AX-158 Proof-of-Mechanism Safety Study: Evaluating a Novel T cell Receptor (TCR) Signal Modulator in Patients with Mild-to-Moderate Plaque Psoriasis (NCT05725057)

D. Scott Batty, Jr., MD[1*], Christopher VanDeusen, PhD[1], Sandra Garcet, PhD[2], James G. Krueger, MD PhD[2]

Artax Biopharma, Inc., Cambridge, MA [1], Rockefeller University, New York, NY[2]

**sbatty@artaxbiopharma.com*

INTRODUCTION

The T cell receptor (TCR) is the sentinel mechanism through which the immune system responds to antigens. In healthy individuals, thymic selection has removed clonal populations of T cells that bind too tightly to self and non-harmful antigens. In some individuals however, molecular mimicry and other drivers can cause overexpansion of T cells with a TCR that binds at an avidity that leads to an unwanted activated Th cell. These activated Th cells then drive autoimmune disease pathologies.

Current therapies for autoimmune diseases focus on the inhibition of cytokines produced by Th cells activated by self antigens. These approaches strive to find a balance of amelioration of symptoms against immune suppression as cytokine directed approaches do not discriminate autoimmune signaling from beneficial immune surveillance or pathogen responses. These therapies are also frequently are limited as they are focused in nature (e.g. anti-cytokine antibodies)

Nck is an adaptor protein that is recruited to the activated TCR and acts as a positive modulator of TCR signaling. AX-158 is a small molecule inhibitor of Nck association into the activated TCR complex and acts as a negative modulator of signaling in preclinical models. In phase I studies, AX-158 was well tolerated with excellent pharmacokinetics. In this Phase IIa study, biomarker responses were assessed in psoriasis patients to provide support for the potential of modulating Nck as an approach to the broad treatment of T cell driven dermatologic diseases.

Mechanism: TCR signal modulation, not inhibition

(A) Resting state: Nck is not associated with resting state T cell receptor (TCR)

(B) In the absence of treatment, on antigen binding (for both strong and weak avidity antigens), Nck is recruited to the activated TCR and acts as a positive modulator of Th activation

(C) In the presence of AX-158, the compound binds to Nck, preventing its recruitment to the activated TCR, for weak antigens this absence of positive modulation results in no Th activation. However for strong antigens (e.g. pathogen) Nck is not required to amplify the signal and Th activation will still occur

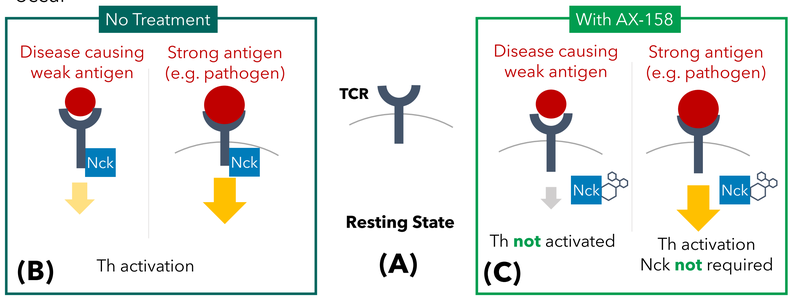


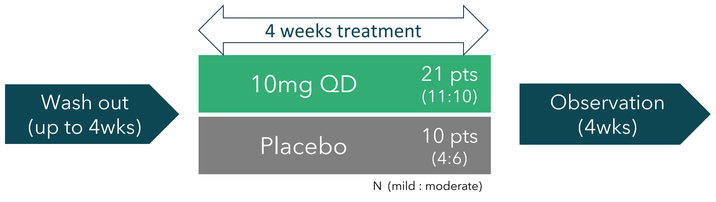
Figure 1. Mechanism of action

HYPOTHESIS

Modulation of Nck activity in mild-to-moderate psoriasis patients through once daily, oral administration of AX-158 will result in a decrease of T cell and disease related mechanistic markers as measured in lesional skin biopsies.

