A Phase 1 Randomized Dose-Escalation Study of a Human Monoclonal Antibody to IL-6 in CKD

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Abstract

Background Chronic systemic inflammation is highly prevalent in patients with CKD (measured as an elevated high-sensitivity C-reactive protein, hsCRP) and independently associated with cardiovascular events and all-cause mortality. An IL-6 blocker to suppress inflammation represents a potential novel paradigm to reduce cardiovascular risk in CKD.

Methods A phase 1 trial of ziltivekimab, a fully human mAb against IL-6, was conducted in patients with moderate-to-severe nondialysis-dependent CKD (eGFR of 20–60 ml/min per 1.73 m²) and evidence of chronic inflammation (hsCRP level >2 mg/L over two consecutive measurements). Three cohorts of n=4 (3:1 active: placebo) were blindly randomized to a single dose of ziltivekimab (5 mg, 15 mg, and 50 mg subcutaneous injection), and followed for 12 weeks for safety and pharmacokinetic/pharmacodynamic assessments, with an additional 20 weeks for safety and antidrug antibody assessments.

Results Participants were 67±11 years old; baseline eGFR: 40±13 ml/min per 1.73 m²; baseline hsCRP: 5.0±2.5 mg/L. Dose escalation was approved, and all adverse events were within the expected range for a CKD population with chronic inflammation. No serious adverse events were reported in any active cohort. hsCRP levels were substantially reduced with ziltivekimab. Of participants, 100% achieved suppression of hsCRP to <2 mg/L with the 15 mg and 50 mg dose, and several patients had undetectable levels of hsCRP with the 50 mg dose. The mean t1/2 ranged from 45 to 65 days.

Conclusions In adults with moderate-to-severe CKD and evidence of chronic inflammation, a single-injection of the IL-6 inhibitor ziltivekimab was safe and highly effective at suppressing hsCRP over 12 weeks.

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Introduction

Risk of cardiovascular diseases (CVD) is significantly elevated in patients with CKD, and increased cardiovascular risk is only partially explained by traditional CVD risk factors (1–6). Chronic systemic inflammation is highly prevalent in patients with CKD (measured as an elevated high-sensitivity C-reactive protein, hsCRP) (7,8) and is an independent predictor of morbidity and mortality, including cardiovascular mortality (7–11). The recently completed Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) trial demonstrated that blocking the proinflammatory cytokine IL-1β reduced major adverse cardiovascular events by 15% in adults with history of acute myocardial infarction and chronic inflammation (n=10,061) (12). However, CANTOS did not include patients with an eGFR <30 ml/min per 1.73 m² (median eGFR in the whole cohort was 79 and the interquartile range [IQR] was 64–93 ml/min per 1.73 m²), and only a few individuals with an eGFR <45 ml/min per 1.73 m² were included (12,13).

IL-6 is a proinflammatory cytokine that occupies a central position in inflammatory signaling pathways related to atherosclerosis downstream of IL-1 (14). Large-scale genetic studies have demonstrated a gene-dosage-dependent relationship between loss of IL-6 signaling and reductions in both hsCRP and cardiovascular events, indicating a strong causal role of IL-6 signaling in promotion of atherosclerosis and cardiovascular events (14–17). Both IL-6 and hsCRP levels are elevated in patients with nondialysis-dependent CKD (7,8,18) and are independently associated with cardiovascular events and all-cause/cardiovascular mortality in this population (10,11,19). Thus, the use of an IL-6 blocker to suppress chronic inflammation represents a potential new paradigm for reducing cardiovascular risks in patients with CKD.

Ziltivekimab is a potent neutralizing, fully human mAb against IL-6. We conducted a phase 1, randomized, double-blind, placebo-controlled trial designed to evaluate the safety, pharmacokinetic (PK), and...
pharmacodynamic (PD) effects of single dose of ziltivekimab or placebo, administered subcutaneously to patients with moderate-to-severe CKD and persistent inflammation.

Materials and Methods
The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Participants
Eligible participants were enrolled at the University of Colorado Anschutz Medical Center between May 2017 and July 2018 (the trial concluded according to enrollment determined by prespecified protocol). Participants eligible for inclusion were men and women ≥18 years of age, with stage III or IV CKD (eGFR by the four-variable Modified Diet Renal Disease prediction equation (20) was 20–60 ml/min per 1.73 m² and stable, defined as a variance of <30% across at least two measurements in the 3 months preceding day 1 of study dosing). Participants demonstrated chronic systemic inflammation, defined as a serum hsCRP >2 mg/L, measured twice during the screening period at least 1 week apart. Additionally, participants had a urine protein excretion <3.5 g/24 h (estimated by a spot urine protein/creatinine ratio), agreed to comply with study contraception and reproduction restrictions, and were able to provide informed consent.

