EVELO

Harnessing the Small Intestinal Axis to Create Big Change

Evelo Corporate Presentation

June 2021

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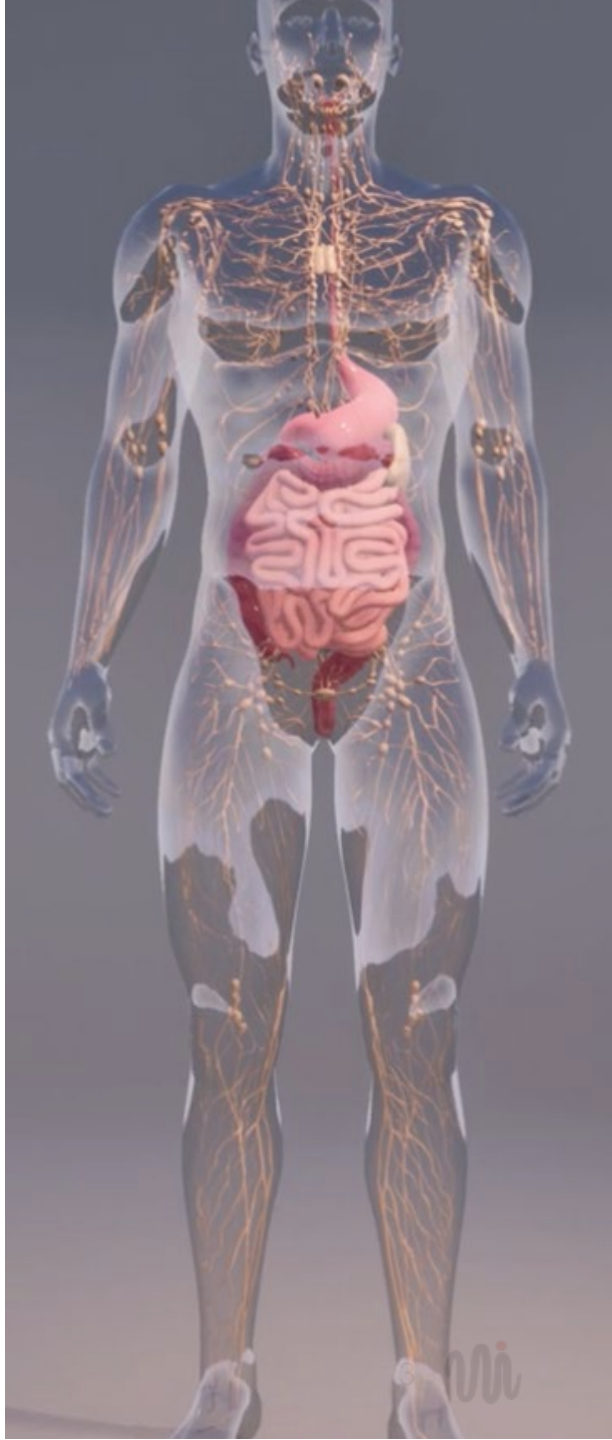
Harnessing the Small Intestinal Axis to Transform Medicine

- The small intestinal axis, SINTAX™ - a newly uncovered area of central biology
- SINTAX is the sensing system in the gut that governs inflammation and immunity throughout the body
- Evelo is harnessing SINTAX to develop a new type of medicine that has the potential to be:
  - Safe, effective, convenient, and affordable for billions of people, and
  - Used at all stages of disease



Five Positive Sets of Clinical Data with Lead Product, EDP1815

- Positive preclinical and Phase 1b clinical results across Th1, Th2, and Th17 inflammation pathways
- Generally well tolerated
- Potential utility across all stages of disease: mild and moderate to severe
- Profile has potential to be used across broad spectrum of inflammatory diseases

Pipeline is Rich in Anticipated Near-Term Clinical Catalysts

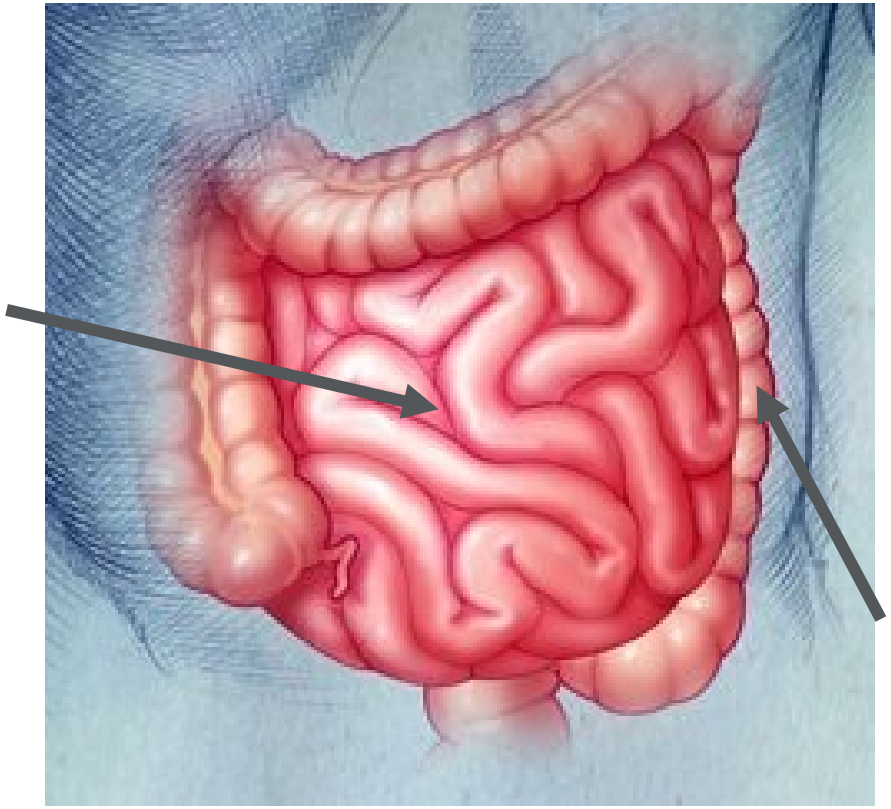
Candidate	Catalyst
EDP1815 Psoriasis	3Q 2021: Phase 2b data 3Q 2021: Data from multiple Phase 1b cohorts aimed at defining formulation and concentration of drug
EDP1815 Atopic dermatitis	3Q 2021: Phase 2 initiation 1Q 2022: Phase 2 interim data
EDP1815–TACTIC-E COVID-19	Phase 2/3 data
EDP1815–Rutgers University COVID-19	Phase 2 data
EDP1867 Atopic dermatitis	4Q 2021: Phase 1b data
EDP2939 Inflammation	2022: Initiation of clinical development
EDP1908 Oncology	2022: Initiation of clinical development

Cells in the Small Intestine are Therapeutic Targets for SINTAX Medicines

Evelo's focus

Small Intestine

- 80-90% of the gut surface area
- Epithelium includes specialized cells
  - *Immune, endocrine, neural*
- Sensing of signals and govern physiology throughout the body
- Very low level of resident gut microbes



The field's focus

Large Intestine

- 10-20% of the gut surface area
- Limited range of specialized cells
- Contains ~99.99% of the gut microbiome

Three-Step Process for Immunomodulation by SINTAX Medicines

1

Interaction between the SINTAX medicine and cells in the small intestine

Effects are believed to be driven by recognition of structural motifs by host intestinal immune cells in the small intestine

