including apheresis, significantly reduced LDL-C in adult patients with HoFH to a similar degree whether the patient was receiving concomitant apheresis or not. Notably, different centres used different apheresis techniques and schedules in a manner analogous to a real-world, non-clinical trial situation. More studies are needed aimed at making substantial, positive qualitative changes for patients who are candidates for

lifelong therapy while not losing any potential beneficial effects of decreased LDL-C. Information of this type could be used to inform the design future of individualised, multimodal pharmacotherapy/ apheresis regimens.

Translational perspective

Due to the difficulties inherent in treating homozygous familial hypercholesterolaenia (HoFH), lipoprotein apheresis (LA) is part of the standard of care. Lomitapide, an oral agent for HoFH, was found to exert a lipid-lowering effect independently of LA. Therefore, both therapies can be applied concurrently without loss of efficacy.

Acknowledgements

Appendix A. Supplementary data

Supplementary data related to this article can be found at http:// dx.doi.org/10.1016/j.atherosclerosis.2015.03.014.

Conflict of interest

C. Stefanutti: Received honoraria and/or grant support from Aegerion, Fresenius Medical Care Deutschland GmbH and Kaneka NV; D.J. Blom: Received honoraria and/or grant support from Aegerion, Amgen AstraZeneca, Merck, Pfizer, Sanofi-Aventis, Ranbaxy, Servier and Unilever; M.R. Averna: Received honoraria and/or grant support from Aegerion, Sanofi, Amgen, MSD, Chiesi, Mediolanum, AZ, and Kowa. E.A. Meagher: Received honoraria and/or grant support from Aegerion; R.A. Hegele: Received honoraria and/ or grant support from Acasti, Aegerion, Amgen, Lilly, Merck, Omthera, Pfizer Tribute and Valeant; C.R. Sirtori: Received honoraria and/or grant support from Aegerion and Fondazione Carlo Sirtori; P.K. Shah: D. Gaudet: Received honoraria and/or grant support from Aegerion, Amgen, Aventis, Catabasis, Cerenis, Chiesi, ISIS Pharmaceuticals, Novartis, Regeneron, Sanofi and UniQure; B.S. Sachais: Received honoraria and/or grant support from Aegerion and Kaneka Pharma America; L.T. Bloedon: Equity-owning employee of Aegerion Pharmaceuticals Inc.; J. Balser: Employee of Veristat contracted by Aegerion Pharmaceuticals Inc.; D.J. Rader: Holds stock options in Aegerion. Received honoraria and/or grant support from Aegerion; M. Cuchel: Received honoraria and/or grant support from Aegerion and Sanofi/Regeneron. All other authors declare no conflicts of interest. None of the authors were paid by Aegerion Pharmaceuticals or any other agency to write this article.

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