Design of VICTORION-2 Prevent: A randomized double-blind, placebo-controlled trial, assessing the impact of inclisiran on major adverse cardiovascular events in patients with established cardiovascular disease

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ABSTRACT

Rationale Inclisiran is a small interfering ribonucleic acid targeting hepatic proprotein convertase subtilisin/kexin type 9 messenger RNA, that effectively reduces low-density lipoprotein cholesterol (LDL-C) levels. The effect of inclisiran on cardiovascular (CV) outcomes has not been formally tested.

Methods VICTORION-2 Prevent (NCT05030428) is an ongoing, Phase 3 randomized, double-blind, placebo-controlled, international trial assessing the efficacy and safety of inclisiran in preventing CV events in patients with established atherosclerotic cardiovascular disease (ASCVD) receiving high-intensity statin therapy. Patients with established ASCVD (history of myocardial infarction [MI], ischemic stroke, or symptomatic peripheral artery disease), and fasting plasma LDL-C $\geq$ 1.8 mmol/L (70 mg/dL) despite high-intensity statin therapy ($\geq$ 20 mg rosuvastatin or $\geq$ 40 mg atorvastatin daily) will be enrolled. Patients will be treated with inclisiran sodium 300 mg or placebo, administered subcutaneously at Day 1, Day 90, and every 6 months thereafter. The primary outcome will include time to first occurrence of 3-point major adverse CV events (3P-MACE; composite of CV death, MI, or ischemic stroke). Secondary outcomes will include time to occurrence of CV death, time to first occurrence of 4P-MACE (composite of 3P-MACE and urgent revascularization), and major adverse limb event (all adjudicated outcomes), time to occurrence of all-cause death, and long-term safety of inclisiran. Safety will be monitored using a selective safety data collection strategy.

Conclusion VICTORION-2 Prevent will provide robust data on CV benefits and safety of inclisiran in patients with established ASCVD and not at guideline-recommended LDL-C goals despite high-intensity statin treatment.

Clinical trial registration https://clinicaltrials.gov/study/NCT05030428. (Am Heart J 2026;300:107493.)

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Although major advances in cardiovascular (CV) risk prevention have been made over the last decades, atherosclerotic cardiovascular diseases (ASCVD), primarily acute myocardial infarction (MI) and stroke, remain the leading causes of death in men and women worldwide.[1,2] Elevated low-density lipoprotein cholesterol (LDL-C) directly correlates to the risk of developing ASCVD in large epidemiological and Mendelian randomization studies.[3-5] Multiple prospective randomized trials have shown that lowering LDL-C levels reduces the risk of CV events (CV death, MI, and stroke), with a direct quantitative relationship between LDL-C lowering and clinical event reduction.[6,7]

Despite the availability of several therapeutic options for LDL-C lowering, including 3–hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) and cholesterol absorption inhibitors (ezetimibe), a majority of the treated patients do not reach the recommended LDL-C goals.[8-11] This is particularly concerning for patients with established ASCVD, as they are at the highest risk of CV events. International guidelines assign the lowest LDL-C goals for treatment and recommend the most intensive management for these patients.[12-14] High-intensity statin therapy can reduce LDL-C levels by up to 50%,[15] is well tolerated and provides additional clinical benefit on CV outcomes.[16] Therefore, the use of intensive statin therapy with atorvastatin or rosuvastatin, is widely recommended in patients with established ASCVD.[12-14] However, recent studies have shown that up to 75% of these patients fail to reach the recommended LDL-C levels,[17-19] and observational studies have repeatedly indicated that many patients do not adhere to statin therapy for more than 6 months, which contributes to the failure to reach guideline-recommended LDL-C goals.[20-22]

Proprotein convertase subtilisin/kexin type 9 (PCSK9), which is expressed and secreted into the bloodstream predominantly by the liver, binds to the LDL receptor both intracellularly and extracellularly and promotes the lysosomal degradation of these receptors in hepatocytes,[23,24] thereby increasing circulating LDL-C levels. Gain-of-function mutations in the *PCSK9* gene result in elevated LDL-C levels and increased CV risk.[25] Conversely, loss-of-function mutations are associated with low LDL-C levels and confer relative protection against the risk of CV events.[26] Monoclonal antibodies (mAbs) against PCSK9 have been developed and tested clinically in patients with established ASCVD or with recent acute coronary syndromes receiving high-intensity statin therapy and shown to markedly reduce LDL-C levels and the risk of CV events, when administered every 2 to 4 weeks.[27-29]