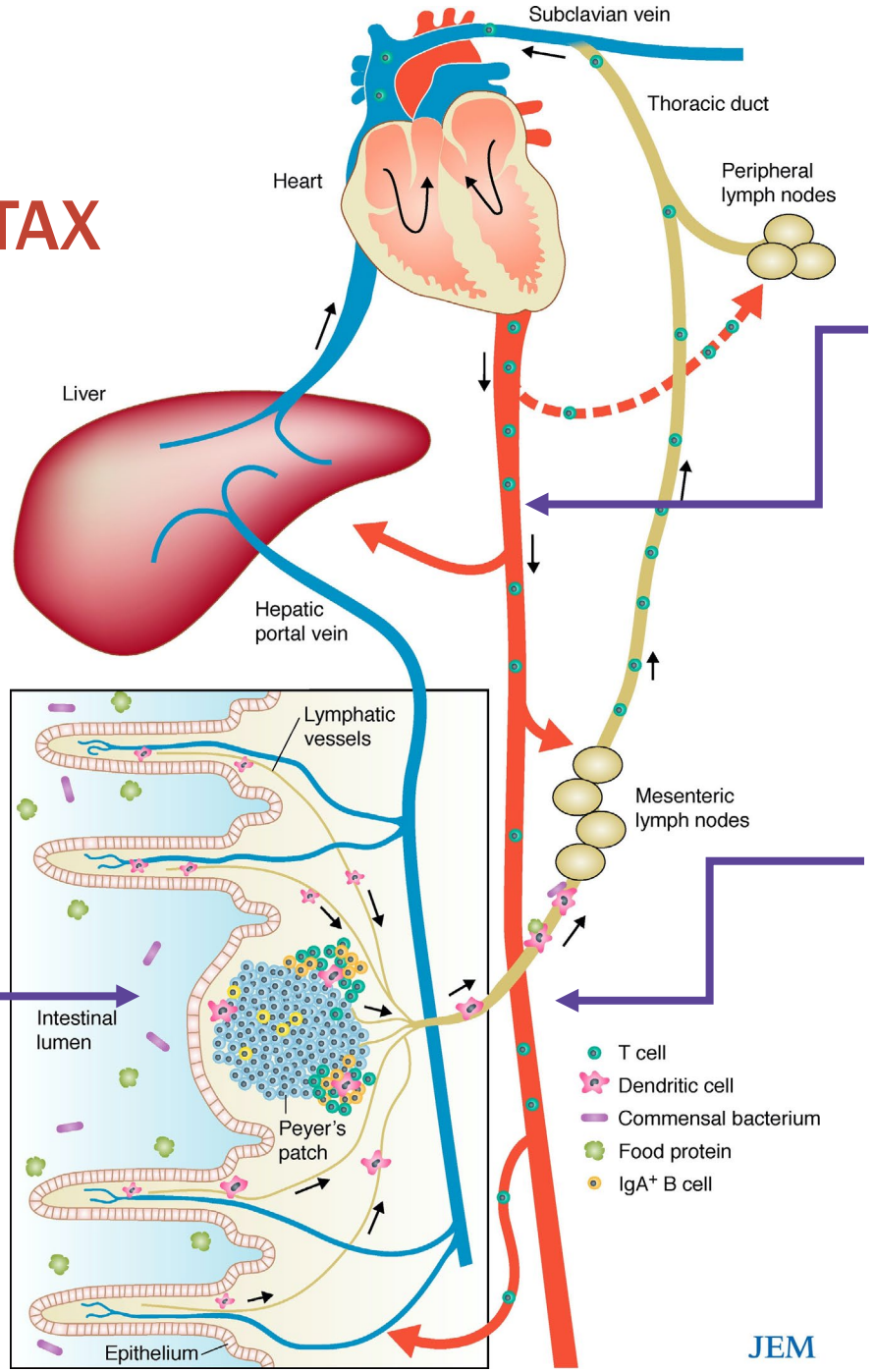
2

Activated T cells trafficking through the mesenteric lymph node encounter gut-migrating dendritic cells, which instruct effector T cells

3

T cells leave the mesenteric lymph node, enter systemic circulation to migrate to peripheral tissue and exert their effects

Depending on the structural motifs of the SINTAX medicine, effects can be inflammation resolving or anti-tumor



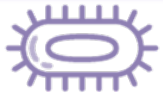
J Exp Med (2006) 203 (3): 497–500.
https://doi.org/10.1084/jem.20060227

JEM

SINTAX Product Candidates: Microbes and Microbial Extracellular Vesicles (EVs)

- Product candidates are pharmaceutical preparations of single strains of microbes and EVs
- Effects are thought to be driven by recognition of structural motifs by immune cells in the small intestine

Whole, inactivated microbes



- Non-replicating, non-colonizing, and gut restricted
- Biomarkers show inflammation resolution without immunosuppression

Microbial Extracellular Vesicles (EVs)

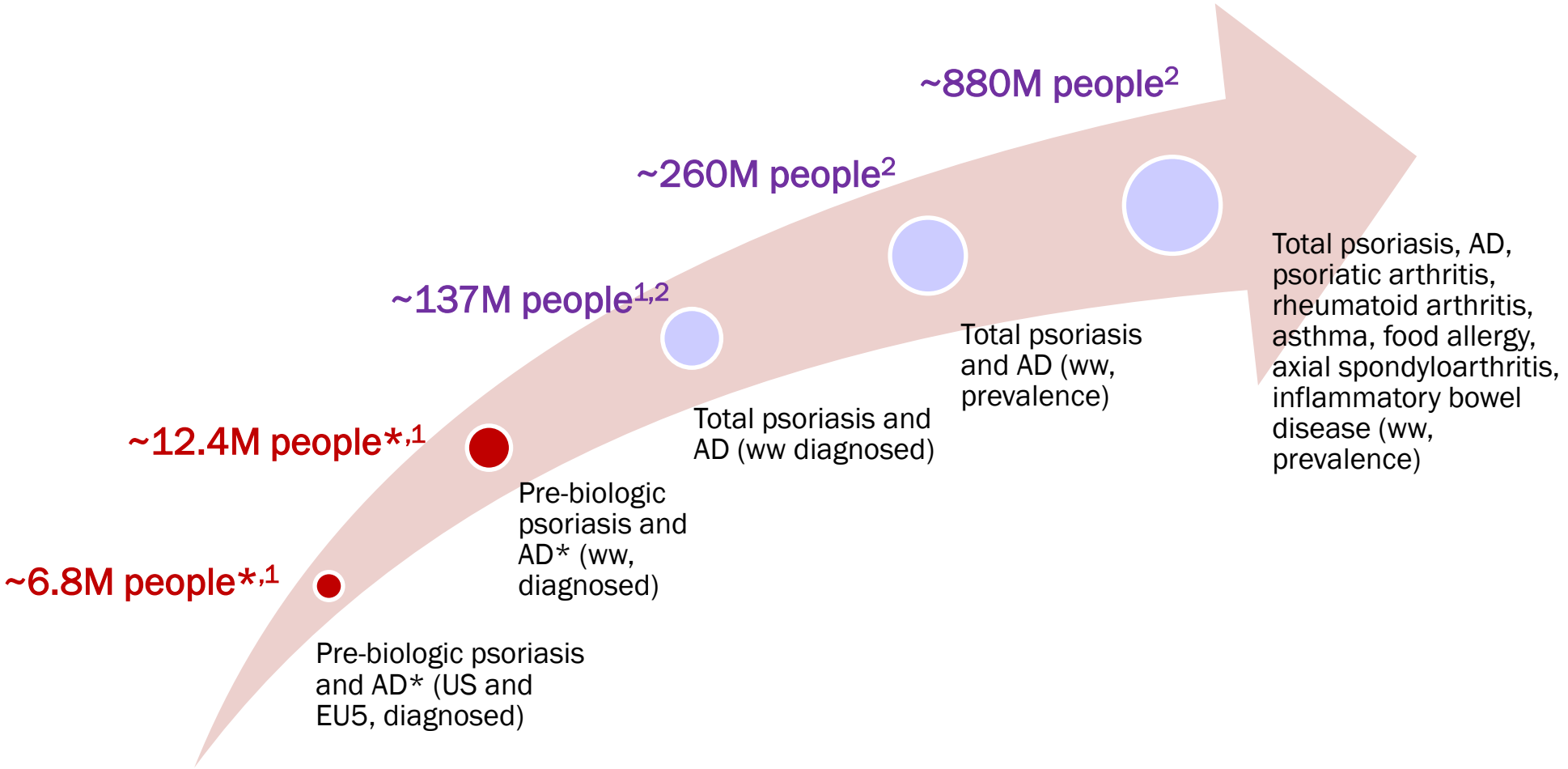
- Lipoprotein nanoparticles naturally produced by some bacteria- macromolecular content is a subset of the parent; non-viable
- 1/1,000th volume of whole microbes, potentially enabling increased target engagement and potency
- Potent efficacy in oncology and inflammation pre-clinical models
- Initiation of clinical development in 2022

