Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol (ORION-3): results from the 4-year open-label extension of the ORION-1 trial

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Summary

Introduction Whether long-term treatment with the twice-yearly, siRNA therapeutic inclisiran, which reduces hepatic production of proprotein convertase subtilisin/kexin type 9 (PCSK9), results in sustained reductions in LDL cholesterol with an acceptable safety profile is not known. The aim of this study was to assess the effect of long-term dosing of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol.

Methods ORION-3 was a 4-year open-label extension study of the placebo-controlled, phase 2 ORION-1 trial, conducted at 52 sites across five countries. Patients with prevalent atherosclerotic cardiovascular disease or high-risk primary prevention and elevated LDL cholesterol despite maximally tolerated statins or other LDL-lowering treatments, or with documented statin intolerance, who had completed the ORION-1 trial were eligible. Patients receiving inclisiran in ORION-1 received twice-yearly 300 mg subcutaneous inclisiran sodium throughout ORION-3 (inclisiran-only arm), whereas patients receiving placebo in ORION-1 first received subcutaneous evolocumab 140 mg every 2 weeks until day 360 thereafter transitioning to inclisiran twice-yearly for the remainder of ORION-3 study (switching arm). The primary efficacy endpoint was the percentage change in LDL cholesterol with inclisiran from the start of ORION-1 through to day 210 of the open label extension phase in the inclisiran-only arm (approximately 570 days of total inclisiran exposure in the modified intention-to-treat population). Secondary and exploratory endpoints included changes in LDL-C cholesterol and PCSK9 concentrations levels up to day 1440 (4 years) in each arm, and safety. ORION-3 is registered with ClinicalTrials.gov, NCT03060577.

Findings Of the original ORION-1 cohort of 497 patients, 290 of 370 patients allocated to drug continued into the inclisiran-only arm and 92 of 127 patients allocated to placebo entered the switching-arm in the ORION-3 extension study conducted between March 24, 2017, and Dec 17, 2021. In the inclisiran-only arm, LDL cholesterol was reduced by 47·5% (95% CI 50·7–44·3) at day 210 and sustained over 1440 days. The 4-year averaged mean reduction of LDL-C cholesterol was 44·2% (95% CI: 47·1–41·4), with reductions in PCSK9 ranging from 62·2% to 77·8%. Adverse events at the injection site were reported in 39 (14%) of 284 patients in the inclisiran-only arm and 12 (14%) of 87 patients in the switching arm. The incidence of treatment-emergent serious adverse events possibly related to the study drug was 1% (three of 284) in the inclisiran-only arm and 1% (one of 87) in the switching arm.

Interpretation Twice-yearly inclisiran provided sustained reductions in LDL cholesterol and PCSK9 concentrations and was well tolerated over 4 years in the extension study. This is the first prospective long-term study to assess repeat hepatic exposure to inclisiran.

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Introduction

Lowering LDL cholesterol is an established, effective, pharmacological approach to reduce the risk of atherosclerotic cardiovascular disease (ASCVD). Current guidelines recommend risk-based LDL cholesterol goals with the aim of maintaining lower LDL cholesterol concentrations long term for those patients at greatest risk of future ASCVD-related events.[1–3] Statin monotherapy results in only 20–40% of very high-risk patients achieving new, lower, recommended LDL cholesterol goals, meaning that those not at goal will not only be required to use combination therapies, but also to be adherent to the additional medication prescribed.[1,3] Injectable therapies directed against proprotein convertase subtilisin/kexin type 9 (PCSK9) have emerged, which further reduce LDL cholesterol concentrations, with two approaches currently available. The most common regimen used globally are monoclonal antibodies (mAbs) that bind circulating PCSK9. These require subcutaneous injections every 2 weeks,

Research in context

Evidence before this study

We searched PubMed on Aug 31, 2022, without any applied restrictions using the search terms "ASCVD", "LDL-C", "atherosclerotic cardiovascular disease", "low density lipoprotein cholesterol", "PCSK9", "proprotein convertase subtilisin/kexin type 9", "inclisiran", "evolocumab", "alirocumab", "guideline", "siRNA", "long term", "efficacy", "effectiveness", and "safety".

In patients at highest risk of atherosclerotic cardiovascular disease (ASCVD), lowering LDL cholesterol reduces the long-term risk of cardiovascular events, hence guidelines recommend lowering LDL cholesterol goals for those at highest risk. However, the vast majority of patients fail to achieve these recommended LDL cholesterol concentrations with statin monotherapy, and require the use of adjunct oral therapies daily (ezetimibe, bempedoic acid, or both) or injectable therapies every 2 weeks (monoclonal antibodies against PCSK9). Inclisiran is a first-in-class small interfering ribonucleic acid (siRNA) therapy which prevents hepatic PCSK9 production and can be administered every 6 months (after initial and 3-month doses) providing a convenient approach to lower LDL cholesterol. In the three phase 3 trials, inclisiran administered on days 1 and 90 and 6 monthly thereafter provided placebo-corrected LDL cholesterol reduction of up to 52% over 18 months and was well tolerated.

Added value of this study

To the best of our knowledge, ORION-3 provides the largest evidence base to date of any siRNA-based therapy showing the safety of repeat exposure to inclisiran over an additional 4 years beyond the original 1-year observation period of ORION-1. It shows that the long-pharmacodynamic effect of inclisiran through its novel mechanism of action is not only well tolerated but makes sustained additional reductions of LDL cholesterol feasible through twice-yearly dosing. There were no additional safety signals observed over approximately 5 years of exposure to inclisiran from the start of ORION-1 through to the end of ORION-3. Furthermore, there were no safety concerns when patients were switched from evolocumab twice a month to inclisiran twice a year.

Implications of all the available evidence

These data provide novel evidence that preventing production of hepatic PCSK9 consistently with the siRNA-therapeutic inclisiran is well tolerated and results in sustained reductions in circulating PCSK9 and LDL cholesterol through twice-yearly dosing for up to 5 years of total observation. For those patients who require additional LDL cholesterol-lowering despite maximally tolerated statins or those who are statin-intolerant, twice-yearly inclisiran could offer a convenient, safe, and potent option as an add-on lipid-lowering therapy. Furthermore, siRNA-based therapies against other biological pathways might offer convenient dosing schedules with a good tolerability profile to manage chronic conditions or risk factors which are amenable to this approach.

cumulating in approximately 26 injections per year. These have been extensively studied with long-term safety and reductions in cardiovascular events shown.[4,5]

More recently, inclisiran has emerged as an alternative approach against PCSK9. It uses small interfering ribonucleic acid (siRNA)-based technology which degrades PCSK9 mRNA in the liver, inhibiting translation, and thus eliminating the main source of PCSK9 in the circulation.[6–11] This novel mechanism allows twice-yearly dosing and has been shown to be well tolerated up to 18 months in the placebo-controlled ORION-9, ORION-10, and ORION-11 trials.[11–13] However, these trials exposed patients to only four inclisiran injections, with the twice-yearly inclisiran dosing interval used from second dose onwards only assessed over a 1-year period in those three trials.