Participants were excluded if they had advanced CKD requiring chronic dialysis, had a history of, or were expected to undergo, living related kidney transplant during the study period, were hospitalized over the 6 weeks before randomization, used systemic immunosuppressive drugs during the screening period, or anticipated use of such drugs during the study (use of otic, ophthalmic, inhaled, and topical corticosteroids or local corticosteroid injections were not exclusionary). Patients were also excluded if they were receiving or planning to receive live or inactivated vaccines, had clinical evidence or suspicion of active or smoldering infection (e.g., diabetic foot ulcer), or used antibiotics during the screening period, had a history of a positive purified protein derivative skin test or prior diagnosis of tuberculosis, or had evidence of HIV or carrier state by serology at screening. Additional exclusions were evidence of hepatitis B or C by serology (i.e., hepatitis B surface antigen or hepatitis C antibody–positive at screening), aspartate aminotransferase or alanine aminotransferase levels >2.5 × the upper limit of normal at screening, history of liver cirrhosis, home oxygen use, gastrointestinal ulceration, or active diverticulitis within 1 year before screening, absolute neutrophil count <2 × 10^9 L at screening, platelet count <100 × 10^9 L at screening, participation in an investigational drug study within 30 days of screening or falling within five 1/2 of an investigational compound, a known allergy to the study drug or any ingredients, and breastfeeding or pregnancy.

Further exclusions included any conditions that could interfere with the conduct of the study, interpretation of the study results, or potentially increase the risk of the patient’s study participation (e.g., alcoholism, drug dependency or abuse, psychiatric disease, epilepsy, anemia attributable to a primary hematologic disease, such as sickle cell anemia), or unexplained blackouts. Actively treated malignancy (other than nonmelanoma skin cancers) during the year before screening, myocardial infarction during the 3 months before screening, and severe arthritis, lupus, inflammatory bowel disease, asthma, and other diseases or medical conditions that could interfere with hsCRP or immune function, and the use of cytochrome P substrates with a narrow therapeutic index, were also exclusionary.

Participants were managed according to best medical practice while enrolled in the study, including a stable antihypertensive, diabetic, and lipid-lowering regimen, as applicable, as follows: control of hypertension with antihypertensives to a goal BP of <130/80 mm Hg (medication choice included angiotensin converting enzyme inhibitor/angiotensin receptor blocker as a first-line agent, diuretic as a second-line agent, calcium channel blocker as a third-line agent, and beta blocker as a fourth-line agent, unless the participant had known CVD and needed to be on a beta blocker regardless of BP), treatment of diabetes to a goal of HbA1C <7%, control of hyperlipidemia with statins to a goal of LDL cholesterol <100 mg/dl, and total cholesterol <200 mg/dl, smoking cessation counseling, control of anemia following the latest recommendations from the National Kidney Foundation (21), and control of hyperphosphatemia with phosphate binders to a goal phosphate of <4.6 mg/dl.

Study Design
This was a randomized, double-blind, placebo-controlled phase 1 trial designed to evaluate the safety, PK, and PD effects of single dose of ziltivekimab (previously COR-001) or placebo, administered subcutaneously to patients with moderate-to-severe CKD and persistent inflammation (defined as a persistently elevated serum hsCRP level). Patients underwent a 2-week screening period, during which two independent serum hsCRP measures were collected per the inclusion criteria detailed above. Four participants meeting eligibility criteria were randomized to ziltivekimab or placebo within each of three dosing cohorts (5 mg, 15 mg, 50 mg) in a ratio of 3:1 (drug to placebo) (Figure 1A). The protocol was written such that the planned doses could be adjusted based on PK, PD, and safety data upon Data Safety Monitoring Board (DSMB) review. Although the protocol originally planned for escalation to a dose of 100 mg, patients treated with the 50 mg dose achieved a significant reduction in hsCRP, thus no participants were escalated to the 100 mg dose. Randomization occurred using a computer-generated procedure run and kept by a statistician. Before dose escalation (i.e., higher total dose than studied in the preceding cohorts), there was a formal safety review and the data were determined to be acceptable by the DSMB. The safety review required for dose escalation included at least 21 days of treatment data from the preceding cohorts. The DSMB also met to review data concerning serious adverse events (SAEs) that were suspected to be study-drug related.

Following a single dose of ziltivekimab or placebo, participants were followed for 12 weeks for primary safety, PK, and PD assessments. Participants continued to be followed for a further 20 weeks (32 weeks of observation in total) for safety and antidrug antibody assessments. Participant visits occurred at baseline, weeks 1, 2, 3, 4, 5, 8, 12, 20, and 32. All
investigators, coordinators, analysts, and participants were blinded to group assignment, with only the nursing staff not affiliated with the study and the statistician aware of the randomization.

