Short Report

Efficacy and safety of inclisiran in patients with cerebrovascular disease: ORION-9, ORION-10, and ORION-11

Wolfgang Koenig [a,b,*], Kausik K. Ray [c], Ulf Landmesser [d], Lawrence A. Leiter [e],
Gregory G. Schwartz [f], R. Scott Wright [g], Lorena Garcia Conde [h], Jackie Han [i], Frederick J. Raal [j]

[a] *Deutsches Herzzentrum München, Technische Universität München, DZHK (German Centre for Cardiovascular Research), Partner Site Munich Heart Alliance, Munich, Germany*
[b] *Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm, Germany*
[c] *Imperial Centre for Cardiovascular Disease Prevention, Department of Primary Care and Public Health, Imperial College, London, UK*
[d] *Department of Cardiology, Charité-University Medicine Berlin, Berlin Institute of Health (BIH), DZHK, Partner Site Berlin, Germany*
[e] *Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto, Canada*
[f] *Division of Cardiology, University of Colorado School of Medicine, Aurora, CO, USA*
[g] *Division of Preventive Cardiology and Department of Cardiology, Mayo Clinic, Rochester, MN, USA*
[h] *Novartis Pharma AG, Basel, Switzerland*
[i] *Novartis Pharmaceutical Corporation, East Hanover, NJ, USA*
[j] *Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*

ARTICLE INFO

ABSTRACT

Patients with cerebrovascular disease (CeVD) have been shown to benefit from lipid-lowering therapies, but guideline-recommended levels of low-density lipoprotein cholesterol (LDL-C) are often not attained with statin treatment alone. The ORION-9, ORION-10, and ORION-11 trials evaluated the efficacy and safety of inclisiran in 3660 primary and secondary prevention patients with hyperlipidemia despite maximum tolerated statin treatment. This pooled *post hoc* analysis comprised 202 randomized patients from those trials with established CeVD who had received either 284 mg inclisiran (equivalent to 300 mg inclisiran sodium, $n = 110$) or placebo ($n = 92$) on Days 1, 90, and 6-monthly thereafter up to Day 540. At baseline, mean (SD) LDL-C was 108.4 (34.3) mg/dL and 110.5 (35.3) mg/dL in inclisiran and placebo arms, respectively. Inclisiran produced a mean (95% CI) placebo-corrected percentage change in LDL-C from baseline to Day 510 of –55.2 (–64.5 to –45.9; $p < 0.0001$); the corresponding time-adjusted percentage change from baseline after Day 90 and up to Day 540 was –55.2 (–62.4 to –47.9; $p < 0.0001$). Treatment-emergent adverse events (TEAEs) and TEAEs at the injection site, mostly mild, were more frequent with inclisiran versus placebo (82.7% vs 70.7% and 3.6% vs 0%, respectively). In patients with CeVD, twice-yearly dosing with inclisiran (after the initial and 3-month doses) in combination with maximally tolerated statins provided effective and consistent LDL-C reductions and was well tolerated.

1. Introduction

Hyperlipidemia is a modifiable risk factor for atherosclerotic cardiovascular disease (ASCVD) including stroke [1]. In ischemic stroke survivors, recurrence of stroke and other vascular events remains high, with the reported 5-year risk of recurrence of stroke varying between 9.5%–26% across studies [1–6]. Statins, are the first line treatment for the management of elevated low-density lipoprotein cholesterol (LDL-C) levels, and significantly reduce the risk of cardiovascular events by 22% and stroke by 16% for every 38.7 mg/dL (1.0 mmol/L) reduction in

LDL-C [7,8]. However, suboptimal long-term adherence to statins or other oral lipid-lowering therapy remains a challenge, and ~70% patients on statins fail to achieve guideline-recommended LDL-C goals [9]. With guidelines increasingly advocating for lower LDL-C levels in secondary prevention, combination therapeutic strategies are needed when patients do not attain the specified LDL-C goals [8,9]. Monoclonal antibodies (mAbs) that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9) have been shown to provide further reduction in LDL-C levels when added to statin therapy, and further reduce the risk of future cardiovascular events including stroke but require subcutaneous

injection once or twice per month [10–13].