See Online for appendix

ORION-1, was a blinded, placebo-controlled, phase 2, dose-finding and dosing schedule study of inclisiran over 1 year,[10] and served as a feeder study into this two-arm, 4-year, open labelled extension study (ORION-3). The primary aim of ORION-3 trial was to evaluate whether twice-yearly inclisiran provided sustained reductions in LDL cholesterol at day 210. Secondary endpoints included whether this reduction was maintained over 4 years, the percentage change of PCSK9 levels over 4 years, and whether repeat exposure to a hepatocyte-directed siRNA therapeutic had an acceptable safety and tolerability profile in patients at increased risk of cardiovascular diseases who have elevated LDL cholesterol concentrations. The exploratory endpoints included evaluating the second arm for the efficacy and safety of switching from one PCSK9 lowering approach to another, namely, patients who are switched from a twice-monthly mAb directed against PCSK9 (evolocumab) to a twice-yearly siRNA (inclisiran).

Methods

Study design and participants

ORION-3 is the open-label, multicenter, long-term (4-year) extension study of the 1-year ORION-1 study conducted across 52 study sites in five countries (figure 1, appendix pp 1–2). ORION-1 was a phase 2, multicenter, 1-year, double-blind, placebo-controlled, dose-finding study of inclisiran administered as a subcutaneous injection in patients at high risk of ASCVD with elevated LDL cholesterol concentrations. Inclisiran sodium was administered as a single dose of 200 mg, 300 mg, or 500 mg on day 1 or two doses of 100 mg, 200 mg, or 300 mg on day 1 and day 90. The study design and results of ORION-1 have been published in detail previously.[10]

ORION-3 was conducted in accordance with the trial protocol, principles of the Declaration of Helsinki, the

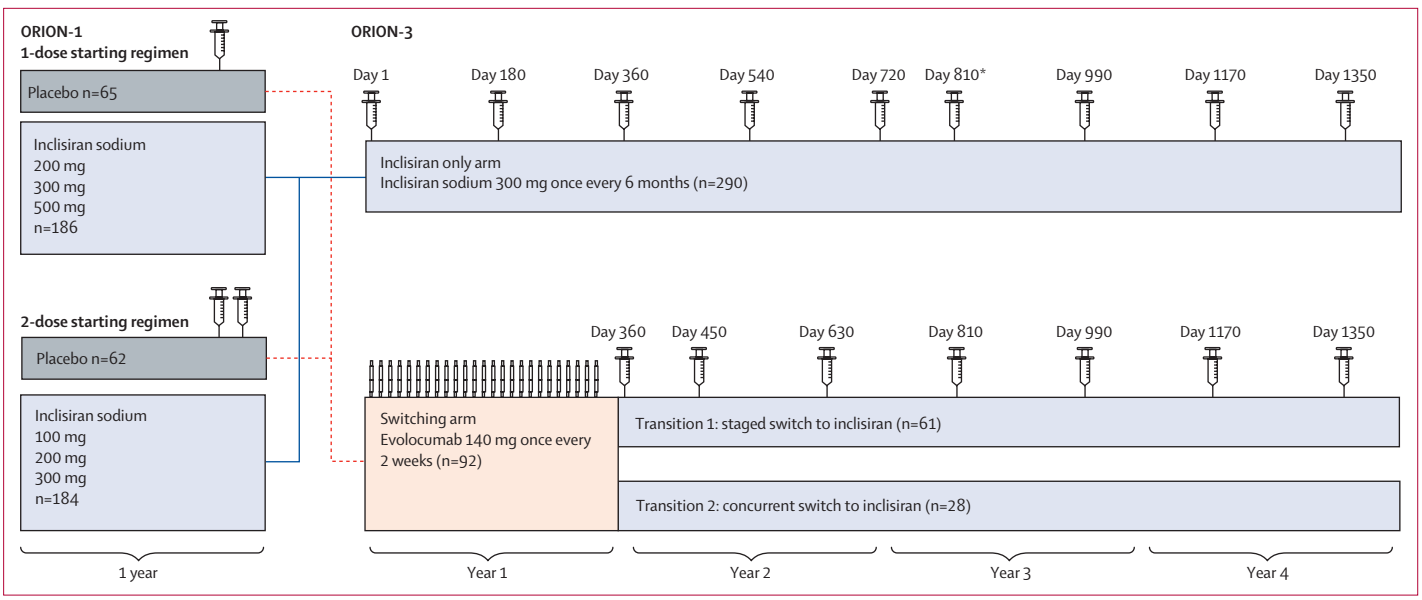

Figure 1: **Study design**
*Day 810 injection in the inclisiran-only arm was administered as a one-time 90-day dosing interval as per the initial study design for exploratory purposes. In the switching arm patients received the second inclisiran dose 90 days apart on day 450.

International Council for Harmonization Good Clinical Practice, and was approved by the Institutional Review Boards of each facility. Written informed consent was required and obtained from each patient for this open-label extension trial before trial enrolment (separate from the informed consent required for the ORION-1 phase 2 trial).

Patients aged 18 years and older with prevalent ASCVD or high-risk primary prevention (defined as either type 2 diabetes, familial hypercholesterolemia, or a 10-year risk of a cardiovascular event >20%) and elevated LDL cholesterol (≥1·8 mmol/L [≥70 mg/dL] for ASCVD patients or ≥2·6 mmol/L [≥100 mg/dL] for high-risk primary prevention in ORION-1) despite maximally tolerated statins or other LDL-lowering treatments, or with documented statin intolerance, who had completed the predefined 1-year of observation in the ORION-1 trial were invited to enroll in ORION-3.

Detailed inclusion and exclusion criteria are provided in the appendix (pp 3–4). Briefly, patients were excluded if they had any uncontrolled or serious medical or surgical condition that reduced life expectancy, or previous or current treatment with a mAb directed against PCSK9. Pregnant or lactating women were also excluded from the trial. Finally, patients randomly assigned in the original ORION-1 trial had to consent to an extended participation in the ORION-3 trial.

Randomisation and masking

The ORION-1 trial has been published,[10] and the randomisation into treatment arms has been explained and discussed in this publication. ORION-3 was an open-label study and included two treatment arms: inclisiran-only arm and switching arm.

Procedures

Patients who received inclisiran sodium (100 mg, 200 mg, or 300 mg in two doses or 200 mg, 300 mg, or 500 mg as a single dose) in ORION-1 received 300 mg subcutaneous inclisiran sodium (equivalent to 284 mg inclisiran; twice-yearly subcutaneous dosing) throughout ORION-3 (inclisiran-only arm). Patients in the inclisiran-only arm received inclisiran on days 1, 180, 360, 540, 720, 810, 990, 1170, and 1350.

