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HPS-4/TIMI 65/ORION-4: A double-blind randomized placebo-controlled trial assessing the effects of inclisiran on clinical outcomes among people with atherosclerotic cardiovascular disease: Trial design, recruitment, and baseline characteristics

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HPS-4/TIMI 65/ORION-4: A double-blind randomized placebo-controlled trial assessing the effects of inclisiran on clinical outcomes among people with atherosclerotic cardiovascular disease: Trial design, recruitment, and baseline characteristics

Running title: ORION-4 baseline paper

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Abstract

Background

Despite widespread statin use, atherosclerotic cardiovascular disease remains a leading cause of morbidity and mortality worldwide. Monoclonal antibodies targeting circulating proprotein convertase subtilisin-kexin type 9 (PCSK9) substantially reduce low-density lipoprotein cholesterol (LDL-C) levels and cardiovascular events. However, the requirement for self-administration every 2-4 weeks may limit adherence to treatment.

Inclisiran, a first-in-class small interfering ribonucleic acid (siRNA) therapy targeting hepatic PCSK9 production, has several potential advantages over the anti-PCSK9 monoclonal antibodies, principally longer duration of action. To date, however, the efficacy and safety of inclisiran have not been proven in a cardiovascular outcomes trial.

Methods

The ORION-4 study is the first large-scale clinical outcomes trial of an siRNA therapy, aiming to assess the efficacy and safety of inclisiran among participants with pre-existing atherosclerotic cardiovascular disease. The primary assessment is an intention-to-treat comparison of the effect of inclisiran sodium 300 mg (equivalent to 284 mg inclisiran), given by subcutaneous injection at randomization, at approximately 3 months and then approximately every 6 months thereafter, on major adverse cardiovascular events (MACE), defined as the composite of coronary death, myocardial infarction, fatal or non-fatal ischaemic stroke, or urgent coronary revascularization. Participants will be followed until the median time since randomization is at least 5 years and at least 1700 participants have a recorded adjudicated MACE. With a planned sample size of ~15,000 participants, ORION-4 was designed to have >99% power to detect a relative reduction in the primary outcome of about one quarter, while also providing an opportunity to assess efficacy in different subgroups as well as on secondary outcomes of interest.

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Results

Between 2019 and 2023 a total of 16,124 participants were randomized in the UK and the US. The mean (SD) age was 70 (8.1) years and 30% were female. At baseline, 78% had a history of coronary heart disease, 22% of ischaemic stroke, 15% of revascularization for peripheral arterial disease, and 23% had diabetes mellitus. 85% were on statin therapy (53% high intensity statin, 29% moderate and 3% low intensity statins). Overall, baseline mean (SD) LDL-C was 96 (32) mg/dL, and was similar among participants on high- and moderate/low-intensity statin regimens (87 (27) mg/dL and 93 (26) mg/dL respectively), with higher levels in those receiving no statin therapy (133 (33) mg/dL). Follow-up will complete during 2026 and results will be available in early 2027.

Interpretation

Inclisiran potentially offers a scalable lipid-lowering treatment, either alone or in combination with other agents. ORION-4 will evaluate the clinical efficacy of inclisiran, and provide a robust assessment of the safety of prolonged use of an siRNA therapeutic.

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BACKGROUND AND RATIONALE

Large-scale randomized controlled trials have shown that lowering blood low-density lipoprotein cholesterol (LDL-C) levels reduces the risks of both coronary events and ischaemic strokes.[1,2] Furthermore, trials have demonstrated that more intensive LDL-C lowering with high-intensity statins, or the addition of non-statin therapies (such as ezetimibe), further reduces these risks.[3-7] However, even with such treatment, the residual risk of cardiovascular events in people with existing atherosclerotic cardiovascular disease remains substantial.[5,6,8]

Around 20 years ago, gain of function mutations in the *proprotein convertase subtilisin-kexin type 9* (*PCSK9)* gene were identified as a cause of familial hypercholesterolaemia,[9] with later studies also demonstrating that loss of function mutations are associated with lower blood LDL-C levels and a reduced risk of coronary events.[10] Circulating PCSK9, a protein of mainly hepatic origin, binds to the low-density lipoprotein (LDL) receptor on the surface of liver cells. The PCSK9-LDL receptor complex is then degraded by hepatic lysosomes, reducing the number of LDL receptors thus reducing uptake of circulating LDL-C.[11,12]

Therapeutic strategies to reduce circulating PCSK9 include binding it in the circulation with monoclonal antibodies or modified binding proteins, and reducing its production in the liver with siRNAs.[9] Monoclonal antibodies to PCSK9 (such as evolocumab and alirocumab) are given by subcutaneous injection every 2-4 weeks and reduce LDL-C by 50-60%.[5,6,13] In the FOURIER and ODYSSEY OUTCOMES trials, allocation to monoclonal antibodies targeting PCSK9 reduced LDL-C by approximately 50 mg/dL (1.3 mmol/L) and produced a 15% proportional reduction in major adverse cardiovascular events (MACE) compared to placebo over a mean follow-up of 2-3 years.[5,6] LDL-C lowering typically has a relatively small effect on

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cardiovascular events in the first year,[1] so the short follow-up in these two studies may have led to an underestimate of the longer-term effects of these agents and limited their ability to detect an effect on cardiovascular mortality.[14] More recently, in the VESALIUS-CV trial conducted in participants with atherosclerosis or diabetes and without a previous myocardial infarction or stroke, the addition of evolocumab to baseline lipid-lowering therapy reduced LDL-C by 63 mg/dL (1.6 mmol/L), leading to a 25% proportional reduction in MACE over a median follow-up of 4.6 years compared to placebo.[7]

