Altasciences, 562 State Road DD, Auxvasse, MO 65231, United States
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Assessments for the *In Vivo* Tolerability and Efficacy of a JAK1-siRNA Being Developed for the Highly Targeted, Infrequent, and Efficacious Treatment of Inflammatory Skin Diseases Using Various Application Techniques

Shanté Nicole Jackson[1], Thomas J. R. Ormsby[2], Mohamad Omar Rachid[2], Carine Blanchard[3], Sylvia Martha Fürst[4], and Julia Frances Alterman[2]
[1]Altascienes Preclinical Columbia, Auxvasse, MO, USA; [2]RNA Therapeutics Institute, University of Massachusetts Chan Medical School, Worcester, MA, USA; [3]Aldena Therapeutics, London, UK; [4]Certara USA Inc., Radnor, PA, USA

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INTRODUCTION

An estimated 20-25% of the global population is affected by inflammatory skin diseases, such as alopecia areata (AA, characterized by patchy hair loss) and atopic dermatitis (AD, also known as eczema).

Many current therapeutics in development for the treatment of these conditions fall into the class of small-molecule, Janus kinase (JAK) inhibitors with a short half-life, which often necessitates daily treatments.

JAK1 is a protein involved in the JAK-STAT signaling pathway, which regulates gene expression, cell growth, and immune responses. Downregulation or silencing of JAK1 can reduce pro-inflammatory signaling cascades and immune overactivation, thereby offering therapeutic benefit for inflammatory skin diseases. Local inhibition of JAK1 in the skin provides the potential to achieve efficacy at the disease site while minimizing systemic drug exposure and associated toxicities **(Fridman *et al.*).**

A small interfering ribonucleic acid (siRNA) that specifically targets JAK1, named ALD-102, is being developed as a highly targeted and efficacious clinical candidate for the infrequent treatment of inflammatory skin diseases such as AA and AD due to the compound's established long-lasting properties. As part of that development, preclinical studies were designed to evaluate the toxicity/tolerability and efficacy of ALD-102 when administered via intradermal (ID) injections or transepidermal (TE) administration in the presence of STAR Particles®.

METHODS

Studies utilizing Göttingen Minipigs® were designed to test the toxicity/tolerability and efficacy for administration of the clinical compound, ALD-102, using the minipig surrogate compound, ALD-105, in parallel via ID injection and TE administration in the presence of STAR Particles® as a skin-delivery enhancement technology.

STAR Particles® **(Figure 1)** are sub-millimetric ceramic particles known to create temporary micropores in the stratum corneum, enhancing permeability and facilitating localized uptake of therapeutic molecules such as siRNA **(Tadros *et al.*, Abideen *et al.*).**

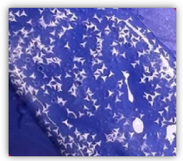

Figure 1: STAR Particles®

To appropriately assess the endpoints of interest, animals were administered the following:

- Efficacy—ID: 200 µM ALD-102 or ALD-105 as a single ID dose.
- Efficacy—TE application: ALD-102 was applied topically at 5 mM in a gel containing 10% w/w STAR Particles®.
- Toxicity/Tolerability—ID: Supra-therapeutic dose (43.04 mg/dose) ALD-102 or ALD-105 as a repeat ID dose (2 doses, once weekly).

RESULTS

- Administration of ALD-102 and ALD-105 was well tolerated across all evaluated dose levels and routes. No ALD-related abnormal clinical signs were noted, and no adverse findings were observed.
- Limited distal exposure/biodistribution of ALD-102 was observed even at supra-therapeutic dose levels following repeat ID injections (minimal systemic exposure), supporting large safety margins for the clinical dose **(Figure 2)**.
- Striking duration of local retention of ALD-102 and ALD-105 was observed in the skin following a single ID injection **(Figure 3)**.
- Quantification of JAK1 mRNA in skin biopsies 28 days post a single ID injection showed downregulation of JAK1 mRNA and the downstream signaling pathway **(Figure 4)**.
- JAK1 mRNA inhibition was sustained at week 4, 3 weeks following the TE loading regimen of ALD-105 on Days 1, 4, and 7 when using STAR Particles® **(Figure 5)**.

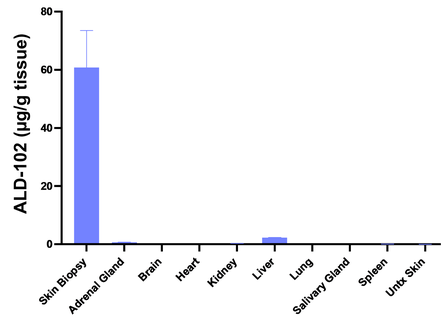

Figure 2: Limited Biodistribution Following Repeat Intradermal Injections

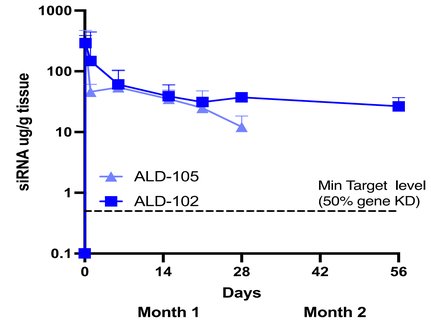

Figure 3: Skin Retention Following a Single ID Injection in Göttingen Minipigs®

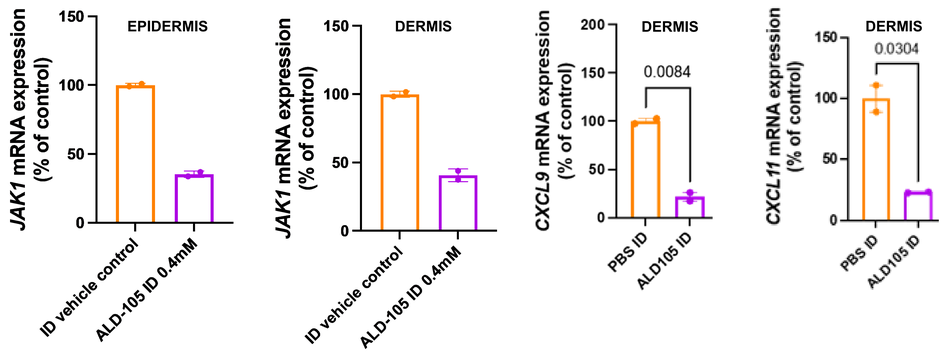

Figure 4: Long-Lasting Efficacy Following a Single ID Injection in Göttingen Minipigs®

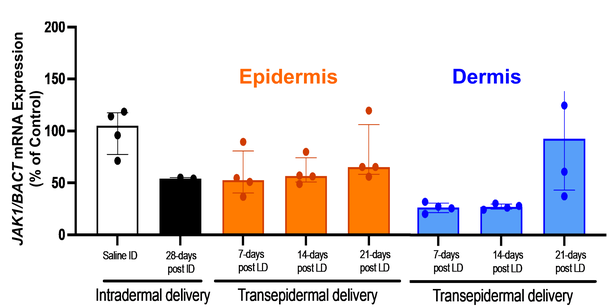

Figure 5: Long-Lasting Functional Efficacy Using STAR Particles®

CONCLUSIONS

ALD-102 shows promise as a targeted, long-lasting treatment for inflammatory skin diseases, based on intradermal delivery and efficacy results in minipig skin 28 days post-injection.

When combined with STAR Particles®, the combination overcomes skin barrier challenges and displays long-lasting efficacy, sustained for 3 weeks post a loading regimen.

ALD-102 is currently in a Phase 1b/2a trial via ID injection for AA patients.

Acknowledgments
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