Atopic Dermatitis Phase 1b Positive Trial Results for EDP1815, An Oral Single-Strain Commensal Microbe

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Introduction

The small intestinal axis (SINTAX™) is a network of anatomic and functional connections with the rest of the body. It acts as a sensory system, integrating environmental signals that link gut mucosal immunology with immunological processes throughout the body.

Evelo Biosciences is developing a new class of oral medicines which engage this immune system in the small intestine, leading to systemic anti-inflammatory effects, including within the skin.

This suggests that SINTAX acts as a control mechanism for systemic immunity and inflammation. SINTAX therapeutics target this mechanism and have novel features of considerable interest for the development of immunomodulatory therapies. They can be delivered orally and are systemically effective without systemic distribution.

EDP1815

EDP1815 is an orally-delivered and gut-restricted anti-inflammatory commensal microbe. It is a pharmaceutical preparation of a single strain of *Prevotella histicola* which is effectively non-viable following the manufacturing process. It is the first known Investigational Medicinal Product (IMP) targeting SINTAX.

EDP1815 has demonstrated potent anti-inflammatory effects in pre-clinical models of Th1-, Th2- (**Fig 1**) and Th17-mediated inflammation. It is able to resolve systemic inflammation without any systemic exposure and without colonizing or modifying the microbiome. In addition to the results shown here, EDP1815 has previously shown clinical efficacy in a phase 1b study of mild and moderate psoriasis.

It achieves these effects via interactions between EDP1815 and antigen presenting cells at the gut epithelial lining, which stimulate trafficking of enteric mucosal immune cells to gut-draining mesenteric lymph nodes, where they interact with circulating T cells.

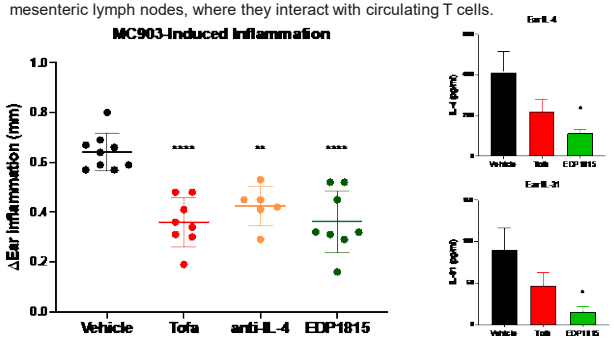

Fig 1. EDP1815 reduces inflammation and cytokine production in the skin in the MC903 model of allergic dermatitis. Mice were gavaged daily from Day 1 to Day 14 with 10 mg of EDP1815, vehicle, tofacitinib (20 mg/kg) or an anti-IL-4 antibody (200 ug/mouse IP every 3 days). Change in ear thickness was expressed as ear thickness at day 14 minus ear thickness at baseline. Panels on the right display absolute levels of cytokines at the site of inflammation (ear).

Phase 1b Clinical Trial - Method

EDP1815 was evaluated in a phase 1b clinical study which included a cohort of 24 participants with mild and moderate atopic dermatitis, randomized 2:1 active:placebo (EudraCT # 2018-002807-32).

The dose of EDP1815 was $8.0x10^{11}$ cells once a day for 56 days, with follow-up off drug at Day 70. Participants could only use emollients if they were part of their care prior to the study and could not use any active topical therapies including topical corticosteroids.

The primary outcome of this phase 1b study was safety and tolerability. Secondary outcomes were the clinical outcomes of EASI, SCORAD, IGA, and IGA*BSA; and the patient-reported outcomes of DLQI, POEM, and Pruritus-NRS.

Results

Baseline mean EASI and IGA scores were 8.31 and 2.63, respectively, for the 16 patients receiving EDP1815, and 9.31 and 2.75, respectively, for the 8 patients receiving Placebo. Only 25% of patients in each treatment group reported using regular emollient during the study.

EDP1815 was very well tolerated in this study with no treatment-related adverse events of moderate or severe intensity, and no serious adverse events.

