Durability and efficacy of solbinsiran, a GalNAc-conjugated siRNA targeting ANGPTL3, in adults with mixed dyslipidaemia (PROLONG-ANG3): a double-blind, randomised, placebo-controlled, phase 2 trial

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Summary

Background Mixed dyslipidaemia, characterised by elevated concentrations of circulating triglycerides and LDL cholesterol (LDL-C), is associated with an increased risk of atherosclerotic cardiovascular disease. Solbinsiran, a GalNAc-conjugated small interfering RNA targeting hepatic angiopoietin-like protein 3 (ANGPTL3), reduced triglycerides and LDL-C concentrations in a phase 1 study. This study aimed to assess the durability and efficacy of solbinsiran in reducing concentrations of atherogenic lipoproteins in adults with mixed dyslipidaemia.

Methods This double-blind, parallel-arm, randomised, placebo-controlled, phase 2 trial enrolled adults (aged ≥18 years) with mixed dyslipidaemia at 41 clinical research units across seven countries. Patients receiving moderate-intensity or high-intensity statins, and with concentrations of fasting triglycerides between 1·69 mmol/L and 5·64 mmol/L, LDL-C of at least 1·81 mmol/L, and non-HDL cholesterol of at least 3·36 mmol/L were included. Using an interactive web-response system, patients were randomly assigned (1:2:2:2) to receive either solbinsiran 100 mg, solbinsiran 400 mg, solbinsiran 800 mg, or placebo, by subcutaneous injection on days 0 and 90. Patients were followed up for at least 270 days. The primary outcome was percent change in apolipoprotein B (apoB) concentration from baseline to day 180 with solbinsiran compared with placebo, analysed under an efficacy estimand (in patients who received at least one dose of the study drug). This trial is completed and registered with ClinicalTrials.gov, NCT05256654.

Findings Of 585 patients screened, 205 patients were enrolled in the study between July 20, 2022, and March 4, 2024. Patients (111 [54%] female and 94 [46%] male; median age 57 years [IQR 49–65]) were randomly assigned to receive solbinsiran 100 mg (n=30), solbinsiran 400 mg (n=58), solbinsiran 800 mg (n=59), or placebo (n=58). At baseline, median concentrations were 111 mg/dL (IQR 96–130) for apoB, 2·64 mmol/L (2·06–3·29) for triglycerides, and 3·16 mmol/L (2·57–3·82) for LDL-C. The placebo-adjusted percent change in apoB concentration from baseline at day 180 was –2·8% (95% CI –15·5 to 11·9; p=0·69) for solbinsiran 100 mg; –14·3% (–23·6 to –3·9; p=0·0085) for solbinsiran 400 mg; and –8·3% (–18·3 to 2·9; p=0·14) for solbinsiran 800 mg. Solbinsiran administration was well tolerated, with a low incidence of adverse events. The number of patients with treatment-emergent adverse events was 18 [60%] of 30 patients in the solbinsiran 100 mg group, 30 [52%] of 58 patients in the solbinsiran 400 mg group, 26 [44%] of 59 patients in the solbinsiran 800 mg group, and 37 [65%] of 57 patients in the placebo group.

Interpretation Solbinsiran 400 mg reduced apoB in patients with mixed dyslipidaemia and was generally well tolerated. The impact of solbinsiran on cardiovascular outcomes remains to be investigated.

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Introduction

Mixed dyslipidaemia, characterised by elevations in concentrations of circulating triglycerides and LDL cholesterol (LDL-C), is common in conditions associated with insulin resistance, type 2 diabetes, and metabolic dysfunction-associated steatotic liver disease.[1,2] Patients also have higher concentrations of non-HDL cholesterol (non-HDL-C) and apolipoprotein B (apoB), and a higher residual risk of atherosclerotic cardiovascular disease, even when LDL-C is controlled.[3,4] Accordingly, prevention guidelines recommend the use of non-HDL-C and apoB as secondary lipid targets.[3,4]

Even though triglyceride-rich lipoprotein particles are considered more atherogenic than LDL particles,[5,6] most of the pharmacological treatments to lower triglycerides have modest effects on triglyceride and very LDL-C (VLDL-C) concentrations and have not been shown to reduce the risk of cardiovascular disease.[7] Although

Research in context

Evidence before this study

Mixed dyslipidaemia is characterised by elevated circulating LDL cholesterol (LDL-C) and triglycerides. Patients with mixed dyslipidaemia are at increased risk of cardiovascular events despite statins. Few therapies directed against lowering triglycerides have resulted in a lowering of cardiovascular events, highlighting the need to investigate novel pathways. Angiopoietin-like protein 3 (ANGPTL3) is a protein encoded by the *ANGPTL3* gene, which is predominantly expressed in the liver and plays an important role in regulating triglyceride-rich lipoprotein metabolism. Individuals with homozygous loss-of-function mutations in the *ANGPTL3* gene have a rare genetic disorder called familial combined hypolipidaemia, which is characterised by abnormally low concentrations of all major lipoproteins (very LDL cholesterol [VLDL-C], LDL-C, and HDL cholesterol [HDL-C]) and a lower risk of cardiovascular events. This suggests that therapies targeting ANGPTL3 lowering might modify triglyceride-related pathways and potentially reduce the risk for cardiovascular events. On March 6, 2025, we searched PubMed using the search term "ANGPTL3 inhibition" for any published randomised controlled trials of ANGPTL3 inhibition published between Jan 1, 2010, and Dec 31, 2024. The search results included 25 articles. Pharmacological inhibition of ANGPTL3 protein by monoclonal antibody or mRNA by antisense oligonucleotide or RNA interference have been shown to reduce triglyceride, LDL-C, and HDL-C concentrations in different types of dyslipidaemias. However, treatment with vupanorsen, an ANGPTL3 antisense oligonucleotide, resulted in increased hepatic fat fraction and marked elevations in liver aminotransferases, leading to termination of the development of the drug due to safety concerns. By comparison, an alternative approach that targets hepatic ANGPTL3 production through RNA interference (zodasiran) reduced concentrations of ANGPTL3, triglycerides, apolipoprotein B (apoB), non-HDL-C, and LDL-C, and it showed no adverse effects on liver function. Rather, reduction in hepatic fat fraction was observed with zodasiran in a subgroup of patients with underlying high baseline liver fat fraction (>8%). Although evinacumab, which reduces circulating ANGPTL3, has not shown adverse effects on biochemical measures of liver function, there are limited data of its effects on hepatic fat fraction.

Added value of this study

This phase 2 clinical trial aimed to ascertain the efficacy, safety, and tolerability of different doses of solbinsiran, a GalNAc-conjugated siRNA targeting hepatic ANGPTL3, for patients with mixed dyslipidaemia. Solbinsiran reduced concentrations of apoB, ANGPTL3, triglycerides, VLDL-C, non-HDL-C, and LDL-C. Hepatic MRI assessment, performed in all patients before and after 6 months of treatment, showed no evidence of dose-dependent adverse effects of solbinsiran on hepatic fat fraction, but it showed a reduction of hepatic fat fraction in adults with mixed dyslipidaemia. This finding was not accompanied by any change in weight, possibly supporting a direct effect of ANGPTL3 inhibition with solbinsiran on hepatic fat reduction, in addition to reductions in all atherogenic apoB-containing lipoproteins and triglycerides.

Implications of all the available evidence

This trial doubles the total number of person-years of exposure in patients with mixed dyslipidaemia studied in phase 2 trials of small interfering RNA (siRNA)-based therapies targeting hepatic ANGPTL3 production to over 400 patients with 270 days of treatment. Together, the available data show consistent effects of RNA-based inhibition on reductions in concentrations of apoB, ANGPTL3, triglycerides, non-HDL-C, and LDL-C. Both siRNA molecules tested to date, solbinsiran and zodasiran, show a potential benefit of reducing liver fat, suggesting that the adverse effect on hepatic fat content observed with an antisense oligonucleotide was not an on-target effect of hepatic ANGPTL3 inhibition itself but rather an off-target effect. Taken together, the available data support further development of ANGPTL3-targeted therapies through siRNA-based approaches as a means to reduce both atherogenic apoB-containing lipoproteins and liver fat in patients with mixed dyslipidaemia, possibly with a dosing frequency of only four times a year.