Targeting hepatic PCSK9 production with an siRNA offers an alternative approach to monoclonal antibodies. Inclisiran is the first chemically synthesized siRNA, administered by subcutaneous injection, designed to target hepatic PCSK9 production.[17] It is covalently linked to a ligand containing three N-acetylgalactosamine (GalNAc) residues. These GalNAc residues bind to abundant liver-expressed asialoglycoprotein receptor, leading to inclisiran uptake specifically into hepatocytes. When introduced into the hepatocyte, inclisiran engages the natural pathway of RNA interference (RNAi) by binding intracellularly to the RNA-induced silencing complex (RISC), enabling it to cleave mRNA molecules encoding PCSK9 specifically. The cleaved PCSK9 mRNA is degraded and thus unavailable for protein translation, resulting in decreased levels of the circulating PCSK9 protein.[17]

A potential key advantage of this mechanism of action is its long duration of effect enabling twice yearly maintenance administration (after an initial and 3-month dose).[15] Inclisiran offers a potentially scalable population intervention in contrast to the anti-PCSK9 monoclonal antibodies, which require frequent self-administration and cold-chain refrigerated storage.[16]

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In the ORION-10 and ORION-11 Phase 3 trials, which included approximately 3000 participants followed for 18 months, allocation to inclisiran sodium 300 mg administered at baseline, 3 months later and then every 6 months reduced blood LDL-C by around 50%.[18] These trials also included detailed assessments of adverse events and biochemical measures, and identified no safety issues other than typically mild injection site reactions in approximately 2-5% of participants. However, these and other studies[19,20] involved relatively small numbers of patients followed for relatively short periods, and, being designed primarily to assess the LDL-C lowering effect of inclisiran, were not expected to have sufficient statistical power to assess clinical outcomes reliably. The HPS-4/TIMI 65/ORION-4 trial ("ORION-4") is the first large-scale clinical outcomes trial conducted to assess the efficacy and safety of any siRNA therapy, and involves placebo-controlled treatment with inclisiran for ~5 years among people with pre-existing atherosclerotic cardiovascular disease. In this manuscript, we describe the trial design, details of the recruitment process, baseline participant characteristics, and the statistical analysis plan.

METHODS

STUDY AIMS

The ORION-4 study[21] aimed to randomize at least 15,000 participants with pre-existing atherosclerotic cardiovascular disease in a 1:1 ratio to either inclisiran sodium 300 mg or matching placebo (given by subcutaneous injection on the day of randomization, at 3 months and then every six months) for a planned median duration of time since randomization of at least 5 years. The primary efficacy outcome is MACE, defined as the composite of coronary heart disease (CHD) death, myocardial infarction (MI), fatal or non-fatal ischaemic stroke or urgent coronary revascularization (Figure 1). Secondary outcomes are: (i) MACE among participants

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recorded at baseline to be taking high-intensity statin; (ii) the composite outcome of CHD death or myocardial infarction; and (iii) cardiovascular death.

STUDY ORGANIZATION

ORION-4 was initiated and is led by independent scientists at the Clinical Trial Service Unit (CTSU) based at the University of Oxford, Oxford, in collaboration with the TIMI Study Group based at Brigham and Women's Hospital, Harvard Medical School, Boston. The trial was designed with input from the Medicines Company (MDCO, which was subsequently acquired in January 2020 by Novartis) and from additional external academic members of the Steering Committee. The trial is co-sponsored by the University of Oxford and Novartis. The University of Oxford is the academic lead for the trial and responsible for data analysis, while Novartis is the regulatory lead. The study is funded by a grant to the University of Oxford from Novartis to cover the costs of central coordination and all costs in the UK, and a grant from Novartis to the TIMI study Group to cover the costs in the US. Packaged inclisiran or placebo and the distribution of the study medication is provided by Novartis. CTSU is responsible for all analyses involving ORION-4 data for publications and regulatory submissions, and the Steering Committee is responsible for reviewing and approving reports arising from such analyses. The study protocol (see Supplementary Materials) was approved by the relevant health regulatory authority and ethics committee or institutional review board for each participating centre. Details of the ORION-4 collaborative group are provided in the Supplementary Materials.

The conduct of the trial is supported by a bespoke web-based information technology (IT) system, designed and developed at CTSU, based on similar systems employed over the last two decades with iterative enhancements in major trials.[8,22]

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The system is used by study staff to manage study appointments and to record clinical information (including medical history, concomitant medications, adverse events, blood sampling, and administration of study treatment). It includes an embedded minimized randomization program for allocation to inclisiran or placebo. The system also includes a suite of administrative applications used by coordinating centre staff to manage study sites and participants, including clinical supervision (e.g., review of serious adverse events and safety blood results), provision of blood sample kits and study treatment to sites, tracking completeness of follow-up and adherence to study treatment, collection of supporting documentation for relevant events, and clinical outcome adjudication. The system incorporates inbuilt data-entry validation rules, logic checks, and prompts for required activities to support study staff, to maximize the quality of data collected during the trial, and to enhance compliance with the protocol.