Inclisiran is a first-in-class small interfering ribonucleic acid (siRNA) therapy that specifically targets PCSK9 mRNA in the liver and reduces PCSK9 protein production. This leads to increased recycling and availability of LDL receptors on the hepatocyte cell surface, thereby decreasing plasma LDL-C [14]. The pivotal Phase 3 studies, ORION-9 (patients with heterozygous familial hypercholesterolemia [HeFH]), ORION-10 (patients with ASCVD), and ORION-11 (patients with ASCVD or ASCVD risk equivalent), comprised a total of 3660 patients, demonstrated that twice-yearly subcutaneous dosing of inclisiran (after initial doses at baseline and 3 months) resulted in significant and consistent reductions in levels of LDL-C and other atherogenic lipoproteins including lipoprotein(a) [Lp(a)], and was well tolerated [15–17].

This pooled *post hoc* analysis evaluated the efficacy and safety of inclisiran in a subgroup of patients with established cerebrovascular disease (CeVD) from the ORION-9, ORION-10, and ORION-11 studies.

2. Methods

2.1. Study design

The ORION-9 (NCT03397121), ORION-10 (NCT03399370), and ORION-11 (NCT03400800) trials were Phase 3, double-blind, randomized, placebo-controlled trials that evaluated the efficacy and safety of inclisiran in patients with elevated LDL-C (≥70 mg/dL for patients with ASCVD, ≥100 mg/dL for patients with ASCVD risk equivalent and those with HeFH) despite receiving maximum tolerated statin therapy. Patients were randomized 1:1 to receive 284 mg inclisiran (300 mg inclisiran sodium) or placebo on Days 1 and 90, and 6-monthly thereafter; they were followed up for 540 days (18 months). Details of the ORION-9, ORION-10, and ORION-11 studies have been published previously [15–17].

2.2. Participants

Patients who had a history of established CeVD (defined as ischemic stroke, carotid artery stenosis by angiography or ultrasound of >70%, or prior percutaneous or surgical carotid artery revascularization) were included in this *post hoc* analysis. History of prior hemorrhagic stroke was not a criterion for inclusion in this subgroup analysis, nor was it an exclusion criterion.

2.3. Endpoints

The co-primary efficacy endpoints included percentage change in LDL-C from baseline to Day 510 and time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540. Key secondary endpoints included absolute change in LDL-C from baseline to Day 510; time-adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540; percentage change from baseline in total cholesterol, non–high-density lipoprotein cholesterol (non–HDL-C), and apolipoprotein B (apoB) to Day 510 and in Lp(a) from baseline to Day 540; proportion of patients achieving prespecified LDL-C thresholds, and overall treatment-emergent adverse events (TEAEs).

2.4. Statistical analysis

The percentage change and absolute change in LDL-C from baseline to Day 510 were analyzed using an analysis of covariance model with a multiple imputation washout model for missing data. The time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 was analyzed by a mixed-effects model for repeated measures (MMRM) with a control-based pattern mixture model for data imputation. Other efficacy outcomes were analyzed using an MMRM without imputation, assuming missing data are missing at random. Statistical tests were performed at a 2-sided 5% alpha level without multiplicity

adjustment.