icosapent ethyl, a highly purified formulation of eicosapentaenoic acid used to treat dyslipidaemia, has been shown to reduce cardiovascular risk, the event reduction did not correlate with the degree of lowering of triglycerides or atherogenic lipoproteins, suggesting that other functional properties are likely to account for the clinical benefit of this drug.[8] A direct molecular approach to reduce triglycerides concentrations might be achieved by inhibition of angiopoietin-like protein 3 (ANGPTL3), a key regulator of triglyceride-rich lipoprotein metabolism. Rare loss-of-function variants in the *ANGPTL3* gene are associated with decreased plasma triglyceride, LDL-C, and HDL-C concentrations and a lower risk of atherosclerotic cardiovascular disease.[9–11] In mice, deletion of the *ANGPTL3* gene resulted in reduced development of atherosclerosis.[12] These data, combined with advances in RNA-based therapies, have resulted in interest in therapeutic inhibition of hepatic ANGPTL3 in patients with mixed dyslipidaemia.[13,14]

The first RNA-based therapy to target ANGPTL3 was the antisense oligonucleotide vupanorsen. In a phase 2b study, vupanorsen administration resulted in dose-dependent reductions in the concentration of ANGPTL3, non-HDL-C, and additional lipid parameters.[15] However, observations of an increase in liver enzymes and a dose-dependent increase in hepatic fat fraction led to termination of vupanorsen development. Administration of zodasiran, a small interfering RNA (siRNA) currently in phase 3

development (NCT06712771), showed dose-dependent decreases in concentrations of ANGPTL3 and atherogenic lipoproteins, with no adverse effects on liver enzymes or hepatic fat recorded.[16] It remains unclear whether targeting the production of hepatic ANGPTL3 is an effective and well tolerated approach to reducing cardiovascular risk.

Solbinsiran (LY3561774) is a GalNAc-conjugated siRNA targeting hepatic ANGPTL3 protein expression. In a phase 1 study, solbinsiran demonstrated dose-dependent reductions in atherogenic lipoprotein parameters up to day 90.[17] This phase 2 study aimed to further assess solbinsiran durability and efficacy in reducing concentrations of atherogenic lipoproteins as well as tolerability, including hepatic fat, in adult patients with mixed dyslipidaemia.

Methods

Study design and participants

This double-blind, randomised, placebo-controlled, phase 2, trial was conducted at 41 clinical research units across seven countries (Argentina, Canada, Japan, Mexico, Poland, Türkiye, and the USA). The study design, protocol, and statistical analysis plan are provided in the appendix (pp 5, 23, 122). The study was conducted in accordance with local regulations, the Declaration of Helsinki, International Ethical Guidelines of the Council for International Organizations of Medical Sciences, and Good Clinical Practice guidelines of the International Conference for Harmonization. The protocol was approved by independent ethics committees or institutional review boards at each site. Ethics Review Board approval numbers are included in the appendix (p 21). All patients provided written informed consent before undertaking any study procedures. This completed study is registered with ClinicalTrials.gov (NCT05256654).

No external data safety monitoring committee was included for this phase 2 study. Based on the phase 1 study results, there were no safety concerns for solbinsiran at the highest dose of 960 mg.[17] Furthermore, siRNA is not a novel mechanism of delivery, and ANGPTL3 is not a novel target, with evinacumab approved in clinical practice for homozygous familial hypercholesterolaemia.[18] Hence, the study sponsor deemed it sufficient to have an internal assessment committee to review the unblinded safety data at interim analysis and the primary outcome lock. Blinded data were reviewed by the study team at the trial-level safety reviews, which were initiated 4 months after the first patient visit and continued quarterly.

The inclusion and exclusion criteria are described in detail in the appendix (p 2). Briefly, adults, aged at least 18 years, with mixed dyslipidaemia treated with stable doses of moderate-intensity or high-intensity statins and a BMI of 18·5–40·0 kg/m², were eligible for enrolment. Patients were required to have triglyceride concentrations of 1·69–5·64 mmol/L, LDL-C concentrations of 1·81 mmol/L or higher, and non-HDL-C concentrations of 3·36 mmol/L or higher on a fasting blood sample. Important exclusion criteria included having uncontrolled type 1 or type 2 diabetes and having either New York Heart Association Class III or IV heart failure or a last known left ventricular ejection fraction lower than 30%.

Randomisation and masking

Patients were stratified according to triglycerides concentrations at screening (<2·82 mmol/L or ≥2·82 mmol/L) and randomly assigned (1:2:2:2) to receive either solbinsiran 100 mg, solbinsiran 400 mg, solbinsiran 800 mg, or placebo, using an interactive web-response system. Within the placebo group, patients were randomly assigned (1:2:2) to receive either 100 mg, 400 mg, or 800 mg of placebo injection volume to maintain the masking of study drug. Although the participant and the investigator knew the injection volume, they did not know whether the injection contained solbinsiran or placebo. To mitigate the risk of unblinding due to colour difference between treatment allocation, staff at sites were trained on additional operational procedures. Unmasked personnel administering study medications to patients at day 0 had no interaction, role, or responsibilities other than receiving, registering, preparing, and administering study medication at day 90 in the trial. Patients were instructed to look away during administration. Those assessing outcomes and those analysing the data were masked to group assignment. We did not assess the success of blinding.

See Online for appendix

Procedures

On days 0 and 90, patients received a dose of solbinsiran (by volume 200 mg/mL) or matching placebo via a subcutaneous injection into the anterior abdominal wall. On days 0, 15, 30, 60, 90, 120, 150, 180, 210, 240, and 270, blood samples were collected to measure concentrations of ANGPTL3, apoB, total cholesterol, triglycerides, LDL-C, and HDL-C. The following analytes were measured using Roche Cobas 8000 (LabCorp, Indianapolis, IN, USA) by either enzymatic (total cholesterol, triglycerides, direct LDL-C, or HDL-C) or immunoturbidimetric (apoB) methods. VLDL-C was calculated as total cholesterol minus LDL-C minus HDL-C, and non-HDL-C was calculated as total cholesterol minus HDL-C.

Before randomisation, all patients completed hepatic MRI for measurement of liver fat. On day 180, patients underwent a second MRI evaluation of liver fat. MRI images were transmitted to one central reader for evaluation of the MRI-based endpoints. For patient safety, images were also read locally to ensure there were no underlying liver pathologies.

Outcomes

The primary endpoint was the percent change in apoB from baseline to day 180. Secondary endpoints were the percent change from baseline to day 180 for ANGPTL3, triglycerides, non-HDL-C, LDL-C, and HDL-C, and the

percent change from baseline to day 270 for apoB, ANGPTL3, triglycerides, non-HDL-C, LDL-C, and HDL-C. Percent change from baseline to days 180 and 270 for VLDL-C was an exploratory endpoint. The evaluation at day 270 was designed to test the efficacy of the second dose 180 days after its administration at day 90. This would allow assessment of whether the third and subsequent doses need to be administered every 90 days (quarterly) or every 6 months (two injections per year long term).

The number and incidence of treatment-emergent adverse events, serious adverse events, and discontinuations due to adverse events were recorded throughout the study and classified by system organ classification using standard terms from the Medical Dictionary for Regulatory Activities. Adverse events of special interest included injection site reactions, hypersensitivity, gallbladder-related disorders, and potentially drug-related hepatic disorders. MRI-proton density fat fraction (proportion of mobile protons in liver tissue attributable to fat) was used to assess fat content. The change in MRI hepatic fat fraction from baseline to day 180 was assessed as an exploratory endpoint. Glycated haemoglobin A1c (HbA_{1c}) and bodyweight were measured on days 0, 90, 180, and 270, and fasting glucose was measured throughout the study on days 0, 15, 30, 60, 90, 120, 150, 180, 210, 240, and 270.

Statistical analysis

The estimated total sample size was 175 participants randomly assigned (1:2:2:2) to solbinsiran 100 mg (n=30), 400 mg (n=58), 800 mg (n=59), or placebo (n=58). Assuming a 20% dropout rate overall, this would result in approximately 20 participants completing the double-blinded treatment period in the solbinsiran 100 mg group and 40 participants completing it in each of the other groups. With a standard deviation of 15%, and a two-sided α level of 0·05, those completing treatment in each group provided more than 99% power to detect a treatment difference of –30% for the primary endpoint. We did not adjust for multiplicity of testing for the secondary endpoints.