ELIGIBILITY

The study aimed to enrol a wide range of participants with a clinical history of atherosclerotic cardiovascular disease (namely, prior MI, ischaemic stroke, or peripheral artery disease with prior lower extremity artery revascularization or aortic aneurysm repair), and none of the exclusion criteria (Figure 2). Men aged at least 40 years (initially at least 55 years: see Supplementary Table 1) and women aged at least 55 years were eligible in order that they would be at sufficient risk of the primary efficacy outcome.

In addition, only participants with a point-of-care (POC) total cholesterol measurement at screening above the protocol defined threshold were eligible for the trial. At the start of recruitment, this threshold was set at ≥155 mg/dL (4.0 mmol/L). However, the Steering Committee subsequently reduced it to ≥135 mg/dL (≥3.5

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mmol/L) in July 2021 (at which point, approximately half the target number of participants had been recruited and mean baseline LDL-C was 104 mg/dL [2.7 mmol/L]), and then to ≥116 mg/dL (≥3.0 mmol/L) in June 2022 (Supplementary Table 1). Simulations based on participant's baseline characteristics blinded to treatment-related effects (including on LDL-C) indicated that these changes would have only a minimal impact on the overall baseline LDL-C among randomized participants (and, hence, on the statistical power of the trial) but would facilitate recruitment of otherwise eligible participants.

INVITATION

Pre-screening efforts were designed to identify large numbers of potentially eligible individuals at each recruiting site from clinical records (including electronic health care records). The exact methods varied by centre and by country (see below), and in all cases were subject to ethics committee or institutional review board approval, and compliance with data privacy regulations. Potentially eligible individuals were invited to take part in the study between October 2018 and March 2023, with a pause in the UK due to the COVID-19 pandemic between March 2020 and October 2021.

In the UK, lists of potentially eligible individuals were generated from electronic searches of centralized coded health records by information specialists in National Health Service (NHS) organizations, such as NHS DigiTrials (part of NHS England), Public Health Scotland, local Health Boards in Wales, and an existing network of Primary Care practices. With appropriate approvals, invitations were mailed on behalf of the local investigator by the University of Oxford (or on its behalf by the University of Dundee in Scotland, and participating Primary Care organizations in some UK sites) to potentially eligible individuals who were asked to contact the

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coordinating centre in Oxford to confirm their study screening appointment if interested in attending. During this telephone call, study staff asked a series of standardized pre-screening questions to identify those who did not meet certain of the eligibility criteria in order to prevent unnecessary clinic attendance for those who could readily be identified as not suitable for the trial.

In the US, sites were asked to pre-screen local hospital/specialist clinic records, on behalf of the local investigator, to generate lists of potentially eligible participants ready to be invited to join the trial once the necessary approvals were in place at the site.

Where available, prior lipid results were obtained from health care records during the pre-screening process, and sites were discouraged from screening individuals whose most recent measure of blood total cholesterol was less than the protocol defined threshold (Supplementary Table 1).

SCREENING, AND RUN-IN PHASE

At the screening visit, relevant medical history, current lipid-lowering therapy (including statin dose), and other factors pertinent to eligibility were recorded in the study IT system. A capillary blood sample was taken for immediate measurement of total cholesterol using a Cardiocheck® PA POC analyser, which is approved for clinical use in the UK and US. Potential participants did not start the pre-randomization run-in period if the POC total cholesterol value was less than the protocol defined threshold (Supplementary Table 1). Use of the POC measurement of total cholesterol at screening aimed to recruit a trial population enriched for higher blood LDL-C levels. It enabled efficient streamlined recruitment: there was no need for participants to fast for study visits, only 20µL of capillary blood was required, and

the eligibility assessment could be made immediately. Individuals who appeared to be eligible had the study explained to them by trained clinic staff and were asked to provide written informed consent to join the trial. In addition, they were asked to indicate on the consent form if their blood samples could be stored long-term for future biochemical and, separately, genetic analyses.

Eligible individuals who consented to join the study received a subcutaneous injection of placebo in a “single-blind” manner, and an appointment was made for a randomization visit in about eight weeks. This pre-randomization run-in phase was intended to help identify, and exclude before randomization, those individuals who would be unlikely to comply with long-term study treatment and follow-up. After the screening visit, guidance for lipid optimization was provided to the participant’s doctor(s) based on guideline recommendations for people with vascular disease.[23,24] Each individual’s responsible doctor (primary care physician, hospital specialist or local investigator, as appropriate) was given the opportunity to indicate whether, in their view, there were any factors that made the participant unsuitable for randomization into the study, as well as to make any adjustments they deemed medically appropriate to optimize non-study lipid-lowering therapy. Prior to randomization, the local site investigator was also required to confirm that they considered the participant suitable for randomization, which was recorded on the study IT system.

RANDOMIZATION VISIT

At the randomization visit, eligibility was re-checked. Details of all non-study medications and information about smoking history and alcohol intake were sought, and an assessment of quality of life was made (using the EQ-5D-5L questionnaire).[25] A non-fasting blood sample was taken for central laboratory analyses and, subject to

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appropriate consent, for long-term storage. Eligible and consenting individuals were allocated to receive inclisiran or placebo using a minimized randomization algorithm that helps maximize balance between the treatment groups with respect to prognostically important baseline variables (age, sex, type of prior vascular disease, diabetes mellitus, statin use, smoking status, and race) and their correlates.[26] The algorithm included a stochastic element (treatment was assigned to the arm determined by the minimization algorithm with a probability of 0.9) in accordance with clinical trial guidelines.[27] The first subcutaneous injection of randomized treatment (inclisiran sodium 300 mg or placebo) was then given and an appointment for the first post-randomization follow-up visit was made at approximately three months. Non-study lipid lowering therapy (including statin treatment) remained the responsibility of the participant's usual doctor throughout the study.