The Opportunity

SINTAX Medicines: Potential to Treat Inflammation, Oncology, and Beyond

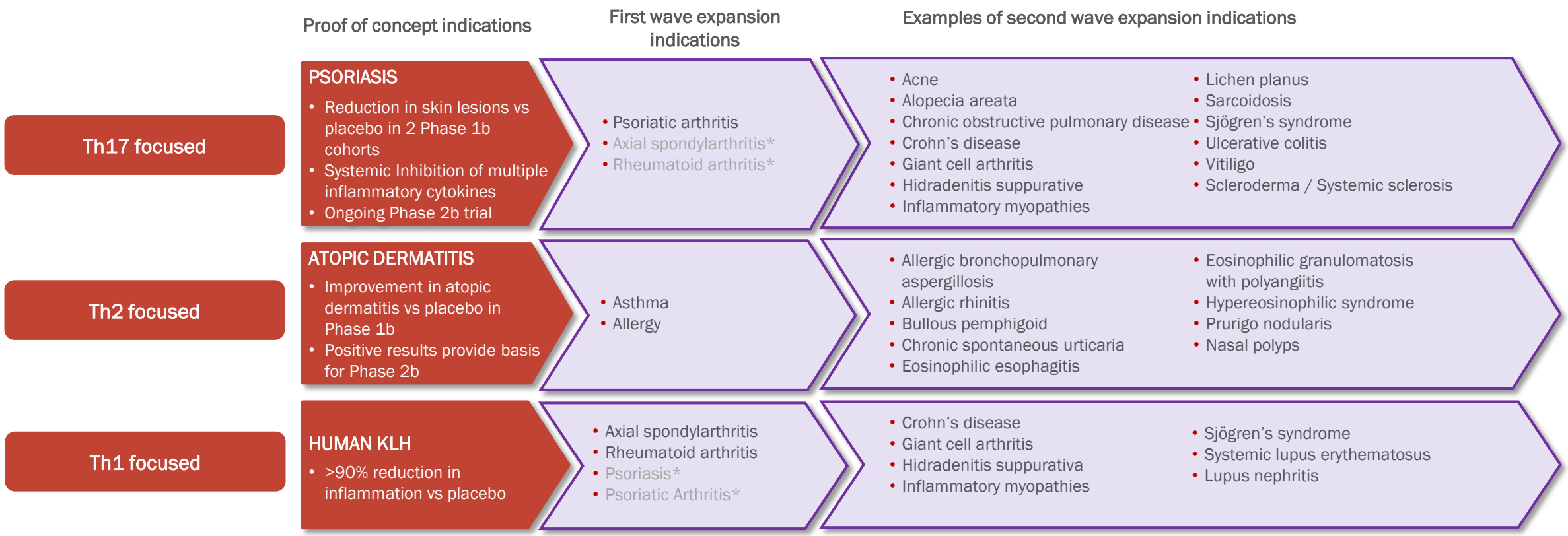
Inflammation	Atopic Dermatitis, Psoriasis, Rheumatoid Arthritis, Inflammatory Bowel Disease
Oncology	Immunologically active tumors (melanoma, lung, renal, bladder) and solid tumors
Metabolism and CV	Type 2 Diabetes, NASH, Obesity, Atherosclerosis
Neuro-Inflammation/ Degeneration	Multiple Sclerosis, Alzheimer's Disease, Parkinson's Disease
Autoimmune	Type 1 Diabetes, ITP, Myasthenia Gravis
Neuro-psychiatric	Autism, Anxiety, Depression
Vaccines	Oral vaccines for autoimmune disease, infectious disease and cancer; conditioning responses to current vaccines

Global Opportunity for SINTAX Medicines: Targeting ~1 Billion People in Inflammation Alone



** Moderate patients not currently taking biologics [1] Celgene VOI in I&I presentation, 2018; Evaluate Pharma, accessed Jul 2018; AstraZeneca Epi Data, Nov 2014; Armstrong A, et al., Dermatol Ther (Heidelb). 2017 Mar; 7(1); Celgene Investor Presentation, Mar 2013; Silverberg JL, et al., Dermatol Clin. 2017. [2] Datamonitor Healthcare, accessed Feb 2020*

SINTAX Medicines Have Potential Use Across Spectrum of Inflammatory Diseases – Evelo Plans to Capture Breadth of Platform in Stages



Simplified and non-exhaustive view of inflammation. Many inflammatory diseases are complex and involve multiple pathways of the immune system.

Pipeline Provides Multiple Diversified Non-Correlated Opportunities

EDP1815: Th17 Effects

*Multiple readouts expected in **3Q 2021**; potential to expand into other Th17-mediated diseases*

Psoriasis

- Phase 2 and series of Phase 1b readouts in **3Q 2021**

Other Potential Indications

- Psoriatic arthritis, axial spondyloarthritis, rheumatoid arthritis, and ulcerative colitis
- Numerous others

EDP1815: Th1/Th2 Effects

*Initiation of Phase 2 in **3Q 2021**; potential to expand in other Th2-mediated diseases*

Atopic Dermatitis

- Initiation of Phase 2 in **3Q 2021**

Other Potential Indications

- Asthma and allergy
- Neuroinflammation
- Numerous others

EDP1815: Integrated Effects

Two COVID-19 trials underway; potential to expand into other viral diseases

COVID-19

- Phase 2/3 TACTIC-E trial ongoing
- Phase 2 Rutgers University trial ongoing

Other Potential Indications

- Influenza
- Future strains of COVID-19
- Future viral infections

EDP1867: Th2 Effects

Strong preclinical activity in Th2-mediated diseases; initial program in atopic dermatitis

Atopic Dermatitis

- Phase 1b data readout in **4Q 2021**

Other Potential Indications

- Asthma and allergy
- Neuroinflammation
- Numerous others

Pipeline Provides Multiple Diversified Non-Correlated Opportunities

EDP2939: EV

Preclinical data suggests broad use across inflammation

Inflammation

- Initiation of clinical development in 2022

Broad use across all inflammatory diseases

EDP1908: EV

Preclinical data suggests broad use across oncology

Oncology

- Initiation of clinical development in 2022

Potential Indications

- Multiple indications in poorly treated solid tumors
- MSS colorectal carcinoma
- Triple-negative breast cancer
- Non-small cell lung cancer
- Numerous others

Next Wave of SINTAX Medicines: EVs

- Pharmacologically active strains of gut mucosa-derived microbes naturally shed EVs
- Small size and diffusion properties enable target engagement in the gut at high potency
- Future EV products should enable greater SINTAX activation for greater efficacy
- Recent data presented demonstrate EVs are generally well tolerated
- EDP2939 in inflammation and EDP1908 in oncology will enter clinical development in **2022**

EDP2939: EV for Inflammation

Orally Delivered Microbial Extracellular Vesicles Modulate Systemic Inflammation Through the Small Intestinal Axis (SINTAX™)

Shannon Argueta*, Adam N. R. Cartwright*, Kritika Ramani, Taylor Cormack, Fabian Romano-Chernac, Kristie Hilliard-Barth, Aula Alami, Divya Raghunathan, Mihika Jalan, Will Caffry, Jake Keats, Krutika Invally, Bin Wang, Valeria Kravitz, Tyler Rommel, Tanmoy Ganguly, Holly Ponichtera, Mark Bodmer, and Andrea Itano

Evelo Biosciences, Cambridge MA

Introduction

Evelo Biosciences is developing a new class of oral medicines which engage the immune system in the small intestine with anti-inflammatory effects throughout the body.

EDP2939 is an orally-delivered and gut-restricted bacterial EV which potently attenuates inflammation in murine models of Th1 and Th17 inflammation.

