EADV CONGRESS
AMSTERDAM 25-28 SEPTEMBER 2024
EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

Abstract N°: 4950

ATTO-1310: A first-in-class anti-IL31 Attobody® for atopic dermatitis and other pruritic diseases

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Introduction & Objectives:

Chronic inflammatory skin diseases such as atopic dermatitis (AD) and prurigo nodularis (PN) lead to intensely pruritic skin lesions resulting in severe scratching. In patients with moderate-to-severe AD and PN, topical steroids and calcineurin inhibitors are not sufficient to achieve symptom control. Nemolizumab, which binds IL31RA, has shown promising anti-pruritic efficacy in clinical trials, providing validation that targeting the IL31 pathway translates to symptom relief in AD and PN patients. We have discovered a high affinity and potent biparatopic Attobody® to the IL31 ligand, which has the potential to induce fast and prolonged control of pruritis in patients with chronic inflammatory skin disease.

Materials & Methods:

ATTO-1310 consists of biparatopic Attobodies® to IL31 fused to human IgG1-Fc engineered for extended half-life. Each Attobody® is comprised of two VHHs, which on their own bind to distinct epitopes on IL31 with medium to low affinity. Our unique linker technology enables the identification of highly potent biparatopic Attobodies® even in the absence of inhibition by its individual component VHHs. The simultaneous engagement of two distinct epitopes on IL31 by each Attobody® drives the exceptional binding affinity to IL31. ATTO-1310 was assessed for its affinity for IL31 and its ability to suppress receptor dimerization and downstream signaling. Further, we examined the anti-pruritic activity in mice and NHP, as well as the pharmacokinetic (PK) profile in NHP. Finally, the manufacturability and immunogenicity of ATTO-1310 was evaluated.

Results:

Functionally, the high affinity of ATTO-1310 leads to potent suppression of IL31-mediated receptor dimerization and downstream signaling *in vitro*. When administered *in vivo*, ATTO-1310 demonstrates the ability to block IL31-induced pruritus in mice and in NHP, with a clear relationship between dose level, serum drug concentration, and extent of anti-pruritic activity. Importantly, pharmacokinetic (PK) assessment of ATTO-1310 in NHP demonstrates low clearance with a long half-life, clear dose linearity, and >80% bioavailability when administered subcutaneously (SC). PK modeling supports the ability to achieve and maintain therapeutic exposures of ATTO-1310 in humans with SC administration every three months. ATTO-1310 displays excellent manufacturability and developability properties and is produced from CHO cells with high productivity and yield. In *ex vivo* assays, ATTO-1310 has not raised any significant risk of immunogenicity.

Conclusion:

Nonclinical efficacy and PK data to date support advancement of ATTO-1310 to first-in-human clinical studies.