IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial

*Paul M Ridker, Matt Devalaraja, Florian M M Baeres, Mads D M Engelmann, G Kees Hovingh, Milana Ivkovic, Larry Lo, Douglas Kling, Pablo Pergola, Dominic Raj, Peter Libby, Michael Davidson, on behalf of the RESCUE Investigators**

Summary

Background IL-6 has emerged as a pivotal factor in atherothrombosis. Yet, the safety and efficacy of IL-6 inhibition among individuals at high atherosclerotic risk but without a systemic inflammatory disorder is unknown. We therefore addressed whether ziltivekimab, a fully human monoclonal antibody directed against the IL-6 ligand, safely and effectively reduces biomarkers of inflammation and thrombosis among patients with high cardiovascular risk. We focused on individuals with elevated high-sensitivity CRP and chronic kidney disease, a group with substantial unmet clinical need in whom previous studies in inflammation inhibition have shown efficacy for cardiovascular event reduction.

Methods RESCUE is a randomised, double-blind, phase 2 trial done at 40 clinical sites in the USA. Inclusion criteria were age 18 years or older, moderate to severe chronic kidney disease, and high-sensitivity CRP of at least 2 mg/L. Participants were randomly allocated (1:1:1:1) to subcutaneous administration of placebo or ziltivekimab 7·5 mg, 15 mg, or 30 mg every 4 weeks up to 24 weeks. The primary outcome was percentage change from baseline in high-sensitivity CRP after 12 weeks of treatment with ziltivekimab compared with placebo, with additional biomarker and safety data collected over 24 weeks of treatment. Primary analyses were done in the intention-to-treat population. Safety was assessed in all patients who received at least one dose of assigned treatment. The trial is registered with ClinicalTrials.gov, NCT03926117.

Findings Between June 17, 2019, and Jan 14, 2020, 264 participants were enrolled into the trial, of whom 66 were randomly assigned to each of the four treatment groups. At 12 weeks after randomisation, median high-sensitivity CRP levels were reduced by 77% for the 7·5 mg group, 88% for the 15 mg group, and 92% for the 30 mg group compared with 4% for the placebo group. As such, the median pairwise differences in percentage change in high-sensitivity CRP between the ziltivekimab and placebo groups, after aligning for strata, were –66·2% for the 7·5 mg group, –77·7% for the 15 mg group, and –87·8% for the 30 mg group (all p<0·0001). Effects were stable over the 24-week treatment period. Dose-dependent reductions were also observed for fibrinogen, serum amyloid A, haptoglobin, secretory phospholipase A2, and lipoprotein(a). Ziltivekimab was well tolerated, did not affect the total cholesterol to HDL cholesterol ratio, and there were no serious injection-site reactions, sustained grade 3 or 4 neutropenia or thrombocytopenia.

Interpretation Ziltivekimab markedly reduced biomarkers of inflammation and thrombosis relevant to atherosclerosis. On the basis of these data, a large-scale cardiovascular outcomes trial will investigate the effect of ziltivekimab in patients with chronic kidney disease, increased high-sensitivity CRP, and established cardiovascular disease.

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*Investigators are listed in the appendix (pp 2–3)

Center for Cardiovascular Disease Prevention (Prof P M Ridker MD) **and the Division of Cardiovascular Medicine** (Prof P M Ridker, Prof P Libby MD), **Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; Corvidia Therapeutics, Waltham, MA, USA** (M Devalaraja PhD, L Lo MD, D Kling MD, Prof M Davidson MD); **Novo Nordisk, Bagsvaerd, Denmark** (F M M Baeres MD, M D M Engelmann MD, Prof G K Hovingh MD, M Ivkovic MSc); **Renal Associates, San Antonio, TX, USA** (Prof P Pergola MD); **Division of Kidney Diseases and Hypertension, George Washington University, Washington, DC, USA** (Prof D Raj MD)

Correspondence to:
Prof Paul M Ridker, Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02215, USA
pridker@bwh.harvard.edu

See Online for appendix

Introduction

Inflammation inhibition targeting the central NLRP3 inflammasome to IL-1 to IL-6 pathway of innate immunity is an emerging method for atherosclerosis treatment and prevention.[1] This principle was first demonstrated in the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) using IL-1β inhibition[2] and has now been confirmed in two trials of colchicine, an agent that through microtubule disruption might indirectly inhibit NLRP3 function.[3,4] These trials share a common mechanistic mediator, which is downstream inhibition of the central signalling cytokine IL-6, in turn reducing the clinical biomarker high-sensitivity CRP.

In CANTOS, the magnitude of atherosclerosis prevention associated with canakinumab was proportional to the magnitude of achieved reduction in IL-6 and high-sensitivity CRP levels following treatment.[5,6] Further, the magnitude of residual inflammatory risk in CANTOS associated with IL-6 was substantially greater than that of IL-18, another cytokine activated by the NLRP3 inflammasome.[7] By contrast, a contemporary inflammation reduction trial using low-dose methotrexate neither

Research in context

Evidence before this study

Recent randomised trials have demonstrated that anti-cytokine and anti-inflammatory therapies can reduce cardiovascular event rates, and evolving genetic, murine, translational, and human epidemiological data suggest that IL-6 might be a causal mediator of this process. However, the safety and efficacy of IL-6 inhibition among individuals at high atherosclerotic risk but without a systemic inflammatory disorder is largely unknown.

Added value of this study

The RESCUE trial data provides the first evidence that inhibition of IL-6 with the novel monoclonal ligand antibody ziltivekimab reduces in a dose-dependent manner multiple inflammatory and thrombotic biomarkers relevant for atherosclerosis, in a critical population of patients with chronic kidney disease and high cardiovascular risk who have considerable unmet need, yet are free of a clinically apparent inflammatory condition.

Implications of all the available evidence

Beyond aggressive lipid lowering, future treatment of atherosclerosis will probably include targeted anti-inflammatory therapy that inhibits the IL-1 to IL-6 pathway of innate immunity. On the basis of these phase 2 efficacy and safety data, a large-scale cardiovascular outcomes trial of ziltivekimab will be conducted among patients with chronic kidney disease, increased CRP, and established cardiovascular disease.

reduced IL-6 nor vascular event rates,[8] suggesting that anti-inflammatory agents that do not reduce IL-6 are unlikely to be effective for atheroprotection.