3. Results

The analysis included 202 patients (*n* = 110 inclisiran arm; *n* = 92 placebo arm) with established CeVD. Baseline demographic and clinical characteristics were generally balanced across both treatment arms (Table 1). The mean ± standard deviation (SD) age of patients was 65.1 ± 8.5 years and 64.2 ± 8.6 years, 48.2% and 45.7% of patients were female in the inclisiran and placebo arms, respectively. At baseline, 90.0% (*n* = 99/110) of patients in the inclisiran arm and 84.8% (*n* = 78/92) in the placebo arm had a history of ischemic stroke(s), 10.9% and 18.5% of patients had carotid artery stenosis, and 13.6% and 17.4% of patients had carotid revascularization, respectively (these categories were not mutually exclusive). Hypertension and diabetes were present in 83.6% and 35.5% of patients in the inclisiran arm, and 90.2% and 32.6% of patients in the placebo arm, respectively. In all, 90.9% and 88.0% of patients in the inclisiran and placebo arms were receiving statins, of whom 69.1% and 69.6% were receiving a high-intensity statin regimen. Ezetimibe was used in 5.5% and 5.4% of patients, respectively. The mean ± SD baseline LDL-C was 108.4 ± 34.3 mg/dL for patients in the inclisiran arm and 110.5 ± 35.3 mg/dL in the placebo arm (Table 1).

Table 1
Demographics and clinical characteristics of patients with CeVD at baseline.

	Inclisiran (*n* = 110)	Placebo (*n* = 92)
Age (years), mean ± SD	65.1 ± 8.5	64.2 ± 8.6
Female, n (%)	53 (48.2)	42 (45.7)
White race, n (%)	94 (85.5)	81 (88.0)
BMI (kg/ m²), mean ± SD	31.0 ± 6.1	30.6 ± 4.8
Lipid modifying therapy, n (%)		
Statin	100 (90.9)	81 (88.0)
High-intensity statin	76 (69.1)	64 (69.6)
Ezetimibe	6 (5.5)	5 (5.4)
ASCVD status, n (%)		
ASCVD	110 (100.0)	92 (100.0)
Medical History, n (%)		
PAD	0 (0.0)	0 (0.0)
CHD	0 (0.0)	0 (0.0)
MI	0 (0.0)	0 (0.0)
CeVD	110 (100.0)	92 (100.0)
CeVD patients: Carotid artery stenosis by angiography or Ultrasound >70%	12 (10.9)	17 (18.5)
CeVD patients: Prior percutaneous or surgical carotid artery revascularization	15 (13.6)	16 (17.4)
Hypertension	92 (83.6)	83 (90.2)
CHF	4 (3.6)	7 (7.6)
Hyperlipidemia	107 (97.3)	85 (92.4)
FH	9 (8.2)	7 (7.6)
Ischemic stroke	99 (90.0)	78 (84.8)
Diabetes	39 (35.5)	30 (32.6)
Smoking	21 (19.1)	14 (15.2)
Lipid measures (mg/dL), mean ± SD		
LDL-C	108.4 ± 34.3	110.5 ± 35.3
Total cholesterol	191.6 ± 42.2	190.3 ± 41.7
Non-HDL-C	138.8 ± 40.3	139.1 ± 37.4
HDL	52.8 ± 17.7	51.3 ± 16.6
ApoB	97.0 ± 23.6	96.5 ± 21.8
Triglycerides	151.5 ± 80.1	142.4 ± 56.1
Lp(a) (nmol/L), median (Q1–Q3)	52.0 (17–157)	31.5 (16–187)
PCSK9 (ng/mL)	382.8 ± 108.8	369.7 ± 123.9

Intention-to-treat population – CeVD only subset.
ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CeVD, cerebrovascular disease; CHF, congestive heart failure; CHD, coronary heart disease; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp (a), lipoprotein(a); PAD, peripheral artery disease; PCSK9, proprotein convertase subtilisin/kexin type 9; SD, standard deviation.

3.1. Efficacy outcomes

The mean percentage change in LDL-C from baseline to Day 510 in patients with CeVD was −45.7% in the inclisiran arm and 9.5% in the placebo arm, resulting in a placebo-corrected difference of −55.2% (95% confidence interval [CI]: −64.5 to −45.9; $p < 0.0001$; Fig. 1A). The time-adjusted percentage change in LDL-C after Day 90 and up to Day 540 was −45.6% with inclisiran and 9.6% with placebo compared with baseline (placebo-corrected difference −55.2%; 95% CI: −62.4 to −47.9; $p < 0.0001$; Fig. 1A).

