The Lancet Diabetes & Endocrinology

-Lomitapide for the treatment of paediatric patients with homozygous familial hypercholesterolaemia: Results from the Efficacy Phase of APH-19, a phase 3, open-label study

--Manuscript Draft--

Manuscript Number:	THELANCETDE-D-24-00282R2
Article Type:	Article (Original Research)
Keywords:	Paediatric; homozygous familial hypercholesterolaemia; HoFH; Lomitapide; phase 3 clinical trial
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Abstract:	Background Homozygous familial hypercholesterolaemia (HoFH) is a rare inherited disorder characterised by extremely high levels of low-density lipoprotein cholesterol (LDL-C), leading to early-onset atherosclerosis. Lomitapide is an orally administered microsomal triglyceride transfer protein inhibitor which effectively lowers LDL-C, approved for adults with HoFH. APH-19 was designed to investigate the efficacy and safety of lomitapide in paediatric patients with HoFH. Methods APH-19 (NCT04681170) is a phase 3, open-label, single-arm trial of lomitapide in paediatric patients with HoFH receiving standard of care lipid-lowering therapy. A Run-in Period was followed by 24-week Efficacy and 80-week Safety Phase. Patients were titrated to maximum tolerated doses of lomitapide, starting at 2mg (patients 5–15 years) or 5mg (patients 16–17 years). The primary endpoint was the percent change from Baseline to Week 24 in LDL-C. Findings Forty-three patients were treated (female: 55.8%; mean age: 10.7 years). Mean change from Baseline in LDL-C at Week 24 was -53.5% (95% CI -61.6; -45.4,

	p<0.0001). Mean percent reductions were observed at Week 24 for non-high-density lipoprotein C (-53.9%, 95% CI -61.7; -46.1, <0.0001), total cholesterol (-50.0%, 95% CI -57.6; -42.4, p<0.0001), very-low-density lipoprotein cholesterol (-50.2%, 95% CI -59.1; -41.2, p<0.0001), apolipoprotein B (-52.4%, 95% CI -60.3; -44.5, p<0.0001) and lipoprotein(a) (-11.3%, 95% CI -32.9; 10.3 [mg/dL]; -23.6%, 95% CI -38.2; -9.0 [nmol/L]; p=0.007 combined). AEs were mostly mild, and gastrointestinal and hepatic in nature. AEs of special interest (AESI) were reported for 5 patients (11.6%); gastrointestinal n=2 and hepatic n=3. One serious related treatment emergent AE was reported (also classed as an AESI) – an increase in hepatic enzymes, resulting in two dose interruptions, two dose reductions and a repeated dose escalation. Interpretation Lomitapide provided statistically significant, clinically meaningful LDL-C reduction and has the potential to be an efficient, LDL receptor-independent option for paediatric patients. Funding Amryt Pharmaceuticals DAC.

Lomitapide for the treatment of paediatric patients with homozygous familial hypercholesterolaemia: Results from the Efficacy Phase of APH-19, a phase 3, open-label study

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Word count: 4540

Panel: Research in context

Evidence before this study

Homozygous familial hypercholesterolaemia (HoFH) causes extremely high levels of low-density lipoprotein C (LDL-C), with the threshold for atherosclerotic cardiovascular disease (ASCVD) being reached at around 12.5 years of age, and life expectancy around 18 years if untreated. Early diagnosis and treatment in childhood is imperative to avoid morbidity and mortality.

Treatment options for children are limited and as a result, young patients with HoFH rarely reach target LDL-C levels, even with maximally tolerated combinations of currently available lipid-lowering therapies (LLTs).

Lomitapide is a microsomal triglyceride transfer protein inhibitor which effectively lowers LDL-C, independently of the LDL receptor function, and is approved for adults with HoFH. Prior to this study, lomitapide was shown to be effective in lowering LDL-C in a case series of paediatric patients with HoFH (N=11), where the mean LDL-C reduction was 58% after 20 weeks of lomitapide therapy.

Added value of this study

APH-19 is the first clinical trial of lomitapide in paediatric patients with HoFH. Results show that lomitapide treatment over 24 weeks provides significant reductions in LDL-C, non-high-density lipoprotein C, total cholesterol, very-low-density lipoprotein cholesterol, ApoB and Lp(a) in patients aged 5–17 years. Forty-two percent of patients were able to reach the pre-specified LDL-C target level of <135 mg/dL by Week 24. No new safety signals were identified, and the majority of adverse events were mild or moderate in severity. Hepatic enzyme elevations occurred in around one-third of patients, were mostly transient and did not necessitate dose modification/therapy interruption with the exception of two cases. These were managed by dose reductions in one patient and therapy interruptions followed by dose reductions in the other.

Implications of all the available evidence

Lomitapide is an effective LDL-C-lowering agent for paediatric patients with HoFH with an acceptable safety and tolerability profile. New therapeutic options in this vulnerable population are urgently needed to address the significant unmet need and potentially reduce morbidity and mortality

Abstract

Background

Homozygous familial hypercholesterolaemia (HoFH) is a rare inherited disorder characterised by extremely high levels of low-density lipoprotein cholesterol (LDL-C), leading to early-onset atherosclerosis. Lomitapide is an orally administered microsomal triglyceride transfer protein inhibitor which effectively lowers LDL-C, approved for adults with HoFH. APH-19 was designed to investigate the efficacy and safety of lomitapide in paediatric patients with HoFH.

Methods

APH-19 (NCT04681170) is a phase 3, open-label, single-arm trial of lomitapide in paediatric patients with HoFH receiving standard of care lipid-lowering therapy. A Run-in Period was followed by 24-week Efficacy and 80-week Safety Phase. Patients were titrated to maximum tolerated doses of lomitapide, starting at 2mg (patients 5–15 years) or 5mg (patients 16–17 years). The primary endpoint was the percent change from Baseline to Week 24 in LDL-C.

Findings

Forty-three patients were treated (female: 55·8%; mean age: 10·7 years). Mean change from Baseline in LDL-C at Week 24 was -53·5% (95% CI -61·6; -45·4, p<0·0001). Mean percent reductions were observed at Week 24 for non-high-density lipoprotein C (-53·9%, 95% CI -61·7; -46·1, <0.0001), total cholesterol (-50 0%, 95% CI -57·6; -42·4, p<0·0001), very-low-density lipoprotein cholesterol (-50·2%, 95% CI -59·1; -41·2, p<0·0001), apolipoprotein B (-52·4%, 95% CI -60·3; -44·5, p<0·0001) and lipoprotein(a) (-11·3%, 95% CI -32·9; 10·3 [mg/dL]; -23·6%, 95% CI -38·2; -9·0 [nmol/L]; p=0·007 combined). AEs were mostly mild, and gastrointestinal and hepatic in nature. AEs of special interest (AESI) were reported for five patients (11·6%); gastrointestinal n=2 and hepatic n=3. One serious related treatment-emergent AE was reported (also classed as an AESI) – an increase in hepatic enzymes, resulting in two dose interruptions, two dose reductions and a repeated dose escalation.

Interpretation

Lomitapide provided statistically significant, clinically meaningful LDL-C reduction and has the potential to be an efficient, LDL receptor-independent option for paediatric patients.

Funding

Amryt Pharmaceuticals DAC.

Introduction

Homozygous familial hypercholesterolaemia (HoFH) is a rare, life-threatening inherited disorder characterised by extremely high levels of low-density lipoprotein cholesterol (LDL-C) and premature atherosclerotic cardiovascular disease (ASCVD).[1] It is estimated that ~30,000 people worldwide have HoFH, but it is widely underdiagnosed, with less than 5% of the estimated number of cases identified.[1-3] The genetics of HoFH are complex with the most common causal pathogenic gene variants occurring in genes involved in the LDL receptor (LDLR) pathway, including *LDLR*, apolipoprotein B (*APOB)*, and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene loci.

The cumulative LDL-C exposure that occurs in HoFH means that the threshold for ASCVD is reached in childhood (approximately 12·5 years of age).[3] As such, the average age of death for people with HoFH, when untreated, is 18 years, although deaths before the age of 5 have been reported.[4] Therefore, early diagnosis and treatment in childhood is imperative to reduce circulating LDL-C, and to delay the development of ASCVD.

Pharmacological reduction of LDL-C using maximum tolerated doses (MTD) of statins and ezetimibe is standard practice, and is recommended to be initiated before the age of 2 years.[5] Unfortunately, these therapies act via the LDLR pathway that is severely impaired in patients with HoFH. Therefore, these individuals rarely reach recommended LDL-C targets on the standard of care therapy, and more intense intervention is required. However, pharmacological treatment options for children are limited, with many therapies lacking regulatory approval or data in paediatric patients, and reduced effectiveness in HoFH if relying on residual LDLR activity e.g., PCSK9 inhibitors.[1,6-9] Lipoprotein apheresis (LA) remains an important non-pharmacological intervention for paediatric patients but is burdensome for patients and relatives, as it may be required up to twice weekly in apheresis centres.[10] It is also not universally available and has only a transient effect on LDL-C.[1,11-13]

With LDL-C levels remaining substantially above recommended goals for most patients, despite the standard of care treatments mentioned above, LDLR-independent therapies are a critical component of the latest HoFH treatment algorithm and are recommended to sufficiently lower LDL-C.[1] These include lomitapide, a microsomal triglyceride transfer protein (MTP) inhibitor, and angiopoietin-like 3 inhibitors (e.g., evinacumab[14,15]). Lomitapide is an oral once daily therapy, which reduces LDL-C levels independently of LDLR by decreasing the secretion of its precursor, very low-density lipoprotein cholesterol (VLDL-C).[16] Lomitapide, in combination with other lipid-lowering medicines and a low-fat diet, effectively reduces LDL-C across genotypes, and is approved for use in adults with HoFH.[17-19] The

current data on lomitapide for paediatric patients is limited to case studies and series, but shows promising reductions in LDL-C levels aligned with that seen in trials of adult patients.[20,21]

The purpose of the APH-19 clinical trial (NCT04681170) was to investigate the clinical efficacy and safety of lomitapide in paediatric patients with HoFH in a statistically powered study.

Methods

Study design and participants

APH-19 is a single-arm, open-label, multi-centre phase 3 study to evaluate the efficacy and long-term safety of lomitapide in paediatric patients with HoFH receiving stable lipid-lowering therapy (LLT). The Efficacy Phase of the study was performed between December 2020 and October 2022, at 12 study centres in Germany, Israel, Italy, Saudi Arabia, Spain, and Tunisia.

APH-19 consists of a 6- to 12-week Run-in Period, followed by a 24-week Efficacy Phase and 80-week Safety Phase. The study design is shown in **Supplementary Figure 1** (appendix p16).

Patients and/or their parent/legal guardian provided informed consent and had to be able and willing to follow study procedures and instructions. Eligible patients were aged 5–17 years on stable LLT, with HoFH diagnosed using the criteria from the 2014 EAS Consensus Panel on HoFH:[22] either (i) a genetic confirmation of two mutant alleles at the *LDLR*, apolipoprotein B (*ApoB*), proprotein convertase subtilisin/kexin type 9 (*PCSK9*) or low-density lipoprotein receptor adapter protein 1 (*LDLRAP1*) gene locus; or (ii) untreated LDL-C ≥500 mg/dL / treated LDL-C ≥300 mg/dL together with cutaneous or tendon xanthoma before age 10 years or untreated LDL-C levels consistent with heterozygous familial hypercholesterolaemia in both parents. Full inclusion and exclusion criteria are shown in **Supplementary Table 1** (appendix p6).

APH-19 was conducted in accordance with the harmonised tripartite ICH Guidelines for good clinical practice, and with the Helsinki Declaration of 1964 and its later amendments. The study was approved by the institutional review board and independent ethics committee at each participating site. The analysis plan was agreed upon by the sponsor and regulators. The analysis was performed by a Contract Research Organization (Veristat LLC, MA, USA), contracted by the sponsor (Amryt Pharma). The results of the analysis were reviewed by the authors. Periodic safety analyses were performed by a Data Safety Monitoring Board

(DSMB), which comprised four members, one of whom was a statistician. The DSMB was independent and not otherwise involved in the conduct of the study.

Randomisation and masking

APH-19 was an open-label study, and as such, was not masked or blinded. Given the existing data to indicate the benefit of lomitapide therapy in HoFH and the rarity of the disease, a randomised two-arm design with placebo was not considered acceptable for these very high-risk patients. Furthermore, the safety profile of lomitapide would potentially unblind both patients and investigators.

Procedures

Lomitapide was administered orally in capsule form for all patients, and the dose was escalated following the applicable titration scheme based on patient age (**Supplementary Table 2;** appendix p7). The dose must have been tolerated for at least four consecutive weeks before escalation to the next higher dose in stepwise increments. MTD definition details can be found on appendix p2. Dosing was stratified into three age groups (5–10, 11–15 and 16–17 years). All patients were placed on a low-fat diet (less than 20% fat or <30g fat, whichever was the lesser amount), supplemented with vitamin E (200 international units [IU] for patients aged 5–8 years, 400 IU for patients aged 9–17 years) and essential fatty acids.[17,18] More details can be found on appendix p2. In addition, during the Efficacy Phase, patients were required to remain on the stable LLT regimen (including LA, when applicable) established during the 6-week Run-in Period.

Blood samples for fasting lipid panel analysis were collected at Baseline and every 4 weeks thereafter. Use of concomitant medications and LLT, including LA, was assessed continuously throughout the study. Blood samples for laboratory safety tests (metabolic panel and liver function tests [LFTs]) were collected at Baseline and every 4 weeks thereafter. More details can be found on appendix p2**.**

Safety was assessed continuously throughout the study from the start of the Run-in Period through to the end of the follow-up period and adverse events (AEs) were followed until resolution or stabilisation. AEs were evaluated by the incidence, severity, and the relationship of AEs to study drug and were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 25.1, and classified by System Organ Class and Preferred Term. Treatment-emergent AEs (TEAEs) were summarised overall and by age group and classified by maximum severity and relationship to study drug.

Outcomes

The primary outcome measure was the percent change from Baseline to Week 24 in LDL-C. Based on the previous pivotal study of lomitapide in adult patients with HoFH,[19] key secondary outcome measures were chosen and tested in order of their clinical relevance. The secondary outcomes were the percent change from Baseline at Week 24 in total cholesterol, non-high-density lipoprotein cholesterol (non-HDL-C), VLDL-C, triglycerides, lipoprotein(a) [Lp(a)], and ApoB. Primary endpoint sub-group analyses were conducted using two age groups (5–10, 11–17 years) instead of the three dosing sub-groups. The change from three to two sub-groups was based on the number of patients who were available to be enrolled into the upper age group and was implemented following a protocol amendment (August 2022) per agreement with the European Medicines Agency Paediatric Committee. Additional exploratory secondary outcome measures were the number and proportion of patients achieving the previous EAS recommended target LDL-C of <135 mg/dL (3.5 mmol/L) at Week 24. Note that at the time of trial design, this was the EAS recommended target LDL-C for children and adolescent patients,[22] with the 2023 update lowering this target to 115 mg/dL (<3.0 mmol/L).[1]

Safety endpoints included incidence of reported AEs including adverse events of special interest (AESIs, including hepatic/gastrointestinal/pancreatic tumours, hepatic abnormalities [e.g., hepatic enzyme increases] and gastrointestinal events; see appendix p3), serious AEs (SAEs), and treatment-related events. Hepatic safety endpoints included hepatic fat assessment by nuclear magnetic resonance (NMR) imaging or ultrasound, and LFTs. Further population-specific safety endpoints were the impact of treatment on patient growth and maturation, which was assessed in terms of patient weight, height, body mass index (BMI), BMI-for-age z-score, BMI percentile, height-for-age z-score and height percentile, hormone levels and Tanner Staging (further details can be found on appendix p4).

Statistical analysis

At least 30 evaluable patients were required to provide 92% power, assuming a 25% reduction from Baseline in LDL-C with a standard deviation (SD) of 40% and a 2-sided α of 0·05, with sampling distribution of the mean assumed to be normal under the central limit theorem; data distributions were also checked through normal quantile-quantile plots to confirm no significant departures from normality for all study endpoints. To allow for up to 33% dropout during the Efficacy Phase (prior to Week 24), an additional 15 patients were enrolled. Enrolment was stratified to ensure approximately equal numbers of patients within

age groups of 5–10 and 11–17 years, in order to facilitate the analysis performed in these two patient groups. The full analysis set was defined as patients who had received ≥1 dose of lomitapide, and who had a Baseline and ≥1 post-Baseline measurement. The safety analysis set was defined as patients who had received ≥1 dose of lomitapide.

The primary efficacy analysis was conducted once all patients completed (or withdrawn prior to Visit 10) at Week 24±3 days (End of the Efficacy Phase). The primary efficacy analysis included the key primary and secondary efficacy data, all safety data available up to the data cut-off date of the last patient reaching Week 24±3 days, and pharmacokinetic parameter analysis. The final statistical analysis was performed when all patients completed the Follow-up Visit (Visit 23) at Week 108±7 days. Efficacy, safety, and exploratory data collected during both the Safety Phase and follow-up were included. Analysis of other secondary endpoints collected during the Efficacy Phase and of endpoints collected during the Safety Phase were analysed without adjustment for multiplicity. All analyses were conducted using SAS version 9.4.

All patients enrolled in the Efficacy Phase with at least one post-Baseline LDL-C observation were included in the efficacy analyses. The key secondary efficacy endpoints were tested sequentially in a pre-specified fixed order, to control the overall type I error. The percent changes from Baseline for the primary and secondary efficacy outcomes at Week 24 were each analysed using a one sample t-test. For the efficacy outcomes, missing data were imputed using the last observation carried forward (LOCF) approach. This (or any other method of data imputation) was not utilised for the sensitivity analyses, which were conducted using a Mixed Models for Repeated Measures approach under the assumption that data were missing at random. Under this approach, time was the fixed effect and subject was the random effect; no other random effects were included. Sub-group analyses were conducted by age group (5–10 and 11–17) using an Analysis of Covariance (ANCOVA) model to estimate the mean percentage change and 2-sided 95% confidence intervals within each sub-group at Week 24±3 days.

Summary statistics (presented for the overall group and by age group) were used to assess safety in the safety population. Events leading to discontinuation as well as SAEs and AESIs (e.g., hepatic abnormalities, gastrointestinal effects) were summarised. Here, 24-week Efficacy Phase and safety endpoints are reported in this paper.

Role of the funding source

Amryt Pharmaceuticals DAC (Dublin, Ireland) funded this study, and was therefore responsible for study design, data collection, analysis and regulatory compliance. The paper was written by the authors with assistance from Alistair Ray, Steven Foster and Jake

Casson of Meridian HealthComms Ltd (Macclesfield, UK), funded by Amryt Pharmaceuticals DAC, who provided editorial and technical support in the preparation of the manuscript.

Results

Patients disposition in APH-19 is shown in **Figure 1**. Forty-six patients entered the Run-in Period, where three patients were lost to follow-up, including one patient in the 5–10-year age group that died prior to starting lomitapide (myocardial ischaemia), which was therefore considered as a non-treatment-emergent serious AE. Two further patients left the study voluntarily owing to withdrawal of parental consent and inability to comply with the study schedule. A total of 43 patients entered the 24-week Efficacy Phase; of these, two adolescent siblings prematurely discontinued from the study due to moderate AESIs of diarrhoea at Week 10–11 and 41 patients entered the Safety Phase, which will be reported at a later date.

Full baseline characteristics can be found in **Table 1**. The majority of patients had a genetic diagnosis of HoFH (n = 38 [88·4%]), and five patients were diagnosed using other criteria from the 2014 EAS Consensus Panel on Homozygous Familial Hypercholesterolemia.[22] The median baseline LDL-C level in the full cohort was 390·5 mg/dL (range: 152·3 to 902·4 mg/dL), with a higher median baseline LDL-C level in patients aged 5–10 years (526·8 mg/dL) compared with patients aged 11–17 years (346·4 mg/dL). Prior/run-in background LLTs were maintained through the Efficacy Phase, with the exception of one patient who discontinued evolocumab at Week 8. Details of other concomitant medications during the study are shown in **Supplementary Table 3** (appendix p8), with a detailed description of cardiovascular (CVD) conditions shown in **Supplementary Table 4** (appendix p9).

Efficacy data are presented for the full analysis set (N = 43); the LOCF approach was utilised for four patients. APH-19 met its primary efficacy endpoint, with a significant overall mean LDL-C percent change from Baseline at Week 24 of -53·5% (95% confidence interval [CI] -61·6, -45·4; p<0·0001; **Figure 2**). A waterfall plot of the patient-level data of the percentage change from Baseline in LDL-C at Week 24 is shown in **Supplementary Figure 2** (appendix p17), mean values at each study visit shown in **Supplementary Figure 3** (appendix p25) and mean LDL-C percentage change from Baseline using LOCF and the sensitivity analysis in **Supplementary Table 5** (appendix p10). The mean (SD) LDL-C of the full cohort decreased from 435·8 (189·5) mg/dL at Baseline to 176·5 (90·4) mg/dL at Week 24. Results were similar when the cohort was split into younger and older patient sub-groups.

Secondary outcomes in the lipid markers non-HDL-C, total cholesterol, VLDL-C, ApoB, triglycerides and Lp(a) were also significantly reduced from Baseline after 24 weeks of lomitapide therapy (**Figure 3**). Mean values at each study visit shown in **Supplementary Figure 3** (appendix p25). Overall, non-HDL-C decreased by -53·9% (95% CI -61·7, -46·1; p<0·0001). Total cholesterol decreased by -50·1% (95% CI -57·6, -42·5; p<0·0001), while VLDL-C decreased -50·2% (95% CI -59·1, -41·2; p<0·0001). ApoB decreased by -52·4% (95% CI -60·3, -44·5; p<0·0001), and triglycerides decreased by -49·9% (95% CI -58·8, -41·0; <0·0001).

Lp(a) was measured in local laboratories, with 21 patients having results measured in mg/dL and 22 patients having results measured in nmol/L. Of the patients with mg/dL measurements, Lp(a) decreased by -11·3% (95% CI -32·9; 10·3). Of the patients with nmol/L measurements, Lp(a) decreased by -23·6% (95% CI -38·2; -9·0). The Fisher combined p-value for the mg/dL and nmol/L datasets was p=0·007.

At any time up to Week 24, a total of 18 patients (41.9%) had achieved the pre-specified EAS recommended target LDL-C level of <135 mg/dL, which comprised seven patients (35·0%) aged 5–10 years and 11 patients (47·8%) aged 11–17 years. A post-hoc analysis with the updated recommended EAS target LDL-C level of <115 mg/dL (<3·0mmol/L)[1] showed that at any time up to Week 24, a total of 16 patients (37·2%) achieved this lower target. This includes five patients aged 5–10 years and 11 (47·8%) aged 11–17 years. Exploratory endpoint results can be found on appendix p3**.**

Twenty-five patients (58·1%) had at least one TEAE considered related to study treatment; 10 patients aged 5–10 years (50·0% of age group) and 15 patients aged 11–17 years (65·2% of age group; **Table 2** with additional safety results shown in **Supplementary Table 6**; appendix p11). The most commonly reported TEAEs were gastrointestinal or hepatic in nature (**Supplementary Table 7**; appendix p12).

Eight events in five patients were considered serious: two in two patients in the 5–10 years age group, and a further six events were recorded in three patients in the 11–17 years age group. Only one of these events was considered related to study treatment (hepatic enzyme increased, occurring in the 5–10 years age group; **Table 2**). One patient experienced two life-threatening TEAEs, of which one was assessed as a major adverse cardiovascular event (MACE); neither of these TEAEs led to study drug discontinuation or was deemed to be related to treatment (**Table 2**). A detailed breakdown of serious TEAEs is shown in **Supplementary Table 8** (appendix p13).

Six AESIs were recorded in five patients: four events in three patients aged 5–10 years and two events in two patients aged 11–17 years (**Table 3**). As previously mentioned, two moderate AESIs of diarrhoea led to study discontinuation, both in the 11–17 years age group.

The most frequently reported TEAEs were gastrointestinal in nature, with diarrhoea (46.5%) and abdominal pain (41.9%) the most common. Both of these occurred at similar frequencies in the 5–10 and 11–17 age sub-groups.

TEAEs related to hepatic enzyme elevation were reported in a total of 16 patients (37·2%), encompassing the preferred terms 'ALT/AST increased', 'hepatic enzyme increased', 'hypertransaminasaemia', and 'transaminases increased.' These were more common in 5–10 years age group than the 11–17 age group (9 patients [45·0%] versus seven patients [30·4%], respectively; **Supplementary Table 9**, appendix p14).

These TEAEs were considered treatment-related in most patients and were mild or moderate in severity, with only one reported as severe (hepatic enzyme increased). This serious related TEAE occurred at Week 32, met the criteria for a level 4 Hepatotoxicity per APH-19 study protocol, and was therefore reported as an AESI to the DSMB. Dosing was interrupted immediately; following this, the only finding from all diagnostic tests was a mild hyperechogenic liver per ultrasound. Subsequently, transaminases started rising again upon re-challenge. Therefore, the DSMB recommended to interrupt lomitapide for a further 6–8 weeks with normal liver function tests before repeating the dose escalation per age group. Shortly after the maximum dose per age group (20 mg/day) had *de novo* been achieved at Week 80, the patient again experienced an AESI of elevated liver enzymes, which required two further dose interruptions with corresponding dose reductions to 10 mg/day and 5 mg/day, respectively and 10 mg/day as final dose.

Considering both ultrasound scans and NMR scans, at Week 24, lipid accumulation data were available for 34 patients; 30 patients had ≤10% liver fat, three patients had >10% and ≤20% liver fat, and one subject had >20% liver fat. Increases from Baseline were reported for overall four patients, one patient 5–10 years and three patients 11–17 years.