POST-RANDOMIZATION FOLLOW-UP VISITS

Following randomization, all participants were scheduled to attend follow-up visits at about three months after randomization and then approximately every six months until the end of the study. Provided that continuation of study treatment remained appropriate, participants were given a subcutaneous injection of their randomly allocated study treatment (inclisiran sodium 300 mg or placebo) at each scheduled study visit. Follow-up information was sought for all study participants, irrespective of whether or not they continued to receive study treatment. Participants were encouraged to attend in-person clinic visits whenever possible; otherwise, follow-up data could be collected by phone or from medical records unless consent is withdrawn. Details on the follow-up visit assessments are provided in the protocol (See Supplementary Materials).

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Non-fasting blood samples have been collected for central laboratory assays and storage from all participants at the randomization and selected follow-up visits (see Supplementary Table 2). Samples were processed at the local sites, and stored at -20°C or lower before frozen transfer to the Wolfson Laboratory at the University of Oxford. Serum, plasma, and buffy coat samples are stored at -165°C or lower in temperature-monitored liquid nitrogen facilities, enabling future biochemical, genetic, or other laboratory analyses, subject to appropriate consents. Creatinine, alanine aminotransferase (ALT) and lipids (total cholesterol, LDL-C [direct enzymatic measurement], HDL cholesterol, triglycerides, apolipoproteins B and A1) in serum have been assayed using Beckman-Coulter AU clinical chemistry analysers. HbA1c analysis was performed by HPLC using EDTA whole blood on an Arkray HA8160 analyser and reagents with International Federation of Clinical Chemistry (IFCC) traceable calibrator. All assays have used methods accredited by the UK Accreditation Service. For participants in the US, ambient samples were also sent to a US central laboratory for ALT and creatinine analysis to ensure timely safety monitoring and reduce logistical delays with international sample shipment.

Recording of adverse events (AEs) and adjudication of potential study outcomes

All serious adverse events (SAEs) and any non-serious AEs that lead to discontinuation of study treatment reported by participants at each follow-up visit were recorded by trained study clinic staff directly in the study IT system. Potential study outcomes have been adjudicated at the University of Oxford by clinicians who have no other involvement in the trial, blind to study treatment allocation and blood lipid values, using standard Outcome Definitions (See Supplementary Materials).

STATISTICAL CONSIDERATIONS

Sample size and predicted number of events

Evidence from randomized trials of statin therapy indicates that, for every 39 mg/dL (1 mmol/L) reduction in LDL-C, the risk of MACE is reduced by about a quarter in each year after the first year, but only about half as much in the first year.[1] Assuming a mean baseline LDL-C of 100 mg/dL (2.6 mmol/L) and average adherence to allocated treatment of 90%, it was anticipated that LDL-C would be reduced by 45 mg/dL (1.2 mmol/L) compared to placebo. Based on data from previous randomized trials of statin therapy,[1] this reduction in LDL-C is predicted to lead to a reduction in MACE of about a quarter over 5 years. With an anticipated rate of MACE in the placebo group of 2.7% per year (estimated from analysis of the ORION-4 primary outcome among participants aged at least 55 years in our previous REVEAL trial in a similar patient population[8]) and a median follow-up of 5 years, a trial of approximately 15,000 participants would have >99% power at a two-tailed P<0.01 to detect a relative risk reduction of at least this magnitude. This sample size also provides reasonable power for key secondary endpoints and pre-specified subgroup analyses. Consequently, follow-up of all randomized participants was planned to continue until both median duration of time since randomization of at least 5 years and at least 1700 participants have been recorded with an unrefuted MACE (primary outcome).

Statistical analysis plan

All participants randomized to inclisiran will be compared with all participants randomized to placebo, irrespective of whether they received all, some or none of their allocated treatment (i.e. intention-to-treat [ITT] analyses). For the time-to-event analyses, survival analytic methods will be used to evaluate the time to the first event

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during the entire study period. The log-rank 'observed minus expected' statistic and its variance will be used both to test the null hypothesis of equal survival curves (i.e., the log-rank test) and to estimate the corresponding average event rate ratio, comparing all participants allocated active inclisiran with all those allocated placebo.[28,29] Estimates of the event rate ratio will be shown with their 95% confidence intervals. A sensitivity analysis will be conducted to assess the impact of modifying the screening cholesterol threshold, adjusted for the average LDL-C differences between those allocated inclisiran and those allocated placebo, and taking account of any differences in duration of follow-up. Full details, including the testing strategy for the primary and secondary outcomes, are provided in the Statistical Analysis Plan (See Supplementary Materials).

Role of the independent Data Monitoring Committee

An independent Data Monitoring Committee (DMC) has been responsible for reviewing interim unblinded analyses of the effect of randomized treatment allocation on all SAEs and other study outcomes at appropriate intervals, including a single interim analysis for efficacy which occurred in 2025. No recommendations for protocol modifications or early stopping were made. Further details are provided in the DMC Charter (See Supplementary Materials).

