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XTMAB-16 IN SARCOIDOSIS: FIRST-IN-PATIENT STUDY RESULTS

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Disclosures

- PI on industry sponsored sarcoidosis studies (aTYR, Kinevant, Novartis, Xentria, Proviant)
- Serve/served on the scientific advisory board of the Foundation of Sarcoidosis Research (FSR) and the Ann Theodore Foundation - Break Through Sarcoidosis initiative (ATF-BSI)
- Provided paid consulting services to & received travel support from Xentria, aTYR, CSL-Behring

Goals of This Session

- Introduce XTMAB-16, a therapeutic antibody targeting inflammatory pathways implicated in the formation and propagation of granulomas in sarcoidosis.
- Provide an overview of the XTMAB-16-201 Part A, the first-in-patient clinical trial.
- Present results on Part A (dose-escalation), focusing on safety, tolerability and pharmacokinetics.
- Discuss implications of Part A results for ongoing clinical development, including dose selection and progression to subsequent study phases.

Sarcoidosis

Rare Inflammatory Disease that Interferes with an Organ's Structure and Function

- Multisystem immune-mediated disease characterized by granulomas developing across one or more organ systems.
- When left untreated, inflammation can lead to fibrosis, organ dysfunction and reduced QoL.

Ongoing Unmet Need

- There are no FDA-approved therapies specifically developed for sarcoidosis.
- Beyond steroids, patients rely on off-label therapies approved for other diseases, highlighting the lack of targeted treatments.
- Patients emphasize the need for accessible therapies with mechanisms of action that target disease etiology and progression.

Drent, et al. NEJM. 2021; Bhargava, et al. Sci Rep. 2020; Judson, et al. Respiratory Medicine 2023

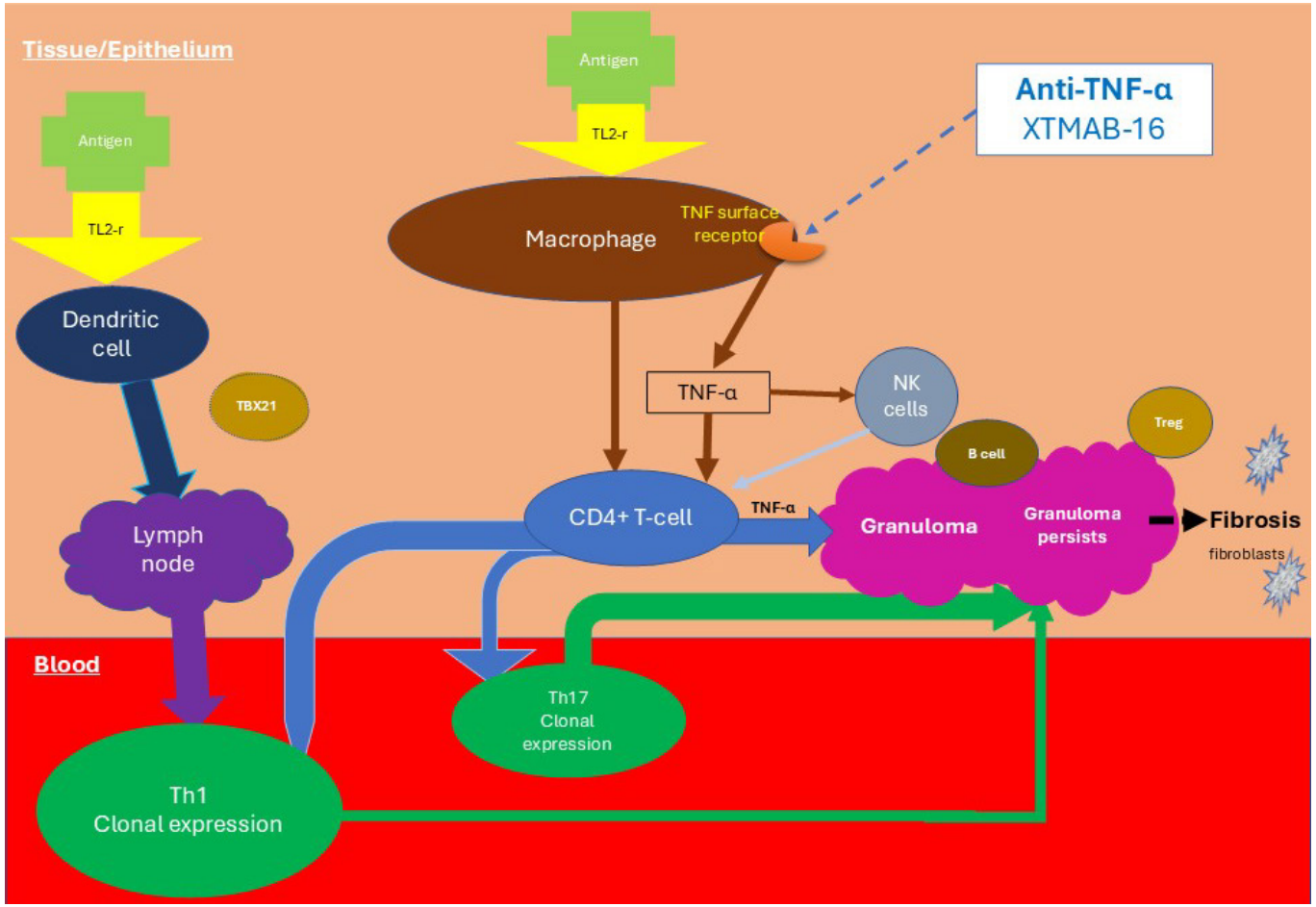
Pathophysiology

TNFα is essential for the:

- **Early recruitment** of macrophages
- **Activation** of immune cells
- **Maintenance** of the granuloma's structural integrity

TNF is upstream in the process of granuloma formation, acting as a crucial initiating and regulatory signal rather than merely a consequence of the structure's formation.

Granuloma Formation and Persistence



Adapted from Obi ,et al., Clin Chest Med. 2024

Broos, et al. Front. Immunol. 2013; Offman, et al. Front Pharmacol. 2023

XTMAB-16 At A Glance

XTMAB-16 is an anti-tumor necrosis factor alpha (TNFα) monoclonal antibody being developed as a novel biologic product for the treatment of pulmonary sarcoidosis with or without extrapulmonary manifestations.

Therapeutic Goal: Disrupt the inflammatory pathway and slow/halt the progress of granuloma formation

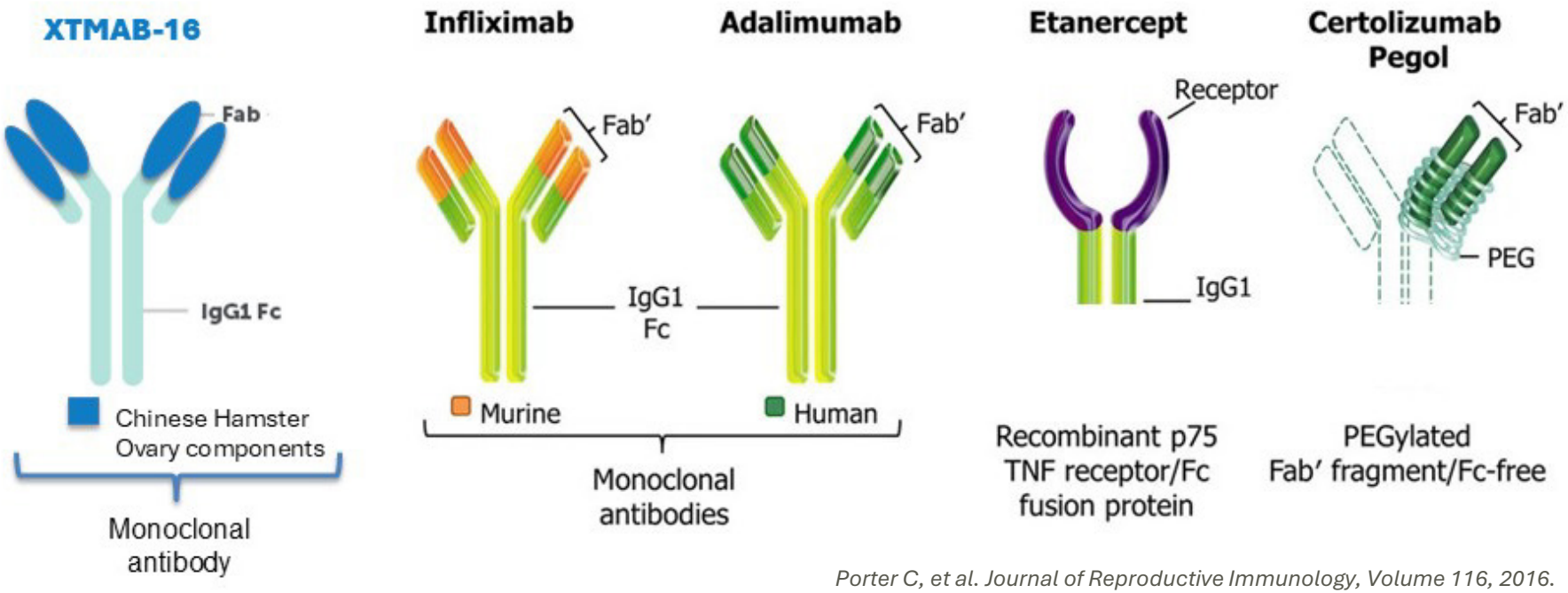
DEVELOPED AS A DISTINCT INVESTIGATIONAL MONOCLONAL ANTIBODY		
Although XTMAB-16 was initially designed with reference to infliximab, it is recognized as a separate molecular entity (with a distinct CAS identifier) and is being advanced under the FDA 351(a) pathway for sarcoidosis, requiring independent evaluation of safety and efficacy rather than demonstration of bio similarity.		
Route	—	IV Infusion
Phase 1 **Healthy volunteers**	—	Overall Safe & Tolerable
Phase 2 **First Inpatient dose ranging Study**	—	Overall Safe & Tolerable

FIP = first-in-patient

Hypothesis

XTMAB-16 is a chimeric human-murine IgG1 anti-TNF mAb targeting soluble TNF-α, a pathway implicated in granuloma formation and persistence in sarcoidosis.