Beyond the internal consistency of these recent clinical trials, it has been known for two decades that IL-6 levels predict vascular events in primary and secondary prevention with at least as much fidelity as the downstream clinical biomarker high-sensitivity CRP.[9–14] Unlike CRP, mendelian randomisation studies indicate that genetic variants in the IL-6 receptor signalling pathway associate with lifelong risks of coronary heart disease, suggesting that IL-6 is likely to be a causal factor for atherosclerotic progression.[15,16] Genetic data have also affirmed a role of IL-6 signalling in multiple forms of atherosclerosis, including myocardial infarction, peripheral arterial disease, and aortic aneurysm formation.[17] In parallel, experimental data have long implicated IL-6 directly in the atherosclerotic process.[18–20] Moreover, genetically modified mice with high IL-6 levels have increased susceptibility to atherogenesis when fed a high-fat diet, yet have fewer atherosclerotic lesions after treatment with an anti-mouse IL-6 receptor antibody.[21]

On the basis of these data, we hypothesised that direct targeting of IL-6 might have the potential to maximise anti-inflammatory atherosclerotic benefit while minimising off-target effects among high atherosclerotic risk individuals who are free of a clinically apparent systemic inflammatory illness.[1,22,23] One agent under investigation is ziltivekimab, a narrow-spectrum fully human monoclonal antibody targeting the IL-6 ligand that, unlike other clinically available IL-6 signalling inhibitors, is being developed specifically for atherosclerosis treatment. As a monoclonal antibody targeting the IL-6 ligand rather than the IL-6 receptor, ziltivekimab used at lower doses could have fewer adverse effects on lipid levels, haematological indices, and hepatic function than other approved IL-6 agents such as tocilizumab and sarilumab.

To address these issues, we conducted a phase 2 trial to assess the effects of ziltivekimab on multiple biomarkers of inflammation and thrombosis, and to address whether there might be dose response effects for safety or efficacy. The population selected for this trial was patients at high cardiovascular risk with chronic kidney disease and elevated high-sensitivity CRP, a group where previous studies indicate that IL-6 levels correlate with severity of renal impairment as well as level of atherosclerotic risk.[24–30] Further, as shown within CANTOS, participants with chronic kidney disease and elevated IL-6 preferentially benefit from targeted anti-inflammatory therapy.[31] In RESCUE, we assessed effects of antibody-mediated IL-6 inhibition on inflammation in patients with advanced chronic renal disease.

Methods

Study design and participants

RESCUE is a parallel-group, double-blind, randomised, placebo-controlled, phase 2 trial done at 40 clinical sites in the USA (appendix pp 3–4). The study protocol was approved by the independent ethics committee of the institutional review board for each centre.

Participants aged 18 years or older were eligible for screening if they had stage 3–5 chronic kidney disease (estimated glomerular filtration rate [eGFR] >10 mL/min per 1·73 m² and <60 mL/min per 1·73 m² using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation) and residual inflammatory risk defined as a high-sensitivity CRP level of 2 mg/L or greater at entry. Major exclusion criteria were an absolute neutrophil count less than $2·0\times10^9$ per L, platelet count less than 120×10^9 per L, spot urine to creatine ratio greater than 4, positive testing for active tuberculosis, HIV, or hepatitis B or C, or the chronic use of immunosuppressive therapies. Full trial inclusion and exclusion criteria are in the trial protocol (appendix pp 56–57). Written informed consent was obtained from participants before participation.

Randomisation and masking

Eligible patients were randomly allocated in a 1:1:1:1 ratio to placebo or ziltivekimab at 7·5 mg, 15 mg, or 30 mg. We used the Clintrak web-based interactive response technology system for central randomisation; this system is

externally validated and Code of Federal Regulations 21 part 11 compliant. The randomisation was stratified by two variables, chronic kidney disease stage (3 or 4 and 5) at screening and haemoglobin (≥11 g/dL or <11 g/dL) at baseline. Once the patient qualified for the study, the central system assigned the randomisation number, which was electronically communicated to the site. All participants and investigators were masked to treatment assignment.

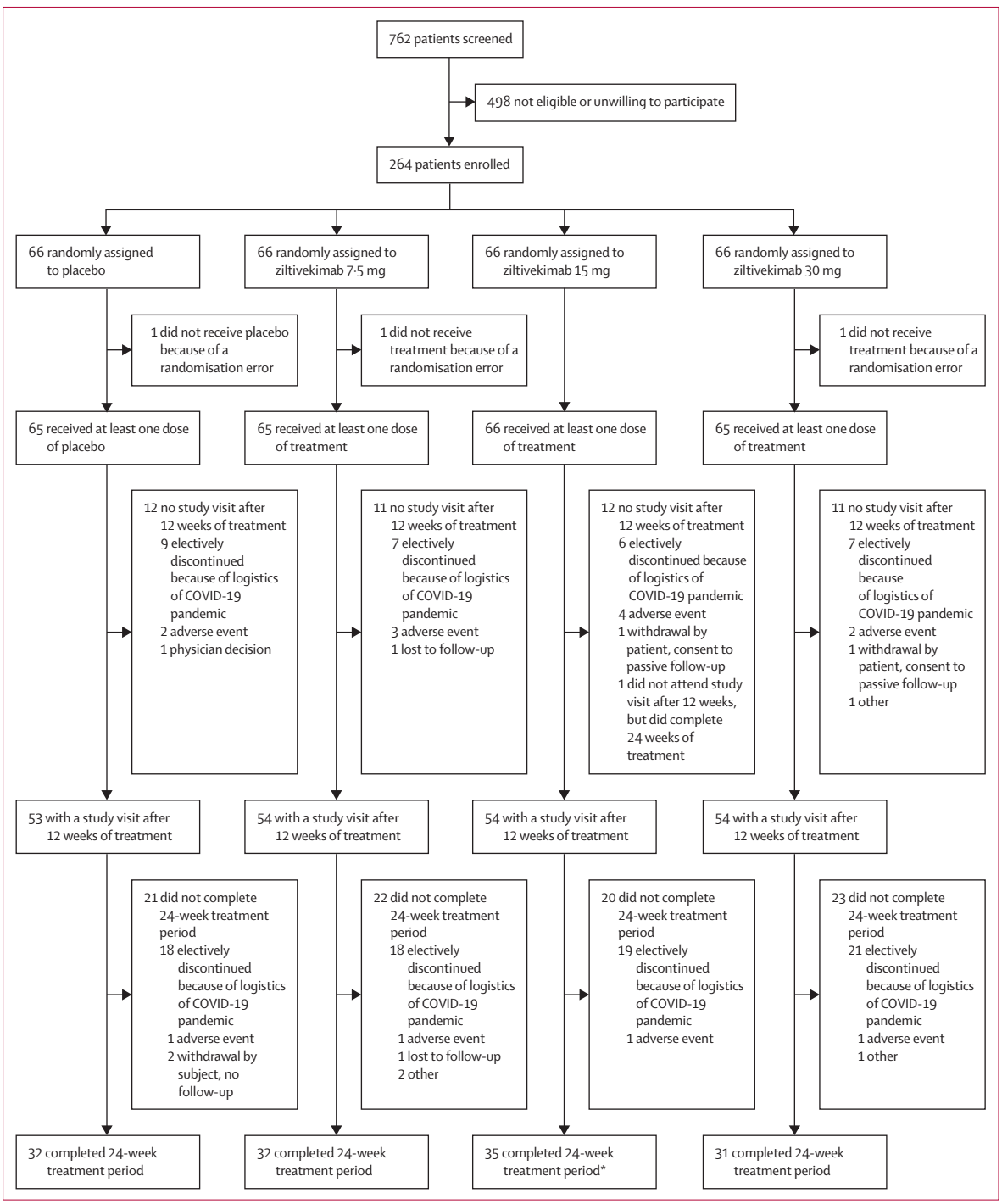

Figure 1: **Trial profile**
No follow-up=participant withdrew consent and refused all further follow-up. Passive follow-up=participant withdrew consent and did not participate further with the trial procedures, but consented to some follow-up. *As noted on the trial profile, one participant did not attend a visit after 12 weeks but did complete the 24 weeks of treatment.