Patients who received placebo in ORION-1 received open-labeled 140 mg subcutaneous evolocumab (dosed every 2 weeks) for up to 1 year and then transitioned to 300 mg subcutaneous inclisiran sodium (equivalent to 284 mg inclisiran) for the remainder of the study (switching arm). In this arm, patients were randomly allocated to either staged switch (day 336, final dose of evolocumab therapy; day 360, first dose of inclisiran) or concurrent switch (day 360, final dose of evolocumab and the first dose of inclisiran at clinic visit). After the first inclisiran dose (day 360), subsequent doses were administered 90 days later (ie, day 450) and 6-monthly thereafter on days 630, 810, 990, 1170, and 1350. All patients received the assigned treatments over an open-label follow-up period of 4 years (figure 1).

Inclisiran was administered as a single subcutaneous injection of 300 mg inclisiran sodium (equivalent to 284 mg inclisiran) through a 1·5 mL solution packaged in a glass vial by a health care professional at the study site. Evolocumab was self-administered by the patient as a single 1·0 ml subcutaneous injection using a single-use auto-injector containing 140 mg of evolocumab.

Fasting blood samples were obtained at each study visit, and LDL cholesterol concentrations were measured by

combining ultracentrifugation with precipitation. PCSK9 analysis was performed using Quantikine ELISA from R&D Systems according to the manufacturer's instructions using a Tecan Sunrise reader and EDTA-plasma. A full description of the methods used to measure prespecified laboratory parameters is available in the appendix (p 5); the methods were the same as in the ORION-1 trial.[10]

Outcomes

The primary endpoint of the ORION-3 trial was the percentage change in LDL cholesterol from baseline of ORION-1 to day 210 in this study for the inclisiran-only arm—ie, an observation period of approximately 570 days from first inclisiran injection. Secondary endpoints included percentage and absolute change from baseline of ORION-1 in LDL cholesterol and PCSK9 over time; percentage and absolute change from baseline of ORION-1 in other lipids and lipoproteins over time; individual response to inclisiran defined as the number of patients achieving prespecified LDL cholesterol thresholds of less than 0·6 mmol/L (<25 mg/dL), less than 1·3 mmol/L (<50 mg/dL), less than 1·8 mmol/L (<70 mg/dL), and less than 2·6 mmol/L (<100 mg/dL) at any time point for the inclisiran-only arm and long-term safety and tolerability (adverse events, laboratory abnormalities and serious adverse events, with their severity and relationship to study treatment) of inclisiran.

In the switching arm, patients were on placebo during ORION-1, thus the ORION-3 baseline data (defined as the last available measurement before the first evolocumab administration in ORION-3) was used to assess change in LDL cholesterol, PCSK9, and other efficacy parameters, instead of the baseline data of ORION-1 (unlike the inclisiran-only arm who received inclisiran in ORION-1). Correspondingly, the exploratory endpoints for the switching arm were the percentage and absolute change from ORION-3 baseline in LDL cholesterol, PCSK9, and other efficacy parameters. An additional exploratory endpoint was the safety of transitioning from evolocumab (mAb) to inclisiran on the day 360 visit.

LDL cholesterol percentage change averaged for each year of the open-labeled extension phase was also evaluated (post-hoc analysis).

Statistical analysis

There was no formal sample size calculation for this study. Data collected were summarised by treatment arm (inclisiran-only arm and switching arm) using descriptive statistics, graphs, or raw data counts, or combination of these metrics, as appropriate. Categorical variables were summarised using numbers and percentages. Percentages were based on the number of patients in the analysis set for whom there was non-missing data, unless otherwise specified. Continuous variables, including changes from baseline of ORION-1 or ORION-3 (inclisiran-only and switching arm respectively), were summarised using descriptive statistics. For the primary endpoint, mean and 95% CI for the percentage change and p value are reported (inclisiran-only arm); for secondary and exploratory efficacy endpoints, 95% CIs for the mean, median, or proportion are provided. The p value for the primary endpoint was based on the t-test for the null hypothesis of mean=0. CIs for the mean were constructed by inverting the t-test statistic, CIs for the median were constructed using the distribution-free method based on binomial probabilities, and CIs for the proportion used Blaker's method. Safety analyses are descriptive and reported as counts and proportions.

As a post-hoc analysis, the mean percentage change from ORION-1 baseline in LDL cholesterol concentration averaged over time for modified ITT (mITT; all patients who received at least one dose of study drug and for whom both baseline and the day 210 follow-up LDL cholesterol concentration measurements were available) population in the inclisiran-only arm were analysed for the entire 4-year duration of ORION-3 and for each of the 4 years. The average over time was calculated as the arithmetic mean of the least squares means at each study visit, estimated using a mixed-effects model for repeated measurements which included study visits as the fixed effect. For the switching arm ITT population, the same was analysed from ORION-3 baseline for year 1, the 3-year period from year 2 to year 4, and each of the last 3 years.

Analyses for the inclisiran-only arm were performed in the ITT and the mITT population; mITT was the primary population used for presentation whenever available. All patients who received at least one dose of inclisiran were included in the safety analysis (safety population). All analyses were performed with SAS software (version 9.4). ORION-3 is registered with ClinicalTrials.gov, NCT0360577.

Role of the funding source

The ORION-3 trial was initiated by The Medicines Company, which was subsequently purchased by Novartis. Novartis continued the ORION-3 trial through to completion. Data analyses were performed by Novartis and a designated external service provider in accordance with the statistical analysis plan prepared by a qualified statistician.

Results

The first patient visit for ORION-3 occurred on March 24, 2017, recruitment continued until Nov 22, 2017, and the last patient visit was on Dec 17, 2021. In the blinded, placebo-controlled ORION-1 trial, 370 patients received inclisiran and 127 received placebo. Of those patients in the inclisiran arms, 290 of 370 agreed to continue into the twice-yearly inclisiran-only open-labelled extension arm for 4 years. In the placebo arms, 92 of 127 agreed to continue the trial and to first have evolocumab twice-monthly for 1 year and then twice-yearly inclisiran for 3 years (switching-arm). Of these, 233 (80%) in the inclisiran-only arm and 80 (87%) in the switching arm completed the full 4-year study

observation period. The ITT population comprised 382 patients (inclisiran-only and switching arm) and of these, the mITT population comprised 277 patients in the inclisiran-only arm and 88 patients in the switching arm. The primary reason for discontinuation irrespective of treatment arm was the withdrawal of consent (25 of total 57 discontinuations in the inclisiran-only arm and five of total 12 discontinuations in the switching arm; appendix p 6).

Patient demographic and clinical characteristics are summarised in table 1. Overall, the mean age of patients in the study was 63·0 years (SD 11·0), 64% (n=243) were men, 94% (n=356) were White, 4% (n=15) Black or African American, 1% (n=4) American Indian or Alaska Native, and 1% (n=4) Asian. The mean baseline LDL cholesterol was 3·33 (SD 1·30) mmol/L for the inclisiran-only arm and 3·17 (1·35) mmol/L for the switching arm (table 1). In the inclisiran-only arm, during the open-label extension phase, there were 1045·5 patient-years of exposure to inclisiran resulting in a total cumulative exposure to inclisiran starting from the beginning of ORION-1 through to the end of ORION-3 of 1209·6 patient-years. In the switching arm, the exposure to inclisiran was 250·2 patient-years.

