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Efficacy and safety of lomitapide in familial chylomicronaemia syndrome

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ABSTRACT

Background and aims: Familial chylomicronaemia syndrome (FCS) is a rare autosomal recessive disorder, resulting in elevated triglycerides (TGs), abdominal pain and pancreatitis. Treatment options are limited. Lomitapide, a microsomal triglyceride transfer protein inhibitor, is approved for the treatment of homozygous familial hypercholesterolaemia. Whether its therapeutic use may be extended to FCS remains unknown. The aim of this study was to evaluate the efficacy and safety of lomitapide in adult patients with FCS.

Methods: The open-label, single-arm 'LOCHNES' study of lomitapide in FCS enrolled patients >18 years with genetically confirmed FCS, elevated fasting TG ≥ 750 mg/dL and history of pancreatitis. Patients were administered lomitapide to the maximum tolerated dose for 26 weeks. The primary endpoint was the percent change in TGs from baseline to Week 26.

Results: Eighteen patients were enrolled with median baseline TG levels 1803.5 mg/dL (97.5% CI, 1452–2391 mg/dL). At Week 26, median fasting TGs were reduced to 305 mg/dL (97.5% CI 219–801 mg/dL; 70.5% reduction); median lomitapide dose was 35 mg/day; 13 patients achieved TGs ≤750 mg/dL. Adverse events were mild to moderate and mainly related to gastrointestinal tolerability. Liver imaging at baseline and Week 26 revealed hepatic fat increases from median 12.0%–32.5%, while median hepatic stiffness remained normal. No patient experienced acute pancreatitis or severe abdominal pain during lomitapide treatment.

Conclusions: Lomitapide is effective and well tolerated in reducing TGs in FCS patients with a history of pancreatitis. Larger studies are warranted to determine lomitapide effectiveness in FCS.

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1. Introduction

Familial chylomicronaemia syndrome (FCS) is a rare, severe, monogenic, recessive disorder caused by loss-of-function mutations in both alleles of one or more of the genes that control the intravascular lipolytic cascade of triglyceride (TG)-rich chylomicrons and large very-low-density lipoproteins [1]. Five genes have been identified as causative of FCS in the presence of biallelic loss-of-function mutations, coding for lipoprotein lipase (*LPL*), apolipoprotein CII (*APOC2*), apolipoprotein AV (*APOA5*), glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (*GPIHBP1*) or lipase maturation factor 1 (*LMF1*). More than 80% of individuals with monogenic chylomicronaemia have biallelic lipoprotein lipase (LPL) mutations, of which more than 100 have been identified [1].

The clinical FCS phenotype is characterized by a very large increase in plasma levels of TGs >10 mmol/L (886 mg/dL) [1,2] and a lipemic appearance of aspirated blood samples due to the accumulation of chylomicrons during fasting. FCS patients also develop eruptive xanthomas, lipemia retinalis, recurrent abdominal pain, acute and/or recurrent pancreatitis, hepato-splenomegaly and memory loss [1–3]. Recurrent abdominal pain, alimentary restrictions and risk of pancreatitis and lipemia retinalis are responsible for the cognitive symptoms and emotional burden that negatively affect the quality of life of patients with FCS [4].

Patients with FCS have a high lifelong risk of developing acute, recurrent and often lethal episodes of pancreatitis [5]. The therapeutic goal in FCS is to permanently lower the TG plasma levels below 10 mmol/L (<886 mg/dL) - and ideally below 5 mmol/L (<443 mg/dL) if possible - in order to reduce the incidence of pancreatitis and to improve quality of life [6]. The standard of care of FCS is based on a strict dietary regimen with <10% of energy from fat and supplementation with medium-chain TGs [7]. Long-term adherence to this diet is poor [7].

Available TG-lowering agents, such as fibrates and high-dose omega-3 fatty acids, are not effective in monogenic FCS [2] and alternatives are being sought. Recent phase III trials have suggested that the antisense oligonucleotide volanesorsen, which inhibits apolipoprotein C-III RNA, may reduce TGs by 77% in patients with FCS [8]. A series of angiopoietin-like protein (ANGPLT3) inhibitors (evinacumab, IONIS-ANGPTL3-LRx and ARO-ANG3) have demonstrated efficacy in reducing TG levels in hypertriglyceridemia [9], but not in FCS due to LPL pathway mutations [10].