	Placebo (n=66)	Ziltivekimab 7·5 mg (n=66)	Ziltivekimab 15 mg (n=66)	Ziltivekimab 30 mg (n=66)
Age, years	66·0 (60·0–74·0)	70·0 (60·0–74·0)	65·5 (59·0–74·0)	68·0 (61·0–76·0)
Gender				
Female	29 (44%)	32 (48%)	36 (55%)	32 (48%)
Male	37 (56%)	34 (52%)	30 (45%)	34 (52%)
Race				
White	50 (76%)	48 (73%)	49 (74%)	52 (79%)
Black or African American	16 (24%)	18 (27%)	12 (18%)	14 (21%)
Other	0	0	5 (8%)	0
Body-mass index, kg/m²	35·90 (29·20–39·50)	32·70 (27·50–40·20)	34·40 (29·60–38·90)	34·85 (31·30–39·80)
Diabetes*	50 (76%)	41 (62%)	48 (73%)	48 (73%)
Hypertension†	62 (94%)	60 (91%)	60 (91%)	60 (91%)
Atherosclerotic cardiovascular disease	37 (56%)	29 (44%)	27 (41%)	33 (50%)
Statin use	45 (68%)	44 (67%)	45 (68%)	45 (68%)
Chronic kidney disease stage‡				
3a	19 (29%)	16 (24%)	23 (35%)	19 (29%)
3b	23 (35%)	30 (45%)	29 (44%)	26 (39%)
4	17 (26%)	16 (24%)	10 (15%)	17 (26%)
5	5 (8%)	3 (5%)	4 (6%)	3 (5%)
eGFR, mL/min per 1·73m²	38·00 (26·33–48·33)	35·33 (26·00–45·33)	37·33 (31·33–50·33)	37·17 (27·67–45·67)
High-sensitivity CRP, mg/L	5·80 (3·25–9·85)	5·53 (3·50–9·25)	5·70 (3·45–8·10)	5·80 (3·65–8·90)
IL-6, pg/mL§	5·24 (3·60–7·62)	4·85 (3·06–8·28)	5·11 (3·79–9·44)	6·63 (4·07–9·01)

Data are median (IQR) or n (%). eGFR=estimated glomerular filtration rate. *Includes patients with glycated haemoglobin >6·5%, those with a history of diabetes at baseline, or those on diabetes medication at baseline; diabetes history of patients was identified using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0. †Includes patients with a history of hypertension at baseline or those on medication for hypertension at baseline, identified using MedDRA. ‡Baseline chronic kidney disease value based on laboratory results and calculated as the average of all eGFR assessments before the first dose. Chronic kidney disease stages 3a and 3b indicate stage 3 patients with baseline GFR of 45–59 mL/min per 1·73m² (stage 3a) and 30–44 mL/min per 1·73m² (stage 3b). §Baseline IL-6 measurements missing for some patients: placebo n=48, ziltivekimab 7·5 mg n=48, ziltivekimab 15 mg n=52, ziltivekimab 30 mg n=54.

Table 1: **Baseline characteristics of the RESCUE trial population**

Procedures

Participants received placebo or ziltivekimab at doses of 7·5 mg, 15 mg, or 30 mg subcutaneously once every 4 weeks for up to 24 weeks. On-treatment analyses were planned for inflammatory biomarkers, lipids, and safety after 12 weeks of treatment. Participants were then to be followed up on treatment up to 24 weeks, after which the study drug was to be discontinued and an additional safety washout period of 2 weeks done at the end of the trial.

Laboratory assessments done throughout the trial included fibrinogen, serum amyloid A (SAA), LDL cholesterol, HDL cholesterol, total cholesterol, triglycerides, lipoprotein(a), apolipoprotein A1 (APOA1), apolipoprotein B (APOB), haptoglobin, and secretory phospholipase A2 (sPLA2). Safety parameters included measures of alanine aminotransferase, aspartate aminotransferase, and indices of complete blood count. All laboratory measures were assessed in a central core laboratory facility (Medpace Reference Laboratories, Cincinnati, OH, USA).

Patient-reported outcomes were assessed with the Patient-Reported Outcomes Measurement Information System, Corvidia electronic patient-reported outcomes, Patient Global Impression of Severity index, Patient Global Impression of Change index, Optum SF-36 version 2, and EQ-5D-5L index.

Endpoints

The trial primary inflammation reduction endpoint was predefined as the change in high-sensitivity CRP from baseline (average of the high-sensitivity CRP value at screening and at the day of randomisation) to the value measured after 12 weeks of treatment (at week 13, because randomisation is at week 1).

We also analysed the proportions of individuals in each group who achieved high-sensitivity CRP reductions of at least 50% or on-treatment high-sensitivity CRP levels less than 2 mg/L at 12 weeks versus baseline.

The trial secondary endpoints were changes in fibrinogen and SAA from baseline to week 13.

Exploratory analyses included longer-term changes in inflammatory, thrombotic, and lipid biomarkers from baseline to week 13 and baseline to week 24 and proportion of patients with a high-sensitivity CRP response (defined as <2·0 mg/L) between week 13 and 24. Change in patient-reported outcomes from baseline to week 13 and baseline to week 24 was an exploratory outcome but results are not presented here.

Statistical analysis

To calculate sample size, we relied on the results of a previous completed single-dose, placebo-controlled, pharmacokinetic and pharmacodynamic study of

ziltivekimab (NCT03126318). On the basis of observed treatment difference in percentage change from baseline in high-sensitivity CRP of –60·74% between the ziltivekimab and placebo groups, and the associated pooled SD of 16·893% in high-sensitivity CRP at week 4 from the final analysis of the previous study, a sample size of 54 per group was estimated to yield more than 99% power at the 0·05 level of significance. With an assumed dropout rate of 10%, a sample size of 60 per group was considered suitable for this study.