METHODS

4-week trial design in mild-to-moderate psoriasis patients focused on safety and biomarker endpoints



Dose selection:
- 10mg QD

Patient population:
- Mild to moderate plaque psoriasis: PASI ≤10, BSA ≤10%

Primary endpoints:
- Safety

Secondary endpoints:
- Clinical scores: PASI, sPGA, DLQI
- Skin biopsy at D1, D15 and D29
- Established biomarkers: RNA and Histology
  - IL-17, IL-12, IFNγ, CD8+ T Cells,

Figure 2. Phase IIa trial design

Baseline Characteristics

	AX-158 10 mg/day (n=21)	Placebo (n=10)
Age in years, mean (SD)	43.6 (9.42)	50.3 (8.43)
Male, n (%)	8 (38.1%)	8 (80.0%)
Race, n (%)		
White	20 (95.2%)	8 (80.0%)
Asian	0 (0.0%)	2 (20.0%)
Other	1 (4.8%)	0 (0.0%)
Weight in kg, mean (SD)	82.6 (18.10)	89.9 (10.40)
Baseline PASI Score, mean (SD)	5.0 (1.99)	4.6 (1.15)
Baseline % of BSA, mean (SD)	5.4 (2.61)	3.9 (2.74)
Baseline sPGA, mean (SD)	2.3 (0.90)	2.4 (0.84)

Table 1. Baseline characteristics. BSA, body surface area; PASI, Psoriasis Area and Severity Index; SD, standard deviation; sPGA, static Physician's Global Assessment.

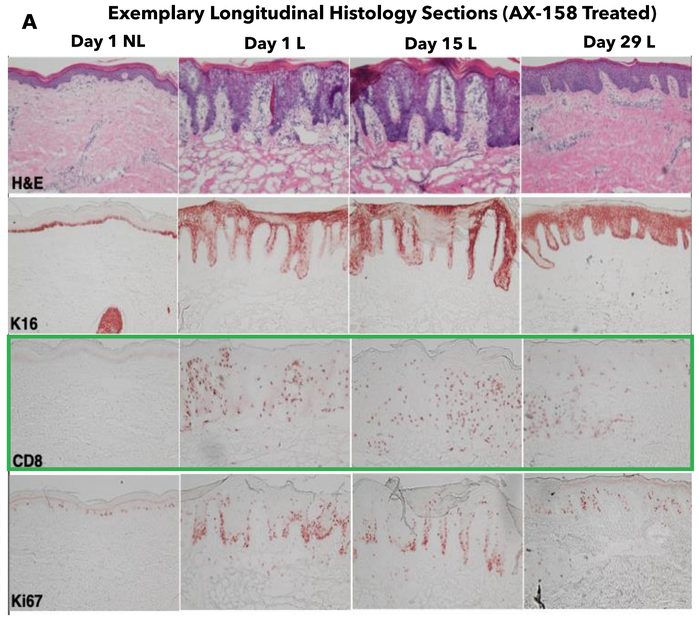
RESULTS

Primary Endpoint: Safety

Number (%) of subjects	AX-158 10 mg/day (n=21)	Placebo (n=10)
With any TEAEs	9 (42.9%)	3 (30.0%)
≥Grade 3	0	0
Treatment-related AE	1 (4.8%)	1 (10.0%)
Neutropenia	1 (4.8%)	0
Oropharyngeal pain	0	1 (10.0%)
Any Serious TEAE	0	0
Leading to study discontinuation	0	0
Treatment-related leading to study discontinuation	0	0

Table 2. Safety summary

Secondary Endpoint: Histology



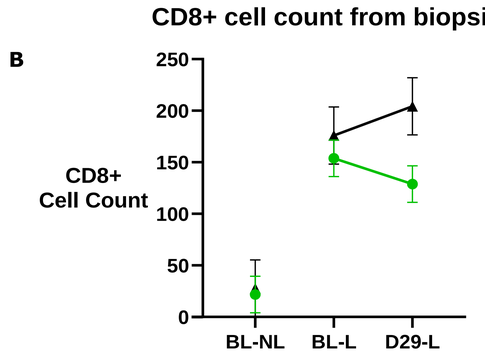


Figure 3. **A)** Exemplary longitudinal histologic sections from a patient treated with AX-158. Noted in patients was a reduction in CD8+ T cell counts, highlighted in green. **B)** LS mean values for sectional CD8+ T cell counts for all patients. BL, baseline; L, Lesional; NL, non-lesional