RESULTS

Screening and run-in

A total of 33,461 individuals attended a screening visit in 206 sites: 28,517 in 112 sites in the UK (approximately 250 people screened per site) and 4944 in 94 sites in the US (approximately 50 people screened per site): Figure 3; Supplementary Table 3. Of those screened, 14,892 (45%) did not enter the run-in period (13,215 [46%] in the UK and 1677 [34%] in the US), and were excluded. Of these, 13,395 individuals

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(90% of those excluded at screening) did not meet the inclusion criteria (including 12,379 (83%) on the basis of their screening POC cholesterol results), and 1324 (9%) met one or more exclusion criteria (including 210 (1%) with a recent MI, acute coronary syndrome or stroke).

Of the 18,569 individuals who entered the single-blind run-in phase on placebo, 2173 (12%) withdrew before attending a randomization visit (Supplementary Table 4). A total of 49 (2% of those who entered the run-in phase but did not attend a randomization visit) died during the run-in period, 116 (5%) withdrew because of a non-fatal SAE, and 23 (1%) withdrew because of a non-serious AE. A total of 1985 (91%) individuals had other reasons for withdrawing from run-in, principally due to not wishing to continue (960 [44% of those withdrawing from the run-in phase]), along with 150 (7%) for whom the local investigator declined approval for randomization, and 350 (16%) who failed to attend the randomization visit without providing a reason for withdrawal.

Of the 16,396 individuals who attended a randomization visit, 272 (2%) were not randomized (Supplementary Table 5). Of these, 156 (57% of those excluded at the randomization visit) were excluded at the discretion of the local staff, usually because of concerns about long-term adherence, and 31 (11% of those excluded at the randomization visit) because they were unwilling to continue in the trial. Thirteen sites (3 UK and 10 US) that screened potential participants subsequently closed before any randomizations took place.

Baseline characteristics of randomized participants

Between March 2019 and September 2023, 16,124 participants were randomized; 13,190 (82%) in 109 sites in the UK (approximately 120 participants per site) and

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2934 (18%) in 84 sites in the US (approximately 35 participants per site). The mean (standard deviation [SD]) age at randomization was 70 (8) years and 4865 (30%) were women (Table 1). Overall, 12,548 (78%) of participants had a history of coronary heart disease, 3517 (22%) had previously experienced an ischaemic stroke, 2461 (15%) met the protocol definition of previous peripheral arterial disease, and 3742 (23%) were known to have diabetes mellitus (with overlap between these groups). At randomization, 13,735 (85%) participants were receiving statin therapy, with 8489 (53%) reporting high-intensity regimens, 4740 (29%) moderate-intensity regimens, and 506 (3%) low-intensity regimens (see Supplementary Table 6 for definitions of statin intensity). 2389 (15%) participants were not receiving statin therapy for a variety of reasons (Supplementary Table 7). Ezetimibe was received by 1273 (8%) participants in addition to any statin regimen (Supplementary Table 8). Overall, mean (SD) blood LDL-C concentration was 96 (32) mg/dL (2.5 [0.8] mmol/L) and mean (SD) blood apo B concentration was 87 (23) mg/dL. Mean (SD) LDL-C levels were similar among participants on high- and moderate/low-intensity statin regimens: 87 (27) mg/dL (2.2 [0.7] mmol/L) and 93 (26) mg/dL (2.4 [0.7] mmol/L) respectively. In contrast, LDL-C levels were substantially higher in the 15% of participants not receiving statin therapy: 133 (33) mg/dL (3.4 [0.9] mmol/L). Consequently, ORION-4 will be able to assess the effects of adding inclisiran to statin therapy for patients with what would be considered well-controlled LDL-C levels (that is, those on high or moderate/low-intensity statin regimens) as well as in those who, for whatever reason, were not taking statin therapy.

DISCUSSION

The ORION-4 trial will provide the first large-scale evidence about the safety and cardiovascular efficacy of adding subcutaneous inclisiran to standard oral LDL-C

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lowering treatment (principally statins and ezetimibe) in individuals with existing atherosclerotic cardiovascular disease. With over 16,000 participants recruited, and median follow-up of at least 5 years, the results will provide robust evidence to inform future clinical guidelines and influence clinical practice. Importantly, the trial includes individuals on different statin regimens, as well as approximately 15% not receiving statins (as is not uncommon in clinical practice),[30] enabling evaluation of inclisiran across a range of baseline lipid-lowering regimens.

Novartis is separately conducting the VICTORION-2 PREVENT trial (NCT05030428) of inclisiran in approximately 17,000 participants with established cardiovascular disease randomized in about 1000 clinical sites in 49 countries, which has a design closely resembling that of ORION-4 with results expected in late 2027. Both trials are collaborating in a prospectively planned individual participant data meta-analysis to provide an even more statistically robust assessment of the efficacy of inclisiran (particularly on cardiovascular mortality and in different patient subgroups), as well as its safety, based on the larger combined numbers of events.

Should ORION-4 demonstrate both the efficacy of inclisiran in reducing major cardiovascular events and the clinical safety of prolonged administration, it would represent a significant advance in lipid management, particularly for high-risk individuals whose LDL-C remains inadequately controlled despite effective statin therapy or who for whatever reason are not taking statins. Results are expected in early 2027.