Microsomal triglyceride transfer protein (MTP) is an intracellular lipid-transfer protein essential for the assembly and secretion of the ApoB-containing lipoproteins; very-low-density lipoprotein (VLDL) in hepatocytes and chylomicrons in enterocytes [11]. Loss of function mutations in the *MTTP* gene results in abetalipoproteinemia [12].

Lomitapide is a small molecule microsomal triglyceride transfer protein (MTP) inhibitor that prevents assembly and secretion of apolipoprotein (apo) B-containing lipoproteins in the liver and intestine [13]. At present, lomitapide is approved by the Food & Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of familial homozygous hypercholesterolaemia (HoFH) on the basis of the results from a pivotal phase III clinical trial [14]. The ability of lomitapide to reduce the assembly and secretion of chylomicrons in the intestine prompted the design of the LOCHNES (LOmitapide for the treatment of patients with Familial CHylomicroNEmia Syndrome) study (EudraCT 2018-002911-80) to evaluate efficacy and safety of lomitapide in FCS.

2. Patients and methods

2.1. Study design, patients and interventions

LOCHNES is a multicenter, open label study to evaluate safety, tolerability, and efficacy of lomitapide in adult patients with FCS. Patients >18 years-old were eligible to participate if FCS was confirmed by genetic testing and fasting triglyceride levels were ≥750 mg/dL (8.5 mmol/L). All patients were required to have a history of pancreatitis consequent to FCS.

Genetic confirmation of FCS was based on detection of homozygosity, compound heterozygosity, or double heterozygosity for loss-of-function mutations in *LPL, APOC2, APOA5, GPIHBP1,* or *LMF1* genes. Exclusion criteria included active pancreatitis within 4 weeks prior to screening, congestive heart failure, history of liver disease or transaminases greater than two times the upper limit of normal (ULN), estimated creatinine clearance <50 mL/min (via Cockcroft-Gault formula), recent malignancy, alcohol or drug abuse, known bowel disease and malabsorption syndromes.

Patients were screened for eligibility 6–12 weeks prior to the first dose of lomitapide. Screening procedures included medical and medication history, review of current lipid-lowering therapies, physical examination, vital signs, 12-lead ECG, fasting lipid panel, safety laboratory assessments, and dietary counselling.

All enrolled patients were required to enter a minimum 6-week run-in phase during which concomitant lipid-lowering therapies and the low-fat diet were stabilized. All patients received detailed dietary counselling at the screening visit and at all subsequent visits until after the study drug was discontinued. The patients were advised to consume a diet containing less than 10% of energy from dietary fat while consuming adequate calories to maintain weight. Daily dietary supplementation of vitamin E and essential fatty acids were initiated. At the end of the run-in phase, patients entered a 26-week efficacy and safety phase, during which they received lomitapide in addition to their current lipid-lowering therapy. Lomitapide was initiated at a starting dose of 5 mg/day for the first two weeks and then escalated to 10, 20, 40, and 60 mg/day at 4-week intervals or until an individually determined maximum dose was reached based on lipid profile (TGs <750 mg/dL), liver safety transaminases, (alanine aminotransferase [ALT]/aspartate aminotransferase [AST] >5xULN) and tolerability (persistent gastrointestinal side effects). Dose adjustments were also made according to liver transaminase levels. If patients experienced ALT or AST elevations between 3-5 x ULN, or >100 IU/L but <200 IU/L above the baseline value (confirmed by central laboratory), the dose of lomitapide was reduced to the previously tolerated dose level, with the possibility to re-escalate dose once transaminase elevations were resolved. Once a maximum dose was established, patients remained on this dose up to Week 26.

Study design is shown in Supplementary Fig. 1.

2.2. Endpoints

The primary endpoint of LOCHNES was percent change in TGs compared to baseline after 26 weeks of treatment at the maximum dose of lomitapide in combination with other lipid-lowering therapy in patients with FCS.