Developed using a CHO cell expression system to support human-compatible glycosylation and controlled product quality – factors associated with reduced immunogenicity risk (pending clinical confirmation).

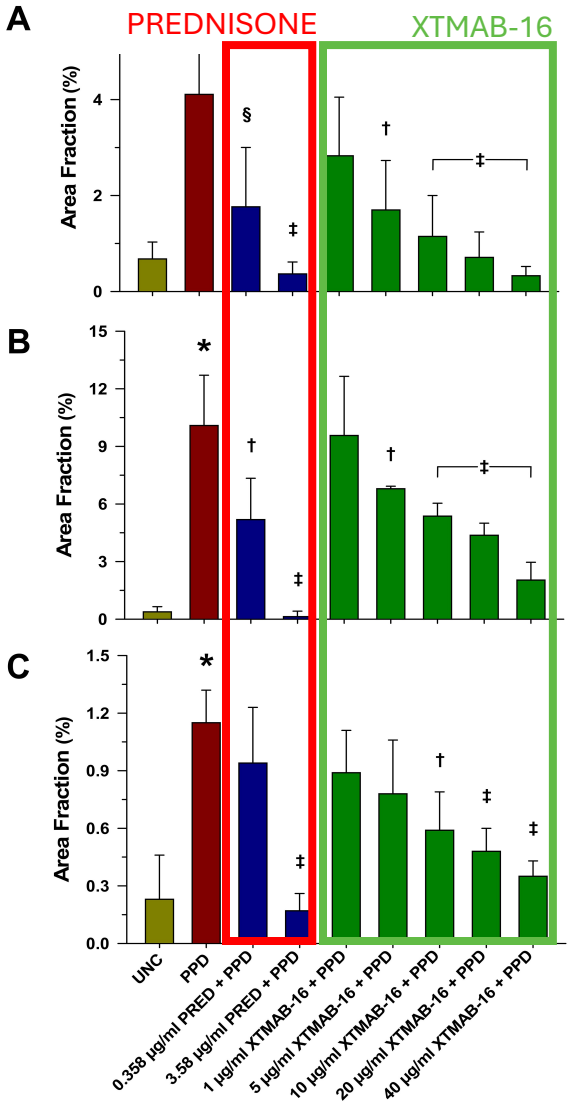


Porter C, et al. Journal of Reproductive Immunology, Volume 116, 2016.

mAb = Monoclonal antibody; CHO = Chinese Hamster Ovary ; Howard, E.I., et al. Biomedicines. 2025; Offman, et al. Front Pharmacol. 2023

Model-Informed Dosing Strategy for Part A Trial Design

- **Mechanistic potential**: Dose-dependent inhibition of granuloma growth observed in vitro.
- XTMAB-16 showed a superior dose effect to standard of care corticosteroids.
  - At doses comparable to therapeutic and supra-therapeutic doses of first-line prednisone; with supra-therapeutic dose of steroids being toxic and infeasible.
- Implementation of this model predicted therapeutically relevant lung tissue drug concentrations for Part A of the study.



XTMAB-16 pretreatment for 30 minutes had a significant dose-response effect to suppress granuloma formation

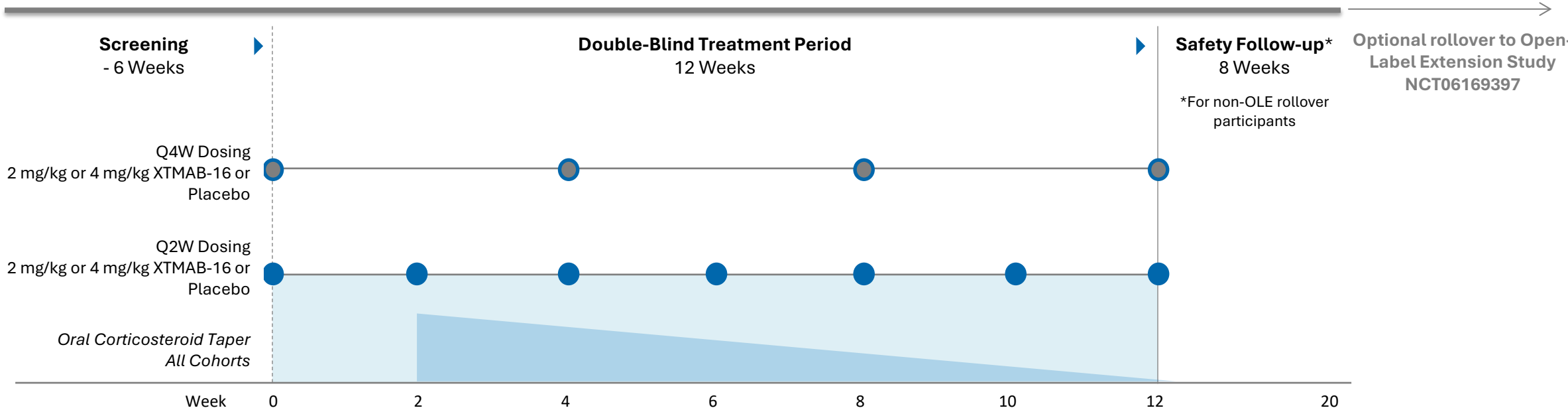
Group analysis of granuloma formation in sarcoid patients (n=15)

Area Fraction (%) = cumulative granuloma area as a percentage of the total area of the image
(A) High Responder
(B) Very High Responder
(C) Low Responder

*p < 0.001 compared to (UNC) Uncoated bead treatment group
†p < 0.01
‡p < 0.001
§p < 0.05 relative to (PPD) PPD-treated group

Singh, et al. Am J Respir Crit Care Med. 2022

Part A (Multiple Ascending Dose-Ranging) Trial Design



Baseline Randomization

- **4 mg/kg** XTMAB-16 or Placebo **Q2W** N=8, (3:1)
- **2 mg/kg** XTMAB-16 or Placebo **Q2W** N=8, (3:1)
- **4 mg/kg** XTMAB-16 or Placebo **Q4W** N=8, (3:1)
- **2 mg/kg** XTMAB-16 or Placebo **Q4W** N=8, (3:1)

Cohort Escalation: *Each subsequent cohort opened only after completion of a predefined safety evaluation.*

Patients with chronic and active pulmonary sarcoidosis

Key Inclusion Criteria	Key Exclusion Criteria
• Patients with pulmonary sarcoidosis (PS), with or without extrapulmonary manifestations • Diagnosis of PS ≥ 6 months prior to screening • No prior anti-TNF use • On 7.5–25 mg/day OCS (or equivalent) and can remain on stable dose during screening period • On stable dose of 2nd-line agent for ≥ 3 months • Parenchymal lung involvement on HRCT • mMRC Dyspnea Scale of ≥ 1 • FVC > 50%	• Extensive Fibrosis (> 20%) • Clinically significant SAPH • Clinically significant Cardiac/ Neurosarcoidosis

SFU = safety follow-up; OLE = open-label extension study; OCS = oral corticosteroid; HRCT = high-resolution computed tomography; mMRC = Modified Medical Research Conference; NCT05890729

