Evaluating TOUR006 in Participants with Chronic Kidney Disease and Elevated Hs-CRP: Rationale and Design of the TRANQUILITY Phase 2 Study

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TOURMALINE

BACKGROUND

- Atherosclerotic cardiovascular disease (ASCVD), including coronary artery disease (CAD), large artery ischemic cerebrovascular disease, and peripheral artery disease (PAD), remains the leading cause of mortality globally. [1]
- Once considered a mere consequence of cholesterol buildup, ASCVD is now recognized as an inflammatory disorder driven by chronic inflammation. Interleukins such as IL-6 as well as other cellular constituents, orchestrate complex inflammatory responses that play pivotal roles in the disease's pathogenesis. [2]
- Human genetic studies have consistently shown associations between genetic variants mimicking (low) dose IL-6 inhibition and a lower risk of ASCVD (Figure 1). [3-6]
- Multiple studies have also demonstrated associations between levels of IL-6 and C-reactive protein (CRP), a key biomarker for IL-6 pathway activity, and ASCVD risk. [7,8]
- Recently, three large analyses of high-risk patient populations have shown that high-sensitivity CRP (hs-CRP) is more strongly associated with risk of major adverse cardiovascular events (MACE) than low-density lipoprotein cholesterol (LDL-C) (Figure 2). [9-11]

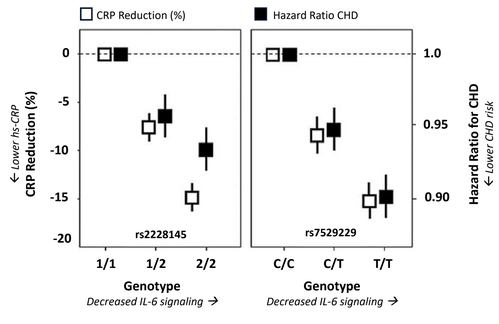

Figure 1. IL-6 genetic variants are associated with hs-CRP levels and CVD risk. Specific genotypes at rs2228145 and rs7529229 are associated with lower hs-CRP levels and lower CHD risk (shown as hazard ratios). Figure was adapted from Ridker, 2016[12]. CHD, coronary heart disease.

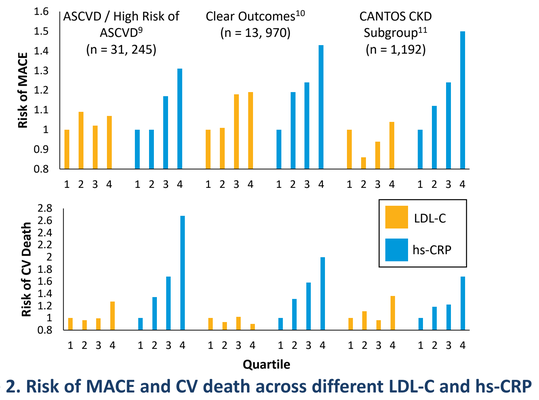

Figure 2. Risk of MACE and CV death across different LDL-C and hs-CRP levels. Analyses of multiple clinical trial populations demonstrated higher risk for MACE and CV death (shown as hazard ratios) for individuals with elevated hs-CRP. [9-11] MACE includes myocardial infarction, stroke, coronary revascularization, and CV death. CV, cardiovascular.

TOUR006

- TOUR006 is a long-acting, fully human, anti-IL-6 monoclonal antibody with unique properties, including a naturally long half-life, low immunogenicity, and high binding affinity to IL-6.
- TOUR006 (formerly known as PF-04236921) has been previously studied in 448 participants, including patients with autoimmune disorders such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and Crohn's disease (CD), across six completed Phase 1/2 trials. [13-15]
- Pharmacokinetic (PK) and pharmacodynamic (PD) modeling in virtual patient populations with systemic inflammation that is comparable to patients with ASCVD showed significant reductions in hs-CRP with both monthly and quarterly subcutaneous (SC) dosing of TOUR006 (Figures 3 & 4). [13]
- To date, the safety profile of TOUR006 has appeared generally similar to other IL-6 pathway inhibitors, and the highest planned Phase 2 dose (50 mg) did not show excess safety risk vs placebo in previous Phase 2 studies in CD and SLE. [14, 15]
  - The most common AEs observed across all six completed Phase 1/2 studies included: headache, nasal congestion, oropharyngeal pain, abdominal pain, diarrhea, pain in extremity, arthralgia, nausea, fatigue, vomiting, and nasopharyngitis/upper respiratory infection.
- Currently, Tourmaline is developing TOUR006 for the treatment of ASCVD and thyroid eye disease, with additional diseases under consideration.

