Human Monoclonal Antibody TRL1068 Disrupts Bacterial Biofilm for Nonsurgical Treatment of Orthopaedic Infections

Sandeep Singh Bains[1], Jeremy Dubin[1], Anton Leighton, Adriane Sara Kisch-Hancock, Stefan - Ryser[2], Lawrence Michael Kauvar, Zhongming Chen, Daniel Hameed[3], Ronald Emilio Delanois[4]
[1]Sinai Hospital, [2]Trellis Bioscience Inc., [3]Rubin Institute For Advanced Orthopaedics, [4]Rubin Institute for Advanced Orthopedics

INTRODUCTION:
Orthopaedic implants are susceptible to biofilm associated bacterial infections that cause significant morbidity, mortality, and treatment costs while decreasing quality of life. TRL1068 extracts a key bacterial protein required for structural integrity of biofilms. The epitope is highly conserved across gram-positive and gram-negative species. Extensive animal data have established utility for restoring antibiotic sensitivity to infections that are clinically refractory due to biofilm. TRL1068-101 is an ongoing Phase 1, first-in-human, double-blind, single ascending dose study to assess the safety, PK, and preliminary activity of TRL1068 in subjects with culture-confirmed periprosthetic joint infection (PJI) of the knee or hip and undergoing primary two-stage exchange arthroplasty.
METHODS:
A total of 8 subjects with a synovial fluid aspirate that identified one or more bacterial pathogens have received a single infusion of TRL1068 on Day 1 in combination with targeted antibiotic treatment for 7 days prior to the first stage of a standard two-stage exchange arthroplasty. Follow-up assessments were performed through study Day 169. At the timepoint of abstract submission, a scheduled interim analysis had been conducted after all subjects recruited into two of the three dose groups (6 and 15 mg/kg) completed 15 days of study participation. Culture of the explanted joints was also performed following standard sonication procedures to release biofilm associated bacteria from the surface.
RESULTS:
Two of the 8 dosed subjects (one with *Pseudomonas aeruginosa*, the other with *Streptococcus agalactiae*) presented with complete eradication of the pathogen on the explanted prosthesis after 7 days and no recurrence to date. Substantial decrease in bacterial burden was also observed for multiple other species in the other subjects. No drug-related adverse events were reported for any of the treated subjects.
DISCUSSION AND CONCLUSION:
The combination of extensive preclinical study results and the preliminary data of the ongoing Phase 1 study warrant design of Phase 2 studies in which repeat dosing with TRL1068 (an initial dose of 15 mg/kg and 3 maintenance doses of 7.5 mg/kg every 3 weeks) is combined with targeted antibiotic therapy instead of any surgical intervention. Because TRL1068 is a fully human monoclonal antibody, repeated systemic dosing is expected to be well tolerated. In addition to PJI, this novel approach has promise for treatment of infected spinal implants and as a prophylaxis for high risk patients such as external fixations of complex fractures.