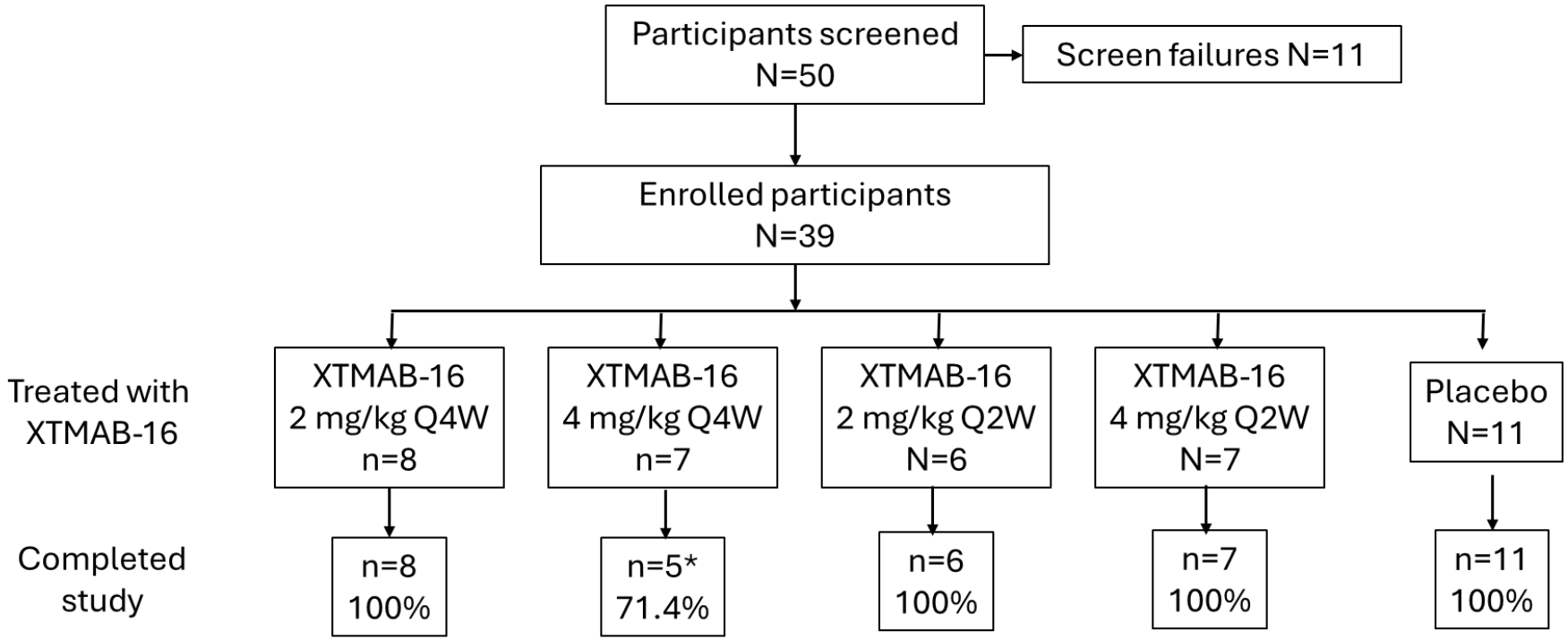
Patients with chronic and active pulmonary sarcoidosis

Primary Objectives	Secondary Objectives
Safety and tolerability • Rate Of Adverse Events (AEs) • Dose Limiting Toxicities (DLTs) • Adverse Events Of Special Interests (AESIs) Recommended dose determination • PK profiling • PD trends • Occurrence of ADA • FVC • OCS reduction	• Proportions of participants who achieve targeted OCS taper (5mg/day or equivalent) by Week 12 • PK clearance, volume, half-life • Accumulation ratio repeat dosing • Immunogenicity profiles • Biomarkers* • HRQoL* • HRCT*

No formal statistical hypothesis was planned due to the exploratory nature of the study and the limited sample size in each treatment group

**Exploratory; HRQoL = Health-related quality of life; HRCT = high-resolution computed tomography; NCT05890729*

Study Period Nov 2023 – Mar 2025



* 1 participant withdrew consent

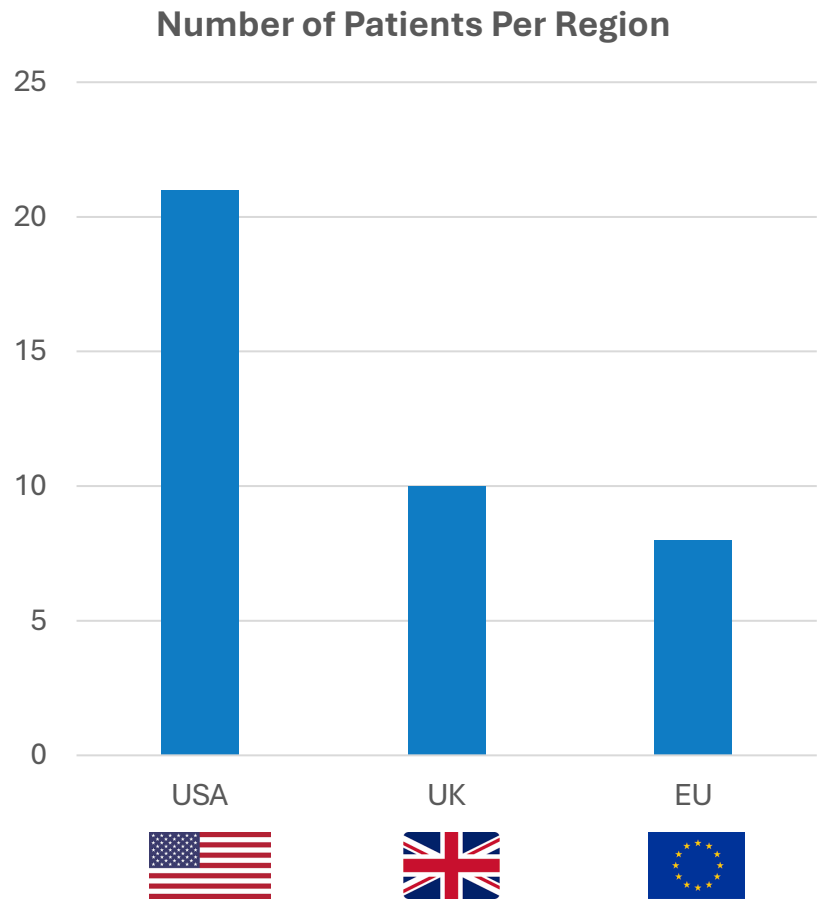
39 Patients were randomized to XTMAB-16 vs. Placebo (3:1);
37 patients completed study

NCT05890729

This presentation was updated on 02JUN2026 to correct the participant disposition statement from "2 participants withdrew consent" to "1 participant withdrew consent." The correction does not affect the study results, safety findings, overall study interpretation, or conclusions.

Demographics

Study XTMAB-16-201	(N=39)
Race	
White	28 (71.8%)
Black	10 (25.6%)
Other	1 (2.6%)
Gender	
Male	23 (59%)
Female	16 (41%)
Age	
Mean (SD)	54.3 (9.0)
BMI	
Mean	31.9 kg/m^2



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Baseline Characteristics

Study XTMAB-16-201	(N=39)
Average duration of disease prior to baseline (years)	8.76
Background immunosuppressant therapy	
Methotrexate	19 (48.7%)
Azathioprine	8 (20.5%)
*Hydroxychloroquine	7 (17.9%)
Mycophenolic Acid	8 (20.5%)
Extrapulmonary manifestation	
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%)

Study XTMAB-16-201	(N=39)
OCS dose (mg/day)	
20	1 (2.6%)
15	2 (5.1%)
10	17 (43.6%)
7.5	17 (43.6%)
FVC % predicted; mean (SD)	87.3% (19)
Pooled Active	83.4 (19)
Pooled Placebo	97.4 (16)
FVC (L); mean (SD)	
Pooled Active	3.42 (2)
Pooled Placebo	4.48 (1)

*OCS = oral corticosteroid; *Combination background therapy with Plaquenil was allowed; NCT05890729*

Safety Profile

XTMAB-16 demonstrated a safety profile consistent with the established class effects of TNFα inhibitors with no unexpected safety signals observed.

