Effect of 1 or 2 Doses of Inclisiran on Low-Density Lipoprotein Cholesterol Levels
One-Year Follow-up of the ORION-1 Randomized Clinical Trial

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IMPORTANCE Sustained reductions in low-density lipoprotein cholesterol (LDL-C) with lipid-lowering therapies that require frequent dosing are reliant on patient adherence, and poor adherence is associated with worse clinical outcomes.

OBJECTIVE To determine whether inclisiran, a small interfering RNA, reduces mean LDL-C exposure with an infrequent dosing regimen.

DESIGN, SETTING, AND PARTICIPANTS Prespecified analysis of a randomized, double-blind, placebo-controlled multicenter phase 2 clinical trial. Participants were followed up monthly for LDL-C levels and proprotein convertase subtilisin-kexin type 9 (PCSK9) measurements as well as safety until their LDL-C levels had returned to within 20% of their change from baseline (maximum 360 days). The study included patients with elevated LDL-C despite maximally tolerated statin therapy. Data were analyzed between January 11, 2016, and June 7, 2017.

INTERVENTIONS One dose (200, 300, or 500 mg on day 1) or 2 doses (100, 200, or 300 mg on days 1 and 90) of inclisiran sodium or placebo.

MAIN OUTCOMES AND MEASURES Duration of time to return to within 20% of change from baseline for LDL-C levels and time-averaged LDL-C reductions over 1 year.

RESULTS At baseline, among the 501 participants, 65% were men (n = 326 of 501), mean age was 63 years, 6% had familial hypercholesterolemia (n = 28 of 501), and 69% had established ASCVD (n = 347 of 501). Baseline LDL-C was 128 mg/dL among 501 randomized participants. The percentage of participants who were followed up to day 360 because their LDL-C levels had not returned to within 20% of their change from baseline ranged from 48.3% to 65.0% for those receiving a single dose and between 55.9% and 83.1% of those receiving 2 doses, with similar effects observed for PCSK9. Time-averaged reduction in LDL-C levels over 1 year after a single dose ranged from 29.5% to 38.7% (P < .001 between groups) and from 29.9% to 46.4% (P < .001 between groups) for those who received 2 doses. The 2-dose 300-mg regimen produced the highest proportion of responders at day 360 and the greatest mean reduction in LDL-C over 1 year. Incidence of adverse events was similar through to 1 year.

CONCLUSIONS AND RELEVANCE Treatment with inclisiran resulted in durable reductions in LDL-C over 1 year. Inclisiran may offer a novel approach to LDL-C reduction with the convenience of infrequent dosing.

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Convergences of data from cohorts, mendelian randomization studies, and randomized clinical trials demonstrate that low-density lipoprotein cholesterol (LDL-C) is not only a causal factor for atherosclerotic cardiovascular disease (ASCVD) but that the cumulative exposure to LDL-C during an individual’s lifetime is a major driver of ASCVD. Hence, lifelong LDL-C reductions from genetic variants confer a larger relative protection against ASCVD than similar reductions in LDL-C achieved with therapies initiated later in life with a shorter duration of exposure. Statins are the first-choice treatment for achieving LDL-C goals with the intensity of therapy being matched to the level of risk to achieve sustained reductions and thus lower cumulative exposure to LDL-C. Many patients who fail to achieve LDL-C goals require additional lipid-lowering therapies ranging from small molecules, such as ezetimibe, which require daily dosing or monoclonal antibodies that require a twice to once monthly dosing regimen. Add-on lipid-lowering therapy places an additional medication burden on the patient. In many areas of health care, higher medication burden has been associated with lower compliance with therapeutic regimens. Further, at least for small molecules that require daily dosing, adherence is associated consistently without comes. 