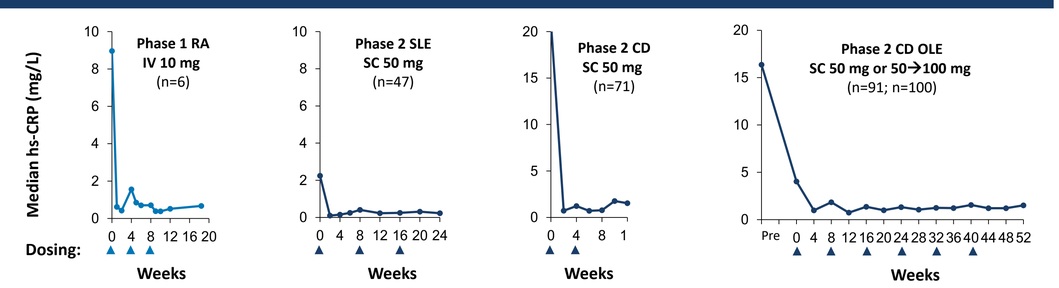

Figure 3. Median hs-CRP concentrations in completed studies of TOUR006 in patients with inflammatory disorders. Median hs-CRP levels over time are shown from four clinical studies in patients with RA, SLE, or CD. IV, intravenous; OLE, open-label extension.

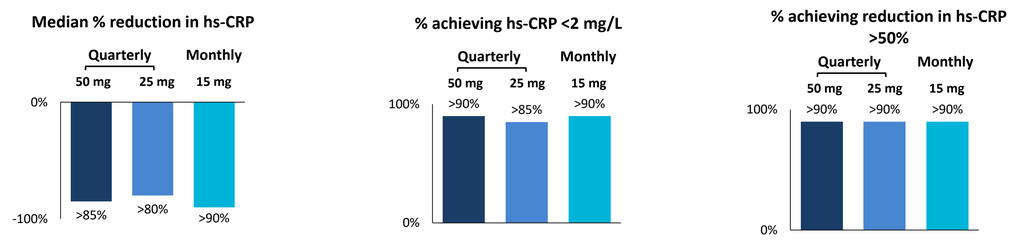

Figure 4. Change in hs-CRP from PK/PD modeling. A PK/PD model developed using data from five studies in patients with RA, SLE, and CD, and healthy volunteers, demonstrated reductions in median hs-CRP (left), achievement of hs-CRP <2mg/L (center), and >50% reductions in hs-CRP (right) with TOUR006 dosed SC 50 mg quarterly, 25 mg quarterly, or 15 mg monthly.

TRANQUILITY STUDY

- TRANQUILITY is an ongoing Phase 2, randomized, double-blind, placebo-controlled, multicenter trial enrolling at ~40 sites located across the United States (Figure 5).
- PURPOSE: The Phase 2 TRANQUILITY Trial is designed to evaluate the safety, PK, PD, and hs-CRP lowering effect of quarterly and monthly subcutaneous administration of TOUR006 in ASCVD defined as patients with chronic kidney disease (CKD) and elevated hs-CRP.
  - The CKD population was chosen for this study due to the high prevalence of elevated hs-CRP and supporting evidence for IL-6 pathway activation leading to increased risk for ASCVD in patients with CKD.