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.

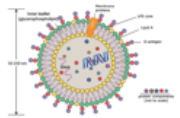
This suggests that SINTAX is a control mechanism for systemic immunity centred in the small intestine. This mechanism has novel features of considerable interest for the development of immunomodulatory therapies. It may be harnessed for orally delivered medicines that are systemically effective without systemic distribution.

We have previously shown clinical proof of the SINTAX mechanism with EDP1815, an orally delivered single strain of commensal bacteria. It has systemic anti-inflammatory effects with a safety profile comparable to placebo. EDP1815 comprises almost entirely non-living bacteria. It exerts its effects through direct action on host cells in the gut with no colonization, alteration of the microbiome, or exposure outside the gut.

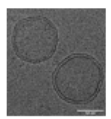
Some bacteria produce extracellular vesicles (EVs) that share molecular content with the parent bacterium in a particle that is roughly 1/1000th the volume in a non-replicating form.

We report here the preclinical pharmacological effects, mechanism of action, and biodistribution of EDP2939, an orally administered preparation of EVs derived from a single gram-negative bacterial strain of the family *Prevotellaceae* that was selected from screens of EVs for anti-inflammatory pharmacology.

Extracellular Vesicles (EVs)



Anand *et al* 2017



Cryo-EM image of EDP2939

- Extracellular vesicles (EV) are lipoprotein nanoparticles naturally produced by some species of bacteria
- Their macromolecular content is a subset of the parent
- EVs enable bacterial communication and survival during stress, host-immune modulation, material exchange, and cell-cell interactions
- Compared to whole microbes EVs are:
  - ~1/1000th volume of microbes enabling improved target engagement
  - Non-viable
  - Incapable of establishing infection or sepsis

EDP2939 is an effective anti-inflammatory drug requiring multiple pathways for efficacy

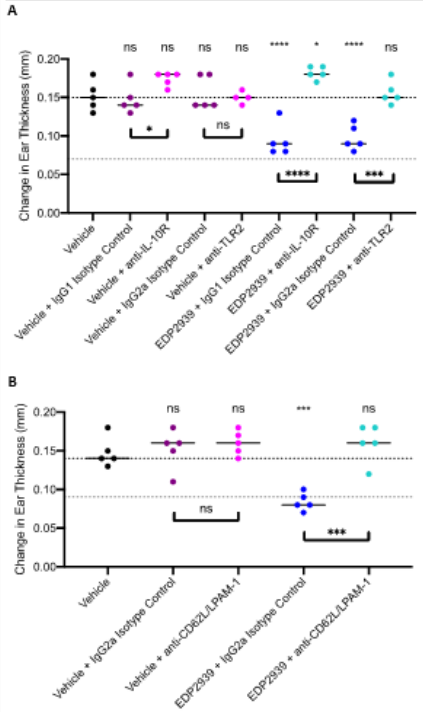


Figure 1: Orally-administered EDP2939 requires multiple pathways for anti-inflammatory effects. Mice undergoing a delayed type hypersensitivity (DTH) reaction against keyhole limpet hemagglutinin (KLH) were dosed with 2E10 particles/dose of EDP2939 by oral gavage on days 5–8. During the study, various mechanisms of action were interrogated by intraperitoneal injection of antibodies as indicated. **A)** Graph shows changes in ear thickness 24 hours after challenge with KLH protein and blockade of TLR2 or IL-10R signaling. **B)** Graph shows changes in ear thickness 24 hours after challenge with KLH protein and inhibition of lymphocyte gut homing. Points indicate individual mice and line shows median change in ear thickness. Data are representative of 2 independent studies. Statistical analyses were performed using a one-way ANOVA (vs. vehicle) or two-tailed unpaired t-test (isotype vs. treated). Ns = not significant, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

Orally administered fluorescently-labelled EDP2939 is gut-restricted

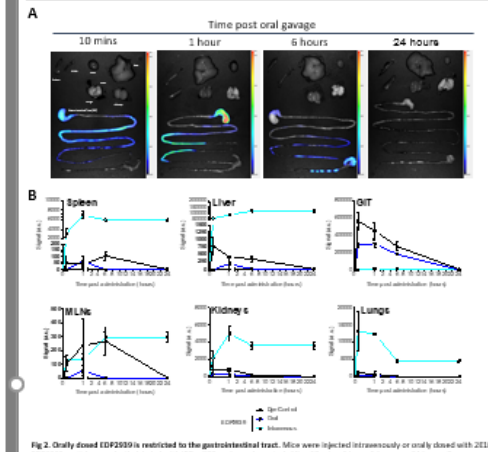


Fig 2. Orally dosed EDP2939 is restricted to the gastrointestinal tract. Mice were injected intravenously or orally dosed with 2E10 EDP2939 particles covalently labeled with IRDye800 or dye-only control. After 10 mins, 1 hour, 6 hours, or 24 hours, fluorescence was measured in the indicated organs using a small animal imaging system (Licor Pearl®). **A)** Representative images showing fluorescence from labelled EDP2939 in various organs at indicated time points post oral gavage. **B)** Graphs showing total signal measured in indicated organs and time points after oral gavage of dye control (Mock) or labelled EDP2939 (dark blue) or intravenous injection of labelled EDP2939 (light blue). Points show fluorescence intensity mean ± SD. Data are representative of 2 independent experiments.

Conclusions

- Orally-delivered microbial extracellular vesicles enact broad-based resolution of inflammation establishing homeostatic inflammatory status
- Efficacy of EDP2939 requires the stimulation of both the TLR2 receptor and the IL-10 receptor in addition to lymphocyte homing to the intestinal lymphoid tissue
- EDP2939 induces TLR2-dependent release of IL-10
- EVs are an orally-dosed, gut-restricted therapeutic with no apparent safety or tolerability issues in animal models, making for a desirable therapeutic profile

These data support the development of EVs as a new class of immunotherapeutic drugs. They are particularly effective at engaging the small intestinal axis, acting locally on host cells in the gut to activate distal immune responses. EDP2939 is in preclinical development for inflammatory disorders involving both aberrant Th1 and Th17 immune responses.

EDP2939 induces the release of IL-10 through TLR2 stimulation

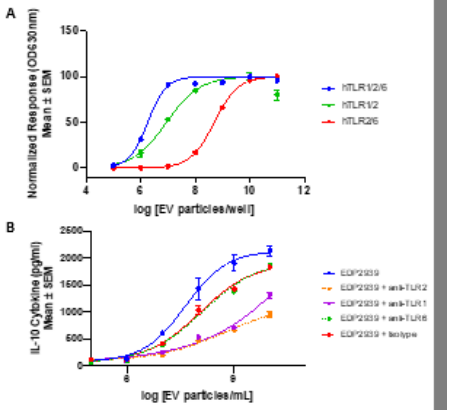


Fig 3. EDP2939 induces release of IL-10 following stimulation of TLR2. A) EDP2939 stimulates both TLR1/2 and TLR2/6 heterodimers, with greater potency towards the TLR1/2 heterodimer. HEK293-SEAP reporter cells (invivogen) expressing human TLR1, TLR2, and TLR6 combinations were incubated for 24 hours with EDP2939 at the indicated concentrations. Supernatants were collected and analyzed for secreted embryonic alkaline phosphatase (SEAP) production to determine stimulation of TLR2 heterodimers. **B)** EDP2939 stimulated IL-10 release from U937 cells is impaired by antibody-mediated blockade of either TLR1 or TLR2, but not TLR6. PMA-differentiated human monocytic U937 cells were incubated with EDP2939 ± 2.5 µg/mL anti-TLR1, TLR2, TLR6 or isotype control antibody for 24 hours. Supernatants were collected and analyzed for IL-10 response by MSD. Data are representative of 2 independent experiments.