Inclisiran is an investigational small interfering RNA that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9) synthesis in the liver and has a long duration of action, which may offer a convenient dosing regimen for patients who require significant LDL-C lowering. We have previously reported that a single dose of 300 mg of inclisiran sodium reduced LDL-C by 38.4% at 180 days of follow-up and a 2-dose starting regimen of inclisiran reduced it by 52.6%. Monthly follow-up in this phase 2 trial, ORION-1, continued for up to 1 year. The objective of this prespecified analysis was to describe the mean reduction in LDL-C exposure over 1 year with single-dose or 2-dose regimen of inclisiran, the within-individual variability in LDL-C, and the persistence of the therapeutic effect at 1 year, as well as overall safety.

Methods

Patient Population and Protocol

The design of the ORION-1 trial protocol has been reported in detail previously. Briefly, ORION-1 was a randomized, double-blind, placebo-controlled phase 2 clinical trial to evaluate the efficacy, safety, and tolerability of different doses of inclisiran (eFigure 1 in the Supplement). Eligible participants had either a history of ASCVD with LDL-C higher than 70 mg/dL (to convert to millimoles per liter, multiply by 0.0259) or ASCVD risk equivalents (eg, type 2 diabetes or familial hypercholesterolemia) with LDL-C higher than 100 mg/dL despite maximally tolerated statin therapy. Patients were randomly assigned to a single dose of inclisiran sodium, 200, 300, or 500 mg, or placebo on day 1 or 2 doses of inclisiran sodium, 100, 200, or 300 mg, or placebo on day 1 and day 90.

The primary efficacy end point of ORION-1 was the percentage change in LDL-C from baseline to day 180. Participants whose LDL-C had not returned to within 20% of their change from baseline had additional monthly follow-up visits until this level had been reached up to a maximum of 360 days. A prespecified secondary end point was the duration of time to return to within 20% of their change from baseline for LDL-C and PCSK9. At each visit, LDL-C and PCSK9 levels, adverse events, and safety laboratory assessments were collected. The protocol and written informed consent documents were approved by the institutional review board or independent ethics committee for each clinical site.

Outcome Assessments

All plasma samples were obtained in a fasting state and analyzed using the laboratory analytical methods described previously at Medpace Reference Laboratories, certified by the Lipid Standardization Part III Program of the US Centers for Disease Control and Prevention–National Heart, Lung, and Blood Institute (NHLBI). The LDL-C levels were measured using β quantification. The PCSK9 levels were measured using enzyme-linked immunosorbent assay.

Adverse events data, vital signs, clinical examinations, electrocardiograms, and laboratory values were obtained for all participants who received at least 1 dose of study drug until the last visit. Laboratory parameters included hematological parameters, renal function, liver function tests, and creatine kinase. Adverse events were classified as mild, moderate, or severe by the investigator with the use of standard Medical Dictionary for Regulatory Activities terms and according to system organ class.

Statistical Analysis

The prespecified secondary study end point of duration of time to return to within 20% of change from baseline LDL-C was visually represented as waterfall plots for each individual in the trial. Additionally, we report the proportions of individuals who at day 360 had not returned to within 20% of their change from baseline LDL-C and PCSK9 after receiving inclisiran. The reduction in LDL-C at day 360 vs baseline was assessed quantitatively for statistical significance using paired t tests. In a post hoc analysis, we calculated the mean percentage change in LDL-C and PCSK9 over the entire first year for each of the dosing groups as the mean of the reductions observed monthly over 1 year. To estimate the mean percentage change...
change in LDL-C potentially achievable with a twice-yearly dosing regimen, we additionally calculated the mean LDL-C reduction over the immediate 6 months following a second dose of inclisiran. Because absolute LDL-C reductions drive clinical benefit of lipid-lowering therapies, we calculated the median number of months that either a single or 2 doses of inclisiran provided LDL-C reductions of at least 39 mg/dL or at least 58 mg/dL up to a maximum of 1 year, which is when follow-up ended. Where appropriate, LDL-C measurements of patients who had returned to within 20% of their change from baseline LDL-C (and therefore no longer had available LDL-C values) were imputed with their individual baseline values. Hence, the primary analyses reported (Figures 1 and 2) provide conservative estimates, using imputed data where appropriate. For comparison, a per protocol analysis including only participants who completed all study-related measures at day 270 and at day 360 (responders) was performed as a sensitivity analysis and is reported separately only as text.