**Procedures**

**Dose Administration and Escalation**

Ziltivekimab or placebo was administered as a single subcutaneous dose at the baseline visit. At the time of intercohort DSMB safety data review, interim PK/PD analysis was conducted based on in-life PK/PD data. This was to target that coverage and safety margins were respected as proposed. Dose escalation proceeded provided the maximum tolerated dose was not reached. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) were used for defining dose-limiting toxicities (DLTs) and individual stopping criteria. For toxicities/events not covered by CTCAE, a qualitative scale that maps to CTCAE was used as follows (qualitative scale, CTCAE grade equivalent): (1) mild, (2) moderate, (3) severe, (4) life-threatening, and (5) fatal. The maximum tolerated dose was defined as a dose in which more than two patients in a given cohort experience a DLT, as determined by the principal investigator or DSMB. DLT was defined as any toxicity of which the relationship to the investigational agent cannot be ruled out as follows: confirmed grade 3 neutropenia and a decline of >25% from baseline, SAEs of infection in the presence of confirmed grade 2 or higher new onset lymphopenia or new onset neutropenia, grade 3 alanine aminotransferase or aspartate aminotransferase, grade 4 hematologic toxicity, or grade 3 nonhematologic toxicity. Grade 3 CTCAE toxicity events having an assessed relationship to the study drug of “definitely,” “probably,” or “unlikely” were also considered DLTs. Grade 3–4 CTCAE toxicities were considered DLTs regardless of the assessed relationship to the study drug. According to the protocol, if a maximum tolerated dose was reached, no further dose escalation would occur.

**Study Endpoints**

**Safety Analyses**

Adverse event reporting, clinical laboratory measurements (chemistry panel, complete blood count, lipid panel, hemoglobin A1C, cardiac biomarkers [lipoprotein-a, N-terminal ProB-type natriuretic peptide, troponin I], serum pregnancy test, spot urine [urine protein and creatinine], and 24-hour urine [urine sodium, protein, creatinine]), a resting 12-lead electrocardiogram, a physical examination, vital

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**Figure 1.** Study design and enrollment. This flow diagram describes (A) the study design and (B) enrollment and randomization (CONSORT diagram). All randomized participants completed the study.
signs, and concomitant medication use were monitored throughout the study period.

**PK Analyses**

Assessment of the PK of ziltivekimab included the drug $t_{1/2}$ area under the curve, maximum concentration, and time to maximum concentration. This was an antibody-based pharmacokinetic assay based on an ELISA format developed and validated to measure ziltivekimab in serum. A one-compartment PK model was tested to describe the data by nonlinear mixed-effects modeling. Noncompartmental analysis and nonlinear mixed-effects modeling were performed using Pumas version 0.10.0 (www.pumas.ai). Data manipulation and graphical analyses were performed using R (version 3.6.1) with the RStudio interface (version 1.2.13351).

**PD Endpoints**

Change from baseline (defined as the mean of two screening values and one baseline) hsCRP during the treatment period was determined as the primary efficacy endpoint. hsCRP was measured by the University of Colorado Hospital Clinical Laboratory using the immunoturbimetry method.

**Statistical Analyses**

All statistical analyses were performed by using SAS version 9.4 (SAS Institute, Cary, NC). The Shapiro–Wilk test was used to evaluate normality. If the Shapiro–Wilk $P$ value was <0.01, then the $P$ value (hsCRP active versus placebo) was obtained from a rank-transformed analysis of covariance model, with the rank-transformed change from baseline values as the response variable and treatments as a factor, and the rank transformed baseline value as its covariate. If the Shapiro–Wilk $P$ value was $\geq0.01$ then the $P$ value (active versus placebo) was obtained from an analysis of covariance model with change from baseline as the response and treatment as a factor and baseline value as a covariate. The trend $P$ value for ordered dose-treatment groups was calculated using Jonckheere–Terpstra test. A responder status analysis (to an hsCRP $>2$ mg/L) was performed using Fisher’s exact test. Given the objective of this phase 1 study, the sample size was not determined based on power calculations. The authors had full access to all of the data in the study, and take responsibility for its integrity and the data analysis.

**Study Approval**

All procedures were approved by the Institutional Review Board of the University of Colorado Anschutz Medical Campus and adhere to the Declaration of Helsinki. The nature, benefits, and risks of the study were explained to the volunteers and their written informed consent was obtained before participation. The trial was registered at ClinicalTrials.gov (NCT03126318).

**Results**

**Enrollment and Baseline Clinical Characteristics**

Of the 32 patients who were screened for participation, 12 were randomized to receive either ziltivekimab or placebo (Figure 1B). The most common reason for screen failure was not meeting the inclusion criteria of an hsCRP $>2$ mg/L measured twice during the screening period at least 1 week apart ($n=15$). All randomized participants completed the study. Participants were 69 ± 13 years old with a baseline eGFR of 41 ± 10 ml/min per 1.73 m$^2$ and hsCRP of 3.9 ± 1.6 mg/L (defined as the mean of two screening values and the baseline value) (Table 1).