Key secondary endpoints included other lipid parameters, percentage hepatic fat, liver stiffness and chylomicron kinetics. Data were also collected on changes in laboratory parameters, vital signs, physical examination and episodes of pancreatitis.

To enable collection of data for the primary and other endpoints a fasting lipid and safety panel, including liver function tests, was obtained at baseline, prior to each dose escalation, and every 4 weeks thereafter until Week 26. Blood was drawn at baseline and at each visit following a 12 h fast. Routine testing included a standard metabolic panel, a complete blood count, urinalysis. Tests were performed at the local central laboratory of each participating centre except for apolipoproteins A-I (ApoA-I) and B (ApoB), lipoprotein-a (Lp(a)) and high-sensitivity C-reactive protein (hsCRP), which were analysed solely at the Core Laboratory, University Hospital of Palermo, Italy. The study protocol included also a metabolic sub-study to determine postprandial chylomicron metabolism [15] and fatty acid profile [16]. These analyses were still under way at the time of manuscript preparation.

Lipid and lipoprotein analyses were conducted on serum samples.

Total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), and TGs were measured enzymatically. Non-HDL-C was calculated by subtracting HDL-C levels from TC levels. ApoA-I, ApoB and Lp(a) were measured by immunonephelometry (Roche Diagnostics, Italy).

Percentage hepatic fat was determined by magnetic resonance imaging (MRI) at baseline and Week 26. The MRI protocol included a dual-phase sequence and the IDEAL IQ sequence. Post-processing software, provided by the manufacturer, was used to generate fat fraction maps. A radiologist trained in abdominal imaging examined four 1 cm^2 regions of interest (ROIs) to measure signal intensities of the liver parenchyma in the in-phase. ROIs were copied from the in-phase images to the opposed-phase to ensure identical size and location. Focal hepatic lesions, major branches of portal or hepatic veins, and artifacts were avoided. The mean of the signal intensity of the liver was calculated as the average value of the four signal intensities of the liver parenchyma both in the in-phase and in the opposed phase. The hepatic fat fraction was then calculated with the following formula: 100 x (signal $intensity_{IP}$ - signal $intensity_{OP}$)/(2 x signal $intensity_{IP}$) [17]. Finally, ROIs were also copied in the HFF Axial IDEAL IQ map to ensure identical size and location (this map was not available in one patient). The liver ROIs placed on the IDEAL-IQ fat fraction reconstruction were used to generate estimates of percentage fat [18].

Non-invasive quantification of liver stiffness, liver stiffness measurement (LSM) in kPa (estimated fibrosis score: F0 to F1: 2–7 kPa; F2: 7.5–10 kPa; F3: 10–14 kPa; F4: >14 kPa) was measured by ultrasound-based transient elastography using FibroScan® (Palermo and Naples Centres) or shear wave elastography (SWE; Rome Centre). Non-alcoholic fatty liver disease fibrosis score (NFS) and fibrosis-4 (FIB-4) score were calculated according to Angulo et al. [19,20].

Adverse events (AEs) were coded using MedDRA, Version 11.0. AEs were judged by the investigators as not related, unlikely, possibly, probably or definitely related to study drug and were reviewed regularly by an independent Data and Safety Monitoring Board.

2.3. Statistical analysis

Numeric parameters were expressed as median values and 97.5% confidence intervals, while dichotomous variables were expressed as proportions. Differences in numeric parameters were evaluated by the Exact Wilcoxon-Mann-Whitney Test (R CRAN "coin" package, https://cran.r-project.org/web/packages/coin/index.html). Differences in proportions were evaluated by the Chi Square test. Percentual reductions of numeric variables at Week 26 were expressed as median values (with 97.5% confidence intervals) of the individual patient's variations from Week 0. Correlation of TG percent reduction with lomitapide dose was calculated by partial Spearman's correlation adjusting for TG baseline absolute values (R CRAN 'ppcor' package, https://cran.rproject.org/web/packages/ppcor/index.html). All calculations were performed by the R statistical software Version 4.04 under the RStudio Version 1.3.1093 interface.