The corresponding placebo-adjusted absolute change in LDL-C with inclisiran at Day 510 was −56.3 mg/dL (95% CI: −65.6 to −46.9 mg/dL; $p < 0.0001$), and the time-adjusted absolute change from baseline after Day 90 and up to Day 540 was −57.0 mg/dL (95% CI: −64.3 to −49.8 mg/dL; $p < 0.0001$; Fig. 1B).

Decreased levels of total cholesterol, apoB, and non–HDL-C from baseline to Day 510 and Lp(a) to Day 540 were observed in patients in the inclisiran arm compared with placebo ($p < 0.0001$ between-group difference for all parameters; Table 2). In the inclisiran arm, 59.4% of patients with CeVD had ≥50% LDL-C reductions from baseline at Day 510 visit (vs 3.6% in placebo); 59.1%, 70.0%, and 79.1% of patients achieved LDL-C threshold levels <50 mg/dL, <70 mg/dL, and <100 mg/dL at Day 510, respectively.

3.2. Safety outcomes

A higher proportion of TEAEs were reported in patients in the inclisiran arm (82.7%; $n = 91$) versus placebo (70.7%; $n = 65$; risk ratio: 1.17; 95% CI: 1.00 to 1.37). Treatment-emergent serious adverse events (TESAE) were reported in 21 patients (19.1%) with inclisiran and 12 (13.0%) patients in placebo (risk ratio: 1.46; 95% CI: 0.76 to 2.81). None of the TESAEs were considered to be drug related in the inclisiran arm; 1 TESAE in the placebo arm was considered drug related. Overall, when assessed by system organ class or preferred term, no increase in any specific safety event was noted between the treatment arms. TEAEs leading to drug discontinuation were reported in 1 (0.9%) patient in the inclisiran arm and by none in the placebo arm; 4 (3.6%) patients in the inclisiran arm reported ≥1 clinically relevant TEAE at the injection site, all mild ($n = 3$) to moderate ($n = 1$). No TEAE of hemorrhagic stroke was reported in this subgroup of patients with CeVD. There was only one TESAE of ischemic stroke in one patient reported in the inclisiran arm and two TESAEs of lacunar stroke reported in two patients in the placebo arm.

4. Discussion

The results of this *post hoc* analysis highlight the beneficial effect of inclisiran in combination with statins on LDL-C levels in patients with established CeVD who require further LDL-C lowering in addition to statin. Consistent with the findings from the overall ORION-9, ORION-10, and ORION-11 trials, the subgroup of patients with established CeVD had substantial and consistent reductions in LDL-C levels with twice-yearly dosing of inclisiran (after the initial and 3-month doses) [15,16]. By Day 510, patients in the CeVD subgroup treated with inclisiran had a mean 55.2% reduction in LDL-C from baseline, compared with 50.7% for the overall pooled ORION-9, ORION-10, ORION-11 cohort [17]. The efficacy of inclisiran has also been evaluated in patients with and without polyvascular disease (PVD), and the results were similar to that observed in this study. The mean percentage reduction in LDL-C in patients with PVD and those without was 48.9% and 51.5% respectively [18]. The results of the current analysis in addition to prior published data, support the consistent effect of inclisiran in different ASCVD sub-populations. In agreement with previous findings, notable improvements in other atherogenic lipids were also observed with inclisiran in patients with CeVD.

Anti-PCSK9 mAbs bind to extracellular PCSK9 protein inhibiting its interaction with LDL receptors, while inclisiran prevents PCSK9 mRNA translation in hepatocytes and thus reduces the production of PCSK9 by the liver. Both approaches result in greater hepatic uptake of circulating LDL-C by LDL receptors [14,19]. The magnitude of LDL-C lowering achieved with inclisiran is similar to that reported with anti-PCSK9 mAbs, but with a less frequent, twice-yearly dosing regimen (after initial and 3-month doses) compared with self-injection of anti-PCSK9 mAb every 2 or 4 weeks [10,11,14,16,17,19]. Moreover, data from the Phase 3 trials and ORION-3 study show that treatment with inclisiran provides a consistent LDL-C−lowering effect sustained for 6 months per dose [16,20]. In this subset of patients with CeVD who had a mean (SD) baseline LDL-C of 108.4 (34.3) mg/dL, 59.1%, 70.0%, and 79.1% of patients achieved LDL-C thresholds of <50 mg/dl, <70 mg/dL, and <100 mg/dL, respectively, with the addition of inclisiran to maximally tolerated statin therapy.