**Safety Analyses**

Throughout the study, dose escalation was approved by the DSMB and all AEs were within the expected range for a CKD population selected based on the presence of inflammation. An overall summary of treatment-emergent AEs (TEAEs) is provided in Table 2. The highest severity of TEAE was one severe event in the 15 mg group (femoroacetabular impingement; not related). Two participants had TEAEs that were considered related to study drug by the investigator (one participant each in the ziltivekimab 5 mg and 15 mg groups). There was one SAE in the placebo group (acute cardiac failure). There were no SAEs in any of the active groups. A summary of AEs reported by one or

![Figure 2. Neutrophil and platelet response to ziltivekimab.](image-url) There was a slight risk of decrease in (A) neutrophils and (B) platelets with the 50 mg dose of ziltivekimab. One participant in the 50 mg group had grade 2 neutropenia ($<1.5-1.0\times10^3/\mu$L). No participants had grade 2 or higher thrombocytopenia.
| Variable                                      | Placebo (n=3) | Ziltivekimab 5 mg (n=3) | Ziltivekimab 15 mg (n=3) | Ziltivekimab 50 mg (n=3) | All Active Groups (n=9) |
|-----------------------------------------------|---------------|-------------------------|--------------------------|--------------------------|------------------------|
| Age, yr, mean±SD                              | 64±2          | 55±12                   | 77±5                     | 74±7                     | 69±13                  |
| Males, n (%)                                  | 1 (33)        | 2 (67)                  | 2 (67)                   | 2 (67)                   | 6 (67)                 |
| White race, n (%)                             | 3 (100)       | 3 (100)                 | 1 (33)                   | 3 (100)                  | 7 (78)                 |
| Diabetes mellitus, n (%)                      | 2 (67)        | 1 (33)                  | 3 (67)                   | 1 (33)                   | 4 (44)                 |
| Hypertension, n (%)                           | 3 (100)       | 3 (100)                 | 3 (100)                  | 3 (100)                  | 3 (100)                |
| CVD or CHF, n (%)                             | 3 (100)       | 0 (0)                   | 0 (0)                    | 2 (67)                   | 2 (22)                 |
| SBP, mm Hg, mean±SD                           | 140±37        | 127±16                  | 146±9                    | 130±17                   | 134±15                 |
| DBP, mm Hg, mean±SD                           | 69±8          | 74±12                   | 62±14                    | 69±10                    | 68±11                  |
| Body mass index, kg/m², mean±SD               | 30.8±2.2      | 32.9±5.2                | 31.1±4.9                 | 31.1±7.9                 | 31.7±5.4               |
| LDL cholesterol, mg/dl, mean±SD               | 134±113       | 61±48                   | 60±18                    | 81±30                    | 68±28                  |
| Total cholesterol, mg/dl, mean±SD            | 228±120       | 165±67                  | 121±16                   | 146±26                   | 144±41                 |
| eGFR, ml/min per 1.73 m², mean±SD             | 33±7          | 43±14                   | 39±11                    | 42±8                     | 41±10                  |
| Urine protein:creatinine ratio, median        | 0.25 (0.23, 0.95) | 0.80 (0.39, 0.89) | 0.11 (0.07, 0.18) | 0.07 (0.07, 0.11) | 0.11 (0.07, 0.39) |
| (interquartile range)                         |               |                         |                          |                          |                        |
| hsCRP, mg/L, mean±SD                          | 8.2±4.9       | 4.0±2.0                 | 4.1±1.5                  | 3.8±2.0                  | 3.9±1.6                |
| ALT, U/L, mean±SD                             | 20.3±7.6      | 44.7±8.3                | 17.7±7.8                 | 17.7±1.5                 | 26.7±26.7              |
| AST, U/L, mean±SD                             | 20.0±2.7      | 29.0±18.2               | 17.7±3.1                 | 16.7±1.5                 | 21.1±11.0              |
| ALP, U/L, mean±SD                             | 67.6±30.8     | 79.0±25.5               | 83.3±17.9                | 67.0±18.0                | 76.4±19.4              |
| Albumin, g/dl, mean±SD                        | 4.3±0.0       | 4.0±0.2                 | 4.1±0.1                  | 4.2±0.1                  | 4.1±0.1                |
| Glucose, mg/dl, mean±SD                       | 168±37        | 116±29                  | 130±46                   | 131±48                   | 126±37                 |
| Hemoglobin, g/dl, mean±SD                     | 13.1±1.5      | 13.7±2.8                | 14.2±2.3                 | 15.4±1.2                 | 14.4±1.9               |

