XmAb564, a Novel Potency-Tuned IL-2 Fc-Fusion Protein Selectively Expands Regulatory T Cells: Results from a Single Ascending-Dose Study in Healthy Adult Volunteers

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Background

• Regulatory T cells (Tregs) are critical for control of autoimmunity and yet no treatments have capitalized on this therapeutic potential.
• Regulatory T cells (Tregs) are potent suppressors of Tregs.

Implications

• Tregs are potent suppressors of inflammation and yet no current treatments capitalize on this mechanism.
• Prior exploratory clinical studies of low-dose recombinant WT IL-2 and a PEGylated IL-2 demonstrated proof-of-concept data for efficacy and Treg expansion in a wide array of indications.
• The potential for best-in-class Treg expansion with XmAb564 may provide an opportunity to further harness the power of Tregs in autoimmune conditions.

Conclusions

• XmAb564 selectively induced Tregs and was well tolerated.
• XmAb564 PK and PD potentially supported extended multi-week dosing intervals and has a Treg induction mechanism.

Study Design

Here Xencor reports the first-in-human, placebo-controlled, double-blind, single-ascending-dose study. Healthy adult volunteers received XmAb564 and were evaluated for safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) for 30-45 days.

Phase 1a Single Ascending Dose (SAD) study

• Randomized and double-blinded
• Subcutaneous administration of XmAb564
• 6 dose-level cohorts

Outcome Measures

• Safety and tolerability
• PK and PD activity

References

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Safety

• A single subcutaneous dose of XmAb564 was well tolerated, with no dose-limiting toxicities, no Grade 3 or greater adverse events (AEs), no serious AEs, no deaths, nor clinically significant laboratory safety abnormalities.
• The most common AE attributed to XmAb564 was mild-to-moderate, self-limited injection site reactions.

Pharmacodynamics

• Terminal half-life of 9-11 days across doses 0.003 - 0.065 mg/kg
• Cmax increased dose proportionally
• AUC increased less than dose proportionally due to target-mediated drug disposition as target population expands
• Follow-up period increased from 30-45 days for Cohorts 4 - 6.

Pharmacokinetics

• The induction of Treg expansion was not paralleled by a concomitant increase in conventional T cells (Tcons) or gamma delta T cells, or a decrease in NK cells. (Figure 5C,D,E) were minimally responsive increase occurred in the CD25 bright Treg:CD4 Tcon ratio from 0.002 at baseline to a maximum mean of 168 ± 122 cells/μl on Day 15 (Figure 5A).