2.4. Ethics

LOCHNES was approved by Italian Medicines Agency (AIFA) and each institution's Institutional Review Board or Ethics Committee and all patients provided written, informed consent. LOCHNES was registered with EudraCT (https://eudract.ema.europa.eu; EudraCT Number: 2018-002911-80).

3. Results

3.1. Patients

Eighteen adult patients with FCS, aged >18 years, were recruited from three specialist lipid clinic centres in Italy (Palermo, Rome and Naples) (Table 1 and Supplementary Table 1).

Table 1
Characteristics of the patients at baseline.

Characteristics	Value
Mean age (range), years	46.55 (19–75)
Sex, M/F, n (%)	8/10 (44.4/55.6)
Median body mass index (97.5% CI), kg/m^2	22.75 (20.2–25.8)
Median triglycerides (97.5% CI), mg/dL	1803.5 (1452–2391)
History of acute pancreatitis, n (%)	18 (100)
Baseline use of n-3 fatty acids, fibrates, or both, n (%)	18 (100)
Genetic mutations, n (%)	
LPL	14 (78)
APOC2	2 (11)
APOA5	0
LMF1	0
GPIHBPI	0
LPL/APOA5	1 (5.5)
LPL/GPIHBP1	1 (5.5)

To convert the values for triglycerides from mg/dL to mmol/L multiply by 0.01129*LPL*, lipoprotein Lipase; *APOC2*, apoprotein C2; *APOA5*, apoprotein A5; *LMF1*, lipase maturation factor 1; *GPIHBP1*, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1.

Of the 19 patients with FCS that were screened for eligibility, 18 entered the run-in phase and were enrolled in the study, with 100% of patients completing the 26 week study. One patient did not meet the eligibility criteria for enrolment because fasting triglyceride levels were <750 mg/dL (8.5 mmol/L) (Supplementary Fig. 2). The baseline characteristics of patients enrolled in the study are reported in Table 1 and Supplementary Table 1. All 18 patients were either homozygotes, compound heterozygotes or double heterozygotes for mutations in genes affecting the intravascular lipolytic chylomicron cascade. All patients were undergoing treatment with omega-3 fatty acids, fibrates, or both (3 g/day of ω-3 fatty acids as eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA] + 145 mg/day of micronized fenofibrate). Despite lipid-lowering treatment, TG levels were markedly elevated at baseline. Compliance with lomitapide dosing, defined as >80% of capsules taken, was 96% during the study. Among the 18 patients who completed the study, maximum dose by Week 26 was 5 mg in one subject; 10 mg in two patients; 15 mg in one subject; 20 mg in three patients; 30 mg in two patients; 40 mg in five patients; 50 mg in one patient and 60 mg in three patients. Median lomitapide maximum dose at Week 26 was 35 mg/day.

3.2. Effects of lomitapide on plasma lipids and lipoproteins

Median TG levels decreased from 1803.5 mg/dL (97.5% CI, 1452–2391 mg/dL) at baseline to 305.0 mg/dL (97.5% CI, 219 to 801) mg/dL at the end of the study (Week 26). No significant differences were observed in median TG reductions in patients ≤40 years of age (n = 7) compared with patients ≥40 years (n = 11) (274.5 mg/dL *vs* 292 mg/dL respectively). There was a statistically significant reduction in TG levels of 70.5% from baseline (97.5% CI, −90.7 to −48.0, $p < 0.0001$) (Table 2, Fig. 1). Changes from baseline to Week 26 for key secondary end points (TC, HDL-C, Non-HDL-C, ApoB, ApoA-I and Lp(a)) are shown in Table 2.

At Week 26, six patients (33.3%) experienced decreases in TG up to 50% (18.25–49.71%). Twelve patients (66.7%) experienced TG reduction >50% and of these, nine patients (50%) underwent a reduction >70%. Thirteen patients achieved TG levels ≤750 mg/dL (≤8.5 mmol/L) at Week 26, with ten (55.6%) of these patients achieving TG levels <500 mg/dL (<5.6 mmol/L). Fig. 2 shows a waterfall plot of the individual percent change in TGs for all 18 patients at Week 26. The individual percent reductions shown in Fig. 2 were not correlated with the lomitapide dose (partial correlation Spearman Rho 0.142, *p*-value 0.587).