- XTMAB-16 was 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

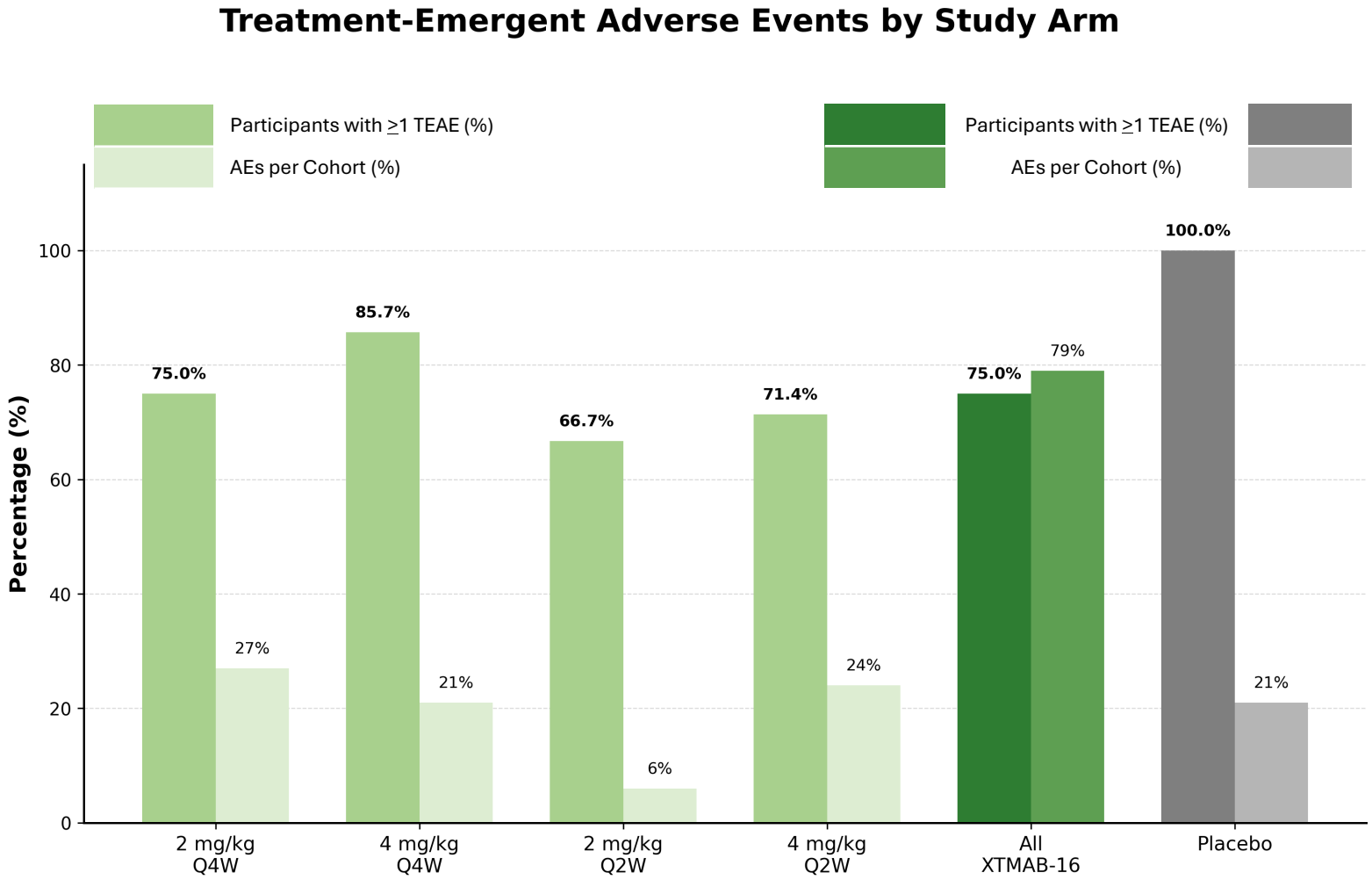
Gerriets V, et al. StatPearls. 2024

TEAEs in >5% of participants across all doses of XTMAB-16 and Placebo

≥ 1 TEAE reported in:

- 100% placebo participants
- 75% of treated participants

Common events were low-grade GI, respiratory (rhinitis, dyspnea) and mild infections Grade 1-2.



TEAE = treatment-emergent adverse event. Dark green indicates pooled XTMAB-16 cohort.

Q2W, every 2 weeks; Q4W, every 4 weeks; *Reports of sarcoidosis exacerbation were documented using the Preferred Term 'sarcoidosis'; *NCT05890729*

TEAEs in >5% of participants across all doses of XTMAB-16 and Placebo

MeDRA Preferred Term n (%)	XTMAB-16 Dose						
	2 mg/kg Q4W N=8	4 mg/kg Q4W N=7	2 mg/kg Q2W N=6	4 mg/kg Q2W N=7	All doses N=28	Placebo N=11	Total N=39
Number of participants with ≥1 TEAE	6 (75.0)	6 (85.7)	4 (66.7)	5 (71.4)	21 (75.0)	11 (100)	32 (82.1)
Fatigue	0	2 (28.6)	0	0	2 (7.1)	0	2 (5.1)
Sarcoidosis exacerbation*	2 (25.0)	0	0	1 (14.3)	3 (10.7)	0	3 (7.7)
Conjunctivitis	1 (12.5)	0	1 (16.7)	0	2 (7.1)	0	2 (5.1)
Postoperative wound infection	1 (12.5)	0	0	0	1 (3.6)	0	1 (2.6)
Nasopharyngitis	0	0	0	0	0	2 (18.2)	2 (5.1)
Pharyngitis	0	0	0	0	0	1 (9.1)	1 (2.6)
Respiratory tract infection viral	0	2 (28.6)	0	0	2 (7.1)	1 (9.1)	3 (7.1)
Elevated serum CPK	2 (25.0)	0	1 (16.7)	1 (14.3)	4 (14.3)	1 (9.1)	5 (12.8)
Myalgia	1 (12.5)	0	0	1 (14.3)	2 (7.1)	0	2 (5.1)
Arthralgia	0	1 (14.3)	0	2 (28.6)	3 (10.7)	1 (9.1)	4 (10.3)
Headache	1 (12.5)	1 (14.3)	0	1 (14.3)	3 (10.7)	1 (9.1)	4 (10.3)
Dyspnea	0	1 (14.3)	0	1 (14.3)	2 (7.1)	0	2 (5.1)
Rash	1 (12.5)	0	0	1 (14.3)	2 (7.1)	0	2 (5.1)

*Reports of sarcoidosis exacerbation were documented using the Preferred Term 'sarcoidosis'.

- Incidence comparable between active and placebo
- No statistically significant differences observed

Q2W, every 2 weeks; Q4W, every 4 weeks; TEAE, treatment emergent adverse events; NCT05890729

PK Profile

- Terminal half-life was approximately 13 days; 14.7 days (ADA-) vs 10.6 days (ADA+) as characterized by two-compartment model.
- Clinical Benchmark: Infliximab ~7-12 days

  - ➢ PK model was unable to distinguish between an ADA mediated clearance and non-ADA mediated clearance – the variability and small sample size may be contributing factors

	Overall	
	ADA non-Positive (N=28)	**ADA Positive (N=19)**
t_half_beta (days)		
Mean (SD)	14.7 (5.57)	10.6 (4.18)
Median [Min, Max]	13.0 [7.57, 30.6]	8.84 [5.49, 18.0]

Table 1. Half-life of each compartmental phase by ADA status

NCT05890729; CarePathRx 2021

PK - Exposure-Response / Trough

Exposures Q2W at Week 10

	Overall (N=13)
AUC (2 week) (hr.ug/mL)	
Mean (SD)	22800 (9210)
Median [Min, Max]	20800 [11500, 35700]
AUC (4 week) (hr.ug/mL)	
Mean (SD)	45600 (18400)
Median [Min, Max]	41600 [23000, 71400]
Cmax (ug/mL)	
Mean (SD)	124 (51.7)
Median [Min, Max]	110 [56.4, 209]
Cmin (ug/mL)	
Mean (SD)	41.8 (17.8)
Median [Min, Max]	46.0 [12.8, 70.0]
Cavg (2 Week) (ug/mL)	
Mean (SD)	68.6 (27.3)
Median [Min, Max]	62.0 [34.3, 106]
Cavg (4 Week) (ug/mL)	
Mean (SD)	137 (54.6)
Median [Min, Max]	124 [68.5, 212]

Exposures Q4W at Weeks 8-12

	Overall (N=14)
AUC (hr.ug/mL)	
Mean (SD)	25500 (14900)
Median [Min, Max]	21300 [8140, 55400]
Cmax (ug/mL)	
Mean (SD)	103 (49.5)
Median [Min, Max]	91.4 [43.6, 190]
Cmin (ug/mL)	
Mean (SD)	17.7 (13.4)
Median [Min, Max]	16.1 [1.50, 46.4]
Cavg (ug/mL)	
Mean (SD)	38.5 (22.2)
Median [Min, Max]	32.9 [12.1, 82.5]

Exposure-Response / anti-TNFs

Prior work in anti-TNF-treated sarcoidosis (n=90) showed that suboptimal dosing, particularly overdosing, can disrupt PK and increase immunogenicity, leading to reduced drug exposure and diminished efficacy (Otten et al.).

Underscores the need for careful evaluation of dose accumulation, dosing frequency and immunogenicity trends.

Infliximab most common dose 5mg/kg Q6W

Table 3

Predictors of infliximab drug levels.

Associated Variable	N (%)	IFX Level (median, IQR)	p-value
Second Line Therapy:			
Yes	36 (56.3 %)	16.2 (17.8)	0.060
No	28 (43.8 %)	8.9 (20.3)	
Prednisone:			
Yes	19 (29.7 %)	6.8 (24.1)	0.877
No	45 (70.3 %)	15.9 (17.5)	
Presence of Anti-drug Antibodies:			
Yes	11 (19.0 %)	1.0 (5.6)	<0.001
No	47 (81.0 %)	16.4 (18.0)	

Adalimumab most common dose 40mg Q1W

Table 4

Predictors of adalimumab drug levels.

