XmAb942, a Novel Potential Best-in-Class, Long-Acting Anti-TL1A Antibody for the Treatment of Inflammatory Bowel Disease: Phase 1 Final Results

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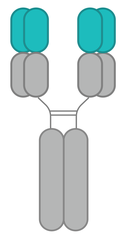
Poster #Mo1538

BACKGROUND

- TL1A mediates pro-inflammatory and pro-fibrotic effects that have been linked to the pathogenesis of IBD, including ulcerative colitis (UC) and Crohn's disease (CD).
- Multiple clinical trials have demonstrated efficacy of anti-TL1A antibodies for the treatment of UC and CD.[1-3]
- XmAb942 demonstrates selective and high-affinity TL1A binding, with potent activity and proprietary half-life extension.



STUDY DESIGN

A randomized, double-blind, placebo-controlled study

- The Phase 1 study was a single ascending-dose (SAD, Part A) and multiple ascending-dose (MAD, Part B) design, conducted in healthy participants (n=64). All cohorts 6 active:2 placebo.
- 3 dose levels with IV and SC administrations each were tested in Part A.
- 2 dose levels with IV administration were tested in Part B.

SAFETY

XmAb942 was safe and well tolerated

- There were no serious or severe TEAEs, and no TEAEs led to drug or study discontinuation.
- All TEAEs were mild or moderate.
- Rates of overall TEAEs were similar in XmAb942 and placebo: 75% (36/48 participants) vs. 69% (11/16 participants).
- Headache was the most common TEAE and occurred in 33% of participants administered XmAb942 vs. 38% of participants administered placebo.
- There were only 2 definite treatment-related AEs: both mild (1 injection site reaction, 1 administration site bruise) and in the highest SC dose.

Acknowledgments: We would like to thank the volunteers, their families, and caregivers who participated in this study, as well as the investigational study teams for support in the conduct of this research.

Author disclosures: All authors are employees of Xencor, Inc.

References: [1]Sands et al, N Engl J Med, 2024 Sep 26; 391(12):1119-1129; [2]Danese et al, Lancet Gastroenterol Hepatol. 2025 Oct; 10(10):882-895; [3]Reinisch et al, J Crohns Colitis, 19(1), 2025 Jan 22, i79–i80.

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RESULTS

Model-based projections of target inhibition for TL1A drug candidates indicated markedly enhanced TL1A inhibition by XmAb942

Table 1: Induction Phase (Week 12)

Drug	Proportion > 90% Inhibition	Proportion > 99% Inhibition
XmAb942	98%	86%
Afimkibart	81%	40%
Tulisokibart	76%	31%

In the **induction phase**, model-based projections indicate that XmAb942 provides markedly enhanced TL1A inhibition, with predicted **>99% inhibition in >80% of patients—compared to only 30–40% for first-generation anti-TL1A antibodies.**

Table 2: Maintenance Phase (Week 52)

Drug	Proportion > 90% Inhibition	Proportion > 99% Inhibition
XmAb942	90%	55%
Afimkibart	68%	25%
Tulisokibart	60%	18%

In the **maintenance phase**, XmAb942 is designed to deliver maximal TL1A inhibition with a single subcutaneous injection every 12 weeks and is projected to achieve **>90% inhibition in ~90% of patients vs. 60–70% for first-generation anti-TL1A antibodies dosed every 4 weeks.**

XmAb942 is predicted to maintain higher exposure compared to other TL1A antibodies during both induction and maintenance

A unified QSP model integrating clinical and published data for XmAb942, afimkibart, and tulisokibart was developed and extended to support virtual population simulations and comparative population-level PK/PD predictions across compounds.