EDP2939 stimulates anti-inflammatory cytokine secretion from human PBMCs

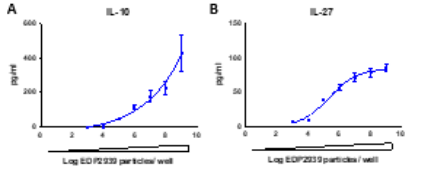


Fig 4. EDP2939 induces IL-10 and IL-27 concentration-dependent production from human PBMCs. PBMCs were isolated from whole blood of six human donors, plated at 100,000 cells per well, rested overnight, and then incubated with varying concentrations of EDP2939 for 24 hours. Supernatants were collected and **A)** IL-10 and **B)** IL-27 concentrations were determined via MSD. Data are representative of 6 independent donors.

EDP1908: EV for Oncology

#695 Oral delivery of a microbial extracellular vesicle induces potent anti-tumor immunity in mice

Loise Francisco, Mary Abdou, Alicia Ballok, Erin Troy, Fabian Romano Chernac, Maria Sizova, Audrey McBride, Michael Goldberg, Shubhra Kashyap, Shannon Argueta, Jessica Tsang, Kristie Barth, Krutika Invally, Holly Ponichtera, Mark Carlson, Tyler Rommel, Kevin Huynh, Valeria Kravitz, Tanmoy Ganguly, and Mark Bodmer
Evelo Biosciences, Cambridge MA

EVELO

INTRODUCTION

Evelo Biosciences is developing a new class of oral medicines which engage the immune system in the small intestine with distal effects throughout the body.

The microbial content of the gut interacts with host cells in the intestine to control systemic immune responses and inflammation. Our approach bypasses the need to modify the microbiota by selecting orally delivered agents which interact directly with host immune cells in the small intestine.

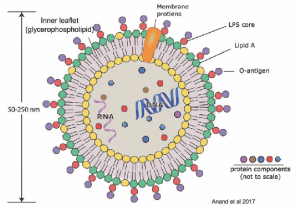
The small intestinal axis (SINTAX™) is a network of anatomic and functional connections with the rest of the body. It acts as an immunosurveillance system, integrating signals from the environment that affect physiological processes throughout the body. It can be harnessed for pharmacological effects of orally delivered agents that are systemically effective without systemic distribution. This is a newly appreciated and potent control system for immunity and inflammation.

This suggests a control mechanism for systemic immunity centered in the small intestine. This mechanism has novel features which are of considerable interest for the development of a new class of immunomodulatory therapies.

The impact of events in the gut on the control of tumor immunity is beginning to be appreciated. We have previously shown that an orally delivered single strain of commensal bacteria induces anti-tumor immunity preclinically via pattern recognition receptor-mediated activation of innate and adaptive immunity.

Some bacteria produce extracellular vesicles (EVs) that share molecular content with the parent bacterium in a particle that is roughly 1/1000th the volume in a non-replicating form.

We report here an orally-delivered and gut-restricted bacterial EV which potently attenuates tumor growth to a greater extent than whole bacteria or checkpoint inhibition.



- Extracellular vesicles (EVs) are lipoprotein nanoparticles naturally produced by some species of bacteria.
- Their macromolecular content is a subset of the parent.
- EVs enable bacterial communication and survival during stress, host-immune modulation, material exchange, and cell-cell interactions.
- Compared to microbes, EVs are:
  - ~1/1000th volume of microbes enabling improved target engagement
  - Non-viable
  - No risk of infection and sepsis

EDP1908 is an extracellular vesicle derived from a strain of Oscillospiraceae

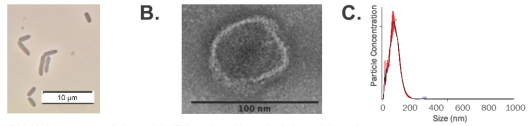


Fig. 1. EDP1908 is an extracellular vesicle (EV) produced by a single bacterial species.

(A) Phase contrast image of the Oscillospiraceae species from which EDP1908 is derived.
(B) TEM image of EDP1908 isolated from the supernatant of a liquid culture of the parent microbe.
(C) EDP1908 comprises a population of EVs with an average diameter of 88nm determined by nanoparticle tracking analysis.

Orally administered EDP1908 has superior anti-tumor efficacy to anti-PD-1 or its parent microbe

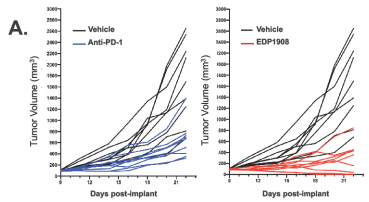
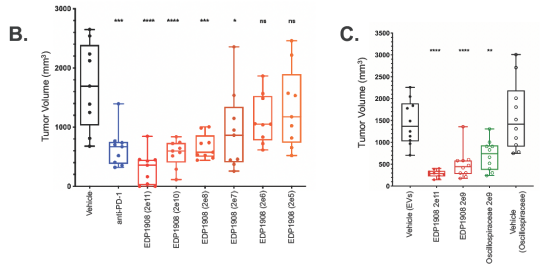


Fig 2. Therapeutic treatment of CT26 tumor-bearing mice with either oral EDP1908 b.i.d., anti-PD-1 i.p., or whole microbe b.i.d.

A) EDP1908 was administered orally at 2e11 particles beginning at day 10 for 12 days vs anti-PD-1. Spider plots show tumor growth for individual mice.
B) Dose-dependent control of tumor growth by EDP1908 doses from 2e5 – 2e11 particles shown at day 21. Data are median and range.
C) The parental Oscillospiraceae strain of EDP1908 was administered at its highest deliverable concentration of 2e9 cells. The 2e11 and 2e9 doses of EVs are shown for reference. Data are median and range.



Oral treatment with EDP1908 distally activates effector lymphocyte populations in the TME

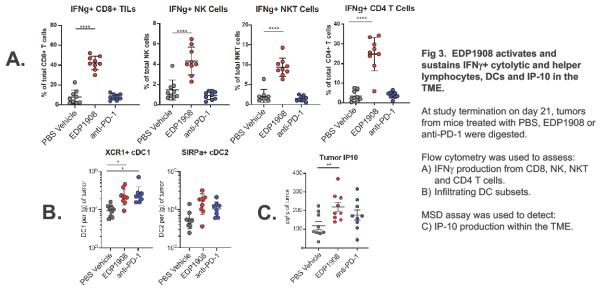


Fig 3. EDP1908 activates and sustains IFNγ+ cytolytic and helper lymphocytes, DCs and IP-10 in the TME.

At study termination on day 21, tumors from mice treated with PBS, EDP1908 or anti-PD-1 were digested.

Flow cytometry was used to assess:
A) IFNγ production from CD8, NK, NKT and CD4 T cells.
B) Infiltrating DC subsets.

MSD assay was used to detect:
C) IP-10 production within the TME.

EDP1908 is not detected outside the GI tract by fluorescent biodistribution

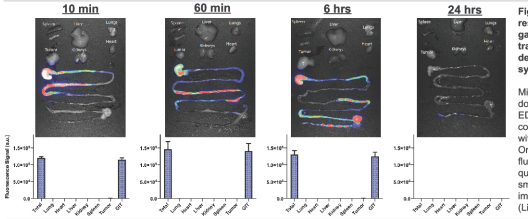


Fig 4. EDP1908 is restricted to the gastrointestinal tract and not detected in systemic organs.

Mice were orally dosed with 2e11 EDP1908 EVs covalently labeled with IRDye800. Organ fluorescence was quantified using a small animal imaging system (Licor Pearl®).

CONCLUSIONS

This is the first report of striking anti-tumor effects of an orally delivered microbial extracellular vesicle. The magnitude of these effects in preclinical models appears to match the reported activity of injected intra-tumoral immunostimulators. The observation that this efficacy can be achieved with an oral agent which does not itself distribute to the tumor is evidence for the level of control that can be exerted via the small intestinal axis, with no apparent safety or tolerability issues in the animal models.

