Targeting TNFα to Preserve Lung Function in Pulmonary Sarcoidosis: Results from a Phase 1b/2a Multiple-Ascending-Dose Trial of XTMAB-16

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BACKGROUND

- Sarcoidosis is a chronic, systemic rare disease with multi-organ involvement and significant quality of life impairment[1].
- Disease course is heterogenous with no sarcoidosis-specific therapies approved to date representing a clear unmet need.

RATIONALE

- Tumor necrosis factor alpha (TNFα) is a key mediator of granuloma formation and disease persistence in sarcoidosis.
- XTMAB-16 is under clinical investigation as an anti-TNF monoclonal antibody.
- In translational preclinical models, XTMAB-16 significantly inhibited non-caseating granuloma formation, supporting mechanistic relevance in sarcoidosis[2].

OBJECTIVES & METHODS

Objectives:

- To evaluate the safety, tolerability and preliminary efficacy of XTMAB-16 in adults with pulmonary sarcoidosis requiring systemic corticosteroids and second-line immunosuppressive therapy
- To inform dose selection for subsequent clinical trials.

Methods

- **Study design**: Part A of this Phase 1b/2a study was a randomized, double-blind, placebo-controlled, multi-ascending-dose trial (NCT05890729).
- **Population:** Adults with pulmonary sarcoidosis (N = 39).
- **Randomization:** 3:1 to XTMAB-16 or placebo.
- **Treatment duration:** 12 weeks.
- **Dose regimens:** XTMAB-16 or placebo 2mg/kg or 4 mg/kg, administered IV Q2W or Q4W.
- **Additional assessments:** pharmacokinetics, pharmacodynamics, immunogenicity, pulmonary function, imaging, quality of life, and oral corticosteroid dose modification.
- Participants were eligible for optional enrollment in an open-label extension study (NCT06169397).

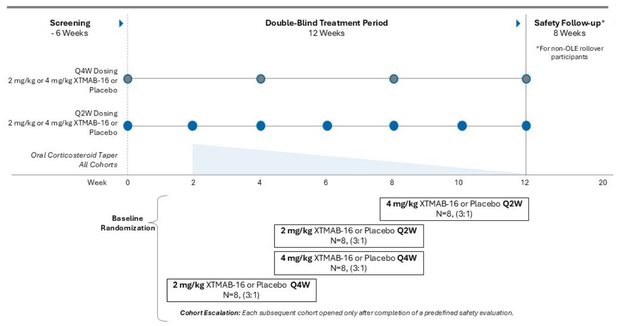


Figure 1. XTMAB-16-201 Part A study design schematic

KEY RESULTS

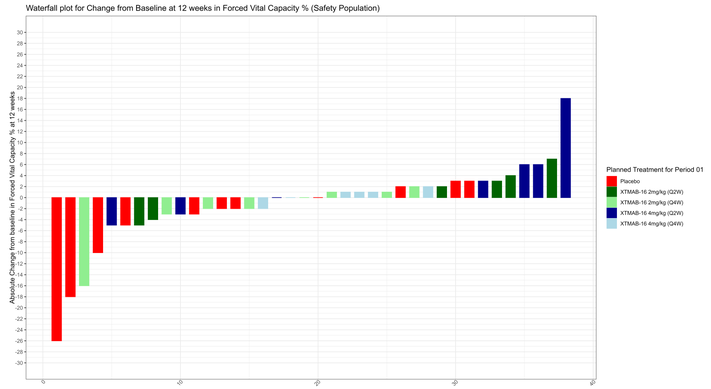
Baseline Characteristics

Study XTMAB-16-201 (Part A)	(N=39)
FVC % predicted, Mean (SD)	87.3% (18.58)
OCS dose, n (%)	
20 mg/day	1 (2.6%)
15 mg/day	2 (5.1%)
10 mg/day	17 (43.6%)
7.5 mg/day	17 (43.6%)
Immunosuppressant background therapy, n (%)	19 (48.7%)
Methotrexate	8 (20.5%)
Azathioprine	7 (17.9%)
Hydroxychloroquine	8 (20.5%)
Mycophenolic Acid	
Extrapulmonary manifestation , n (%)	
No	16 (57.1%)
Yes	12 (42.9%)
Cutaneous	5 (12.8%)
Ocular	7 (17.9%)
Neurological	1 (2.6%)
Musculoskeletal	2 (5.1%)
Renal	1 (2.6%)

Table 1. XTMAB-16-201 Part A baseline characteristics
FVC = Forced Vital Capacity; OCS = Oral corticosteroids;

FVC% Predicted – Change from Baseline

- Mean forced vital capacity percent predicted remained stable or showed modest improvement in XTMAB-16-treated participants, whereas placebo participants experienced a decline at Week 12 (-5.3%).



Safety Summary

- XTMAB-16 was overall well tolerated with mild to moderate adverse events generally consistent across all dose groups.
  - No unexpected treatment-emergent adverse events (TEAEs) observed
  - No dose-limiting toxicities (DLTs) identified
  - No deaths occurred
  - No serious adverse events (SAEs) related to study intervention
  - No opportunistic infections, lymphomas or hepatotoxicity reported
- TEAEs reported in:
  - 100% placebo participants
  - 75% of treated participants
  - Common events were low-grade GI, respiratory (rhinitis, dyspnea) and mild infections Grade 1-2

DOSE SELECTION FRAMEWORK

- **Dose selected for further investigation**: 4 mg/kg administered Q4W.
- Dose concentration and dosing frequency were selected to balance tolerability while maintaining pharmacologic activity and practical feasibility of administration.
- Participants receiving XTMAB-16 achieved greater corticosteroid reduction than placebo. The largest percent reduction from baseline occurred in the 4 mg/kg Q4W group (-85.0%), with all active treatment groups outperforming placebo.
- Although placebo participants reduced steroid dose (mean -4.45 mg), pulmonary function declined.
- Biomarker analyses demonstrated reductions in inflammatory biomarkers, including soluble TNFα in XTMAB-16-treated participants, consistent with on-target TNF blockade.

Steroid Withdrawal	Physiological Impact	Response to Treatment
Immunogenicity	Pharmacokinetics (PK)	Quality of Life (QoL)

Future commercial use of XTMAB-16 is contingent upon positive clinical trial results and regulatory approval

References:

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2. Gerriets V, Goyal A, Khaddour K. Tumor necrosis factor inhibitors. StatPearls. Treasure Island (FL): StatPearls Publishing; 2024.
3. Offman, E., et al. "Leveraging in Vitro and Pharmacokinetic Models to Support Bench to Bedside Investigation of XTMAB-16 as a Novel Pulmonary Sarcoidosis Treatment." Frontiers in Pharmacology, vol. 14, 2023, article 1066454. impairment

Acknowledgements: Medical writing support was provided by Erin Paynich[1] and biostatistical support was provided by Scigenix.

This study was funded by Xentria, Inc.

KEY POINTS

- XTMAB-16 was well tolerated across multiple dose regimens in pulmonary sarcoidosis, with a safety profile consistent with the established class effects of TNFα inhibitors and no unexpected safety signals[3].
- Treatment demonstrated exploratory signals of corticosteroid reduction, maintenance of lung function and on-target TNFα blockade.
- Integrated safety, PK/PD, biomarker and clinical data from Part A support selection of 4mg/kg Q4W for continued evaluation.

CONCLUSIONS

- **XTMAB-16 shows an acceptable safety profile and early efficacy signals in pulmonary sarcoidosis, supporting continued development and advancement of the 4mg/kg Q4W regimen for further evaluation.**

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