The statistical analysis methods were prespecified in the statistical analysis plan (appendix p 122). The primary efficacy estimand and the treatment regimen estimand both targeted the populations of patients meeting the inclusion criteria and receiving at least one dose of study drug. The primary efficacy estimand handled the intercurrent events of treatment discontinuation or prohibited medications using a hypothetical strategy (ICH E9 [R1])[19] and compared the average treatment effect of solbinsiran with that of placebo on all lipid-related measures at days 180 and 270.[20,21] A supplemental treatment regimen estimand handled these intercurrent events using a treatment policy strategy (ICH E9 (R1))[19] and was applied to both the primary outcome as well as liver fat. The related efficacy analysis set included these study participants and excluded timepoints after discontinuation of treatment or initiation of lipid-lowering or per protocol prohibited medications. Safety analyses, including the MRI liver fat analysis, were

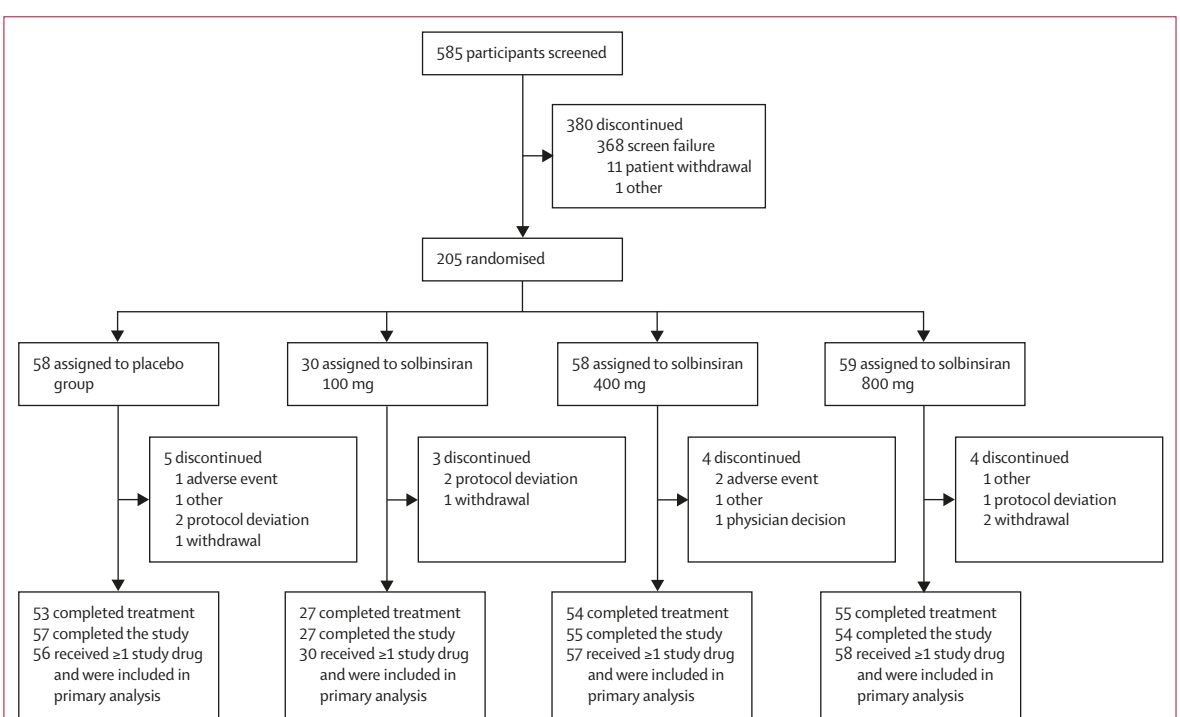


Figure 1: **Trial profile**

	Placebo group (n=58)	Solbinsiran 100 mg group (n=30)	Solbinsiran 400 mg group (n=58)	Solbinsiran 800 mg group (n=59)
Sex				
Female	35 (60%)	18 (60%)	29 (50%)	29 (49%)
Male	23 (40%)	12 (40%)	29 (50%)	30 (51%)
Median age, years	57 (47–63)	58 (51–66)	57 (48–66)	58 (51–63)
Median BMI, kg/m²	28 (27–32)	30 (27–34)	31 (27–36)	30 (27–34)
Race				
White	25 (43%)	13 (43%)	34 (59%)	28 (47%)
Native American	21 (36%)	11 (37%)	14 (24%)	22 (37%)
Asian	11 (19%)	6 (20%)	10 (17%)	9 (15%)
Black or African American	1 (2%)	0	0	0
Hispanic or Latino	36 (62%)	20 (67%)	39 (67%)	44 (75%)
Type 2 diabetes	26 (45%)	10 (33%)	26 (45%)	30 (51%)
Mean HbA_{1c} (SD), %	6·40% (1·30)	6·05% (0·91)	6·12% (0·85)	6·36% (1·19)
Lipid-lowering therapy				
Statins				
Moderate intensity	32 (55%)	17 (57%)	34 (59%)	35 (59%)
High intensity	22 (38%)	12 (40%)	22 (38%)	22 (37%)
Ezetimibe	2 (4%)	3 (10%)	3 (5%)	1 (2%)
Levothyroxine	12 (21%)	4 (13%)	12 (21%)	6 (10%)
SGLT2 inhibitors	7 (12%)	4 (13%)	7 (12%)	8 (14%)
GLP-1 receptor agonists	3 (5%)	0	2 (3%)	2 (3%)
Lipid profile*				
Triglycerides (mmol/L)	2·85 (1·90–3·55)	2·73 (1·94–3·19)	2·51 (2·08–3·43)	2·64 (2·11–3·17)
Triglycerides (mg/dL)	252 (168–314)	242 (172–283)	222 (184–304)	234 (187–281)
VLDL-C (mmol/L)†	1·06 (0·80–1·63)	1·01 (0·78–1·35)	1·09 (0·75–1·34)	1·04 (0·85–1·29)
VLDL-C (mg/dL)†	41 (31–63)	39 (30–56)	42 (29–52)	40 (33–50)
LDL-C (mmol/L)‡	3·03 (2·69–3·60)	3·26 (2·56–3·94)	3·11 (2·49–3·78)	3·26 (2·59–4·09)
LDL-C (mg/dL)‡	117 (104–139)	126 (99–152)	120 (96–146)	126 (100–158)
HDL-C (mmol/L)	1·09 (0·93–1·27)	1·14 (0·98–1·42)	1·06 (0·88–1·32)	1·06 (0·96–1·24)
HDL-C (mgdL)	42 (36–49)	44 (38–55)	41 (34–51)	41 (37–48)
Non-HDL-C (mmol/L)	4·20 (3·68–5·00)	4·27 (3·78–5·18)	4·17 (3·55–5·21)	4·66 (3·68–5·26)
Non-HDL-C (mg/dL)	162 (142–193)	165 (146–200)	161 (137–201)	180 (142–203)
ApoB (mg/dL)	111 (96–124)	109 (99–136)	112 (95–130)	114 (94–133)
ANGPTL3 (ug/L)	238 (184–272)	221 (188–287)	199 (170–267)	210 (165–272)
Hepatic fat (%)	11% (7–20)	12% (4–17)	9% (6–16)	11% (8–18)
Hepatic steatosis§	38 (66)	17 (57)	36 (62)	45 (76)