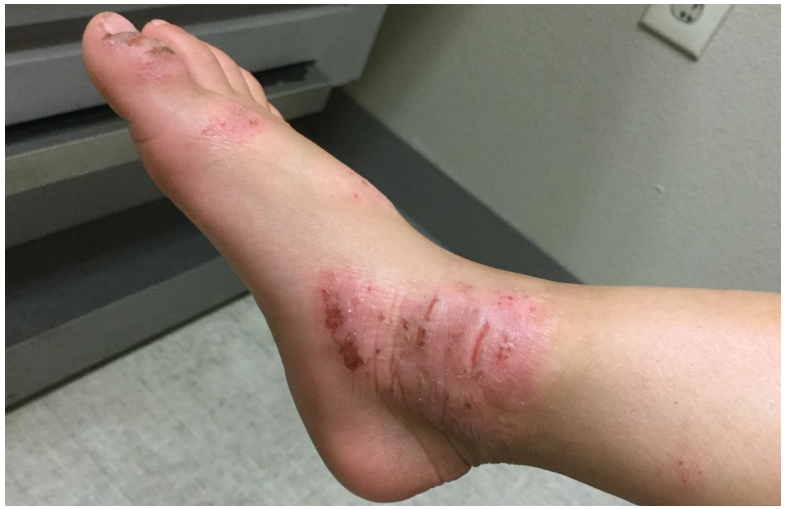
These data point to oral EVs as a new class of immunotherapeutic drugs. They are particularly effective at engaging the small intestinal axis, acting locally on host cells in the gut to activate distal immune responses within the tumor microenvironment. EDP1908 is in preclinical development for the treatment of cancer.

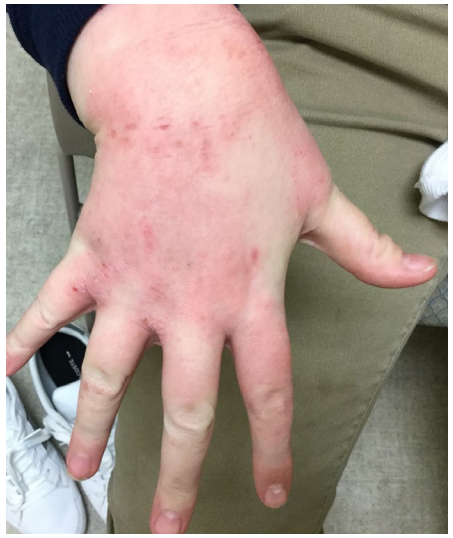
EDP1815

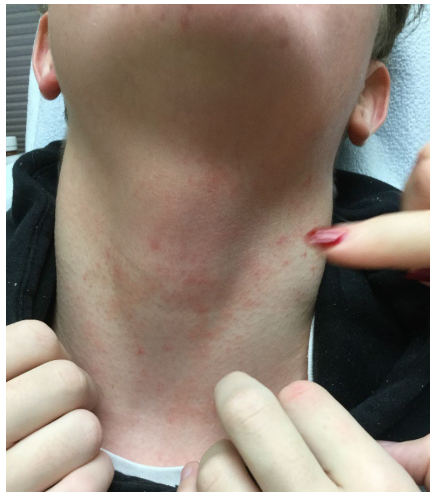
- EDP1815 has shown positive preclinical and Phase 1b clinical results across Th1, Th2, and Th17 inflammation pathways
- Generally well tolerated
- Broad potential applicability across inflammatory diseases: dermatology, rheumatology, inflammatory bowel disease, and beyond
- Potential utility across all stages of disease: mild and moderate to severe

Atopic Dermatitis

Mild and Moderate Atopic Dermatitis: Significant Disease Burden







Patients in these pictures have mild and moderate disease

- Atopic dermatitis is the most common chronic inflammatory disease affecting an estimated 10% of adults and 25% of children worldwide [1]
- Characterized by a cycle of intense itching and scratching that leads to red, cracked, scaly, and oozing skin [2]
- Range of symptoms creates significant physical and psychosocial burden on patients[3]
- Standard of care is topical treatments with low adherence due to inconvenient/burdensome application

[1] Eichenfield LF, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol. 2014;70(2):338-351. doi:10.1016/j.jaad.2013.10.010
[2] Nutten S. Atopic Dermatitis: Global Epidemiology and Risk Factors. Ann Nutr Metab 2015;66(suppl 1):8–16.
[3] EFA. Atopic Eczema: Itching for Life Report. 2018. Available at: https://www.efanet.org/images/2018/EN_-_Itching_for_life_Quality_of_Life_and_costs_for_people_with_severe_atopic_eczema_in_Europe_.pdf.

Hundreds of Millions of Cases of Atopic Dermatitis Worldwide with Few Acceptable Treatment Options

- 15-20% of children and 3-6% of adults worldwide[1] are estimated to suffer from atopic dermatitis
- Of all diagnosed atopic dermatitis patients in the U.S., 43% are not taking any medications for their disease[2]

Oral medications

Treatments include azathioprine, cyclosporine, methotrexate*, oral steroids
44% are dissatisfied with treatment
77% experience side effects
*Not approved for AD in US

Topical medications

Prescription topical steroids
52% are dissatisfied with treatment
60% experience side effects
Topical calcineurin inhibitors
63% are dissatisfied with treatment
40% experience side effects

Phototherapy

60% are dissatisfied with treatment
33% experience side effects

Atopic Dermatitis: Survey of 192 patients from the National Eczema Association, 2016
https://nationaleczema.org/in-your-words-survey-series

"Lack of safe and effective treatments"

"It takes 1 in 3 people one or more hours per day to treat their AD"

[1] Datamonitor Healthcare; DaVeiga, 2012; GBD, 2018; Nutten, 2015, National Eczema Foundation
[2] Evaluate Pharma, accessed Jul 2018

EDP1815 Phase 1b in Atopic Dermatitis

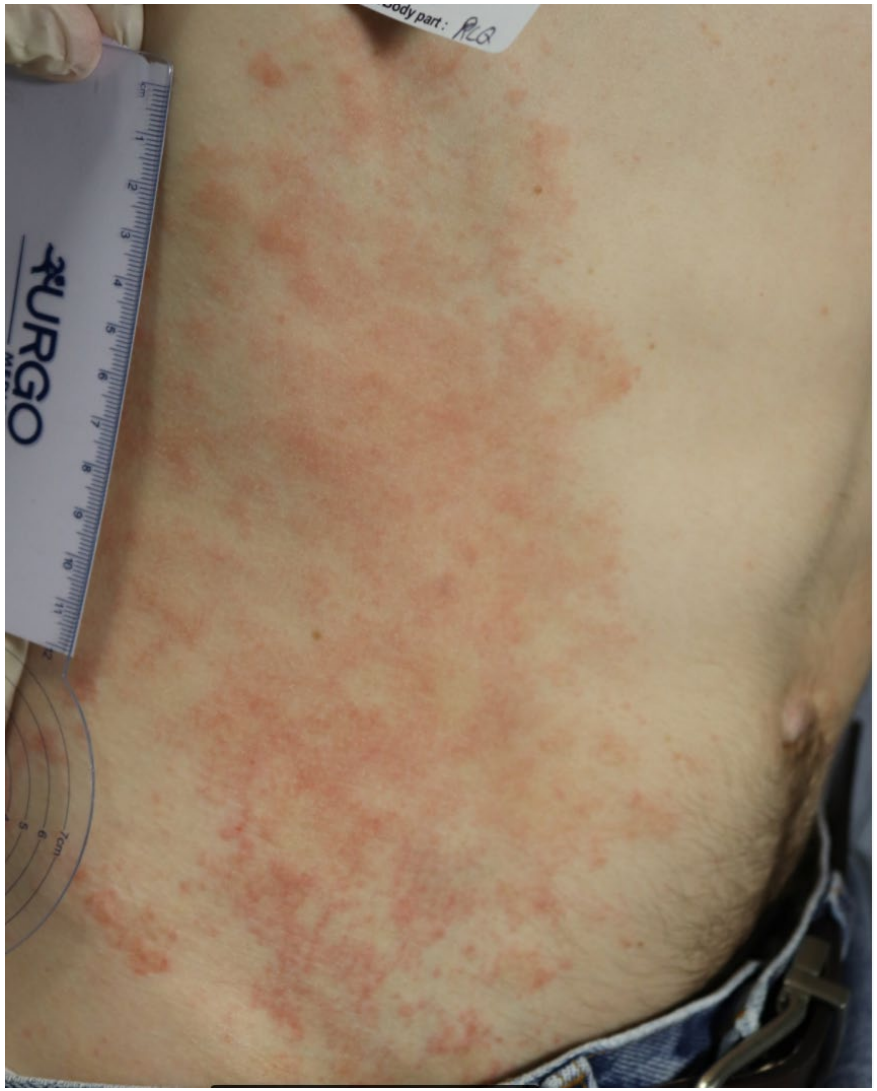
Trial Summary

- Double-blind, placebo-controlled trial of 24 patients
- Mild and moderate atopic dermatitis, randomized 2:1 (active:placebo)
- 56 days of oral administration of EDP1815 in a capsule, follow-up at day 70
- Once daily
- No active topical treatments, no requirement to use emollients