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Table 1: Baseline characteristics of randomized participants, by region

Baseline characteristic	Region					
	UK (N=13190)		USA (N=2934)		Total (N=16124)	
Age at randomization (years)						
Mean (SD)	70.4	(8.0)	68.2	(8.2)	70.0	(8.1)
<65	3432	(26%)	1004	(34%)	4436	(28%)
≥65 <75	5636	(43%)	1215	(41%)	6851	(42%)
≥75	4122	(31%)	715	(24%)	4837	(30%)
Sex						
Male	9565	(73%)	1694	(58%)	11259	(70%)
Female	3625	(27%)	1240	(42%)	4865	(30%)

Statin intensity*						
Intensive	6893	(52%)	1596	(54%)	8489	(53%)
Moderate/low	4581	(35%)	665	(23%)	5246	(33%)
None	1716	(13%)	673	(23%)	2389	(15%)
Prior disease†						
Coronary heart disease‡	10134	(77%)	2414	(82%)	12548	(78%)
Ischaemic stroke§	2795	(21%)	722	(25%)	3517	(22%)
Peripheral arterial disease‖	1948	(15%)	513	(17%)	2461	(15%)
Diabetes	2650	(20%)	1092	(37%)	3742	(23%)
Race						
White	12926	(98%)	2626	(90%)	15552	(96%)
Any other race	264	(2%)	308	(10%)	572	(4%)
Smoking						
Current	1081	(8%)	379	(13%)	1460	(9%)
Former	6665	(51%)	1202	(41%)	7867	(49%)
Never	5443	(41%)	1353	(46%)	6796	(42%)
Alcohol intake						
Current	6844	(52%)	706	(24%)	7550	(47%)
Former	3070	(23%)	656	(22%)	3726	(23%)
Never	3275	(25%)	1572	(54%)	4847	(30%)
Total cholesterol (mg/dL)#						
Mean (SD)	184	(38)	199	(50)	186	(41)
<166	4497	(34%)	762	(26%)	5259	(33%)
≥166 <197	4770	(36%)	875	(30%)	5645	(35%)
≥197	3849	(29%)	1231	(42%)	5080	(32%)
Unavailable	74	(1%)	66	(2%)	140	(1%)
LDL cholesterol (mg/dL)#						
Mean (SD)	94	(30)	105	(38)	96	(32)
<89	6460	(49%)	1145	(39%)	7605	(47%)
≥89 <112	3662	(28%)	702	(24%)	4364	(27%)

Results are count (%) unless otherwise stated.

HDL, high density lipoprotein; LDL, low density lipoprotein; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; GLP, glucagon like peptide; SGLT, sodium glucose transporter.

* Definitions of intensive/moderate/low therapy based on statin dose (see Supplementary Table 6).

† Participants may have a history of more than 1 of these conditions.

‡ Patient-reported history of previous MI or coronary revascularization.

§ Patient-reported history of ischaemic stroke, including 'presumed ischaemic' strokes (i.e. not known to be haemorrhagic).

‖ Patient-reported history of lower limb arterial revascularization (i.e. angioplasty or stent or bypass procedure), non-coronary non-carotid revascularization, or aortic aneurysm repair.

Based on blood lipid profile at the Randomization visit, measured in the central Oxford laboratory. To convert total, LDL or HDL cholesterol from mg/dL to mmol/L, divide by 38.67. To convert triglycerides from mg/dL to mmol/L, divide by 88.57.

** Other diabetes medication excludes SGLT2 inhibitors and GLP-1 receptor agonists.

(Continued)

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Table 1: Baseline characteristics of randomized participants, by region

Baseline characteristic	Region					
	UK		USA		Total	
	(N=13190)		(N=2934)		(N=16124)	
≥112	2994	(23%)	1021	(35%)	4015	(25%)
Unavailable	74	(1%)	66	(2%)	140	(1%)
HDL cholesterol (mg/dL)[#]						
Mean (SD)	51	(13)	48	(13)	50	(13)
<43	3756	(28%)	1084	(37%)	4840	(30%)
≥43 <54	4892	(37%)	1020	(35%)	5912	(37%)
≥54	4468	(34%)	764	(26%)	5232	(32%)
Unavailable	74	(1%)	66	(2%)	140	(1%)
Apolipoprotein B (mg/dL)[#]						
Mean (SD)	84.8	(21.1)	94.9	(27.0)	86.7	(22.6)
<76	4688	(36%)	723	(25%)	5411	(34%)
≥76 <93	4512	(34%)	838	(29%)	5350	(33%)
≥93	3914	(30%)	1307	(45%)	5221	(32%)
Unavailable	76	(1%)	66	(2%)	142	(1%)
Apolipoprotein A1[#]						
Mean [mg/dL] (SD)	141.6	(26.7)	139.5	(28.3)	141.2	(27.0)
Non-HDL cholesterol[#]						
Mean [mg/dL] (SD)	133	(37)	151	(49)	136	(40)
Triglycerides[#]						
Median [mg/dL] (IQR)	142	(99-206)	155	(105-231)	143	(100-210)
Medication						
Statin	11474	(87%)	2261	(77%)	13735	(85%)
Ezetimibe	824	(6%)	449	(15%)	1273	(8%)
Fibrate	207	(2%)	180	(6%)	387	(2%)
Bempedoic acid	4	(0%)	4	(0%)	8	(0%)
Icosapent ethyl	0	(0%)	36	(1%)	36	(0%)
Diabetes medication						
Insulin	489	(4%)	320	(11%)	809	(5%)
Metformin	1447	(11%)	505	(17%)	1952	(12%)
Other diabetes medication[~]	637	(5%)	295	(10%)	932	(6%)
Antiplatelet therapy	10520	(80%)	2224	(76%)	12744	(79%)
ACE Inhibitor or ARB	9228	(70%)	1579	(54%)	10807	(67%)
Beta-blocker	7540	(57%)	1787	(61%)	9327	(58%)
Calcium channel blocker	3297	(25%)	778	(27%)	4075	(25%)
Mineralocorticoid receptor antagonist	839	(6%)	183	(6%)	1022	(6%)
SGLT2 inhibitor	494	(4%)	174	(6%)	668	(4%)
GLP-1 receptor agonist	144	(1%)	119	(4%)	263	(2%)