As prespecified in the statistical analysis plan (appendix p 340), should the primary and secondary endpoints not meet the normality assumption, comparison of percentage change from baseline to 12 weeks since randomisation between ziltivekimab and placebo was analysed using the Wilcoxon two-sample test and the location shift between each ziltivekimab group and placebo, with the associated 95% CI, using the Hodges-Lehmann estimator. The analyses accounted for baseline haemoglobin (≥11 g/dL or <11 g/dL) and chronic kidney disease stage (3, 4, or 5). Likewise, the non-parametric analysis was done for other continuous endpoints and, post hoc, for LDL cholesterol, HDL cholesterol, sPLA2, haptoglobin, the total cholesterol to HDL cholesterol ratio, and the APOB to APOA1 ratio.

Comparison of binary variables was done using a 2×2 table χ^2 test. In addition to prespecified endpoints, analysis of the proportion of participants who had high-sensitivity CRP reductions of at least 50% and high-sensitivity CRP levels less than 2 mg/L after 12 weeks of treatment was done.

p values are two-sided, with a level of 0·05 considered to indicate statistical significance, unless indicated otherwise. No adjustment for multiplicity has been done. The primary endpoint was analysed on an intention-to-treat basis that included all randomly assigned patients. Safety was assessed in all patients who received at least one dose of assigned treatment. Missing values were not imputed, and only participants without missing values at the landmark visit contributed to the non-parametric analyses. Sensitivity analyses were also conducted to assess the robustness of the primary analysis to the possible violation of the missing-at-random assumption (appendix p 5).

SAS software (version 9.3 or later) was used for statistical analysis. The trial is registered at ClinicalTrials.gov, NCT03926117.

Role of the funding source

The funder of the study was involved in study design, data collection, data analysis, and data interpretation but not writing of the report.

Results

Between June 17, 2019, and Jan 14, 2020, 264 participants were enrolled into the trial, of whom 66 were randomly assigned to each of the four treatment groups (figure 1). One patient in each of the placebo, ziltivekimab 7·5 mg,

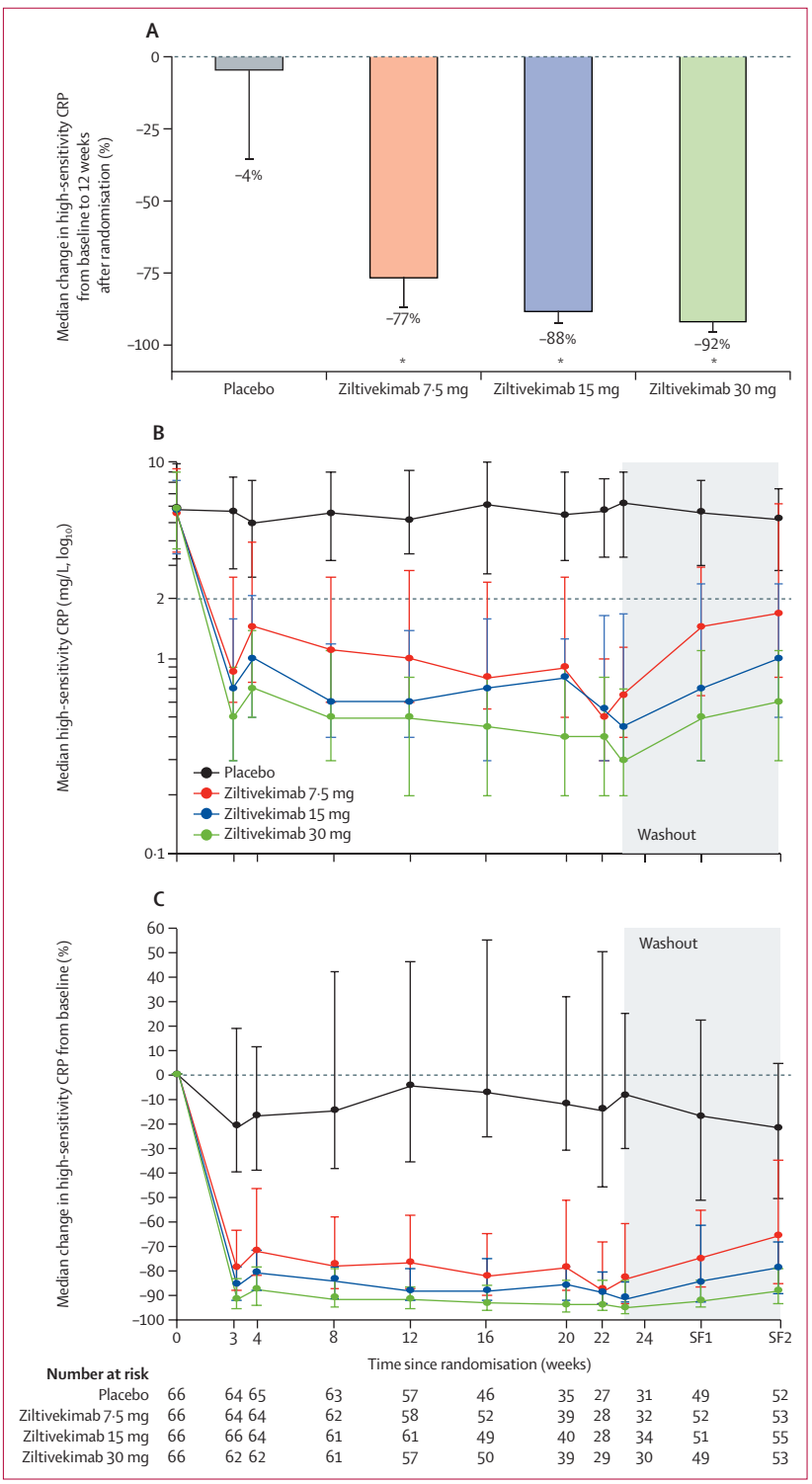

Figure 2: **Effects on high-sensitivity CRP in the ziltivekimab and placebo groups**
(A) Median percentage change in high-sensitivity CRP from baseline to 12 weeks of treatment. (B) Median high-sensitivity CRP over the 24-week treatment period. (C) Median percentage change from baseline in high-sensitivity CRP over the 24-week treatment period. SF=safety follow-up. *p<0·0001.

