

**Abstract N°: 7417****Evaluation of AX-158, a first-in-class Nck modulator, in patients with mild-to-moderate plaque psoriasis**

D. Scott Batty Jr MD^{*1}, Christopher Vandeusen¹, Sandra Garcet², James Krueger²

¹Artax Biopharma, Inc., Cambridge, MA, United States

²Rockefeller University, Center of Clinical and Translational Science, New York, NY, United States

Introduction & Objectives:

The T cell receptor (TCR) is central to a well-functioning immune system which responds appropriately to the wide variation in the avidity of antigens. Nck binds directly to the TCR and amplifies T cell responses to low-affinity antigens, contributing to autoimmune diseases. AX-158 is a first-in-class oral candidate that inhibits the interaction between Nck and the TCR by binding specifically to the SH3.1 domain to selectively disrupt Nck-TCR interaction, thereby helping to prevent self-reactive T cell responses that drive autoimmune pathobiology. The goal of this study was to validate biological responses to AX-158 in subjects with autoimmune disease.

Materials & Methods:

Patients were randomized to receive 10mg QD AX-158 (N=21) or placebo (N=10) for 28 days.** The primary endpoint was the safety and tolerability of AX-158 vs. placebo, and secondary endpoints evaluated both standard psoriasis efficacy endpoints. Additionally, biomarkers relevant to psoriasis and immune activity were evaluated (NCT05725057).

Results:

AX-158 met the primary endpoint of safety and tolerability. Across all participants, few treatment emergent adverse events (TEAEs) were reported, and only one was found to be related to AX-158, namely a single incidence (4.8%) of Grade 2 neutropenia. No serious AEs were reported, and there were no serious or opportunistic infections.** At the end of the treatment period only patients treated with AX-158 achieved a PASI50 response or higher; however, the study was not powered for statistical significance on this endpoint.

Using RT-PCR to quantify expression of IL-17A and IL-17F, a group of 12/21 (57%) progressive responders (wk 4 < wk2 < baseline values) were identified on AX-158 treatment; this was statistically significant vs. placebo treatment. Using gene set variance analysis (GSVA), multiple psoriasis-related gene sets were significantly modulated in patients who received AX-158. Ingenuity® Pathway Analysis of RNAseq data identified that IL-17 pathways in psoriasis and neutrophil trap pathways were significantly modulated in patients who received AX-158.

Conclusion:

In line with the previous Phase 1 experience¹, AX-158 administration was found to be safe and well-tolerated with no serious AEs, and no serious or opportunistic infections. The results on the psoriasis biomarker endpoints, confirm that Nck modulation has a biological effect in this disease population, as well as showing early favorable trends in clinical efficacy measures. Therefore, these data support further investigation of the role of AX-158 as a therapeutic with potential universal applicability to autoimmune diseases.

1. VanDeusen C, Gagete A, Koch A, Batty Jr D. First-in-Human Evaluation of the Safety, Tolerability and Pharmacokinetics of the T Cell Receptor Signal Modulator AX-158 [abstract]. *Arthritis Rheumatol.* 2024; 76

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