Inclisiran is a chemically modified small interfering ribonucleic acid (siRNA), conjugated on the sense strand with triantennary *N*-acetylgalactosamine to facilitate its specific uptake by hepatocytes.[30] In hepatocytes, the siRNA duplex is recognized by the RNA-induced silencing complex, where it is unwound, the passenger strand removed, and the retained antisense guide strand directs the catalytic breakdown of PCSK9 messenger RNA, preventing the subsequent production of the PCSK9 protein.[30] Reduced levels of intrahepatic PCSK9 increase LDL-C receptor recycling and expression on the hepatocyte cell surface, thereby increasing LDL-C uptake and lowering LDL-C levels in the bloodstream.[11] Multiple studies have shown that inclisiran, when administered twice-yearly (after the initial and 3-month doses), in addition to high-intensity statin therapy, can lead to sustained placebo-adjusted reductions in LDL-C levels up to 50%, in diverse patient populations, including those with ASCVD, ASCVD risk equivalent, and/or adult heterozygous familial hypercholesterolemia.[31-34] The safety profile of inclisiran does not show meaningful differences with placebo, with the exception of injection site reactions, which tend to be mostly mild, transient, and resolve without sequelae.[31-34]

Inclisiran has been approved for clinical use in many regions, including United States,[35] European Union,[36] Japan,[37] and China.[38] A prespecified, nonadjudicated exploratory analysis from a patient-level ($n = 3{,}655$) pooled analysis from three Phase 3 studies of inclisiran suggested a lower rate of major adverse CV events (MACE) with inclisiran than with placebo.[39] However, large long-term outcome trials are needed to establish the effects of inclisiran treatment on CV risk reduction. The VICTORION-2 Prevent (NCT05030428) trial tests the hypothesis that inclisiran, when compared with placebo, reduces morbidity and mortality in patients with established ASCVD who have LDL-C $\geq$ 1.8 mmol/L (70 mg/dL) despite receiving high-intensity statin therapy.

Methods

Study design

VICTORION-2 Prevent (https://clinicaltrials.gov/study/NCT05030428) is an ongoing randomized, double-blind, parallel-group, placebo-controlled, international multicenter, event-driven trial conducted in participants with established ASCVD as evidenced by a history of MI, ischemic stroke, or symptomatic peripheral artery disease, and elevated levels of LDL-C despite being on a well-tolerated dose of a high-intensity statin therapy.

The protocol was approved by the Ethics Committee and Institutional Review Board affiliated to each investigative site. The study is being conducted in accordance with good clinical practice, Declaration of Helsinki 2002.

Study population

The trial will enroll approximately 16,500 patients across 49 countries. The detailed inclusion and exclusion criteria are summarized in Table I. Briefly, participants are required to provide signed informed consent, have a fasting LDL-C level of $\geq$ 1.8 mmol/L (70 mg/dL), and have established ASCVD at the screening visit. Moreover,

Table I. Patient selection criteria

Inclusion criteria

Participants must meet all of the following criteria:

1. Signed informed consent must be obtained before participation in the study.
2. Male or female aged ≥ 40 y at the time of signing the informed consent.
3. Fasting LDL-C ≥ 1.8 mmol/L (70 mg/dL) measured at the central laboratory.
4. At the screening visit, participants must be on a stable (≥ 4 wk) and well-tolerated lipid-lowering regimen (with or without ezetimibe) that must include a high-intensity statin therapy with either atorvastatin ≥ 40 mg QD or rosuvastatin ≥ 20 mg QD.
5. Established ASCVD defined as any of the following 3 conditions:
    a) MI: spontaneous MI (either ST-elevation MI or non-ST-elevation MI), which was not the result of a percutaneous coronary intervention or a coronary artery bypass graft and which occurred in the period ≥ 4 wk before the first study visit.
    b) Stroke: history of ischemic stroke (an acute episode of focal cerebral, spinal, or visual dysfunction caused by infarction of central nervous system tissues) occurred 4 wk before the first study visit documented by computerized tomography scan, magnetic resonance imaging, or other visualization method. Transient ischemic attack, lacunar infarction, or embolic stroke (not of atherosclerotic origin) are not qualifying events.
    c) Symptomatic PAD, as evidenced by either intermittent claudication with (ABI) < 0.85, prior peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease.