There were no other clinically significant mean changes related to treatment in other safety endpoints, e.g., growth and maturity/Tanner Staging and fat-soluble vitamins. ECG/echocardiograph findings were consistent with CVD histories. These and other additional safety findings are on appendix p4**.**

Overall, no new safety signals were identified, and the results were consistent with the known safety profile of lomitapide.

Discussion

Results from the APH-19 study demonstrate the efficacy of lomitapide in paediatric patients, with a statistically significant 53·5% overall reduction in LDL-C after 24 weeks of treatment and an acceptable safety profile. LDL-C reduction was consistent as evidenced by the narrow confidence intervals, and apparent in younger paediatric (aged 5–10 years) and older adolescent (aged 11–17 years) analysis sub-groups. The degree of LDL-C reduction is marked in the context of a cohort that was receiving maximally tolerated statin/ezetimibe LLT, with LA use widespread among the cohort (~44% at Baseline).

The substantial percentage reduction in LDL-C at Week 24 observed in APH-19 is similar to that seen in the pivotal phase 3 adult study of lomitapide, with a 50% LDL-C reduction observed after 26 weeks of treatment in adults receiving background LLTs.[19] The present study builds on published evidence from a case series in paediatric patients by Ben-Omran *et al.*, where a mean LDL-C reduction of 58% was reported after a mean of 20 weeks of lomitapide therapy.[20] This was similar to the LDL-C reduction seen in the present study at 24 weeks.

The clinical impact of lomitapide in combination with standard LLTs was emphasised by the substantial proportion of patients (41·9%) that met the previous EAS target LDL-C threshold of <135 mg/dL.[22] A similar proportion reached the more stringent <115 mg/dL threshold set for paediatric patients in the recent 2023 EAS statement.[1] This is encouraging, although it should be noted that 65·1% of patients had an ongoing cardiovascular medical history at Screening, and the EAS guidelines recommend lower goals for these patients (specific targets not given).[1] Nevertheless, it is becoming apparent that targets for LDL-C reduction in children with HoFH are not achievable without LDLR-independent therapies such as lomitapide or evinacumab (a monoclonal antibody inhibitor of angiopoietin-like 3). Evinacumab was recently FDA-approved as an adjunct to LLTs for the treatment of HoFH in children 5–11 years of age.[1] The reported LDL-C reduction by evinacumab (-48·0%) in this age group is similar to that in APH-19, although the evinacumab trial was smaller than APH-19 (N = 14) and recruited patients only between the ages of 5–11.[23] Evinacumab was previously approved in patients from 12 years of age on the basis of an earlier trial in adults and adolescents.[24]

The magnitude of the reductions in secondary lipid/lipoprotein endpoints were consistent with the reduction in LDL-C, supporting the overall lipid-lowering efficacy in this paediatric population. Total cholesterol, triglycerides, ApoB, non-HDL-C, VLDL-C and Lp(a) were all significantly reduced with 24 weeks of lomitapide treatment. These markers are known to be important indicators of ASCVD risk in familial hypercholesterolaemia.[25-27] The reduction in

VLDL-C reflects a key stage in the mechanism of action of lomitapide, i.e., blockade of triglyceride transport to VLDL by MTP, which subsequently leads to reduced LDL-C.[28] The significant reduction in ApoB also reflects the reduced burden of atherogenic lipoproteins characterising children with HoFH who have been treated with lomitapide.

The potential hepatic effects of lomitapide are of clinical interest. It is encouraging that the majority of patients showed hepatic fat below 10% in the Efficacy Phase of APH-19, with only four patients showing increases in hepatic fat. This is consistent with findings in the pivotal registration phase 3 study in adults, which showed an initial increase in hepatic fat at Week 26, but no further increases were reported for the remainder of the study.[19] Furthermore, 20% of patients experienced related aspartate transferase (AST) or alanine aminotransferase (ALT) elevations, which were mostly mild or moderate in severity. This proportion is also smaller than the 34% of patients that had elevations in ALT in the Phase 3 adult study.[28] One SAE of hepatic enzyme increased led to dose interruptions, dose reductions, and a repeated dose escalation with recurrence of an AESI of hepatic enzyme increased, and lomitapide treatment at a lower dose. Three of the eleven patients treated with lomitapide (27%) in the case series experienced LFT elevations which resolved without intervention in one patient, and required dose reduction in the other two patients.[20] A recent integrated hepatic safety analysis of clinical trial and observational data showed that lomitapide treatment was not associated with progressive liver disease and the long-term safety profile of lomitapide remained favourable.[29] Longer-term hepatic safety in paediatric patients will be evaluated in the APH-19 open-label Safety Phase.

In addition to inhibiting hepatic VLDL formation, lomitapide reduces chylomicron synthesis in enterocytes, limiting fat absorption and potentially leading to diarrhoea. This can cause vitamin E deficiency alongside reductions in essential fatty acids, hence patients treated with lomitapide need to follow a low-fat diet (less than 20% fat) with additional vitamin and essential fatty acid supplements, in accordance with the prescribing information.[17,18] Results thus far from the APH-19 trial also suggest no childhood-specific developmental concerns relating to lomitapide treatment, as evidenced by no clinically significant changes in parameters such as osteocalcin & vitamin D levels, height, weight, BMI and sexual maturation.

Safety findings from APH-19 were, overall, aligned with studies of lomitapide in adults with HoFH; most AEs were mild or moderate in nature and involved gastrointestinal symptoms, resolving most frequently without any intervention, or with lomitapide temporary dose reduction or interruption.[19,30] This is also similar to the paediatric case series reported by Ben-Omran *et al.*, in which adverse events occurred early in the treatment course, were

mostly gastrointestinal in nature and manageable.[20] The number of serious TEAEs was low in the APH-19 trial; there was one episode of MACE in the Efficacy Phase and a death occurred in the Run-in Period before treatment commenced. Neither were related to treatment and were likely a result of the substantial atherosclerotic burden observed in children with HoFH. These major cardiovascular events are emblematic of the very high risk of morbidity/mortality that children with HoFH live with, underlining the need for early and aggressive therapeutic intervention. Owing to when the trial was conducted, 11 COVID-19-related AEs were reported in nine patients and led to two patients interrupting their LA for 14 days. The principal limitation of APH-19 was its open-label, non-randomised design, with no control group utilised. The design was justified on the basis of lomitapide having a well-established efficacy profile in adults, HoFH being an orphan disease that limits trial recruitment, and the risk of unblinding due to the known tolerability profile of lomitapide. Nevertheless, the lack of a control group could have introduced bias into APH-19 and the interpretation of the results. For example, the contribution of measures such as low-fat diet and vitamin supplementation to the reduction in lipid/lipoproteins cannot be assessed. However, this limitation is inherent to prior clinical studies of lomitapide and patients with HoFH are generally advised to follow a low-fat diet irrespective of their treatment. Furthermore, HoFH is a chronic condition and, therefore, a further limitation of this study is the 24-week assessment period; however, long-term data on the safety of lomitapide will be assessed in these patients at Week 104.

Conclusion

Results from the Efficacy Phase of APH-19 demonstrate that in paediatric patients with HoFH, lomitapide treatment resulted in statistically significant reductions in LDL-C and reductions from Baseline in total cholesterol, VLDL-C, ApoB and triglycerides comparable to that observed for LDL-C, with an acceptable safety profile. The EAS have acknowledged that lomitapide has potential as a paediatric treatment, but data was limited in children with HoFH.[1] The findings from APH-19 bridge the gap in terms of demonstrating lomitapide to be both acceptably tolerated and efficacious in patients aged 5 years and above. Lomitapide provides an LDL receptor-independent treatment option that may help to address the considerable unmet needs present in this highly vulnerable patient group, helping them to achieve recommended target LDL-C levels.

Acknowledgments

Funding

This study was funded by Amryt Pharmaceuticals DAC., Dublin, Ireland.

Medical Writing, Editorial, and Other Assistance

Medical writing assistance was provided by Alistair Ray, Steven Foster and Jake Casson of Meridian HealthComms Ltd, Macclesfield, UK, in accordance with good publication practice (GPP4), funded by Amryt Pharmaceuticals DAC.

Author Contributions

All authors made substantial contributions to the conception and design of the study, the acquisition, analysis and interpretation of data. Data were analysed by Veristat LLC, with statistical support provided by B.M.; data were verified by T.C. and S.L., and all authors were able to access the raw data. All authors reviewed the analyses, contributed toward the drafting of the article and revising it critically for important intellectual content. The authors had joint responsibility for the decision to submit for publication, and all authors provided their approval of the final version to be published. The authors are accountable for the accuracy and integrity of this work.

Disclosures

Luis Masana received fees for lectures or advisory work from Amarin, Amryt, Daiichi-Sankyo, Ferrer, Novartis, Sanofi, Servier and Viatris.

Claus Peter Schmitt received lecturing honoraria from Fresenius Medical Care; advisory fees from Baxter, Stada and Iperboreal Pharma; and research funding from Invizius.

Alberto Zambon received personal speaker fees from AlfaSigma, Amryt, Amarin, Sobi, Sanofi-Aventis, Servier, Amgen, Mylan, Abbott, Novartis, Fidia; and personal Consultancy/Advisory Board fees from Abbott, Amarin, Novartis.

Christina Taylan received honoraria from Novartis, Sanofi and Danone.

Hofit Cohen received consultation fees from Sanofi; lecture fees from Novartis, Sanofi, Medison Pharma, Abbott, Neopharm, Organon; and research support from Medison Pharma.

José Luis Diaz-Diaz received honoraria for speaker or researcher activities from Merck Sharp and Dohme, Amgen and Sanofi.

Sergio Martinez-Hervas received fees for speaker or advisory work from Amarin, Amryt, Daiichi-Sankyo, MSD, Novartis, Sanofi and Ultragenyx.

Brian Mangal is a Consultant for Amryt Pharma.

Tracy Cunningham and Sandra Löwe are employees of Amryt Pharmaceuticals DAC.

Naji Kholaif reports financial support and honoraria from Amryt.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

Figure 1 Patient disposition

AESI, adverse event of special interest; SAE, serious adverse event; y, years.

608 **Figure 2** Mean LDL-C at Baseline and Week 24: overall and by age group (full analysis set)
609
610

611 N = 43, n = 20 for 5–10 years sub-group, and n = 23 for 11–17 years sub-group. LOCF was utilised for four patients.*p<0·0001; difference between Baseline and follow-up not
612 assessed for age sub-groups. Error bars represent standard deviation.

613 CI, confidence interval; LDL-C, low-density lipoprotein C; LOCF, last observation carried forward.

Figure 3 Mean values at Baseline and at Week 24 for total cholesterol (**A**), non-HDL-C (**B**), VLDL-C (**C**), triglycerides (**D**), Lp(a) measured in mg/dL (**E**), Lp(a) measured in nmol/L (**F**)[a], and ApoB (**G**) (full analysis set)

[a]N = 43 for all outcomes apart from the Lp(a), which was measured in local laboratories, with 21 patients having results measured in mg/dL and 22 patients having results measured in nmol/L. LOCF was utilised for four patients.

*p<0·0001. The Fisher combined p-value for the Lp(a) mg/dL and nmol/L datasets was p=0·007 (Fisher Combined p-value for mg/dL and nmol/L datasets – individual p-values were 0·29 and 0·003 for data reported in mg/dL and nmol/L, respectively). Error bars represent standard deviation.

ApoB, apolipoprotein B; LOCF, last observation carried forward; Lp(a), lipoprotein (a); non-HDL-C, non-high-density lipoprotein C; VLDL-C, very low-density lipoprotein C.

Tables

Table 1 Patient characteristics

Characteristic	**N = 43**
Sex, n (%)	
Female	24 (55.8)
Male	19 (44.2)
Median (IQR) age, years	10.7 (7.0–14.0)
5–10, n (%)	20 (46.5)
11–17, n (%)	23 (53.5)
Race, n (%)	
White	42 (97.7)
Black or African American	1 (2.3)
Geographic location, n (%)	
Germany	7 (16.3)
Italy	7 (16.3)
Spain	7 (16.3)
Saudi Arabia	13 (30.2)
Tunisia	6 (14.0)
Israel	3 (7.0)
Diagnosis of HoFH, n (%)	
Genetic confirmation of biallelic pathogenic variants	38 (88.4)
LDLR gene locus	33 (76.7)
LDLRAP1 gene locus	1 (2.3)
Other	4 (9.3)
Clinical diagnosis based on EAS consensus panel criteria on HoFH[22]	5 (11.6)
Median (IQR) HoFH diagnosis, weeks	254.9 (123.1–340.7)
Median (IQR) Baseline LDL-C mg/dL	390.5 (279.5–571.9)
Median (IQR) Baseline non-HDL-C mg/dL	407.5 (292.3–583.8)

Median (IQR) Baseline total cholesterol mg/dL	440.8 (328.7–600.9)
Median (IQR) Baseline VLDL-C mg/dL	17.0 (12.0–22.0)
Median (IQR) Baseline ApoB mg/dL	291.0 (216.0–400.0)
Median (IQR) Baseline triglycerides mg/dL	85.8 (60.2–108.0)
Median (IQR) Baseline Lp(a) mg/dL	25.3 (10.0–36.0)
Median (IQR) Baseline Lp(a) nmol/L	127.6 (39.0–195.3)
Median (IQR) duration of cardiovascular disease, months	38.6 (26.9–67.5)
Any ongoing cardiovascular medical condition, n (%)	28 (65.1)
Prior and Run-in LLT medications, n (%)	
Any	43 (100)
Statins	39 (90.7)
Ezetimibe	32 (74.4)
Evolocumab	5 (11.6)
Combination ezetimibe + rosuvastatin zinc	1 (2.3)
LDL-apheresis	19 (44.2)
Concomitant LLT during Efficacy Phase, n (%)	
Any	43 (100)
Statins	39 (90.7)
Ezetimibe	32 (74.4)
Evolocumab	4 (9.3)
Combination ezetimibe + rosuvastatin zinc	1 (2.3)
LDL-apheresis	19 (44.2)

ApoB, apolipoprotein B; EAS, European Atherosclerosis Society; HoFH, homozygous familial hypercholesterolaemia; IQR, interquartile range; LDLR, low-density lipoprotein receptor; LDLRAP1, low-density lipoprotein receptor adapter protein 1; LLT, lipid-lowering therapy; Lp(a), lipoprotein (a); non-HDL-C, non-high-density lipoprotein C; SD, standard deviation; VLDL-C, very low-density lipoprotein C.

Table 2 Summary of safety results (Efficacy Phase)

	5–10 years (N=20)			11–17 years (N=23)			Overall (N=43)		
	Events	Patients n (%)	95% CI	Events	Patients n (%)	95% CI	Events	Patients n (%)	95% CI
Total number of non-TEAEs	12	9 (45.0)	23.1, 68.5	11	10 (43.5)	23.2, 65.5	23	19 (44.2)	29.1, 60.1
Total number of TEAEs	168	18 (90.0)	68.3, 98.8	160	22 (95.7)	78.1, 99.9	328	40 (93.0)	80.9, 98.5
Serious TEAEs	2	2 (10.0)	1.2, 31.7	6	3 (13.0)	2.8, 33.6	8	5 (11.6)	3.9, 25.1
Serious related TEAEs	1	1 (5.0)	0.1, 24.9	0	0 (0)	0.0, 14.8	1	1 (2.3)	0.1, 12.3
TEAEs leading to study discontinuation	0	0 (0)	0.0, 16.8	2	2 (8.7)	1.1, 28.0	2	2 (4.7)	0.6, 15.8
Related TEAEs leading to study discontinuation	0	0 (0)	0.0, 16.8	2	2 (8.7)	1.1, 28.0	2	2 (4.7)	0.6, 15.8
Serious related TEAEs leading to study discontinuation	0	0 (0)	0.0, 16.8	0	0 (0)	0.0, 14.8	0	0 (0)	0.0, 8.2
TEAEs leading to death	0	0 (0)	0.0, 16.8	0	0 (0)	0.0, 14.8	0	0 (0)	0.0, 8.2
AESI	4	3 (15.0)	3.2, 37.9	2	2 (8.7)	1.1, 28.0	6	5 (11.6)	3.9, 25.1
Related AESI	4	3 (15.0)	3.2, 37.9	2	2 (8.7)	1.1, 28.0	6	5 (11.6)	3.9, 25.1
Major adverse cardiac events	0	0 (0)	0.0, 16.8	1	1 (4.3)	0.1, 1.9	1	1 (2.3)	0.1, 12.3

AESI, adverse event of special interest; CI, confidence interval; TEAE, treatment-emergent adverse event.

Table 3 Adverse events of special interest (Safety Analysis set)

	5–10 years (N=20)			11–17 years (N=23)			Overall (N=43)		
	Events	Patients n (%)	95% CI	Events	Patients n (%)	95% CI	Events	Patients n (%)	95% CI
AESI	4	3 (15.0)	3.2, 37.9	2	2 (8.7)	1.1, 28.0	6	5 (11.6)	3.9, 25.1
Gastrointestinal disorders	0	0 (0)	0.0, 16.8	2	2 (8.7)	1.1, 28.0	2	2 (4.7)	0.6, 15.8
Diarrhoea	0	0 (0)	0.0, 16.8	2	2 (8.7)	1.1, 28.0	2	2 (4.7)	0.6, 15.8
Hepatobiliary disorders	3	2 (10.0)	1.2, 31.7	0	0 (0)	0.0, 14.8	3	2 (4.7)	0.6, 15.8
Hepatic steatosis	2	2 (10.0)	1.2, 31.7	0	0 (0)	0.0, 14.8	2	2 (4.7)	0.6, 15.8
Hepatomegaly	1	1 (5.0)	0.1, 24.9	0	0 (0)	0.0, 14.8	1	1 (2.3)	0.1, 12.3
Investigations	1	1 (5.0)	0.1, 24.9	0	0 (0)	0.0, 14.8	1	1 (2.3)	0.1, 12.3
Hepatic enzyme increased	1	1 (5.0)	0.1, 24.9	0	0 (0)	0.0, 14.8	1	1 (2.3)	0.1, 12.3

AESIs are defined as hepatic, small bowel/intestinal, pancreatic and colorectal tumours, hepatic abnormalities, gastrointestinal effects and major congenital abnormality adverse events.
If a patient experienced more than 1 TEAE, the patient is counted once for each system organ class and once for each preferred term.
Adverse events were coded using the MedDRA Dictionary, version 25.1.

AESI, adverse event of special interest; CI, confidence interval; TEAE, treatment-emergent adverse event.

Figure 1

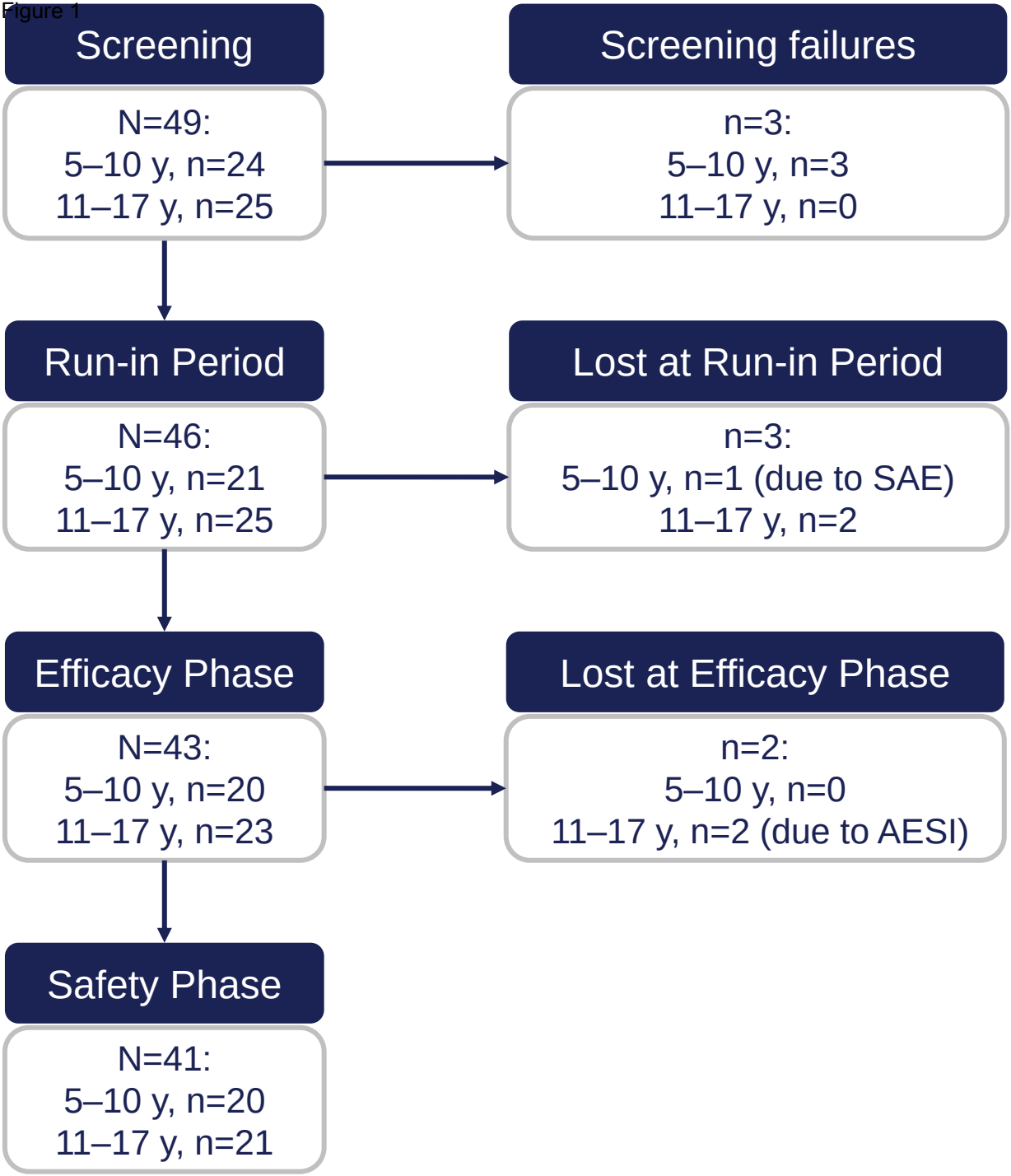

Screening
N=49:
5–10 y, n=24
11–17 y, n=25
Screening failures
n=3:
5–10 y, n=3
11–17 y, n=0
Run-in Period
N=46:
5–10 y, n=21
11–17 y, n=25
Lost at Run-in Period
n=3:
5–10 y, n=1 (due to SAE)
11–17 y, n=2
Efficacy Phase
N=43:
5–10 y, n=20
11–17 y, n=23
Lost at Efficacy Phase
n=2:
5–10 y, n=0
11–17 y, n=2 (due to AESI)
Safety Phase
N=41:
5–10 y, n=20
11–17 y, n=21