To assess interindividual variation in response at day 360, waterfall plots of individual percentage changes in LDL-C levels were created for those who had not returned to within 20% of the change from baseline at day 330 and thus returned for a final visit. To assess the effect of a single or 2 doses of inclisiran vs placebo on month-to-month variability in LDL-C levels as a reflection of usual LDL-C exposure for inclisiran vs placebo, we created box-and-whisker plots of on-treatment LDL-C levels (each box represents a patient’s median and interquartile range [IQR] of LDL-C throughout the study, and whiskers represent the patient’s maximum and minimum observed LDL-C values). However, because placebo-treated participants were only followed up until day 210, box-and-whisker plots reflect each participant’s repeated measure at days 30, 60, 90, 120, 150, 180, and 210. For convenience, we provide data on the 300-mg single or 2-dose regimens of inclisiran sodium and matching placebo.

We also performed a post hoc evaluation of adverse event frequencies during the extended follow-up period. Adverse event rates are presented for the overall safety population (all participants who received at least 1 dose of inclisiran or placebo).

Continuous variables were summarized using means and standard deviations or medians and IQR. Categorical variables at baseline were expressed as counts and percentages. Time courses are presented as means and 95% confidence intervals. Analyses were performed using SAS software, version 9.2 and higher (SAS Institute), with a P value of less than .05 considered significant using a 2-sided test.

The data points are means, and the bars indicate 95% confidence intervals. Where appropriate, LDL-C measurements of patients who had returned to within 20% of their change from baseline LDL-C (and therefore no longer had available LDL-C values) were imputed with their individual baseline values.

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Original Investigation Research

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Reduction of PCSK9 and LDL-C Over Time

The time courses of percentage change in PCSK9 and LDL-C were observed with the 2-dose starting regimen of 300 mg.

Time-Averaged Biomarker Reductions Over 1 Year

The time-averaged reductions in PCSK9 levels from day 30 to day 360 ranged from 15.4% to 21.6% at day 360 (Figure 1B; P < .001 for all groups at day 360). In the 2-dose group, the percentage reduction in PCSK9 ranged from 17.5% to 29.7% at day 360 (Figure 1A), with corresponding reductions in LDL-C ranging from 15.4% to 21.6% at day 360 (Figure 1B; P < .001 for all groups at day 360). In the 2-dose group, the percentage reduction in PCSK9 ranged from 15.8% to 37.7% at day 360 (Figure 1B), and reductions in LDL-C ranged from 12.6% to 31.4% at day 360 (Figure 1B; P < .001 for all groups at day 360 from baseline). The greatest reductions in PCSK9 and LDL-C were observed with the 2-dose starting regimen of 300 mg.

Persistence of LDL-C and PCSK9 Reductions

Time taken to return to within 20% of change from baseline LDL-C following a single dose or 2 doses of inclisiran is shown as waterfall plots in Figure 3. At day 180, among patients who received at least 1 dose of study drug and had both the baseline and the 180-day follow-up LDL-C assessment available, the percentage of patients who had a persistent response (ie, had not returned to within 20% of change from baseline LDL-C level) ranged between 90.0% (n = 54) and 100.0% (n = 60) and between 96.6% (n = 57) and 100.0% (n = 59) following a single dose or 2 doses of inclisiran. At day 330, the corresponding figures were 60.0% to 75.0% and 69.5% to 86.3% of those receiving a single dose or 2 doses, respectively. The duration of time to return to within 20% of change from baseline LDL-C was dose dependent and at day 360, most participants still had not returned to within 20% of their change from baseline LDL-C and PCSK9 levels (eTable 2 in the Supplement). eFigure 2 in the Supplement shows waterfall plots of individual percentage change in LDL-C levels at day 360.