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Results are count (%) unless otherwise stated.
HDL, high density lipoprotein; LDL, low density lipoprotein; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; GLP, glucagon like peptide; SGLT, sodium glucose transporter.
* Definitions of intensive/moderate/low therapy based on statin dose (see Supplementary Table 6).
† Participants may have a history of more than 1 of these conditions.
‡ Patient-reported history of previous MI or coronary revascularization.
§ Patient-reported history of ischaemic stroke, including 'presumed ischaemic' strokes (i.e. not known to be haemorrhagic).
‖ Patient-reported history of lower limb arterial revascularization (i.e. angioplasty or stent or bypass procedure), non-coronary non-carotid revascularization, or aortic aneurysm repair.
Based on blood lipid profile at the Randomization visit, measured in the central Oxford laboratory. To convert total, LDL or HDL cholesterol from mg/dL to mmol/L, divide by 38.67. To convert triglycerides from mg/dL to mmol/L, divide by 88.57.
** Other diabetes medication excludes SGLT2 inhibitors and GLP-1 receptor agonists.
Source: [CTSU_MDCO_PCS-17-01: ADSL]
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Figure 1: Efficacy assessments

Intention-to-treat comparison among all randomized participants of the effects of allocation to inclisiran versus placebo on time to first occurrence during the scheduled treatment period of:
Primary efficacy assessment
Major adverse cardiovascular event ('MACE' defined as: coronary heart disease [CHD] death*, non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, or urgent coronary revascularization procedure).
Secondary efficacy assessments
(i) MACE among participants recorded at baseline to be taking high-intensity statin;
(ii) The composite outcome of CHD death or myocardial infarction; and
(iii) Cardiovascular death.
* CHD death includes deaths due to myocardial infarction, other consequences of coronary atherosclerosis (such as ischaemic heart failure) and sudden cardiac death.

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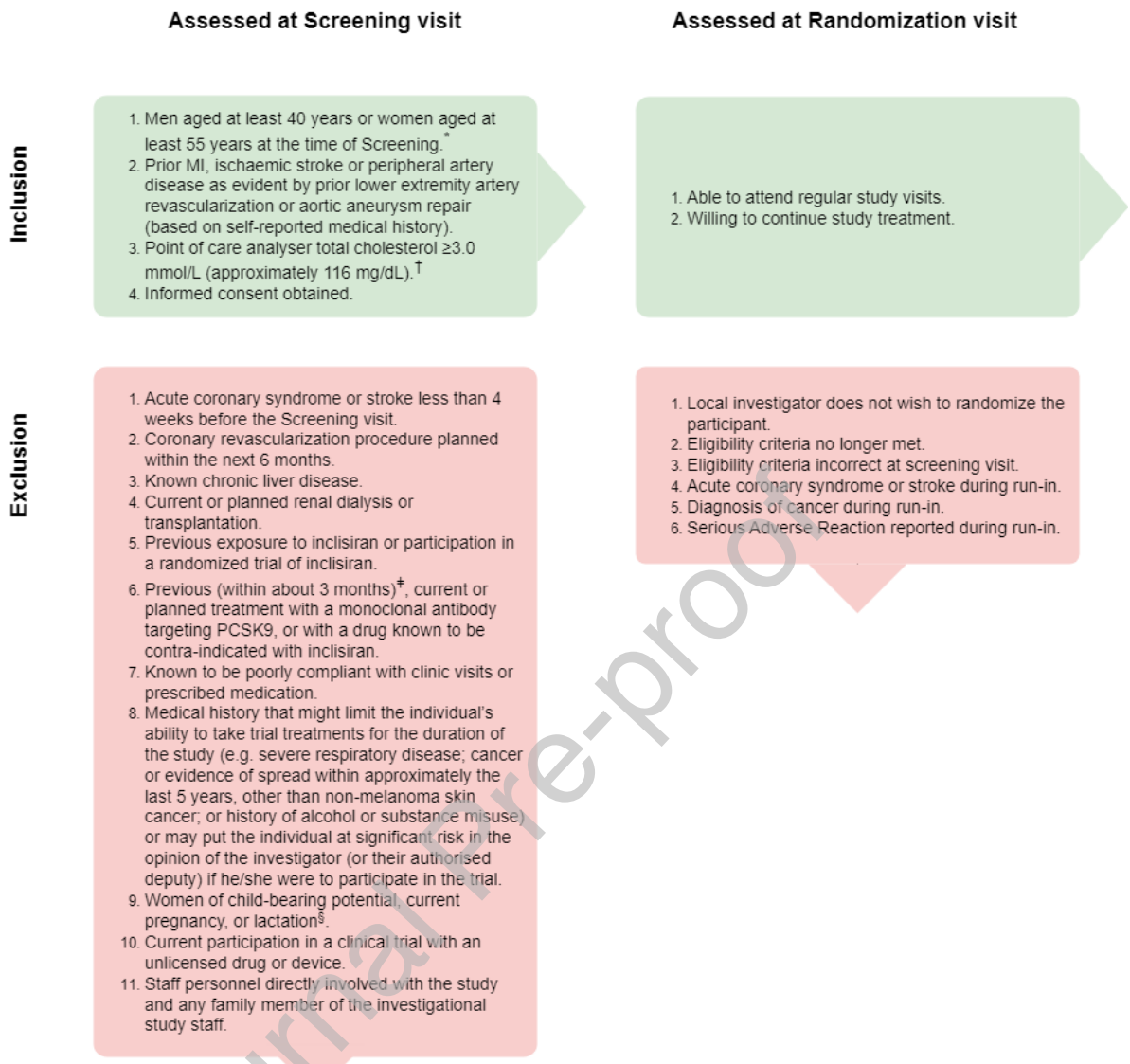
Figure 2: Inclusion and exclusion criteria for entry into the ORION-4 trial