Figure 2

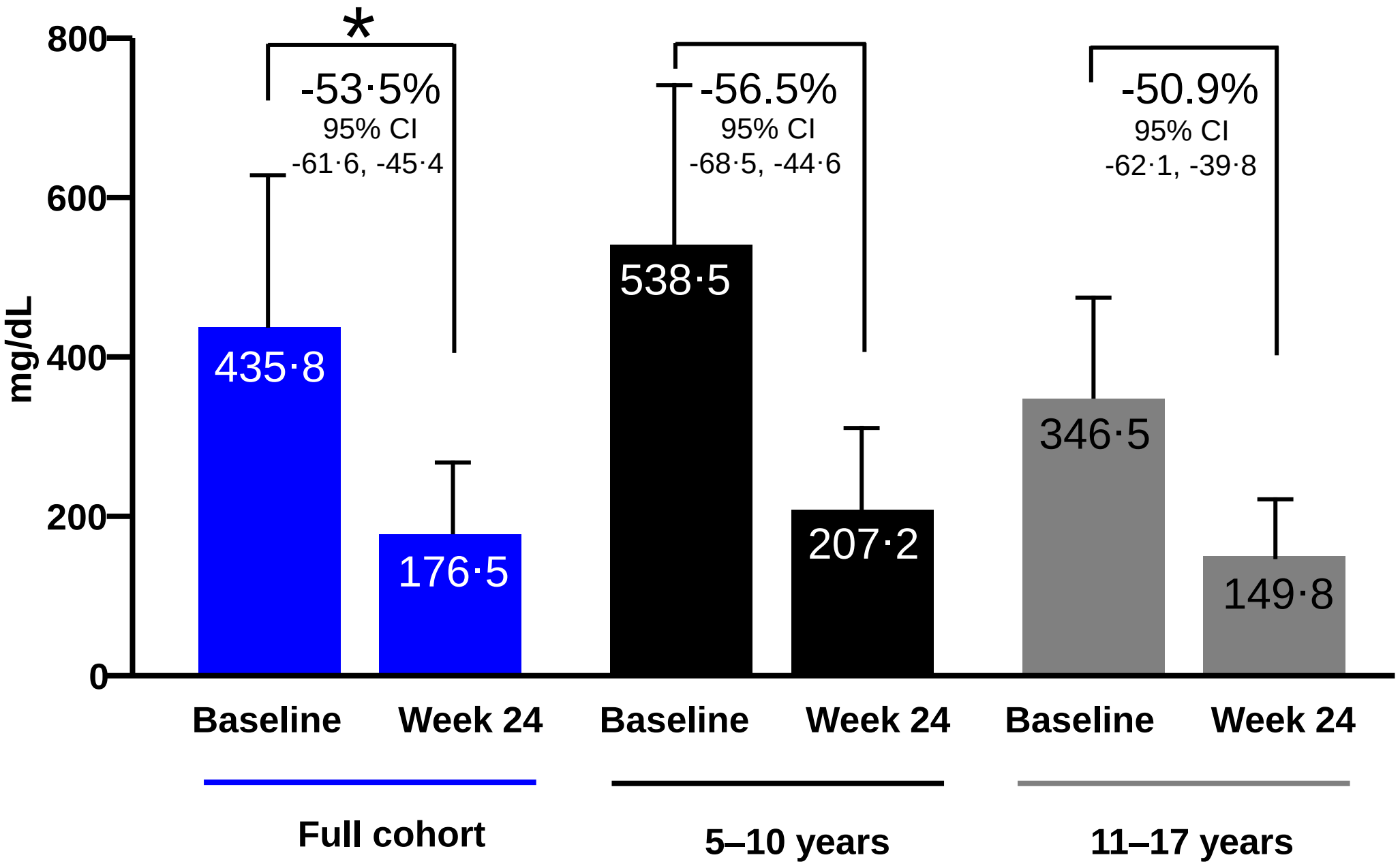
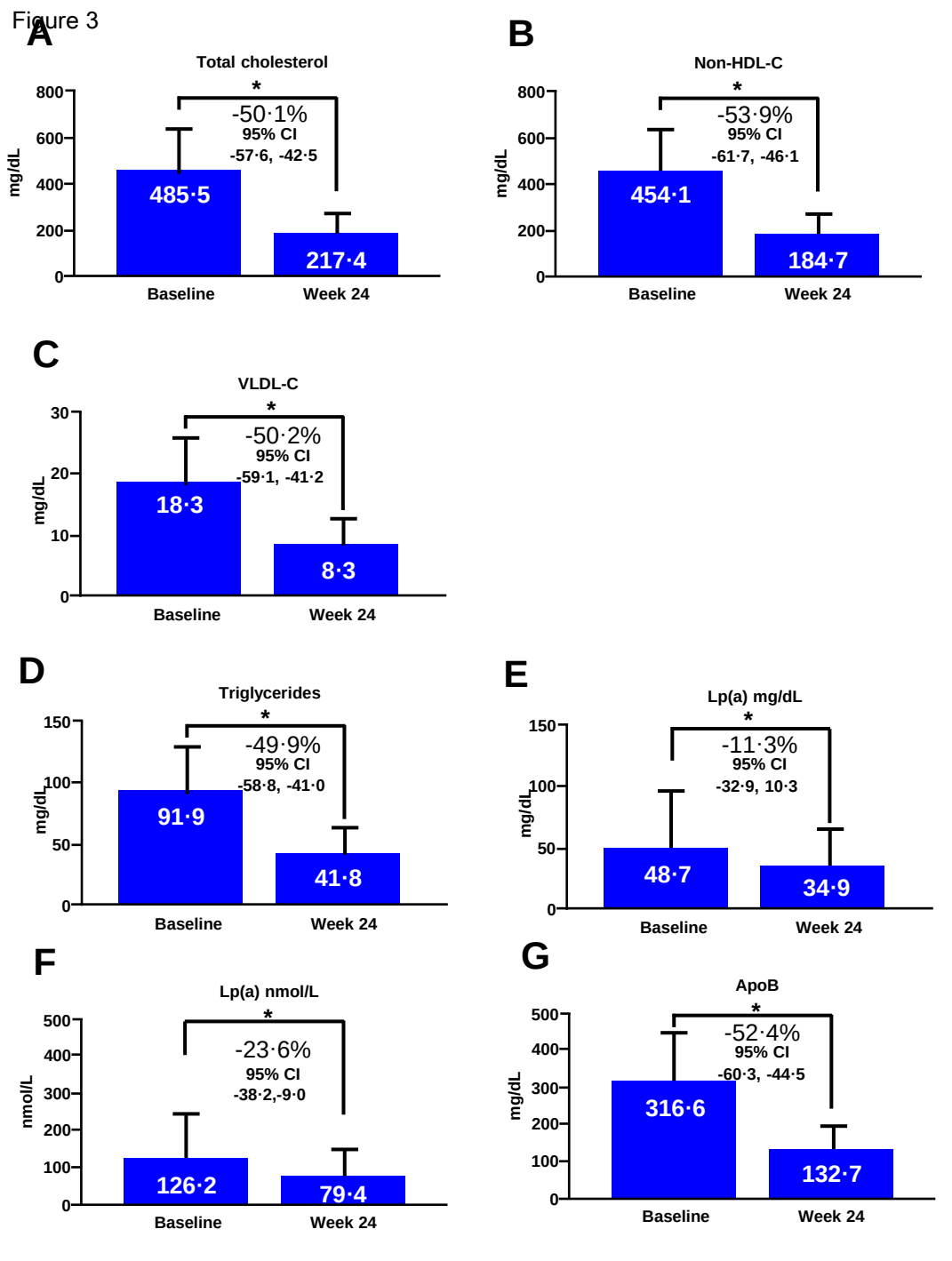

*
-53·5%
95% CI
-61·6, -45·4
-56.5%
95% CI
-68·5, -44·6
-50.9%
95% CI
-62·1, -39·8
800
600
400
200
0
mg/dL
435·8
176·5
538·5
207·2
346·5
149·8
Baseline
Week 24
Baseline
Week 24
Baseline
Week 24
Full cohort
5–10 years
11–17 years

Figure 3


A
Total cholesterol
*
-50·1%
95% CI
-57·6, -42·5
485·5
217·4
mg/dL
800
600
400
200
0
Baseline
Week 24
B
Non-HDL-C
*
-53·9%
95% CI
-61·7, -46·1
454·1
184·7
mg/dL
800
600
400
200
0
Baseline
Week 24
C
VLDL-C
*
-50·2%
95% CI
-59·1, -41·2
18·3
8·3
mg/dL
30
20
10
0
Baseline
Week 24
D
Triglycerides
*
-49·9%
95% CI
-58·8, -41·0
91·9
41·8
mg/dL
150
100
50
0
Baseline
Week 24
E
Lp(a) mg/dL
*
-11·3%
95% CI
-32·9, 10·3
48·7
34·9
mg/dL
150
100
50
0
Baseline
Week 24
F
Lp(a) nmol/L
*
-23·6%
95% CI
-38·2,-9·0
126·2
79·4
nmol/L
500
400
300
200
100
0
Baseline
Week 24
G
ApoB
*
-52·4%
95% CI
-60·3, -44·5
316·6
132·7
mg/dL
500
400
300
200
100
0
Baseline
Week 24

appendix

Lomitapide for the treatment of paediatric patients with homozygous familial hypercholesterolaemia: Results from the Efficacy Phase of APH-19, a phase 3, open-label study

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Word count: 4540

Panel: Research in context

Evidence before this study

Homozygous familial hypercholesterolaemia (HoFH) causes extremely high levels of low-density lipoprotein C (LDL-C), with the threshold for atherosclerotic cardiovascular disease (ASCVD) being reached at around 12.5 years of age, and life expectancy around 18 years if untreated. Early diagnosis and treatment in childhood is imperative to avoid morbidity and mortality.

Treatment options for children are limited and as a result, young patients with HoFH rarely reach target LDL-C levels, even with maximally tolerated combinations of currently available lipid-lowering therapies (LLTs).

Lomitapide is a microsomal triglyceride transfer protein inhibitor which effectively lowers LDL-C, independently of the LDL receptor function, and is approved for adults with HoFH. Prior to this study, lomitapide was shown to be effective in lowering LDL-C in a case series of paediatric patients with HoFH (N=11), where the mean LDL-C reduction was 58% after 20 weeks of lomitapide therapy.

Added value of this study

APH-19 is the first clinical trial of lomitapide in paediatric patients with HoFH. Results show that lomitapide treatment over 24 weeks provides significant reductions in LDL-C, non-high-density lipoprotein C, total cholesterol, very-low-density lipoprotein cholesterol, ApoB and Lp(a) in patients aged 5–17 years. Forty-two percent of patients were able to reach the pre-specified LDL-C target level of <135 mg/dL by Week 24. No new safety signals were identified, and the majority of adverse events were mild or moderate in severity. Hepatic enzyme elevations occurred in around one-third of patients, were mostly transient and did not necessitate dose modification/therapy interruption with the exception of two cases. These were managed by dose reductions in one patient and therapy interruptions followed by dose reductions in the other.

Implications of all the available evidence

Lomitapide is an effective LDL-C-lowering agent for paediatric patients with HoFH with an acceptable safety and tolerability profile. New therapeutic options in this vulnerable population are urgently needed to address the significant unmet need and potentially reduce morbidity and mortality

Abstract

Background

Homozygous familial hypercholesterolaemia (HoFH) is a rare inherited disorder characterised by extremely high levels of low-density lipoprotein cholesterol (LDL-C), leading to early-onset atherosclerosis. Lomitapide is an orally administered microsomal triglyceride transfer protein inhibitor which effectively lowers LDL-C, approved for adults with HoFH. APH-19 was designed to investigate the efficacy and safety of lomitapide in paediatric patients with HoFH.

Methods

APH-19 (NCT04681170) is a phase 3, open-label, single-arm trial of lomitapide in paediatric patients with HoFH receiving standard of care lipid-lowering therapy. A Run-in Period was followed by 24-week Efficacy and 80-week Safety Phase. Patients were titrated to maximum tolerated doses of lomitapide, starting at 2mg (patients 5–15 years) or 5mg (patients 16–17 years). The primary endpoint was the percent change from Baseline to Week 24 in LDL-C.

Findings

Forty-three patients were treated (female: 55·8%; mean age: 10·7 years). Mean change from Baseline in LDL-C at Week 24 was -53·5% (95% CI -61·6; -45·4, p<0·0001). Mean percent reductions were observed at Week 24 for non-high-density lipoprotein C (-53·9%, 95% CI -61·7; -46·1, <0.0001), total cholesterol (-50 0%, 95% CI -57·6; -42·4, p<0·0001), very-low-density lipoprotein cholesterol (-50·2%, 95% CI -59·1; -41·2, p<0·0001), apolipoprotein B (-52·4%, 95% CI -60·3; -44·5, p<0·0001) and lipoprotein(a) (-11·3%, 95% CI -32·9; 10·3 [mg/dL]; -23·6%, 95% CI -38·2; -9·0 [nmol/L]; p=0·007 combined). AEs were mostly mild, and gastrointestinal and hepatic in nature. AEs of special interest (AESI) were reported for five patients (11·6%); gastrointestinal n=2 and hepatic n=3. One serious related treatment-emergent AE was reported (also classed as an AESI) – an increase in hepatic enzymes, resulting in two dose interruptions, two dose reductions and a repeated dose escalation.

Interpretation

Lomitapide provided statistically significant, clinically meaningful LDL-C reduction and has the potential to be an efficient, LDL receptor-independent option for paediatric patients.

Funding

Amryt Pharmaceuticals DAC.

Introduction

Homozygous familial hypercholesterolaemia (HoFH) is a rare, life-threatening inherited disorder characterised by extremely high levels of low-density lipoprotein cholesterol (LDL-C) and premature atherosclerotic cardiovascular disease (ASCVD).[1] It is estimated that ~30,000 people worldwide have HoFH, but it is widely underdiagnosed, with less than 5% of the estimated number of cases identified.[1-3] The genetics of HoFH are complex with the most common causal pathogenic gene variants occurring in genes involved in the LDL receptor (LDLR) pathway, including *LDLR*, apolipoprotein B (*APOB)*, and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene loci.

The cumulative LDL-C exposure that occurs in HoFH means that the threshold for ASCVD is reached in childhood (approximately 12·5 years of age).[3] As such, the average age of death for people with HoFH, when untreated, is 18 years, although deaths before the age of 5 have been reported.[4] Therefore, early diagnosis and treatment in childhood is imperative to reduce circulating LDL-C, and to delay the development of ASCVD.

Pharmacological reduction of LDL-C using maximum tolerated doses (MTD) of statins and ezetimibe is standard practice, and is recommended to be initiated before the age of 2 years.[5] Unfortunately, these therapies act via the LDLR pathway that is severely impaired in patients with HoFH. Therefore, these individuals rarely reach recommended LDL-C targets on the standard of care therapy, and more intense intervention is required. However, pharmacological treatment options for children are limited, with many therapies lacking regulatory approval or data in paediatric patients, and reduced effectiveness in HoFH if relying on residual LDLR activity e.g., PCSK9 inhibitors.[1,6-9] Lipoprotein apheresis (LA) remains an important non-pharmacological intervention for paediatric patients but is burdensome for patients and relatives, as it may be required up to twice weekly in apheresis centres.[10] It is also not universally available and has only a transient effect on LDL-C.[1,11-13]

With LDL-C levels remaining substantially above recommended goals for most patients, despite the standard of care treatments mentioned above, LDLR-independent therapies are a critical component of the latest HoFH treatment algorithm and are recommended to sufficiently lower LDL-C.[1] These include lomitapide, a microsomal triglyceride transfer protein (MTP) inhibitor, and angiopoietin-like 3 inhibitors (e.g., evinacumab[14,15]). Lomitapide is an oral once daily therapy, which reduces LDL-C levels independently of LDLR by decreasing the secretion of its precursor, very low-density lipoprotein cholesterol (VLDL-C).[16] Lomitapide, in combination with other lipid-lowering medicines and a low-fat diet, effectively reduces LDL-C across genotypes, and is approved for use in adults with HoFH.[17-19] The

current data on lomitapide for paediatric patients is limited to case studies and series, but shows promising reductions in LDL-C levels aligned with that seen in trials of adult patients.[20,21]

The purpose of the APH-19 clinical trial (NCT04681170) was to investigate the clinical efficacy and safety of lomitapide in paediatric patients with HoFH in a statistically powered study.

Methods

Study design and participants

APH-19 is a single-arm, open-label, multi-centre phase 3 study to evaluate the efficacy and long-term safety of lomitapide in paediatric patients with HoFH receiving stable lipid-lowering therapy (LLT). The Efficacy Phase of the study was performed between December 2020 and October 2022, at 12 study centres in Germany, Israel, Italy, Saudi Arabia, Spain, and Tunisia.

APH-19 consists of a 6- to 12-week Run-in Period, followed by a 24-week Efficacy Phase and 80-week Safety Phase. The study design is shown in **Supplementary Figure 1** (appendix p16~~20~~).

Patients and/or their parent/legal guardian provided informed consent and had to be able and willing to follow study procedures and instructions. Eligible patients were aged 5–17 years on stable LLT, with HoFH diagnosed using the criteria from the 2014 EAS Consensus Panel on HoFH:[22] either (i) a genetic confirmation of two mutant alleles at the *LDLR*, apolipoprotein B (*ApoB*), proprotein convertase subtilisin/kexin type 9 (*PCSK9*) or low-density lipoprotein receptor adapter protein 1 (*LDLRAP1*) gene locus; or (ii) untreated LDL-C ≥500 mg/dL / treated LDL-C ≥300 mg/dL together with cutaneous or tendon xanthoma before age 10 years or untreated LDL-C levels consistent with heterozygous familial hypercholesterolaemia in both parents. Full inclusion and exclusion criteria are shown in **Supplementary Table 1** (appendix p6~~9~~).

APH-19 was conducted in accordance with the harmonised tripartite ICH Guidelines for good clinical practice, and with the Helsinki Declaration of 1964 and its later amendments. The study was approved by the institutional review board and independent ethics committee at each participating site. The analysis plan was agreed upon by the sponsor and regulators. The analysis was performed by a Contract Research Organization (Veristat LLC, MA, USA), contracted by the sponsor (Amryt Pharma). The results of the analysis were reviewed by the authors. Periodic safety analyses were performed by a Data Safety Monitoring Board

(DSMB), which comprised four members, one of whom was a statistician. The DSMB was independent and not otherwise involved in the conduct of the study.

Randomisation and masking

APH-19 was an open-label study, and as such, was not masked or blinded. Given the existing data to indicate the benefit of lomitapide therapy in HoFH and the rarity of the disease, a randomised two-arm design with placebo was not considered acceptable for these very high-risk patients. Furthermore, the safety profile of lomitapide would potentially unblind both patients and investigators.

Procedures

Lomitapide was administered orally in capsule form for all patients, and the dose was escalated following the applicable titration scheme based on patient age (**Supplementary Table 2;** appendix p7~~11~~). The dose must have been tolerated for at least four consecutive weeks before escalation to the next higher dose in stepwise increments. MTD definition details can be found on appendix p2. Dosing was stratified into three age groups (5–10, 11–15 and 16–17 years). All patients were placed on a low-fat diet (less than 20% fat or <30g fat, whichever was the lesser amount), supplemented with vitamin E (200 international units [IU] for patients aged 5–8 years, 400 IU for patients aged 9–17 years) and essential fatty acids.[17,18] More details can be found on appendix p2. In addition, during the Efficacy Phase, patients were required to remain on the stable LLT regimen (including LA, when applicable) established during the 6-week Run-in Period.

Blood samples for fasting lipid panel analysis were collected at Baseline and every 4 weeks thereafter. Use of concomitant medications and LLT, including LA, was assessed continuously throughout the study. Blood samples for laboratory safety tests (metabolic panel and liver function tests [LFTs]) were collected at Baseline and every 4 weeks thereafter. More details can be found on appendix p2**.**

Safety was assessed continuously throughout the study from the start of the Run-in Period through to the end of the follow-up period and adverse events (AEs) were followed until resolution or stabilisation. AEs were evaluated by the incidence, severity, and the relationship of AEs to study drug and were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 25.1, and classified by System Organ Class and Preferred Term. Treatment-emergent AEs (TEAEs) were summarised overall and by age group and classified by maximum severity and relationship to study drug.

Outcomes

The primary outcome measure was the percent change from Baseline to Week 24 in LDL-C. Based on the previous pivotal study of lomitapide in adult patients with HoFH,[19] key secondary outcome measures were chosen and tested in order of their clinical relevance. The secondary outcomes were the percent change from Baseline at Week 24 in total cholesterol, non-high-density lipoprotein cholesterol (non-HDL-C), VLDL-C, triglycerides, lipoprotein(a) [Lp(a)], and ApoB. Primary endpoint sub-group analyses were conducted using two age groups (5–10, 11–17 years) instead of the three dosing sub-groups. The change from three to two sub-groups was based on the number of patients who were available to be enrolled into the upper age group and was implemented following a protocol amendment (August 2022) per agreement with the European Medicines Agency Paediatric Committee. Additional exploratory secondary outcome measures were the number and proportion of patients achieving the previous EAS recommended target LDL-C of <135 mg/dL (3.5 mmol/L) at Week 24. Note that at the time of trial design, this was the EAS recommended target LDL-C for children and adolescent patients,[22] with the 2023 update lowering this target to 115 mg/dL (<3.0 mmol/L).[1]

Safety endpoints included incidence of reported AEs including adverse events of special interest (AESIs, including hepatic/gastrointestinal/pancreatic tumours, hepatic abnormalities [e.g., hepatic enzyme increases] and gastrointestinal events; see appendix p3), serious AEs (SAEs), and treatment-related events. Hepatic safety endpoints included hepatic fat assessment by nuclear magnetic resonance (NMR) imaging or ultrasound, and LFTs. Further population-specific safety endpoints were the impact of treatment on patient growth and maturation, which was assessed in terms of patient weight, height, body mass index (BMI), BMI-for-age z-score, BMI percentile, height-for-age z-score and height percentile, hormone levels and Tanner Staging (further details can be found on appendix p43).

Statistical analysis

At least 30 evaluable patients were required to provide 92% power, assuming a 25% reduction from Baseline in LDL-C with a standard deviation (SD) of 40% and a 2-sided α of 0·05, with sampling distribution of the mean assumed to be normal under the central limit theorem; data distributions were also checked through normal quantile-quantile plots to confirm no significant departures from normality for all study endpoints. To allow for up to 33% dropout during the Efficacy Phase (prior to Week 24), an additional 15 patients were enrolled. Enrolment was stratified to ensure approximately equal numbers of patients within

age groups of 5–10 and 11–17 years, in order to facilitate the analysis performed in these two patient groups. The full analysis set was defined as patients who had received ≥1 dose of lomitapide, and who had a Baseline and ≥1 post-Bbaseline measurement. The safety analysis set was defined as patients who had received ≥1 dose of lomitapide.

The primary efficacy analysis was conducted once all patients completed (or withdrawn prior to Visit 10) at Week 24±3 days (End of the Efficacy Phase). The primary efficacy analysis included the key primary and secondary efficacy data, all safety data available up to the data cut-off date of the last patient reaching Week 24±3 days, and pharmacokinetic parameter analysis. The final statistical analysis was performed when all patients completed the Follow-up Visit (Visit 23) at Week 108±7 days. Efficacy, safety, and exploratory data collected during both the Safety Phase and follow-up were included. Analysis of other secondary endpoints collected during the Efficacy Phase and of endpoints collected during the Safety Phase were analysed without adjustment for multiplicity. All analyses were conducted using SAS version 9.4.

All patients enrolled in the Efficacy Phase with at least one post-Baseline LDL-C observation were included in the efficacy analyses. The key secondary efficacy endpoints were tested sequentially in a pre-specified fixed order, to control the overall type I error. The percent changes from Baseline for the primary and secondary efficacy outcomes at Week 24 were each analysed using a one sample t-test. For the efficacy outcomes, missing data were imputed using the last observation carried forward (LOCF) approach. This (or any other method of data imputation) was not utilised for the sensitivity analyses, which were conducted using a Mixed Models for Repeated Measures approach under the assumption that data were missing at random. Under this approach, time was the fixed effect and subject was the random effect; no other random effects were included. Sub-group analyses were conducted by age group (5–10 and 11–17) using an Analysis of Covariance (ANCOVA) model to estimate the mean percentage change and 2-sided 95% confidence intervals within each sub-group at Week 24±3 days.

Summary statistics (presented for the overall group and by age group) were used to assess safety in the safety population. Events leading to discontinuation as well as SAEs and AESIs (e.g., hepatic abnormalities, gastrointestinal effects) were summarised. Here, 24-week Efficacy Phase and safety endpoints are reported in this paper.

Role of the funding source

Amryt Pharmaceuticals DAC (Dublin, Ireland) funded this study, and was therefore responsible for study design, data collection, analysis and regulatory compliance. The paper was written by the authors with assistance from Alistair Ray, Steven Foster and Jake

Casson of Meridian HealthComms Ltd (Macclesfield, UK), funded by Amryt Pharmaceuticals DAC, who provided editorial and technical support in the preparation of the manuscript.

Results

Patients disposition in APH-19 is shown in **Figure 1**. Forty-six patients entered the Run-in Period, where three patients were lost to follow-up, including one patient in the 5–10-year age group that died prior to starting lomitapide (myocardial ischaemia), which was therefore considered as a non-treatment-emergent serious AE. Two further patients left the study voluntarily owing to withdrawal of parental consent and inability to comply with the study schedule. A total of 43 patients entered the 24-week Efficacy Phase; of these, two adolescent siblings prematurely discontinued from the study due to moderate AESIs of diarrhoea at Week 10–11 and 41 patients entered the Safety Phase, which will be reported at a later date.

Full baseline characteristics can be found in **Table 1**. The majority of patients had a genetic diagnosis of HoFH (n = 38 [88·4%]), and five patients were diagnosed using other criteria from the 2014 EAS Consensus Panel on Homozygous Familial Hypercholesterolemia.[22] The median baseline LDL-C level in the full cohort was 390·5 mg/dL (range: 152·3 to 902·4 mg/dL), with a higher median baseline LDL-C level in patients aged 5–10 years (526·8 mg/dL) compared with patients aged 11–17 years (346·4 mg/dL). Prior/run-in background LLTs were maintained through the Efficacy Phase, with the exception of one patient who discontinued evolocumab at Week 8. Details of other concomitant medications during the study are shown in **Supplementary Table 3** (appendix p8~~12~~), with a detailed description of cardiovascular (CVD) conditions shown in **Supplementary Table 4** (appendix p9~~13~~).

Efficacy data are presented for the full analysis set (N = 43); the LOCF approach was utilised for four patients. APH-19 met its primary efficacy endpoint, with a significant overall mean LDL-C percent change from Baseline at Week 24 of -53·5% (95% confidence interval [CI] -61·6, -45·4; p<0·0001; **Figure 2**). A waterfall plot of the patient-level data of the percentage change from Baseline in LDL-C at Week 24 is shown in **Supplementary Figure 2** (appendix p~~2~~17), mean values at each study visit shown in **Supplementary Figure 3** (appendix p25~~30~~) and mean LDL-C percentage change from Baseline using LOCF and the sensitivity analysis in **Supplementary Table 5** (appendix p104). The mean (SD) LDL-C of the full cohort decreased from 435·8 (189·5) mg/dL at Baseline to 176·5 (90·4) mg/dL at Week 24. Results were similar when the cohort was split into younger and older patient sub-groups.

Secondary outcomes in the lipid markers non-HDL-C, total cholesterol, VLDL-C, ApoB, triglycerides and Lp(a) were also significantly reduced from Baseline after 24 weeks of lomitapide therapy (**Figure 3**). Mean values at each study visit shown in **Supplementary Figure 3** (appendix p25~~30~~). Overall, non-HDL-C decreased by -53·9% (95% CI -61·7, -46·1; p<0·0001). Total cholesterol decreased by -50·1% (95% CI -57·6, -42·5; p<0·0001), while VLDL-C decreased -50·2% (95% CI -59·1, -41·2; p<0·0001). ApoB decreased by -52·4% (95% CI -60·3, -44·5; p<0·0001), and triglycerides decreased by -49·9% (95% CI -58·8, -41·0; <0·0001).

Lp(a) was measured in local laboratories, with 21 patients having results measured in mg/dL and 22 patients having results measured in nmol/L. Of the patients with mg/dL measurements, Lp(a) decreased by -11·3% (95% CI -32·9; 10·3). Of the patients with nmol/L measurements, Lp(a) decreased by -23·6% (95% CI -38·2; -9·0). The Fisher combined p-value for the mg/dL and nmol/L datasets was p=0·007.

