Design of the ZEUS trial: interleukin 6 inhibition with ziltivekimab for cardiovascular protection in chronic kidney disease

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The phase 3 ZEUS trial is evaluating the efficacy and safety of ziltivekimab in participants with CKD, ASCVD and elevated hsCRP levels; endpoints include MACE and kidney outcomes

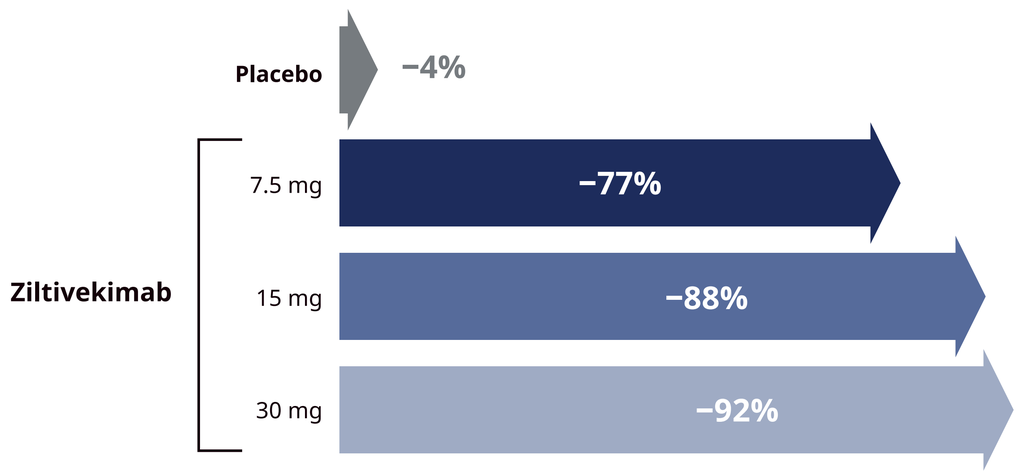
Atherosclerotic cardiovascular disease, chronic kidney disease and systemic inflammation

- Inflammation is an established and common cardiovascular (CV) risk factor.[1]
- Inflammation is involved in the pathogenesis of atherosclerotic cardiovascular disease (ASCVD) and chronic kidney disease (CKD), and inflammation likely also has an important role in the progression of both diseases.[2,3]
  - Systemic inflammation, typically defined as high-sensitivity C-reactive protein (hsCRP) levels ≥2 mg/L, is particularly common in people with CKD.[4]
- People with established CVD are at high risk of secondary CV events. In patients with established CVD, low-dose colchicine (0.5 mg once daily) may be considered for secondary prevention of CV events.[5]
  - However, low-dose colchicine is contraindicated in patients with significantly reduced kidney function, and people with CKD should be monitored closely for adverse effects.[5]
  - Better tolerated methods of reducing CV risk in people with ASCVD and CKD are therefore required.
- Levels of interleukin 6 (IL-6), an inflammatory cytokine, are a strong predictor of future CV events in people with ASCVD[6] and with CKD.[7]
- IL-6 may therefore be an important target for anti-inflammatory therapy for CV risk reduction in patients with ASCVD and CKD.

Ziltivekimab is a human monoclonal antibody that targets the IL-6 ligand

- In the phase 2 RESCUE trial (NCT03926117), ziltivekimab significantly reduced hsCRP levels by up to 92% compared with placebo, in patients with CKD stages 3–5 and hsCRP ≥2 mg/L (**Figure 1**).[8]
  - Dose-dependent reductions were also observed for other inflammatory biomarkers: fibrinogen, serum amyloid A, haptoglobin, secretory phospholipase A2 and lipoprotein(a).
- Ziltivekimab was well tolerated and did not affect the ratio of total cholesterol to high-density lipoprotein cholesterol.[8]
- There were no serious injection-related reactions, or sustained neutropenia or thrombocytopenia events of grade 3 or 4.[8]

Figure 1: Median change in hsCRP from baseline to week 12 in the RESCUE trial[8]