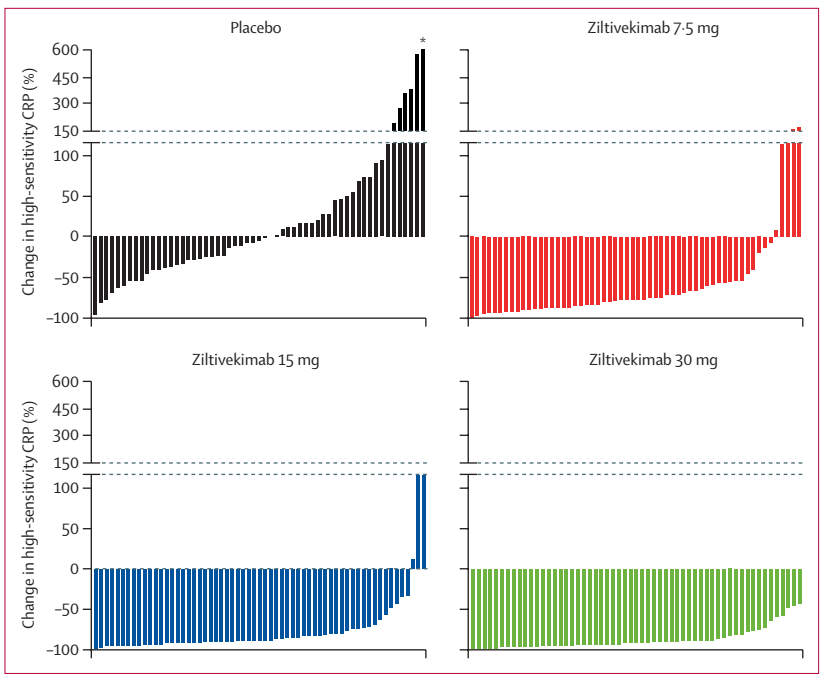

Figure 3: **Waterfall plots showing individual high-sensitivity CRP percentage changes from baseline to 12 weeks in the four treatment groups**
*One patient in the placebo group had a high-sensitivity CRP increase from baseline greater than 600%.

and ziltivekimab 30 mg groups did not start treatment and were not included in safety analyses.

With the onset of the COVID-19 pandemic and concern that an exogenous cause of CRP increase in the general population could skew outcomes for the trial primary inflammation endpoints, a decision was made by the sponsor and Executive Committee to terminate the trial at a time when 215 participants had completed the 12-week primary treatment and efficacy period. This decision was made without knowledge by the investigators, sponsor, or any study personnel of any outcome data in the trial, which was fully masked at that time.

We present data in this report for the 215 trial participants who completed the 12-week primary efficacy period as well as all available data from participants who completed the full 24-week secondary efficacy period at the time of trial closure because of the COVID-19 pandemic.

Baseline clinical characteristics were similar across treatment groups (table 1). The median age of the patient population was 68 years (IQR 60·0–74·5) and 129 (49%) of the 264 participants were women, 65 (25%) were non-White, 187 (71%) had diabetes, 126 (48%) had known atherosclerotic disease, and 179 (68%) were taking statin therapy. 77 (29%) patients had stage 3a, 108 (41%) had stage 3b, 60 (23%) had stage 4, and 15 (6%) had stage 5 chronic kidney disease. Median baseline high-sensitivity

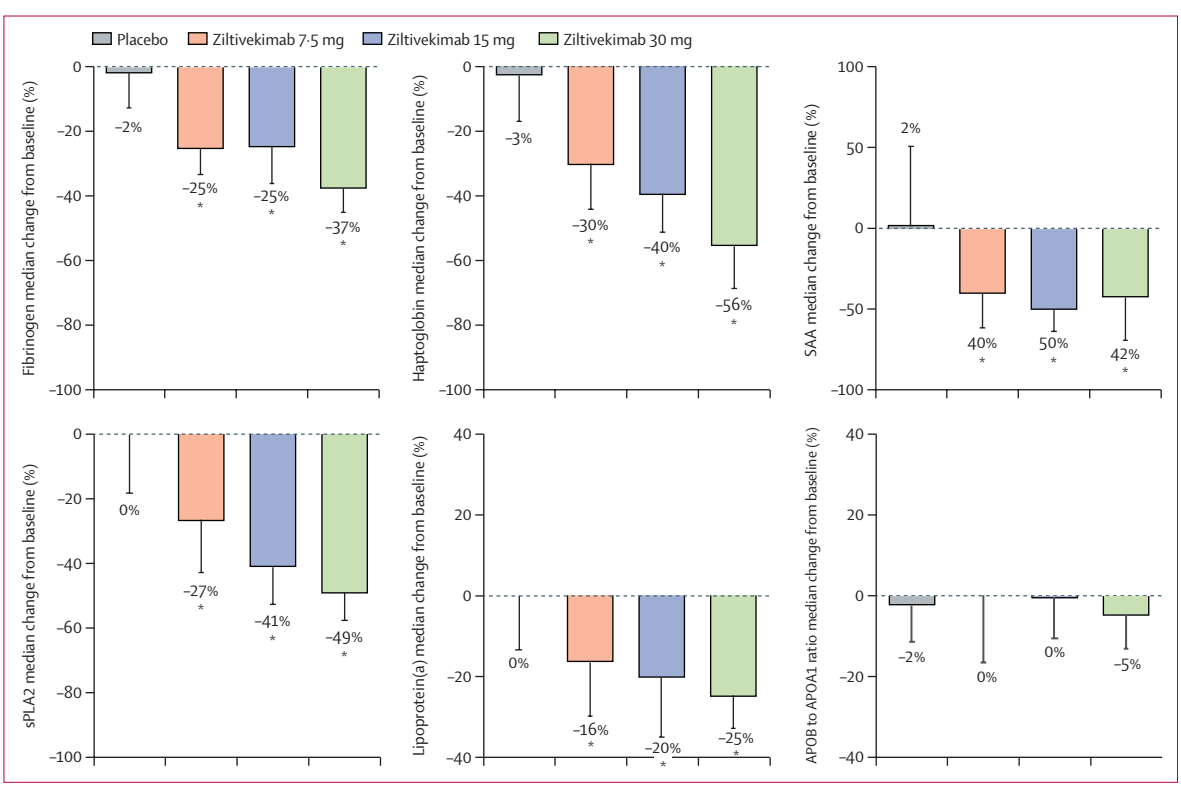

Figure 4: **Median percentage changes from baseline to 12 weeks of treatment for fibrinogen, haptoglobin, serum amyloid A (SAA), secretory phospholipase A2 (sPLA2), lipoprotein(a), and the apolipoprotein A1 (APOA1) to apolipoprotein B (APOB) ratio**
*p<0·0001.

CRP was 5·75 mg/L (3·45–9·00), median IL-6 was 5·55 pg/mL (3·70–8·85), and median eGFR was 36·83 mL/min per 1·73 m² (27·67–47·50; table 1).

For the primary endpoint of percentage median change in high-sensitivity CRP at 12 weeks of treatment, all ziltivekimab treatment groups had significantly greater reductions than the placebo group (figure 2A; appendix p 8). Among those allocated to placebo, there was a 4% reduction in median high-sensitivity CRP at 12 weeks. By contrast, the reductions in the ziltivekimab groups were 77% for the 7·5 mg group, 88% for the 15 mg group, and 92% for the 30 mg group (all p<0·0001). As such, the median pairwise differences in percentage change in high-sensitivity CRP between the placebo and ziltivekimab groups were, after aligning for strata, –66·2 for the 7·5 mg group, –77·7 for the 15 mg group, and –87·8% for the 30 mg group (all p<0·0001).