At any time up to Week 24, a total of 18 patients (41.9%) had achieved the pre-specified EAS recommended target LDL-C level of <135 mg/dL, which comprised seven patients (35·0%) aged 5–10 years and 11 patients (47·8%) aged 11–17 years. A post-hoc analysis with the updated recommended EAS target LDL-C level of <115 mg/dL (<3·0mmol/L)[1] showed that at any time up to Week 24, a total of 16 patients (37·2%) achieved this lower target. This includes five patients aged 5–10 years and 11 (47·8%) aged 11–17 years. Exploratory endpoint results can be found on appendix p3~~4~~**.**

Twenty-five patients (58·1%) had at least one TEAE considered related to study treatment; 10 patients aged 5–10 years (50·0% of age group) and 15 patients aged 11–17 years (65·2% of age group; **Table 2** with additional safety results shown in **Supplementary Table 6**; appendix p1~~5~~). The most commonly reported TEAEs were gastrointestinal or hepatic in nature (**Supplementary Table 7**; appendix p1~~6~~).

Eight events in five patients were considered serious: two in two patients in the 5–10 years age group, and a further six events were recorded in three patients in the 11–17 years age group. Only one of these events was considered related to study treatment (hepatic enzyme increased, occurring in the 5–10 years age group; **Table 2**). One patient experienced two life-threatening TEAEs, of which one was assessed as a major adverse cardiovascular event (MACE); neither of these TEAEs led to study drug discontinuation or was deemed to be related to treatment (**Table 2**). A detailed breakdown of serious TEAEs is shown in **Supplementary Table 8** (appendix p1~~7~~).

Six AESIs were recorded in five patients: four events in three patients aged 5–10 years and two events in two patients aged 11–17 years (**Table 3**). As previously mentioned, two moderate AESIs of diarrhoea led to study discontinuation, both in the 11–17 years age group.

The most frequently reported TEAEs were gastrointestinal in nature, with diarrhoea (46.5%) and abdominal pain (41.9%) the most common. Both of these occurred at similar frequencies in the 5–10 and 11–17 age sub-groups.

TEAEs related to hepatic enzyme elevation were reported in a total of 16 patients (37·2%), encompassing the preferred terms 'ALT/AST increased', 'hepatic enzyme increased', 'hypertransaminasaemia', and 'transaminases increased.' These were more common in 5–10 years age group than the 11–17 age group (9 patients [45·0%] versus seven patients [30·4%], respectively; **Supplementary Table 9**, appendix p1~~4~~8).

These TEAEs were considered treatment-related in most patients and were mild or moderate in severity, with only one reported as severe (hepatic enzyme increased). This serious related TEAE occurred at Week 32, met the criteria for a level 4 Hepatotoxicity per APH-19 study protocol, and was therefore reported as an AESI to the DSMB. Dosing was interrupted immediately; following this, the only finding from all diagnostic tests was a mild hyperechogenic liver per ultrasound. Subsequently, transaminases started rising again upon re-challenge. Therefore, the DSMB recommended to interrupt lomitapide for a further 6–8 weeks with normal liver function tests before repeating the dose escalation per age group. Shortly after the maximum dose per age group (20 mg/day) had *de novo* been achieved at Week 80, the patient again experienced an AESI of elevated liver enzymes, which required two further dose interruptions with corresponding dose reductions to 10 mg/day and 5 mg/day, respectively and 10 mg/day as final dose.

Considering both ultrasound scans and NMR scans, at Week 24, lipid accumulation data were available for 34 patients; 30 patients had ≤10% liver fat, three patients had >10% and ≤20% liver fat, and one subject had >20% liver fat. Increases from Baseline were reported for overall four patients, one patient 5–10 years and three patients 11–17 years.

There were no other clinically significant mean changes related to treatment in other safety endpoints, e.g., growth and maturity/Tanner Staging and fat-soluble vitamins. ECG/echocardiograph findings were consistent with CVD histories. These and other additional safety findings are on appendix p4~~5~~**.**

Overall, no new safety signals were identified, and the results were consistent with the known safety profile of lomitapide.

Discussion

Results from the APH-19 study demonstrate the efficacy of lomitapide in paediatric patients, with a statistically significant 53·5% overall reduction in LDL-C after 24 weeks of treatment and an acceptable safety profile. LDL-C reduction was consistent as evidenced by the narrow confidence intervals, and apparent in younger paediatric (aged 5–10 years) and older adolescent (aged 11–17 years) analysis sub-groups. The degree of LDL-C reduction is marked in the context of a cohort that was receiving maximally tolerated statin/ezetimibe LLT, with LA use widespread among the cohort (~44% at Baseline).

The substantial percentage reduction in LDL-C at Week 24 observed in APH-19 is similar to that seen in the pivotal phase 3 adult study of lomitapide, with a 50% LDL-C reduction observed after 26 weeks of treatment in adults receiving background LLTs.[19] The present study builds on published evidence from a case series in paediatric patients by Ben-Omran *et al.*, where a mean LDL-C reduction of 58% was reported after a mean of 20 weeks of lomitapide therapy.[20] This was similar to the LDL-C reduction seen in the present study at 24 weeks.

The clinical impact of lomitapide in combination with standard LLTs was emphasised by the substantial proportion of patients (41·9%) that met the previous EAS target LDL-C threshold of <135 mg/dL.[22] A similar proportion reached the more stringent <115 mg/dL threshold set for paediatric patients in the recent 2023 EAS statement.[1] This is encouraging, although it should be noted that 65·1% of patients had an ongoing cardiovascular medical history at Screening, and the EAS guidelines recommend lower goals for these patients (specific targets not given).[1] Nevertheless, it is becoming apparent that targets for LDL-C reduction in children with HoFH are not achievable without LDLR-independent therapies such as lomitapide or evinacumab (a monoclonal antibody inhibitor of angiopoietin-like 3). Evinacumab was recently FDA-approved as an adjunct to LLTs for the treatment of HoFH in children 5–11 years of age.[1] The reported LDL-C reduction by evinacumab (-48·0%) in this age group is similar to that in APH-19, although the evinacumab trial was smaller than APH-19 (N = 14) and recruited patients only between the ages of 5–11.[23] Evinacumab was previously approved in patients from 12 years of age on the basis of an earlier trial in adults and adolescents.[24]

The magnitude of the reductions in secondary lipid/lipoprotein endpoints were consistent with the reduction in LDL-C, supporting the overall lipid-lowering efficacy in this paediatric population. Total cholesterol, triglycerides, ApoB, non-HDL-C, VLDL-C and Lp(a) were all significantly reduced with 24 weeks of lomitapide treatment. These markers are known to be important indicators of ASCVD risk in familial hypercholesterolaemia.[25-27] The reduction in

VLDL-C reflects a key stage in the mechanism of action of lomitapide, i.e., blockade of triglyceride transport to VLDL by MTP, which subsequently leads to reduced LDL-C.[28] The significant reduction in ApoB also reflects the reduced burden of atherogenic lipoproteins characterising children with HoFH who have been treated with lomitapide.

The potential hepatic effects of lomitapide are of clinical interest. It is encouraging that the majority of patients showed hepatic fat below 10% in the Efficacy Phase of APH-19, with only four patients showing increases in hepatic fat. This is consistent with findings in the pivotal registration phase 3 study in adults, which showed an initial increase in hepatic fat at Week 26, but no further increases were reported for the remainder of the study.[19] Furthermore, 20% of patients experienced related aspartate transferase (AST) or alanine aminotransferase (ALT) elevations, which were mostly mild or moderate in severity. This proportion is also smaller than the 34% of patients that had elevations in ALT in the Phase 3 adult study.[28] One SAE of hepatic enzyme increased led to dose interruptions, dose reductions, and a repeated dose escalation with recurrence of an AESI of hepatic enzyme increased, and lomitapide treatment at a lower dose. Three of the eleven patients treated with lomitapide (27%) in the case series experienced LFT elevations which resolved without intervention in one patient, and required dose reduction in the other two patients.[20] A recent integrated hepatic safety analysis of clinical trial and observational data showed that lomitapide treatment was not associated with progressive liver disease and the long-term safety profile of lomitapide remained favourable.[29] Longer-term hepatic safety in paediatric patients will be evaluated in the APH-19 open-label Safety Phase.

In addition to inhibiting hepatic VLDL formation, lomitapide reduces chylomicron synthesis in enterocytes, limiting fat absorption and potentially leading to diarrhoea. This can cause vitamin E deficiency alongside reductions in essential fatty acids, hence patients treated with lomitapide need to follow a low-fat diet (less than 20% fat) with additional vitamin and essential fatty acid supplements, in accordance with the prescribing information.[17,18] Results thus far from the APH-19 trial also suggest no childhood-specific developmental concerns relating to lomitapide treatment, as evidenced by no clinically significant changes in parameters such as osteocalcin & vitamin D levels, height, weight, BMI and sexual maturation.

Safety findings from APH-19 were, overall, aligned with studies of lomitapide in adults with HoFH; most AEs were mild or moderate in nature and involved gastrointestinal symptoms, resolving most frequently without any intervention, or with lomitapide temporary dose reduction or interruption.[19,30] This is also similar to the paediatric case series reported by Ben-Omran *et al.*, in which adverse events occurred early in the treatment course, were

mostly gastrointestinal in nature and manageable.[20] The number of serious TEAEs was low in the APH-19 trial; there was one episode of MACE in the Efficacy Phase and a death occurred in the Run-in Period before treatment commenced. Neither were related to treatment and were likely a result of the substantial atherosclerotic burden observed in children with HoFH. These major cardiovascular events are emblematic of the very high risk of morbidity/mortality that children with HoFH live with, underlining the need for early and aggressive therapeutic intervention. Owing to when the trial was conducted, 11 COVID-19-related AEs were reported in nine patients and led to two patients interrupting their LA for 14 days. The principal limitation of APH-19 was its open-label, non-randomised design, with no control group utilised. The design was justified on the basis of lomitapide having a well-established efficacy profile in adults, HoFH being an orphan disease that limits trial recruitment, and the risk of unblinding due to the known tolerability profile of lomitapide. Nevertheless, the lack of a control group could have introduced bias into APH-19 and the interpretation of the results. For example, the contribution of measures such as low-fat diet and vitamin supplementation to the reduction in lipid/lipoproteins cannot be assessed. However, this limitation is inherent to prior clinical studies of lomitapide and patients with HoFH are generally advised to follow a low-fat diet irrespective of their treatment. Furthermore, HoFH is a chronic condition and, therefore, a further limitation of this study is the 24-week assessment period; however, long-term data on the safety of lomitapide will be assessed in these patients at Week 104.

Conclusion

Results from the Efficacy Phase of APH-19 demonstrate that in paediatric patients with HoFH, lomitapide treatment resulted in statistically significant reductions in LDL-C and reductions from Baseline in total cholesterol, VLDL-C, ApoB and triglycerides comparable to that observed for LDL-C, with an acceptable safety profile. The EAS have acknowledged that lomitapide has potential as a paediatric treatment, but data was limited in children with HoFH.[1] The findings from APH-19 bridge the gap in terms of demonstrating lomitapide to be both acceptably tolerated and efficacious in patients aged 5 years and above. Lomitapide provides an LDL receptor-independent treatment option that may help to address the considerable unmet needs present in this highly vulnerable patient group, helping them to achieve recommended target LDL-C levels.

Acknowledgments

Funding

This study was funded by Amryt Pharmaceuticals DAC., Dublin, Ireland.

Medical Writing, Editorial, and Other Assistance

Medical writing assistance was provided by Alistair Ray, Steven Foster and Jake Casson of Meridian HealthComms Ltd, Macclesfield, UK, in accordance with good publication practice (GPP4), funded by Amryt Pharmaceuticals DAC.

Author Contributions

All authors made substantial contributions to the conception and design of the study, the acquisition, analysis and interpretation of data. Data were analysed by Veristat LLC, with statistical support provided by B.M.; data were verified by T.C. and S.L., and all authors were able to access the raw data. All authors reviewed the analyses, contributed toward the drafting of the article and revising it critically for important intellectual content. The authors had joint responsibility for the decision to submit for publication, and all authors provided their approval of the final version to be published. The authors are accountable for the accuracy and integrity of this work.

Disclosures

Luis Masana received fees for lectures or advisory work from Amarin, Amryt, Daiichi-Sankyo, Ferrer, Novartis, Sanofi, Servier and Viatris.

Claus Peter Schmitt received lecturing honoraria from Fresenius Medical Care; advisory fees from Baxter, Stada and Iperboreal Pharma; and research funding from Invizius.

Alberto Zambon received personal speaker fees from AlfaSigma, Amryt, Amarin, Sobi, Sanofi-Aventis, Servier, Amgen, Mylan, Abbott, Novartis, Fidia; and personal Consultancy/Advisory Board fees from Abbott, Amarin, Novartis.

Christina Taylan received honoraria from Novartis, Sanofi and Danone.

Hofit Cohen received consultation fees from Sanofi; lecture fees from Novartis, Sanofi, Medison Pharma, Abbott, Neopharm, Organon; and research support from Medison Pharma.

José Luis Diaz-Diaz received honoraria for speaker or researcher activities from Merck Sharp and Dohme, Amgen and Sanofi.

Sergio Martinez-Hervas received fees for speaker or advisory work from Amarin, Amryt, Daiichi-Sankyo, MSD, Novartis, Sanofi and Ultragenyx.

Brian Mangal is a Consultant for Amryt Pharma.

Tracy Cunningham and Sandra Löwe are employees of Amryt Pharmaceuticals DAC.

Naji Kholaif reports financial support and honoraria from Amryt.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1 Patient characteristics

Characteristic	**N = 43**
Sex, n (%)	
Female	24 (55·8)
Male	19 (44·2)
Median (IQR) age, years	10·7 (7·0–14·0)
5–10, n (%)	20 (46·5)
11–17, n (%)	23 (53·5)
Race, n (%)	
White	42 (97·7)
Black or African American	1 (2·3)
Geographic location, n (%)	
Germany	7 (16·3)
Italy	7 (16·3)
Spain	7 (16·3)
Saudi Arabia	13 (30·2)
Tunisia	6 (14·0)
Israel	3 (7·0)
Diagnosis of HoFH, n (%)	
Genetic confirmation of biallelic pathogenic variants	38 (88·4)
LDLR gene locus	33 (76·7)
LDLRAP1 gene locus	1 (2·3)
Other	4 (9·3)
Clinical diagnosis based on EAS consensus panel criteria on HoFH[22]	5 (11·6)
Median (IQR) HoFH diagnosis, weeks	254·9 (123·1–340·7)
Median (IQR) Baseline LDL-C mg/dL	390·5 (279·5–571·9)
Median (IQR) Baseline non-HDL-C mg/dL	407·5 (292·3–583·8)

Median (IQR) Baseline total cholesterol mg/dL	440·8 (328·7–600·9)
Median (IQR) Baseline VLDL-C mg/dL	17·0 (12·0–22·0)
Median (IQR) Baseline ApoB mg/dL	291·0 (216·0–400·0)
Median (IQR) Baseline triglycerides mg/dL	85·8 (60·2–108·0)
Median (IQR) Baseline Lp(a) mg/dL	25·3 (10·0–36·0)
Median (IQR) Baseline Lp(a) nmol/L	127·6 (39·0–195·3)
Median (IQR) duration of cardiovascular disease, months	38·6 (26·9–67·5)
Any ongoing cardiovascular medical condition, n (%)	28 (65·1)
Prior and Run-in LLT medications, n (%)	
Any	43 (100)
Statins	39 (90·7)
Ezetimibe	32 (74·4)
Evolocumab	5 (11·6)
Combination ezetimibe + rosuvastatin zinc	1 (2·3)
LDL-apheresis	19 (44·2)
Concomitant LLT during Efficacy Phase, n (%)	
Any	43 (100)
Statins	39 (90·7)
Ezetimibe	32 (74·4)
Evolocumab	4 (9·3)
Combination ezetimibe + rosuvastatin zinc	1 (2·3)
LDL-apheresis	19 (44·2)

ApoB, apolipoprotein B; EAS, European Atherosclerosis Society; HoFH, homozygous familial hypercholesterolaemia; IQR, interquartile range; LDLR, low-density lipoprotein receptor; LDLRAP1, low-density lipoprotein receptor adapter protein 1; LLT, lipid-lowering therapy; Lp(a), lipoprotein (a); non-HDL-C, non-high-density lipoprotein C; SD, standard deviation; VLDL-C, very low-density lipoprotein C.

Table 2 Summary of safety results (Efficacy Phase)

	5–10 years (N=20)			11–17 years (N=23)			Overall (N=43)		
	Events	Patients n (%)	95% CI	Events	Patients n (%)	95% CI	Events	Patients n (%)	95% CI
Total number of non-TEAEs	12	9 (45·0)	23·1, 68·5	11	10 (43·5)	23·2, 65·5	23	19 (44·2)	29·1, 60·1
Total number of TEAEs	168	18 (90·0)	68·3, 98·8	160	22 (95·7)	78·1, 99·9	328	40 (93·0)	80·9, 98·5
Serious TEAEs	2	2 (10·0)	1·2, 31·7	6	3 (13·0)	2·8, 33·6	8	5 (11·6)	3·9, 25·1
Serious related TEAEs	1	1 (5·0)	0·1, 24·9	0	0 (0)	0·0, 14·8	1	1 (2·3)	0·1, 12·3
TEAEs leading to study discontinuation	0	0 (0)	0·0, 16·8	2	2 (8·7)	1·1, 28·0	2	2 (4·7)	0·6, 15·8
Related TEAEs leading to study discontinuation	0	0 (0)	0·0, 16·8	2	2 (8·7)	1.1, 280	2	2 (4·7)	0·6, 15·8
Serious related TEAEs leading to study discontinuation	0	0 (0)	0·0, 16·8	0	0 (0)	0·0, 14·8	0	0 (0)	0·0, 8·2
TEAEs leading to death	0	0 (0)	0·0, 16·8	0	0 (0)	0·0, 14·8	0	0 (0)	0·0, 8·2
AESI	4	3 (15·0)	3·2, 37·9	2	2 (8·7)	1·1, 28·0	6	5 (11·6)	3·9, 25·1
Related AESI	4	3 (15·0)	3·2, 37·9	2	2 (8·7)	1·1, 28·0	6	5 (11·6)	3·9, 25·1
Major adverse cardiac events	0	0 (0)	0·0, 16·8	1	1 (4·3)	0·1, 1·9	1	1 (2·3)	0·1, 12.3

AESI, adverse event of special interest; CI, confidence interval; TEAE, treatment-emergent adverse event.

Table 3 Adverse events of special interest (Safety Analysis set)

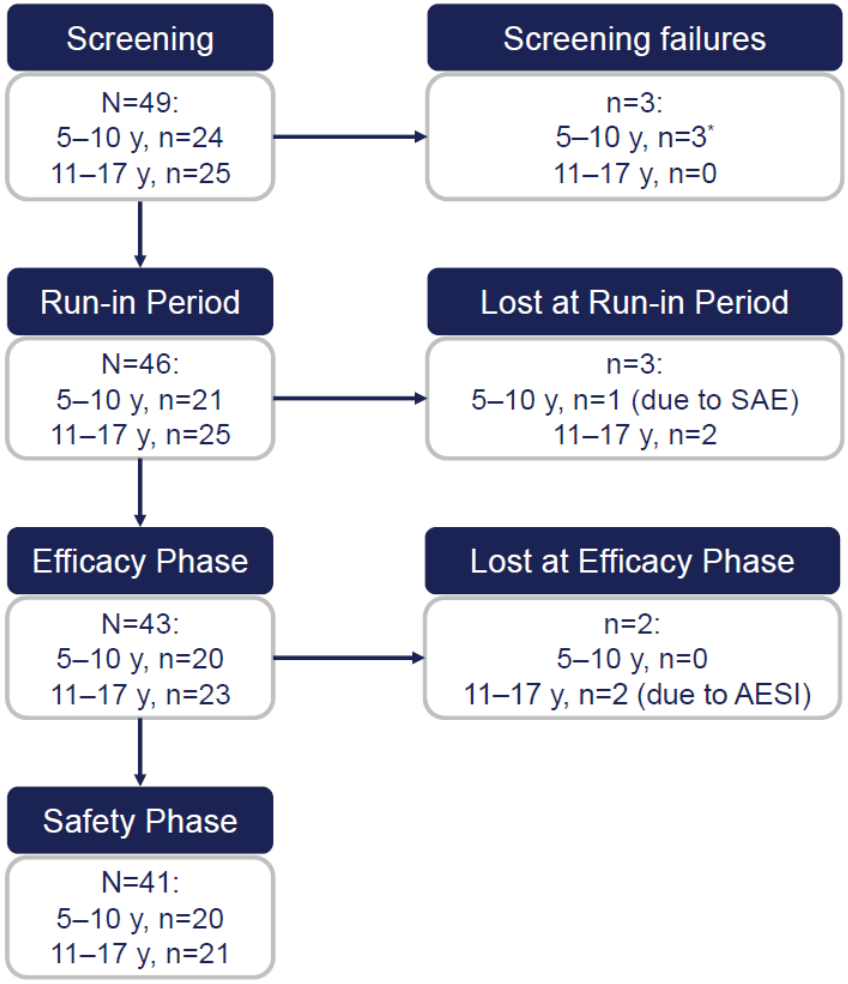
	5–10 years (N=20)			11–17 years (N=23)			Overall (N=43)		
	Events	Patients n (%)	95% CI	Events	Patients n (%)	95% CI	Events	Patients n (%)	95% CI
AESI	4	3 (15·0)	3·2, 37·9	2	2 (8·7)	1·1, 28·0	6	5 (11·6)	3·9, 25·1
Gastrointestinal disorders	0	0 (0)	0·0, 16·8	2	2 (8·7)	1·1, 28·0	2	2 (4·7)	0·6, 15·8
Diarrhoea	0	0 (0)	0·0, 16·8	2	2 (8·7)	1·1, 28·0	2	2 (4·7)	0·6, 15·8
Hepatobiliary disorders	3	2 (10·0)	1·2, 31·7	0	0 (0)	0·0, 14·8	3	2 (4·7)	0·6, 15·8
Hepatic steatosis	2	2 (10·0)	1·2, 31·7	0	0 (0)	0·0, 14·8	2	2 (4·7)	0·6, 15·8
Hepatomegaly	1	1 (5·0)	0·1, 24·9	0	0 (0)	0·0, 14·8	1	1 (2·3)	0·1, 12·3
Investigations	1	1 (5·0)	0·1, 24·9	0	0 (0)	0·0, 14·8	1	1 (2·3)	0·1, 12·3
Hepatic enzyme increased	1	1 (5·0)	0·1, 24·9	0	0 (0)	0·0, 14·8	1	1 (2·3)	0·1, 12·3

AESIs are defined as hepatic, small bowel/intestinal, pancreatic and colorectal tumours, hepatic abnormalities, gastrointestinal effects and major congenital abnormality adverse events.
If a patient experienced more than 1 TEAE, the patient is counted once for each system organ class and once for each preferred term.
Adverse events were coded using the MedDRA Dictionary, version 25.1.

AESI, adverse event of special interest; CI, confidence interval; TEAE, treatment-emergent adverse event.

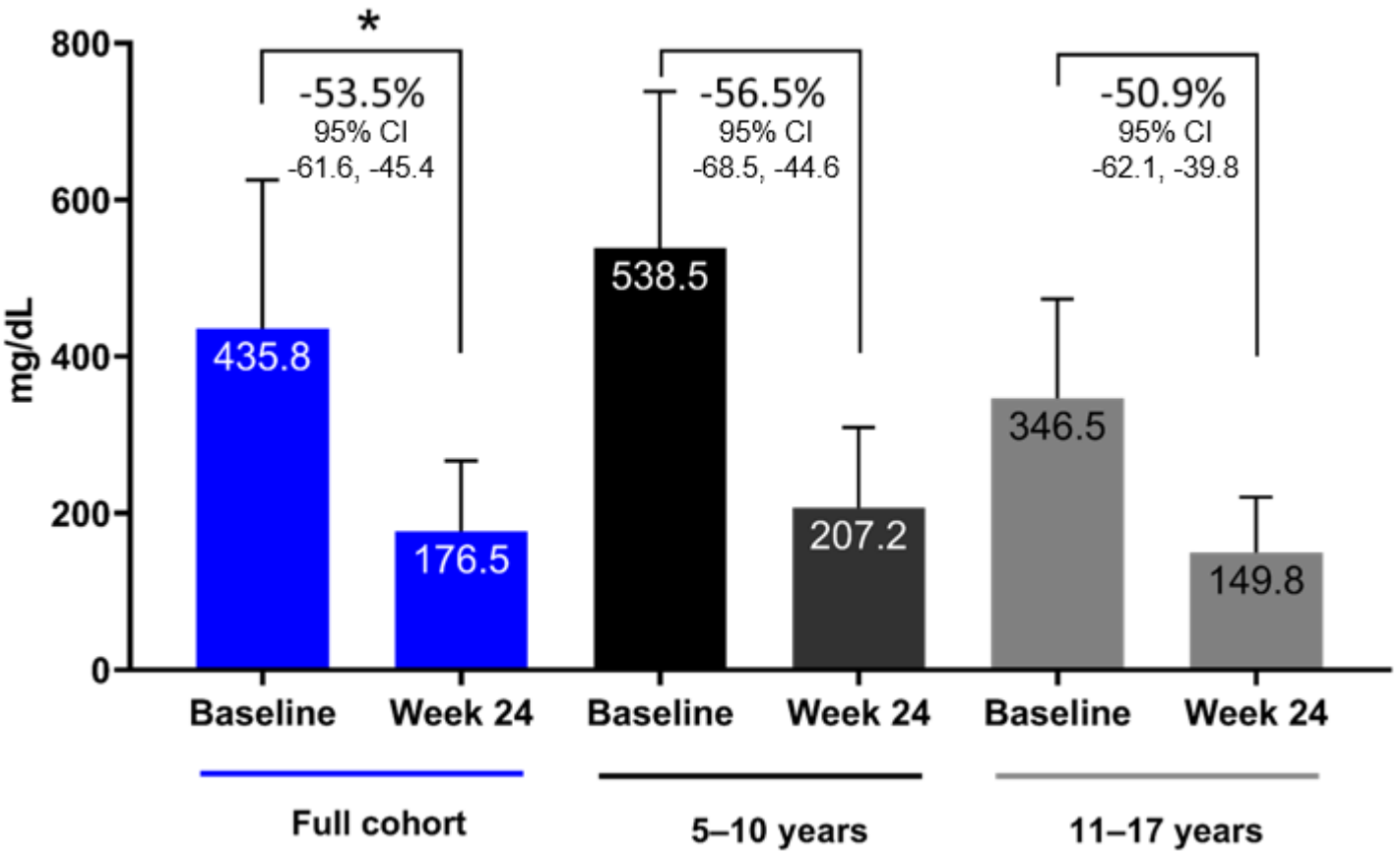
Figures

Figure 1 Patient disposition



AESI, adverse event of special interest; SAE, serious adverse event; y, years.