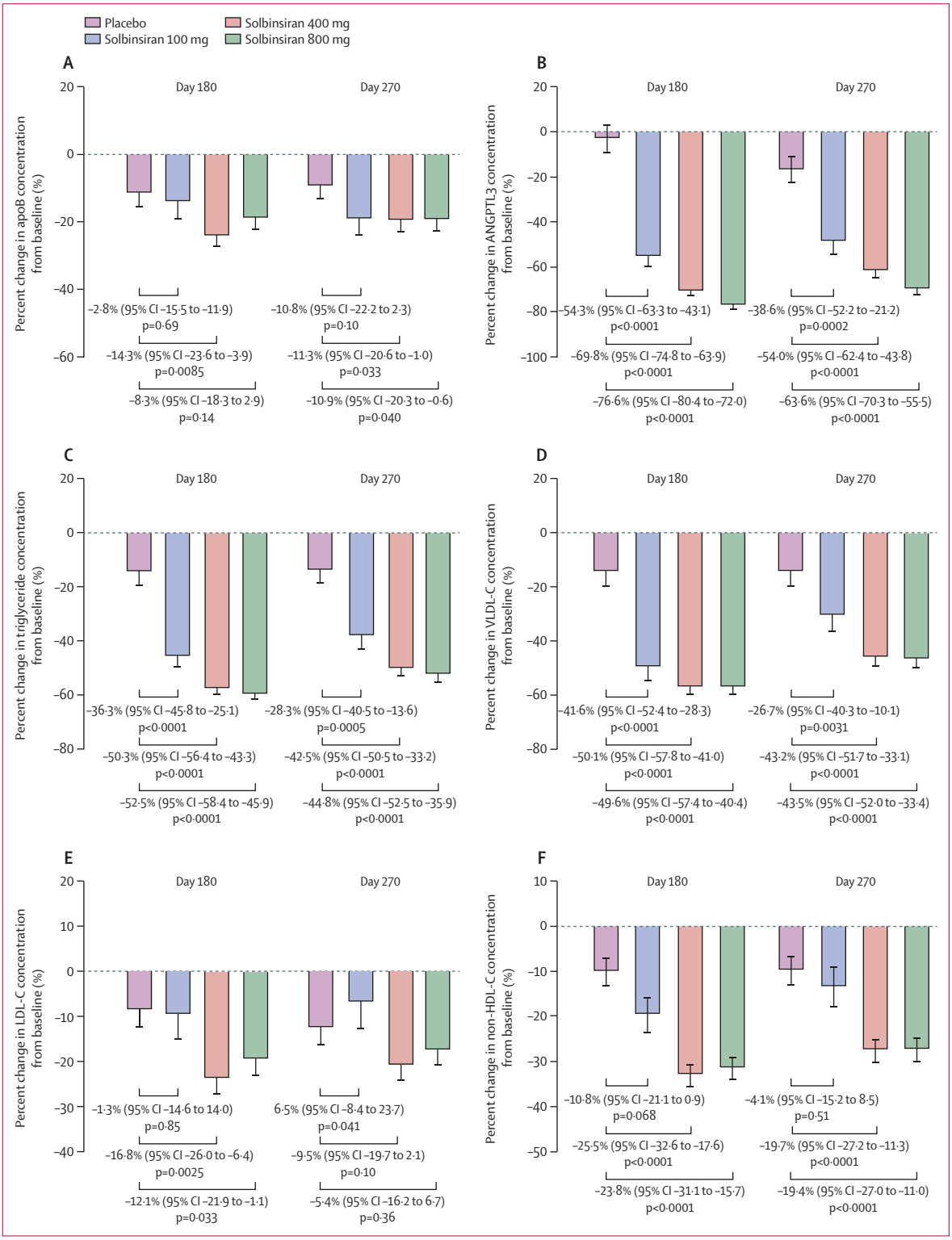
Data are presented as n (%) or median (IQR), unless otherwise stated. ApoB=apolipoprotein B. HbA_{1c}=glycated haemoglobin. HDL-C=HDL cholesterol. LDL-C=LDL cholesterol. VLDL-C=very LDL cholesterol. *400 mg solbinsiran: n=57, apoB: placebo n=56 and total n=203. †VLDL-C was calculated as total cholesterol minus HDL-C minus LDL-C. ‡LDL-C was directly measured. §Hepatic steatosis defined as baseline hepatic fat ≥8%.

Table 1: **Baseline demographics and participant characteristics**

guided by an estimand that included all randomised participants who were exposed to at least one dose of study drug, regardless of adherence to intervention. The related safety analysis set included these study participants and all available timepoints.

To estimate the efficacy estimand, all data up to treatment discontinuation or initiation of prohibited medication was used. The analysis model for primary and secondary endpoints under this estimand used a mixed model for repeated measures to implicitly handle missing data. The model terms were treatment, visit, treatment-by-visit interaction, baseline measurement, and screening triglycerides stratum (<2·82 mmol/L or ≥2·82 mmol/L). The treatment regimen estimand was estimated using all available data, regardless of treatment discontinuation or prohibited medication, using ANCOVA, with multiple imputation within treatment groups for missing baseline or post-baseline measurements. Contrast-based tests were used to compare each treatment group versus placebo at the indicated timepoint for both ANCOVA and mixed model for repeated measures analyses. No multiplicity

adjustments were performed. All lipid-related parameters and ANGPTL3 concentrations were log-transformed before the analysis to diminish the impact of skewness. A post-hoc sensitivity analysis was also performed to exclude a single study site that enrolled approximately 26% of the study population.



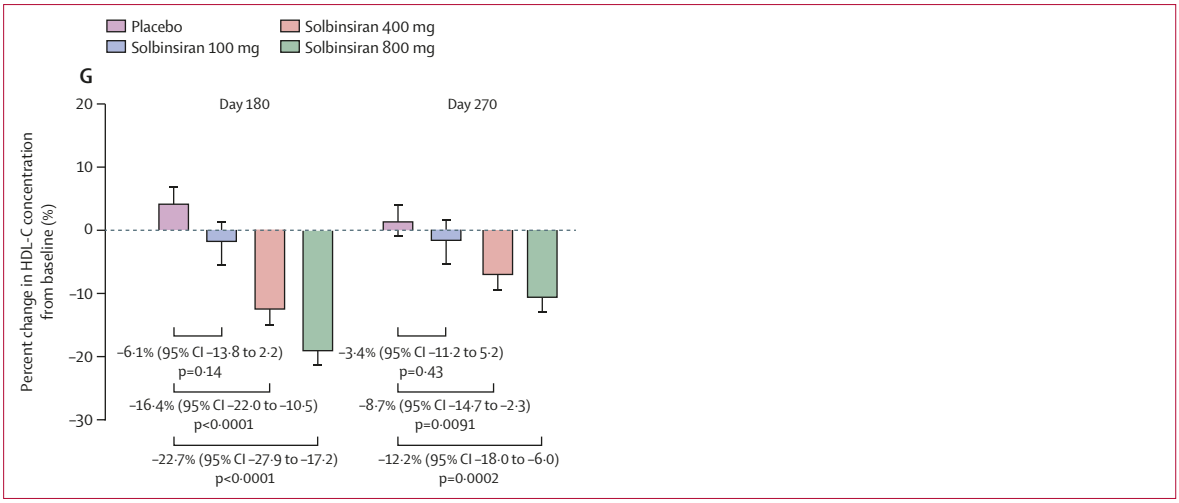


Figure 2: **Percent change from baseline in apoB (A), ANGPTL3 (B), triglycerides (C), VLDL-C (D), LDL-C (E), non-HDL-C (F), and HDL-C (G) over time**
Data are estimates (SD). apoB=apolipoprotein B. ANGPTL3=angiopoietin 3. LDL-C=LDL cholesterol. HDL=C=HDL cholesterol. VLDL-C=very LDL cholesterol.

For other endpoints which do not fall into the categories listed above, the following general statistical methods were used. Continuous data were summarised by the sample size, mean and SD if normally distributed, and median and interquartile range if the distribution was skewed. Categorical data were summarised by sample size, frequency, and percentage. Fisher's exact test or Pearson's χ^2 test were used to examine the treatment difference in categorical outcomes. Statistical analysis was completed using SAS version 9.4.

Role of the funding source

The study's funder designed the trial and was responsible for data collection, data analysis, and, in conjunction with an academic steering committee, data interpretation and writing of the report.

Results

Of the 585 patients screened between July 20, 2022, and May 23, 2024, 205 were randomly assigned (1:2:2:2) to receive either solbinsiran 100 mg (n=30), solbinsiran 400 mg (n=58), solbinsiran 800 mg (n=59), or placebo (n=58; figure 1) and followed up over 270 days. All randomised patients received at least one dose of study drug, and 189 (92%) completed the treatment period, without discontinuing treatment (figure 1). The median age of patients was 57 years (IQR 49–65), 111 (54%) participants were female and 94 (46%) male, the median BMI was 30 kg/m² (26·9–33·9), 92 (45%) patients had diabetes, and the mean concentration of HbA_{1c} was 6·3% (SD 1·1; 45·4 mmol/mol [12·0]) at baseline (table 1). In this cohort of patients with mixed dyslipidaemia, median baseline concentrations of atherogenic lipoproteins were high, with concentrations of apoB of 111 mg/dL (IQR 96–130), triglycerides 2·64 mmol/L (2·06–3·29), VLDL-C 1·04 mmol/L (0·80–1·37), LDL-C 3·16 mmol/L (2·58–3·83), and non-HDL-C 4·30 mmol/L (3·68–5·19).

Within the placebo group, apoB concentrations were significantly reduced at day 180 (–11·6%; p=0·0031) and day 270 (–9·5%; p=0·013) compared with baseline (figure 2A, appendix p 6). Compared with baseline, ANGPTL3 concentrations were not significantly lower at day 180 (–3·2%; p=0·62) in the placebo group, but they were significantly lower at day 270 (–17·0%; p=0·011; figure 2B, appendix p 6). Significant reductions in triglycerides were observed for the placebo treatment group at both day 180 (–15·1%; p=0·0007) and day 270 (–13·9%; p=0·0059) compared with baseline (figure 2C). Additionally, VLDL-C was significantly lower in the placebo group at day 180 (–14·5%; p=0·010) but not at day 270 (–5·4%; p=0·35) compared with baseline (figure 2D). The placebo group demonstrated significant reductions in non-HDL-C concentrations at day 180 (–10·2%; p=0.0033) and day 270 (–9·8%; p=0.0041) compared with baseline (figure 2E). Similarly, LDL-C was significantly reduced in the placebo group at day 180 (–8·7%; p=0.034) and day 270 (–12·7%; p=0.0020; figure 2F). There were no significant changes in HDL-C in the placebo treatment group at day 180 (4·3%; p=0·091) or day 270 (1·5%; p=0·54) compared with baseline (figure 2G).