Baseline hsCRP was defined as the average of two screening values and the baseline value. CVD, cardiovascular disease; CHF, congestive heart failure; SBP, systolic blood pressure; DBP, diastolic blood pressure; hsCRP, high-sensitivity C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase.
Table 2. Overall adverse event summary

| Treatment-Emergent Adverse Events | Placebo (n=3) | Ziltivekimab 5 mg (n=3) | Ziltivekimab 15 mg (n=3) | Ziltivekimab 50 mg (n=3) | All Active Groups (n=9) |
|-----------------------------------|-------------|-------------------------|--------------------------|--------------------------|------------------------|
| Any TEAE, n (%)                   | 3 (100)     | 2 (67)                  | 3 (100)                  | 3 (100)                  | 8 (89)                 |
| TEAE by highest severity          |             |                         |                          |                          |                        |
| Mild                              | 0           | 0                       | 0                        | 1 (33)                   | 1 (11)                 |
| Moderate                          | 2 (67)      | 2 (67)                  | 2 (67)                   | 2 (67)                   | 6 (67)                 |
| Severe                            | 1 (33)      | 0                       | 1 (33)                   | 0                        | 1 (11)                 |
| Life threatening                  | 0           | 0                       | 0                        | 0                        | 0                      |
| Fatal                             | 0           | 0                       | 0                        | 0                        | 0                      |
| TEAE by highest relationship      |             |                         |                          |                          |                        |
| Not related                       | 3 (100)     | 1 (33)                  | 2 (67)                   | 3 (100)                  | 6 (67)                 |
| Related                           | 0           | 1 (33)                  | 1 (33)                   | 0                        | 2 (22)                 |
| AE leading to study drug          |             |                         |                          |                          |                        |
| discontinuation                   |              |                         |                          |                          |                        |
| Any SAE, n (%)                    | 1 (33)      | 0                       | 0                        | 0                        | 0                      |
| SAE by highest severity           |             |                         |                          |                          |                        |
| Mild                              | 0           | 0                       | 0                        | 0                        | 0                      |
| Moderate                          | 0           | 0                       | 0                        | 0                        | 0                      |
| Severe                            | 1 (33)      | 0                       | 0                        | 0                        | 0                      |
| Life threatening                  | 0           | 0                       | 0                        | 0                        | 0                      |
| Fatal                             | 0           | 0                       | 0                        | 0                        | 0                      |
| SAE by highest relationship       |             |                         |                          |                          |                        |
| Not related                       | 1 (33)      | 0                       | 0                        | 0                        | 0                      |
| Related                           | 0           | 0                       | 0                        | 0                        | 0                      |