Associated variable	N (%)	Adalimumab Level (median, IQR)	p-value
Second Line Therapy:			
Yes	8 (30.8 %)	9.7 (7.1)	0.683
No	18 (69.2 %)	12.1 (20.9)	
Prednisone:			
Yes	10 (38.5 %)	7.3 (12.1)	0.150
No	16 (61.5 %)	12.5 (15.0)	
Presence of Anti-drug Antibodies:			
Yes	8 (32 %)	3.1 (6.9)	<0.001
No	17 (68 %)	14.0 (17.3)	

Otten, et al. Respir Med. 2025

Model Predicted Exposure for 201 Patients

- Observed ADA formation showed trends towards reduced terminal half-life
  - Terminal ½ life : 14.7 days (ADA-) vs 10.6 days (ADA+)

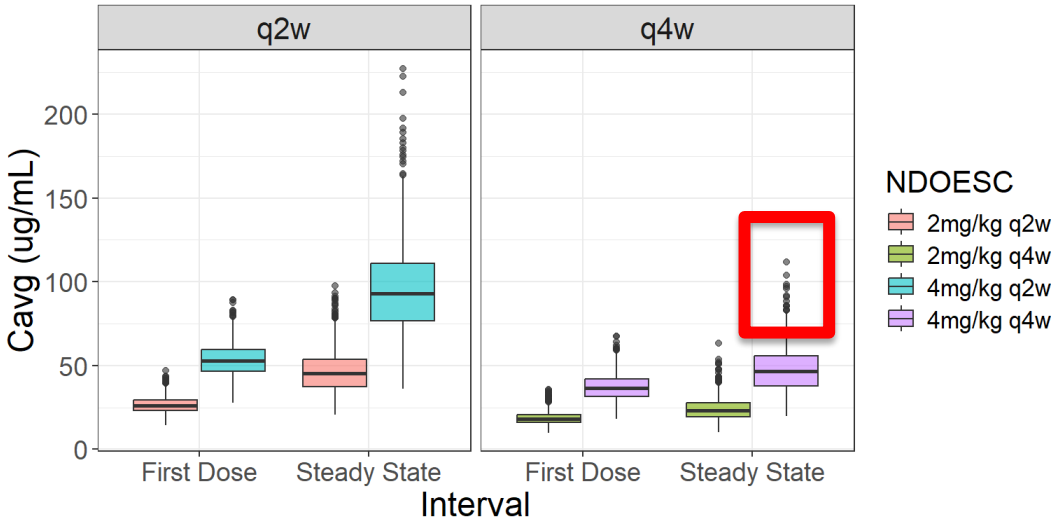


Figure 1. XTMAB-16 Average Concentration Q2W vs Q4W

- **Q4W dosing demonstrates minimal accumulation with stable trough levels**
- Q2W dosing shows modest accumulation with repeated dosing

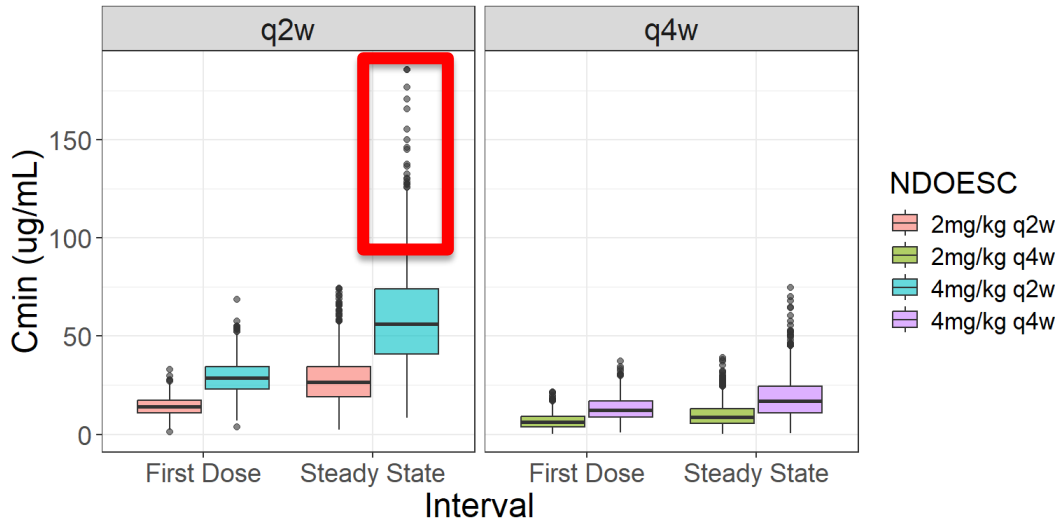


Figure 2. XTMAB-16 Minimum Concentration Q2W vs Q4W

Crommelin, et al. 2014 Immunotherapy; NCT05890729

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Immunogenicity

Anti-Drug Antibodies and Neutralizing Antibodies by Dose Level and Dosing Regimen for XTMAB-16

	2 mg/kg Q4W (N=8)	4 mg/kg Q4W (N=7)	2 mg/kg Q2W (N=6)	4 mg/kg Q2W (N=7)
Anti-drug antibody (subject level)				
Non-Positive	2 (25.0%)	6 (85.7%)	4 (66.7%)	5 (71.4%)
Positive	6 (75.0%)	1 (14.3%)	2 (33.3%)	2 (28.6%)
Neutralizing antibody (subject level)				
Negative	5 (62.5%)	2 (28.6%)	2 (33.3%)	1 (14.3%)
Positive	0 (0%)	0 (0%)	0 (0%)	1 (14.3%)
Not assessed /ADA non-positive	3 (37.5%)	5 (71.4%)	4 (66.7%)	5 (71.4%)

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PK Profiles by Confirmed Anti-Drug Antibody (Positive) Status

- P1 Single Ascending Dose in healthy volunteers (101)
  - All ADA+ participants were NAb+
- Part A (active group)
  - Minimal NAb+ in 201 (n = 1) in 4mg/kg Q2W dose group confirmed at Wk 12
  - ADA+ linked to lower XTMAB-16 exposure compared to ADA- participants
  - **ADA most frequent in 2mg/kg Q4W dosing group**

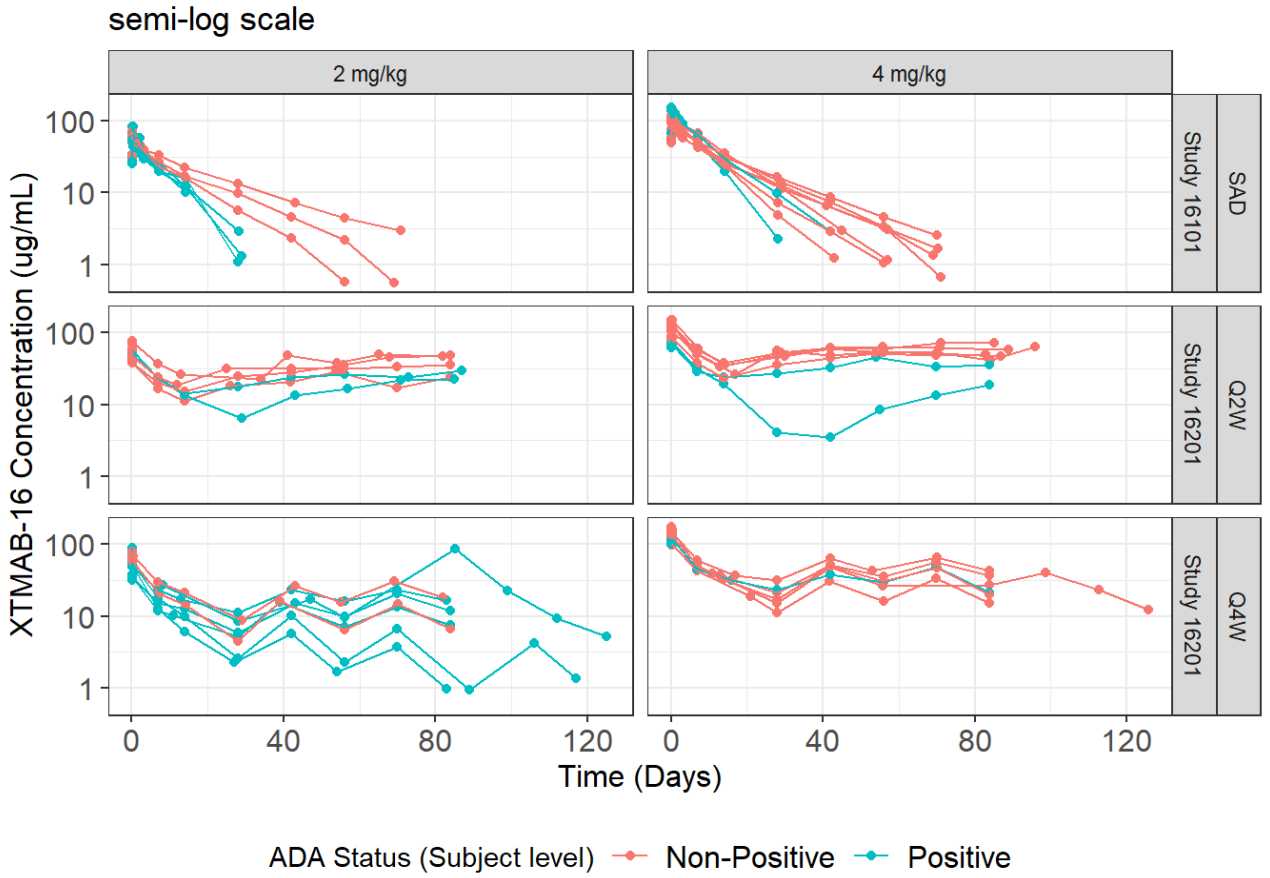
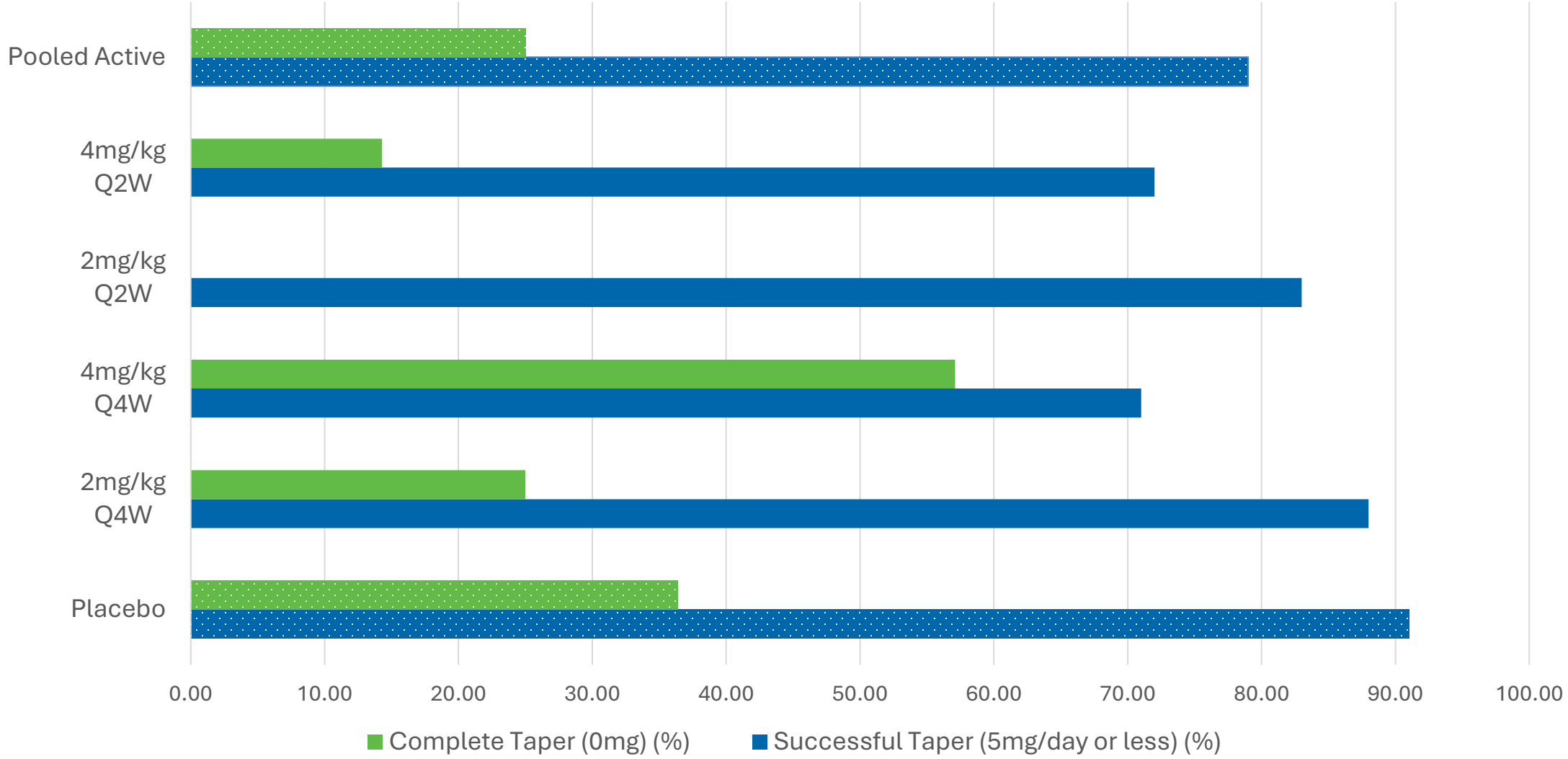


