POSIBIL6 Study: Cardiovascular Outcome Study for Patients with Cardiovascular Disease and/or End Stage Kidney Disease Receiving Maintenance Dialysis: An Evaluation of Inflammation Reduction by Clazakizumab

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POSIBIL6 ESKD™
PREVENTION OF SERIOUS CARDIAC EVENTS BY TARGETING IL-6 IN ESKD

Background

Patients with end-stage kidney disease (ESKD) experience unacceptably high rates of mortality and morbidity despite the provision of dialysis . A majority of the deaths are attributable to cardiovascular causes.

Inflammatory markers, including serum concentrations of IL-6 and C-reactive protein (CRP), are typically elevated in ESKD and are associated with mortality and cardiovascular events in this population.

A therapeutic approach targeting the IL-6 pathway could reduce cardiovascular events and mortality in patients receiving maintenance dialysis.

Clazakizumab (CSL300) is a high-affinity humanized monoclonal antibody that targets the IL-6 ligand and inhibits downstream IL-6 function.

It was hypothesized that CSL300 could reduce the occurrence of cardiovascular events in patients receiving maintenance dialysis by modulating excess IL-6-dependent inflammation.

Protocol Overview & Study Design

This is a 2-part (phase 2b/3) prospective, interventional, multicenter, randomized, double blind, placebo controlled study.

- Part 1 (phase 2b) is a dose-finding study for CSL300 (Clazakizumab) vs placebo to examine safety and efficacy of three doses of CSL300 on markers of inflammation associated with major adverse cardiovascular events.
- Part 2 (phase 3) aims to assess the efficacy of CSL300 (Clazakizumab) on CV outcomes and safety in subjects with ASCVD or diabetes mellitus and evidence of systemic inflammation who are undergoing maintenance dialysis.

Drug Administration

- Experimental – IV administration of CSL300
- Placebo– IV administration of placebo that is matching content and concentration of the CSL300 product minus the active ingredient

MORE INFORMAITON

- **med.stanford.edu/sccr**
- **Clinicaltrials.gov: NCT05485961**
- **Phase 2b published manuscript in Nature Medicine:** *https://doi.org/10.1038/s41591-024-03043-1*

Clinical Events Committee (CEC)

Clinical Endpoint Adjudication is an important feature of large, randomized CV clinical trials like the POSIBIL6 study

CEC member roles:

- ❑ Adjudication experience and therapeutic expertise to independently assess potential clinical endpoints
- ❑ Adhere to pre-specified event definitions documented in the CEC Charter for classifying clinical events in an unbiased way
- ❑ Adjudication results add validity to the final analyses of clinical trial outcomes to improve treatment of cardiovascular diseases
- ❑ CEC operates independently of sites and study Sponsor

CEC MEMBER OVERVIEW

CEC Chair: Dr. Tara Chang

- Nephrologists
- Neurologists
- Cardiologists
- Infectious Disease

- Independent
- Systematic
- Unbiased
- Blinded
- Consistent

Clinical Endpoint Adjudication

Adjudicated events for this study are adverse medical events that have been independently evaluated by a CEC to ensure their accuracy and consistency.

Phase 3, Target enrollment 2,190 patients
5 year Duration/4,500 clinical events expected

Clinical Endpoints to be Adjudicated based on phase 3 study outcome measures:

1. Cardiovascular
- Myocardial Infarction
- Stroke/Suspected Cerebrovascular Ischemic Event
- Major Adverse Limb Event
- Heart Failure Hospitalization and Urgent Heart Failure Visit

2. Death
- Cardiovascular, Non-Cardiovascular, and Undetermined Causes

3. Major Infection

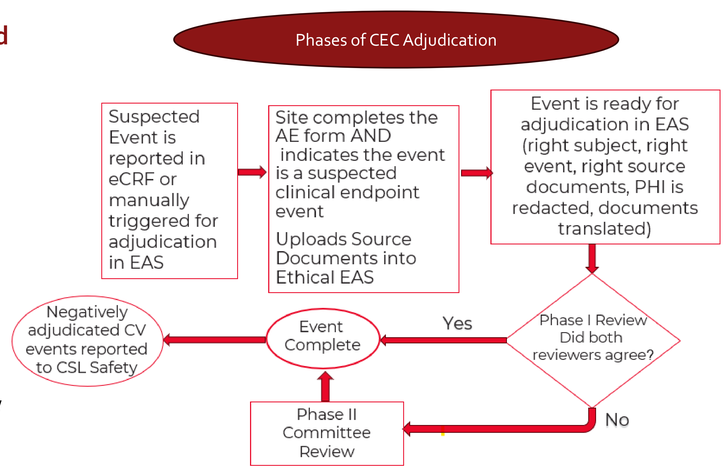
Verification of clinical event information using Supplemental Source Documents included in CEC event dossiers

Endpoint Event	CRF Page	Source Docs
Death	Death Details	✓ Death Summary ✓ Autopsy Report (if applicable)
Myocardial Infarction	Myocardial Infarction	✓ Discharge Summary ✓ Procedure Reports (PCI/CABG) ✓ Event ECGs (pre-event, event, post-event) ✓ Cardiac markers, with URL
Stroke/ Cerebrovascular Event	Suspected Cerebrovascular Ischemic Event	✓ Discharge Summary ✓ Neurology Consult Notes ✓ CT/MRI Report
Major Adverse Limb Event	Major Adverse Limb Event	✓ Imaging Report ✓ Discharge Summary ✓ CT Report ✓ Surgical / Procedure reports
Heart Failure Hospitalization or Urgent Visit for Heart Failure	Heart Failure	✓ Discharge Summary ✓ Admission History and Physical ✓ Medication Records ✓ Chest X-ray Reports ✓ BNP results ✓ Cardiovascular imaging reports ✓ Dialysis run sheets ✓ Nephrology notes ✓ Cardiology consult notes
Major Infection	Major Infection	✓ Discharge Summary ✓ Admission History and Physical ✓ Medication Records ✓ Lab Results (CBC, Viral loads, ✓ cultures, etc) ✓ Imaging ✓ Infectious disease consult notes

CEC Adjudication Process Overview

Identification and Reporting of Suspected Endpoint Events

- Identified by investigative sites during medical review of records or through patient contacts
- Identified during Monitoring visits or Medical Data Review
- Identified by SCCR Operations Team
- Identified by Adjudicators during review of assigned events-



Summary

Phase 2b of this study demonstrated dose-dependent efficacy and safety profile based on three doses of clazakizumab (2.5 mg, 5 mg, and 10 mg), which all showed reduction in hs-CRP concentrations, with more frequent serious infections in the high dose treatment group.

Phase 3 of this study will evaluate the potential cardiovascular benefit of longer term clazakizumab (5 mg) treatment by reducing hs-CRP and limiting serious adverse events such as major infections.

Inflammatory biomarkers and cardiovascular endpoints, major infections and all cause deaths will be further quantified to determine if clazakizumab is beneficial for the treatment of CV events in this high-risk patient population.

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- **Study Sponsor: CSL Behring**