Overall, the safety profile of inclisiran in patients with established CeVD was generally consistent with that reported for the pooled population from the Phase 3 studies, although rates of TEAEs and TSEAEs were numerically higher with inclisiran than with placebo. This finding is likely due to the lower rate of TEAEs and TSEAEs among placebo-treated individuals with CeVD (70.7%) compared to the aggregate placebo groups from the 3 trials (77.3%) [17], which in turn may be related to the relatively small size of the CeVD subgroup. TEAEs at the injection site were few and mostly mild; none were severe with inclisiran.

Limitations include the *post hoc* nature of this analysis, the small sample size of the subgroup of patients with established CeVD, and the lack of longer-term efficacy and safety data. Patients were not randomized according to a history of CeVD, resulting in a modest imbalance in the numbers of patients in the inclisiran versus placebo groups. Furthermore, the effect of inclisiran in lowering the risk of stroke and other cardiovascular events in these patients needs to be determined. Although the incidence of major adverse cardiovascular events was less frequent with inclisiran compared with placebo in the ORION-10 and ORION-11 trials, the analysis was exploratory [16,21,22]. The ongoing cardiovascular outcomes trials, ORION-4 NCT03705234) and VICTORION-2 Prevent (NCT05030428), will provide further insights into the long-term efficacy of inclisiran in improving cardiovascular outcomes in patients with ASCVD, including CeVD [23,24]. There is also a need for real-world data to understand the effectiveness of inclisiran in routine clinical settings.

In conclusion, in addition to maximally tolerated statin therapy, twice-yearly dosing with inclisiran (after the initial and 3-month doses) is an effective option for LDL-C lowering and is well tolerated in adults with established CeVD.