Durability of Absolute Reductions

Patients maintained an LDL-C reduction of at least 39 mg/dL from baseline for a median of 6 to 9 months (P < .001 for 500 mg vs 200 mg) with a single dose and from 5 to 10 months with 2 doses of inclisiran (P < .001 for 100 mg vs 300 mg) (eTable 3 in the Supplement). In the study cohort, an LDL-C reduction of at least 39 mg/dL from baseline was maintained from 2 to 5 months (P = .002) for 500 mg vs 200 mg and between 1 to 6 months (P < .001 for 300 mg vs 100 mg for those receiving a single dose or 2 doses of inclisiran) (eTable 3 in the Supplement).

Individual Variability

Month-to-month variation in LDL-C levels between day 30 and day 210 for every patient who received either placebo or a
300-mg dose of inclisiran sodium as a single dose or 2 doses on day 1 and day 90 are shown in Figure 4 as the median, IQR, and minimum—maximum and maximum—measured LDL-C levels during the treatment window. One dose of 300 mg of inclisiran sodium administered on day 1 or 2 doses on days 1 and 90 appeared in general to not only reduce LDL-C levels more than placebo but to maintain lower LDL-C levels consistently despite the infrequent dosing regimen.

**Sensitivity Analyses**

In the sensitivity analyses (ie, including only patients with available measurements), reductions in LDL-C at day 270 and day 360 in the single-dose groups ranged between 25.3% and 32.4% and between 29.8% and 28.4%, respectively. In the 2-dose groups, the corresponding reductions ranged between 25.2% and 43.4% and between 17.6% and 33.8%, respectively. The time-averaged LDL-C reductions over 1 year ranged between 31.6% and 39.8% in the single-dose groups. For the 2-dose groups, the time-averaged LDL-C reductions over 1 year ranged between 31.0% and 46.8%.

**Rationale for Dosing Interval for Phase 3 Studies**

The greatest reduction in LDL-C appeared to occur with the 300-mg 2-dose regimen. Following the second 300-mg injection at day 90, the percentage reduction in LDL-C at day 270 was similar to the reduction at day 90 after a single dose. The reduction in LDL-C between day 90 and day 270 after a single or 2 300-mg doses is shown in eFigure 3 in the Supplement. For the single dose, the mean reduction in LDL-C declined predictably but steadily, with a time-averaged LDL-C reduction between days 90 and 270 of 39%. Among those, given the second dose at day 90, the time-averaged reduction over the same period was 50% (P value for comparison <.001).

**Safety and Tolerability**

Adverse event rates are shown in eTable 4 in the Supplement. Adverse event rates in placebo-treated and inclisiran-treated patients were generally similar to the end-of-study visit at day 210 and stable in inclisiran-treated patients during continued follow-up to day 360. There were 2 deaths within the first 210 days that were not attributed to inclisiran by the investigators. There were no further deaths in the 360-day observation window.

**Discussion**

This analysis of the ORION-1 trial extends our prior observations through to 1 year and provides the largest and longest safety data set, to our knowledge, to date for a small interfering RNA in any given therapeutic area. We observed that 1 year after administration of a single dose of inclisiran there was a dose-dependent persistence of response with approximately 50% to 65% of participants not having returned to within 20% of their change from baseline LDL-C. Following a second dose of inclisiran at day 90 the proportion of participants whose response persisted at day 360 increased also in a dose-dependent fashion from 48% (n = 29 of 60) and was highest overall (83%; n = 49 of 59) with the 300-mg 2-dose starting regimen. Notably, the lowest of the 2-dose starting regimen (100 mg) was comparable with the persistence of response observed in the 2 highest single-dose regimens (300 mg or 500 mg).

