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ORIGINAL RESEARCH

Efficacy and Safety of Inclisiran in Asian Patients

Results From ORION-18

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ABSTRACT

BACKGROUND Management of low-density lipoprotein cholesterol (LDL-C) in Asia remains suboptimal, with ~50% of patients who are treated with lipid-lowering therapies (LLTs) unable to achieve their guideline-recommended LDL-C goals. Asian-representative studies of the use of inclisiran are needed.

OBJECTIVES The authors sought to evaluate the efficacy and safety of inclisiran in Asian patients with atherosclerotic cardiovascular disease (ASCVD) or high risk of ASCVD, as an adjunct to diet and maximally tolerated statin dose, with or without additional LLTs.

METHODS The ORION-18 was a phase 3 double-blind trial in which patients were randomized 1:1 to receive either 300 mg inclisiran sodium or matching placebo on days 1, 90, and 270. Percentage change in LDL-C from baseline to day 330 was the primary endpoint.

RESULTS A total of 345 patients (mean age 59.5 years, mean baseline LDL-C 109 mg/dL, 74.7% male) were randomized to inclisiran or placebo. Baseline characteristics were similar in both groups. The percentage decrease in LDL-C from baseline to day 330 was 57.2% ($P < 0.001$); proprotein convertase subtilisin/kexin type 9 was reduced by 78.3% ($P < 0.001$). Time-adjusted percentage reduction in LDL-C from baseline after day 90 and up to day 360 was 56.3%. At day 330, 71.7% of participants with inclisiran achieved ≥50% reduction in LDL-C compared with 1.5% with placebo. Over the study period, total cholesterol, apolipoprotein B, and non–high-density lipoprotein cholesterol (HDL-C) levels were decreased significantly, and HDL-C levels increased. The incidence of adverse events with inclisiran was similar to that with placebo.

CONCLUSIONS In Asian patients with ASCVD or high risk of ASCVD, inclisiran was effective and safe. (Study of Efficacy and Safety of Inclisiran in Asian Participants With Atherosclerotic Cardiovascular Disease [ASCVD] or ASCVD High Risk and Elevated Low-Density Lipoprotein Cholesterol [LDL-C] [ORION-18]; NCT04765657)
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ABBREVIATIONS AND ACRONYMS

ApoB = apolipoprotein B

ASCVD = atherosclerotic cardiovascular disease

HDL-C = high-density lipoprotein cholesterol

LDL-C = low-density lipoprotein cholesterol

LLT = lipid-lowering therapy

Lp(a) = lipoprotein(a)

mAb = monoclonal antibody

SAE = serious adverse event(s)

siRNA = small interfering RNA

TEAE = treatment-emergent adverse event

According to the World Health Organization (WHO), cardiovascular (CV) disease is the leading cause of death worldwide, with 58% of deaths occurring in Asia.[1,2] Elevated low-density lipoprotein cholesterol (LDL-C) leads to CV disease, and cumulative exposure to elevated LDL-C is causal to atherosclerotic cardiovascular disease (ASCVD).[3,4] LDL-C–lowering therapy has been shown to reduce the risk of CV events.[5]

The Asian Pacific Society of Cardiology consensus recommendations on dyslipidemia recommend LDL-C levels of <1.8 mmol/L and <1.4 mmol/L for high-risk and very-high-risk patients, respectively.[6] However, the management of elevated LDL-C in Asia remains suboptimal, and treatment approaches are limited by patient awareness of CV disease risk, treatment adherence, and health care costs.[6-8] It has been observed that around 50% of the patients undergoing lipid-lowering therapies (LLTs) in Asian countries do not achieve their guideline-recommended LDL-C goals.[9-11]

To appropriately reduce the CV disease risk in Asian patients, novel LLTs are required in addition to existing therapies. Inclisiran, a small interfering RNA (siRNA), inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9) synthesis in hepatocytes and has a long duration of action. It offers a convenient dosing regimen (twice yearly after initial and 3-month doses) for patients who require significant LDL-C lowering.[12-14] Inclisiran also provides consistent LDL-C reduction with long-term use.[15] Unfortunately, Asian patients were not well represented in the clinical program for inclisiran.

ORION-18 (Study of Efficacy and Safety of Inclisiran in Asian Participants With Atherosclerotic Cardiovascular Disease [ASCVD] or ASCVD High Risk and Elevated Low-Density Lipoprotein Cholesterol [LDL-C]; NCT04765657), the first large-scale study for inclisiran in Asia, aims to evaluate the efficacy and safety of inclisiran in Asian patients with atherosclerotic cardiovascular disease (ASCVD) or high risk of ASCVD and elevated LDL-C, as an adjunct to diet and maximally tolerated dose of statins, with or without additional LLTs.

METHODS

STUDY DESIGN AND PARTICIPANTS. ORION-18 was a randomized, placebo-controlled, parallel-group, double-blinded phase 3 study comprising a 2-week screening period and a 12-month double-blinded treatment period (core part of the study) (**Figure 1**). It was conducted across 45 study sites in 4 countries or regions (China, South Korea, Singapore, and Taiwan) (Supplemental Appendix). The study was conducted in accordance with the trial protocol, principles of the Declaration of Helsinki, and the International Council for Harmonization Good Clinical Practice; and it was approved by the institutional review boards of each participating facility. Written informed consent was obtained from each patient before or at screening. The results from the double-blinded treatment period are reported here. ORION-18 will be continued with open-label administration of inclisiran.

Adult patients aged at least 18 years with prevalent ASCVD (including acute coronary syndrome, stable chronic heart disease, post-revascularization, ischemic cardiomyopathy, ischemic stroke, transient ischemic attack, and peripheral atherosclerosis) and serum LDL-C ≥1.8 mmol/L (≥70 mg/dL) or high risk of ASCVD (LDL-C ≥4.9 mmol/L, diabetes, high 10-year ASCVD risk assessed by Chinese ASCVD Risk Assessment Flow Chart, or high risk per local guidelines with a target LDL-C of <100 mg/dL) and serum LDL-C ≥2.6 mmol/L (≥100 mg/dL) were enrolled. Detailed inclusion and exclusion criteria are provided in Supplemental Appendix. Briefly, patients were required to be on the maximally tolerated dose of statins and were excluded if they had any major adverse CV event within the 3 months before randomization, history of homozygous familial hypercholesterolemia, severe concomitant non-CV disease that reduced life expectancy during the trial (<2 years), or active liver disease. Pregnant and lactating women also were excluded from the trial.