Figure 1: QSP Model-Predicted Pharmacokinetics (PK)

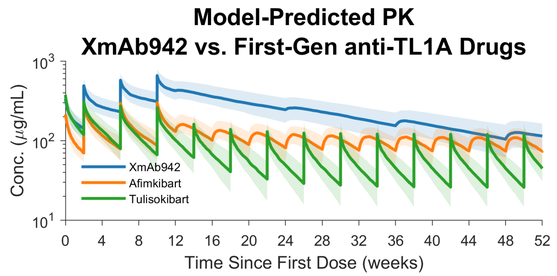


Figure 2: QSP Model-Predicted Pharmacodynamics (PD)

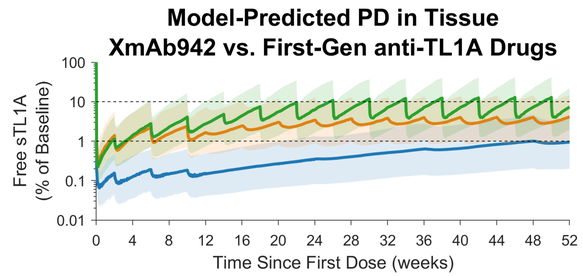


Figure 3: PK Profile (SAD IV + SC)

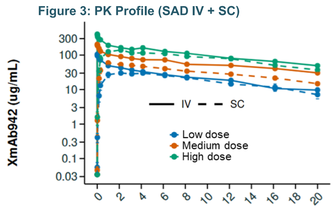


Figure 4: PK Profile (MAD IV)

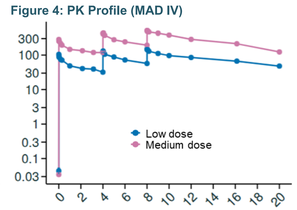


Figure 5: Complexed soluble TL1A (SAD IV + SC)

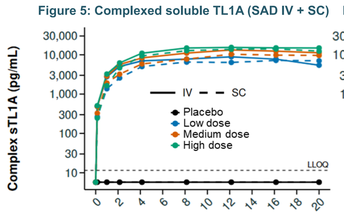


Figure 6: Complexed soluble TL1A (MAD IV)

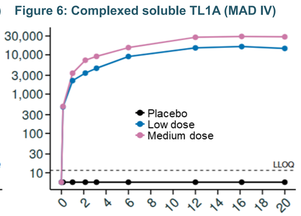


Figure 7: Free soluble TL1A (SAD IV + SC)

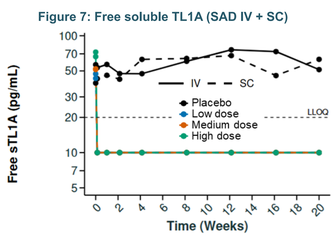
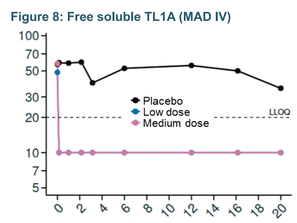


Figure 8: Free soluble TL1A (MAD IV)



XmAb942 demonstrated significantly extended serum exposure

- Pooled analysis of single-dose cohorts results in an **estimated terminal half-life of 74.1 days**, which supports the 12-week dosing interval during maintenance treatment in Phase 2b.

XmAb942 increases complexed TL1A and decreases free TL1A in serum with extended durability

- Dose-dependent increases in target engagement represented by complexed soluble TL1A (sTL1A) noted with a **durability of effect for 20 weeks after single dose.**
- **Rapid and sustained reduction of free soluble TL1A** achieved below LLOQ for 20 weeks after single dose.
- Plot symbols and lines for free sTL1A for all XmAb942 cohorts overlap at LLOQ/2, per convention for below LLOQ data.

Plot lines represent median value per cohort
LLOQ Lower Limit of Quantification

Immunogenicity

- The incidence of ADA was 57% (27/47) in healthy participants administered XmAb942 as determined in a high sensitivity ECL assay aligned to FDA guidance. Incidence and magnitude of ADA decreased with increasing drug exposure.
- 1 out of 47 healthy participants (~2%) administered XmAb942 had neutralizing antibodies, with no observed impact on suppression of free soluble TL1A.
- No impact of ADA on XmAb942 clearance was seen in the population PK model.
- No impact of ADA on safety or tolerability was observed.

CONCLUSIONS

- XmAb942 has the potential to deliver best-in-class drug exposure and TL1A target inhibition with convenient Q12W SC maintenance period dosing.
- In Phase 1, XmAb942 was shown to be safe and well-tolerated in single and multiple doses in healthy participants.
- The XENITH-UC Phase 2b study of XmAb942 in patients with ulcerative colitis (NCT06619990) is ongoing.