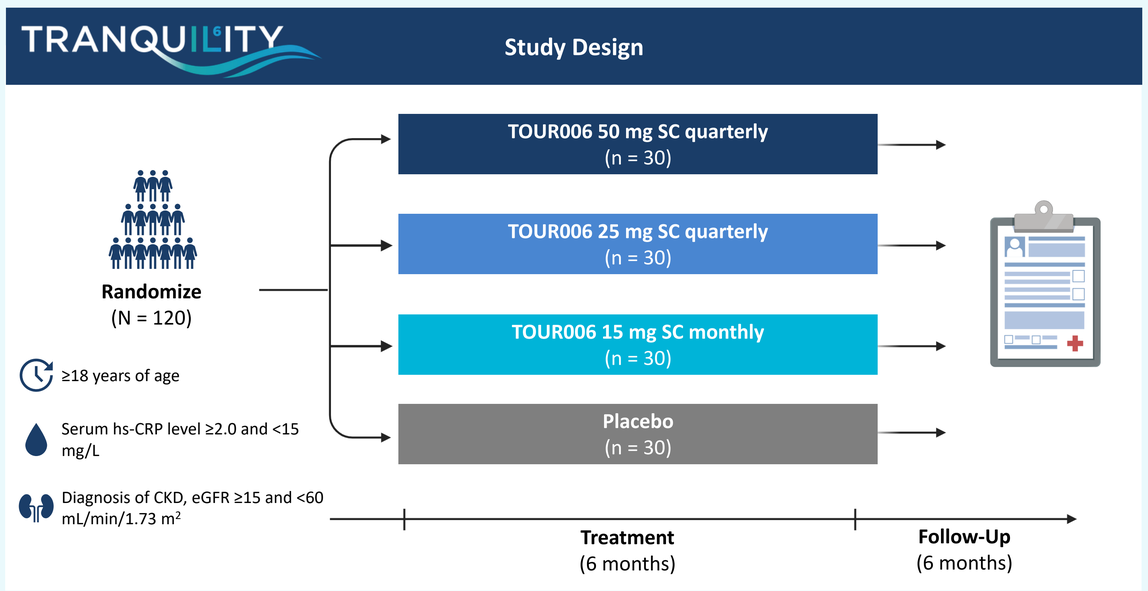

Figure 5. TRANQUILITY study design overview. Approximately 120 patients with CKD stage 3 or 4 and hs-CRP≥2 and <15 mg/L are planned for enrollment. Patients will be stratified by CKD stage and randomized to receive SC TOUR006 50 mg quarterly, 25 mg quarterly, 15 mg monthly, or placebo for 6 months. Assessments will continue for 6 months following completion of treatment. eGFR, estimated glomerular filtration rate.

Table 1. Key outcome measures for the Phase 2 TRANQUILITY Study.

Primary Outcome Measures
• Change from baseline in hs-CRP after 90 days of treatment
Secondary Outcome Measures
• Change from baseline in hs-CRP after 180 days of treatment • Serum drug concentrations of TOUR006 at baseline and after 30, 60, 90, 120, 150, and 180 days of treatment • Serum drug concentrations of TOUR006 at 210, 240, 330, and 365 days
Safety Outcome Measures
• Proportion of participants with AEs, SAEs, severe AEs, and AEs leading to discontinuation • Description and frequency of events of special interest by treatment group • Description of additional safety assessments by treatment group and dose (e.g., vital signs, electrocardiogram, and anti-drug antibodies)
Exploratory Outcome Measures
• Change from baseline in serum amyloid A, lipoprotein (a), neutrophil-to-lymphocyte ratio, fibrinogen, oxidized low-density lipoprotein, plasminogen activator inhibitor-1, and IL-6

CONCLUSIONS

- As a fully human, anti-IL-6 monoclonal antibody, TOUR006 introduces a novel approach to targeting key inflammatory pathways implicated in the progression ASCVD.
- TOUR006 is being developed and investigated towards an aim of addressing persistent cardiovascular risk in patients despite lifestyle modification and existing pharmacologic interventions.
- TOUR006 is being evaluated in the ongoing TRANQUILITY study to characterize the safety and tolerability, PK, and hs-CRP-lowering effect of TOUR006, and to inform the dosing and design of future Phase 3 outcome studies in CV indications.

ACKNOWLEDGEMENTS

- Writing and editorial support was provided by Talisa Silzer, PhD and Holly Szczepanski, MSc of sixsense strategy group inc., Toronto, Ontario, Canada, and funded by Tourmaline Bio, Inc.

DISCLOSURES

- ED, YC, KE, JW, and RI are employees of Tourmaline Bio, Inc. MDS is a consultant for Tourmaline Bio, Inc.

MORE INFORMATION

- To **learn more**, please visit: https://www.tourmalinebio.com/science/
- For more information on the **Phase 2 TRANQUILITY Study** (NCT06362759), please visit: www.clinicaltrials.gov

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