The mean reduction in PCSK9 levels over 1 year ranged from 44.5% to 55.9% with a single dose and from 43.1% to 60.5% with 2 doses of inclisiran. This translated into a time-averaged reduction in LDL-C levels of 30% and 39% for a single 200-mg and 500-mg injection over 1 year and a 30% and 46% reduction for 100 mg and 300 mg administered at day 1 and day 90. The rate at which LDL-C returned toward baseline was similar after repeated dosing. The 500-mg dose did not materially increase the magnitude or the duration of response compared with 300 mg. In contrast, lower dosing regimens of inclisiran resulted in more modest reductions in

300-mg dose of inclisiran sodium as a single dose or 2 doses on day 1 and day 90 are shown in Figure 4 as the median, IQR, and minimum—maximum and maximum—measured LDL-C levels during the treatment window. One dose of 300 mg of inclisiran sodium administered on day 1 or 2 doses on days 1 and 90 appeared in general to not only reduce LDL-C levels more than placebo but to maintain lower LDL-C levels consistently despite the infrequent dosing regimen.

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PCSK9, proprotein convertase subtilisin-kexin type 9.

FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; index (calculated as weight in kilograms divided by height in meters squared);

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared);

Table. Baseline Characteristics*

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<th>Characteristic</th>
<th>Single-Dose Groups</th>
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<tr>
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<td>Placebo (n = 62)</td>
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<td>200 mg (n = 60)</td>
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Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin-kexin type 9.

Si conversion factor: To convert low-density lipoprotein cholesterol to millimoles per liter, multiply by 0.0259.

* Data reflect the intention-to-treat population (N=501).
time-averaged LDL-C and PCSK9. Hence, the 300-mg dose appears to have the optimal profile. Following the second 300-mg dose at day 90, the median reduction in LDL-C over the following 180 days was 50%. Therefore, it is estimated that following the 2-dose starting regimen of 300 mg administered on days 1 and 90, it should be feasible for maintenance doses of 300 mg to be administered 180 days apart from day 270, which would allow for a twice-a-year dosing regimen after the second dose. This regimen is being evaluated in an ongoing pivotal registration program, which has enrolled approximately 3600 participants (NCT03397121, NCT03399370, and NCT03400800).
We previously reported safety data to day 210. During the additional 150 days of safety follow-up observation through to 1 year, there were no additional deaths observed. The adverse event profile and the incidence of adverse events were similar across placebo-treated and inclisiran-treated participants without notable safety observations through to day 360. With longer exposure, the proportions of events observed at day 360 were not dissimilar to those reported to day 210.

A potential advantage of inclisiran compared with therapies with a shorter duration of action is the relative stability in achieved LDL-C levels over time that can be achieved despite the infrequent dosing regimen. When given in addition to statin therapy, inclisiran could theoretically attenuate short-term fluctuations in LDL-C that may result from intermittent statin use (eg, owing to poor adherence) because those fluctuations will occur from a lower baseline. Variability in LDL-C over time, even among patients prescribed stable doses of high-intensity statins, has been reported and may be associated with poor adherence.10 In our previous analysis of the difference in LDL-C at day 180 as compared with baseline among patients randomized to placebo injections, LDL-C values among individuals who were receiving a stable background dose of lipid-modifying therapy (per protocol prior to study entry) varied considerably. For instance, between these 2 times, among the placebo group, some patients’ LDL-C levels went up by as much as 40% while others’ went down by as much as 40%. About half the placebo group had an LDL-C rise while the other half had a fall, and the mean change (difference) in LDL-C levels over these 2 times in the overall placebo group was approximately zero. Such variability is unlikely to result from natural biological variation among individuals receiving stable dosing regimens and likely to result from variability in adherence between 2 times. Importantly, during a period of 5 or more years of treatment, those with the greatest variability in LDL-C levels have associated worse cardiovascular outcomes.11,12 With each 1 SD increase in visit-to-visit LDL-C variability associated with a 16% increased risk of coronary events independent of achieved LDL-C levels.11 Large observational studies have also shown that greater variations in lipids are associated with higher risk of ASCVD and all-cause mortality.13 Genetic studies and trial data have shown that when scaled for magnitude and duration, the benefit of lowering LDL-C through different pathways is similar. This suggests that benefits depend on LDL-C exposure (reduction) rather than the mechanism by which it is achieved.1,14 It could be speculated that any therapy that conveniently attenuates absolute month-to-
month fluctuations in LDL-C over a long time offers advantages vs regimens that require much more rigorous adherence to treatment regimens to achieve the same. The ongoing ORION-4 cardiovascular outcomes trial (NCT03705234) could provide a hint as to whether the more stable LDL-C reductions produced by inclisiran may yield greater benefit than would be expected for any given reduction in LDL-C at a fixed point in time. Because poor adherence contributes to real-world fluctuations in LDL-C levels and good adherence is often artificially inflated in the context of clinical trials, it will be impossible to draw conclusions about the benefits of an infrequent dosing regimen until real-world evidence becomes available.