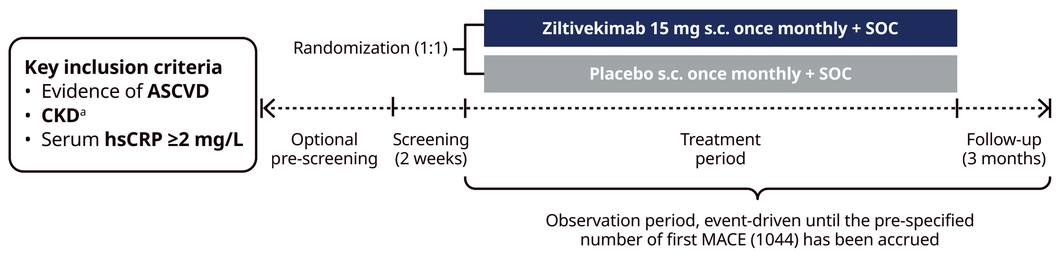


hsCRP, high-sensitivity C-reactive protein.

ZEUS study design

- ZEUS (NCT05021835) is a randomized, parallel-group, double-blind, placebo-controlled CV outcomes trial including people with established ASCVD, CKD and hsCRP ≥2 mg/L (**Figure 2**).

Figure 2: ZEUS study design



[a]Defined as UACR ≥200 mg/g and eGFR ≥60 mL/min/1.73 m^2, or eGFR ≥15 and <60 mL/min/1.73 m^2.
ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; MACE, major cardiovascular adverse events; s.c., subcutaneously; SOC, standard of care; UACR, urine albumin to creatinine ratio.

- Approximately 6400 participants were recruited between 2021 and 2024 from more than 30 countries and territories (**Figure 3**).
  - Participants will be followed up until 1044 primary outcomes have accrued.
  - This will provide 95% power to detect a 20% relative risk reduction in the primary outcome, with a one-sided α level of 2.5%.
- The study duration is expected to be approximately 4 years.
- The primary endpoint is major adverse cardiovascular events (MACE; defined as CV death, non-fatal myocardial infarction [MI] or non-fatal stroke) in time-to-first-event analysis (from randomization to end of study).
- Confirmatory secondary endpoints are the following (from randomization to end of study):
  - expanded MACE (CV death, non-fatal MI, non-fatal stroke or hospitalization for unstable angina pectoris requiring urgent coronary revascularization) in time-to-first-event analysis
  - number of hospitalizations for heart failure or urgent heart failure visits or CV deaths
  - composite CKD endpoint (kidney failure [initiation of chronic kidney replacement therapy or onset of persistent estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2], ≥40% reduction in eGFR, death from kidney failure or CV causes) in time-to-first-event analysis
  - all-cause mortality in time-to-event analysis.

Figure 3: ZEUS is a large-scale global study involving 38 countries and territories



Why is ZEUS important?

- People with CKD are at high risk of CV events.
- Markers of systemic inflammation, including IL-6, are strong, modifiable risk factors for the development and progression of cardiovascular disease[9] as well as CKD.
  - People with CKD have systemic inflammation and high CV and CKD progression risk,[10,11] and IL-6 may play a particularly important role in this population.
- Targeting systemic inflammation has the potential to improve CV outcomes.[12]
  - The ZEUS trial will evaluate the effect of ziltivekimab, an anti-inflammatory drug targeting the IL-6 ligand, on CV and kidney outcomes in participants with ASCVD, CKD and elevated hsCRP levels, as well as additional efficacy and safety endpoints.

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References: (**1**) Ridker PM et al. N Engl J Med 1997;336:973–9; (**2**) Komada T, Muruve DA. Nat Rev Nephrol 2019;15:501–20; (**3**) Baragetti A et al. Int J Mol Sci 2020;21:4459; (**4**) Ridker PM. J Am Coll Cardiol 2018;72:3320–31; (**5**) Agepha Pharma. Prescribing information, Lodoco (colchicine). FDA, 2023. Available from www.accessdata.fda.gov/drugsatfda_docs/label/2023/215727s000lbl.pdf (Accessed 9 January 2025); (**6**) Kaptoge S et al. Eur Heart J 2014;35:578–89; (**7**) Kreiner FF et al. Expert Rev Clin Immunol 2022;18(4):377–89; (**8**) Ridker PM et al. Lancet 2021;397:2060–9; (**9**) Alfaddagh A et al. Am J Prev Cardiol 2020;4:100130; (**10**) Foley RN et al. Am J Kidney Dis 1998;32(5 Suppl 3):S112–19; (**11**) Alani H et al. World J Nephrol 2014;3:156–68; (**12**) Lawler PR et al. Eur Heart J 2021;42:113–31.

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