RANDOMIZATION AND MASKING. Patients were randomized in a 1:1 ratio to receive either inclisiran or placebo. Randomization was performed with an automated interactive response technology for eligible patients. Patients, investigators, site staff,

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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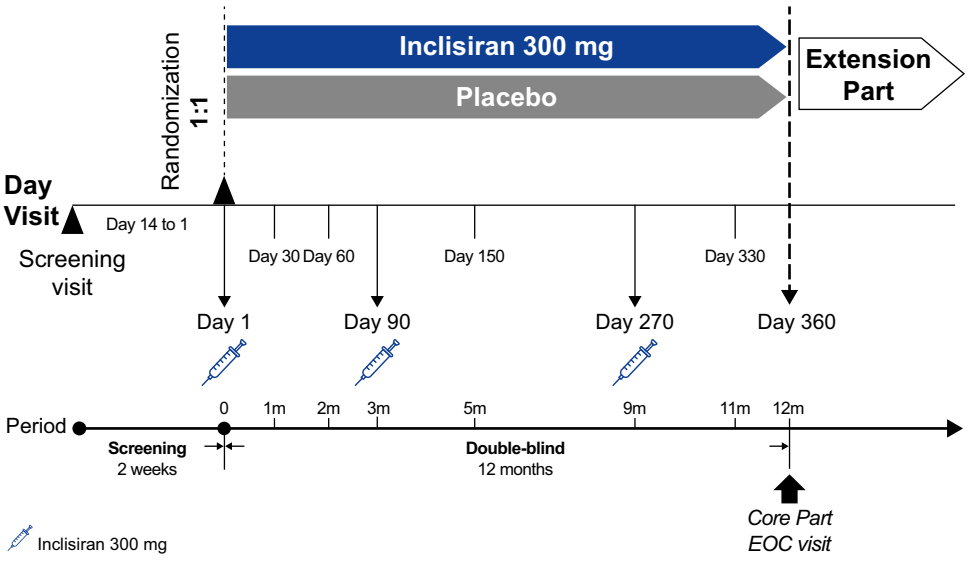
FIGURE 1 Study Design



The core part of ORION-18 comprised a 2-week screening period and a 12-month double-blinded treatment period. The last visit of the core part of the study was on day 360. EOC = end of core.

and the clinical trial team were blinded to the treatment allocation.

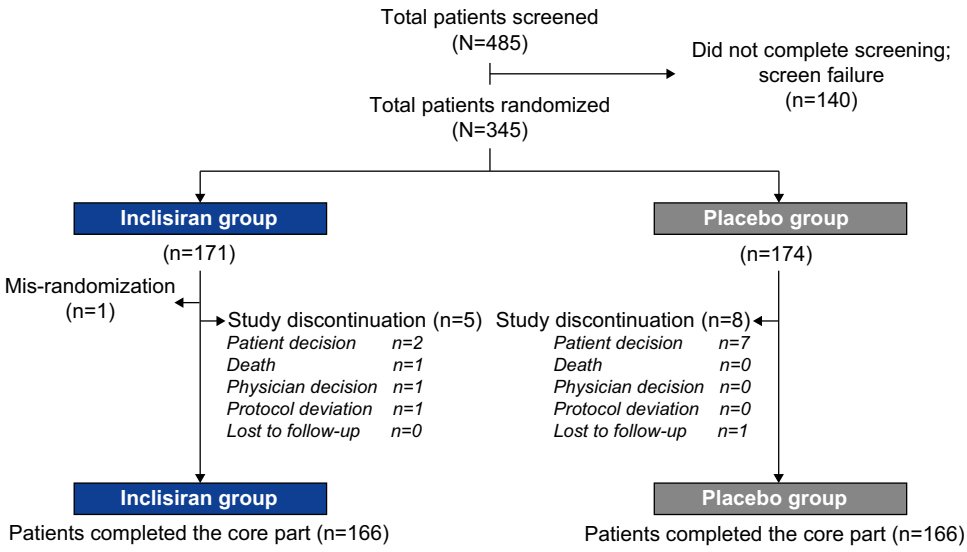
PROCEDURES AND TREATMENT COMPLIANCE. Inclisiran was administered as a single subcutaneous (SC) injection of 300 mg inclisiran sodium (equivalent to 284 mg inclisiran) in a 1.5 mL solution through a prefilled syringe at days 1, 90, and 270, and patients were required to maintain their background LLTs. The last patient visit was on day 360. Placebo was also administered as an SC injection via a prefilled syringe on days 1, 90, and 270. Study treatment was administered at designated study visits at the study site by qualified personnel. All efficacy parameters were laboratory assessments analyzed at a central laboratory. Samples were obtained at prespecified time points. Participants were required to be in a fasted state for at least 10 hours before efficacy laboratory assessments.

OUTCOMES. The primary endpoint of the trial was the percentage change in LDL-C from baseline to day 330. Key secondary endpoints included time-adjusted percentage and absolute change in LDL-C from baseline after day 90 and up to day 360; absolute change from baseline to day 330 in LDL-C; percentage and absolute change from baseline to day 330 in PCSK9, other lipids, and lipoproteins; and proportion of patients reaching LDL-C levels of <25 mg/dL, <50 mg/dL, and <70 mg/dL at day 330. Other secondary endpoints included proportion of patients in each group with ≥50% LDL-C reduction from baseline at day 330, proportion of patients in each group who attained global lipid targets for their level of ASCVD risk at each scheduled visit (day 330), and safety and tolerability (adverse events, laboratory abnormalities, and serious adverse events [SAEs], with their severity and relationship to study treatment) of inclisiran.