Exclusion criteria

Participants who meet any of the following criteria are not eligible for inclusion in this study:

1. Acute coronary syndrome, ischemic stroke, peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease < 4 wk before the first study visit.
2. Planned or expected cardiac, cerebrovascular, or peripheral artery surgery or re-vascularization within the 6 mo after the first study visit.
3. Heart failure NYHA class III or IV before randomization
4. Active liver disease, defined as any known current infectious, neoplastic, or metabolic pathology of the liver.
5. Previous (within 90 d before the first study visit) or planned treatment with an mAb directed toward PCSK9 (eg, evolocumab and alirocumab).
6. Previous exposure to inclisiran or any other non-mAb PCSK9-targeted therapy, either as an investigational or marketed drug within 2 y before the first study visit.
7. History of hypersensitivity to the study drug, its excipients, or other siRNA drugs.
8. Use of other investigational drugs within 5 half-lives, 30 d, or until the expected pharmacodynamic effect has returned to baseline (eg, biologics), whichever is longer, or longer if required by local regulation, before the first study visit.
9. Severe concomitant non-CV disease that is expected to reduce life expectancy to less than 5 y.
10. History of malignancy that required surgery (excluding local and wide-local excision), radiation therapy, and/or systemic therapy during the 3 y before the study.
11. Any surgical or medical condition that may place the participant at higher risk from their participation in the study or is likely to prevent the participant from complying with the requirements of the study or completing the study.
12. Unwillingness or inability (eg, physical or cognitive) to comply with the study procedures and medication administration (injections) and schedule.
13. Pregnant or nursing (lactating) women.
14. Women of child-bearing potential unless they are using effective methods of contraception during dosing of the study treatment.

ABI, ankle brachial index; *ASCVD*, atherosclerotic cardiovascular disease; *CV*, cardiovascular; *LDL-C*, low-density lipoprotein cholesterol; mAb, monoclonal antibody; *MI*, myocardial infarction; *NYHA*, New York Heart Association; *PAD*, peripheral artery disease; *PCSK9*, proprotein convertase subtilisin/kexin type 9; *QD*, quaque die (daily); *siRNA*, small interfering RNA.

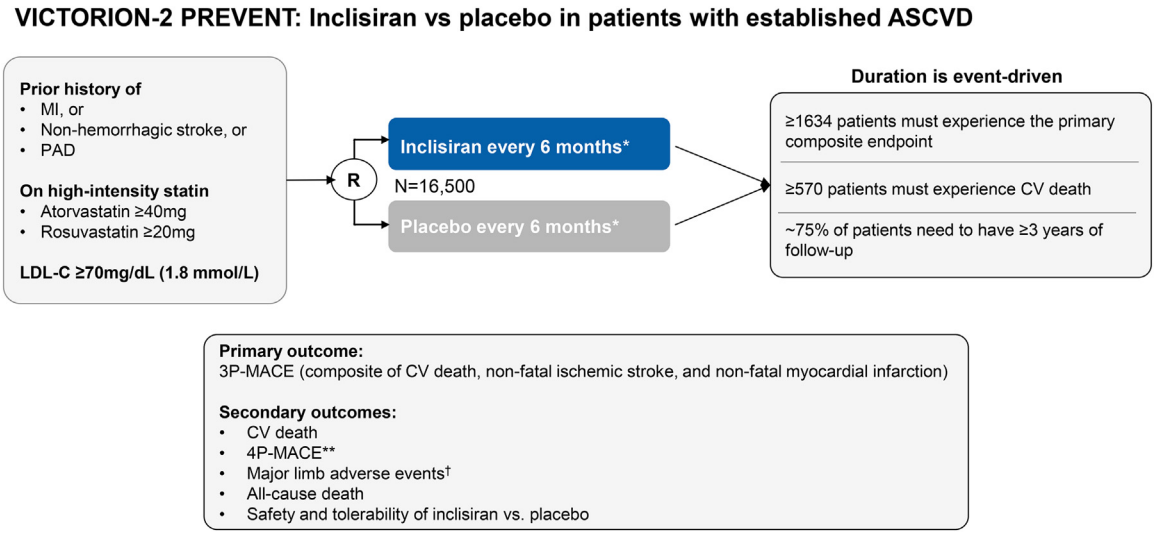
all participants randomized in the trial should be on a stable (≥ 4 weeks), well-tolerated lipid-lowering regimen that includes high-intensity statin therapy, defined as either ≥ 40 mg of atorvastatin once-daily or ≥ 20 mg of rosuvastatin once-daily (Figure). Participants can receive additional lipid-lowering therapy (LLT) according to local guidelines before and after randomization, but treatment optimization before randomization is recommended.