In the inclisiran-only arm, LDL cholesterol concentrations at day 210 were –1·56 (95% CI –1·68 to –1·44) mmol/L reflecting a reduction of 47·5% (95% CI –50·7 to –44·3; p<0·0001 [approximately 570 days after first inclisiran exposure in ORION-1]). The percentage change in LDL cholesterol over time in the inclisiran-only arm is shown in figure 2A and the percentage and absolute changes are shown in table 2. During the 4 years of the open-labeled extension, the mean percentage change and mean absolute change in LDL cholesterol concentrations ranged between –34·3% to –53·8%, and –1·13 mmol/L to –1·76 mmol/L, respectively with upper bounds of 95% CIs at all time points being lower than –30% and excluded zero (figure 2 and table 2). Two injections of inclisiran per year provided annual average reductions in LDL cholesterol of 42·5%, 44·5%, 49·4%, and 45·4% in each year of the open-label extension, and an overall 4-year time-averaged reduction of 44·2% through 9 injections (table 3).

The mean percentage change in PCSK9 concentrations ranged between –62·2% to –77·8% over 4 years in the inclisiran-only arm (appendix pp 7–8). Following the first dose of inclisiran during the open-label extension, the mean percentage change (95% CI) in PCSK9 concentrations 30 days later was –71·8% (–73·2 to –70·4), and was –69·5% (–71·2 to –67·9) at 1440 days with twice-yearly dosing. The percentage and absolute change in PCSK9 concentrations are shown in the appendix (p 8).

The mean percentage change in non-HDL cholesterol and apoB concentrations ranged between –41·7% and –30·0%, and –40·4% and –26·5%, respectively, throughout the study period, with mean absolute change for the same parameters ranging from –1·72 mmol/L to

	Inclisiran-only arm (n=290)	Switching arm (n=92)	Total (n=382)
Characteristics			
Age, years	63·3 (11·1)	61·9 (10·6)	63·0 (11·0)
Age ≥65 years	145/290 (50%)	39/92 (42%)	184/382 (48%)
Female	102/290 (35%)	37/92 (40%)	139/382 (36%)
Male	188/290 (65%)	55/92 (60%)	243/382 (64%)
White	271/289 (94%)	85/91 (93%)	356/380 (94%)
Black or African American	10/289 (3%)	5/91 (5%)	15/380 (4%)
American Indian or Alaska Native	3/289 (1%)	1/91 (1%)	4/380 (1%)
Asian	4/289 (1%)	0/91	4/380 (1%)
BMI, kg/m²	29·1 (5·6), n=286	29·7 (4·9), n=91	29·2 (5·4), n=377
Baseline eGFR (mL/min per 1·73 m²)	79·4 (19·0), n=284	81·0 (18·5), n=90	79·8 (18·9), n=374
Baseline of efficacy evaluations*			
PCSK9, µg/L	432·7 (141·8), n=277	413·1 (130·7), n=77	..
LDL cholesterol, mmol/L†	3·33 (1·30), n=277	3·17 (1·35), n=90	..
Medical history and comorbidities‡			
Hypertension	187/283 (66%)	61/90 (68%)	248/373 (67%)
Family history of coronary artery disease	147/257 (57%)	52/82 (63%)	199/339 (59%)
Family history of dyslipidemia	122/231 (53%)	46/76 (61%)	168/307 (55%)
Diabetes mellitus	69/283 (24%)	18/89 (20%)	87/372 (23%)
ASCVD	185/284 (65%)	62/87 (71%)§	247/371 (67%)
ASCVD risk equivalent (high-risk primary prevention)	99/284 (35%)	25/87 (29%)§	124/371 (33%)
Lipid-lowering therapy‡			
Any lipid-lowering therapy	216/284 (76%)	70/90 (78%)	286/374 (77%)
Ezetimibe	84/284 (30%)	31/90 (34%)	115/374 (31%)
Any statin therapy	186/284 (66%)	63/90 (70%)	249/374 (67%)
Atorvastatin (high and moderate intensity)	76/284 (27%)	24/90 (27%)	100/374 (27%)
Rosuvastatin (high, moderate, and low intensity)	47/284 (17%)	13/90 (14%)	60/374 (16%)
Simvastatin (high, moderate, and low intensity)	28/284 (10%)	10/90 (11%)	38/374 (10%)

Data are mean (SD), n/N (%), or mean (SD), n. ASCVD=atherosclerotic cardiovascular disease. BMI=body-mass index. eGFR=estimated glomerular filtration rate. ITT=intention-to-treat. LDL=low-density lipoprotein. mITT=modified intention-to-treat. PCSK9=proprotein convertase subtilisin/kexin type 9. *For the inclisiran-only arm, the efficacy baseline is for the mITT population; for the switching arm, the efficacy baseline is for the ITT population. The inclisiran-only arm uses ORION-1 baseline and the switching arm uses ORION-3 baseline. †To convert mmol/L cholesterol data to mg/dL, multiply each value by 38·67. ‡In the safety population. §87 patients in the switching arm switched to inclisiran on the day 360 visit.

Table 1: **Baseline demographic and clinical characteristics for the ORION-3 study participants**