Declaration of Competing Interest

Wolfgang Koenig reports receiving consulting fees and lecture fees from AstraZeneca, Novartis, and Amgen; consulting fees from Pfizer, The Medicines Company, DalCor Pharmaceuticals, Kowa, Corvidia Therapeutics, Esperion, Genentech, OMEICOS, Novo Nordisk, LIB Therapeutics, TenSixteen Bio, New Amsterdam Pharma and Daiichi Sankyo; lecture fees from Berlin-Chemie, Bristol-Myers Squibb, and Sanofi; and grant support and provision of reagents from Singulex,
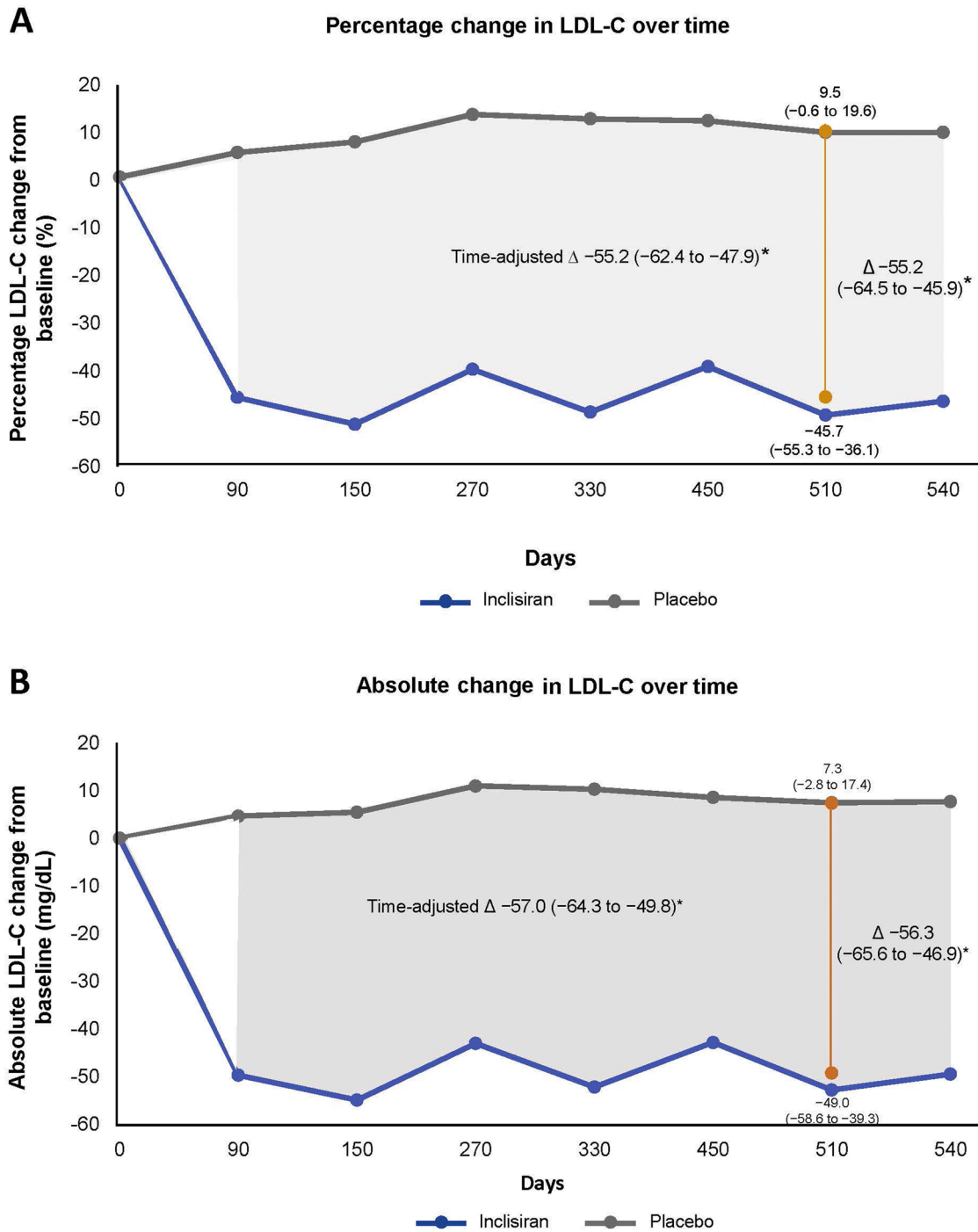
A

B

Fig. 1. Change in LDL-C over time. A) Percentage change in LDL-C from baseline to Day 510 (vertical line) was analyzed using ANCOVA model with a multiple imputation washout model for missing data,the time-adjusted percentage change from baseline after Day 90 and up to Day 540 was analyzed by MMRM with a controlbased pattern mixture model for data imputation (shaded gray area) Percentage change in LDL-C for post-baseline visits from Day 90 to Day 540 (gray line for placebo group and blue line for inclisiran group) is based on observed data analyzed using MMRM without imputation. (B) Absolute change in LDL-C from baseline to Day 510 (yellow line) was analyzed using ANCOVA model with a multiple imputation washout model for missing data. Absolute time-adjusted change from baseline after Day 90 and up to Day 540 (shaded gray area) and absolute change in LDL-C for post-baseline visits from Day 90 up to Day 540 (gray line for placebo group and blue line for inclisiran group) is based on observed data analyzed using MMRM without imputation assuming missing data MAR. Efficacy analyses were performed on the intention-to-treat population – CeVD only subset that included all randomized patients with established CeVD in the 3 trials. ANCOVA, analysis of covariance; CeVD, cerebrovascular disease; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; LS, least square; MMRM, mixed-effects model for repeated measures; MAR, missing at random.

*Inclisiran vs placebo, $p < 0.0001$.

Table 2

Percentage change in other atherogenic lipids and lipoproteins from baseline to Day 510.