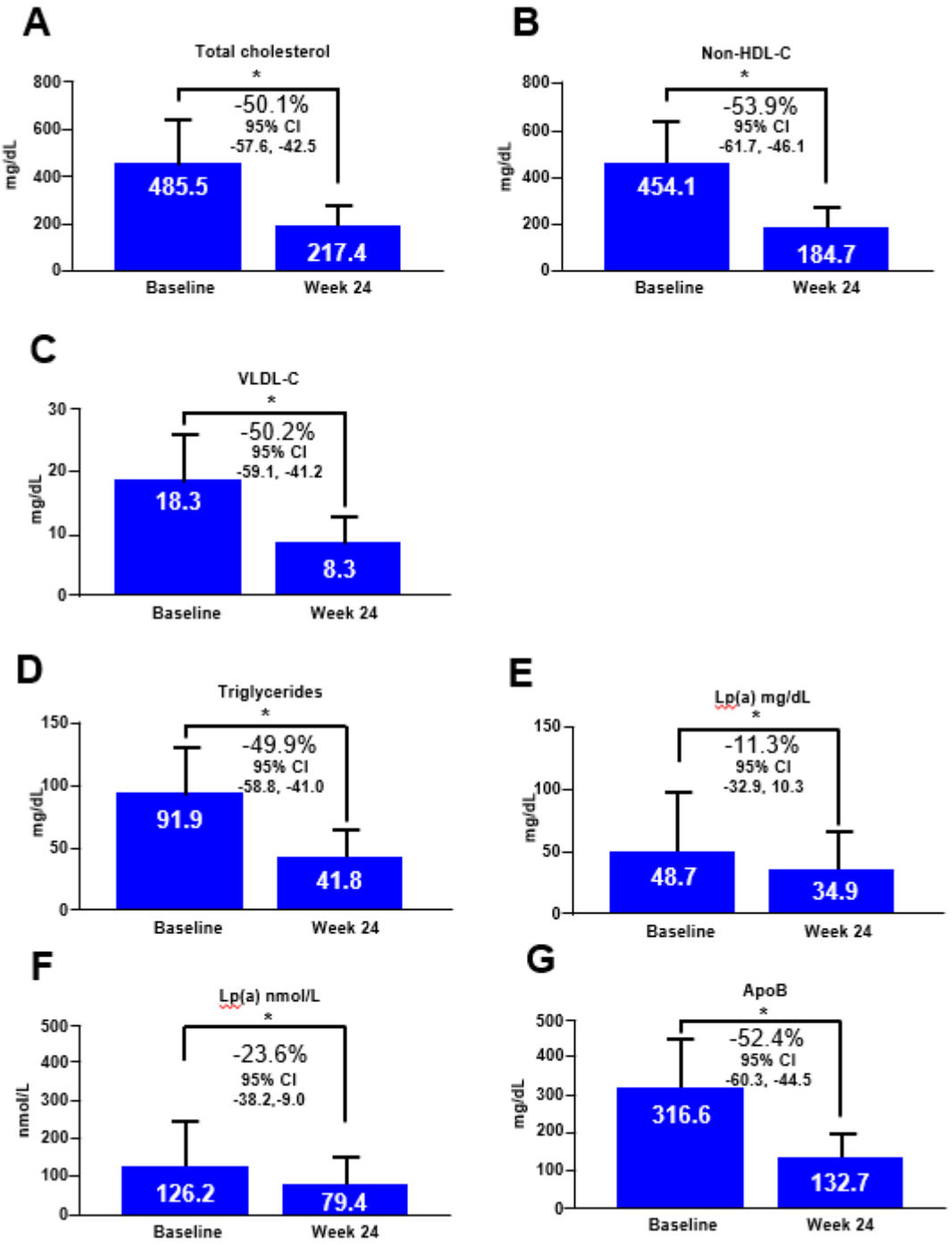
Figure 2 Mean LDL-C at Baseline and Week 24: overall and by age group (full analysis set)



N = 43, n = 20 for 5–10 years sub-group, and n = 23 for 11–17 years sub-group. LOCF was utilised for four patients.*p<0·0001; difference between Baseline and follow-up not assessed for age sub-groups. Error bars represent standard deviation.

CI, confidence interval; LDL-C, low-density lipoprotein C; LOCF, last observation carried forward.

Figure 3 Mean values at Baseline and at Week 24 for total cholesterol (**A**), non-HDL-C (**B**), VLDL-C (**C**), triglycerides (**D**), Lp(a) measured in mg/dL (**E**), Lp(a) measured in nmol/L (**F**)[a], and ApoB (**G**) (full analysis set)



[a]N = 43 for all outcomes apart from the Lp(a), which was measured in local laboratories, with 21 patients having results measured in mg/dL and 22 patients having results measured in nmol/L. LOCF was utilised for four patients.

*p<0·0001. The Fisher combined p-value for the Lp(a) mg/dL and nmol/L datasets was p=0·007 (Fisher Combined p-value for mg/dL and nmol/L datasets – individual p-values were 0·29 and 0·003 for data reported in mg/dL and nmol/L, respectively). Error bars represent standard deviation.

ApoB, apolipoprotein B; LOCF, last observation carried forward; Lp(a), lipoprotein (a); non-HDL-C, non-high-density lipoprotein C; VLDL-C, very low-density lipoprotein C.

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Appendix

Supplementary Methods

Maximum tolerated dose definition

The maximum tolerated dose (MTD) was defined as the highest dose of lomitapide through Week 24 that did not result in tolerability or safety concerns. Each patient continued to receive the MTD established during the Efficacy Phase for an additional 80 weeks in the Safety Phase, although a protocol amendment allowed eligible patients aged 5–15 years to have further escalation of the lomitapide dose beyond the age group recommended maximum dose. This was at the discretion of the investigator, and in agreement with the sponsor, if dose escalation was deemed safe and potentially efficacious for the patient. After Week 56, if a patient had crossed over into the next age category, the study medication was allowed to be further escalated to the maximum dose applicable for the new age category. In each case of dose escalation, if the patient tolerated this new dose for at least 4 weeks, this was then considered the new MTD.

For patients not taking part in the Expanded Access Programme, the lomitapide dose would be discontinued at the End of Treatment visit in patients <18 years (with patients remaining on concomitant lipid-lowering therapy [LLT] including lipoprotein apheresis [LA], when applicable), while patients >18 years may choose to transition to lomitapide under its adult indication.

Diet, vitamin E and essential fatty acids

During the Run-in Period, patients were established on a diet supplying <20% of energy (calories) from fat or <30 g fat, whichever was the lesser amount. Patients also returned to the study centre for a compliance visit between Week -3 and Week -2. From this visit, patients' diets were also supplemented with essential fatty acids (EFA), and 200 international units (IU) vitamin E for patients aged 5–8 years or 400 IU for those aged 9–to ≤17 years.

Assessments

Blood samples/laboratory tests

Blood samples for laboratory safety tests (metabolic panel and liver function tests [LFTs]) were collected at Baseline and every 4 weeks. Blood samples were analysed for complete blood count and hormone levels at Baseline, Week 56 and End of Treatment. Serum lipase was analysed at Baseline, Week 24 and 56, and End of Treatment, and EFAs and fat-soluble vitamins were analysed at Baseline, Weeks 24, 56, 80 and End of Treatment.

Electrocardiograms, standard of care echocardiography, pulmonary function tests, and lipid accumulation in the liver

Electrocardiograms (ECGs) were performed at Baseline, Weeks 24, 56, and 80, and at End of Treatment. Information in relation to the most recent standard of care echocardiography was collected at Baseline, Weeks 24 and 56, and at End of Treatment, if available. Pulmonary function tests (PFTs) were performed at Baseline, Weeks 24 and 56, and at End of Treatment. Lipid accumulation in the liver (nuclear magnetic resonance [NMR] or ultrasound) was assessed at Baseline, Weeks 24 and 56, and at End of Treatment and the Follow-up Visit, if applicable. Urinalysis was performed at Baseline, Week 56, End of Treatment or the Follow-up Visit, if applicable

Pharmacokinetics

Pharmacokinetic samples were collected from Baseline through Week 24. These were used to evaluate plasma levels of lomitapide but results were analysed separately and are not reported in this manuscript.

Patient maturation

Assessments of patient growth and maturation included vital signs at every visit, Tanner Staging at Weeks 12, 24, 56, and End of Treatment and measurements of hormones (thyroid-stimulating hormone, follicle-stimulating hormone, luteinising hormone, adrenocorticotropic hormone and serum cortisol) in all patients and sex hormones (serum testosterone for male patients, serum oestradiol for female patients) in patients Tanner Stage ≥2 at Baseline, Week 56 and End of Treatment.

Xanthomas

Xanthomas (tendon and cutaneous, size and location) were evaluated during physical examinations at Screening and at every visit from Baseline.

Supplementary methods - Endpoints

Safety endpoints

Other safety endpoints included nutrient levels, such as EFA and fat-soluble vitamin levels. Vital signs, ECG, echocardiography, PFT and physical examinations were also performed, and laboratory tests including haematology, a metabolic panel and serum lipase measurements were additional safety endpoints.

Adverse events of special interest were defined as:

- Hepatic, small bowel/intestinal, pancreatic and colorectal tumours
- Hepatic abnormalities
    - Elevations of hepatic transaminases resulting in discontinuation of lomitapide
    - Elevations of hepatic transaminases >3 × upper limit of normal (ULN) that persist despite dose reduction or interruption
    - Elevations of hepatic transaminases ≥5 × ULN symptomatic liver injury
    - Other hepatic evaluation and testing or any histology obtained from liver biopsy and imaging evaluations
- Gastrointestinal effects
    - Events that led to permanent treatment discontinuations
    - Events that led to hospitalisation due to gastrointestinal events
    - Events that triggered additional investigations, such as endoscopy
- Major congenital anomalies

Exploratory endpoints

Exploratory endpoints at later timepoints (outside the Efficacy Phase) included the change from Baseline at Week 56 and 104 in mean carotid intima media thickness (CIMT) and flow mediated dilatation (FMD), and the resolution or regression of pre-existing xanthomas at Week 56 and at Week 104.

Of the endpoints listed above, those occurring up to Week 24 are reported in this manuscript. Those after Week 24 will be reported in a separate manuscript when these data are analysed. Pharmacokinetics from this study are also being analysed separately and are not covered in this paper.

Palatability/ease of administration endpoints

Five-point facial hedonic scales were used in conjunction with parents' or guardians' interpretation to assess palatability and ease of administration of lomitapide. An example of the 5-point hedonic scale used is shown in Supplementary Figure 4 .

Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) was responsible for reviewing the clinical trial data on an ongoing basis to assure the safety of participants in this trial, as well as the validity and integrity of the data generated.

Statistical analysis

Mean changes from Baseline were analysed using a restricted maximum likelihood (REML)-based repeated measures approach in combination with the Newton Raphson algorithm. Analyses included visit as a fixed categorical effect. A common unstructured covariance structure to model the within-patient errors was used first, but the model failed to converge. The following structures were then applied in the subsequent order; Toeplitz, Autoregressive(1), and Compound Symmetry, with model-convergence being achieved under Compound Symmetry. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Significance tests were based on least-squares means using a two-sided $\alpha = \cdot 05$ (two-sided 95% confidence intervals). Analyses were implemented using the MIXED procedure in SAS v9.4.

Supplementary Results

Xanthoma assessment

At Week 24, pre-existing xanthomas had changed in 13/27 patients (48·1%) who had xanthomas at Baseline. Reductions in the size of xanthomas were reported for 11 of the 27 patients (40·7%) who had xanthomas at Baseline. Increases in size of xanthomas and new xanthomas were reported for 2 patients, both in the 5–10 years age group. Both of these patients had a slow dose escalation of lomitapide.

Palatability/ease of administration

Overall, palatability was reported as 'good', with no issues of vomiting or refusal to take lomitapide. Of the 40 patients with data available at Baseline, only one patient (aged 5–10 years) was unable to swallow the capsule, but they were able to take the study drug with mashed banana (as allowed per protocol). From Week 16, this patient was able to swallow the capsule. The majority of parents/guardians reported a pleasant reaction from their child on taking the study drug and did not report issues with refusal to take lomitapide.

Lipid accumulation in the liver

Although all patients were to undergo NMR imaging unless it was contraindicated or not feasible, when ultrasound scans could have been used at the discretion of the Investigator, NMR imaging was used for hepatic fat assessment in only 24/43 patients (55·8%), predominantly in patients 11–17 years of age (21/24, 87·5%).

Vice versa, ultrasound scans were performed in 19/43 patients (44·2%), mainly in those 5–10 years of age (17/19, 89·5%). All except one patient aged 5–10 years (17/17, 100·0% at Baseline, 15/15 and 100·0% at Week 24) and both patients aged 11–17 years, for whom hepatic fat assessments were based on ultrasound had a liver fat content below 10% at Baseline and Week 24 respectively. Results are shown in Supplementary Table 10.

Safety

Fat-soluble vitamins

All mean fat-soluble vitamin levels were within paediatric reference ranges at Baseline and at Week 24 except for vitamin E levels, which were well above the reference range at Baseline. These decreased as expected by Week 24, but were still above the ULN. Correspondingly, the vitamin E to total cholesterol, the vitamin E to total lipids, and the vitamin E to triglycerides ratios were all above the ULN both at Baseline and at Week 24. With the exception of four patients who had low vitamin E values at Screening, no clinically significantly abnormal values for vitamin E were reported. Two patients had treatment-emergent adverse events (TEAEs) of Vitamin E increased during the study; both were mild in severity and considered not related to lomitapide. Mean levels of the fat-soluble vitamins A and D increased within reference ranges from Baseline to Week 24. One patient had clinically significantly low levels of vitamin A, but this was present at Screening. Three patients had clinically significantly low vitamin D levels during the study, one of which was considered a TEAE of mild vitamin D deficiency, but not related to lomitapide. Twelve additional patients had low vitamin D at Screening or Baseline, one of whom was reported as having a TEAE of vitamin D deficiency, which was also unrelated to lomitapide. No clinically significantly abnormal values were reported for the fat-soluble vitamins osteocalcin, uncarboxylated osteocalcin:total osteocalcin ratio, or uncarboxylated osteocalcin.

Growth and maturation

There were no clinically significant mean changes in weight, height, body mass index (BMI), BMI-for-age z-score, BMI percentile, height-for-age z-score or height percentile from Baseline to Week 24. Patients 5–10 years of age had normal mean weight, height and BMI scores which remained stable or increased up to Week 24, indicating normal growth. However, there was considerable variability across all parameters including categories ranging from wasting to obesity. Patients 11–17 years of age had higher mean BMIs and BMI percentiles at Baseline compared to the 5–10 years sub-group, but still normal. Patients in the 11–17 age sub-group lost slightly more weight up to Week 24 compared to the younger patients, but weight loss did not reach levels of clinical concern.

All patients in the 5–10 years age group had a Tanner Stage of 1 throughout the study. The majority of patients in the 11–17 years age group were Tanner Stage 4 or 5 at Baseline and at Week 24.

Electrocardiograms, Echocardiography, Vital Signs and Pulmonary Function Tests

No clinically significant ECG abnormalities were identified, with any changes being considered consistent with the course of homozygous familial hypercholesterolemia (HoFH) and the patients' cardiovascular disease (CVD) history. Abnormal non-clinically significant ECG findings were reported for 11/43 patients (25·6%) at Baseline and seven patients at Week 24. Signs of left ventricular hypertrophy at Baseline in one patient normalised by Week 24. In 5 other patients, ECG changes appeared to reflect progressive CVD that was already reported as ongoing CVD history at Baseline. Echocardiography findings of atherosclerotic aortic valve disease, thickening of the aortic valve leaflets, thickening of the aortic root, flow acceleration or turbulence over the aortic valve, and/or aortic valve regurgitation were identified in 16/43 patients (37·2%) at Baseline. Six patients had TEAEs related to abnormal ECGs, which had been identified due to protocol-mandated procedures. However, none were considered related to study treatment and lomitapide was continued unchanged for each patient. Similarly, echocardiography findings were considered consistent with the progression of HoFH. There were no clinically meaningful changes from Baseline to Week 24 for any PFT assessment.

Supplementary References

1. Guinard J-X. Sensory and consumer testing with children. *Trends in Food Science & Technology* 2000; **11**(8): 273–83.

Supplementary Tables

Supplementary Table 1 APH-19 inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
1. Male and female patients aged 5–17 years with HoFH as defined by any of the following criteria recommended by the Consensus Panel on Familial Hypercholesterolaemia of the EAS[22] a. Genetic confirmation of 2 mutant alleles at the LDLR, ApoB, PCSK9, or LDLRAP1 gene locus, or b. An untreated LDL-C >500 mg/dL (13 mmol/L) or treated LDL-C ≥300 mg/dL (8 mmol/L) together with either - Cutaneous or tendon xanthoma before age 10 years or - Untreated LDL-C levels consistent with heterozygous FH in both parents	1. Other forms of primary hyperlipoproteinaemia and secondary causes of hypercholesterolaemia (e.g., nephrotic syndrome, hypothyroidism)
2. Baseline LDL-C on LLT (C_{max} of LDL-C immediately prior to LA, if applicable): a. >160 mg/dL (4.1 mmol/L, no documented CVD) or b. >130 mg/dL (3.4 mmol/L, established CVD defined as aortic valve disease and/or coronary atherosclerosis)	2. Contraindications for the use of lomitapide such as hypersensitivity to the active substance or to any of the excipients, known significant or chronic inflammatory bowel disease or malabsorption
3. Body weight ≥15 kg or BMI and height both >10th percentile according to WHO Growth Charts for Boys and Girls 5–19 Years of Age	3. Moderate (Child Pugh B) or severe hepatic impairment (Child Pugh C), active liver disease and/or abnormal liver function tests at Screening (AST or ALT >1·5 x ULN and/or total bilirubin >1·5 x ULN in the absence of Gilbert's syndrome or AP >1.5 x ULN [based on appropriate age and gender normal values])
4. Patient and/or their legal representative has given informed consent	4. Serum CK >2 x ULN
5. Patient and/or his/her legal representative able and willing to follow study procedures and instructions	5. Chronic renal insufficiency with GFR <70 mL/min/1·73 m^2 calculated using the Schwartz formula
6. Postmenarchal female adolescents had to be willing to use highly effective methods of birth control that, alone or in combination, resulted in a low failure rate (i.e., <1% per year)	6. Uncontrolled hypertension (defined as mean systolic and/or diastolic blood pressure ≥95% of normal for age and sex) despite medical therapy
7. Patient was in stable physical and mental health at Screening	7. NYHA Class III or IV congestive heart failure
	8. Precocious/delayed puberty or endocrine disorder affecting growth (e.g., hypothyroidism, premature adrenarche)
	9. History of drug abuse within the last 3 years or habitual alcohol consumption
	10. Life expectancy predicted to be <5 years
	11. History of a non-skin malignancy (with the exception of cervical cancer in situ) within 3 years prior to enrolment
	12. Treatment with any IMP within 6 months or 5 times the terminal half-life of the corresponding IMP, whichever was longer, before the Screening visit
	13. Patient was related to the sponsor or member of the investigational team
	14. Pregnant or nursing women

ALT, alanine aminotransferase; AP, alkaline phosphatase; ApoB, apolipoprotein B; AST, aspartate transaminase; BMI, body mass index; CK, creatinine kinase; CVD, cardiovascular disease; EAS, European Atherosclerosis Society; FH, familial hypercholesterolemia; GFR, glomerular filtration rate; HoFH, homozygous familial hypercholesterolemia; IMP, investigational medicinal product; LA, low-density lipoprotein apheresis; LDL-C, low-density lipoprotein A; LDLR, low-density lipoprotein receptor; LDLRAP1, Low-Density Lipoprotein Receptor Adaptor Protein 1; LLT, lipid-lowering therapy; NYHA, New York Heart Association; PCSK9, proprotein convertase subtilisin/kexin type 9; ULN, upper limit of normal; WHO, World Health Organization.

Supplementary Table 2 Dosing schedule for patients in different age groups

Age Group (years)	Lomitapide Dose (mg)					
	Day 0	Week 4	Week 8	Week 12	Week 16	Maximum
5–10	2	2	5	10	20	20[a] (10, in Child-Pugh A)
11–15	2	5	10	20	40	40[b] (20, in Child-Pugh A)
16–17	5	10	20	40	60	60[c] (40, in Child-Pugh A)

[a]95% of patients in this age group achieved maximum dose; [b]70.6% of patients in this age group achieved maximum dose; [c]50.0% of patients in this age group achieved maximum dose.

Supplementary Table 3 Concomitant medications

Concomitant medication (except for LLT)	n (%)
Any concomitant medication	32 (74·4)
Vitamin D and analogues	14 (32·6)
Anilides	10 (23·3)
Iron bivalent, oral preparations	8 (18·6)
Platelet aggregation inhibitors excluding heparin	8 (18·6)
Propionic acid derivatives	7 (16·3)
Combinations of penicillins, including beta-lactamase inhibitors	5 (11·6)
Iron, parenteral preparations	5 (11·6)
Other viral vaccines	4 (9·3)
Beta blocking agents, selective	3 (7·0)
ACE inhibitors, plain	2 (4·7)
Beta-lactamase sensitive penicillins	2 (4·7)
Expectorants	2 (4·7)
Glycopeptide antibacterials	2 (4·7)
Iron trivalent, oral preparations	2 (4·7)
Other antiemetics	2 (4·7)
Sympathomimetics	2 (4·7)

Medications were coded using World Health Organization Drug Dictionary, version B3Mar20.

Medication classes and standardised medication names are ordered by descending frequency.

ACE, angiotensin-converting enzyme; LLT, lipid-lowering therapy.

Supplementary Table 4 Cardiovascular conditions

Characteristic	N = 43
Any ongoing cardiovascular medical condition, n (%)*	28 (65·1)
Aortic valvular disorders	15 (34·9)
Mitral valvular disorders	7 (16·3)
Cardiac valve disorders NEC	4 (9·3)
Tricuspid valvular disorders	3 (7·0)
Coronary artery disorders NEC	2 (4·7)
Ischaemic coronary artery disorders NEC	2 (4·7)
Cardiac conduction disorders	1 (2·3)
Myocardial disorders NEC	1 (2·3)
Aortic necrosis and vascular insufficiency	5 (11·6)
Vascular hypertensive disorders NEC	4 (9·3)
Non-site-specific necrosis and vascular insufficiency NEC	1 (2·3)
Site specific necrosis and vascular insufficiency NEC	1 (2·3)
Site specific vascular disorders NEC	1 (2·3)
ECG investigations	1 (2·3)

*Cardiovascular medical history events were coded using the MedDRA Dictionary, Version 25.1, MedDRA Higher Level Terms are reported.

ECG, echocardiogram; NEC, not elsewhere classified.

Supplementary Table 5 LDL-C change from Baseline at 24 weeks (full analysis set)

Visit	Overall (N = 43) Change from Baseline (%)
Primary analysis Week 24[a]	
Mean	-53·5
95% CI	-61·6, -45·4
P-value	<0·0001
Sensitivity analysis[b]	
Mean	-55·5
95% CI	-63·6, -47·4
P-value	<0·0001

[a]Missing data has been imputed using last observation carried forward (LOCF) for four patients; [b]A sensitivity analysis was conducted using a mixed model repeated measures model with missing at random assumption. Model includes visit as a categorical fixed effect. A Compound Symmetry covariance structure was used in the model.

CI, confidence interval; LDL-C, low-density lipoprotein cholesterol.

856 **Supplementary Table 6 Additional safety results (Efficacy Phase)**

	5–10 years (N = 20)		11–17 years (N = 23)		Overall (N = 43)	
	Events	**Patients n (%)**	**Events**	**Patients n (%)**	**Events**	**Patients n (%)**
Severity						
Mild	153	12 (60)	101	9 (39·1)	254	21 (48·8)
Moderate	13	4 (20)	48	9 (39·1)	61	13 (30·2)
Severe	2	2 (10)	9	3 (13·0)	11	5 (11·6)
Life-threatening	0	0 (0)	2	1 (4·3)	2	1 (2·3)
Death	0	0 (0)	0	0 (0)	0	0 (0)
Relationship to study treatment						
Related	53	10 (50·0)	55	15 (65·2)	108	25 (58·1)
Unrelated	115	8 (40·0)	105	7 (30·4)	220	15 (34·9)
Action taken with study treatment						
Dose decreased	0	0 (0)	9	4 (17·4)	9	4 (9·3)
Dose unchanged	149	18 (90·0)	141	14 (60·9)	290	32 (74·4)
Drug withdrawn	0	0 (0)	2	2 (8·7)	2	2 (4·7)
Not applicable	4	0 (0)	1	0 (0)	5	0 (0)
Other	15	0 (0)	7	2 (8·7)	22	2 (4·7)

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Supplementary Table 7 Treatment-emergent adverse events in >5% of patients overall (Safety Analysis set)

	5–10 years N = 20 n (%)	11–17 years N = 23 n (%)	Overall N = 43 n (%)
Patients with any TEAEs	18 (90·0)	22 (95·7)	40 (93·0)
Diarrhoea	8 (40·0)	12 (52·2)	20 (46·5)
Abdominal pain	8 (40·0)	10 (43·5)	18 (41·9)
Pyrexia	10 (50·0)	3 (13·0)	13 (30·2)
Alanine aminotransferase increased	6 (30·0)	6 (26·1)	12 (27·9)
Vomiting	9 (45·0)	2 (8·7)	11 (25·6)
Aspartate aminotransferase increased	4 (20·0)	6 (26·1)	10 (23·3)
COVID-19	4 (20·0)	5 (21·7)	9 (20·9)
Cough	6 (30·0)	1 (4·3)	7 (16·3)
Anaemia	2 (10·0)	3 (13·0)	5 (11·6)
ECG signs of ventricular hypertrophy	2 (10·0)	3 (13·0)	5 (11·6)
Nasopharyngitis	3 (15·0)	2 (8·7)	5 (11·6)
Abdominal pain upper	2 (10·0)	2 (8·7)	4 (9·3)
Blood creatine phosphokinase increased	4 (20·0)	0	4 (9·3)
C-reactive protein increased	2 (10·0)	2 (8·7)	4 (9·3)
Headache	2 (10·0)	2 (8·7)	4 (9·3)
Decreased appetite	2 (10·0)	1 (4·3)	3 (7·0)
Nausea	1 (5·0)	2 (8·7)	3 (7·0)
Upper respiratory tract infection	2 (10·0)	1 (4·3)	3 (7·0)
Viral infection	2 (10·0)	1 (4·3)	3 (7·0)

If a patient experienced more than 1 TEAE, the patient is counted once for each system organ class and once for each preferred term.
Adverse events were coded using the MedDRA, version 25.1.
COVID-19, coronavirus disease 2019; ECG, electrocardiogram; TEAE, treatment-emergent adverse event.