Although not formally powered for efficacy, statistical testing was performed on the estimated treatment difference between EDP1815 and Placebo at day 56, via MMRM analysis. The difference in percentage decrease from baseline in EASI, IGA*BSA and SCORAD were 52% (p=0.062), 65% (p=0.022), and 55% (p=0.043) respectively **(Fig 2).** Ten out of 16 patients receiving EDP1815 saw improvements in their EASI score at day 56, compared to 1 out of 8 patients receiving placebo (**Fig 3).**

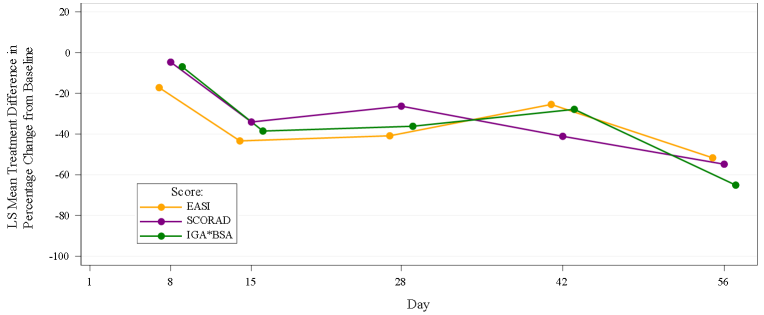

Fig 2. Treatment Difference between EDP1815 and Placebo for EASI, IGA*BSA, and SCORAD throughout the study treatment period.

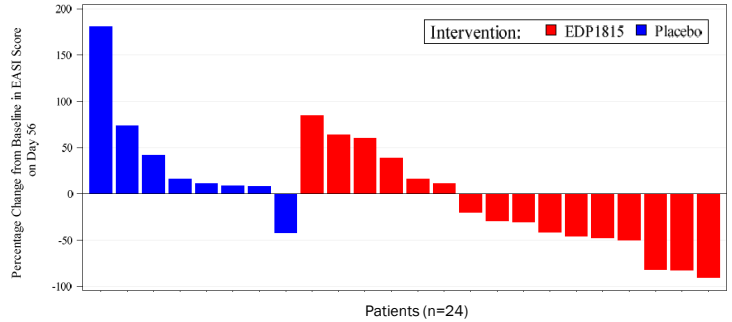

Fig 3. Individual percentage change from baseline in EASI score at day 56

At the day 70 follow-up visit, the percentage of patients receiving EDP1815 achieving EASI50 was 44% compared with 0% in the placebo group; and the proportion achieving an IGA score of 0 or 1 was 31% with 19% also having a 2 point improvement, again compared with 0% in the placebo group **(Table 1).**

Clinical Score (Day 70)	Active Group (n=16)	Placebo Group (n=8)
IGA 0 or 1	31%	0%
IGA 0 or 1 with 2 point improvement	19%	0%
EASI50	44%	0%

Table 1. Proportion of active and placebo patients achieving clinical milestones within IGA and EASI score, from baseline to end of study visit.

Finally, with regard to patient-reported outcomes, the mean individual improvement from baseline in the DLQI (3.6) and POEM (4.1) in EDP1815-treated patients at day 56 exceeded the minimally clinically important difference thresholds; and exceeded placebo changes (-0.3 and +1.6, respectively). Improvements in itch and sleep were seen within all scales (Pruritus-NRS, DLQI, SCORAD and POEM) at the end of the treatment period.

Conclusions

EDP1815 is Evelo's first anti-inflammatory SINTAX therapeutic to enter phase 2 development. It is a pharmaceutical preparation of an oral, gut-restricted non-viable microbe targeting a novel mechanism of inflammation control. The SINTAX mechanism operates within the lumen of the gut driving systemic inflammation resolution without systemic exposure to the drug or overt immunosuppression.

The phase 1b clinical data presented here provide proof of concept for further clinical development of EDP1815 in the treatment of atopic dermatitis. Together with previous data demonstrating efficacy in psoriasis, this adds to the potential of EDP1815 as a safe, well-tolerated and effective treatment for a broad spectrum of inflammatory conditions.