SAMPLE SIZE CALCULATION. Assuming a within-treatment-group SD of 30% for the percentage change from baseline in LDL-C and a dropout rate of 5%, a sample size of 320 participants was determined to provide >90% power for a between-treatment difference of 30% at a 1-sided significance level of 0.025. This planned sample size was also based on the consideration to collect additional safety data.

STATISTICAL ANALYSIS. Data analysis was performed by the sponsoring company. The full analysis set comprised all patients randomized to the study (intent-to-treat population). Efficacy variables were analyzed for the full analysis set. Patients who received at least 1 dose of the study treatment were included in the safety analysis (safety set). Patients who discontinued prematurely for treatment in the core part continued to be followed in the study unless informed consent was withdrawn. For baseline demographics and disease characteristics, categoric variables were summarized as n (%) and continuous

FIGURE 2 Disposition of Study Participants



After a 2-week screening period, 345 patients were randomized to receive either 300 mg SC inclisiran sodium or placebo; 166 patients in both groups completed the study. N = number of patients in the study population within the treatment group, regardless of data availability; n = number of patients with available data/records/measurements for a particular evaluation. One patient was misrandomized in the inclisiran group and was therefore excluded from the analysis.

variables summarized descriptively with nonmissing observations. Mixed model for repeated measures (MMRM) analyses was used for the primary endpoint in which the response variable was the LDL-C percentage change from baseline, with treatment, visit, and treatment-by-visit interaction as fixed-effect factors and baseline LDL-C as a covariate. The analysis included all scheduled visits from day 60 to day 360. The adjusted mean within a treatment group and adjusted mean difference between treatments and the related 95% CIs and *P* values from this model are reported. The primary objective would be achieved if the null hypothesis was rejected at the 1-sided significance level of 0.025. The same MMRM models were used for the key secondary endpoints and other continuous secondary endpoints, from which the adjusted means and mean differences within/between treatments were reported for these endpoints. Nominal 2-sided *P* values also were provided. Owing to the skewed distribution of lipoprotein(a) [Lp(a)], data were log-transformed before using the MMRM model. Specifically, the log-transformed ratio [ratio of post-baseline Lp(a) to baseline Lp(a)] was calculated for each scheduled visit from day 60 to day 360. These endpoints were then analyzed in the MMRM model as response variableswith treatment, visit, and treatment-by-visit interaction as fixed-effect factors and log-transformed baseline Lp(a) as a covariate. The estimates and related 95% CIs for each group and for the difference between groups (inclisiran minus placebo) were presented in back-transformed values. Other binary secondary efficacy endpoints were analyzed separately with the use of frequencies and percentages by visit and treatment group. The estimates and the 95% CIs were provided for the proportion differences (inclisiran minus placebo). Safety analyses are descriptive and reported as n (%).

RESULTS

The first patient visit for the core part of ORION-18 occurred on March 1, 2021; the last patient visit was on July 8, 2022. In total, 345 patients were randomized to receive either 300 mg SC inclisiran sodium (equivalent to 284 mg inclisiran) or placebo after a 2-week screening period. Among the randomized patients, 171 patients received inclisiran and 174 patients received placebo. A total of 97.1% of patients (n = 166) in the inclisiran group and 95.4% (n = 166) in the placebo group completed the core part of the study. Patient disposition is shown in **Figure 2**. The median duration of treatment exposure over the follow-up duration of 360 days in both groups was 363.0 days.

Patient demographic and clinical characteristics are summarized in **Table 1** and were well balanced

between the inclisiran and placebo groups. The mean age of patients was 59.5 ± 10.9 years, 74.7% were male, and 74.7% were Chinese. The mean baseline LDL-C levels for patients in the inclisiran and placebo groups were 108.8 ± 38.3 mg/dL and 109.1 ± 42.3 mg/dL, respectively (**Table 1**).

At day 330, the placebo-adjusted percentage change in LDL-C level from baseline was −57.2% ($P < 0.001$) and the absolute change was −60.5 mg/dL ($P < 0.001$) (**Figure 3**). Variability in the percentage change in LDL-C from baseline to day 330 among patients is shown in a waterfall plot in Supplemental Figure 1. The percentage and absolute change in LDL-C level from baseline for all study visits are presented in Supplemental Table 1. Similar results favoring inclisiran were observed in all subgroups analyzed (Supplemental Figure 2). The time-adjusted percentage and absolute change in the LDL-C level from baseline from day 90 and to day 360 were −56.3% and −59.0 mg/dL, respectively ($P < 0.001$ for both), compared with placebo (Supplemental Table 2). The efficacy of inclisiran treatment in terms of time-adjusted percentage and absolute LDL-C change from baseline after day 90 and to day 330 was consistent across all subgroups (Supplemental Figure 3). Similar results were seen for absolute LDL-C change from baseline to day 330 for all subgroups (Supplemental Figure 4).

The placebo-adjusted percentage change in PCSK9 from baseline to day 330 was −78.3% ($P < 0.001$). The mean difference in the percentage change in PCSK9 levels ranged from −66.5% to −83.3% over the study period between the inclisiran and the placebo groups. Both the percentage and absolute change in PCSK9 levels are presented in Supplemental Table 3. Over the study period, inclisiran treatment significantly decreased the levels of total cholesterol by 33.0%, apolipoprotein B (ApoB) by 42.3%, and non-high-density lipoprotein cholesterol (non-HDL-C) by 47.4% from baseline ($P < 0.001$ for all). At day 330, levels of HDL-C were significantly increased from baseline by 9.1% ($P < 0.001$). There were no significant changes in triglyceride levels. The absolute changes in total cholesterol, ApoB, non-HDL-C, HDL-C, and triglycerides were consistent with the percentage changes (**Figure 4**, Supplemental Table 4). At day 330, the descriptive median percentage and absolute changes in Lp(a) in the inclisiran group were lower than that of the placebo group (Supplemental Table 5). The ratio of Lp(a) to baseline levels was approximately 41% lower in the inclisiran group than in the placebo group at day 330 ($P < 0.001$) (**Figure 5**, Supplemental Table 6). At day 330, the majority (80.7%) of patients in the inclisiran group attained an LDL-C level of <70 mg/dL; in the placebo group, that target was achieved by 15.7% of patients. Similarly, the numbers of patients achieving the LDL-C target goals of <50 mg/dL and <25 mg/dL were higher in the inclisiran group than those in the placebo group