No significant differences were observed for Lp(a) and hsCRP levels from baseline to Week 26 (Table 2). A significant increase of 20.7% in

Table 2
Changes in lipid parameters and hsCRP from baseline to Week 26.

Parameter	Baseline (n = 18)	Week 26 (n = 18)	Median of individual changes from baseline % (97.5% CI)[a]	*p* value[b]
Primary endpoint				
TG, mg/dL	1803.5 (1452–2391)	305.0 (219–801)	−70.5 (−90.7, −48.0)	<0.0001
Secondary endpoints				
TC, mg/dL	205.5 (176–252)	94 (69–132)	−51.7 (−60.8, −33.7)	<0.0001
HDL-C, mg/dL	16 (14–17)	18 (16–22)	+20.7 (+33.3, 15.0)	<0.01
non-HDL-C, mg/dL	184 (148–234)	90.0 (44–109)	−50.0 (−66.5, −26.4)	<0.0001
Lp(a), nmol/L	6 (3–11)	5.5 (3–30)	+40.5 (−20, +200)	ns
ApoB, mg/dL	81.85 (64.7–87.2)	39.25 (25.0–50.6)	−43.8 (−66.3, −25.2)	<0.0001
ApoA-I, mg/dL	93.7 (86.1–99.1)	74.95 (68.7–87.5)	−23.0 (−31.8, −4.6)	<0.0001
hsCRP, mg/L	1.2 (0.15–4.15)	1.24 (0.3–2.32)	+9.8 (−0.7, +0.8)	ns

Data expressed as median with 97.5% confidence intervals (CI) in brackets.
TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; non-HDL-C, non-HDL cholesterol; Lp(a), lipoprotein (a); ApoB, apolipoprotein B; ApoA-I, apolipoprotein A-I; hsCRP, high-sensitivity C-reactive protein; ns, not significant.
[a] Percentage reductions in numeric variables at Week 26 were expressed as median values (with 97.5% confidence intervals) of the individual patients' variations from Week 0.
[b] Exact Wilcoxon-Mann-Whitney Test.

HDL cholesterol was observed ($p < 0.012$) at Week 26, while ApoA-I levels were significantly reduced by −23% (97.5% CI, −31.8 to −4.6, $p < 0.0001$; Table 2).

3.3. Safety and tolerability

A summary of AEs reported during the study is presented in Supplementary Table 2. Most patients (15 of 18; 83.3%) experienced at least one AE during the study. Most of the AEs were assessed as mild to moderate in intensity. The most common types of AE reported during treatment with lomitapide were gastrointestinal (GI) in nature (55.6%). None of the patients discontinued the study due to GI events or permanently stopped lomitapide. There were no deaths during the study. Three of the 18 patients (16.7%) experienced serious AEs (SAEs) - all of these were recurrent episodes of pancreatitis in the run-in period and therefore considered to be unrelated to study treatment. All episodes resolved with standard-of-care treatment.

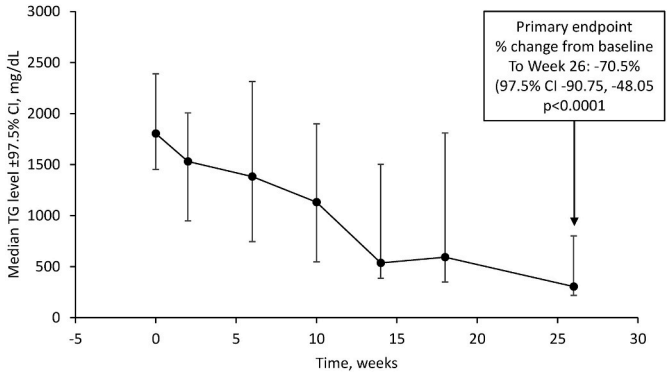

Fig. 1. Median triglyceride levels in FCS patients receiving lomitapide.
TG, triglycerides.