All comparisons between the three ziltivekimab groups and the placebo group for reduction in high-sensitivity CRP of at least 50% at 12 weeks, on-treatment high-sensitivity CRP less than 2 mg/L at 12 weeks, and both of these on-treatment parameters were significant (p<0·0001; appendix p 6).

Similar findings were observed among trial participants who completed the 24-week secondary efficacy treatment period, with resolution back towards baseline levels during the subsequent 2-week washout period (figure 2B, C). Dose-dependent effects of zilitivekimab on high-sensitivity CRP were observed over time in terms of both absolute levels (figure 2B) and median percentage change (figure 2C), though formal statistical testing across doses was not prespecified in the protocol.

Waterfall plots of high-sensitivity CRP percentage change for individual trial participants in the four groups at 12 weeks showed a wide distribution of changes in the placebo group, but most participants receiving ziltivekimab had large and persistent reductions in high-sensitivity CRP (figure 3).

Compared with placebo, ziltivekimab was associated with similar significant dose-dependent reductions for the secondary biomarker endpoints of fibrinogen and SAA, and the exploratory endpoints of sPLA2 and haptoglobin (figure 4; appendix pp 8–9).

Ziltivekimab significantly reduced levels of lipoprotein(a) by 16·4–25·0% and resulted in small increases in APOB, HDL cholesterol, and APOA1 such that there was no substantive shift in either the total cholesterol to HDL cholesterol ratio or in the APOB to APOA1 ratio (figure 4; appendix pp 6, 9–11). Triglycerides were increased in the ziltivekimab groups compared with the placebo group. No differences between ziltivekimab and placebo were observed after 12 weeks of treatment with respect to eGFR or the urine albumin to creatinine ratio (appendix p 14).

One case of grade 2 neutropenia in the ziltivekimab 7·5 mg group was reported and no cases of sustained (ie, on two consecutive visits) grade 3 or 4 neutropenia. Ziltivekimab had minimal effect on platelet counts, with no cases of sustained grade 2–4 thrombocytopenia.

No increases of aspartate aminotransferase or alanine aminotransferase to more than three times the upper limit of normal were observed in any of the ziltivekimab groups. Throughout the course of the trial, no serious injection-related reactions were observed. One participant

	Placebo (n=65)	Ziltivekimab 7·5 mg (n=65)	Ziltivekimab 15 mg (n=66)	Ziltivekimab 30 mg (n=65)
Any treatment-emergent adverse events	45 (69%)	43 (66%)	44 (67%)	47 (72%)
Mild	19 (29%)	15 (23%)	18 (27%)	16 (25%)
Moderate	18 (28%)	16 (25%)	19 (29%)	23 (35%)
Severe	8 (12%)	12 (18%)	7 (11%)	8 (12%)
Serious injection-related reactions	0	0	0*	0
Any infection or infestation	19 (29%)	18 (28%)	21 (32%)	14 (22%)
Any serious infection	3 (5%)	7 (11%)	3 (5%)	2 (3%)
Anaphylaxis	0	0	0	0
Sustained neutropenia†				
Grade 1 (1500 to <2000 cells per mm³)	1 (2%)	1 (2%)	2 (3%)	1 (2%)
Grade 2 (1000 to <1500 cells per mm³)	0	1 (2%)	0	0
Grade 3 or 4 (<1000 cells per mm³)	0	0	0	0
Sustained thrombocytopenia†				
Grade 1 (75 000 to <100 000 cells per mm³)	0	0	2 (3%)	1 (2%)
Grade 2, 3, or 4 (<75 000 cells per mm³)	0	0	0	0

Treatment-emergent adverse events are adverse events that initiated or worsened on or after the date of first dose of study drug up to the end of safety follow-up. Mild, moderate, and severe were as defined by the investigator. CTCAE=Common Terminology Criteria for Adverse Events. *One participant in the ziltivekimab 15 mg group reported short-term discomfort at the injection site. †By CTCAE grade; denominators are numbers of patients with at least two non-missing values after the first dose of study drug (placebo n=65, ziltivekimab 7·5 mg n=65, ziltivekimab 15 mg n=66, ziltivekimab 30 mg n=64); CTCAE grade is assigned as the grade from the second value; sustained indicates abnormal values on at least two consecutive study visits.

Table 2: **Adverse events**

in the ziltivekimab 15 mg group reported short-term discomfort at the injection site. Treatment-emergent adverse events considered to be mild, moderate, or severe, were similar between the placebo and ziltivekimab groups (table 2).

During the course of the trial, there was one cardiovascular death in the placebo group, one non-fatal myocardial infarction in the ziltivekimab 7·5 mg group, and one non-fatal myocardial infarction in the ziltivekimab 15 mg group.

As the non-parametric tests do not account for baseline measures and interaction terms, sensitivity analyses that account for this as well as the impact of missing data were done for the primary endpoint, including an analysis on a logarithmic scale (appendix p 13). None of these analyses altered interpretation of the trial data.

Discussion

In the RESCUE trial, which was done in individuals with chronic kidney disease who are at high atherosclerotic risk yet free of any clinically apparent inflammatory conditions, the IL-6 ligand monoclonal antibody ziltivekimab (developed specifically for atherosclerosis) markedly reduced multiple biomarkers of systemic inflammation associated with the atherothrombotic process. Furthermore, the anti-inflammatory benefits of ziltivekimab were achieved without substantive toxicity or adverse change in either the total cholesterol to HDL cholesterol ratio or in the APOB to APOA1 ratio, and no serious injection-site reactions.

The magnitude of change with ziltivekimab on high-sensitivity CRP was nearly twice as large in RESCUE as that observed in the recent CANTOS trial of canakinumab in which cardiovascular event rates were reduced by 15–20%.[2] Indeed, the percentage median change in CRP with ziltivekimab ranged 77–92% across the 7·5–30 mg once monthly dose groups. These effects are substantially larger than the 35–40% reductions in high-sensitivity CRP observed in CANTOS.[2] Yet, within CANTOS, individuals who achieved greater than 50% reductions in high-sensitivity CRP or on-treatment high-sensitivity CRP levels less than 2 mg/L were less likely to have a recurrent cardiovascular event.[6] These data have been interpreted to suggest that, at least for canakinumab (an IL-1β inhibitor), there is a wide range of individual responses at the level of IL-6 and that the magnitude of this response is directly related to the magnitude of clinical benefit that can be anticipated for individual patients.[5–7] In RESCUE, we used a direct IL-6 monoclonal antibody rather than indirect inhibition with an IL-1β inhibitor, and individual variation in downstream high-sensitivity CRP was minimal and the intermediate 15 mg dose of ziltivekimab was nearly as effective as the higher 30 mg dose.