Nonstatin lipid-lowering therapies, such as ezetimibe and monoclonal antibodies to PCSK9, improve outcomes when added to statins proportional to the absolute reduction in LDL-C levels and the duration of therapy, with around one-fifth lowering of risk per 39 mg/dL reduction in LDL-C levels.4,14-16 In contrast to these large outcome studies, our study was not powered for outcomes, but we did demonstrate the potential for inclisiran to sustain clinically meaningful reductions in absolute LDL-C levels with an infrequent dosing regimen. A large cardiovascular outcomes trial (NCT03705234) is testing whether lowering LDL-C with inclisiran reduces cardiovascular outcomes.

Limitations

There are several limitations that merit consideration. First, because the placebo group was not followed up beyond day 210, no direct comparisons to placebo can be made at day 360. Second, patients whose LDL-C levels had returned to within 20% of their change from baseline were no longer followed up after day 210, which limits the number of patients with available data. A conservative approach was taken to estimate the effect of inclisiran on LDL-C by assuming that all patients without available measurements had returned to baseline. This assumption did not materially affect the results as demonstrated by the sensitivity analysis, which included only patients with available data (ie, best-case analysis). Notably, all patients in the 300-mg 2-dose group with measurement data at day 240 continued to be followed up through to day 360. Although this analysis extends the observation period to 1 year of follow-up, results from the larger and longer ongoing ORION-9, ORION-10, and ORION-11 trials are required to confirm the findings of this analysis. Finally, further data on longer-term safety, adherence/persistence, and clinical event reduction are required.

Conclusions

In conclusion, a single 300-mg dose of inclisiran sodium provides a mean reduction in LDL-C of 36.6% over 1 year, and a 50% LDL-C reduction in LDL-C can be maintained for at least 6 months after 2 doses of 300 mg at day 1 and day 90. Therefore, inclisiran administered at day 1, day 90, and twice a year thereafter should enable patients to achieve stable and meaningful reductions in LDL-C. The ongoing phase 3 trials of inclisiran will provide longer-term follow-up data in larger numbers of patients.
of inclisiran with the second injection given at 3 months and LDL-C reduction at 6 months following either 1 or 2 injections of inclisiran (with the second injection given at 3 months) and safety data up to 7 months after randomization. For this study, follow-up was extended beyond 7 months for participants who received the active treatment and who had LDL-C levels that had not returned to within 20% of change from baseline at 7 months to assess the durability of response (for all other patients, LDL-C levels were imputed using the baseline LDL-C value). For most participants (49 [83%]) who received the repeated 300-mg dosing regimen, LDL-C levels had not returned to within 20% of their change from baseline at 1 year. Time-averaged LDL-C levels were reduced by 46% using this dosing regimen over the 1-year follow-up period. Presented safety data were limited to absolute numbers of adverse events at 1 year follow-up among those with sustained LDL-C lowering. In line with the 7 months of safety data presented in the original article, the differences in adverse event rates at 1 year between randomized groups were not formally tested. Crude serious adverse event rates among those treated with inclisiran were similar at 0 to 7 months (20 per 100 person-years) and 7 to 12 months (21 per 100 person-years). The safety data were based on only 341 person-years of inclisiran treatment.

The data presented by Ray and colleagues provide a solid basis for the ongoing phase 3 TIMI 63/ORION-4 trial (NCT03705234). This study aims to compare clinical outcomes for 5 years among 15,000 adults with established ASCVD.