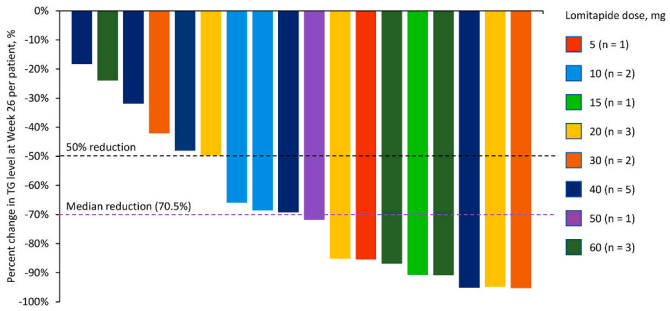

Fig. 2. Percent change in triglyceride levels at Week 26 for each FCS patient receiving lomitapide.
FCS, familial chylomicronaemia syndrome; TG, triglycerides.

3.4. Hepatic safety

Median ALT and AST levels over time are shown in Fig. 3. Four patients experienced elevations of ALT and/or AST >3xULN one or more times during the study. No patients exhibited ALT increases >5x ULN. The elevations >3xULN occurred at lomitapide doses 10 mg, 20 mg, 40 mg and 60 mg. No subject discontinued treatment permanently due to liver transaminase elevations and all increases were managed either by dose reduction or temporary interruption of lomitapide as per protocol. No subject experienced elevations in bilirubin or alkaline phosphatase levels. Hepatic fat was measured non-invasively using MRI. In the nine patients that had evaluable MRI scans at baseline and Week 26, median hepatic fat was 12% (97.5% CI 2%–30%) at baseline and 32.5% (97.5% CI 6–50%) at Week 26 ($p < 0.041$; Table 3). Three patients with baseline hepatic fat >20% (range 22–30%), experienced increases to 30–50% hepatic fat at Week 26. No significant changes were seen for non-invasive liver fibrosis measurements including quantification of liver stiffness, FIB-4 and non-alcoholic fatty liver disease fibrosis score (NFS) scores. Median FIB-4 score increased 38.44% from 0.76 at baseline to 1.03 (p = 0.0538, not significant). Median hepatic stiffness (n = 14) remained normal at 5.7 kPa–5.5 kPa (Table 3).

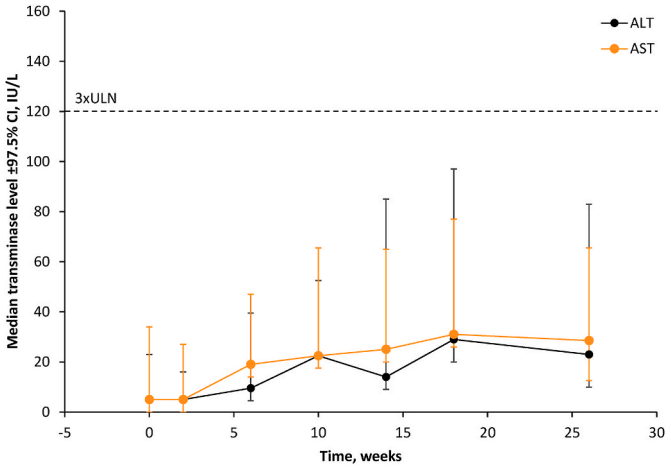

Fig. 3. Liver transaminase levels in FCS patients receiving lomitapide.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Table 3
Changes in markers of liver fibrosis from baseline to Week 26.

Parameter (N*)	Baseline	Week 26	Individual change from baseline, % (95% CI)	*p*-value[a]
LSM, kPa (14)	5.7 (5.0–6.6)	5.5 (4.6–7.5)	0.0 (−38.46, +5.63)	ns
Hepatic fat content on MRI, % (9)	12.0 (2–30)	32.5 (6–50)	+146.4 (+14.3, +900)	<0.04
NFS (18)	0.786 (0.208–1.760)	0.428 (0.112–1.247)	−51.69 (−0.41, −86.06)	ns
FIB-4 (18)	0.76 (0.48–1.12)	1.03 (0.58–1.76)	+38.44 (−18.40, +106.00)	ns

Data expressed ad median with 97.5% confidence intervals (CI) in brackets.
LSM: liver stiffness measurement; kPa: kilopascals; MRI: magnetic resonance imaging; non-alcoholic fatty liver disease (NAFLD) fibrosis score (NFS); FIB-4: fibrosis-4; (N*): number of subjects with data available at baseline and at 26 weeks; ns, not significant.
[a] Exact Wilcoxon-Mann-Whitney Test.