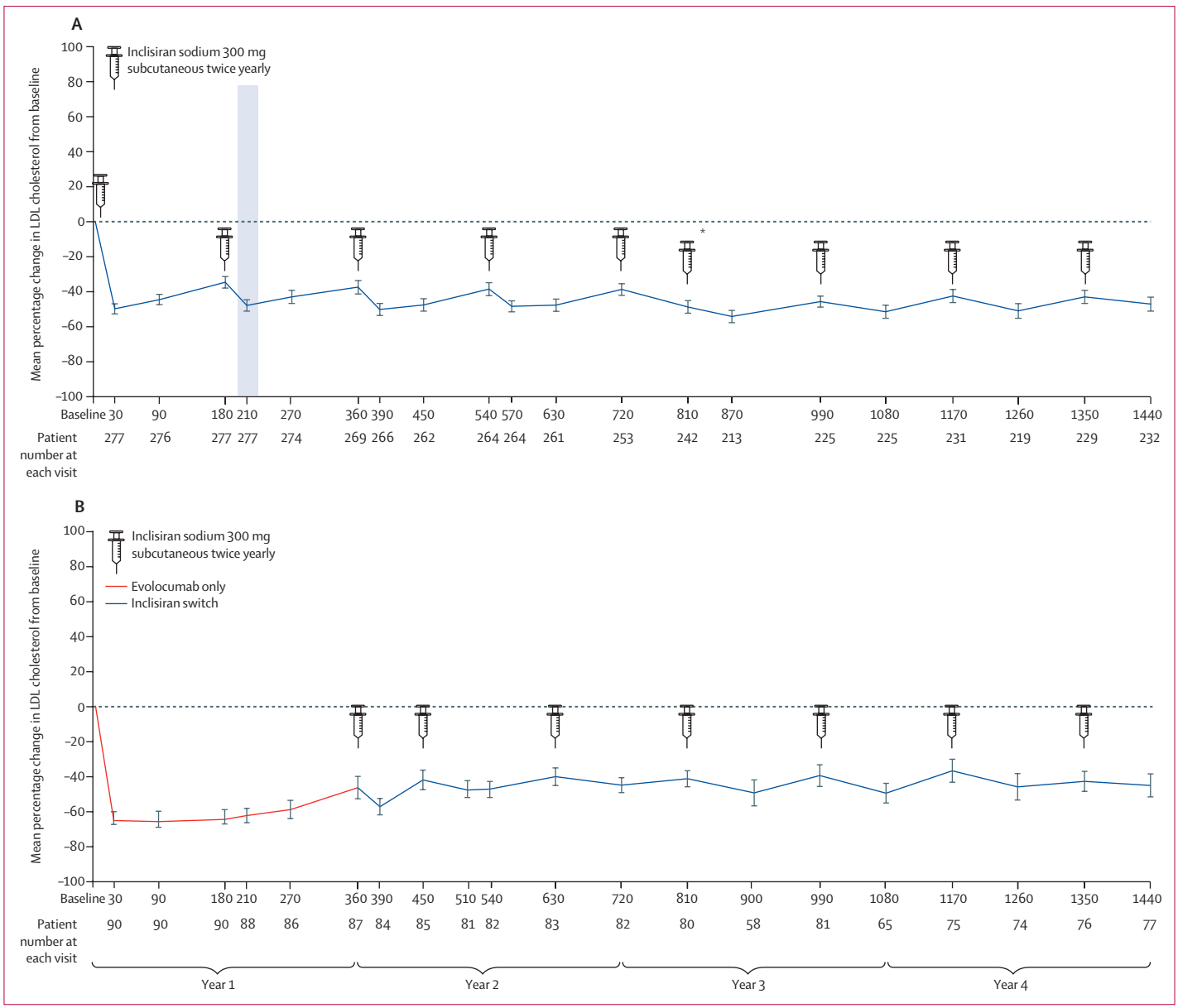

Figure 2: **Mean percentage change in LDL cholesterol (A) from ORION-1 baseline to day 1440 (4 years) of ORION-3 (inclisiran-only arm), and from (B) ORION-3 baseline to day 1440 (4 years) of ORION-3 (switching arm)**

LDL=low-density lipoprotein. *D810 injection was administered as a one-time 90-day dosing interval as per the initial study design for exploratory purposes. (A) The vertical rectangle denotes the primary endpoint at day 210; baseline is representative of ORION-1 baseline; analysis was carried out in the modified intention-to-treat population. (B) Baseline is representative of ORION-3 baseline; the analysis was carried out in the intention-to-treat population.

–1·23 mmol/L, and –42·6 mg/dL to –27·9 mg/dL, respectively (appendix, pp 8–10) with changes observed early and maintained throughout the study. Percentage and absolute change in lipoprotein(a) [Lp(a)], triglycerides, very low-density lipoprotein cholesterol (VLDL cholesterol) calculated, VLDL cholesterol directly measured, and high-sensitivity C-reactive protein (hsCRP) over the study period are shown in the appendix (pp 8–10). Most patients (93%) in the inclisiran-only arm achieved an LDL cholesterol level of less than 2·6 mmol/L at any time point during the study, and 79% of patients achieved LDL cholesterol concentrations of less than 1·8 mmol/L and 62% that of less than 1·3 mmol/L (appendix p 10).

In the switching arm, treatment with evolocumab resulted in percentage LDL cholesterol reductions ranging between 47·8% and 65·7% (figure 2B and table 2) and a time-averaged reduction during that year of 61·0% (95% CI 64·5–57·4) through 25 injections (table 3). After switching to inclisiran, the time-averaged reduction in LDL cholesterol in each subsequent year was

	Inclisiran-only arm (n=277)			Switching arm (n=92)		
	N	Percentage change, % (95% CI)	Absolute change, mmol/L (95% CI)†	N	Percentage change, % (95% CI)	Absolute change, mmol/L (95% CI)†
Day 30	277	−49·4% (−52·3 to −46·6)	−1·62 (−1·73 to −1·51)	90	−65·1% (−68·7 to −61·4)	−1·98 (−2·13 to −1·82)
Day 90	276	−44·2% (−47·1 to −41.2)	−1·44 (−1·55 to −1·34)	90	−65·7% (−70·3 to −61·2)	−2·00 (−2·19 to −1·81)
Day 180	277	−34·3% (−37·6 to −31·0)	−1·13 (−1·24 to −1·02)	90	−64·4% (−68·4 to −60·3)	−2·00 (−2·19 to −1·81)
Day 210	277	−47·5% (−50·7 to −44·3)	−1·56 (−1·68 to −1·44)	88	−63·6% (−67·7 to −59·6)	−1·95 (−2·13 to −1·77)
Day 270	274	−42·6% (−46·4 to −38·9)	−1·42 (−1·55 to −1·30)	86	−60·2% (−65·4 to −55·0)	−1·88 (−2.09 to −1·67)
Day 360	269	−37·1% (−41·0 to −33·3)	−1·24 (−1·36 to −1·12)	87	−47·8% (−54·1 to −41·4)	−1·47 (−1·69 to −1·25)
Day 390	266	−49·8% (−53·2 to −46·4)	−1·63 (−1·75 to −1·51)	84	−58·6% (−63·2 to −53·9)	−1·75 (−1·94 to −1·56)
Day 450	262	−47·2% (−50·7 to −43·7)	−1·55 (−1·67 to −1·43)	85	−43·4% (−48·9 to −37·8)	−1·32 (−1·50 to −1·14)
Day 510	NA	NA	NA	81	−49·1% (−53·4 to −43·8)	−1·45 (−1·62 to −1·28)
Day 540	264	−38·2% (−41·9 to −34·5)	−1·26 (−1·38 to −1·15)	82	−48·6% (−53·4 to −44·3)	−1·45 (−1·61 to −1·28)
Day 570	264	−48·0% (−51·1 to −44·9)	−1·59 (−1·71 to −1·48)	NA	NA	NA
Day 630	261	−47·4% (−50·8 to −43·9)	−1·55 (−1·67 to −1·43)	83	−41·6% (−46·6 to −36·6)	−1·29 (−1·47 to −1·11)
Day 720	253	−38·4% (−41·8 to −35·1)	−1·28 (−1·40 to −1·15)	82	−46·4% (−50·6 to −42·1)	−1·42 (−1·59 to −1·24)
Day 810	242	−48·4% (−51·9 to −44·8)	−1·57 (−1·70 to −1·44)	80	−42·7% (−47·3 to −38·2)	−1·31 (−1·49 to −1·12)
Day 870 or 900‡	213	−53·8% (−57·3 to −50·3)	−1·76 (−1·91 to −1·62)	58	−50·7% (−58·1 to −43·4)	−1·53 (−1·82 to −1·25)
Day 990	225	−45·3% (−48·5 to −42·2)	−1·46 (−1·58 to −1·35)	81	−40·9% (−47·1 to −34·8)	−1·22 (−1·42 to −1·02)
Day 1080	225	−51·1% (−54·8 to −47·4)	−1·64 (−1·78 to −1·50)	65	−50·9% (−56·5 to −45·3)	−1·49 (−1·68 to −1·29)
Day 1170	231	−42·1% (−45·9 to −38·4)	−1·38 (−1·52 to −1·24)	75	−38·2% (−44·7 to −31·6)	−1·20 (−1·43 to −0·98)
Day 1260	219	−50·6% (−54·8 to −46·5)	−1·63 (−1·77 to −1·48)	74	−47·3% (−54·8 to −39·8)	−1·44 (−1·68 to −1·19)
Day 1350	229	−42·6% (−46·4 to −38·9)	−1·39 (−1·53 to −1·25)	76	−44·2% (−49·9 to −38·5)	−1·35 (−1·54 to −1·15)
Day 1440	232	−46·7% (−50·7 to −42·8)	−1·55 (−1·70 to −1·40)	77	−46·5% (−53·0 to −40·0)	−1·46 (−1·71 to −1·22)