Figure 1. Pharmacokinetic Profile, Single Ascending Dose in Healthy Volunteers vs Q2W and Q4W Dosing in Pulmonary Sarcoidosis Patients

If a subject had a positive ADA sample at any time on study, then coded as positive for this plot

SAD = single-ascending dose; NCT05890729

Achievement of Complete Steroid Taper (0 mg/day) at Week 12



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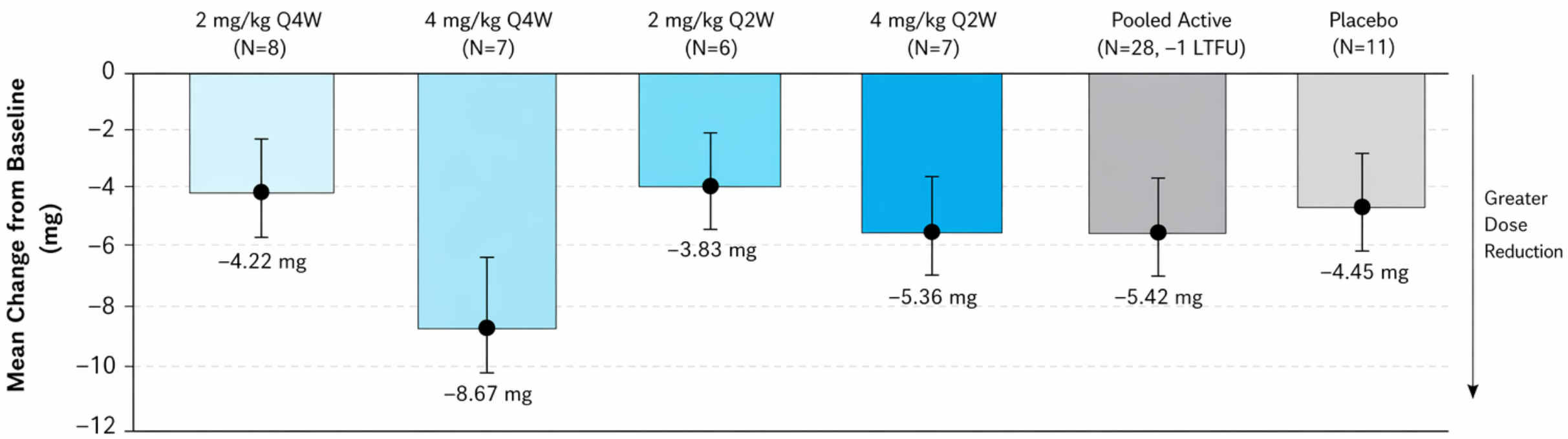
Corticosteroid Mean Reduction at Week 12



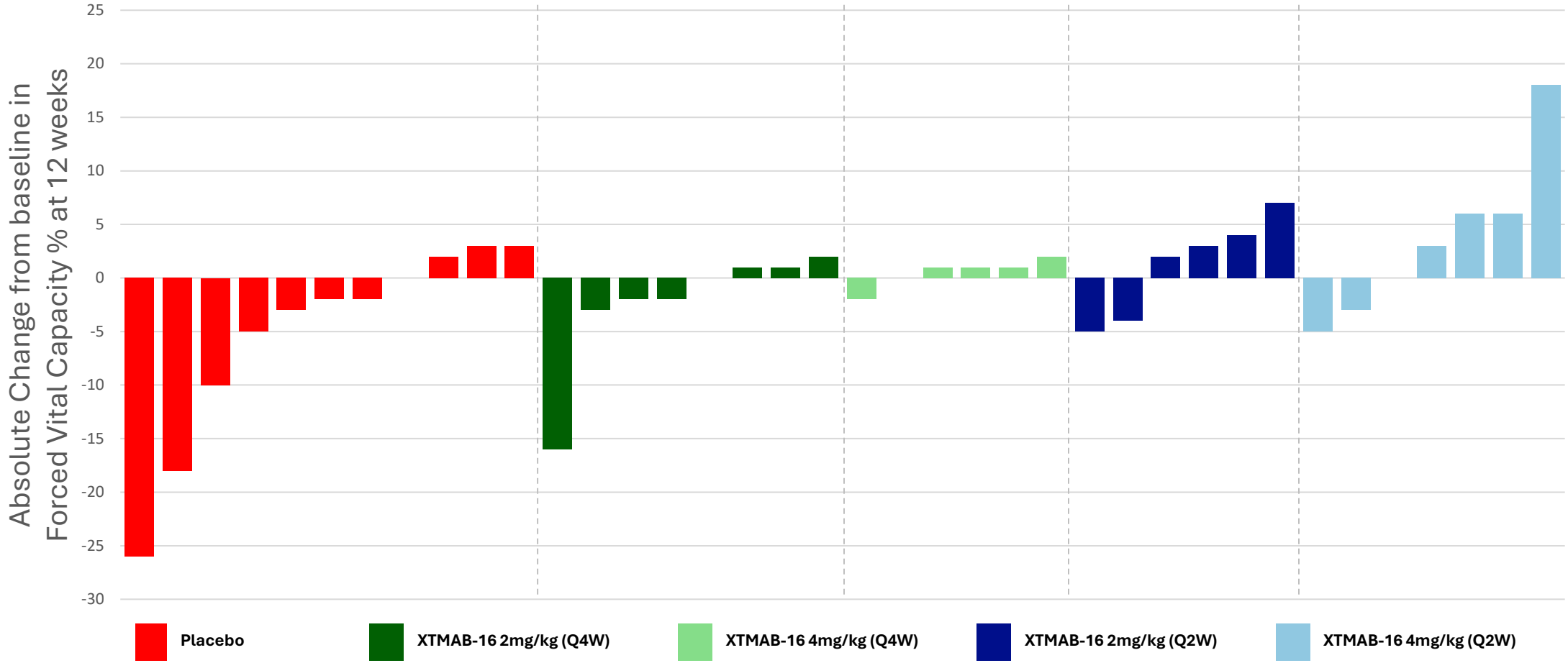
Q4W = every 4 weeks; Q2W = every 2 weeks; LTFU = lost to follow-up; SD = standard deviation; CI = confidence interval.