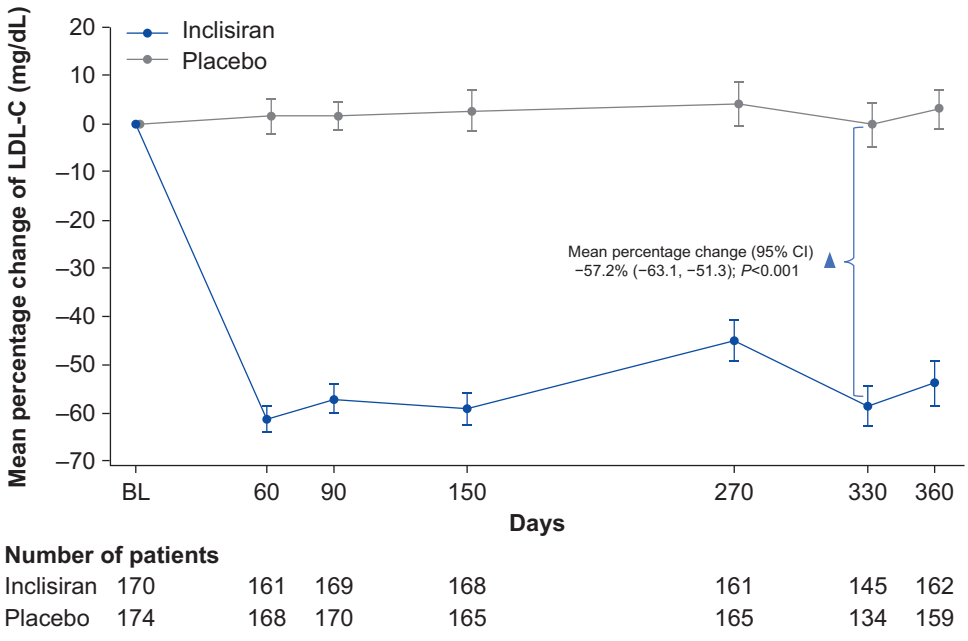
TABLE 1 Baseline Demographics and Clinical Characteristics for the ORION-18 Study Participants

	Inclisiran (n = 170)	Placebo (n = 174)	Total (n = 344)	*P* Value
Age, y	58.8 ± 11.2	60.1 ± 10.5	59.5 ± 10.9	0.236
Age group				0.335
<65 y	114 (67.1)	107 (61.5)	221 (64.2)	
≥65 y	56 (32.9)	67 (38.5)	123 (35.8)	
Sex				0.536
Female	40 (23.5)	47 (27.0)	87 (25.3)	
Male	130 (76.5)	127 (73.0)	257 (74.7)	
Race				0.962
Asian	170 (100.0)	174 (100.0)	344 (100.0)	
Nationality				
Chinese	126 (74.1)	131 (75.3)	257 (74.7)	
Indian	2 (1.2)	1 (0.6)	3 (0.9)	
Korean	41 (24.1)	42 (24.1)	83 (24.1)	
Body mass index, kg/m^2	26.2 ± 3.5	26.1 ± 3.1	26.1 ± 3.3	0.778
Smoking history, yes	100 (58.8)	93 (53.4)	193 (56.1)	0.370
eGFR, mL/min/1.73 m^2	85.1 ± 17.9	83.4 ± 19.6	84.2 ± 18.8	0.421
Baseline eGFR group, mL/min/1.73 m^2				0.125
≥30 to <60	10 (5.9)	15 (8.6)	25 (7.3)	
≥60 to <90	89 (52.4)	104 (59.8)	193 (56.1)	
≥90	71 (41.8)	55 (31.6)	126 (36.6)	
Baseline of efficacy evaluations				
PCSK9, ng/mL	458.0 ± 208.0	436.6 ± 113.9	447.2 ± 167.2	0.238
LDL-C, mg/dL	108.8 ± 38.3	109.1 ± 42.3	109.0 ± 40.3	0.935
Triglycerides, mg/dL	138.9 ± 90.1	142.3 ± 73.4	140.6 ± 82.0	0.705
Medical history and comorbidities				
Hypertension	111 (65.3)	112 (64.4)	223 (64.8)	0.947
History of coronary artery disease	75 (44.1)	78 (44.8)	153 (44.5)	0.981
History of dyslipidemia	16 (9.4)	19 (10.9)	35 (10.2)	0.776
HeFH	17 (10.0)	19 (10.9)	36 (10.5)	0.918
Diabetes	71 (41.8)	74 (42.5)	145 (42.2)	0.973
ASCVD status				0.372
ASCVD	163 (95.9)	162 (93.1)	325 (94.5)	
ASCVD risk equivalent (high risk primary prevention)	7 (4.1)	12 (6.9)	19 (5.5)	
LLTs				
Use of other LLTs	55 (32.4)	60 (34.5)	115 (33.4)	0.761
Use of statin therapy	168 (98.8)	168 (96.6)	336 (97.7)	0.284
Statin intensity[a]				0.311
None/low	3 (1.8)	8 (4.6)	11 (3.2)	
Moderate	49 (28.8)	46 (26.4)	95 (27.6)	
High	118 (69.4)	120 (69.0)	238 (69.2)	

Values are mean ± SD or n (%). Fisher exact test was used for nationality and use of statin therapy, chi-square test for other categoric variables, and 2-sample Student's *t*-test for continuous variables. [a]High intensity: atorvastatin 40-80 mg, rosuvastatin 20-40 mg; moderate intensity: atorvastatin 10 to <40 mg, rosuvastatin 5 to <20 mg, pitavastatin 2-4 mg, lovastatin 40-80 mg, fluvastatin ≥80 mg, simvastatin 20-40 mg, pravastatin 40-80 mg; low intensity: pitavastatin 1 mg, lovastatin 10 to <40 mg, fluvastatin 20 to <80 mg, simvastatin 5 to <20 mg, pravastatin 10 to <40 mg.

