**Inclisiran Lowers LDL-C and PCSK9 Irrespective of Diabetes Status: The ORION-1 Randomized Clinical Trial**

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**Running title:** Inclisiran lowers LDL-C in subjects with diabetes

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**Abbreviations**

ASCVD atherosclerotic cardiovascular disease

HDL-C high-density lipoprotein cholesterol

LDL-C low-density lipoprotein cholesterol

LDLR low-density lipoprotein receptors

PCSK9 proprotein convertase subtilisin/kexin type 9

siRNA small interfering RNA

VLDL very low-density lipoprotein cholesterol

**Abstract**

**Objective**

To evaluate the efficacy and safety of inclisiran by diabetes status.

**result design and Methods**

ORION-1 (ClinicalTrials.gov NCT02597127) randomized 501 subjects with ASCVD or ASCVD-risk equivalents, and high LDL-C despite maximally tolerated LDL-C lowering therapies, to 1 or 2 doses of placebo or inclisiran. Levels of lipids and PCSK9 at baseline and day 180 were compared.

**Results**

Inclisiran was associated with marked declines in LDL-C (median -28% to -52%, *P*<.0001 and -28% to -55%, *P*<.005 for all doses in the without and with diabetes groups respectively) and PCSK9. The inclisiran-treated groups also had lower apolipoprotein B, non-HDL-C and lipoprotein (a) but higher HDL-C. Inclisiran had a similar adverse profile to that of placebo, and adverse events were proportionally balanced in the with and without baseline diabetes groups.

**Conclusion**

PCSK9-targeted siRNA-driven strategies may provide a novel therapeutic option for managing dyslipidemia in the presence and absence of diabetes.

**Introduction**

Many individuals at high cardiovascular risk have low-density lipoprotein cholesterol (LDL-C) levels exceeding recommended targets ([1](#_ENREF_1),[2](#_ENREF_2)). Diabetes is a risk factor for atherosclerotic cardiovascular disease (ASCVD), and guidelines underscore timely initiation of appropriately aggressive LDL-C lowering pharmacotherapy in individuals who co-present with diabetes and dyslipidemia ([3-5](#_ENREF_3)).

Although statins remain the cornerstone of LDL-C lowering strategies, maximally tolerated doses of statins are not always sufficiently efficacious even when used with non-statin lipid-lowering agents. The discovery that proprotein convertase subtilisin/kexin type 9 (PCSK9) modulates the degradation of LDL receptors (LDLR) ([6](#_ENREF_6)), and the linking of PCSK9 polymorphisms with serum LDL-C levels and cardiovascular outcomes ([7](#_ENREF_7)) signaled a new era of lipid-lowering options. Novel approaches involving monoclonal antibodies that interfere with PCSK9-LDLR interaction or RNA interference preventing PCSK9 synthesis are associated with substantial LDL-C declines among individuals with suboptimal LDL-C levels despite being on optimal background statin therapy with or without other lipid-lowering agents ([8-13](#_ENREF_8)). Furthermore, interventions targeting PCSK9 have demonstrated cardiovascular benefit in individuals with stable cardiovascular disease ([9](#_ENREF_9),[10](#_ENREF_10)) and recent acute coronary syndromes ([12](#_ENREF_12),[13](#_ENREF_13)) regardless of whether they have diabetes or not ([10](#_ENREF_10),[12](#_ENREF_12)).

Inclisiran is a synthetic small interfering RNA (siRNA) that drives PCSK9-specific mRNA degradation in the liver. The ORION-1 trial (ClinicalTrials.gov NCT02597127) reported that people with ASCVD or ASCVD-risk equivalents along with high LDL-C, despite management with maximally tolerated LDL-C-lowering therapies, had significantly lower LDL-C following inclisiran therapy ([8](#_ENREF_8),[11](#_ENREF_11)). This post hoc analysis evaluated if ORION-1 subjects with and without diabetes at baseline responded differently to inclisiran with respect to changes in lipid profiles, safety and glycemic control.

**research design and Methods**

Details for the ORION-1 trial have been published ([8](#_ENREF_8)). Subjects were randomized to either 1 dose of placebo or inclisiran (200, 300, or 500 mg) on day 1, or 2 doses of placebo or inclisiran (100, 200, or 300 mg of inclisiran on days 1 and 90). For this analysis, the subjects were divided into those with or without diabetes at baseline. The primary efficacy endpoint was the percent change from baseline LDL-C at day 180. Secondary efficacy endpoints included the percent change in lipid measures. Adverse events were documented up to day 210.

**Results**

Of the 501 subjects randomized, 497 received their assigned study agent. A total of 67 had diabetes at baseline (n=25 and 42 for the 1-dose and 2-dose sub-studies respectively) and 415 did not (n=218 and 197 for the 1-dose and 2-dose sub-studies respectively). The baseline clinical characteristics were generally similar between the placebo- and inclisiran-treated groups with minor exceptions. The placebo group tended to have higher body mass indexes and the inclisiran group with diabetes tended to be older. Median HbA1c values in the groups without diabetes were approximately 5.6% (36 mmol/mol) while those in the groups with diabetes ranged between 7.6% (60 mmol/mol) and 8.5% (69 mmol/mol).

