# 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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## Summary and Key Findings


- XmAb564 is a potency-tuned, monomeric human IL-2 heterodimeric Fc-fusion protein with extended half-life and increased binding affinity for IL-2 receptor alpha (CD25) designed to selectively expand regulatory T cells (Tregs).
- Single-dose XmAb564 in healthy adult volunteers induced Tregs and CD25$^{bright}$ Tregs 8-fold and 117-fold above baseline, respectively, and expansion persisted at least 21 days.


## Conclusions

- XmAb564 selectively induced Tregs and was well tolerated.
- XmAb564 PK and PD potentially support extended multi-week dosing intervals and has a Treg induction magnitude and durability that may be competitive or superior to other engineered IL-2 candidates in clinic.

## Implications

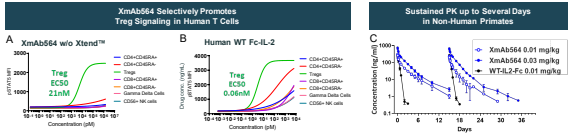
- Tregs are potent suppressors of inflammation and yet no current treatments capitalize on this mechanism.
- Prior exploratory clinical studies of low-dose recombinant WT IL-2[1] and a PEGylated IL-2[2,3] demonstrated proof-of-concept data for efficacy and Treg expansion in a wide array of indications.
- The potential for best-in-class Treg expansion with XmAb564 may provide an opportunity to further harness the power of Tregs in autoimmune conditions.



## Background

- Regulatory T cells (Tregs) are critical for control of autoimmunity and yet no treatments have capitalized on this therapeutic potential. Interleukin 2 (IL-2) signaling is essential for the development, survival, and suppressive function of Tregs.
- Diminished IL-2 signaling and Treg functional impairment are associated with the development of autoimmune diseases.
- XmAb564 is a potency-tuned, monomeric human IL-2 heterodimeric Fc-fusion protein with extended half-life and increased binding affinity for IL-2 receptor alpha (CD25) designed to selectively expand Tregs, being developed for the treatment of autoimmune diseases.
- ~1000X reduction in binding of XmAb564 to IL2-Rβγ results in tuned overall potency and greater selectivity for Treg activation over conventional T cells (Tcons) and natural killer (NK) cells (Figure 1A,B).
- The loss of internalization in vivo through IL-2Rβγ results in large gains in pharmacological exposure (Figure 1C).

**Figure 1: XmAb564 Design Reduces Potency and Enhances Treg Selectivity and Pharmacologic Exposure**




(A,B) In vitro stimulation of human PBMCs with either XmAb564 (A) or Fc-WT-IL-2 (B) reveals ~400-fold potency reduction for IL-2 signaling in human Tregs (phosphorylated STAT5 induction), with enhanced Treg selectivity over Tcons, gamma delta T cells, or NK cells. (C) Comparison of pharmacologic half-lives in cynomolgus macaques shows prolonged exposure of low-potency XmAb564 vs. WT Fc-IL-2.

## Study Design

Here Xencor reports the first-in-human, placebo-controlled, double-blind, single ascending-dose study.

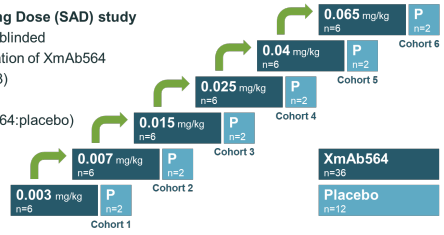
Healthy adult volunteers received XmAb564 and were evaluated for safety, tolerability, pharmacokinetics (PK), and pharmacodynamic (PD) for 30-45 days.

### Phase 1a Single Ascending Dose (SAD) study

- Randomized and double-blinded
- Subcutaneous administration of XmAb564
- Heathy volunteers (n = 48)
- 6 dose-level cohorts
- Randomized 6:2 (XmAb564:placebo)

### Outcome Measures

- Safety and tolerability
- PK and PD activity




## Results

### Demographics

**Table 1: Subject Baseline Characteristics**

| | Placebo (N=12) | 0.003 (N=6) | 0.007 (N=6) | 0.015 (N=6) | 0.025 (N=6) | 0.040 (N=6) | 0.065 (N=6) |
|---|---|---|---|---|---|---|---|
| Age (yrs), median (range) | 42.5 (26-55) | 42 (25-51) | 38 (33-47) | 44.5 (19-54) | 32.5 (22-55) | 46.5 (23-53) | 40.5 (24-49) |
| Sex | | | | | | | |
| Male | 4 | 6 | 1 | 3 | 1 | 1 | 3 |
| Female | 8 | 0 | 5 | 3 | 5 | 5 | 3 |
| Race | | | | | | | |
| White | 8 | 5 | 5 | 4 | 3 | 4 | 4 |
| Black | 2 | 1 | 1 | 2 | 2 | 2 | 1 |
| Asian | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| Other | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| BMI (kg/m2), median (range) | 27.8 (18.9-34.4) | 28.65 (26.4-30.2) | 29.8 (19.1-32.3) | 30.25 (24.9-32.0) | 21.8 (25.8-34.2) | 26.25 (20.2-32.7) | 27.55 (22.1-32.1) |

BMI = body mass index. Unit for dose level is mg/kg.

