Safety and tolerability of 514G3, a True Human Anti-Protein A Monoclonal Antibody for the treatment of S. aureus Bacteremia.

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Background
Novel therapeutic approaches are urgently needed for the treatment of serious infections due to S. aureus. 514G3 is a True Human Monoclonal antibody (lgG3), targeting Staphylococcus Protein A (SpA), which was isolated and cloned from a healthy human donor. Treatment of S. aureus infection with a True Human Antibody is expected to be safe, with minimal side effects.

Staphylococcus Protein A: Immune Evasion

514G3: True Human Antibody

• 514G3 was cloned from the B-Cell of a healthy human donor with pre-existing antibodies against SpA

• 514G3 binds with high affinity via the Fab region to SpA

Methods
This was a Phase I, double blind, multicenter, randomized, placebo controlled, dose escalation study of 514G3 in patients hospitalized with S. aureus bacteremia.

• Eligible subjects received a single intravenous dose of 514G3 at 2, 10, or 40 mg/kg or placebo (3:1) along with standard antibiotic therapy.

• Key Inclusion: positive blood culture for S. aureus

• Key Exclusion: polymicrobial bacteremia, complicated bacteremia, septic shock

Results
• 12 subjects received 514G3, and 4 placebo. Median age was 60, and 39% were female.

• Infection source was skin and soft tissue infection (6), phlebitis or catheter associated (4), unknown (3), and hemodialysis vascular access (3).

• MRSA was identified in 6 of 16 patients (38%).

• No DLTs occurred.

• The MTD was undefined, and 40 mg/kg was designated as the recommended phase 2 dose.

• The incidence of SAEs was lower in the 514G3 group than placebo, with 3 of 12 (25%) and 2 of 4 (50%) experiencing SAEs respectively.

• All SAEs were deemed to be related to worsening of the patients’ underlying condition.

Conclusions
514G3 was safe and well tolerated at all dose levels tested. While the numbers are small, fewer SAEs in the 514G3 treatment group suggest a favorable side effect and tolerability profile. Safety of 514G3 and reduction of complications from S. aureus bacteremia will be explored further in a randomized controlled trial utilizing the 40 mg/kg dose that is adequately powered to demonstrate differences between treatment arms.

514G3: True Human Antibody

Subjects were followed for at least 14 days to assess adverse events (AEs), potential dose-limiting toxicities (DLTs), and determine the maximum tolerated dose (MTD).

• DLTs were defined as any grade 3 or greater AE assessed as probably or definitely related to therapy. The MTD was defined as the highest dose level with ≤1 DLT.

514G3 True Human Antibody

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