TEAE, treatment-emergent adverse events; AE; adverse event; SAE; serious adverse event.
| System Organ Class                              | Preferred Term                          | Placebo (n=3) | Ziltivekimab 5 mg (n=3) | Ziltivekimab 15 mg (n=3) | Ziltivekimab 50 mg (n=3) | All Active Groups (n=9) |
|------------------------------------------------|-----------------------------------------|---------------|------------------------|-------------------------|-------------------------|------------------------|
| **Cardiac disorders, n (%)**                    | Cardiac failure acute                   | 1 (33)        | 0                      | 1 (33)                  | 0                       | 1 (11)                 |
|                                                | Sinus arrhythmia                        | 0             | 0                      | 1 (33)                  | 0                       | 1 (11)                 |
|                                                | Sinus bradycardia                       | 0             | 0                      | 1 (33)                  | 0                       | 1 (11)                 |
| **Gastrointestinal disorders, n (%)**          | Diarrhea                                | 0             | 1 (33)                 | 0                       | 0                       | 1 (11)                 |
|                                                | Nausea                                  | 1 (33)        | 0                      | 0                       | 0                       | 0                      |
| **General disorders and administration site conditions, n (%)** | Edema                                   | 1 (33)        | 0                      | 0                       | 0                       | 0                      |
| **Infections and infestations, n (%)**         | Bronchitis                              | 1 (33)        | 0                      | 0                       | 0                       | 0                      |
|                                                | Localized infection                     | 0             | 1 (33)                 | 0                       | 0                       | 1 (11)                 |
|                                                | Upper respiratory infection             | 1 (33)        | 1 (33)                 | 1 (33)                  | 0                       | 2 (22)                 |
| **Injury, poisoning, and procedural complication, n (%)** | Fall                                    | 1 (33)        | 0                      | 0                       | 0                       | 0                      |
|                                                | Post-procedural contusion               | 1 (33)        | 0                      | 1 (33)                  | 0                       | 1 (33)                 |
|                                                | Road traffic accident                   | 0             | 0                      | 0                       | 1 (33)                  | 1 (33)                 |
|                                                | Skin abrasion                           | 1 (33)        | 0                      | 0                       | 1 (33)                  | 1 (33)                 |
| **Investigations, n (%)**                      | ECG ST segment abnormal                 | 0             | 0                      | 0                       | 1 (33)                  | 1 (11)                 |
|                                                | ECG T wave abnormal                     | 0             | 0                      | 0                       | 1 (33)                  | 1 (11)                 |
|                                                | Weight increased                       | 1 (33)        | 0                      | 0                       | 0                       | 0                      |
| **Metabolism and nutrition disorders, n (%)**  |                                        | 1 (33)        | 0                      | 0                       | 1 (33)                  | 1 (11)                 |
|                                                | Gout                                    | 1 (33)        | 0                      | 0                       | 0                       | 0                      |
|                                                | Hyperglycemia                           | 0             | 0                      | 0                       | 1 (33)                  | 1 (11)                 |
|                                                | Hypoglycemia                            | 0             | 0                      | 0                       | 1 (33)                  | 1 (11)                 |
| **Musculoskeletal and connective tissue disorders, n (%)** | Back pain                              | 0             | 0                      | 0                       | 2 (67)                  | 2 (22)                 |
|                                                | Femoracetabular impingement             | 0             | 0                      | 1 (33)                  | 0                       | 1 (11)                 |
|                                                | Neck pain                               | 0             | 0                      | 0                       | 1 (33)                  | 1 (11)                 |
| **Neoplasms, n (%)**                           | Basal cell carcinoma                    | 0             | 0                      | 1 (33)                  | 0                       | 1 (11)                 |
|                                                | Squamous cell carcinoma of skin         | 0             | 0                      | 1 (33)                  | 0                       | 1 (11)                 |
| **Nervous system disorders, n (%)**            |                                        | 1 (33)        | 0                      | 0                       | 1 (33)                  | 1 (11)                 |
|                                                | Cerebral hemorrhage                     | 0             | 0                      | 0                       | 1 (33)                  | 1 (11)                 |
|                                                | Syncope                                 | 1 (33)        | 0                      | 0                       | 0                       | 0                      |
| **Renal and urinary disorders, n (%)**         |                                        | 1 (33)        | 0                      | 0                       | 0                       | 0                      |
|                                                | AKI                                     | 1 (33)        | 0                      | 0                       | 0                       | 0                      |
| System Organ Class Preferred Term                  | Placebo (n=3) | Ziltivekimab 5 mg (n=3) | Ziltivekimab 15 mg (n=3) | Ziltivekimab 50 mg (n=3) | All Active Groups (n=9) |
|--------------------------------------------------|---------------|-------------------------|--------------------------|--------------------------|-------------------------|
| Respiratory, thoracic, and mediastinal disorders, n (%) |               |                         |                          |                          |                         |
| Cough                                            | 1 (33)        | 0                       |                          |                          | 1 (33)                  |
| Paranasal sinus hypersecretion                   | 0             | 0                       |                          |                          | 0                       |
| Vascular disorders, n (%)                        | 0             | 0                       | 1 (33)                   |                          | 1 (11)                  |
| Hypertension                                     | 0             | 0                       | 1 (33)                   |                          | 0                       |

ECG, electrocardiogram.
more subjects according to system organ class is provided in Table 3.

There was a slight risk of decrease in neutrophils and platelets with the 50 mg dose (Figure 2). One participant in the 50 mg group developed grade 2 neutropenia ($<1.5$–$1.0 \times 10^9/\mu l$). No participants developed thrombocytopenia. Changes in eGFR and albumin according to ziltivekimab dose and placebo treatment are shown in Supplemental Figures 1 and 2. Additional clinical laboratory measurements and vital signs are provided in Supplemental Table 1. No other clinically significant changes in laboratory parameters (including liver function), vital signs, or physical assessments as related to safety were noted.

Pharmacokinetic Analyses
A one-compartment model with first-order absorption and elimination adequately described the time-course of ziltivekimab concentrations after a subcutaneous injection (Figure 3). Table 4 presents the area under the curve, maximum concentration, apparent clearance, and apparent volume of distribution. Ziltivekimab concentrations exhibited dose proportional PK. Potential prognostic factors such as body size, age, eGFR, serum creatinine, and sex did not demonstrate any influence on apparent clearance or apparent volume of distribution. No confirmed neutralizing antidrug antibodies were detected. The mean $t_{1/2}$ ranged from 45 to 65 days.

PD Endpoints
A single dose of ziltivekimab substantially reduced hsCRP levels in a dose-dependent manner (Figure 4A). In total, 100% of participants achieved suppression of hsCRP to <2 mg/L with the 15 mg and 50 mg doses (Figure 4B). Several subjects had undetectable levels of hsCRP with the 50 mg dose.