### 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.
- Asymptomatic transient elevations of peripheral eosinophils were seen in a dose-dependent manner, similar to those reported with other biologics in the class.

**Table 2: Treatment-related Adverse Events**

| AEs, Number of Subjects | Placebo (N=12) | 0.003 (N=6) | 0.007 (N=6) | 0.015 (N=6) | 0.025 (N=6) | 0.040 (N=6) | 0.065 (N=6) |
|---|---|---|---|---|---|---|---|
| Injection site reaction | 0 | 4 | 2 | 3 | 5 | 5 | 6 |
| Headache | 0 | 0 | 0 | 0 | 1 | 1 | 1 |
| Arthralgia | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Bursitis | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Musculoskeletal stiffness | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Nausea | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Pruritus | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Urticaria | 0 | 0 | 1 | 0 | 0 | 0 | 0 |

Unit for dose level is mg/kg.

### Pharmacokinetics

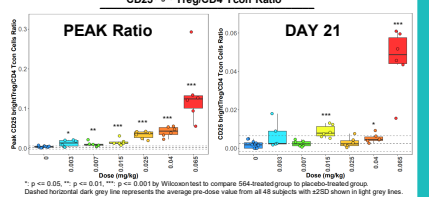
**Figure 3: Potency Reduction Improves Exposure**




- 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.

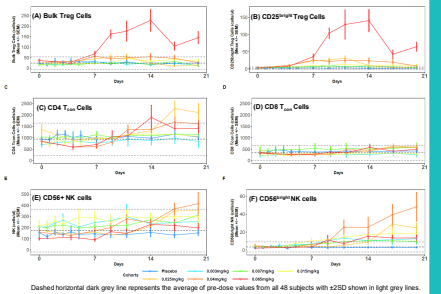
### Pharmacodynamic Activity

**Figure 4: Selective and Durable Expansion and Activation of Tregs Through Day 21**




*: p <= 0.05, **: p <= 0.01, ***: p <= 0.001 by Wilcoxon test to compare 564-treated group to placebo-treated group.
Dashed horizontal dark grey line represents the average pre-dose value from all 48 subjects with ±2SD shown in light grey lines.

**Figure 5: Treg, Tcon, and NK Cells Responses After a Single Subcutaneous Dose of XmAb564 in Healthy Volunteers**




Dashed horizontal dark grey line represents the average of pre-dose values from all 48 subjects with ±2SD shown in light grey lines.

- As a single index of Treg selectivity and potential anti-inflammatory benefit, a dose-responsive increase occurred in the CD25$^{bright}$ Treg:CD4 Tcon ratio from 0.002 at baseline to a peak ratio of 0.14 on treatment, an increase largely maintained at 0.05 on Day 21 (Figure 4).
- At the highest dose level of 0.065 mg/kg, the peak total Tregs increased by 8.31-fold, corresponding to a mean increase of 193 ± 122 cells/microliter on Day 15 (Figure 5A).
- The majority of these Tregs were CD25$^{bright}$ Tregs (Figure 5B), which were present at very low levels at baseline (mean of 2 ± 1 cells/microliter) and were 117-fold induced to a maximum mean of 168 ± 98 cells/microliter. CD25$^{bright}$ Tregs are thought to be functionally highly immunosuppressive Tregs.
- The induction of Treg expansion was not paralleled by a concomitant increase in effector lymphocyte expansion. Consistent with the intended Treg selectivity of XmAb564, CD4+ or CD8+ Tcon or total NK cells (Figure 5C,D,E) were minimally increased (< 2-fold) and without clear dose-responsive behavior at higher doses.
- CD56$^{bright}$ NK cells, a potentially immunosuppressive cell type, were increased in a dose-dependent manner, as reported with other biologics in the class (Figure 5F).

**References**

(1) Groeschel H, et al., Low-dose IL-2 therapy in autoimmune and rheumatic diseases, Frontiers in Immunology (2021) ; (2) Schleicher, S., et al. Efficacy and Safety of a Selective Regulatory T-Cell Inducing IL-2 Conjugate (LY3471851) in the Treatment of Atopic Dermatitis: A Phase 1 Randomised Study, Abstract P1242. EADV Congress, (2022). (3) Forman, S. et a., "Efficacy and Safety of a Selective Regulatory T-Cell Inducing IL-2 Conjugate (LY3471851) in the Treatment of Psoriasis: A Phase 1 Randomised Study, Abstract P161. EADV Congress (2022).