4. Discussion

LOCHNES met its primary efficacy endpoint of reduction in TG levels at Week 26. The median reduction in fasting TG levels *versus* baseline was 70.5% (median TGs levels 1803.5 mg/dL at baseline *versus* 305.0 mg/dL at Week 26). Most patients (14/18, 77.8%) achieved reductions in triglycerides to <1000 mg/dL. In 13 of these patients, median TG plasma levels were ≤750 mg/dL at Week 26. According to the study design, the daily dose of lomitapide was titrated up or down in the range 5–60 mg/day on the basis of efficacy and safety assessments to determine the maximum-tolerated dose. The median dose of lomitapide in LOCHNES was 35 mg/day. This is slightly lower than the median dose of 40 mg/day observed in the phase 3 trial of lomitapide in HoFH, which featured a similar dose escalation protocol [14]. In HoFH patients treated in a real-world setting, lomitapide doses are even lower (~20 mg/day) [21], and this might also be expected in the real-world use of lomitapide in FCS.

In the present study, adherence to treatment was high (97%). Individual TG reductions varied between patients. Most patients were able to achieve TG levels <750 mg/dL, with no clear association between target attainment and lomitapide dose. Similar variability was observed in the phase 3 trial of lomitapide in HoFH [14]. The reasons for variability of individual responses are currently unknown and may be due to characteristic lack of compliance to dietary counselling in patients with FCS, or variations in the background genetic profile of the patients with FCS, such as MTP gene expression [22].

In the present study, lomitapide did not result in significant alterations to Lp(a) or hsCRP levels by Week 26, although median levels of hsCRP were elevated above normal at baseline (1.2 mg/dL). A 20.7% increase in HDL cholesterol was observed, along with a 23.0% decrease in ApoA-I levels, both statistically significant.

Previous studies have shown that lomitapide-treated HoFH patients can have a small initial decrease in levels of both HDL-C and ApoA-I during up-titration of the drug - these levels returned to baseline levels at the end of the study [13,14].

There is some evidence of a shift to larger buoyant HDL subclasses (HDL_2) in lomitapide treated HoFH patients and the total cholesterol efflux capacity (CEC) is unaffected in lomitapide treated patients [23]. In the context of this study, elevations in HDL-C may be due to the inverse relationship between levels of TG and HDL-C driven by cholesterol ester transfer protein exchange [24]. The decreased ApoA-I levels may be related to both an increased catabolic rate and decreased production rate of ApoA-I messenger RNA levels fostered by MTP inhibition [25,26]. Further studies are needed to explore the composition and functional properties of HDL in FCS patients treated with lomitapide.

Most patients in LOCHNES (83.3%) experienced at least one AE. Most of these were GI in nature (55.6%), and most were mild or moderate. No patients discontinued lomitapide due to an AE. This pattern of mild/moderate GI adverse events that resolve with dose adjustment of lomitapide are common to almost all reports of lomitapide use in the clinic [21,27]. In LOCHNES, only three SAEs were reported, but all of these were episodes of pancreatitis, which is a common finding in uncontrolled FCS. All of these SAEs occurred in the run-in period before lomitapide treatment.