ASCVD = atherosclerotic cardiovascular disease; eGFR = estimated glomerular filtration rate; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; PCSK9 = proprotein convertase subtilisin/kexin type 9.

FIGURE 3 Primary Endpoint



Placebo-adjusted mean percentage change in low-density lipoprotein cholesterol (LDL-C) from baseline to day 330 was −57.2% (95% CI: −63.1% to −51.3%; $P < 0.001$) with inclisiran.

(Supplemental Table 7). At day 330, 71.7% of patients in the inclisiran group achieved ≥50% reduction in LDL-C level, compared with 1.5% in the placebo group (Supplemental Table 8). At day 330, 69.7% of patients in the inclisiran group attained their global LDL-C goals (<55 and <70 mg/dL for patients with ASCVD and high risk of ASCVD, respectively), compared with 6.0% in the placebo group (**Figure 6**).

Over the study period of 1 year, treatment-emergent adverse events (TEAEs) were reported in 73.5% of patients in the inclisiran group and 66.7% patients in the placebo group (**Table 2**). The majority were mild to moderate in nature. Severe TEAEs were reported in 4.7% (n = 8) and 2.3% (n = 4) in the inclisiran and placebo groups, respectively (Supplemental Table 9). No trends in TEAE incidence were observed. The most common TEAEs (≥5%) in both treatment arms were diabetes mellitus, increased blood creatinine phosphokinase, inadequate control of diabetes mellitus, upper respiratory tract infection, urinary tract infection, and insomnia (Supplemental Table 9). TEAEs related to study drug (as determined by the investigator) occurred in 11.8% and 10.3% in the inclisiran and placebo groups, respectively (**Table 2**). In the inclisiran group, the most common drug-related TEAEs were injection-site pain, abnormal hepatic function (increase in aspartate transaminase and/or alanine transaminase by <3× upper limit of normal), and increased body weight (1.2% for all 3 TEAEs). There was a higher incidence of TEAEs at the injection site in the inclisiran group compared with the placebo group (2.9% vs 0.6%) (**Table 2**, Supplemental Table 10). However, all of these were mild in nature and the majority resolved without sequelae. In the placebo group, the most common TEAE related to study drug was increased blood creatine phosphokinase (2.3%) (Supplemental Table 10). The incidence of serious TEAEs was 16.5% and 9.8% in the inclisiran and placebo groups, respectively (**Table 2**). There were no serious TEAEs related to the study medication.

One death due to acute myocardial infarction was reported in the inclisiran group, which was not considered to be related to inclisiran treatment. TEAEs associated with hepatic safety were balanced between the treatment groups (inclisiran group: 12.4%; placebo group: 10.9%). A summary of clinically significant liver chemistry abnormalities is presented in **Table 2**.

DISCUSSION

The ORION-18 study demonstrated that 300 mg SC inclisiran sodium was well tolerated and exhibited

FIGURE 4 Percentage and Absolute Change in Other Efficacy Parameters From Baseline