The safety and efficacy data shown here also suggests that ziltivekimab (a monoclonal antibody targeting the IL-6 ligand) could have a superior clinical profile compared with other approved and clinically available monoclonal antibodies that target the IL-6 receptor such as tocilizumab and sarilumab. Both tocilizumab and sarilumab are associated with sustained neutropenia, increases in hepatic enzymes, and increased triglycerides. The safety profile of ziltivekimab within RESCUE also appears superior to that of two other IL-6 ligand monoclonal antibodies, sirukumab and siltuximab, with which neutropenia and thrombocytopenia are common, increases of hepatic enzyme levels often limit doses, and adverse effects on cholesterol and triglycerides have been large enough to require clinical intervention. Further, tocilizumab, sarilumab, sirukumab, and siltuximab have all been associated with injection-site reactions, whereas no serious injection-site events were seen in our study with ziltivekimab.

The reduction of lipoprotein(a) by ziltivekimab is of additional cardiovascular interest and consistent with previous work indicating that IL-6 induces *LPA* mRNA expression in human hepatocytes.[32] Although lowering lipoprotein(a) has been hypothesised to be a potential mechanism for cardiovascular event reduction, we note that the median pairwise differences in percentage change in lipoprotein(a) between the ziltivekimab groups and the placebo group in our study, after aligning for strata, were modest in magnitude (–16·4% for 7·5 mg, –20·4% for 15 mg, and –25·0% for 30 mg; all p<0·0001). Current trials directly inhibiting lipoprotein(a) might clarify this issue.

We believe our data support the advancement of ziltivekimab into formal investigation of clinical cardiovascular outcomes in a population with chronic kidney disease, high residual inflammatory vascular risk, and established cardiovascular disease. First, individuals with moderate chronic kidney disease and increases of IL-6 or high-sensitivity CRP have markedly increased rates of major adverse cardiovascular events and comprise a group with substantial unmet needs for treatment; in moderate to severe chronic kidney disease, both IL-6 and high-sensitivity CRP are powerful predictors of adverse cardiovascular outcomes, suggesting that residual inflammatory risk might disproportionately contribute in this setting.[24–30] Second, data from a CANTOS substudy focused on patients with chronic kidney disease demonstrated a greater absolute benefit from targeted anti-inflammatory therapy than in those with normal renal function.[31] Third, chronic kidney disease is a disease state in which the anti-inflammatory agent colchicine, a renally excreted agent, is generally contraindicated and therefore unlikely to be used for atherosclerosis treatment.

Although atherosclerotic event reduction in patients with high-risk chronic kidney disease is an attractive initial target for ziltivekimab, IL-6 inhibition might also prove useful in acute coronary ischaemia.[33] Other vascular settings associated with a proinflammatory response linked to IL-6 include heart failure, peripheral arterial disease, aortic aneurysm, and arrythmia.[17]

Limitations of our study merit consideration. The total sample size and duration of therapy was modest; thus, the safety results need external validation in larger groups. Equally important, although we achieved our full anticipated enrolment for the 12-week primary prespecified treatment period, participant safety concerns raised at the onset of the COVID-19 pandemic made it impossible to maintain face-to-face trial visits for all participants up to the secondary 24-week endpoint. Furthermore, we had concern during the COVID-19 pandemic that an exogenous cause of CRP increase in the general population could skew outcomes for the trial primary inflammation endpoints. For these reasons, a decision was made to terminate the study before formal completion. Although this decision was made at a time when all data were fully masked, the magnitude of effects noted here after trial unmasking suggest that this decision was unlikely to introduce bias or alter interpretation. In our trial, we prespecified using the change in CRP as our primary endpoint rather than the change in IL-6 itself. This a priori decision was made because of the inability of total IL-6 assays to distinguish differences between free IL-6 (which is reduced) and ziltivekimab-bound IL-6 (which is increased) in the setting of antibody treatment. Furthermore, when measuring total IL-6, levels might appear to counterintuitively increase after IL-6 inhibition because of the prolongation of the elimination half-life of the therapeutic antibody–IL-6 receptor complex. As our trial was done exclusively in the USA, data may not be fully generalisable to populations in other countries.

In summary, in the RESCUE trial, the novel IL-6 ligand monoclonal antibody ziltivekimab was highly effective at reducing multiple inflammatory and thrombotic biomarkers relevant to atherosclerosis without the adverse effects associated with other agents in its class. On the basis of these data, a large-scale cardiovascular outcomes trial of ziltivekimab compared with placebo in patients with chronic kidney disease who have increased high-sensitivity CRP and established cardiovascular disease will be done to establish whether this novel anti-inflammatory approach reduces rates of recurrent vascular events.

Contributors

PMR and PL provided scientific input towards the design and conduct of the trial as well as academic oversight. PMR further oversaw analyses, had access to all study data, wrote the manuscript, and made and was responsible for the decision to submit for publication. PP and DR were site leads who enrolled participants in the trial and provided intellectual input to analyses. MDe, LL, DK, and MDa were employees of Corvidia and involved in trial design, conduct, and data collection. FMMB, MDME, GKH, and MI are employees of Novo Nordisk and provided input into analyses and interpretation, and assistance with statistical inferences. MI, LL, MDa, and PMR accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

During the course of this trial, PMR received research grant support from Novartis, Kowa, Amarin, Pfizer, and the National Heart, Lung, and Blood Institute; served as a consultant to Corvidia, Novartis, Novo Nordisk, Flame, Agepha, Inflazome, AstraZeneca, Jannsen, Civi Biopharm, SOCAR, and Omeicos; and has a financial interest in Uptton, a company developing unrelated anti-inflammatory therapy. MDe, LL, DK, and MDa were employees of and held equity in Corvidia Therapeutics. FMMB, MDME, GKH, and MI are employees of and hold equity in Novo Nordisk. PP has served as a consultant to Corvidia and was a trial investigator whose employer received trial funds. DR is supported by National Institutes of Health grants 1 R01 DK125256-01, U01DK099914, and U01DK099924. PL is an unpaid consultant to, or involved in clinical trials for Amgen, AstraZeneca, Baim Institute, Beren Therapeutics, Esperion, Therapeutics, Genentech, Kancera, Kowa Pharmaceuticals, Medimmune, Merck, Norvo Nordisk, Merck, Novartis, Pfizer, and Sanofi-Regeneron; is a member of scientific advisory boards for Amgen, Corvidia Therapeutics, DalCor Pharmaceuticals, Kowa Pharmaceuticals, Olatec Therapeutics, Medimmune, Novartis, and XBiotech, a company developing therapeutic human antibodies; has received laboratory research funding in the past 2 years from Novartis; is on the Board of Directors of XBiotech; has a financial interest in Xbiotech, a company developing therapeutic human antibodies; and receives research funding support from the National Heart, Lung, and Blood Institute (1R01HL134892), the American Heart Association (18CSA34080399), the RRM Charitable Fund, and the Simard Fund.