Some degree of hepatic fat accumulation is expected in accordance with the mechanism of action of lomitapide that reduces ApoB-containing lipoprotein formation in the liver and small intestine. In Massachusetts, USA, lomitapide has been used over a 14-year period for the treatment of a patient with recurrent pancreatitis secondary to severe hypertriglyceridemia [28]. After a near fatal episode of pancreatitis, lomitapide was commenced, and TG levels fell from 3000 mg/dL to 908 mg/dL (70%) with a mean lomitapide dose of 30 mg/day. TG levels were further reduced to 524 mg/dL (83% decrease) on lomitapide 40 mg/day. Over 12–13 years on lomitapide, the patient developed steatohepatitis and fibrosis in the context of a fatty liver prior to lomitapide use [28,29]. In LOCHNES, liver safety was evaluated via liver function tests and hepatic imaging, and baseline levels were higher than that seen in HoFH (12% *versus* 1%), which is not an unexpected finding in FCS. Elevations in liver transaminases - ALT levels >3xULN were recorded at least once in four patients, but no patients exhibited ALT increases >5x ULN. There was no pattern evident around liver transaminase elevations and dose of lomitapide. Median hepatic fat increased from 12% at baseline to 32.5% at Week 26. There were no significant changes in markers of hepatic pathology, including liver stiffness, FIB-4 and NFS scores.

It is well known that conventional therapies based on the use of very low-fat diets and/or of fibrates and omega-3 fatty acids are either difficult to accept by patients or have limited effectiveness in FCS [2]. Recently, volanesorsen, an antisense oligonucleotide targeting apoCIII mRNA, has become available for the treatment of this condition [30]. The placebo-controlled APPROACH study reported that patients receiving volanesorsen showed a reduction in serum TG levels of ~60% after 52 weeks of therapy [31]. Among the most common adverse events associated with volanesorsen were local irritation at the site injection and thrombocytopenia, as 15 patients (45%) receiving volanesorsen reached a platelet count less than 100,000 per mm^3 and 2 (6%) had a count of less than 25,000 per mm^3 [31].

According to the conditional marketing authorization granted by the European Medicines Agency (EMA), if the platelet count is below 140×10^9/L on two consecutive evaluations while being treated with volanesorsen, patients should have platelet monitoring increased from every two weeks to every week [32]. Therefore, while the approval of volanesorsen for FCS by the EMA is welcome, it may not be considered a suitable treatment option for all FCS patients.

For lomitapide, an extensive pre-treatment and on-treatment hepatological monitoring is mandatory if physicians decide to use lomitapide to manage FCS [28,29]. As both treatments are for a rare disease, the costs are likely to be similar and the decision to treat with volanesorsen or lomitapide should be made by balancing the potential patient-based development of side effects and the known risk of developing episodes of pancreatitis if patients remain untreated.

LOCHNES is limited by a small sample size with heterogenous phenotypes, short follow up and incomplete liver imaging results in a subset of patients. Additionally, the dose adjustment protocol was based on the holistic physician assessment of efficacy and tolerability, and while lomitapide was titrated to a maximum-tolerated dose for transaminase

results, there were no algorithm-based rules for dose adjustment *vis a vis* TG levels. Only 9 patients had evaluable MRI scans due to difficulties for patients accessing the clinics during the COVID-19 pandemic. FIB-4 scores, which were used to assess risk of fibrosis, are known to be inaccurate in patients with low platelet levels and in patients aged ≥65 years [33,34]. Many of the patients treated in this study continue to be treated through a lomitapide expanded access programme, which has the potential to provide longer-term data in these FCS patients.

In summary, lomitapide demonstrated a high level of efficacy in reducing TG levels in patients with FCS over 26 weeks. Median lomitapide dose was slightly lower than that observed in the phase 3 dose escalation study in HoFH. Lomitapide was generally well tolerated. The findings of the LOCHNES study indicate that MTP inhibition warrants further exploration in FCS, possibly with multivariate analyses designed to determine the cause of inter-patient variability. Long-term assessment of hepatic safety should also be conducted.

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Authors contribution

ABC, LDE, GI, DN and MAv contributed to study design, patients' recruitment, data collection, data analysis, data interpretation and writing.

MC, RC: centralized laboratory parameters assessment, draft revision, and final approval for submission.

FV: imaging analysis, draft revision, and final approval for submission.

All other authors contributed to patient recruitment, data collection, data analysis, data interpretation, draft revision, and final approval for submission.

Author declarations

All authors meet all four criteria for authorship in the ICMJE Recommendations.

All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

MA, GI, DN and ABC have directly accessed and verified the underlying data reported in the manuscript.

None of the authors are from a commercial sponsor.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2022.08.017.

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