Supplementary Table 8 Summary of serious adverse events (Safety Analysis set)

	5–10 years N = 20 n (%)	11–17 years N = 23 n (%)	Overall N = 43 n (%)
Patients with any serious adverse event	2 (10·0)	3 (13·0)	5 (11·6)
Infections and infestations	0	2 (8·7)	2 (4·7)
Vascular device infection	0	2 (8·7)	2 (4·7)
Injury, poisoning and procedural complications			
Subdural haematoma	0	1 (4·3)	1 (2·3)
	0	1 (4·3)	1 (2·3)
Investigations	1 (5·0)	0	1 (2·3)
Hepatic enzyme increased	1 (5·0)	0	1 (2·3)
Musculoskeletal and connective tissue disorders			
Tendon disorder	0	1 (4·3)	1 (2·3)
	0	1 (4·3)	1 (2·3)
Product issues	1 (5·0)	0	1 (2·3)
Device occlusion	1 (5·0)	0	1 (2·3)
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism	0	1 (4·3)	1 (2·3)
	0	1 (4·3)	1 (2·3)
Vascular disorders	0	1 (4·3)	1 (2·3)
Aortic arteriosclerosis	0	1 (4·3)	1 (2·3)

Adverse events were coded using the MedDRA, version 25.1.

Supplementary Table 9 AEs related to hepatic enzyme abnormalities (Safety Analysis set)

Preferred term	5–10 years N = 20 n (%)	11–17 years N = 23 n (%)	Overall N = 43 n (%)
All causality			
Alanine aminotransferase increased	6 (30·0)	6 (26·1)	12 (27·9)
Aspartate aminotransferase increased	4 (20·0)	6 (26·1)	10 (23·3)
Hepatic enzyme increased	2 (10·0)	0	2 (4·7)
Hypertransaminasaemia	1 (5·0)	0	1 (2·3)
Transaminases increased	1 (5·0)	0	1 (2·3)
Treatment related			
Alanine aminotransferase increased	4 (20·0)	4 (17·4)	8 (18·6)
Aspartate aminotransferase increased	4 (20·0)	4 (17·4)	8 (18·6)
Hepatic enzyme increased	2 (10·0)	0	2 (4·7)
Hypertransaminasaemia	1 (5·0)	0	1 (2·3)
Transaminases increased	1 (5·0)	0	1 (2·3)

If a patient experienced more than 1 TEAE, the patient is counted once for each preferred term.
Related events are those classified as having a reasonable causal relationship to the study treatment.
Adverse events were coded using the MedDRA Dictionary, version 25.1.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent AE.

Supplementary Table 10 Summary of lipid accumulation in the liver at Baseline and Week 24 (Safety Analysis set)

	NMR scan (N = 24)		Ultrasound scan (N = 19)		
	5–10 years (N = 3)	**11–17 years (N = 21)**	**5–10 years (N = 17)**	**11–17 years (N = 2)**	**Overall (N = 43)**
Baseline					
Total	3 (100·0)	19 (100·0)	17 (100·0)	2 (100·0)	41 (100·0)
≤10% liver fat	2 (66·7)	16 (84·2)	17 (100·0)	2 (100·0)	37 (90·2)
>10% liver fat	0 (0)	1 (5·3)	0 (0)	0 (0)	1 (2·4)
>20% liver fat	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
No result	1 (33·3)	2 (10·5)	0 (0)	0 (0)	3 (7·3)
Week 24[a]					
Total	4 (100·0)	19 (100·0)	15 (100·0)	2 (100·0)	40 (100·0)
≤10% liver fat	1 (25·0)	12 (6·3)	15 (100·0)	2 (100·0)	30 (75·0)
>10% liver fat	1 (25·0)	2 (10·5)	0 (0)	0 (0)	3 (7·5)
>20% liver fat	0 (0)	1 (5·3)	0 (0)	0 (0)	1 (2·5)
No result	2 (50·0)	4 (21·1)	0 (0)	0 (0)	6 (15·0)

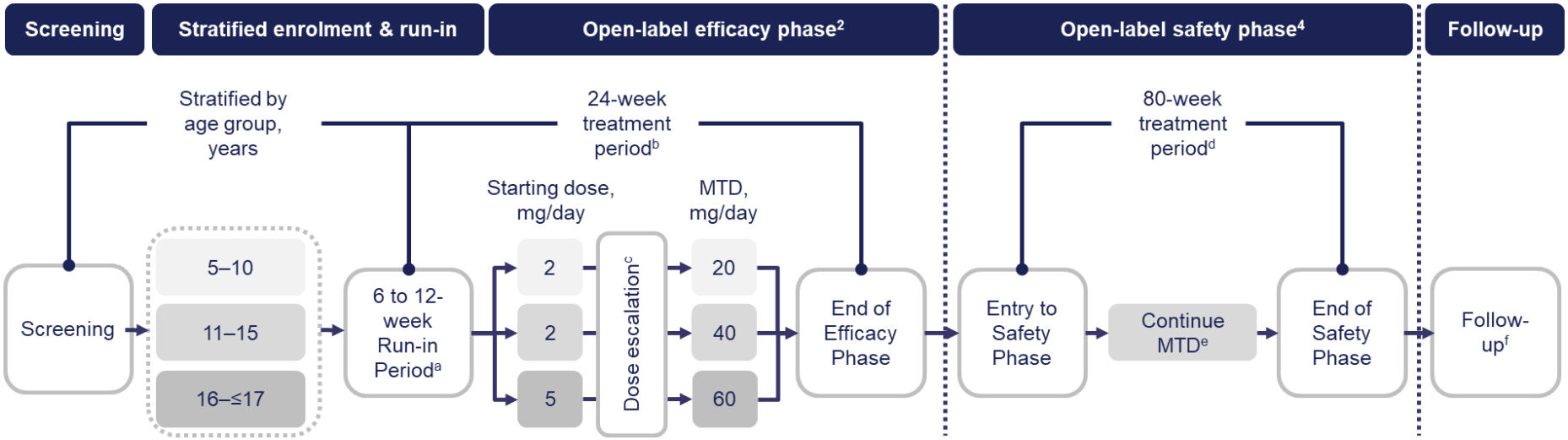
Data are n (%).

[a]One patient switched from ultrasound at Baseline to NMR at Week 24.

NMR, nuclear magnetic resonance.

Supplementary Figures

Supplementary Figure 1 Study design



[a]Stabilised current LLT (including LA, when applicable), establish diet <20% energy from fat or <30 g fat, whichever is the lesser amount, dietary supplementation from Week -2 (daily 200 IU [5 to 8 years of age] 400 IU [≥9 years of age] vitamin E and EFA supplement [approx. 200 mg linoleic acid, 210 mg ALA, 110 mg EPA, and 80 mg DHA]).

[b]During the 24-week Efficacy Phase, patients were required to remain on the stable LLT regimen (including LA, when applicable) established during the 6-week Run-in Period.

[c]Based on safety, tolerability and efficacy parameters.

[d]Adjustments to background LLT (including LA, when applicable) will be allowed at the discretion of the investigator.

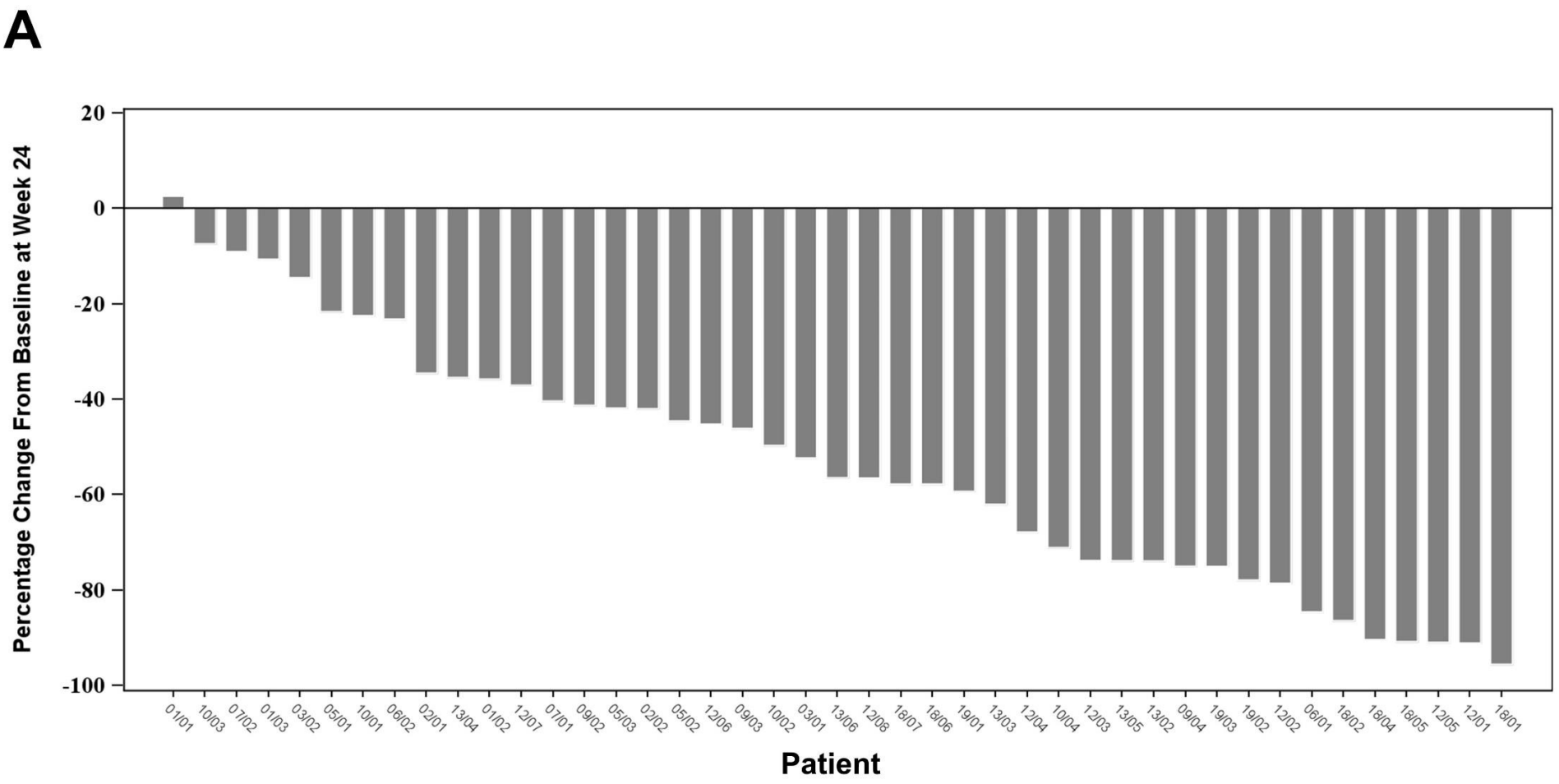
[e]Dose adjustment rules apply.

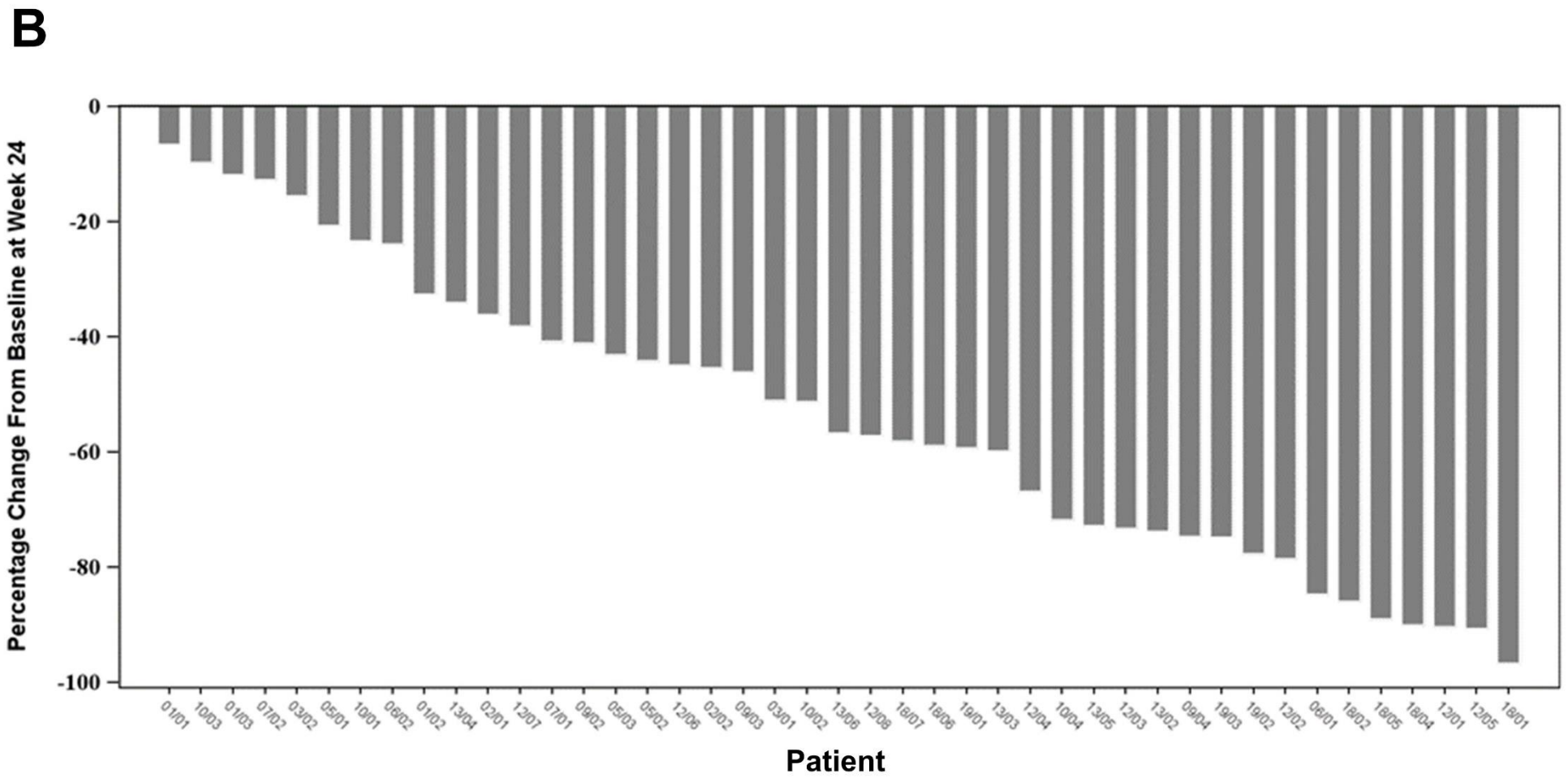
[f]Eligible patients who complete the study per protocol at Week 104 and are <18 years of age may choose to enter the Early Access Programme. Patients ≥18 years of age may opt to transition to commercial product under the approved product label for adults. For both these patient groups, a follow-up phone call will be conducted at Week 108±1 week to monitor safety including AE and concomitant medication reporting. Patients who opt not to participate in or are unsuitable for the Early Access Programme, or patients ≥18 years of age who opt not to transition to commercial product will discontinue lomitapide treatment at Week 104±1 week and enter a 4-week follow-up period during which they will remain on concomitant LLT (including LA, when applicable). These patients will attend in person for a Week 108±1 week visit.

AE, adverse event; ALA, alpha-linoleic acid; DHA, docosahexaenoic acid; EFA, essential fatty acids; EPA, eicosapentaenoic acid; LA, lipoprotein apheresis; LLT, lipid-lowering therapy; MTD, maximum tolerated dose.

Supplementary Figure 2 Change in individual patient lipoprotein levels from Baseline to Week 24 for LDL-C (A), non-HDL-C (B), total cholesterol (C), VLDL-C (D), ApoB (E), triglycerides (F), Lp(a) measured in mg/dL (G), and Lp(a) measured in nmol/L (H) – Full Analysis set

ApoB, apolipoprotein B; LDL-C, low-density lipoprotein C; Lp(a), lipoprotein (a); non-HDL-C, non-high-density lipoprotein C; VLDL-C, very low-density lipoprotein C.

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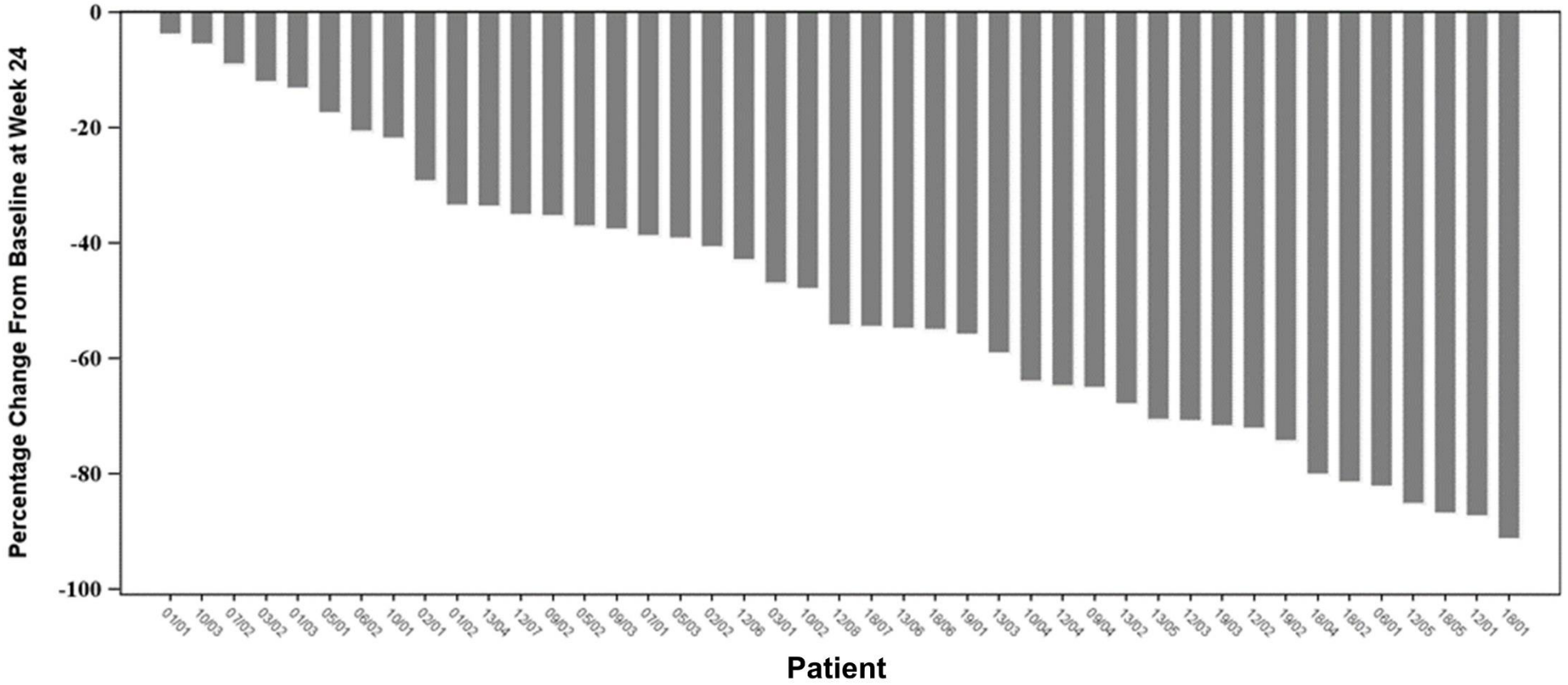
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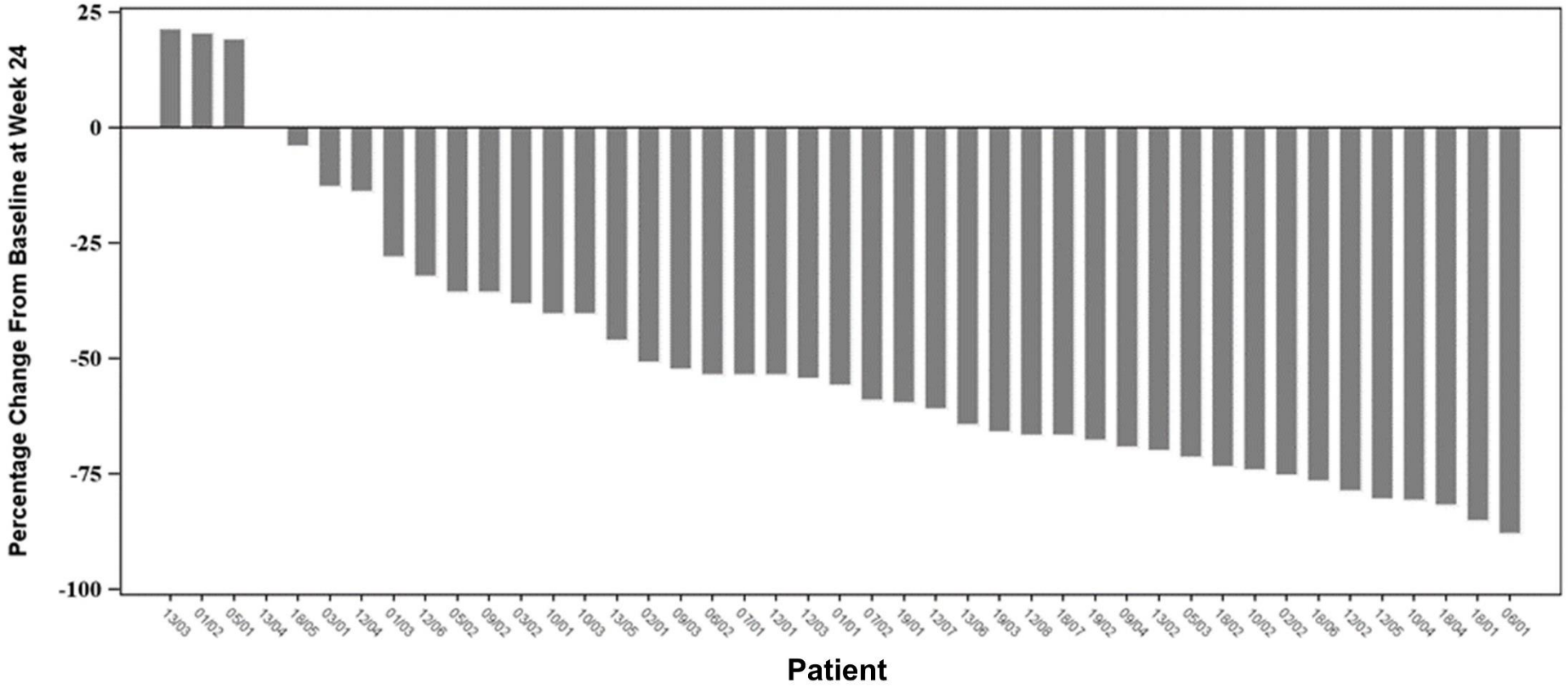
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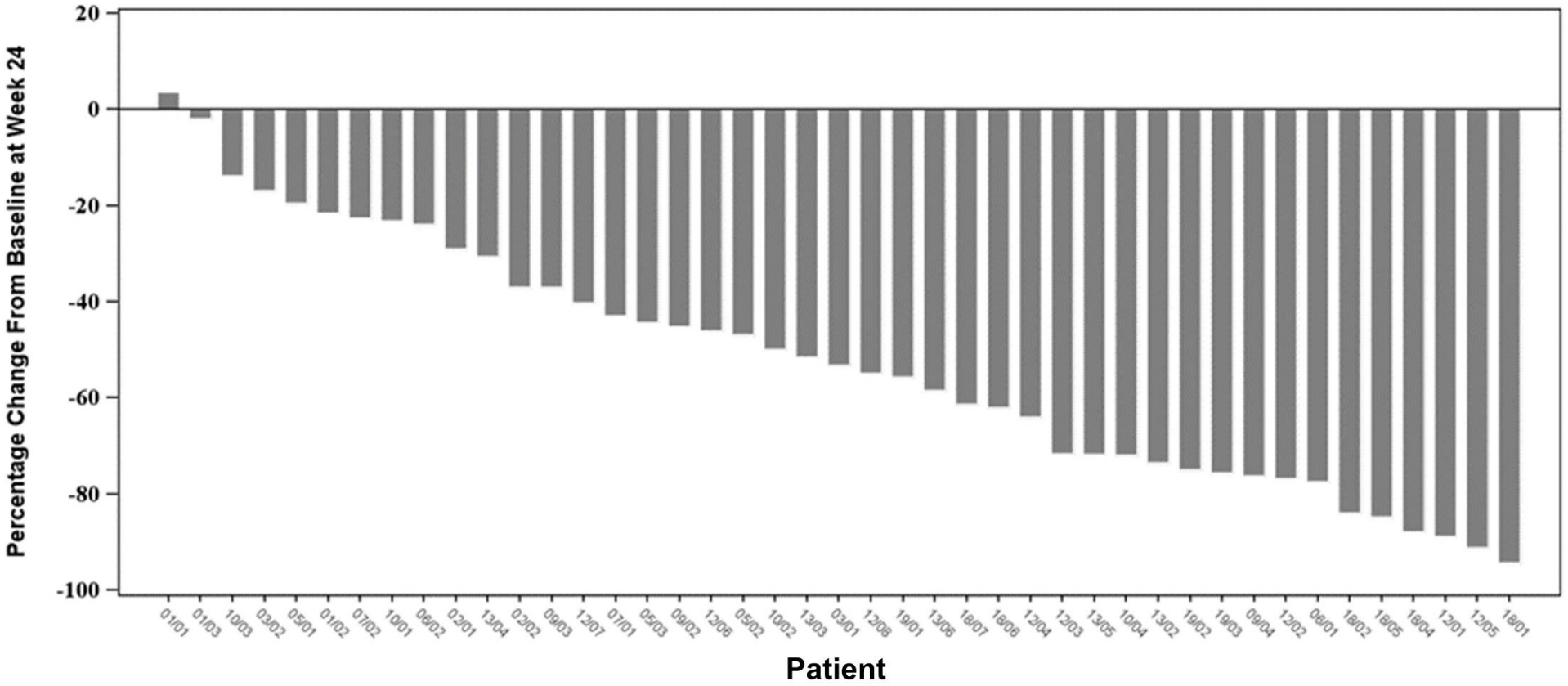
Percentage Change From Baseline at Week 24
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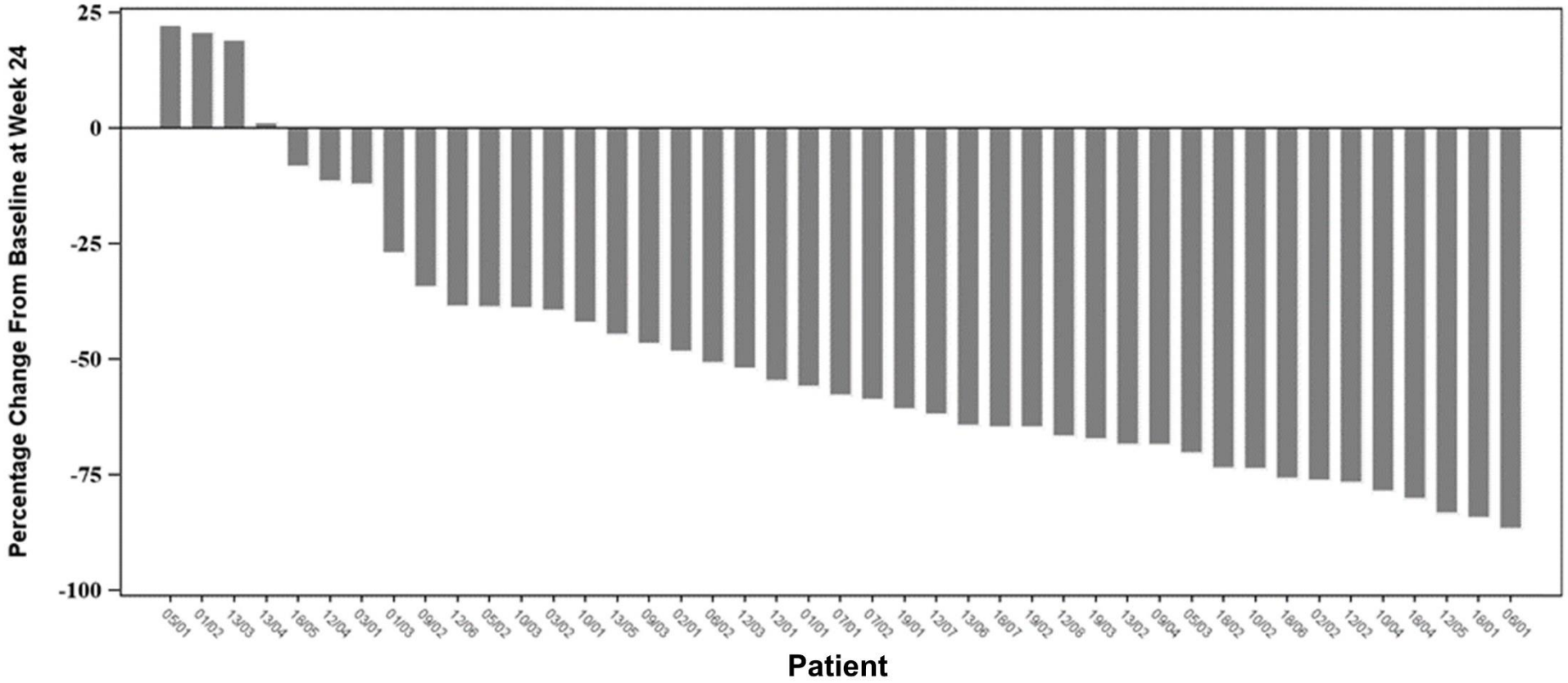
07/01
05/03
09/02
12/06
05/02
10/02
13/03
03/01
12/08
19/01
13/06
18/07
18/06
12/04
12/03
13/05
10/04
13/02
19/02
19/03
09/04
12/02
06/01
18/02
18/05
18/04
12/01
12/05
18/01
Patient