The placebo-adjusted percent change in apoB concentration from baseline at day 180 was –2·8% (95% CI –15·5 to 11·9; p=0·69) for solbinsiran 100 mg; –14·3% (–23·6 to –3·9; p=0·0085) for solbinsiran 400 mg; and –8·3% (–18·3 to 2·9; p=0·14) for solbinsiran 800 mg (figure 2A; appendix p 6). The results for the treatment regimen estimand (appendix p 7) were consistent with those of the efficacy estimand. At day 270, the placebo-adjusted percent changes from baseline in apoB concentration were –10·8% (–22·2 to 2·3; p=0·10)

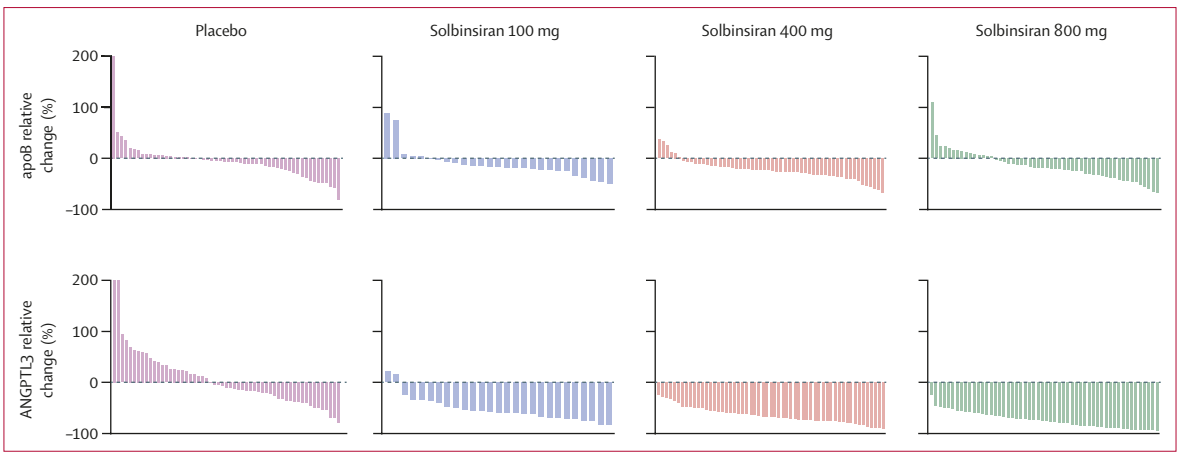


Figure 3: **Waterfall plot of relative change in apoB (top) and ANGPTL3 (bottom) at day 180**
apoB=apolipoprotein B. ANGPTL3=angiopoietin 3.

for solbinsiran 100 mg, –11·3% (–20·6 to –1·0; p=0·033) for solbinsiran 400 mg, and –10·9% (–20·3 to –0·6; p=0·040) for solbinsiran 800 mg.

Dose-dependent, placebo-adjusted reductions in ANGPTL3 concentrations with solbinsiran at day 180 were –54·3% (95% CI –63·3 to –43·1) with 100 mg to –69·8% (–74·8 to –63·9) with 400 mg, and –76·6% (–80·4 to –72·0) with 800 mg (all p<0·0001; figure 2B, appendix p 6). At day 270, 180 days after the second dose, smaller but still significant placebo-adjusted reductions in ANGPTL3 concentrations were observed with solbinsiran (figure 2B).

Figure 2C–G and the appendix (p 8) show the percent change from baseline for other lipid parameters. All three doses of solbinsiran provided significant dose-dependent, placebo-adjusted reductions in triglycerides at days 180 and 270 (figure 2C; all p≤0·0005). The magnitude of reductions in triglycerides were similar to the placebo-adjusted percentage reductions in VLDL-C at day 180 (figure 2D). Placebo-adjusted reductions in VLDL-C at day 270 were smaller than at day 180, but still significant (all p≤0·0031).

At day 180 solbinsiran 100 mg did not demonstrate significant placebo-corrected reductions in LDL-C (figure 2E). However, both solbinsiran 400 mg and 800 mg demonstrated significant reductions in LDL-C from baseline to day 180. These differences, compared with placebo, were not observed at day 270 for the 100 mg, 400 mg, or 800 mg doses.

The placebo-adjusted percent changes in non-HDL-C for solbinsiran at day 180 ranged between –10·8% and –25·5%. At day 270, these reductions were smaller, ranging between –4·1% and –19·7%. These changes at day 180 and day 270 were significant for the two highest doses, but not for the 100 mg dose (figure 2F)

There was no difference in the placebo-adjusted percent change in HDL-C for solbinsiran 100 mg at day 180, but both 400 mg and 800 mg doses demonstrated significant reductions (figure 2G). The placebo-adjusted reduction observed with the solbinsiran 100 mg group at day 270 was not significant. However, the significant difference in percent change for HDL-C from baseline was maintained at day 270 for 400 mg and 800 mg (figure 2G). Significant placebo-adjusted reductions in apoA-I concentrations were also observed for solbinsiran 400 mg and 800 mg at days 180 and 270 (appendix p 10) in line with the observed reductions in HDL-C. All three doses of solbinsiran also demonstrated significant placebo-adjusted percent reductions from baseline for apoC-III at days 180 and 270 (appendix p 10).

Waterfall plots of between-person variation in the change in apoB and ANGPTL3 suggest that, in the placebo group, more patients had a reduction from baseline in apoB than an increase (skewed towards overall reduction), whereas for ANGTL3, the number and magnitude of the changes from baseline (increases or decreases) appeared more balanced (figure 3). The between-person variation in apoB and ANGPTL3 seemed similar between the 400 mg and 800 mg groups, with greater and more consistent effects seen in those groups than in the 100 mg group. Unlike in the placebo group, ANGPTL3 concentrations were reduced in all the patients in the solbinsiran 400 mg and 800 mg groups. The between-person variation for triglycerides and VLDL-C concentrations resembled the variation pattern seen in ANGPTL3 concentrations (in the placebo and solbinsiran groups), while LDL-C and non-HDL-C plots more closely resembled those of apoB (appendix p 11).

The incidence of treatment-emergent adverse events in the solbinsiran 100 mg (18 [60%] of 30 patients), 400 mg (30 [52%] of 58 patients), 800 mg (26 [44] of 59 patients), and placebo (37 [65%] of 57 patients) groups were generally similar (table 2). The most common adverse events, occurring in more than 2% of patients, were COVID-19 (13 [6%] patients), gastroenteritis (eight [4%] patients), nasopharyngitis (eight [4%] patients),

	Placebo (n=57)	Solbinsiran 100 mg (n=30)	Solbinsiran 400 mg (n=58)	Solbinsiran 800 mg (n=59)	Total (n=204)
Deaths	0	0	0	0	0
Serious adverse events	5 (9%)	1 (3%)	3 (5%)	2 (3%)	11 (5%)
Discontinuations from study due to an adverse event	0	0	1 (2%)	0	1 (<1%)
Discontinuations from study treatment due to an adverse event	1 (2%)	0	2 (3%)	0	3 (1%)
Treatment-emergent adverse events	37 (65%)	18 (60%)	30 (52%)	26 (44%)	111 (54%)
Treatment-emergent adverse events related to study treatment	5 (9%)	2 (7%)	7 (12%)	5 (8%)	19 (9%)
Adverse events of special interest					
Participants with ≥1 treatment-emergent adverse event: gallbladder-related disorders	0	0	1 (2%)	1 (2%)	2 (1%)
Cholelithiasis	0	0	1 (2%)	1 (2%)	2 (1%)
Participants with ≥1 treatment-emergent adverse event: hypersensitivity reactions	1 (2%)	2 (7%)	2 (3%)	3 (5%)	8 (4%)
Cough	0	1 (3%)	1 (2%)	0	2 (1%)
Rhinitis allergic	0	0	0	2 (3%)	2 (1%)
Conjunctivitis allergic	0	1 (3%)	0	0	1 (<1%)
Dermatitis atopic	0	0	1 (2%)	0	1 (<1%)
Dyspnoea	0	0	1 (2%)	0	1 (<1%)
Oedema peripheral	0	0	0	1 (2%)	1 (<1%)
Rash	1 (2%)	0	0	0	1 (<1%)
Injection site reactions	0	1 (3%)	3 (5%)	1 (2%)	5 (2%)
Erythema	0	0	2 (3%)	0	2 (1%)
Induration	0	0	0	0	0
Pain	0	0	2 (3%)	1 (2%)	3 (1%)
Pruritus	0	1 (3%)	1 (2%)	0	2 (1%)
Oedema	0	0	0	0	0
Most common adverse events (occurring in >2% of total patients)					
COVID-19	4 (7%)	4 (13%)	3 (5%)	2 (3%)	13 (6%)
Gastroenteritis	3 (5%)	3 (10%)	2 (3%)	0	8 (4%)
Nasopharyngitis	2 (4%)	1 (3%)	3 (5%)	2 (3%)	8 (4%)
Hypertension	2 (4%)	2 (7%)	1 (2%)	2 (3%)	7 (3%)
Influenza	0	2 (7%)	2 (3%)	2 (3%)	6 (3%)
Urinary tract infection	3 (5%)	1 (3%)	1 (2%)	1 (2%)	6 (3%)
Injection site reactions	0	1 (3%)	3 (5%)	1 (2%)	5 (3%)

Data are number of participants (%).