Inclisiran treatment was associated with robust reductions in mean LDL-C levels from day 14 until day 210 regardless of baseline diabetes status. The LDL-C nadirs with the 1-dose inclisiran regimens normally occurred at day 30; LDL-C remained significantly below baseline levels at day 180. The groups assigned to the 2-dose inclisiran regimens demonstrated further LDL-C lowering after the second dose of inclisiran. The maximal changes in LDL-C between the baseline visits and those after the second inclisiran doses were greater than those noted for the 1-dose regimens and displayed a slower return to baseline values for up to 210 days.

 Inclisiran therapy was also associated with decreases in total cholesterol, atherogenic apolipoprotein B, non-high-density lipoprotein cholesterol (non-HDL-C), and lipoprotein (a), as well as trend toward increases in HDL-C regardless of baseline diabetes status, or if they were assigned to the 1-dose or 2-dose regimen (Supplementary Table).

There were no clinically meaningful changes in HbA1c 180 days after treatment initiation and this persisted over the course of the study. The overall occurrences of adverse events were similar in subjects with and without diabetes. There were no cases of myopathy and no persistent elevations of liver function tests considered related to inclisiran in subjects with or without diabetes.

**discussion**

We report that, regardless of diabetes status, silencing of the PCSK9 pathway via siRNA technology on a maximally tolerated statin background (1) yields rapid, significant and extended lowering of LDL-C levels with 1-2 injections; (2) improves atherogenic lipid and lipoprotein profiles; (3) is safe and well tolerated including neutral effects on glycemia and inflammatory markers.

The novel approach of using PCSK9-directed monoclonal antibodies provides an option for people who are at very high-risk and who have been unable to achieve their LDL-C goals. Importantly, the available data indicate that the PCSK9 inhibitor strategy, when applied to a statin background, can lower LDL-C by as much as an additional 60% and is associated with clinically significant reductions of cardiovascular events ([9](#_ENREF_9),[13-15](#_ENREF_13)). Enthusiasm for and uptake of PCSK9-directed monoclonal antibodies has, however, been dampened by cost, limited indications for coverage and the need to self-inject every 2-4 weeks.

Rather than targeting the downstream PCSK9 protein like monoclonal antibodies do, inclisiran acts upstream to inhibit PCSK9 synthesis. Inclisiran was associated with sustained declines in LDL-C ([8](#_ENREF_8)) and atherogenic lipoproteins ([11](#_ENREF_11)) that were comparable to those observed with the PCSK9-directed monoclonal antibody evolocumab ([9](#_ENREF_9)). The current analysis extends the primary ORION-1 findings by demonstrating that inclisiran therapy, especially the 2-dose regimens, was associated with substantial and sustained LDL-C reductions in the subjects with diabetes. Our findings that targeting PCSK9 signalling positively alters the lipid profiles of individuals without and with diabetes aligns with the diabetes analysis from the Further cardiovascular Outcomes Research with PCSK9 Inhibition in subjects with Elevated Risk (FOURIER) ([10](#_ENREF_10)) and Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY Outcomes) trials ([12](#_ENREF_12)). Subjects in the FOURIER and ODYSSEY Outcomes trials who were randomized to evolocumab and alirocumab, respectively, exhibited considerable cardiovascular risk reduction regardless of whether they had diabetes or not at baseline ([10](#_ENREF_10),[12](#_ENREF_12)). Whether or not the ORION-1 subjects assigned to inclisiran would also experience diminished cardiovascular risk and if this phenomenon would present in individuals with and without diabetes to the same magnitude as that observed among the FOURIER subjects, remains to be determined.

The main limitation of this analysis is the small numbers of subjects with diabetes in each subgroup which limited the power to make specific conclusions. That said, the sustained reduction in clinically meaningful LDL-C is notable. Given the greater and sustained LDL-C lowering outcome observed with the 2-dose regimens and the fact that the 2-dose 300 mg regimen was at least as effective as the 1-dose 500 mg regimen, the inclisiran dosing regimen in all studies moving forward will be a 300 mg dose administered on day 1, day 90 and then q180days. The use of a twice a year therapy for LDL-lowering on top of a daily statin has the potential for improved adherence and more complete LDL-C goal attainment.

In conclusion, this analysis suggests that inclisiran may be a viable lipid-lowering alternative in people with and without diabetes.