Parameter	Inclisiran ($n = 110$)	Placebo ($n = 92$)	Between-group difference[*]
Total cholesterol	−29.5 (−34.8, −24.1)	3.9 (−1.8, 9.6)	−33.4 (−39.2, −27.5)
Non–HDL-C	−44.0 (−51.0, −37.1)	4.7 (−2.7, 12.0)	−48.7 (−56.4, −41.0)
ApoB	−41.1 (−47.3, −34.9)	3.0 (−3.6, 9.5)	−44.0 (−50.7, −37.3)
Triglycerides	−9.1 (−17.4, −0.9)	−7.1 (−15.9, 1.7)	−2.0 (−11.4, 7.4)
Lp(a)[†]	−16.6 (−27.0, −6.2)	1.0 (−9.3, 11.4)	−17.6 (−25.8, –9.4)

[*] Inclisiran vs placebo, $p < 0.0001$ for all atherogenic lipids and lipoproteins except triglycerides where $p = 0.6714$; [†]Lp(a) assessed at Day 540.

Efficacy analyses were performed on the intention-to-treat population – CeVD only subset that included all randomized patients with established CeVD in the 3 trials. Data shown are LS mean (95% CI), except for Lp(a) which is median (95% CI).

ApoB, apolipoprotein B; CeVD, cerebrovascular disease; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); LS, least squares; HDL-C, high-density lipoprotein cholesterol.

References

[1] Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart disease and stroke statistics-2021 Update: a Report from the American heart association. Circulation 2021;143(8):e254–743. https://doi.org/10.1161/CIR.0000000000000950.

[2] Amarenco P, Lavallee PC, Monteiro Tavares L, Labreuche J, Albers GW, Abboud H, et al. Five-year risk of stroke after TIA or minor ischemic stroke. N Engl J Med 2018;378(23):2182–90. https://doi.org/10.1056/NEJMoa1802712.

[3] Flach C, Muruet W, Wolfe CDA, Bhalla A, Douiri A. Risk and secondary prevention of stroke recurrence: a population-base cohort study. Stroke 2020;51(8):2435–44. https://doi.org/10.1161/STROKEAHA.120.028992.

[4] Mohan KM, Wolfe CD, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and cumulative risk of stroke recurrence: a systematic review and meta-analysis. Stroke 2011;42(5):1489–94. https://doi.org/10.1161/STROKEAHA.110.602615.

[5] Rucker V, Heuschmann PU, O'Flaherty M, Weingartner M, Hess M, Sedlak C, et al. Twenty-year time trends in long-term case-fatality and recurrence rates After ischemic stroke stratified by etiology. Stroke 2020;51(9):2778–85. https://doi.org/10.1161/STROKEAHA.120.029972.

[6] Zhao W, Wu J, Liu J, Wu Y, Ni J, Gu H, et al. Trends in the incidence of recurrent stroke at 5 years after the first-ever stroke in rural China: a population-based stroke surveillance from 1992 to 2017. Aging 2019;11(6):1686–94. https://doi.org/10.18632/aging.101862 (Albany NY).

[7] Cholesterol Treatment Trialists C, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376(9753):1670–81. https://doi.org/10.1016/S0140-6736(10)61350-5.

[8] Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41(1):111–88. https://doi.org/10.1093/eurheartj/ehz455.

[9] Ray KK, Molemans B, Schoonen WM, Giovas P, Bray S, Kiru G, et al. EU-Wide cross-sectional observational study of lipid-modifying therapy use in secondary and primary care: the DA VINCI study. Eur J Prev Cardiol 2021;28(11):1279–89. https://doi.org/10.1093/eurjpc/zwaa047.

[10] Giugliano RP, Pedersen TR, Saver JL, Sever PS, Keech AC, Bohula EA, et al. Stroke prevention with the PCSK9 (Proprotein Convertase Subtilisin-Kexin Type 9) inhibitor evolocumab added to statin in high-risk patients with stable atherosclerosis. Stroke 2020;51(5):1546–54. https://doi.org/10.1161/STROKEAHA.119.027759.