Table 2: **Adverse events**

hypertension (seven [3%] patients), influenza (six [3%] patients), urinary tract infection (six [3%] patients), and injection site reaction (five [3%] patients); the incidence of these events were similar between groups. The incidence of injection site reactions was generally low in the solbinsiran groups (one [3%] patient with 100 mg, three [5%] patients with 400 mg, and one [2%] patient with 800 mg) and were mild or moderate in severity. There were no reports of injection site reactions in the placebo group. Numerically, more serious adverse events and more treatment-emergent adverse events were reported for the placebo group than in the solbinsiran groups. No deaths occurred throughout the study.

Three patients developed increased concentrations of hepatic aspartate aminotransferase (≥3 times the upper limit of the normal range [ULN]), all in the solbinsiran 800 mg group. Four patients had increased hepatic alanine aminotransferase (≥3×ULN), two in the solbinsiran 800 mg group, one in the solbinsiran 400 mg group, and one in the placebo group. The increase in transaminase concentrations was transient and rapidly normalised. No participants demonstrated increased bilirubin concentrations. High-sensitivity C-reactive protein (hsCRP) concentrations fell in the placebo and all three solbinsiran-treated groups, with no difference in the placebo-corrected percent changes from baseline at any solbinsiran dose (appendix p 12).

Absolute hepatic fat fractions at baseline as assessed via MRI were different across the four groups. There was a reduction from baseline to day 180 in hepatic fat in all solbinsiran groups (–26·8% for 100 mg to –42·4% for 400 mg, and 35·9% for 800 mg; all p<0·0001) and

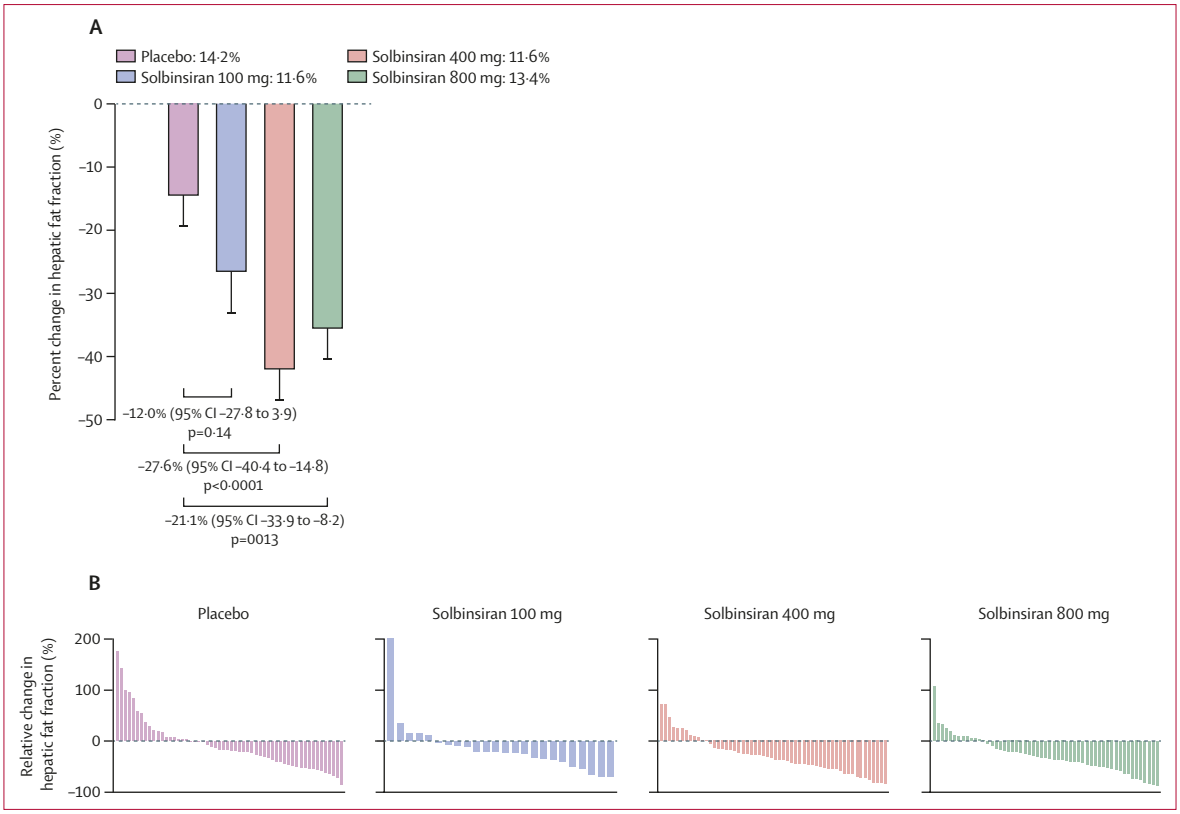


Figure 4: **Percent change from baseline in hepatic fat fraction as measured by MRI (A) and waterfall plot of relative change in hepatic fat fraction at day 180**
Data are estimates (SD).

placebo (–14·8%; p=0·0013) treatment groups (figure 4A). The placebo-adjusted percent change in hepatic fat from baseline to day 180 was –27·6% (95% CI –40·4 to –14·8) in the solbinsiran 400 mg group (p<0·0001) and –21·1% (–33·9 to –8·2) in the solbinsiran 800 mg group (p=0·0013). The waterfall plots of individual change in patient hepatic fat fraction suggested that although some patients in the placebo group had an increase in hepatic fat over 180 days, this increase was less frequent with the solbinsiran groups, in which most patients had a reduction, with less between-person variation at the two higher doses (figure 4B).

There were no significant differences in change from baseline in HbA_{1c} throughout the study for the placebo, solbinsiran 100 mg, and solbinsiran 400 mg groups (appendix p 13). The solbinsiran 800 mg group showed a transient increase in HbA_{1c} at day 180 (0·18% [2·0 mmol/mol]; p=0·043), which was resolved by day 270. Similarly, there were transient significant reductions in fasting glucose for the solbinsiran 800 mg group on day 15 (–4·7 mg/dL [0·26 mmol/L]; p=0·043) and for the placebo group at day 180 (–10·2 mg/dL [0·57 mmol/L]; p=0·0007; appendix p 14). Bodyweight was significantly reduced at day 180 in the placebo group (–1·0 kg; p=0·039) and at day 90 (–1·1 kg; p=0·0015), day 180 (–1·6 kg; p=0·0015), and day 270 (–1·6 kg; p=0·012) in the solbinsiran 400 mg group, but placebo-corrected differences were not significant, for any of the solbinsiran doses (appendix p 14).

The results from the post-hoc sensitivity analysis, which excluded a single study site that had recruited approximately 26% of all study patients, was consistent with the results of the full analysis set. Specifically, reductions in apoB concentrations (appendix p 15) and trends in lipid changes (appendix p 16) were similar between the full analysis and the sensitivity analysis. However, in the sensitivity analysis, there was no reduction in the placebo group hepatic fat fraction, and the solbinsiran treatment groups showed significant reductions in hepatic fat fraction, as was observed in the full population (appendix p 17).