Data sharing

Individual participant data will be shared in datasets in a deidentified and anonymised format, including datasets from Novo Nordisk-sponsored clinical research completed after 2001 for product indications approved in both the EU and the USA. The redacted clinical study report will be available according to Novo Nordisk data sharing commitments. Data will be available permanently after research completion and approval of product and product use in the EU and the USA. Data will only be shared with bona fide researchers submitting a research proposal and requesting access to data, for use as approved by the independent review board and according to its charter. The access request proposal form and the access criteria can be found online. Data will be made available on a specialised Statistical Analysis System data platform.

For more on **Novo Nordisk data sharing policies** see https://www.novonordisk-trials.com

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References

1 Ridker PM. Anticytokine agents: targeting interleukin signaling pathways for the treatment of atherothrombosis. *Circ Res* 2019; **124:** 437–50.
2 Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017; **377:** 1119–31.
3 Tardif JC, Kouz S, Waters DD, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med* 2019; **381:** 2497–505.
4 Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in patients with chronic coronary disease. *N Engl J Med* 2020; **383:** 1838–47.
5 Ridker PM, Libby P, MacFadyen JG, et al. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). *Eur Heart J* 2018; **39:** 3499–507.
6 Ridker PM, MacFadyen JG, Everett BM, et al. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. *Lancet* 2018; **391:** 319–28.
7 Ridker PM, MacFadyen JG, Thuren T, Libby P. Residual inflammatory risk associated with interleukin-18 and interleukin-6 after successful interleukin-1β inhibition with canakinumab: further rationale for the development of targeted anti-cytokine therapies for the treatment of atherothrombosis. *Eur Heart J* 2020; **41:** 2153–63.
8 Ridker PM, Everett BM, Pradhan A, et al. Low-dose methotrexate for the prevention of atherosclerotic events. *N Engl J Med* 2019; **380:** 752–62.
9 Kaptoge S, Seshasai SR, Gao P, et al. Inflammatory cytokines and risk of coronary heart disease: new prospective study and updated meta-analysis. *Eur Heart J* 2014; **35:** 578–89.

10 Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation* 2000; **101:** 1767–72.

11 Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000; **342:** 836–43.

12 Held C, White HD, Stewart RAH, et al. Inflammatory biomarkers interleukin-6 and C-reactive protein and outcomes in stable coronary heart disease: experiences from the STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) Trial. *J Am Heart Assoc* 2017; **6:** e005077.

13 Fanola CL, Morrow DA, Cannon CP, et al. Interleukin-6 and the risk of adverse outcomes in patients after an acute coronary syndrome: observations from the SOLID-TIMI 52 (Stabilization of Plaque Using Darapladib-Thrombolysis in Myocardial Infarction 52) Trial. *J Am Heart Assoc* 2017; **6:** e005637.

14 Lindmark E, Diderholm E, Wallentin L, Siegbahn A. Relationship between interleukin 6 and mortality in patients with unstable coronary artery disease: effects of an early invasive or noninvasive strategy. *JAMA* 2001; **286:** 2107–13.

15 Sarwar N, Butterworth AS, Freitag DF, et al. Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. *Lancet* 2012; **379:** 1205–13.

16 Swerdlow DI, Holmes MV, Kuchenbaecker KB, et al. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. *Lancet* 2012; **379:** 1214–24.

17 Cai T, Zhang Y, Ho Y-L, et al. Association of interleukin 6 receptor variant with cardiovascular disease. Effects of interleukin 6 receptor blocking therapy: a phenome-wide association study. *JAMA Cardiol* 2018; **3:** 849–57.

18 Loppnow H, Libby P. Adult human vascular endothelial cells express the IL6 gene differentially in response to LPS or IL1. *Cell Immunol* 1989; **122:** 493–503.

19 Loppnow H, Libby P. Proliferating or interleukin 1-activated human vascular smooth muscle cells secrete copious interleukin 6. *J Clin Invest* 1990; **85:** 731–38.

20 Huber SA, Sakkinen P, Conze D, Hardin N, Tracy R. Interleukin-6 exacerbates early atherosclerosis in mice. *Arterioscler Thromb Vasc Biol* 1999; **19:** 2364–67.

21 Akita K, Isoda K, Sato-Okabayashi Y, et al. An interleukin-6 receptor antibody suppresses atherosclerosis in atherogenic mice. *Front Cardiovasc Med* 2017; **4:** 84.

22 Ridker PM. From C-reactive protein to interleukin-6 to interleukin-1: moving upstream to identify novel targets for atheroprotection. *Circ Res* 2016; **118:** 145–56.

23 Libby P, Rocha VZ. All roads lead to IL-6: a central hub of cardiometabolic signaling. *Int J Cardiol* 2018; **259:** 213–15.

24 Spoto B, Mattace-Raso F, Sijbrands E, et al. Association of IL-6 and a functional polymorphism in the IL-6 gene with cardiovascular events in patients with CKD. *Clin J Am Soc Nephrol* 2015; **10:** 232–40.

25 Yeun JY, Levine RA, Mantadilok V, Kaysen GA. C-reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis* 2000; **35:** 469–76.

26 Barreto DV, Barreto FC, Liabeuf S, et al. Plasma interleukin-6 is independently associated with mortality in both hemodialysis and pre-dialysis patients with chronic kidney disease. *Kidney Int* 2010; **77:** 550–56.

27 Krane V, Winkler K, Drechsler C, Lilienthal J, März W, Wanner C. Association of LDL cholesterol and inflammation with cardiovascular events and mortality in hemodialysis patients with type 2 diabetes mellitus. *Am J Kidney Dis* 2009; **54:** 902–11.

28 Gupta J, Mitra N, Kanetsky PA, et al. Association between albuminuria, kidney function, and inflammatory biomarker profile in CKD in CRIC. *Clin J Am Soc Nephrol* 2012; **7:** 1938–46.

29 Amdur RL, Feldman HI, Gupta J, et al. Inflammation and progression of CKD: the CRIC study. *Clin J Am Soc Nephrol* 2016; **11:** 1546–56.

30 Upadhyay A, Larson MG, Guo C-Y, et al. Inflammation, kidney function and albuminuria in the Framingham Offspring cohort. *Nephrol Dial Transplant* 2011; **26:** 920–26.

31 Ridker PM, MacFadyen JG, Glynn RJ, et al. Inhibition of interleukin-1β by canakinumab and cardiovascular outcomes in patients with chronic kidney disease. *J Am Coll Cardiol* 2018; **71:** 2405–14.

32 Müller N, Schulte DM, Türk K, et al. IL-6 blockade by monoclonal antibodies inhibits apolipoprotein (a) expression and lipoprotein (a) synthesis in humans. *J Lipid Res* 2015; **56:** 1034–42.

33 Kleveland O, Kunszt G, Bratlie M, et al. Effect of a single dose of the interleukin-6 receptor antagonist tocilizumab on inflammation and troponin T release in patients with non-ST-elevation myocardial infarction: a double-blind, randomized, placebo-controlled phase 2 trial. *Eur Heart J* 2016; **37:** 2406–13.