Discussion
In this phase 1 study in adults with moderate-to-severe CKD and evidence of chronic inflammation, a single injection of the IL-6 inhibitor ziltivekimab was safe and highly effective at suppressing hsCRP over a long period (12 weeks). Throughout the study period, dose escalation was approved and AEs were within the expected range for a CKD population with chronic inflammation. No SAEs were reported in any active cohort. hsCRP levels were substantially reduced with ziltivekimab treatment. All participants achieved suppression of hsCRP to <2 mg/L with the 15 mg and 50 mg dose, and several subjects had undetectable levels of hsCRP with the 50 mg dose.

Chronic low-grade inflammation is highly prevalent in patients with CKD and an independent predictor of morbidity and mortality, including cardiovascular mortality (7–11). Patients with CKD are more likely to die of CVD than to progress to ESKD (22,23). IL-6 is a proinflammatory cytokine that occupies a central position in inflammatory signaling pathways related to atherosclerosis (14), thus represents a potential novel target to reduce cardiovascular risk in patients with CKD. Although blocking the proinflammatory cytokine IL-1β reduced major adverse cardiovascular events in the CANTOS trial, patients with an eGFR <30 ml/min per 1.73 m² were not included (median eGFR in the whole cohort was 79 [IQR, 64 – 93] ml/min per 1.73 m²), and only few individuals had an eGFR <45 ml/min per 1.73 m² (median eGFR of those with CKD was 51 [IQR, 43 – 56] ml/min per 1.73 m²) (12,13).

Notably, in CANTOS, only patients who achieved an on-treatment hsCRP level of <2 mg/L or a reduction in serum IL-6 levels to <1.65 ng/L experienced a reduction in major cardiovascular events, whereas those patients who did not achieve these targets had no reduction in major cardiovascular events (24,25). These effects were magnified in patients

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**Figure 3.** Time course of ziltivekimab concentrations after a subcutaneous injection. Observed mean (points) and SD (error bar), model-predicted population mean (lines) of ziltivekimab concentration time profiles after single doses of 5 mg, 15 mg, and 50 mg subcutaneous administration from nine patients. Lower error bar at day 49 of 50 mg dose was not displayed due to negative value obtained by large SD.
Table 4. Pharmacokinetics parameters of ziltivekimab by noncompartmental analysis and pharmacokinetic modeling

| Parameters       | 5 mg   | 15 mg  | 50 mg  |
|------------------|--------|--------|--------|
| Noncompartmental analysis |        |        |        |
| $C_{max}$, μg/ml, mean (CV%) | 0.34 (26) | 0.82 (23) | 3.92 (94) |
| $T_{max}$, d, median (min–max) | 6.0 (4.0–14.0) | 14.0 (10.0–30.0) | 27.0 (10.0–49.0) |
| AUCinf, d, μg/ml, mean (CV%) | 21.3 (6) | 76.9 (18) | 320.8 (76) |
| AUClast, d, μg/ml, mean (CV%) | 22.3 (10) | 85.9 (18) | 355.4 (74) |
| $t_{1/2}$, d, mean (CV%) | 45.4 (30) | 64.6 (12) | 63.0 (7) |
| Modeling        |        |        |        |
| CL/F, L/d, mean (CV%) | 0.19 (37) |        |        |
| V/F, L, mean (CV%) | 16.5 (37) |        |        |

$C_{max}$, maximum concentration; $T_{max}$, time to reach $C_{max}$; AUCinf, area under the concentration–time curve from the time of last dosing to the last measurable concentration; AUClast, AUC from the last dosing time extrapolated to infinity; $t_{1/2}$, terminal elimination $t_{1/2}$; CL/F, apparent clearance; V/F, apparent volume of distribution.

with CKD, strongly suggesting that suppression of hsCRP via a reduction in IL-6 (e.g., with ziltivekimab) may translate to significant cardiovascular benefit in patients with mild-to-moderate renal dysfunction. Specifically, in the subgroup with an eGFR < 60 ml/min per 1.73 m², the reduction in major cardiovascular events was doubled in those participants who achieved an on-treatments hsCRP < 2 mg/L (13). Although the efficacy data should be interpreted cautiously given the small sample size in this phase 1 trial, we observed better suppression of hsCRP than with IL-1β inhibition in both CANTOS with canakinumab (12), and in our previous study with the IL-1 trap, rilonacept (26).