Based on protocol version 7.0 onwards (see Supplementary Table 1).
* At least 55 years for both sexes prior to protocol version 7.0.
† ≥4.0 mmol/L (approximately 155 mg/dL) prior to protocol version 6.0; ≥3.5 mmol/L (approximately 135 mg/dL) under protocol version 6.0.
‡ '(within about 3 months)' added in protocol version 5.1.
§ Women of child-bearing potential are defined as women less than 55 years of age unless surgically sterile or with history of a postmenopausal state.

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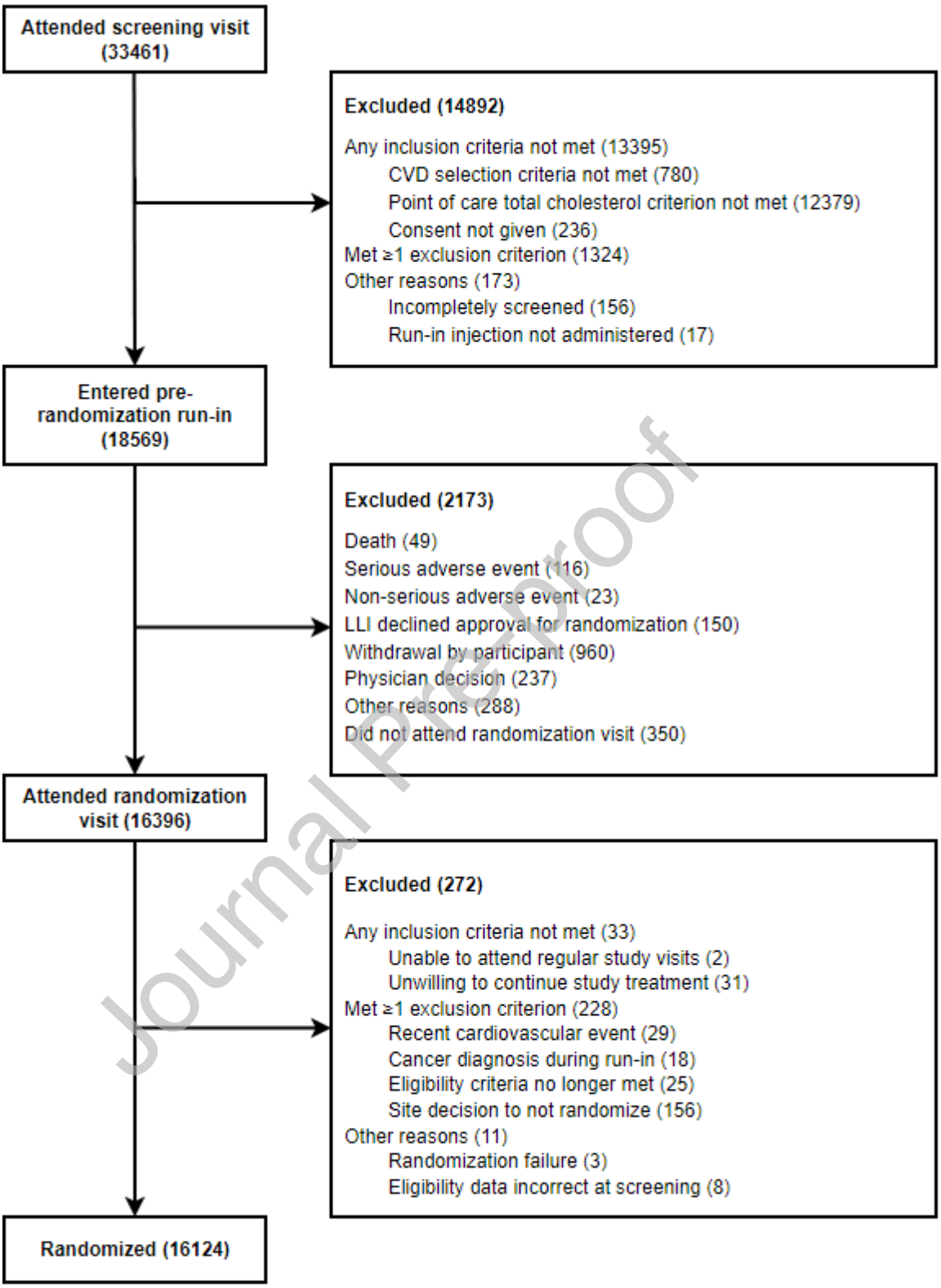
Figure 3: Trial profile



LLI: Local Lead Investigator; CVD: cardiovascular disease.

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