Secondary Endpoints: Biomarker Analyses

RNAseq Measurements in Longitudinal Lesional Biopsies

A) Ingenuity Pathway Analysis was used to identify impacts on key dysregulated cytokine signaling pathways (IL-17 and IL-12).

IL-17 signaling pathway, p<0.001

Genes contributing to signal include
- IL-17A
- IL-36A
- MMP3
- IL-12B

IL-12 signaling pathway, p<0.02

Genes contributing to signal include
- IL-12B
- E Selectin

	AX-158 10 mg/day (n=21)	Placebo (n=10)
Psoriasis Gene dataset	p-Values (baseline vs Day 29)	
MAD3[1]	**0.04**	0.49
MAD5[1]	**0.04**	0.52
Yao[2]	**0.05**	0.74
Gudjonsson[3]	**0.02**	0.34

Table 3. Gene Set Variance Analysis: impact of AX-158 on established gene panels of psoriatic lesions versus healthy skin

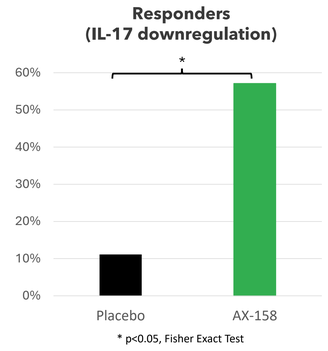


Figure 4. Responder analysis of RT-PCR levels of IL17A in longitudinal skin biopsies.

Figure 4 shows the responder analysis demonstrating significant directional responses of AX-158 treated patients in IL-17A levels vs placebo. A responder is defined as a patient where IL-17A levels are lower at week 2 than at baseline, and lower at week 4 than both baseline and week 2

The same result was seen for IL-17F levels.

Additionally, in the full population, trends of reductions in the following disease-related cytokines were observed, those in bold showed a statistically significant reduction (p<0.05) in the IL-17A responder population in Figure 4

- **IL-17F**
- IFNg
- **β-defensin**
- IL-22
- IL-17A
- **IL-23p19**
- **IL-12p40**

Secondary Endpoints: Clinical

PASI50 and PASI75 scores were evaluated after 4 weeks of AX-158 treatment. A greater proportion of patients achieved PASI50 or PASI75 in the AX-158 treated patients, but did not reach statistical significance..

	AX-158 10 mg/day (n=21)		Placebo (n=10)	
	D29	**End of Study**	**D29**	**End of Study**
All Patients				
PASI50, N (%)	2 (10%)	2 (10%)	0 (0%)	0 (0%)
PASI75, N (%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)
Moderate Patients (PASI ≥ 5, n=10)				
PASI50, N (%)	1 (10%)	2 (20%)	0 (0%)	0 (0%)
PASI75, N (%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)

Table 4. PASI analysis

CONCLUSIONS

- AX-158 10 mg QD administration was found to be safe and well-tolerated compared with placebo, matching previous Phase 1 experience
- Biomarker analyses revealed significant and consistent and favourable responses to validate Nck immunomodulation as an approach in T cell driven dermatologic disease
  - Statistically significant impacts on IL-17 and IL-12 pathways
  - Statistically significant impact on established disease marker gene panels
- Short term efficacy evaluations support additional investigational studies with AX-158
  - Longer duration studies will help identify full depth of response in autoimmune diseases

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3. Gudjonsson JE, et al. J Invest Dermatol. 2009;129(12):2795–804

Disclosures

D. Scott Batty Jr and Christopher VanDeusen are employees of Artax Biopharma Inc. This study was commissioned and sponsored by Artax Biopharma Inc.