909

F


Percentage Change From Baseline at Week 24
25
0
-25
-50
-75
-100
05/01
01/02
13/03
13/04
18/05
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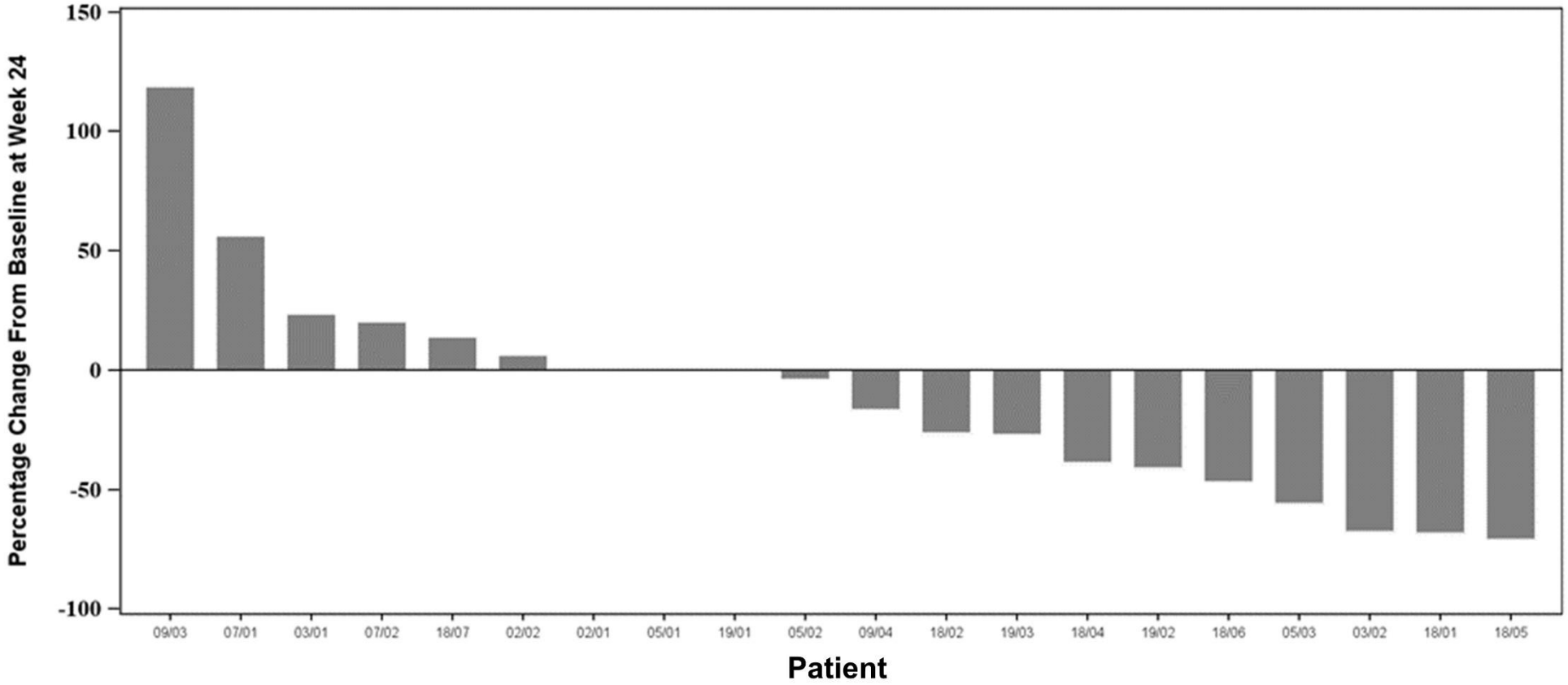
03/01
01/03
09/02
12/06
05/02
10/03
03/02
10/01
13/05
09/03
02/01
06/02
12/03
12/01
01/01
07/01
07/02
19/01
12/07
13/06
18/07
19/02
12/08
19/03
13/02
09/04
05/03
18/02
10/02
18/06
02/02
12/02
10/04
18/04
13/05
18/01
06/01
Patient

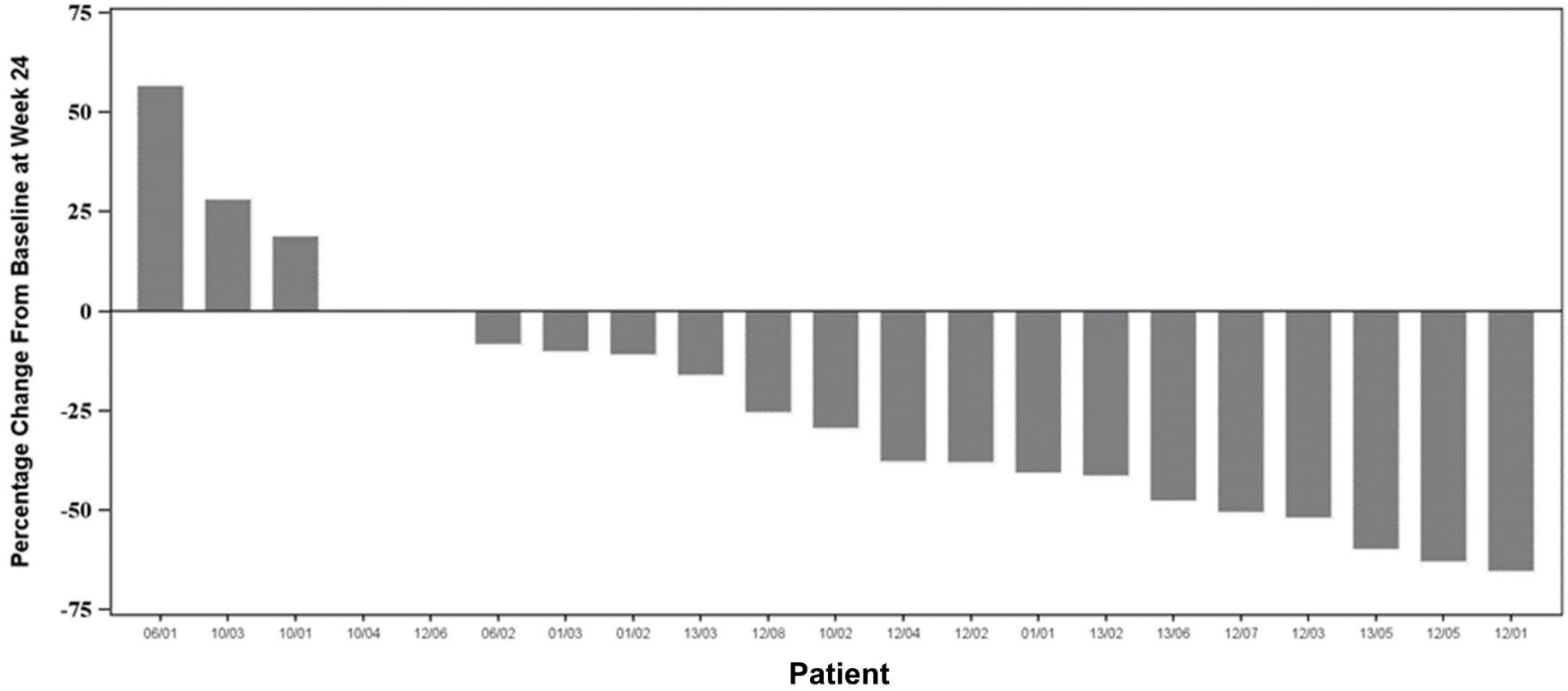
910

G


150
100
50
0
-50
-100
Percentage Change From Baseline at Week 24
09/03
07/01
03/01
07/02
18/07
02/02
02/01
05/01
19/01
05/02
09/04
18/02
19/03
18/04
19/02
18/06
05/03
03/02
18/01
18/05
Patient

911

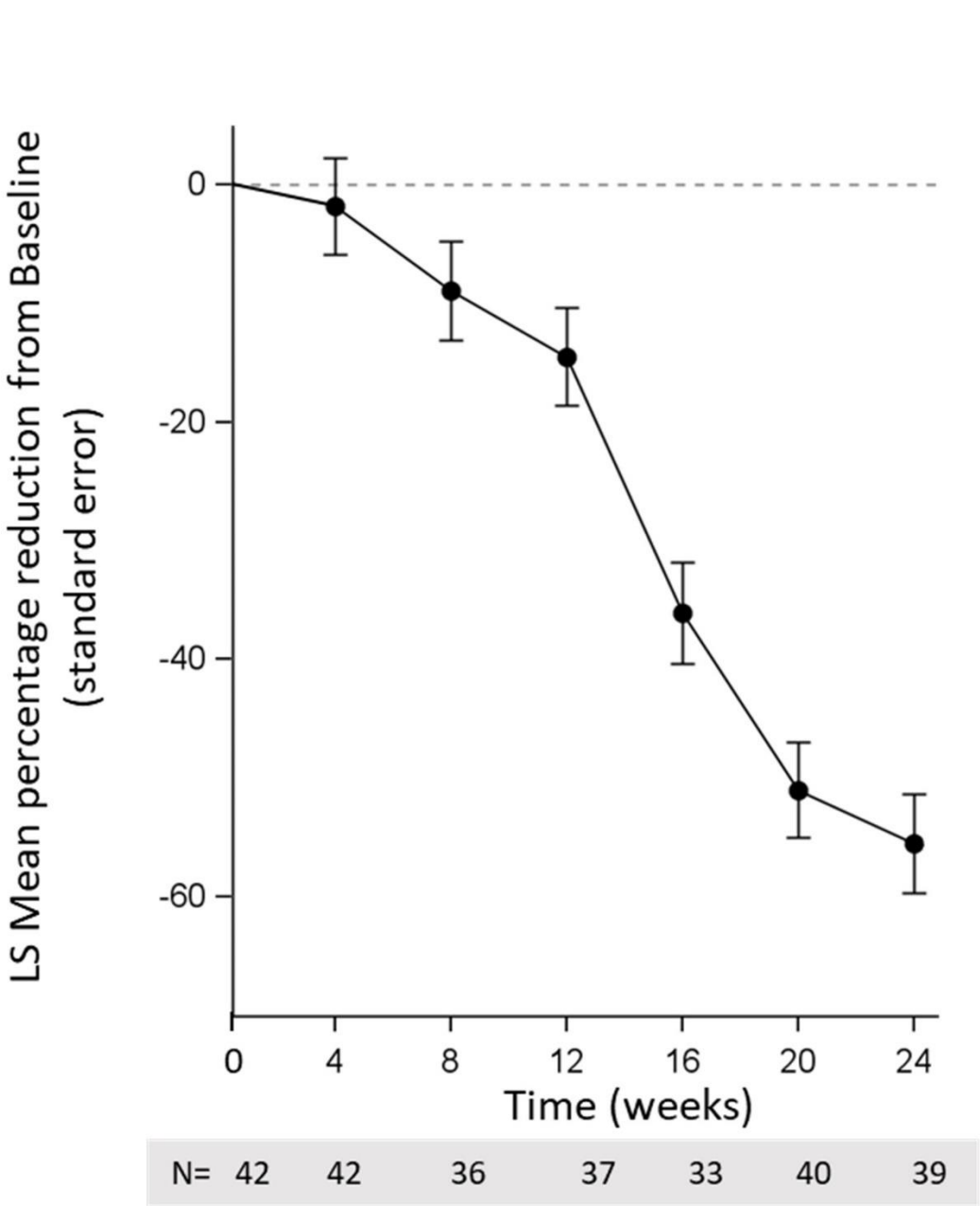
H


Percentage Change From Baseline at Week 24
75
50
25
0
-25
-50
-75
06/01
10/03
10/01
10/04
12/06
06/02
01/03
01/02
13/03
12/08
10/02
12/04
12/02
01/01
13/02
13/06
12/07
12/03
13/05
12/05
12/01
Patient

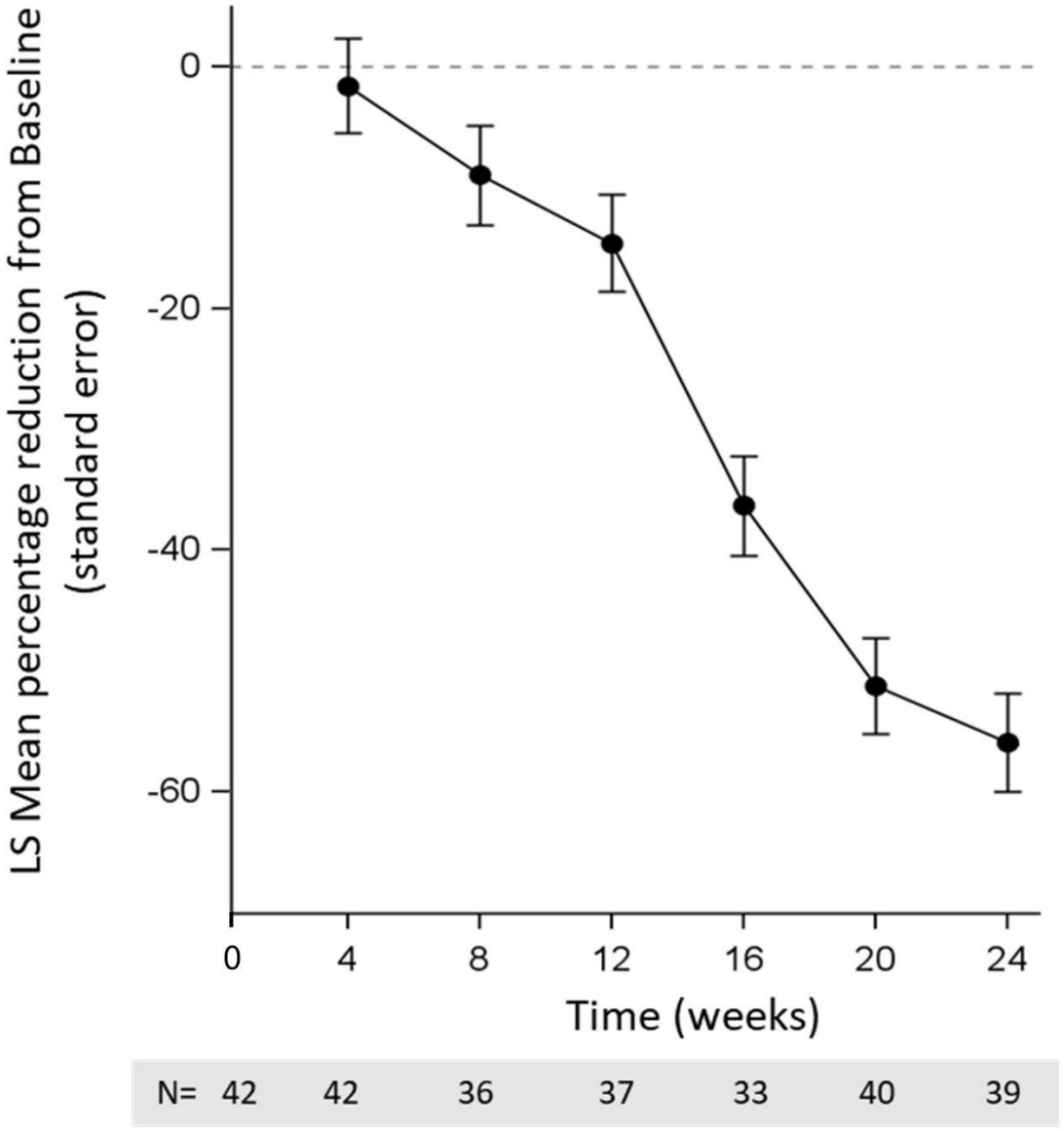
912

Supplementary Figure 3 Mean change in lipoproteins from Baseline to Week 24 for LDL-C (A), non-HDL-C (B), total cholesterol (C), VLDL-C (D), ApoB (E), triglycerides (F), Lp(a) measured in mg/dL (G), and Lp(a) measured in nmol/L (H) – Full Analysis set

ApoB, apolipoprotein B; LDL-C, low-density lipoprotein C; LS, least squares; Lp(a), lipoprotein (a); non-HDL-C, non-high-density lipoprotein C; VLDL-C, very low-density lipoprotein C.

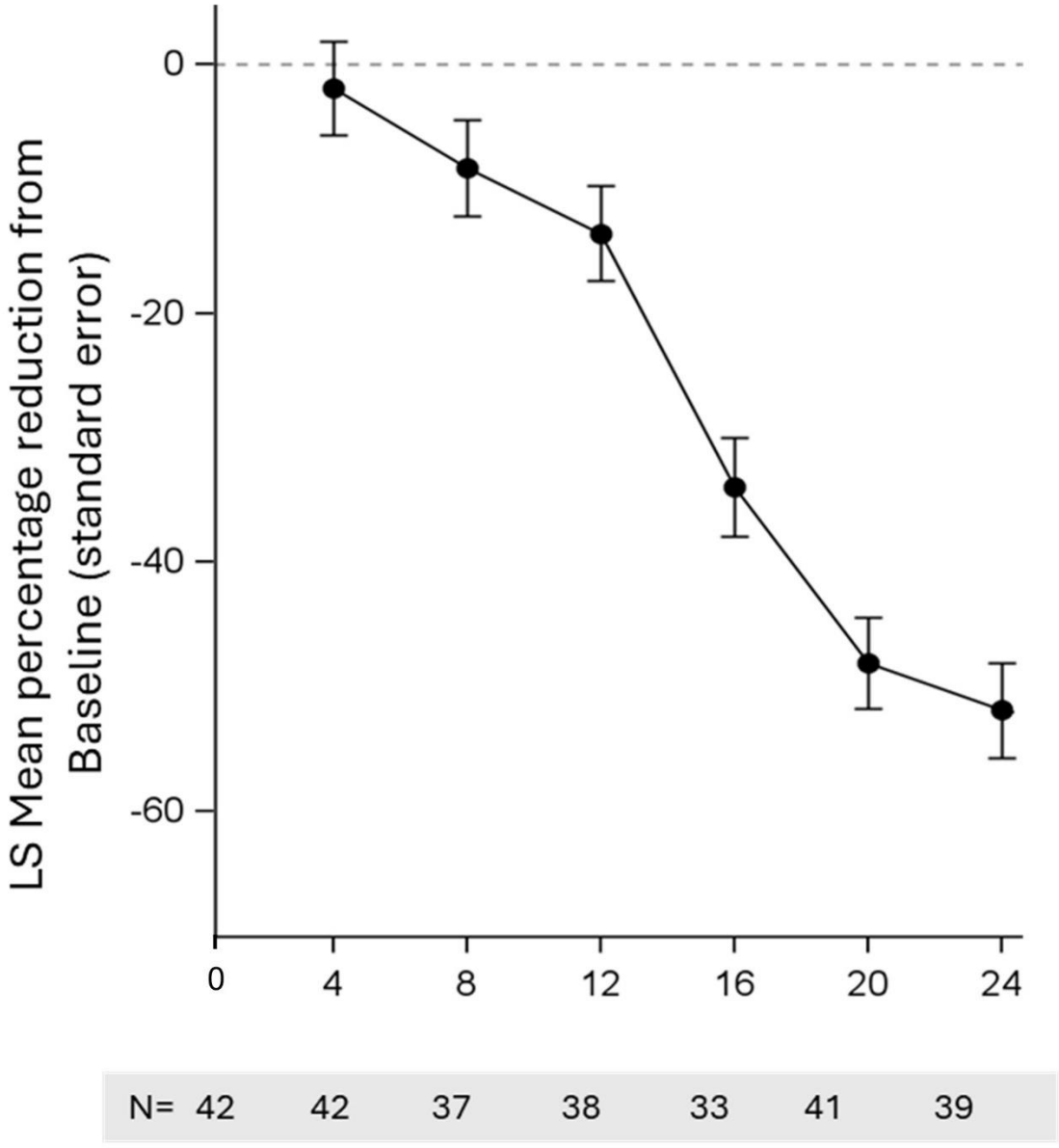


B


LS Mean percentage reduction from Baseline (standard error)
0
-20
-40
-60
0
4
8
12
16
20
24
Time (weeks)
N= 42 42 36 37 33 40 39