Participants who are on moderate-intensity statin, as defined in the American College of Cardiology and the American Heart Association Cholesterol guidelines.[13] Must enter a statin optimization period of approximately 5 to 7 weeks to ensure that they are stabilized on high-intensity statin therapy for at least 4 weeks before screening.

Procedures

Participants will be randomized in a 1:1 ratio to receive inclisiran sodium 300 mg (equivalent to 284 mg inclisiran) or matching placebo, administered subcuta-

Figure. VICTORION-2 Prevent trial design. Patients are randomized 1:1 to receive inclisiran sodium 300 mg (equivalent to 284 mg inclisiran) or matching placebo on Day 1, Day 90, and every 6 months thereafter. *R*, randomization; *after the initial and 3-month doses; **composite of CV death, nonfatal ischemic stroke, nonfatal myocardial infarction, and urgent coronary revascularization; †MALE; composite of acute lower limb ischemia, lower limb amputation due to ischemia, or urgent lower limb revascularization for ischemia). *3P-MACE*, 3-point major adverse cardiovascular events; *4P-MACE*, 4-point major adverse cardiovascular events; *ASCVD*, atherosclerotic cardiovascular disease; *CV*, cardiovascular; *LDL-C*, low-density lipoprotein cholesterol; *MACE*, major adverse cardiovascular events; *MI*, myocardial infarction; *PAD*, peripheral artery disease.



neously on Day 1, Day 90, and every 6 months thereafter. The study drug will be administered in addition to a stable and well-tolerated dose of a high-intensity statin with or without other LLT (eg, ezetimibe).

Participants will be given lifestyle instructions at each follow-up visit during double-blind treatment period, and fasting lipid panel and liver function tests will be performed at baseline, month 3, and every 12 months until the end of the study. They will be assessed for concomitant medications and surgical procedures at each visit throughout the study. Adverse events (AEs) will be monitored and recorded at each visit.

Background lipid-lowering therapy

Background LLT should be maintained unchanged during the entire duration of the trial. Changes are only allowed for the management of pre-existing medical conditions or in case of AEs requiring such changes, or in case of an LDL-C alert (see below).

The use of any PCSK9-targeted therapy, lomitapide, mipomersen, or any investigational agent is prohibited during the trial.

LDL-C alerts

Participants, investigators, and care teams will remain blinded to the lipid levels obtained after baseline and will be discouraged from obtaining lipid panels during the entire duration of the trial to minimize risk of unblinding caused by lack of anticipated LDL-C lowering effects of the study medication.

After baseline, lipid assessment is performed at month 3 and annually thereafter. If the LDL-C values measured by the study central laboratory are over the prespecified limit of $\geq$ 3.4 mmol/L (130 mg/dL) and if there is an increase of $\geq$ 50% relative to baseline, the investigators will be alerted and asked to review patient adherence to background LLT and, if appropriate, adjust background treatment accordingly to best clinical judgement, including the addition of an additional LLT (eg, ezetimibe or bempedoic acid if not already used). Upon receipt of a lipid alert, the frequency of lipid assessment is increased from annually to every 6 months. The trial team will remain blinded to these alerts.

Outcomes

Efficacy

The primary objective of the VICTORION-2 Prevent trial is to demonstrate the superiority of inclisiran compared with placebo in reducing the risk of 3-point MACE (3P-MACE; composite of CV death, nonfatal MI, and nonfatal ischemic stroke) in participants with established ASCVD and LDL-C $\geq$ 1.8 mmol/L (70 mg/dL) on a high-intensity statin. Thus, the primary outcome is time to first occurrence of 3P-MACE (Table II).