* Mean difference (Active – Placebo). Negative values favor active treatment (greater dose reduction).

NCT05890729

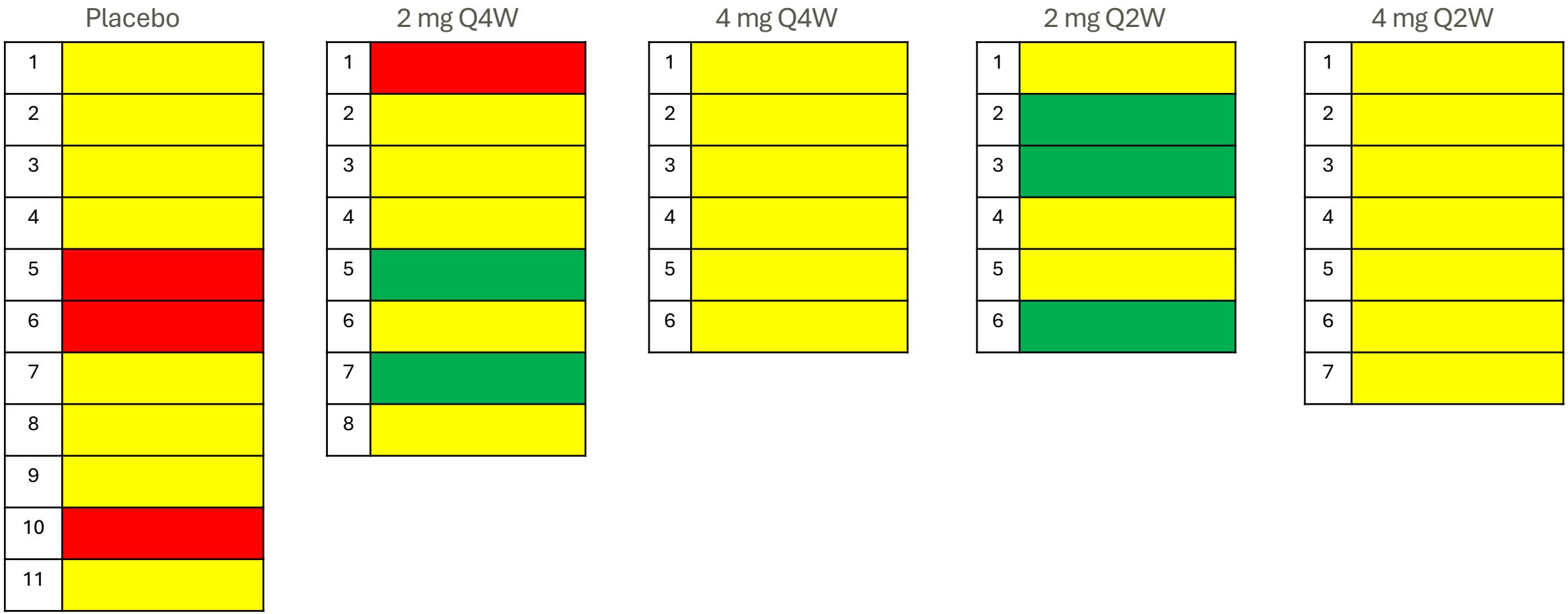
FVC % – Change from Baseline (Safety Population)

	XTMAB-16 Dose				
	Placebo N=11	**2 mg/kg/Q4W** N=8	**4 mg/kg/Q4W** N=6	**2 mg/kg/Q2W** N=6	**4 mg/kg/Q2W** N=7
Mean (SD)	**-5.3** (9.26)	**-2.4** (5.78)	**0.5** (1.38)	**1.2** (4.71)	**3.6** (7.63)



NCT05890729; Q2W: every 2 weeks; Q4W: every 4 weeks; SD: standard deviation.

HRCT & Structural Changes at Week 12



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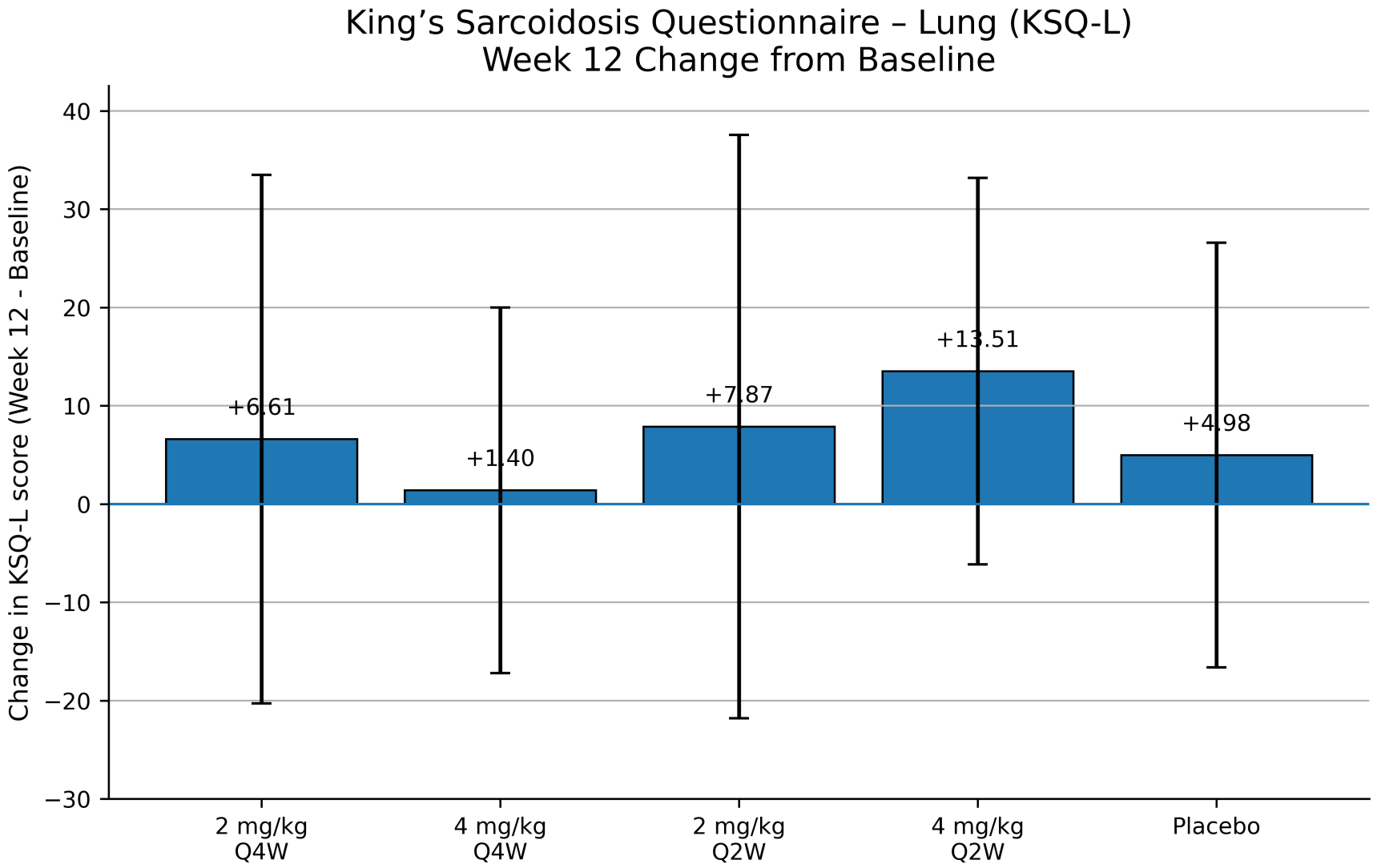
Kings Sarcoidosis Questionnaire –Lung (KSQ-L)