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**Conflicts of Interest.** L. A. L. reports receiving personal fees from The Medicines Company during the conduct of the study, as well as grants and personal fees from Amgen, AstraZeneca, Eli Lilly and Company, Merck, and Sanofi-Regeneron, and grants from Esperion, Kowa, and The Medicines Company. D. K. reports other support from The Medicines Company outside of this submitted work. R. S. W. reports receiving personal fees and non-financial support from The Medicines Company during the conduct of the study, and personal fees and non-financial support from AstraZeneca, Boehringer Ingelheim, and Sanofi-Regeneron outside of this submitted work. U. L. reports lecture or advisory honorary fees from Amgen, Berlin Chemie, The Medicines Company, and Sanofi. P. W. reports other support from The Medicines Company outside of this submitted work. J. J. P. K. reports personal fees from Sanofi during the conduct of the study, as well as personal fees from Affiris, Amgen, Akama, AstraZeneca, Catabasis, Cerenis, Corvidia, CSL-Behring, Cymabay, Esperion, Gemphire, Ionis, Kowa, Madrigal, Novartis, Eli Lilly, Pfizer, Regeneron, Roche, and Sanofi outside of this submitted work. K. K. R. reports receiving personal fees from The Medicines Company during the conduct of the study, as well as grants from Amgen, MSD, Pfizer, Regeneron, and Sanofi, personal fees from Abbvie, Algorithm, Amgen, AstraZeneca, Boehringer Ingelheim, Cerenis, Cipla, Esperion, IONIS, Janssen, Kowa, Lilly, Mylan, Novo Nordisk, Pfizer, Regeneron, Reserverlogix, Sanofi, and Takeda outside of this submitted work. No relevant conflicts of interest exist for H. T.

**Author contributions.** The trial was designed by the study steering committee and the sponsor. The first two authors wrote the first draft of the manuscript. All the authors had full access to the study data, contributed to the interpretation of the data, critically revised the manuscript and approved the final version for submission. L. A. L. is the guarantor of this work and, as such, takes full responsibility for the integrity of the data and the accuracy of the data analysis.

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**Table ― Similar lowering of LDL-C levels between the baseline and day 180 visits for the groups without and with diabetes**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  |  | **Without Diabetes (*N*=415; 86% of Cohort)** |  | **With Diabetes (*N*=67; 14% of Cohort)** |
|   |   |   | ***n* (%)** | **Baseline LDL-C (mmol/L) [Median, IQR]** | **% LDL-C Change (LS mean [95% CI])** | ***P* value vs. Placebo** | ***n* (%)** | **Baseline LDL-C (mmol/L) [Median, IQR]** | **% LDL-C Change (LS mean [95% CI])** | ***P* value vs. Placebo** |
| **1-dose** | **Placebo** |  | 57 (26) | 3.1 (2.5, 3.8) | 2.8 (-2.5, 8.2) | NA | 6 (24) | 2.3 (2.1, 2.9) | -4.3 (-20.9, 12.2) | NA |
| **Inclisiran** | **200 mg** | 53 (24) | 3.1 (2.6, 3.5) | -28.0 (-33.6, -22.4) | <.0001 | 7 (28) | 2.9 (2.7, 3.0) | -27.6 (-42.9, -12.3) | .0670 |
| **300 mg** | 54 (25) | 2.8 (2.2, 3.8) | -36.9 (-42.4, -31.4) | <.0001 | 6 (24) | 2.7 (2.2, 3.4) | -52.0 (-68.5, -35.5) | .0009 |
| **500 mg** | 54 (25) | 3.5 (2.7, 4.4) | -41.4 (-47.0, -35.9)  |  <.0001 | 6 (24) | 3.6 (2.3, 4.3) | -45.8 (-62.3, -29.3) |  .0031 |
| **2-dose** | **Placebo** |  | 52 (26) | 2.8 (2.3, 3.8) |  2.3 (-2.4, 7.1)  |  NA | 9 (21) | 3.3 (3.0, 3.6) | -1.2 (-12.7, 10.3) | NA  |
| **Inclisiran** | **100 mg** | 49 (25) | 3.1 (2.3, 3.8) | -35.1 (-40.0, -30.2)  | <.0001 | 10 (24) | 3.3 (3.0, 3.6) | -37.2 (-48.1, -26.3) | .0001 |
| **200 mg** | 44 (22) | 3.1 (2.3, 4.4) | -43.6 (-48.8, -38.4)  | <.0001 | 16 (38) | 3.0 (2.8, 3.8) | -48.3 (-57.0, -39.7) | <.0001 |
| **300 mg** | 52 (26) | 3.1 (2.5, 4.1) | -52.3 (-57.1, -47.5)  |  <.0001 | 7 (17) | 2.9 (2.5, 4.7) | -55.0 (-68.0, -42.0) |  <.0001 |

Abbreviations: IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; LS, least squares.

Data are presented for the MITT population. Subjects excluded because of missing data at day 180 were as follows: 1-dose regimens, 1 in the placebo group (2%), 2 in the 300 mg inclisiran group (3%) and 6 in the 500 mg inclisiran group (9%); for the 2-dose regimens, 1 in the placebo group (2%), 3 in the 100 mg inclisiran group (5%), 3 in the 200 mg inclisiran group (5%), and 6 in the 300 mg inclisiran group (10%).

LS means from mixed model with treatment, visit, Diabetes(Y/N) and their interactions, and baseline value effects.

*P* values, Dunnett’s one–sided adjusted pairwise comparison vs. Placebo.