Secondary outcomes are time to occurrence of CV death, time to first occurrence of 4P-MACE (composite of CV death, nonfatal MI, nonfatal ischemic stroke, and ur-

Table II. Primary and secondary outcomes

Primary outcome
• Time to first occurrence of 3P-MACE (composite of CV death, nonfatal MI, and nonfatal ischemic stroke).
Secondary outcomes
• Time to occurrence of CV death. • Time to first occurrence of 4P-MACE (composite of CV death, nonfatal MI, nonfatal ischemic stroke, and urgent coronary re-vascularization). • Time to first occurrence of major adverse limb events (MALE: including acute lower limb ischemia, lower limb amputation due to ischemia, or urgent lower limb revascularization for ischemia). • Time to occurrence of all-cause death. • Long-term safety and tolerability of inclisiran compared with placebo.

3P-MACE, 3-point major adverse cardiovascular events; *4P-MACE*, 4-point major adverse cardiovascular events; *CV*, cardiovascular; *MALE*, major adverse limb events; *MI*, myocardial infarction.

gent coronary revascularization), and major adverse limb events (MALE), time to occurrence of all-cause death, and long-term safety and tolerability of inclisiran (Table II). MALE includes acute lower limb ischemia, lower limb amputation due to ischemia, or urgent lower limb revascularization for ischemia.

Components of the primary and secondary efficacy outcomes will be adjudicated by a central blinded clinical event committee independent of the investigators and the sponsor's personnel, and the data monitoring committee.

Safety

The study will evaluate the long-term safety and tolerability of inclisiran compared with placebo. Given that the safety of inclisiran has been well-characterized in prior Phase 3 studies,[31-34] a selective safety data collection strategy will be used in the present study,[40] with monitoring of serious AEs (SAEs), AEs leading to discontinuation of study the drug, and occurrence of new onset of diabetes mellitus.

Liver function tests will be assessed after randomization in a subset of participants. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and alkaline phosphatase will be evaluated at baseline, month 3, month 15, and yearly thereafter and at the end-of-study visit in all participants who had an AST or ALT $>1 \times$ upper limit of normal at the screening visit (estimated to be approximately 5% of the study population), and in a subset of approximately 15% of the other participants.

Statistical analysis

The trial is event-driven and designed to complete when at least 1,634 participants have experienced a primary composite endpoint and at least 570 CV deaths have occurred, and approximately 75% of the randomized participants have completed a minimum follow-up of 3 years. Assuming an annual event rate in the placebo group of approximately 3% for the 3P-MACE primary endpoint and 1% for the CV death endpoint, a total sample size of approximately 16,500 participants (8,250 per group) would enable the targeted numbers of 3P-MACE and CV death events accumulated over an expected follow-up of up to 6 years. This provides more than 99% and 70% power to detect a 20% risk reduction in the primary endpoint and CV death, respectively. The aggregate event rates of the primary endpoint and the CV death endpoint will be monitored in a blinded manner. The study duration may be adjusted to ensure that assumptions are met.

One formal interim analysis (IA) of efficacy will be performed by an independent data monitoring committee (DMC) when approximately 75% of the target number of primary endpoint events and CV deaths have accumulated. The 1-sided alpha assigned to the IA is set at 0.005. The alpha available at the final analysis is determined using the Haybittle-Peto boundary. The DMC will make a recommendation on whether the study should be stopped based on the totality of the data and the early stopping guidelines prespecified in the protocol and the DMC Charter. An early stop for efficacy will require exceeding the stopping boundaries for 3P-MACE and CV death or exceeding the stopping boundary for 3P-MACE and 4P-MACE and meeting the futility criterion for CV death. Futility will be determined on the basis of conditional power.

The primary efficacy endpoint will be evaluated by a treatment policy estimand, irrespective of treatment adherence and changes to the background LLT. The null hypothesis of the primary endpoint will be tested based on a score test from a Cox regression model stratified by the geographic region and with treatment group as the only factor. This model will also estimate the treatment effect expressed as a hazard ratio and the corresponding 95% CI.