Summary of Endpoints

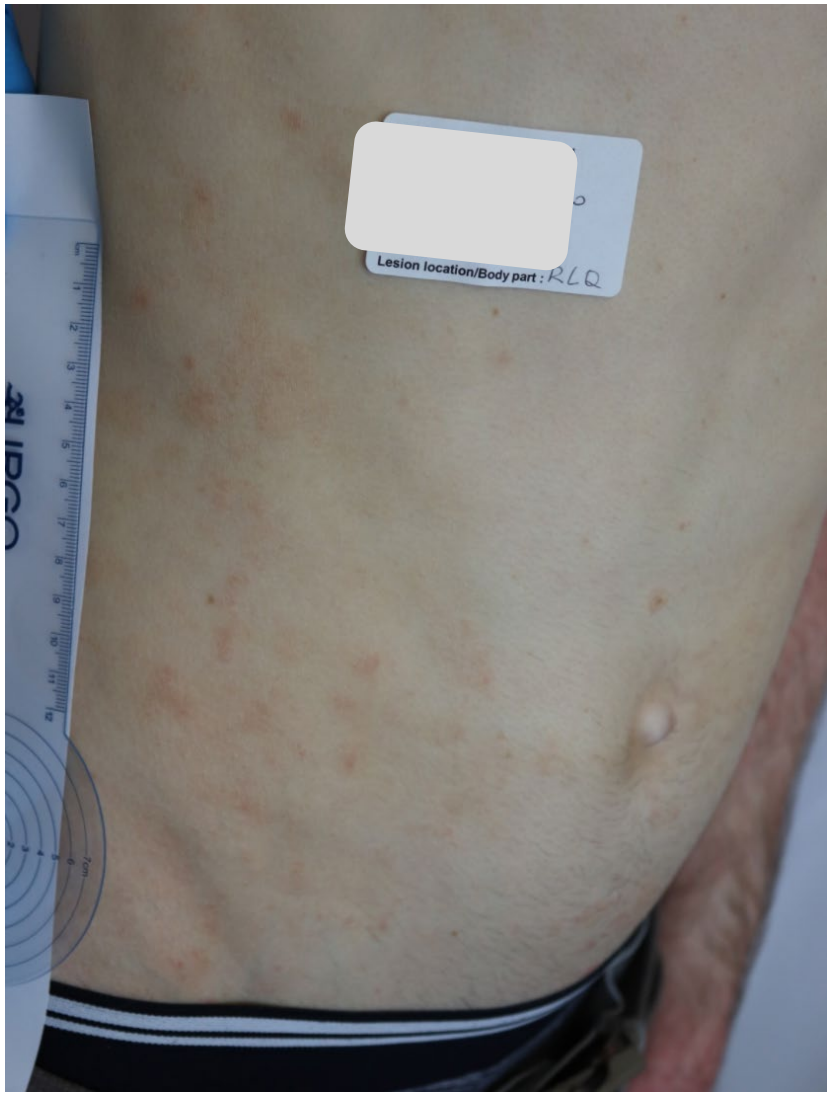
- Primary endpoint: Safety and tolerability
  - EDP1815 was well tolerated with no treatment related adverse events of moderate or severe intensity, and no serious adverse events
- Key physician-reported secondary endpoints:
  - EASI (Eczema Area and Severity Index)
  - IGA*BSA (Investigator Global Assessment x Body Surface Area)
  - SCORAD (SCORing Atopic Dermatitis)
- Key patient-reported secondary endpoints:
  - DLQI (Dermatology Life Quality Index)
  - POEM (Patient-Oriented Eczema Measure)
  - Pruritus-NRS (Numerical Rating Scale)

Efficacy of EDP1815 in Atopic Dermatitis



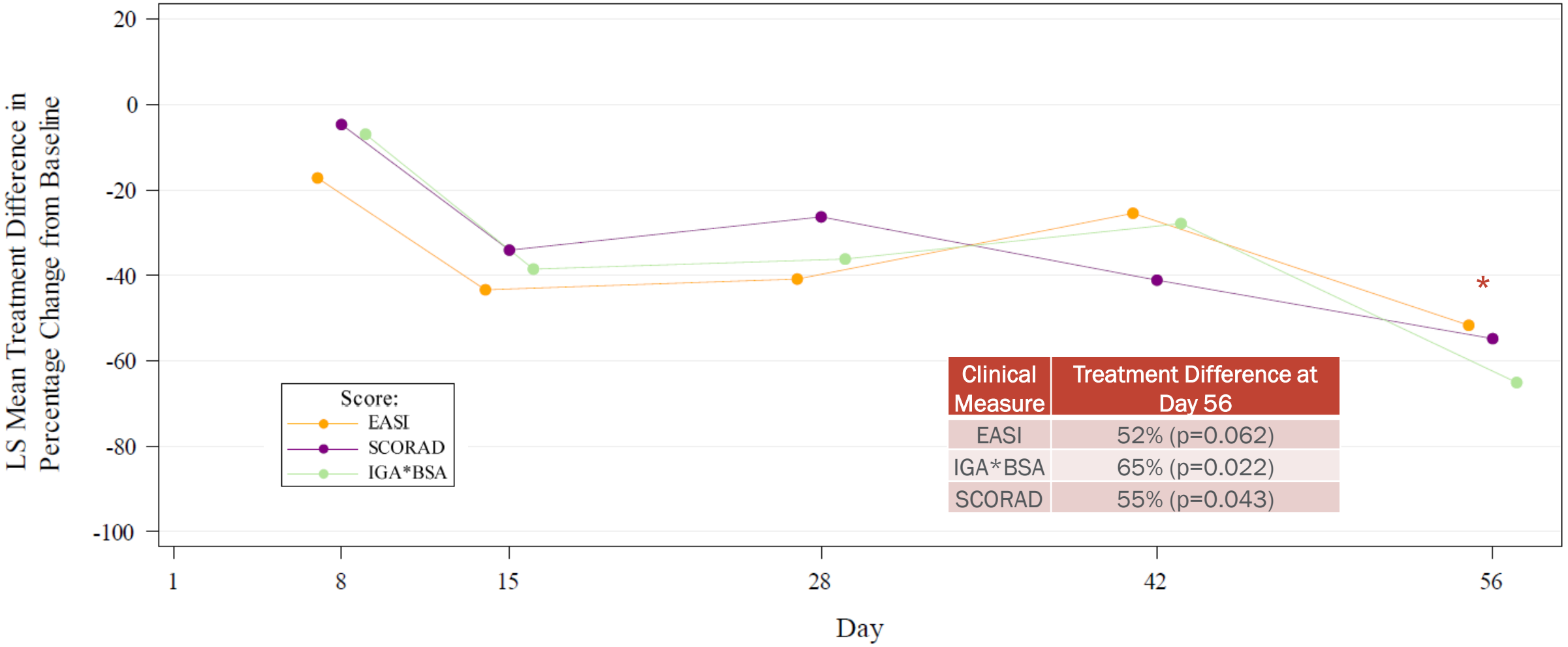
Before, day 0

Patient on once daily EDP1815 and no topical treatments: before and after (patient achieved EASI50 score)