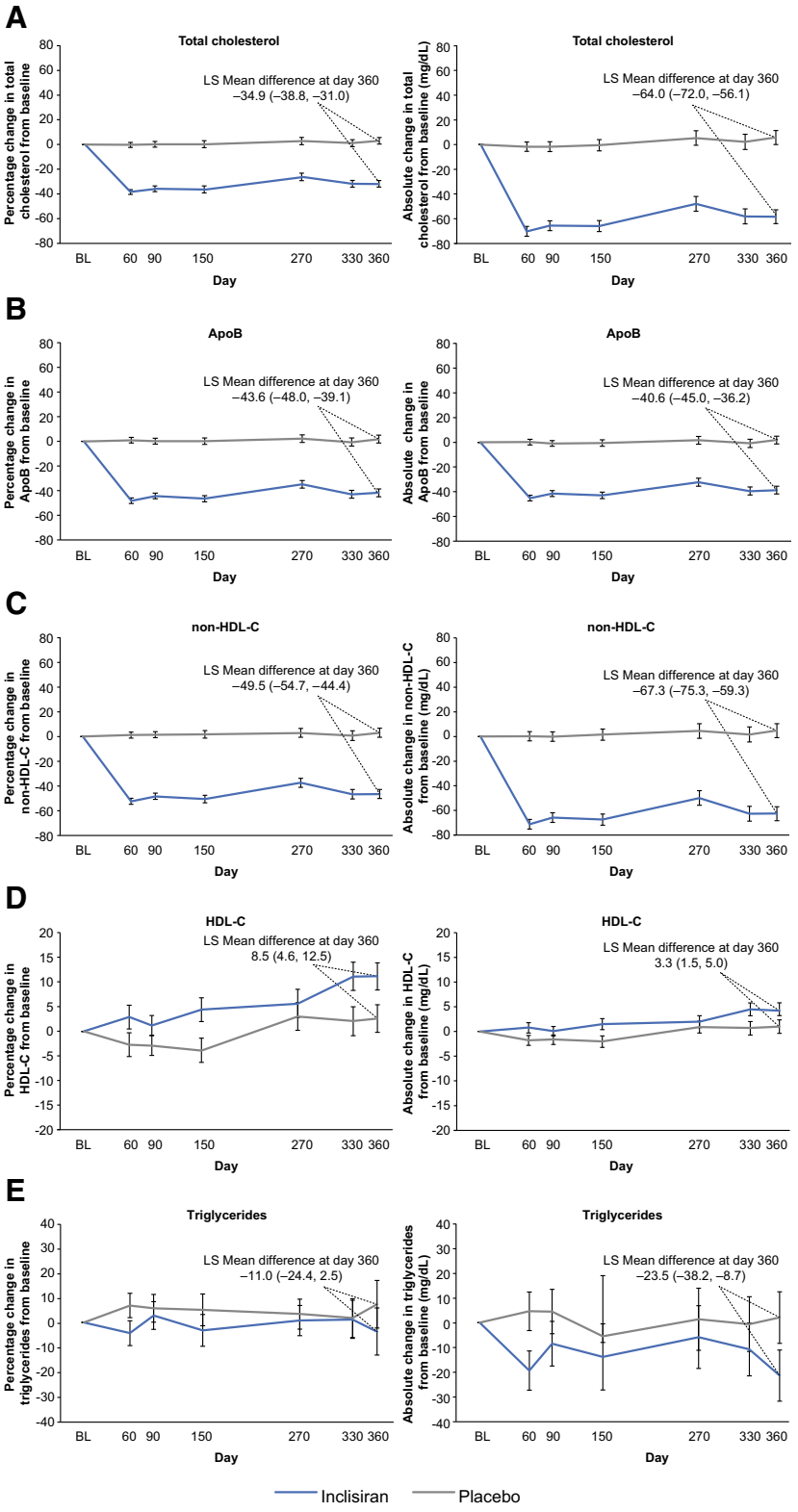


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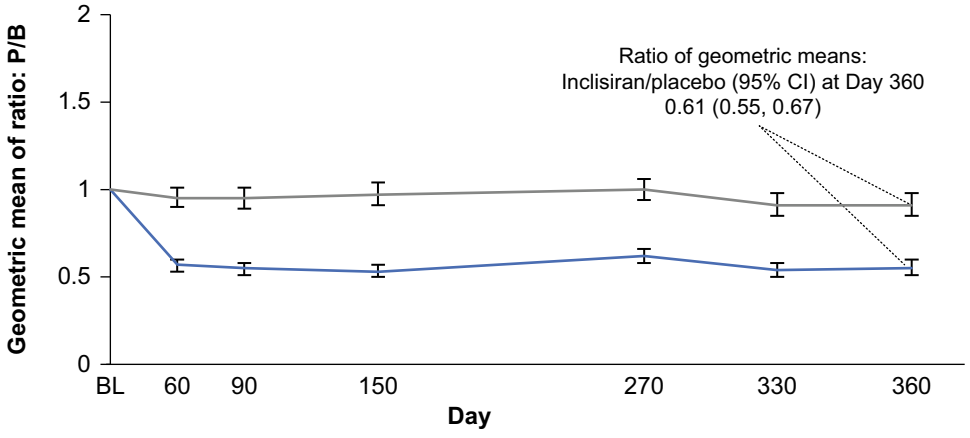
FIGURE 5 Geometric Mean of Lipoprotein(a) Ratio to Baseline From Day 60 to 360



The ratio of geometric means for inclisiran:placebo at day 360 is 0.61 (95% CI: 0.55-0.67; $P < 0.001$). Data are presented as geometric mean (95% CI). BL = baseline; P/B = post-baseline/baseline.

consistent and effective reductions in LDL-C levels over 12 months in Asian patients with ASCVD or high risk of ASCVD and elevated LDL-C, including those with heterozygous familial hypercholesterolemia, as an adjunct to diet and maximally tolerated statins with or without additional LLTs. ORION-18 is the first large-scale study for inclisiran in Asia, and the results are consistent with the global studies.[12-14]

The results of this study showed that treatment with inclisiran leads to a placebo-adjusted percentage reduction of 57.2% in LDL-C from baseline to day 330. This is consistent with the results of pivotal global trials, which show an LDL-C reduction up to 52% with twice-yearly inclisiran (after the initial and 3-month doses) vs placebo when added to maximally tolerated doses of statins.[13,14]

A pooled analysis of ORION-9, ORION-10, and ORION-11 comprising 3,660 patients showed that the mean placebo-corrected percentage reduction in LDL-C with inclisiran at day 510 was 50.7%.[12] The time-adjusted percentage reduction in LDL-C level from baseline from day 90 to day 360 was 56.3% in this study with twice-yearly SC inclisiran administration; similar results were reported in the pooled analysis, where the LDL-C reduction from baseline from day 90 and to day 540 was 50.5%.[12]

Similarly to the global studies, LDL-C lowering was observed across all subgroups of patients in ORION-18.[13] PCSK9 levels were consistently reduced over the 12-month study period, with a reduction of ~70% observed at day 360 in the inclisiran arm, which was consistent with the recently published ORION-3 trial, a long-term safety study for inclisiran.[15] The reductions in other atherogenic lipids and lipoproteins, such as non-HDL-C and ApoB, observed in ORION-18 are in line with those observed in global studies.[12,14-16]

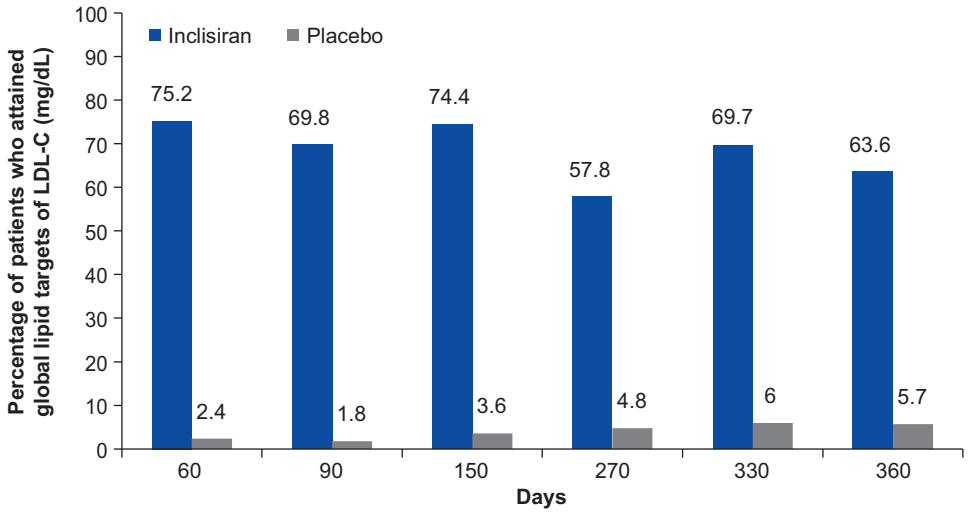
The safety profile of inclisiran reported in ORION-18 is in line with that reported in pivotal trials and in the long-term study with inclisiran.[12,15] Adverse events at the injection site reported in ORION-18 were nonserious, mild, and mostly resolved without sequelae.