Data are n or mean (95% CI). ITT=intention-to-treat. mITT= modified intention-to-treat. NA=not applicable. *For the inclisiran-only arm, data were analysed in the mITT population; for the switching arm, data were analysed in the ITT population. The inclisiran-only arm uses ORION-1 baseline and the switching arm uses ORION-3 baseline. †To convert mmol/L cholesterol data to mg/dL, multiply each value by 38·67. Absolute changes in LDL cholesterol mmol/L are provided up to two decimal points. ‡Day 870 for inclisiran-only arm and day 900 for the switching arm. As per the study protocol, patients in the inclisiran-only arm did not have a day 510 visit, and patients in the switching arm did not have the day 570 visit.

Table 2: **Percentage and absolute change in LDL cholesterol from baseline* by treatment arm and visit day**

47·9% (–51·8 to –44·0), 45·4% (–50·8 to –40·1), and 43·9% (–49·5 to –38·3), respectively, reflecting a time-averaged 3-year LDL cholesterol reduction of 45·3% (–49·7 to –40·9) through 7 injections (figure 2B, table 2 and table 3).

Irrespective of the timing of the switch from evolocumab to inclisiran (staged or concurrent), LDL cholesterol concentrations and PCSK9 reductions on inclisiran were generally similar over years 2–4 (appendix pp 10–12) and similar to the inclisiran-only arm (table 3). Similarly, during years 2–4, changes in other lipids and lipoproteins in the switching arm resembled changes observed with the inclisiran-only arm (appendix pp 12–14). The proportion of patients achieving >50% lowering of LDL cholesterol varied in the switching arm and was higher during evolocumab treatment (appendix pp 14–15).

Over the follow-up period, treatment-emergent adverse events were reported in 275 (97%) of 284 patients in the inclisiran-only arm and 80 (92%) of 87 patients in the switching arm. Although spanning a large array of system categories in a patient population with many comorbidities at baseline, these treatment-emergent adverse events were for the majority, single cases,

	Inclisiran-only arm (n=277)*		Switching arm (n=92)*	
	N	Least squares mean (95% CI)	N	Least squares mean (95% CI)
Year 1	277	−42·5 (−45·3 to −39·7)	90	−61·0 (−64·5 to −57·4)
Year 2	271	−44·5 (−47·6 to −41·4)	87	−47·9 (−51·8 to −44·0)
Year 3	252	−49·4 (−52·5 to −46·3)	84	−45·4 (−50·8 to −40·1)
Year 4	242	−45·4 (−48·9 to −41·9)	80	−43·9 (−49·5 to −38·3)
Year 1–4	277	−44·2 (−47·1 to −41·4)	87	−45·3 (−49·7 to −40·9)†

Data are n or least squares mean (95% CI). ITT=intention-to-treat. LDL=low-density lipoprotein. mITT=modified intention-to-treat. *For the inclisiran-only arm, data were analysed in the mITT population; for the switching arm, data were analysed in the ITT population. The inclisiran-only arm uses ORION-1 baseline and the switching arm uses ORION-3 baseline. †For the switching arm, the time period was year 2–4.

Table 3: **Mean percentage change from baseline in LDL cholesterol averaged over time by treatment group**

	Inclisiran-only arm (n=284)	Switching arm* (n=87)
Patients with ≥1 treatment-emergent adverse event	275 (97%)	80 (92%)
Patients with ≥1 treatment-emergent adverse event possibly related to study drug	79 (28%)	22 (25%)
Patients with ≥1 treatment-emergent serious adverse event	104 (37%)	30 (34%)
Patients with ≥1 treatment-emergent serious adverse event possibly related to the study drug	3 (1%)	1 (1%)
Patients with treatment-emergent adverse event of fatal outcome	7 (2%)	1 (1%)
Patients discontinued study drug due to treatment-emergent adverse event	19 (7%)	5 (6%)
Patients discontinued study drug due to treatment-emergent serious adverse event	12 (4%)	3 (3%)
Patients with ≥1 treatment-emergent adverse event at the injection site	39 (14%)	12 (14%)
Clinically relevant laboratory measurements		
Alanine aminotransferase (U/L)	5 (2%)	1 (1%)
3–5 × upper limit of normal	1 (<1%)	0
5–10 × upper limit of normal	4 (1%)	1 (1%)
10–20 × upper limit of normal	0	0
20 × upper limit of normal	0	0
Alkaline phosphatase (U/L)	3 (1%)	1 (1%)
>2 × upper limit of normal	3 (1%)	1 (1%)
Aspartate aminotransferase (U/L)	8 (3%)	1 (1%)
3–5 × upper limit of normal	6 (2%)	0
5–10 × upper limit of normal	2 (1%)	0
10–20 × upper limit of normal	0	1 (1%)
>20 × upper limit of normal	0	0
Bilirubin (mg/dL)	1 (<1%)	1 (1%)
>2 × upper limit of normal	1 (<1%)	1 (1%)

Data are n (%). UMC=Uppsala Monitoring Centre. *Treatment-emergent adverse events and liver tests after the day 360 visit—ie, after switching to inclisiran. Events related to study drugs are events with a reasonable possibility of a causal relationship between the event and investigational medicinal product, as determined by the investigator following the general principles of causality assessment (as proposed by WHO and UMC as well as the Food and Drug Administration). For alanine aminotransferase and aspartate transaminase, the most severe result for each patient is shown. For the inclisiran-only arm, data were analysed in the safety population; for the switching arm, data were analysed in the safety population who transitioned to inclisiran.