[11] Guedeney P, Giustino G, Sorrentino S, Claessen BE, Camaj A, Kalkman DN, et al. Efficacy and safety of alirocumab and evolocumab: a systematic review and meta-analysis of randomized controlled trials. Eur Heart J 2019. https://doi.org/10.1093/eurheartj/ehz430.

[12] Schwartz GG, Bessac L, Berdan LG, Bhatt DL, Bittner V, Diaz R, et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY outcomes trial. Am Heart J 2014;168(5):682–9. https://doi.org/10.1016/j.ahj.2014.07.028.

[13] Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379(22):2097–107. https://doi.org/10.1056/NEJMoa1801174.

[14] Kosmas CE, Munoz Estrella A, Skavdis A, Pena Genao E, Martinez I, Guzman E. Inclisiran for the treatment of cardiovascular disease: a short review on the emerging data and therapeutic potential. Ther Clin Risk Manag 2020;16:1031–7. https://doi.org/10.2147/TCRM.S230592.

[15] Raal FJ, Kallend D, Ray KK, Turner T, Koenig W, Wright RS, et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. N Engl J Med 2020;382(16):1520–30. https://doi.org/10.1056/NEJMoa1913805.

[16] Ray KK, Wright RS, Kallend D, Koenig W, Leiter LA, Raal FJ, et al. Two Phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med 2020;382(16):1507–19. https://doi.org/10.1056/NEJMoa1912387.

[17] Wright RS, Ray KK, Raal FJ, Kallend DG, Jaros M, Koenig W, et al. Pooled patient-level analysis of inclisiran trials in patients with familial hypercholesterolemia or atherosclerosis. J Am Coll Cardiol 2021;77(9):1182–93. https://doi.org/10.1016/j.jacc.2020.12.058.

[18] Koenig, W., L.G. Conde, U. Landmesser, L.A. Leiter, K.K. Ray, G.G. Schwartz, et al., Efficacy and safety of inclisiran in patients with polyvascular disease: pooled, post hoc analysis of the ORION-9, ORION-10, and ORION-11 Phase 3 randomized controlled trials. Cardiovasc Drugs Ther 2022. DOI: 10.1007/s10557-022-07413-0.

[19] Nishikido T, Ray KK. Inclisiran for the treatment of dyslipidemia. Expert Opin Investig Drugs 2018;27(3):287–94. https://doi.org/10.1080/13543784.2018.1442435.

[20] Ray KK, Troquay RPTV, LA Leiter FLJ, Wright SV, Talloczy S, Zang ZX, Maheux P, et al. Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated low-density lipoprotein cholesterol (ORION-3): results from the 4-Year open-label extension of the ORION-1 Trial. Lancet 2022. DOI: Available at SSRN: https://ssrn.com/abstract=4252675.

[21] Ray KK, Kallend D, Leiter LA, Raal FJ, Koenig W, Jaros MJ, et al. Effect of inclisiran on lipids in primary prevention: the ORION-11 trial. Eur Heart J 2022. https://doi.org/10.1093/eurheartj/ehac615.

[22] Ray KK, Raal FJ, Kallend DG, Jaros MJ, Koenig W, Leiter LA, et al. Inclisiran and cardiovascular events: a patient-level analysis of phase III trials. Eur Heart J 2023;44(2):129–38. https://doi.org/10.1093/eurheartj/ehac594.

[23] ClinicalTrial.gov. A randomized trial assessing the effects of inclisiran on clinical outcomes among people with cardiovascular disease (ORION-4). [Accessed September.2022]; Available from: https://clinicaltrials.gov/ct2/show/NCT03705234.

[24] ClinicalTrial.gov. Study of inclisiran to prevent cardiovascular (CV) events in participants with established cardiovascular disease (VICTORION-2P). [Accessed September.2022]; Available from: https://clinicaltrials.gov/ct2/show/NCT05030428?term=VICTORION-2+Prevent&draw=2&rank=1.