ORION-18 was designed before the European Society of Cardiology/European Atherosclerosis Society lipid guideline update in 2019, which recommended an LDL-C level of ≤55 mg/dL (≤1.4 mmol/L), and therefore that cutoff point was not a prespecified analysis in the trial; instead, the analysis of the

FIGURE 4 Continued

Over time, inclisiran treatment significantly decreased the levels of (A) total cholesterol by 33.0%, (B) apolipoprotein B (ApoB) by 42.3%, and (C) non-high-density lipoprotein cholesterol (HDL-C) by 47.4% from baseline ($P < 0.001$ for all). At day 330, levels of (D) HDL-C were significantly increased from baseline by 9.1% ($P < 0.001$). No significant changes in (E) triglyceride levels were observed. The absolute changes in total cholesterol, ApoB, non-HDL-C, HDL-C, and triglycerides were consistent with the percentage changes. Data are presented as mean (95% CI).

FIGURE 6 Attainment of Global Lipid Targets of LDL-C (mg/dL) at Day 330



A total of 69.7% patients in the inclisiran group attained their global low-density lipoprotein cholesterol (LDL-C) goals (<55 mg/dL and <70 mg/dL for patients with atherosclerotic cardiovascular disease (ASCVD) and high risk of ASCVD, respectively) compared with 6.0% in the placebo group.

prespecified LDL-C goal of <50 mg/dL (<1.3 mmol/L) showed that 64.1% of patients achieved this goal at any time point during inclisiran treatment.[17] The European guidelines are consistent with Asian ones, and considering the recommendations of the different professional organizations across Asia, it is worth noting that at the end of the trial, 91.7% and 80.7% of patients in ORION-18 achieved the LDL-C goals of <100 mg/dL (2.6 mmol/L) and <70 mg/dL (1.8 mmol/L), respectively.[5,6,18-25]

Despite statins being the standard of care for lipid lowering, the majority of Asian patients do not achieve their LDL-C goals, as observed in both clinical and observational trials, and might require additional LLTs.[26-29] Anti-PCSK9 monoclonal antibodies (mAbs; alirocumab and evolocumab), which bind to circulating PCSK9, help lower LDL-C by ~60%, are well tolerated, and reduce CV events compared with placebo.[30-34] However, with SC injections every 2 weeks, patient adherence to 13-26 injections per year with anti-PCSK9 mAbs can pose a challenge for treatment compliance.[35]

Inclisiran, a novel siRNA, has recently emerged as an alternative to anti-PCSK9 mAbs, targeting PCSK9 mRNA and preventing the production of PCSK9 protein. Multiple studies have shown that twice-yearly inclisiran (after the initial and 3-month doses) provides effective and consistent LDL-C lowering up to 52%.[12-15] Inclisiran is well tolerated in the long term (4

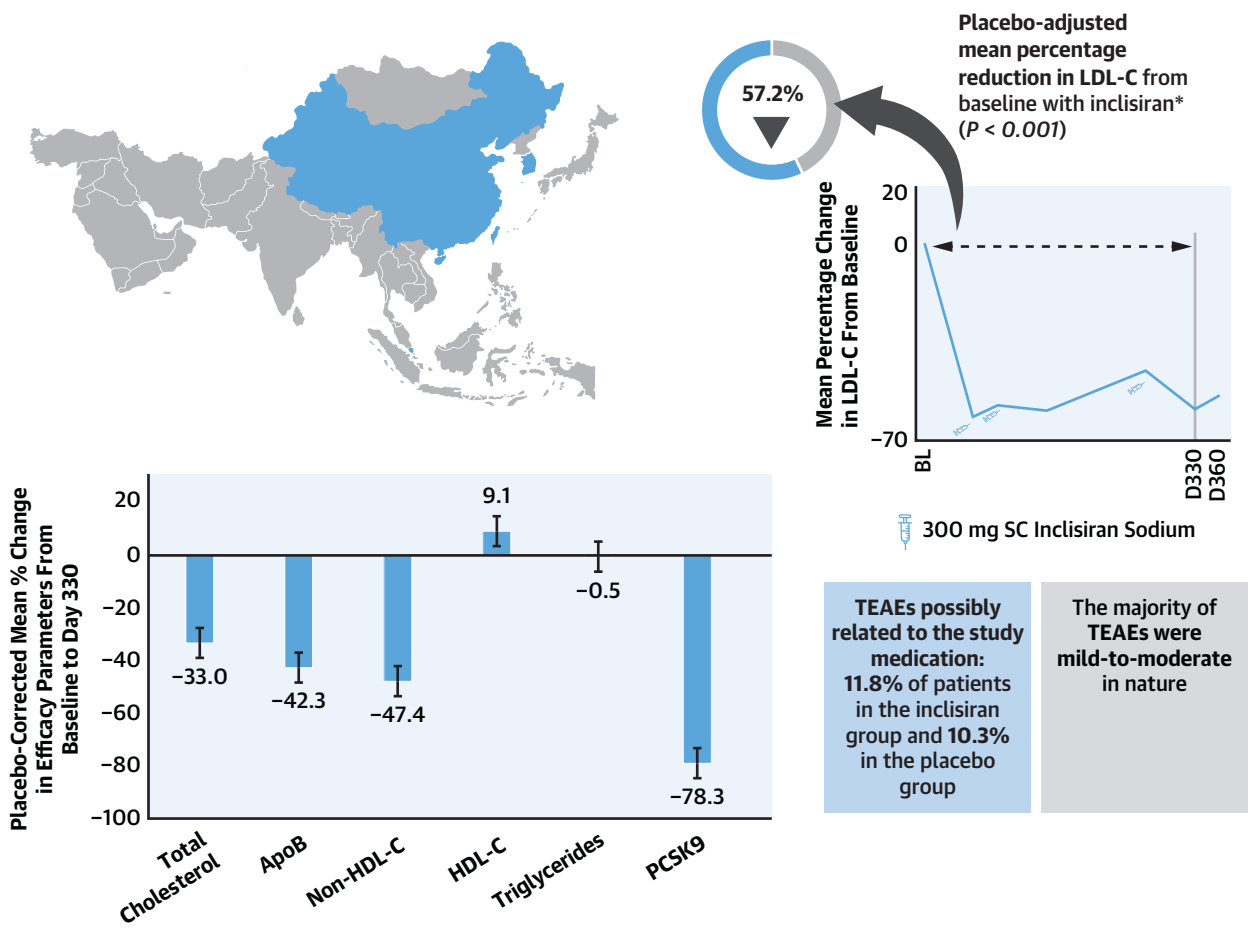
TABLE 2 Summary of Adverse Events and Clinically Relevant Laboratory Measurements by Treatment Arm