Table 4: **Summary of adverse events and clinically relevant laboratory measurements by treatment arm**

mild-to-moderate in severity, and self-limited. The most common treatment-emergent adverse event was nasopharyngitis (55 [19%] of 284) in the inclisiran-only arm and hypertension (17 [20%] of 87) in the switching arm (appendix pp 15). Treatment-emergent adverse events possibly related to study medication (as determined by the investigator) occurred in 79 (28%) of 284 patients in the inclisiran-only arm and 22 (25%) of 87 patients in the switching arm; most were general disorders and administration site reactions that included injection site pain, injection site reaction, injection site erythema etc (appendix pp 16–17). Three patients (3%) in the switching arm had increases in hepatic enzymes that were felt to be related to the study medication. No new safety signals were detected in either of the transition arms upon switching from evolocumab to inclisiran (appendix p 16). The proportion of patients with at least one treatment-emergent adverse event at the injection site was 14% (39 of 284) in the inclisiran-only arm over the entire 4-year duration of the trial. In the switching-arm, the proportion of patients with at least one treatment-emergent adverse event at the injection site was 8% (seven of 90; appendix p 17) during the first year on evolocumab and 14% (12 of 87) for the 3 years following the transition to inclisiran (appendix p 18).

The incidence of treatment-emergent serious adverse events was 37% (104 of 284) in the inclisiran-only arm and 34% (30 of 87) in the switching arm. A total of eight deaths (2%) were reported during the study, seven deaths (2%) in the inclisiran-only arm and one death (1%) in the evolocumab switched to inclisiran arm: none were considered to be related to the study medication but included a variety of conditions such as COVID-19 infection, respiratory failure, ischemic stroke, coronary artery event as well as aortic aneurysm rupture (appendix p 18). Treatment-emergent serious adverse events possibly related to study drug (as reported by the investigator) occurred in three patients (1%) in the inclisiran-only arm and in one patient (1%) in the switching arm (appendix pp 18–19). These four adverse events included one patient with an accessory pathway-mediated tachycardia considered to be exacerbated by study medication, one acute cholecystitis in a patient known with gallstones, one case of hepatic fibrosis in a patient with fatty liver disease at baseline, and one case of peak increases in alanine aminotransferase (ALT) and aspartate transaminase (AST) greater than than 5 × upper limit of normal in a patient with chronic hepatitis C as well as high alcohol intake. Treatment-emergent hepatic events were carefully examined during the study: 28 (10%) of 284 patients in the inclisiran-only arm and eight (9%) of 87 patients in the switching arm experienced at least one treatment-emergent hepatic event. Aside from the two hepatic treatment-emergent serious adverse events described above, most treatment-emergent hepatic events were increases in liver enzymes reported as mild or moderate in severity. The summary of clinically significant liver chemistry abnormalities is also presented in table 4, and no single case reported in this study met the criteria for Hy's Law.[14]

Discussion

ORION-3 provides the first prospective long-term evaluation of the durability and safety of an siRNA-based therapy to provide clinically meaningful reductions in LDL cholesterol with a convenient dosing schedule. At the primary endpoint day 210 of this study, inclisiran administered by a health-care professional twice-yearly provided sustained reductions in circulating PCSK9 concentrations of 76·4%, which, in turn, resulted in reductions in LDL cholesterol concentrations of 47·5%. In addition, the ORION-3 trial confirmed the durability of reductions in other atherogenic lipids and lipoproteins such as non-HDL cholesterol and apoB over 4 years,

compared to the reductions observed over 6 months and 18 months in previous trials.[10,11,15] Thus, this open-label extension study shows that twice-yearly dosing of an siRNA targeting hepatic PCSK9 synthesis is a feasible therapeutic option by which sustained LDL cholesterol-lowering can be achieved. With 4 years of extended exposure, the most common adverse events in the inclisaran only arm observed were nasopharyngitis reported in 19% of patients and adverse events at the injection site in 14% of patients. In phase 3 trials of 3600 patients, nasopharyngitis and adverse events at the injection site were reported in 7·6% and 5·0% of inclisiran-treated patients, respectively, over 18 months with adverse events at the injection site also common during 8 months of treatment in phase 2 trials (3·8–6·5%).[11]

There are several nuances to the design of this extension trial which were necessary based on the mechanism of action, the long duration of effect of inclisiran, and what was known about inclisiran when this trial was conceived. First, in the inclisiran-only arm, which was an open-label extension of patients who had received different doses of inclisiran in the phase 2 ORION-1 trial, it would have been difficult to establish a true baseline for LDL cholesterol at the start of the open-label-phase since 48% to 65% of patients who had received a single dose of inclisiran sodium and 56% to 83% of patients who had received two doses had at least 20% reduction in LDL cholesterol concentrations at the end of the ORION-1 observation period of 1 year.[16] Thus, the primary endpoint of ORION-3 compared LDL cholesterol concentrations after 210 days of the open-label phase following two inclisiran injections, with LDL cholesterol concentrations at the start of ORION-1 when patients were inclisiran naive. Second, as an open-label extension study, there was no placebo comparator, hence the LDL cholesterol reduction of 47·5% was not corrected for placebo, unlike the pooled analyses of 3600 patients where the placebo-corrected time-adjusted reduction observed was 50·5%.[11] The reductions in LDL cholesterol observed at day 210 of the open-labeled extension phase and maintained up to day 1440 are consistent with reductions in LDL cholesterol in the inclisiran-treated patients over 18 months in the earlier trials prior to placebo correction. Hence the efficacy estimates reported here over 4 years of open-label extension and approximately 5 years of total inclisiran exposure are likely to reflect study design rather than loss of biological efficacy.

A major challenge in controlling any long-term risk factor through a pharmacological approach is adherence to any medication regimen with poor adherence adversely impacting cardiovascular outcomes.[17] First-line and add-on therapies have nearly always been small molecules such as statins, which require daily dosing, with the advantage that if an adverse event occurs, it would probably resolve quickly with discontinuation of the medication. With an increasing understanding of complex biological pathways in cholesterol metabolism, therapies have emerged with novel mechanisms of actions allowing them to be dosed less frequently. First among these approaches were monoclonal antibodies against PCSK9 such as evolocumab self-administered every 2 weeks with a 1 ml injection or monthly with three 1 ml injections or an infusion device. Monoclonal antibodies have been shown to be safe and effective in reducing LDL cholesterol concentrations, by about 60% versus placebo, and to reduce cardiovascular events.[18–20] These treatments bind circulating PCSK9 including hepatic and non-hepatic sources and in long-term extension studies, no loss of efficacy has been observed.[21]

In the switching-arm, open label evolocumab twice-monthly lowered LDL cholesterol concentrations by approximately 61% over 1 year through 25 injections. As would be expected from the biology, after switching to twice-yearly inclisiran in year 2 and onwards, LDL cholesterol concentrations were higher with a time-averaged reduction of approximately 45% over 3 years, achieved through 7 injections, which was similar to the time-averaged reductions in the inclisiran-only arm, suggesting that past exposure or treatment with a mAb against PCSK9 did not alter the efficacy of inclisiran. Two approaches to transition from evolocumab to inclisiran were tested (staged or concurrent), with no meaningful differences observed between the two modalities of inclisiran transition with respect to safety or efficacy, meaning that there are no special considerations when transitioning from evolocumab to inclisiran. This finding is supported by the biology whereby a monoclonal antibody resides in blood, but a GalNAc-conjugated siRNA is rapidly taken up by the liver. As the circulating monoclonal antibody PCSK9 complex are removed from the circulation and the effect of the monoclonal antibody diminishes, these patients transition to lower circulating PCSK9 concentrations through inhibition of hepatic PCSK9 production.