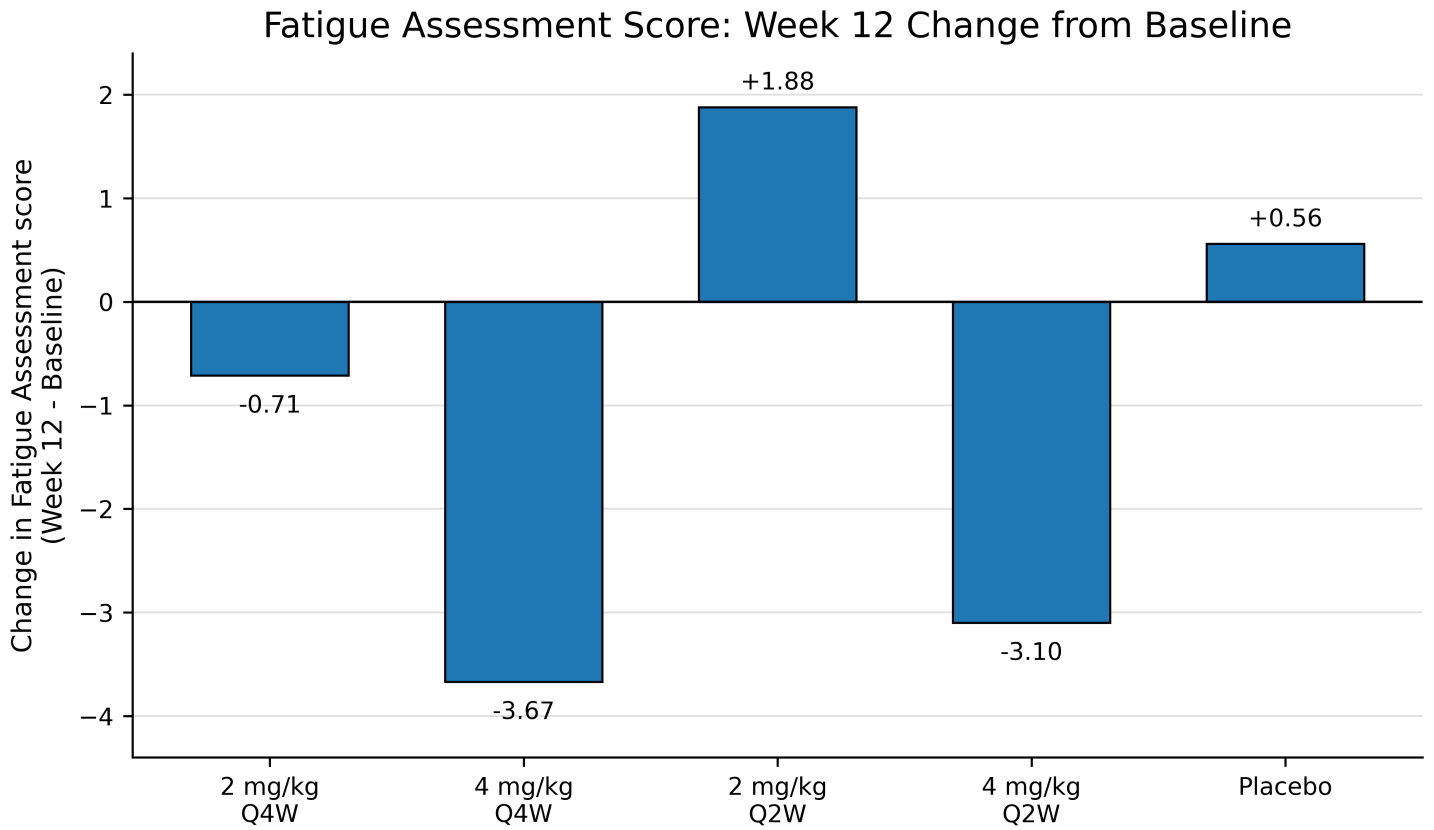
CID 4 = better health

CID = Clinically important difference; Møller J, et al. Eur Respir J. 2024;63(6):00160-2024; NCT05890729

Fatigue Assessment Score (FAS)

	2 mg/kg Q4W	4 mg/kg Q4W	2 mg/kg Q2W	4 mg/kg Q2W	Placebo
Mean Observed Score Baseline	24.8	30	23.5	29.9	26.8

22-50 = Substantial Fatigue



CID 4 or 10% change = better health

Observed means only. Negative values indicate improvement as lower FAS score represents less fatigue

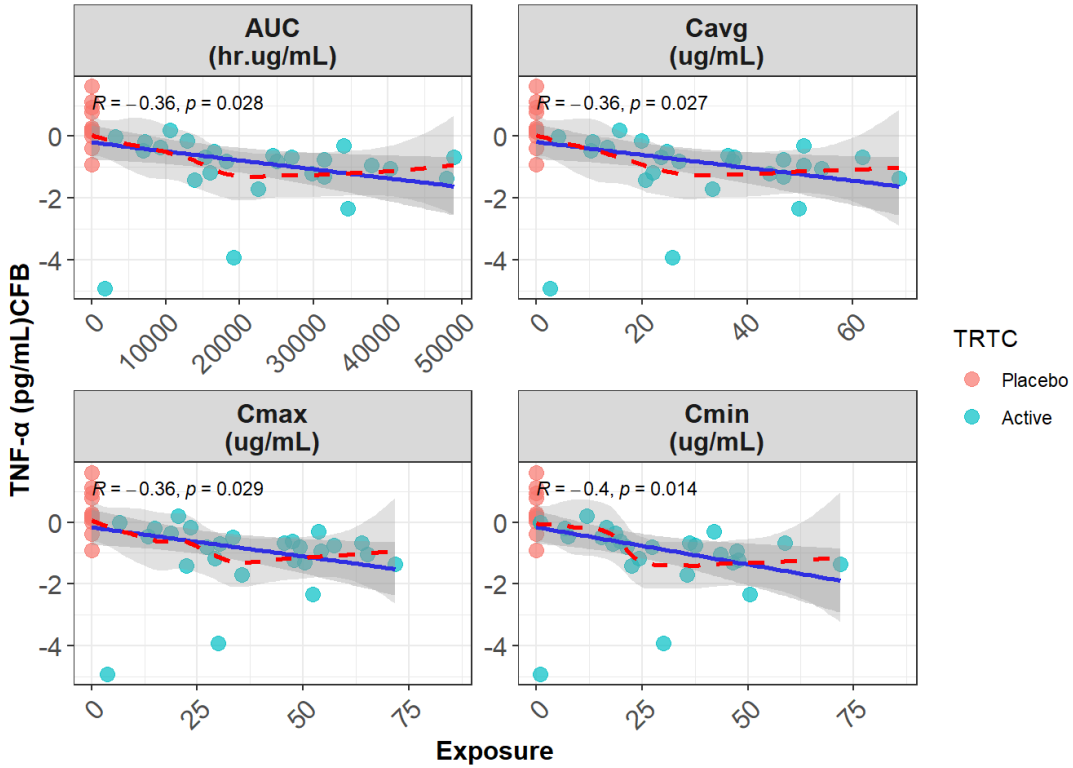
CID = Clinically important difference; de Kleijn WPE, et al. Respir Med. 2011; NCT05890729

sTNFα vs Week 12 PK Exposure

Emerging signal: Directional trend between TNF-α, and exposure levels → requires further investigation

Exposure-response: No strong linear correlations for most biomarkers

	2 mg/kg Q4W	4 mg/kg Q4W	2 mg/kg Q2W	4 mg/kg Q2W	Pooled Active	Placebo
Mean Observed Concentration (pg/mL) Baseline	1.89	1.15	2.23	1.23	1.61	1.59
Mean Observed Concentration (pg/mL) Week 12	1.00	0.44	0.44	0.28	0.56	1.95
Change From Baseline	-0.89	-0.71	-1.79	-0.95	-1.05	0.36
% Change From Baseline	-47%	-62%	-80%	-77%	-65%	+23%



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Qualitative Side-by-Side

	2 mg/kg Q4W	4 mg/kg Q4W	2 mg/kg Q2W	4 mg/kg Q2W
Steroid Sparring	Patients achieved modest steroid tapering (~5 mg/d reduction). Some maintained on >7.5 mg/d, suggesting incomplete effect.	Produced highest reduction in steroid dose; highest proportion of patients to wean completely off steroids	Lowest rate of steroid reduction.	Modest rate of steroid reduction comparable with 2 mg/kg cohorts
Lung Function	Small reduction in FVC	Stable FVC, no decline, minimal improvement	Stable FVC, no decline, minimal improvement	Small improvement in lung function, not clinically meaningful.
Quality of Life	Small improvements in KSQ General and LCQ, not clinically meaningful thresholds	Improvement in KSQ General above the MCID	Improvements in KSQ General below the MCID	Improvements in KSQ General well above MCID
Biomarkers	Modest CRP reduction, ACE and IL-6 unchanged	Highest reduction in IL-1b; variable data in other assays	CRP lowered by 50%, IL-6 trended down	Strong biomarker response in all assays
Safety	Tolerable	Tolerable	Tolerable	Tolerable
Immunogenicity	Significantly higher prevalence of ADA	Lowest incidence of ADA	Higher immunogenicity than 4 mg dosing, lower than 2 mg Q2W dosing	Low Incidence of ADA
Interpretation	Safe, not effective, higher immunogenicity	Safe, effective, KSQ-Lung outliers to be examined	Safe, not effective, higher immunogenicity	Safe, effective, KSQ-Lung outliers to be examined; potentially burdensome treatment schedule.

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Factors Considered for Dose Selection

Dose-ranging design enabled integrated assessment across key domains

- **Selection criteria**: Safety, steroid tapering, physiologic impact, biomarkers, PK, immunogenicity, and QoL
- **DSMC determination**: 4 mg/kg Q4W identified as optimal balance of efficacy, safety, and exposure
- **Investigative plan:** 4 mg/kg Q4W advanced for further evaluation

Summary

- Limitations:
  - Not powered for efficacy
  - Small sample size (n = 39)
  - Absence of validated efficacy endpoints in sarcoidosis hinders interpretation of trial outcomes

- Overview:
  - Evidence of a clinically meaningful signal observed in this first-in-patient trial of XTMAB-16
  - Investigational drug was generally well tolerated
  - Changes in biomarkers and exposure-response trends are consistent with expected TNFa pathway modulation for sarcoidosis
  - Results support dose of 4mg/kg Q4W for further evaluation in clinical trials
  - XAtlas is a planned efficacy study evaluating XTMAB-16 in patients with pulmonary sarcoidosis, with enrollment anticipated to begin in 2026

Q&A

Thank you for your attention.

Extended thanks to all patients and families who participated in this study, as well as the Principal Investigators, study coordinators, site staff.