	Inclisiran (n = 170)	Placebo (n = 174)
Patients with ≥1 TEAE	125 (73.5)	116 (66.7)
Patients with ≥1 drug-related TEAE	20 (11.8)	18 (10.3)
Patients with ≥1 TESAE	28 (16.5)	17 (9.8)
Patients with ≥1 drug-related TESAE	0	0
Patients with TEAE of fatal outcome	1 (0.6)	0
Patients with drug-related TEAE of fatal outcome	0	0
Patients discontinued study drug due to TEAE	2 (1.2)	2 (1.1)
Patients discontinued study drug due to drug-related TEAE	0	1 (0.6)
Patients with ≥1 TEAE at the injection site	5 (2.9)	1 (0.6)
Clinically relevant laboratory measurements		
Alanine transaminase		
3-5 × ULN	0	1 (0.6)
>5 × ULN	0	0
Alkaline phosphatase		
>2 × ULN	0	0
Aspartate transaminase		
3-5 × ULN	0	1 (0.6)
>5 × ULN	0	0
Bilirubin		
>2 × ULN	0	0

Values are n (%). Events with a reasonable possibility of a causal relationship between the event and investigational medicinal product are drug-related events, as determined by the investigator following the general principles of causality assessment (as proposed by the WHO/Uppsala Monitoring Center as well as the FDA). For alanine transaminase and aspartate transaminase, the most severe result for each patient is shown.

TEAE = treatment-emergent adverse event(s); TESAE = serious treatment-emergent adverse event(s); ULN = upper limit of normal.

CENTRAL ILLUSTRATION **Results From ORION-18**



Huo Y, et al. JACC: Asia. 2024;4(2):123-134.

Efficacy and safety of inclisiran in Asian patients with atherosclerotic cardiovascular disease (ASCVD) or high risk of ASCVD. *Inclisiran is administered at days 1, 90, and 270, and was added as an adjunct to diet and maximally-tolerated statin dose. ORION-18 was conducted across 45 study sites in four countries/regions (China, South Korea, Singapore, and Taiwan). ApoB = apolipoprotein B; BL = baseline; D = day; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; SC = subcutaneous; TEAE = treatment emergent adverse event(s).

years of follow-up), and early insights from a pooled safety analysis suggest potential benefits with inclisiran in the reduction of major adverse CV events.[15,36] In addition, the infrequent dosing schedule of inclisiran is an advantage over anti-PCSK9 mAbs, which might make it able to improve the typical below-par adherence rates for prescribed medications in the developing nations, substantially lessening the health care burden of these nations.[37,38] Therefore, in Asian patients with ASCVD or high risk of ASCVD who require additional LDL-C lowering despite maximally tolerated statins or those who are statin intolerant, twice-yearly inclisiran administration is an effective, well-tolerated, and convenient option as an add-on LLT.

STUDY STRENGTHS AND LIMITATIONS. The observed LDL-C-lowering effect of inclisiran in the ORION-18 study confirms the clinical applicability of the results of the global studies of inclisiran to Asian patients with ASCVD or high risk of ASCVD. The study's inclusion and exclusion criteria ensured that a broad population was included that was representative of the target populations likely to be treated with inclisiran; however, the majority of the participants were of Chinese or other east Asian descent, with limited representation from south or southeast Asia. This

study had few patients with high risk of ASCVD (n = 19), so those data should be interpreted with caution. However, different results are not expected for those patients based on subgroup analyses comparing the ASCVD and high risk of ASCVD populations in the global program.

The follow-up time for the present study was relatively short, given that LLTs are expected to be used for longer periods of time in clinical practice. The open-label extension part of this study will allow for a better understanding of the safety and efficacy of inclisiran in the Asian population over a longer time. The study does not demonstrate the impact of inclisiran in the reduction of CV outcomes, which is currently being studied in CV outcomes trials ORION-4 (NCT03705234) and VICTORION-2 Prevent (NCT05030428), each enrolling ~15,000 participants.

CONCLUSIONS

ORION-18 is the first large-scale study for inclisiran in Asia. The results of this study confirmed that inclisiran may help to minimize long-term exposure to elevated LDL-C over time. Inclisiran was effective and well tolerated in Asian patients with ASCVD or high risk of ASCVD and elevated LDL-C, including those with heterozygous familial hypercholesterolemia, as an adjunct to diet and maximally tolerated statin dose (**Central Illustration**). These results also support a positive benefit-risk profile for inclisiran in these patients.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: Asian patient populations respond differently to a variety of CV medicines, including statins, compared with populations of European descent. This is generally due to polymorphisms in drug metabolism genes that may lead to either poor or extensive metabolizing of the therapeutic drug. Typically in Asians, benefits similar to Westerners are observed at lower statin doses, and studies demonstrate Asian patients to have a "hyper-response" to statins compared with Westerners at the same therapeutic dose. Doses of CV medicines approved in Asian countries are generally similar to those in Western countries, which may increase the risk of adverse events in Asian patients.

TRANSLATIONAL OUTLOOK: The results of this study show that inclisiran administered at the same dose used in the global studies (in predominantly Western populations) has similar efficacy and safety in Asian patients who are at an increased risk of CV disease, with consistent LDL-C lowering.

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KEY WORDS ASCVD, Asia, inclisiran, LDL-C lowering, lipid-lowering therapies, PCSK9, siRNA

APPENDIX For a list of the study countries/regions and patient eligibility criteria as well as supplemental figures and tables, please see the online version of this paper.

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