Repeat exposure to inclisiran, which is taken up by the endogenous cytosolic RNA-induced silencing complex in hepatocytes, resulted in sustained lowering of circulating PCSK9 with effects ranging from 62·2% to 77·8% over 4 years, without evidence of any compensatory or escape phenomena resulting in a loss of efficacy in LDL cholesterol lowering with no new safety signals identified. Adverse events at the injection site were predominantly mild or occasionally moderate, resolved without sequelae, and did not worsen with long-term treatment. Hepatic data were consistent with that reported previously with inclisiran versus placebo in phase 3 trials.[10–13] Taken together, the present study provides new data to support the potential use of inclisiran as a convenient approach to provide sustained reductions in LDL cholesterol. Beyond targeting PCSK9 and LDL cholesterol, several siRNA-based therapies using GalNAc modification to enhance hepatic uptake have already been approved, with many more in development.[22–26] Although each of these target different

pathways and long-term safety data will be needed to test for on-target as well as off-target effects, our findings offer promise of infrequent dosing with a good tolerability profile for other siRNA-based therapies in development.

As guidelines evolve and recommend increasingly lower LDL cholesterol targets for those at highest risk, it is sobering to note that implementation of these guidelines remains suboptimal, with many contributing factors, including low use of combination therapies and poor patient-adherence to treatment regimens.[3] Oral medications such as ezetimibe lower LDL cholesterol concentrations by up to 25%, and, more recently, bempedoic acid has been found to lower LDL cholesterol by 18–28% as add-on therapy to statins but require daily dosing.[27] Latest evidence suggests that even if oral medications are optimised, combination therapy with use of a therapy directed against PCSK9 will be required in as many as half of patients for whom an LDL cholesterol goal of 1·4 mmol/L (≤55 mg/dL) or less is recommended.[1,3] ORION-3 was designed before the ESC/EAS lipid guideline update in 2019 recommending ≤1·4 mmol/L (≤55 mg/dL)[28] and so this cut-point was not a prespecified analysis, but instead analysis of the prespecified goal of less than 1·3 mmol/L (<50 mg/dL) showed that at any time point during inclisiran treatment, more than 60% of patients attained these concentrations. Statins, ezetimibe, and bempedoic acid all upregulate LDL receptors, thus lowering circulating LDL cholesterol. Their efficacy is tempered through the opposing effects of circulating PCSK9 on LDL receptor concentration. Combining therapies that lower free PCSK9 concentrations and thus increase LDL receptor concentration together with therapies that increase transcription of LDL receptors offer the opportunity for biological synergy and combined LDL cholesterol reductions approaching 75–80%.[19] At an individual level, with perfect adherence, mAbs against PCSK9 could provide approximately 61% LDL cholesterol lowering annually, but to do so over 4 years would require strict adherence to 104 injections. Taking real world considerations into account, the emergence of siRNA-based therapies offers physicians and patients another method of targeting PCSK9 and LDL cholesterol lowering at the level of the population, whereby nine injections administered by a health-care professional could provide approximately 44% LDL cholesterol lowering over an average of 4 years. Health-care systems and patients would be better served if there were greater availability and uptake of both of these injectable therapies as an adjunct to oral medications to better control LDL cholesterol concentrations.

This study has several limitations. Common to any extension study, patients entered on a voluntary basis, and only patients who completed ORION-1 were eligible for participation. This voluntary enrolment might have potentially introduced a selection bias which should be considered when interpreting the results. Furthermore, patients who tolerated blinded study-drug during the original randomised phase of the study might have been more likely to be adherent long-term to the study protocol. In addition, the absence of a placebo-control arm makes the interpretation of safety difficult in such a high-risk cohort with multiple comorbidities on multiple medications. This study also did not formally provide a randomised comparison between evolocumab and inclisiran but instead used switching to assess ease, safety, and efficacy of treatment transition in a single arm. Formal comparisons of efficacy would require a dedicated 3-arm trial with two active comparator arms and placebo. Finally, it is worth noting that patients in the inclisiran-only arm of ORION-3 received their last injection of inclisiran in ORION-1 at least 9 months to 1 year earlier, and did not receive the normal day 90 dose that is used de-novo to initiate inclisiran. Instead, patients went straight to a 6-monthly maintenance dosing regimen. Although inclisiran is approved for LDL cholesterol-lowering, it has not yet been established whether this approach will result in a reduction in clinical events as has been shown with other therapies targeting PCSK9. Inclisiran is being tested in the ongoing ORION-4 (NCT03705234) and VICTORION-2 Prevent (NCT05030428) trials in this respect. These studies will further provide a greater absolute number of patients exposed to inclisiran, although median follow up will be similar to the present study.

In conclusion, twice-yearly subcutaneous dosing of inclisiran was well tolerated and resulted in sustained and effective reductions in LDL cholesterol and PCSK9 concentrations over 4 years. The findings from the ORION-3 study provide assurance that siRNA-based therapies are safe and have the potential to provide a convenient approach to managing risk factors such as LDL cholesterol lifelong.

Contributors

KKR wrote the first draft of the manuscript and edited subsequent drafts. All authors collaborated in the preparation of the manuscript, contributed to its revision, and approved the final version. KKR, ZT, and XZ directly accessed and verified the underlying data reported, and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors had full access to all the study data and take responsibility for the decision to submit for publication.

Declaration of interests

KKR reports grants from Amgen, Sanofi, Daiichi Sankyo, Regeneron, and Pfizer; consulting fees from Daiichi Sankyo, Silence Therapeutics, Novartis, SCRIBE, CRISPR, VAXXINITY, Cargene, Novo Nordisk, Sanofi, Astra Zeneca, Eli Lilly, Silence Therapeutics, Resverlogix, New Amsterdam, Kowa, Bayer, Amarin, and Esperion; and personal fees from Novartis, Amgen, Viatris, Novo Nordisk, Boehringer Ingelheim, Daiichi Sankyo, Kyrka, and Astra Zeneca. RPTT reports grants from Amgen, Esperion, KOWA, CLS Behring, DalCor Pharma UK, Astra Zeneca, Medtronic, Biotronik, Boehringer Ingelheim, and Celecor Therapeutics. SRW report consulting fees from Boehringer Ingelheim. SV, ZT, XZ, PM, and AL were employed by Novartis at the time of manuscript development. UL reports grants from Novartis; consulting fees from Novartis, Amgen, Sanofi, and Bayer; and personal fees from Novartis, Amgen, Sanofi, Bayer, and Daiichi Sankyo. FLJV and LAL report no competing interests.

Data sharing

Elements of the information presented in this publication are available at ClinicalTrials.gov (NCT03060577). Qualified researchers can request access to patient-level data and related study documents after publication, including the clinical study report, study protocol with any amendments, blank case-report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymised, and study documents will be redacted to protect the privacy of the trial participants.

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