Ziltivekimab has notable advantages over other anti-IL-6 therapies. Unlike other anti-IL-6 therapies, which can induce significant neutropenia, ziltivekimab can provide an anti-inflammatory effect without immune suppression (neutrophil stability at 5 mg and 15 mg doses). Additionally, ziltivekimab did not elicit a dyslipidemic response, which is observed with other anti-IL-6 therapies, such as tocilizumab, via upregulation of apo B (no increase in LDL cholesterol). These key safety findings suggest ziltivekimab dosage can be tailored for efficacy without clinically significant effects on important hematology or lipidology parameters. Additionally, although based on very preliminary, short-term data, ziltivekimab may potentially attenuate the decline in kidney function in patients with CKD.

The major strengths of this study are the novelty of targeting IL-6 inhibition in patients with moderate-to-severe CKD and the attractive safety profile and substantial inhibition of hsCRP observed with this approach. The major limitation is the small sample size due to the nature of a phase 1 trial. Furthermore, data are based on only a single dose of ziltivekimab, with follow-up for a total of 32 weeks. Additionally, because IL-6 is downstream of IL-1, ziltivekimab may act more narrowly than IL-1 inhibition, and hsCRP levels are a single marker of inflammation, which may or may not correlate with the inflammatory processes mediating worsening CVD. Although our study demonstrates initial feasibility and safety of ziltivekimab in patients with stage 3 and 4 CKD, subsequent and ongoing clinical trials are needed to better establish feasibility and tolerability in patients with kidney disease.

Finally, as ziltivekimab is not yet approved by the Food and Drug Administration and trials are ongoing, pricing is not established. Notably, biologic agents are expensive. For example, tocilizumab, another IL-6 inhibitor approved for the treatment of rheumatoid arthritis, is estimated to cost approximately $22,000 annually (27). Economic models evaluating the use of monoclonal antibodies (including tocilizumab) to treat chronic diseases such as rheumatoid arthritis suggest cost effectiveness, although models are inconsistent (28–31). Randomized comparisons evaluating the long-term efficacy and safety follow-up of ziltivekimab in patients with CKD are needed to establish comparative effectiveness. Importantly, the combination of favorable safety data and significant suppression of hsCRP with a single dose of ziltivekimab support the translation of these findings to a subsequent phase 2 trial with once-a-month dosing in a similar dose range in individuals with moderate-to-severe CKD.

Disclosures

D. Kling reports having an ownership interest with Corvidia. D. Kling, L. Lo, M. Davidson, and M. Devalaraja are employees of Corvidia Therapeutics. J. Gobburu reports having an ownership interest with Pumas-AI Inc. K.L. Nowak reports receiving research funding from Corvidia Therapeutics and Verdue Sciences, and reports having other interests/relationships in an interaction with the PKD Foundation. M. Chonchol reports consultancy agreements with Amgen, Corvidia, Otsuka, Reata, Tricidia, and Vifor; receiving research funding from Corvidia, Otsuka, Reata, and Sanofi; receiving honoraria from Amgen, Corvidia, Reata, Tricidia, and Vifor; and being a scientific advisor or member of the CJASN Editorial Board. M. Davidson reports consultancy agreements with Novo Nordisk. R. Kakkar is an employee of Pandion Therapeutics. All remaining authors have nothing to disclose.

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Corvidia Therapeutics performed the data analysis.

Author Contributions

D. Kling, M. Davidson, M. Devalaraja, and R. Kakkar were responsible for the conceptualization and resources; J. Gobburu was...
Ziltivekimab Responder Rate

Baseline hsCRP 3.9 mg/L
Responder defined as Week 12 average hsCRP < 2 mg/L

hsCRP Responder Rate

50 mg (N=3) 5 mg (N=3) 15 mg (N=3) Placebo (N=3)

| Day | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 14 | 16 | 19 | 21 | 24 | 28 | 32 | 36 | 40 | 44 | 49 | 53 | 57 | 61 | 65 | 70 | 74 | 78 |
|-----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LOQ | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 | 36 | 38 | 40 | 42 | 44 | 46 | 48 | 50 | 52 | 54 | 56 | 58 |

Figure 4. | Efficacy of ziltivekimab, as measured by high-sensitivity C-reactive protein (hsCRP) suppression. (A) Ziltivekimab was highly effective at suppressing hsCRP levels, particularly with the 15 mg and 50 mg doses; P value for trend = 0.007 at 12 weeks and 0.004 at 32 weeks (log scale). As defined as week 12 average hsCRP levels <2 mg/L, 100% of participants in the 15 mg and 50 mg group responded to ziltivekimab, defined as a decrease in hsCRP to <2 mg/L at week 4. The responder rate with the 5 mg dose was 33.3% and no participants in the placebo group responded. (B) The P value for responder status across all active groups was 0.033.

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Supplemental Figure 1. Change in eGFR in response to Ziltivekimab.

Supplemental Figure 2. Change in albumin in response to Ziltivekimab.

Supplemental Table 1. Additional Clinical Parameters.

Supplemental Material

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Supplemental Table 1. Additional Clinical Parameters.
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