Discussion

This phase 2 trial provides a more detailed understanding of the potential of solbinsiran as an siRNA therapeutic targeting hepatic ANGPTL3 for mixed dyslipidaemia. Solbinsiran 100 mg was well tolerated but did not show significant reductions in apoB, non-HDL-C, or LDL-C (or HDL-C) concentrations, despite reductions in ANGPTL3, triglycerides, and VLDL-C concentrations. The higher

doses of solbinsiran of 400 mg and 800 mg were more potent but only the 400 mg dose reduced apoB concentration (14·3%), despite the 400 mg and 800 mg doses producing generally similar peak reductions in ANGPTL3 concentrations of 69·8% and 76·6%, respectively, 90 days after the second injection. The 400 mg dose also reduced the concentration of other atherogenic lipoproteins, including non-HDL-C (25·5%) and LDL-C (16·8%). Triglyceride and VLDL-C concentrations were reduced by 50·3% and 50·1%, respectively, and HDL-C by 16·4%, with a waning of the treatment effect by day 270 across the lipid spectrum. Additionally, the 400 mg dose was associated with reductions in hepatic fat fraction of 27·6%. The highest dose of 800 mg did not significantly reduce apoB concentration at day 180, and the magnitude of the effect on other lipids assessed and hepatic fat fraction was generally similar to the 400 mg dose over the study. Incidence of injection site adverse events and transient elevations in liver transaminases were low at the highest doses.

The present study extends previous observations in a small phase 1 trial of solbinsiran, where dose-dependent reductions in ANGPTL3 and circulating lipoprotein concentrations were observed.[17] However, there was no clear consistency of a dose relationship and the follow-up was too short (160 days) to inform safety, which meant a larger study was needed. In the present study, the 100 mg dose of solbinsiran, despite lowering ANGPTL3 concentration by about half, was ineffective at lowering apoB, non-HDL-C, and LDL-C concentrations, suggesting that greater reductions in ANGPTL3 concentrations are needed for meaningful changes in atherogenic lipoproteins. Of the two higher doses, the 400 mg dose provided similar reductions in ANGPTL3 concentration and appeared more effective across the spectrum of lipids than the 800 mg dose, with a similar safety profile.

The peak placebo-corrected reduction in apoB concentration observed with the 400 mg dose might appear lower than the reduction observed with the siRNA zodasiran (where a 22% reduction was observed with the 200 mg dose at week 24).[16] Although indirect comparisons between therapies should be interpreted with caution, it is of note that, in the present trial, the placebo comparator group had a reduction in apoB concentrations from baseline of –11·6 at day 180 and –9·5 at day 270, which would attenuate the estimates of efficacy between solbinsiran and placebo. Common to both siRNA-based therapies targeting ANGPTL3 concentration is the durability of the effect. The placebo-corrected reduction of apoB concentration observed 180 days after the second injection was lower than the peak effect 90 days after the second injection, suggesting an optimal frequency of dosing to maintain meaningful reductions of apoB concentration might be every 3 months with siRNA-based approaches targeting ANGPTL3.

Safety concerns were raised about targeting hepatic ANGPTL3 production after an evaluation of the effects of vupanorsen showed that injection site reactions and significant liver enzyme elevations occurred more frequently at higher total monthly doses in up to 33·3% and 44·4% of participants, respectively, with an antisense oligonucleotide targeting mRNA degradation within hepatocytes over 24 weeks of follow-up.[15] Similarly, a dose-dependent increase in hepatic fat fraction of up to 76% was observed with vupanorsen, despite reductions in concentrations of ANGPTL3 of up to 95·2%, apoB of up to 27·7%, and triglycerides of up to 56·8%.

The present study, together with the ARCHES-2 trial of zodasiran,[16] provides evidence based on 409 patients with mixed dyslipidaemia of the safety of targeting hepatic ANGPTL3 production through RNA interference targeting cytoplasmic mRNA degradation over 36 weeks of follow-up. In both trials, the incidence of liver enzyme abnormalities was low. In ARCHES-2, only a subgroup of patients who had liver steatosis at baseline underwent further MRI of the liver at week 24, where dose-dependent reductions in liver fat content were observed, reaching 28% with the highest dose compared with a 2% reduction with placebo. In the present study, all patients underwent serial MRI assessment, with the 400 mg dose of solbinsiran demonstrating a reduction in hepatic fat fraction of 29·8% compared with a reduction in 1·9% in the placebo group. These two studies are not only reassuring for siRNA-based approaches, but also to target hepatic ANGPTL3 as a therapeutic approach for lipid modification. Moreover, the changes in hepatic fat occurred without a change in weight or hsCRP, which distinguishes the present findings from GLP-1 agonists, which reduce both weight and hepatic fat. This might implicate hepatic ANGPTL3 itself in metabolic steatotic liver disease. ANGPTL3 inhibition can lead to a decreased supply of free fatty acids to the liver and enhanced fatty acid oxidation. For instance, low concentrations of free fatty acids and increased ketone body production (and thus enhanced hepatic fatty acid β-oxidation) are observed in patients with ANGPTL3 deficiency, supporting a potential biological mechanism for our clinical findings.[22,23] We also observed a 50·0% decrease of apoC-III concentration with solbinsiran 400 mg, which can contribute to the lipid and hepatic changes, and we cannot disentangle apoC-II effects from ANGPTL3 effects in this study.

Observational data demonstrate the high unmet need and residual risk of atherosclerotic cardiovascular disease events in patients with elevated triglyceride concentrations, despite LDL-C lowering with statins.[24] Mendelian randomisation supports the concept of a causal link between triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease,[25] as do mendelian randomisation studies of specific molecular regulatory pathways in triglyceride metabolism such as ANGPTL3, ANGPTL4, and apoC-III and apoA-V.[26–28] However, the complexity of triglyceride metabolism and differential changes in the various lipid fractions through different

therapeutic approaches have made the development of novel therapies challenging in contrast to therapies for lowering LDL-C concentrations. As LDL particles account for approximately 90% of circulating apoB, when triglycerides concentrations are normal, the LDL-C to non-HDL-C ratio or LDL-C to apoB closely approximate to one. Therefore, therapies such as statins that lower LDL-C concentration by around 47% will also lower concentrations of non-HDL-C by 43% and apoB by 37%, with a reduction of 23% in triglyceride concentration.[29] This contrasts with therapies directed against triglycerides pathways, as there are fewer apoB-containing triglyceride-rich lipoproteins. This means that for triglyceride lowering therapies, the reductions in triglyceride concentrations are much greater than observed changes in LDL-C, non-HDL-C, and apoB concentrations with these approaches.

Triglycerides per se do not appear to cause atherosclerosis, but the cholesterol that is carried in these apoB-containing triglyceride-rich lipoproteins can penetrate the arterial subendothelial space, bind to proteoglycans, and initiate foam-cell formation, with resultant progression of atherosclerosis. Mendelian randomisation suggests that in patients with high LDL-C but low triglyceride concentrations and in those with high triglyceride but low LDL-C concentrations, risk of atherosclerotic cardiovascular disease is similar when standardised per unit change in apoB,[30] which explains the choice of apoB as the primary efficacy estimand in this study. Whether the magnitude of the changes in apoB concentration observed with solbinsiran will ultimately translate into reductions in risk of atherosclerotic cardiovascular disease is yet to be validated in cardiovascular outcome trials. For comparison, contemporary trials of fibrates in mixed dyslipidaemia demonstrated reductions in triglyceride and VLDL-C concentrations by approximately 25%, but increased LDL-C and apoB concentrations modestly and did not result in reductions in atherosclerotic cardiovascular disease events. By contrast, solbinsiran reduced triglycerides and VLDL-C by approximately 50%, and reduced apoB and LDL-C. As triglyceride-rich lipoproteins are believed, per apoB particle, to be more atherogenic than LDL particles,[5,6] and as triglyceride-rich lipoproteins numerically reflect a smaller portion of the total apoB pool, the reductions in apoB observed with solbinsiran and other therapies targeting ANGPTL3 might underestimate the potential clinical benefit of this approach. In this regard, we have previously shown, using nuclear magnetic resonance, that solbinsiran reduces the absolute number of triglyceride-rich lipoprotein particles and of LDL particle numbers.[17]

This study has limitations that merit consideration. First, siRNA-based therapies have a long duration of action, which means that, over 9 months, no patient received more than two doses. Therefore, the long-term safety of repeat dosing and the durability of the effect is unknown. Second, we observed a reduction in hepatic fat fraction, which, although encouraging, requires validation in prospective efficacy studies given the commonality of biological pathways involved in metabolic dysfunction-associated steatotic liver disease and mixed dyslipidaemia. Third, representing diverse groups in clinical trials was a challenge in this study. There was only one Black patient enrolled in this study, and approximately two-thirds of participants were Hispanic or Latino. However, differently from previous studies, half of the participants were women. Moreover, one site recruited approximately 26% of all patients. In sensitivity analyses, exclusion of this site improved the primary efficacy estimand, but did not change the overall findings. Fourth, we had several secondary outcomes that were analysed and we did not use multiplicity control, which might have resulted in an elevated type 1 error.[31] Fifth, although the magnitude of the placebo-corrected difference in concentrations of apoB and other atherogenic lipids with solbinsiran 400 mg were more modest than reported in other trials, it was of note that, in the placebo group, concentrations of apoB, hepatic fat, and hsCRP were all significantly lower at 180 days than at baseline. Such a finding was not seen in the placebo group of other trials. Sixth, waterfall plots of between-person variation suggested that in the placebo group, changes in concentrations of ANGPTL3, triglycerides, and VLDL-C were random with no net change in the group. By contrast, findings for apoB, non-HDL-C, and LDL-C were skewed towards lower concentrations. This finding might reflect a drop in lipid-lowering medications. Waterfall plots of solbinsiran at higher doses showed consistent reductions in concentrations of ANGPTL3 and all lipid fractions, which is consistent with an on-target effect of ANGPTL3 inhibition. Finally, although the present trial did not detect any differences in HbA_{1c} concentration, some trials of other pathways have suggested that there might be adverse effects of this drug class on HbA_{1c}. As key regulators mediating triglyceride concentrations vary in their biological effects between fasting and fed status, future trials should evaluate each target in the fasting and fed state.