Secondary efficacy endpoints will be analyzed similarly as for the primary endpoint. If the superiority of inclisiran over placebo for the primary endpoint is established, then the treatment effects in the secondary efficacy endpoints will be tested using the following approach to control the type 1 error: first, the CV death endpoint and the composite 4P-MACE endpoint will be tested using a weighted Bonferroni-Holm procedure, with a weight of 90% for CV death and 10% for 4P-MACE. If both CV death and 4P-MACE endpoints achieve statistical significance, then the remaining secondary efficacy endpoints will be tested in a hierarchical order: first MALE, then all-cause mortality. Additional details of the testing procedure are described in Appendix A and Appendix B.

Safety will be analyzed in all randomized participants who received at least one dose of the study drug. Participants will be analyzed according to the treatment received.

Discussion

Therapies targeting PCSK9 have proven to be well-tolerated and effective in lowering LDL-C levels and improving CV outcomes in patients with established ASCVD or acute coronary syndrome, with an approximately 15% to 20% relative risk reduction in CV outcomes.[27,28] However, the relatively short follow-up periods in outcome trials with PCSK9 inhibitors may have resulted in some underestimation of clinical benefit, as the CV benefit observed during the first year was lower than that observed in subsequent years.[27,28,41] In the ODYSSEY OUTCOMES trial, the treatment benefit may have also been blunted because of the deliberate down-titration or treatment interruption in patients who reached very low LDL-C values.[42] A recent analysis suggests that even transient achievement of very low LDL-C levels was associated with persistent large outcome benefits.[43] Furthermore, unequivocal benefit on CV or all-cause mortality was not demonstrated, although signals were observed, including nominally lower all-cause mortality in ODYSSEY OUTCOMES, and lower CV mortality in the FOURIER Open-Label Extension.[41] The perception that PCSK9 inhibitors provide moremodest-than-expected CV outcome benefits, together with the common access barriers, may have been a reason for the low acceptance of these treatments, despite their remarkable efficacy in reducing LDL-C levels and safety profile.[46,47] These limitations highlight the need for an alternative approach to PCSK9 inhibition that can maintain durable lipid lowering and be evaluated over a longer follow-up period.

Inclisiran is a siRNA directed against PCSK9, which is effective at lowering LDL-C and has potential advantages over anti-PCSK9 mAbs, providing long-term and sustained LDL-C lowering with infrequent dosing (twice-yearly after initial and 3-month doses), which could improve adherence to treatment.[44,45] The CV benefits of inclisiran are hypothesized to be driven primarily by sustained LDL-C lowering. In addition, prior PCSK9 inhibitor outcome trials suggested that, among patients with elevated baseline lipoprotein(a) (Lp[a]), PCSK9 inhibitor-associated reductions in Lp(a) may contribute to the clinical benefit.[46,47] Beyond these effects, inclisiran administration is not associated with "scalloping" of LDL-C levels between injections as seen with anti-PCSK9 mAbs, which require injections every 2 to 4 weeks. However, the clinical impact of the modest Lp(a) lowering produced by PCSK9 inhibition and of the absence of LDL-C "scalloping" remains uncertain.[45] A trial of prolonged PCSK9 inhibition with inclisiran could address possible limitations of previous trials,[27,28] by allowing sufficient follow-up time and accrual of endpoint events. This would enable assessment of whether potential mechanistic advantages translate into reductions in CV events, including CV mortality, particularly if adherence is maintained over the long term. Clear evidence of CV events and mortality reduction may allow more patients to benefit from this treatment.

VICTORION-2 Prevent is a large, placebo-controlled long-term trial with a sufficient number of CV outcomes to provide robust evidence regarding the clinical benefit and safety of inclisiran. This trial will compare inclisiran to placebo while ensuring that all patients are on high intensity statins, with or without additional LLT before trial initiation, and receive standard of care treatment. Given the cost and barriers to access to PCSK9 inhibitors, it is particularly important that inclisiran was tested in patients who are all receiving high intensity statin therapy at baseline, whereby all patients were receiving a minimum of 20 mg rosuvastatin or 40 mg atorvastatin, ensuring that any potential benefit observed in the trial could not have been achieved by mere intensification of statin therapy. The trial is placebo-controlled as using a noninferiority design to compare inclisiran to an active control of PCSK9 inhibition would have required an extremely large sample size, becoming impractical.