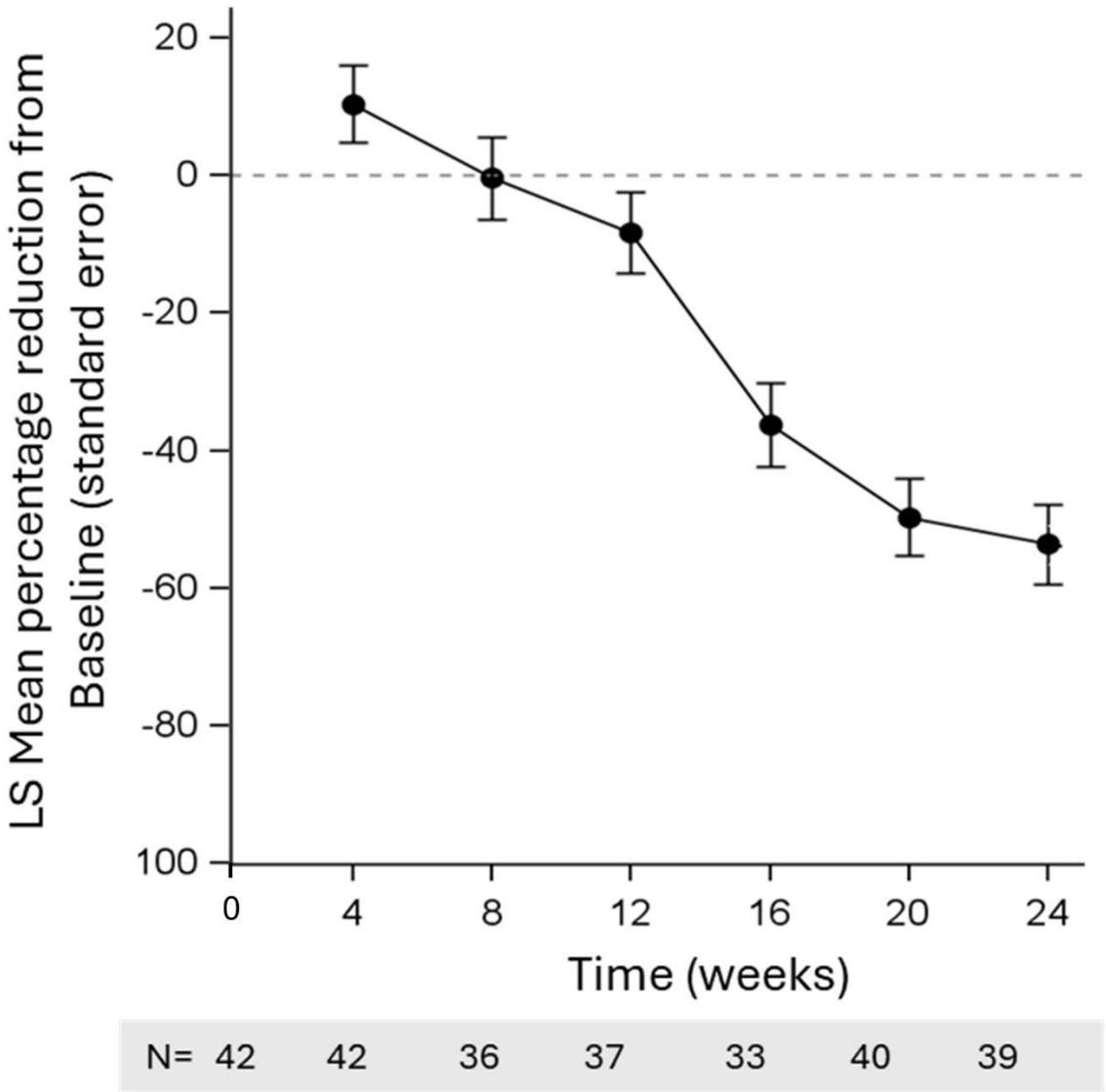
919
920

C


LS Mean percentage reduction from Baseline (standard error)
0
-20
-40
-60
0
4
8
12
16
20
24
N= 42 42 37 38 33 41 39

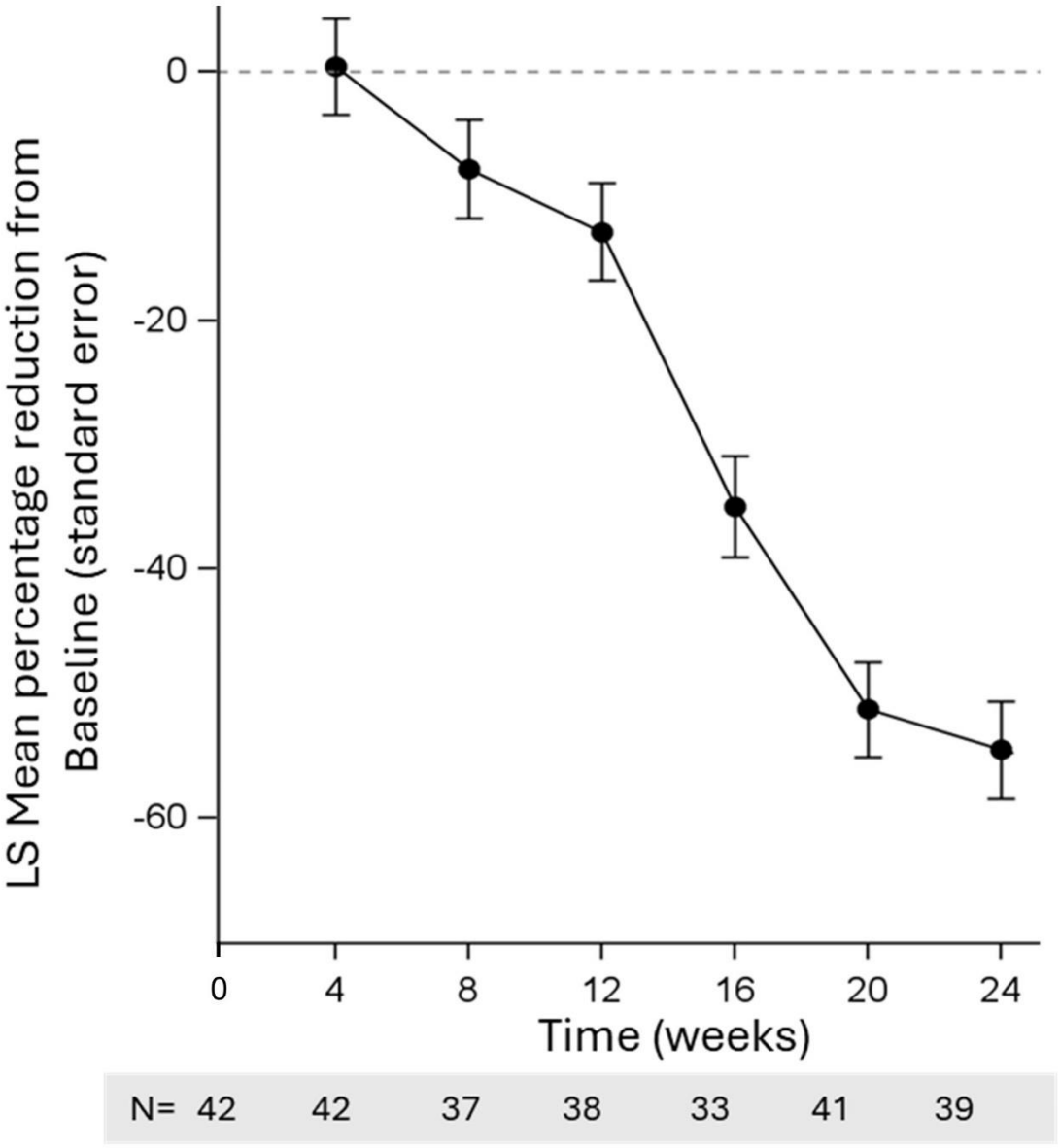
921

D


LS Mean percentage reduction from Baseline (standard error)
20
0
-20
-40
-60
-80
100
0
4
8
12
16
20
24
Time (weeks)
N= 42 42 36 37 33 40 39

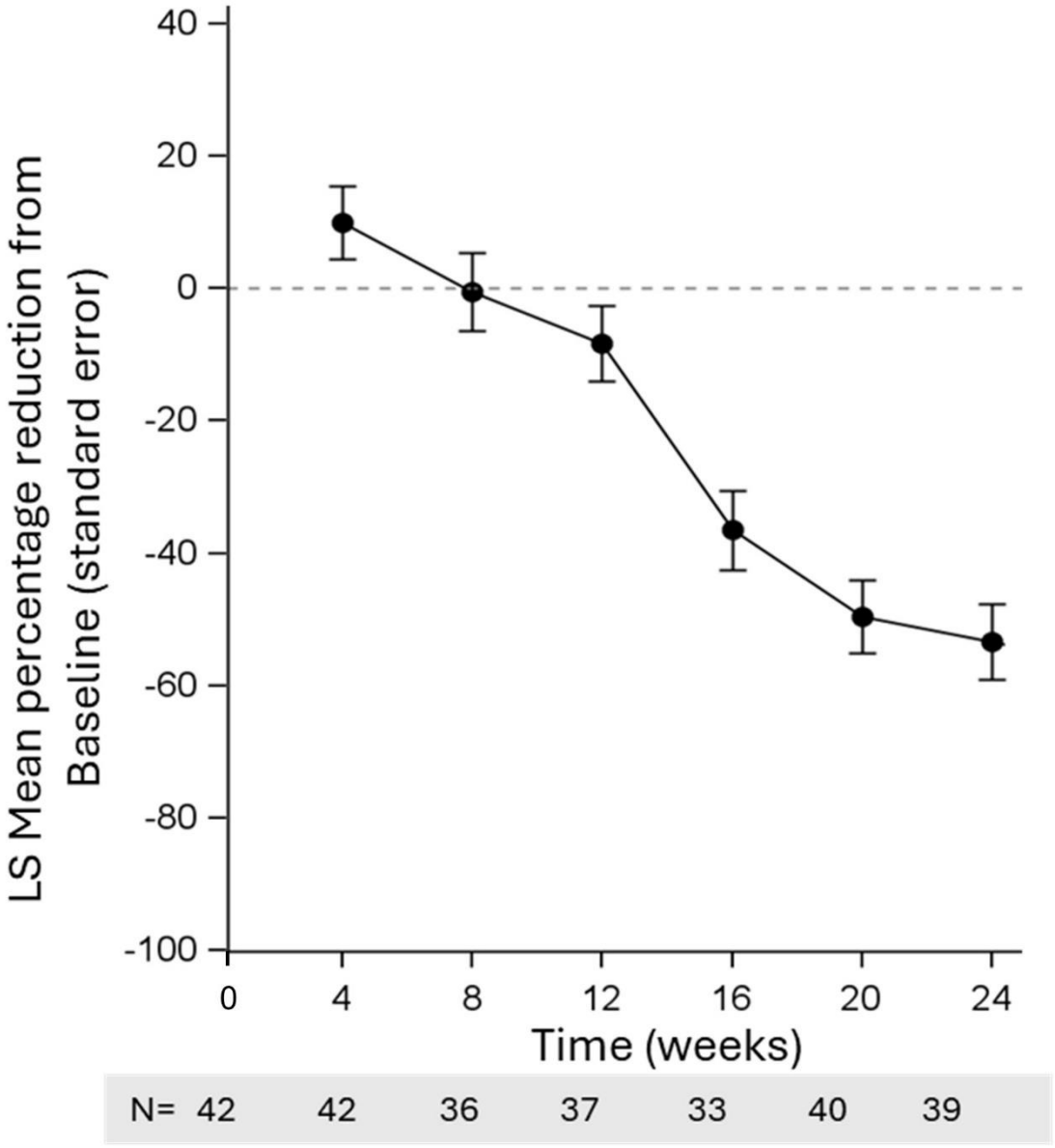
922

E


LS Mean percentage reduction from Baseline (standard error)
0
-20
-40
-60
0
4
8
12
16
20
24
Time (weeks)
N= 42 42 37 38 33 41 39

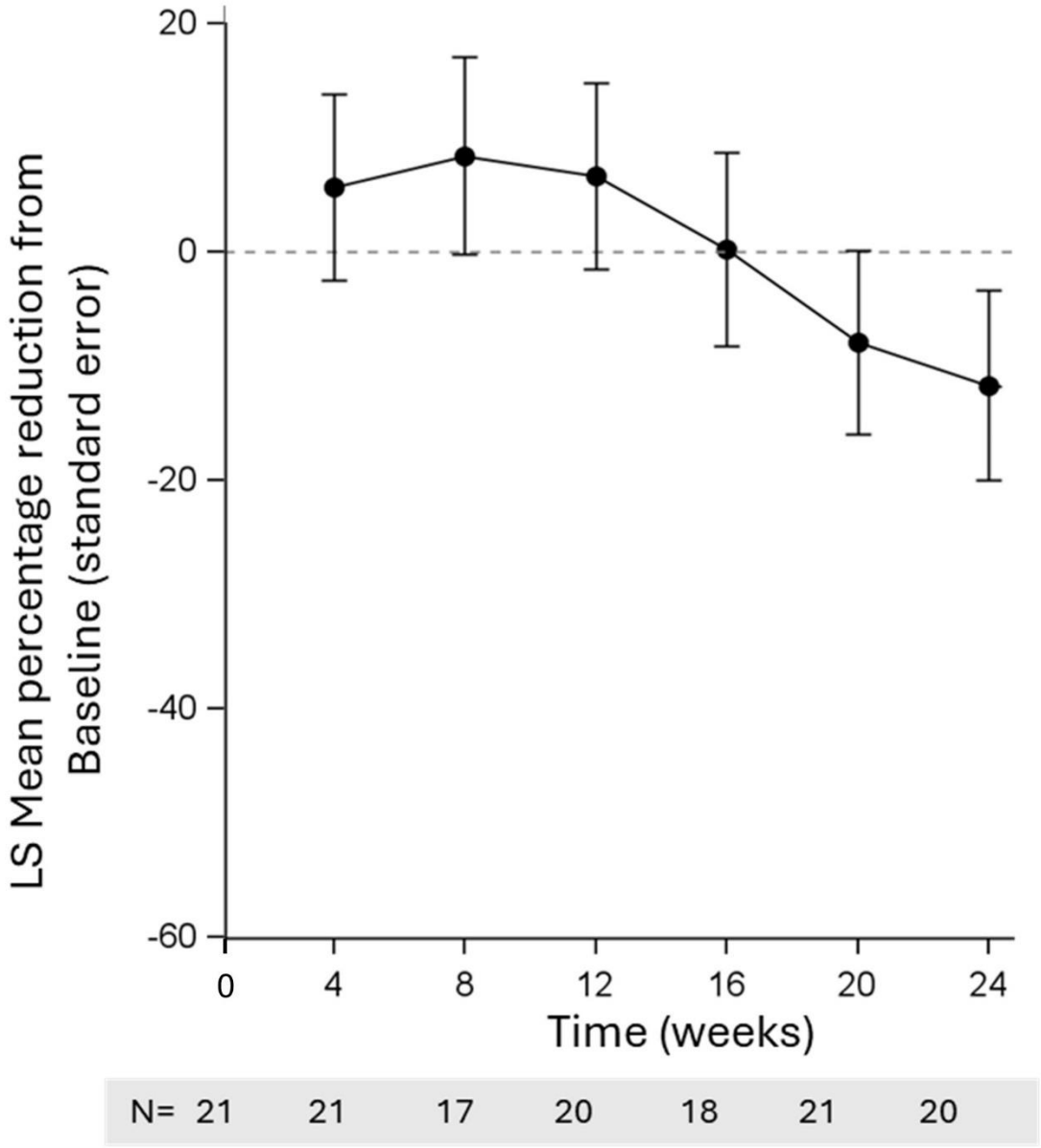
923

F


LS Mean percentage reduction from Baseline (standard error)
40
20
0
-20
-40
-60
-80
-100
0
4
8
12
16
20
24
Time (weeks)
N= 42 42 36 37 33 40 39

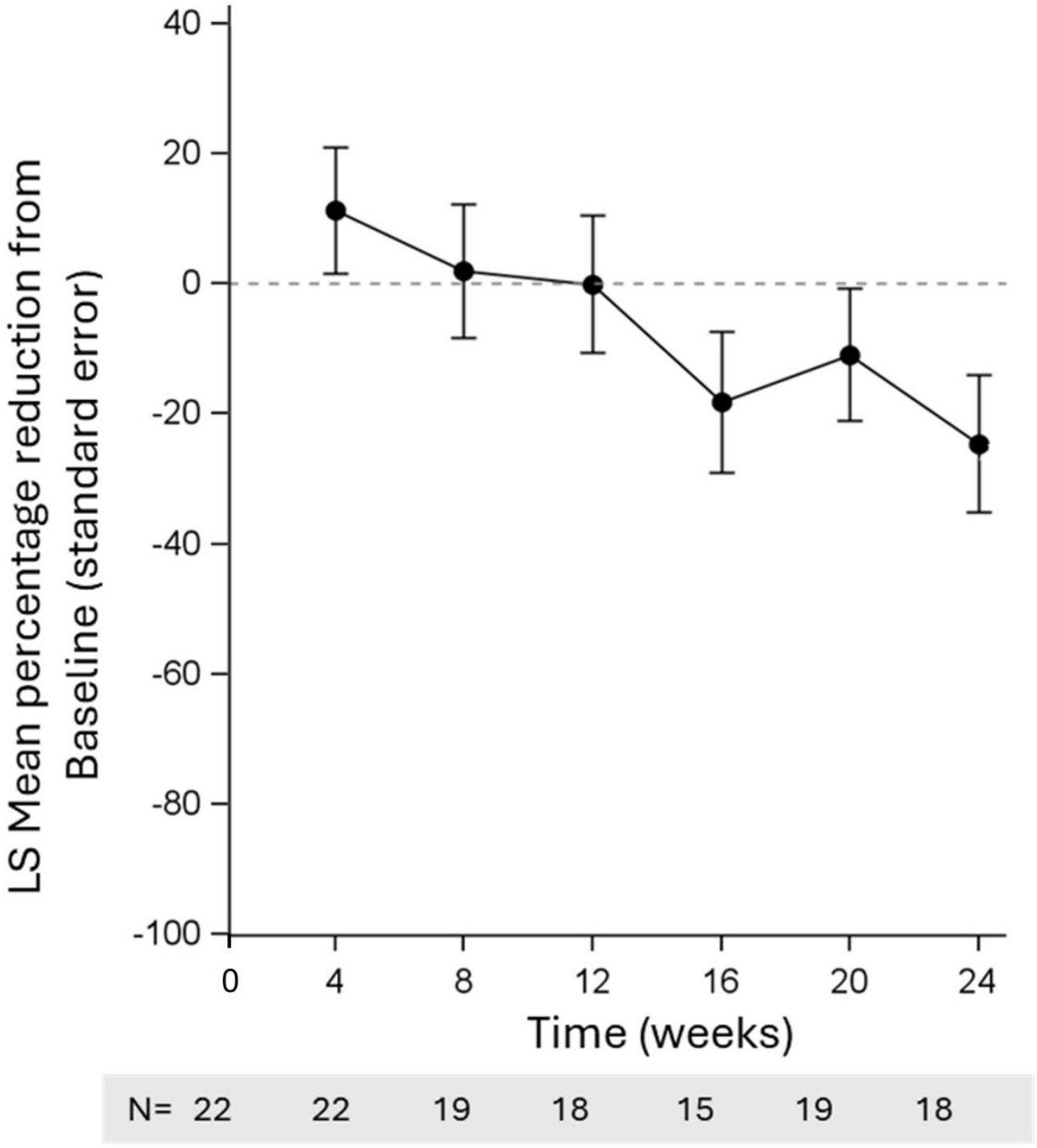
924

G


LS Mean percentage reduction from Baseline (standard error)
20
0
-20
-40
-60
0
4
8
12
16
20
24
Time (weeks)
N= 21 21 17 20 18 21 20

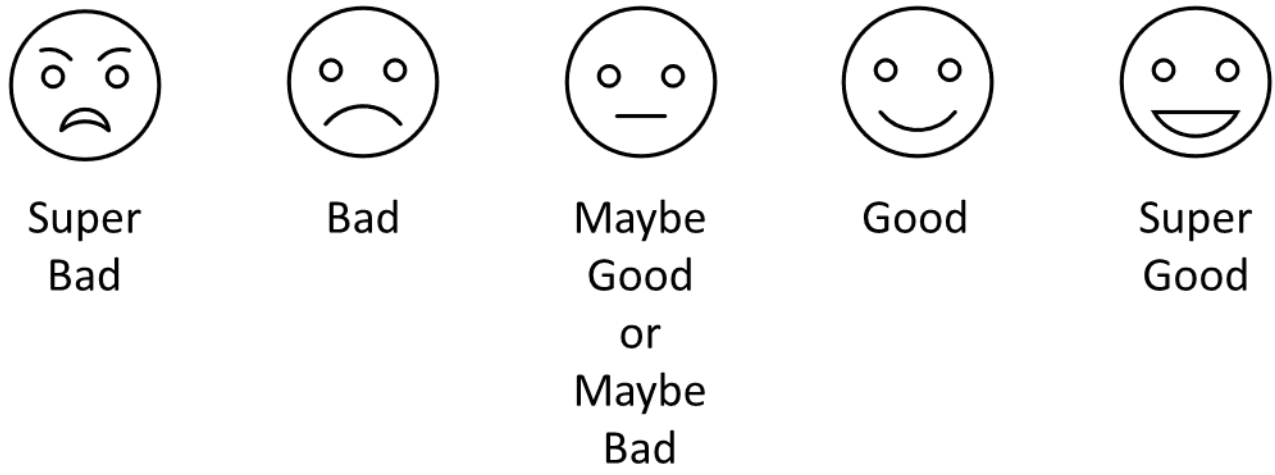
925

H


LS Mean percentage reduction from Baseline (standard error)
40
20
0
-20
-40
-60
-80
-100
0
4
8
12
16
20
24
Time (weeks)
N= 22 22 19 18 15 19 18

926

Supplementary Figure 4 Example of the 5-point hedonic scale



Adapted from Guinard 2000, Trends Food Sci Technol.[1]

Submission: THELANCETDE-D-24-00282R1

Title: Lomitapide for the treatment of paediatric patients with homozygous familial hypercholesterolaemia: Results from the Efficacy Phase of APH-19, a phase 3, open-label study

Editors' specific points

1. In the Abstract, please state the route of administration of lomitapide.

Response: We have now added “orally administered” to line 76 (tracked document) in the abstract introduction.

2. Please add an ethics statement to the Methods section of the article stating which ethics board approved this study.

Response: We have now added a statement to line 165–167 (tracked document) of the Methods.

3. In Table 1, please add data for Male sex below that for Female sex.

Response: We have now added these data to Table 1.

4. Figures 2 and 3 are not editable. Please provide each figure in fully editable format (normally editable pdf or eps formats work best).

Response: We have now provided editable PDFs with the submitted documents

5. Please provide email confirmation from any persons named in the Acknowledgements section confirming that they are happy to be named in the paper.

Response: Attached to the submission are emails with the required permissions from the acknowledged persons.

6. Should Steven Foster also be named in the Acknowledgments section? If so, email confirmation will need to be provided.

Response: Steven Foster has been included in the acknowledgements as providing editorial and technical support – attached to the submission is an email providing their permission

7. The Lancet Diabetes & Endocrinology encourages the submission of translated summaries (abstracts) in languages that are relevant to the country where the research was done. Translated summaries are published unedited and unformatted, as a separate supplementary file. If you are interested in submitting a translation of your summary, please let me know. We will expect to receive the text once your manuscript is accepted and edited, at proof stage.

Response: We do not wish to submit a translated summary.

Reviewer #3 (Lancet Statistical Advisor)

Overall Comments

The authors have addressed the points around central limit theorem but the additional points have not been fully addressed.

Comments

[Original]. Can you please complete the new CONSORT Harms checklist which has recently come out

a. The checklist can be got from Equator (https://www.equator-network.org/reporting-guidelines/consort-harms/)

b. For information the last update was 2010 and this checklist is an interim checklist to this is updated. The elaboration makes the recommendation

""Until future work from the CONSORT group produces an updated checklist, trial authors, journal reviewers, and editors should use the integrated checklist presented in this paper"

i. Please read the elaboration document as this provides important additional information and explanation (will expand on later)

ii. There needs now to be additional information in the CONSORT and also there must now be confidence intervals for Harms as well as benefits - see items 17a and 17b

iii. The CONSORT trumps a protocol and a SAP so event if not stipulated in these documents then there must be CI for safety (will revisit)

c. The main difference in checklist is the better reporting of safety which will revisit when discussing the tables. Safety reporting is important and seen by many reviewers as co-primary to efficacy. This paper is one of the better at reporting safety

[Original]. Can the CONSORT checklist for abstracts please be completed

[Additional]. I see the pushback on not completing but this is still a trial. For the items pertinent to randomisation - 8 to 11 - just need to enter as NA [Editor: The checklists requested by the statistical advisor must be provided.]

Response: We have now completed the CONSORT harms and abstract checklists where possible and provided the document with the submitted manuscript.

[Original]. For Table 2 and 3

i. For all the rows in Table 2 and 3, deaths and all AESI please provide point estimates and CI

ii. Wilson CI can be used

[Additional]. CI have not been done. Given the data these can be CI per group [Editor: As with the checklists, CIs need to be provided.]

Personally I would have Table 2 and 3 in one table

Response: We thank the reviewer for this suggestion and have now included 95% Cis as requested; however, as Table 2 describes the Efficacy Phase and Table 3 the Safety Analysis Set we have kept them separate.

[Original] For Figure 2

i. When graphs are presented side by side they must have the same y-axis scale e.g. 0 to 500 for C and D

ii. If can not have the same y-axis scale then can not be side be side

[Additional]. This has not been fully done. As said can be under each other though here could have G and D side by side (0 to 500 on the scale) and C at the bottom on its own

Response: We thank the reviewer for this suggestion, we have now reorganized the figure to match the order of secondary outcomes listed in the Methods section. As such we were able to align the Y-axes as requested.

acknowledgement permission

acknowledgement permission

acknowledgement permission