In conclusion, solbinsiran, at a dose of 400 mg, provided durable reductions in serum ANGPTL3 concentrations in adults with mixed dyslipidaemia, resulting in significant and sustained reductions in apoB, triglyceride, non–HDL-C, and LDL-C concentrations, and it was well tolerated, with a reassuring hepatic safety profile. These data support further evaluation of solbinsiran in patients with mixed dyslipidaemia at high risk of atherosclerotic cardiovascular disease.

Contributors

KKR, RSR, SJN, EO, AH, and GR conceptualised the study. RSR, DG, and SV were investigators in the study. JJ conducted the statistical analysis. All authors participated in the interpretation of data outputs and study results, and in the drafting, critical revision, and approval of the final version of the manuscript. All authors had access to all the

included data and permission to access the raw data. KKR, JJ, and GR directly accessed and verified the data. All authors accept final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Lilly will provides access to all individual participant data collected during the trial, after anonymisation, with the exception of pharmacokinetic data. Data can be requested 6 months after the indication studied has been approved in the USA and EU or after publication of the primary trial report, whichever occurs later. No expiration date of data requests once data are made available is currently set. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at http://www.vivli.org.

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References

1 Ormazabal V, Nair S, Elfeky O, Aguayo C, Salomon C, Zuniga FA. Association between insulin resistance and the development of cardiovascular disease. *Cardiovasc Diabetol* 2018; **17:** 122.

2 Gurevitz C, Chen L, Muntner P, Rosenson RS. Hypertriglyceridemia and multiorgan disease among US adults. *JACC Adv* 2024; **3:** 100932.

3 Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. *Endocr Pract* 2017; **23** (suppl 2)**:** 1-87.

4 Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J* 2016; **37:** 2999–3058.

5 Bjornson E, Adiels M, Gummesson A, et al. Quantifying triglyceride-rich lipoprotein atherogenicity, associations with inflammation, and implications for risk assessment using non-HDL cholesterol. *J Am Coll Cardiol* 2024; **84:** 1328–38.

6 Björnson E, Adiels M, Taskinen MR, et al. Triglyceride-rich lipoprotein remnants, low-density lipoproteins, and risk of coronary heart disease: a UK Biobank study. *Eur Heart J* 2023; **44:** 4186–95.

7 Das Pradhan A, Glynn RJ, Fruchart JC, et al. Triglyceride lowering with pemafibrate to reduce cardiovascular risk. *N Engl J Med* 2022; **387:** 1923–34.

8 Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med* 2019; **380:** 11–22.

9 Dewey FE, Gusarova V, Dunbar RL, et al. Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. *N Engl J Med* 2017; **377:** 211–21.

10 Minicocci I, Montali A, Robciuc MR, et al. Mutations in the *ANGPTL3* gene and familial combined hypolipidemia: a clinical and biochemical characterization. *J Clin Endocrinol Metab* 2012; **97:** E1266–75.

11 Helgadottir A, Gretarsdottir S, Thorleifsson G, et al. Variants with large effects on blood lipids and the role of cholesterol and triglycerides in coronary disease. *Nat Genet* 2016; **48:** 634–39.

12 Ando Y, Shimizugawa T, Takeshita S, et al. A decreased expression of angiopoietin-like 3 is protective against atherosclerosis in apoE-deficient mice. *J Lipid Res* 2003; **44:** 1216–23.

13 Graham MJ, Lee RG, Brandt TA, et al. Cardiovascular and metabolic effects of ANGPTL3 antisense oligonucleotides. *N Engl J Med* 2017; **377:** 222–32.

14 Stitziel NO, Khera AV, Wang X, et al. ANGPTL3 deficiency and protection against coronary artery disease. *J Am Coll Cardiol* 2017; **69:** 2054–63.

15 Bergmark BA, Marston NA, Bramson CR, et al. Effect of vupanorsen on non-high-density lipoprotein cholesterol levels in statin-treated patients with elevated cholesterol: TRANSLATE-TIMI 70. *Circulation* 2022; **145:** 1377–86.

16 Rosenson RS, Gaudet D, Hegele RA, et al. Zodasiran, an RNAi therapeutic targeting ANGPTL3, for mixed hyperlipidemia. *N Engl J Med* 2024; **391:** 913–25.

17 Ray KK, Linnebjerg H, Michael LF, et al. Effect of ANGPTL3 inhibition with solbinsiran in preclinical and early human studies. *JACC* (in press) 10.1016/j.jacc.2025.03.005.

18 Blom DJ, Marais AD, Raal FJ. Homozygous familial hypercholesterolemia treatment: new developments. *Curr Atheroscler Rep* 2025; **27:** 22.

19 ECDC. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Feb 17, 2020. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-and-sensitivity-analysis-clinical-trials-guideline-statistical-principles-clinical-trials-step-5_en.pdf (accessed March 20, 2025).

20 Nicholls SJ, Ni W, Rhodes GM, et al. Oral muvalaplin for lowering of lipoprotein(a): a randomized clinical trial. *JAMA* 2025; **333:** 222–31.

21 Wharton S, Blevins T, Connery L, et al. Daily oral GLP-1 receptor agonist orforglipron for adults with obesity. *N Engl J Med* 2023; **389:** 877–88.

22 Robciuc MR, Maranghi M, Lahikainen A, et al. Angptl3 deficiency is associated with increased insulin sensitivity, lipoprotein lipase activity, and decreased serum free fatty acids. *Arterioscler Thromb Vasc Biol* 2013; **33:** 1706–13.

23 Tikkanen E, Minicocci I, Hällfors J, et al. Metabolomic signature of angiopoietin-like protein 3 deficiency in fasting and postprandial state. *Arterioscler Thromb Vasc Biol* 2019; **39:** 665–74.

24 Miller M, Cannon CP, Murphy SA, et al. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol* 2008; **51:** 724–30.

25 Nordestgaard BG, Langsted A. Lipoprotein(a) and cardiovascular disease. *Lancet* 2024; **404:** 1255–64.

26 Maidman SD, Hegele RA, Rosenson RS. The emerging potential of apolipoprotein C-III inhibition for ASCVD prevention: a state-of-the-art review. *Curr Atheroscler Rep* 2024; **27:** 3.

27 Gagnon E, Arsenault B. Drug target mendelian randomization supports apolipoprotein C3-lowering for lipoprotein-lipid levels reductions and cardiovascular diseases prevention. *Atherosclerosis* 2024; **391:** 117501.

28 Landfors F, Henneman P, Chorell E, Nilsson SK, Kersten S. Drug-target mendelian randomization analysis supports lowering plasma ANGPTL3, ANGPTL4, and APOC3 levels as strategies for reducing cardiovascular disease risk. *Eur Heart J Open* 2024; **4:** oeae035.

29 Ballantyne CM, Stein EA, Paoletti R, Southworth H, Blasetto JW. Efficacy of rosuvastatin 10 mg in patients with the metabolic syndrome. *Am J Cardiol* 2003; **91**(5a)**:** 25C–27.

30 Ference BA, Kastelein JJP, Ray KK, et al. Association of triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants with risk of coronary heart disease. *JAMA* 2019; **321:** 364–73.

31 Pocock SJ, Rossello X, Owen R, Collier TJ, Stone GW, Rockhold FW. Primary and secondary outcome reporting in randomized trials: JACC state-of-the-art review. *J Am Coll Cardiol* 2021; **7**: 827–39.