The LDL-C eligibility threshold of $\geq$ 1.8 mmol/L (70 mg/dL) was selected because it reflected the standard of care for secondary prevention at the time VICTORION-2 PREVENT was designed and because it is the level that often determines reimbursement eligibility for PCSK9 inhibitors in many countries.

An additional design feature of VICTORION-2 PREVENT is the use of LDL-C alerts to trigger more frequent lipid testing and to prompt investigators to review patients' adherence to background LLT and, when appropriate, to intensify therapy in accordance with clinical practice to support patient safety. Inclisiran provides sustained and effective LDL-C reduction and hence these alerts are anticipated to occur more frequently in the placebo arm, potentially leading to greater background LLT optimization, more frequent lipid monitoring, and enhanced adherence assessment among control patients. This potential between-group difference could attenuate differences between the treatment arms in CV outcomes and bias estimated treatment effects toward the null. Accordingly, the primary and secondary efficacy analyses use a treatment policy estimand to handle changes in background LLT, thereby providing a conservative estimate of treatment benefit associated with inclisiran. This analytic approach is also intended to reflect real-world practice and help ensure that the trial's findings are implementable. They also minimize the risk of leaving high-risk participants with untreated extremely high LDL-C levels for up to several years without intervening. Moreover, all modifications to background LLTs are

prospectively captured, and additional sensitivity and supplementary analyses are planned to assess the robustness of the primary analysis, including analysis under hypothetic strategy for handing the intercurrent events of switching to commercially available PCSK9-targeted therapy and analysis under multiple imputation to assess the impact of the noninformative censoring assumption in the primary analysis. This approach balances methodological rigor with real-world relevance.

In addition to VICTORION-2 Prevent, another large, randomized trial, ORION-4, explores the CV outcome benefits and safety of inclisiran for secondary prevention in patients with ASCVD (NCT03705234). Having two large outcome trials increases the robustness of the results.[48] Differences in trial design, including inclusion criteria, geographical range, and primary outcomes, will allow for the generation of complementary evidence on the impact of inclisiran on CV outcomes in the ASCVD population. The VICTORION-2 Prevent inclusion criteria and age range are broader, with patients enrolled from 49 countries, while ORION-4 enrolment focused on patients from the United Kingdom and the United States. Moreover, in the VICTORION-2 Prevent trial, all patients are on high-intensity statins and the primary outcome is limited to 3-P MACE, whereas the ORION-4 trial allows enrolment of patients on moderate-intensity statin and uses a 4-P MACE primary outcome. Finally, both trials have planned a longer follow-up than those trials on the anti-PCSK9 mAbs, which may increase the likelihood of demonstrating a CV mortality benefit. A pooled patient data level analysis of both trials is planned.

An interesting additional feature of VICTORION-2 Prevent is the selective safety data collection, which was implemented with the approval of regulatory agencies.[40] given that inclisiran has already accumulated substantial evidence of LDL-C–lowering efficacy and safety in prior trials[31-33] and is approved for clinical use in many countries.[35-38] The safety profile of inclisiran in the Phase 3 pivotal studies has been well-established, with injection site reactions being the most commonly reported adverse drug reaction.[31-33] Selective safety data collection means collecting SAEs, AEs leading to drug discontinuation and occurrence of new onset of diabetes mellitus) instead of collecting all AEs, and conducting limited safety assessments related to liver function as described above. This approach will improve the efficiency of the trial and lessen the burden on study participants and investigators by reducing the frequency of patient visits, routine laboratory tests, electrocardiograms, physical examinations and the collection of nonserious AEs.

In conclusion, VICTORION-2 Prevent is an ongoing, large, placebo-controlled, randomized trial that evaluates the CV benefits and safety of inclisiran for patients with established ASCVD who are not at the recommended LDL-C goal despite high-intensity statin treatment. The study includes an extended follow-up and no down-titration of treatment, both of which increase the likelihood of observing an effect on CV mortality.

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CRediT authorship contribution statement

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Conflict of interest

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Supplementary materials

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