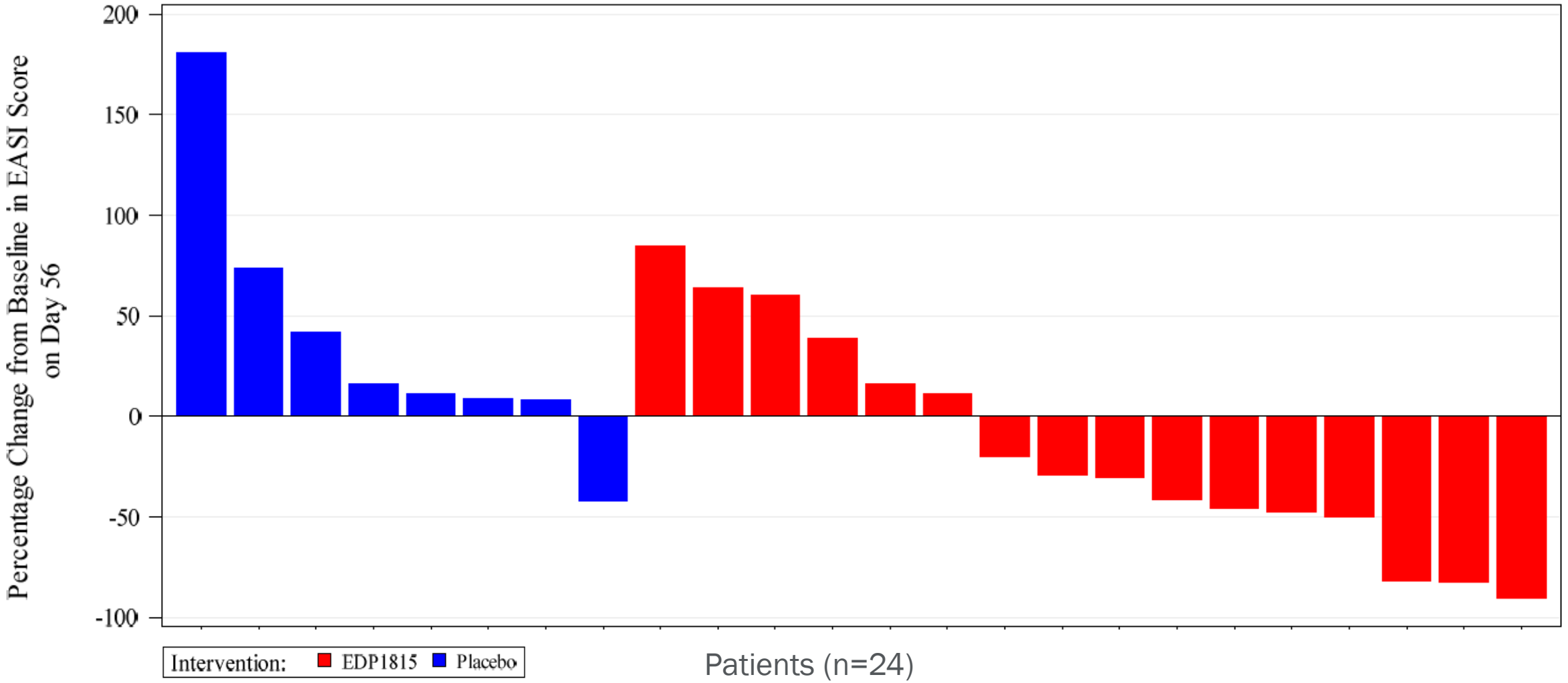
After, day 56

Improvements in EASI, IGA*BSA, and SCORAD with EDP1815 at Day 56



Clinical Measure	Treatment Difference at Day 56
EASI	52% (p=0.062)
IGA*BSA	65% (p=0.022)
SCORAD	55% (p=0.043)

EASI: 10/16 Patients on EDP1815 Improved at Day 56



Clinically Meaningful Improvements in Patient-Reported Outcomes Including Itch and Sleep

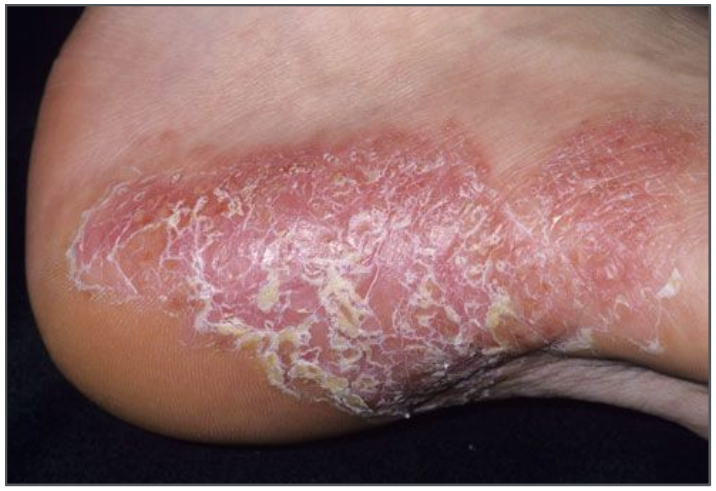
For EDP1815-treated patients at day 56:

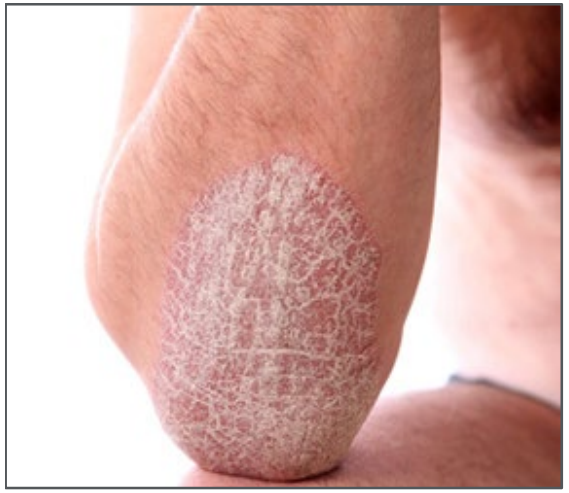
- DLQI (Dermatology Life Quality Index) mean improvement exceeded the clinically validated threshold[1]
- POEM (Patient-Oriented Eczema Measure) mean improvement exceeded the clinically validated threshold[2]
- Improvement in itch across all measured scores (including Pruritus-NRS and within SCORAD)
- Improvement in sleep across all measured scores (including POEM and within SCORAD)

1. Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. Dermatology. 2015;230(1):27-33. doi: 10.1159/000365390. Epub 2015 Jan 20. PMID: 25613671.
2. Schram ME, Spuls PI, Leeflang MM, Lindeboom R, Bos JD, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. Allergy. 2012 Jan;67(1):99-106. doi: 10.1111/j.1398-9995.2011.02719.x. Epub 2011 Sep 27. PMID: 21951293.

Psoriasis

Mild and Moderate Psoriasis is a Serious Condition with Few Existing Effective Treatments





- While characterized as mild and moderate in terms of body surface area, individual lesions can be severe
- ~49% of mild and ~24% of moderate patients do not initiate or maintain treatment due to concerns about long-term safety, tolerability, or efficacy of currently available therapies[1]
- Along with the cosmetic, emotional, and functional disease burden of psoriasis are comorbidities such as psoriatic arthritis, increased risk of depression, inflammatory bowel disease, and ischaemic heart disease

Evelo's initial commercial focus is on mild to moderate population with potential to address over 3.5 million[2] of these individuals in U.S. and EU5 and then expand globally

[1] Armstrong AW, Robertson AD, Wu J, Schupp C, Lebwohl MG. Undertreatment, Treatment Trends, and Treatment Dissatisfaction Among Patients With Psoriasis and Psoriatic Arthritis in the United States: Findings From the National Psoriasis Foundation Surveys, 2003-2011. JAMA Dermatol. 2013;149(10):1180–1185. doi:10.1001/jamadermatol.2013.5264

[2] 2018 company-sponsored market research; EU5 consisting of France, Germany, Italy, Spain and the UK

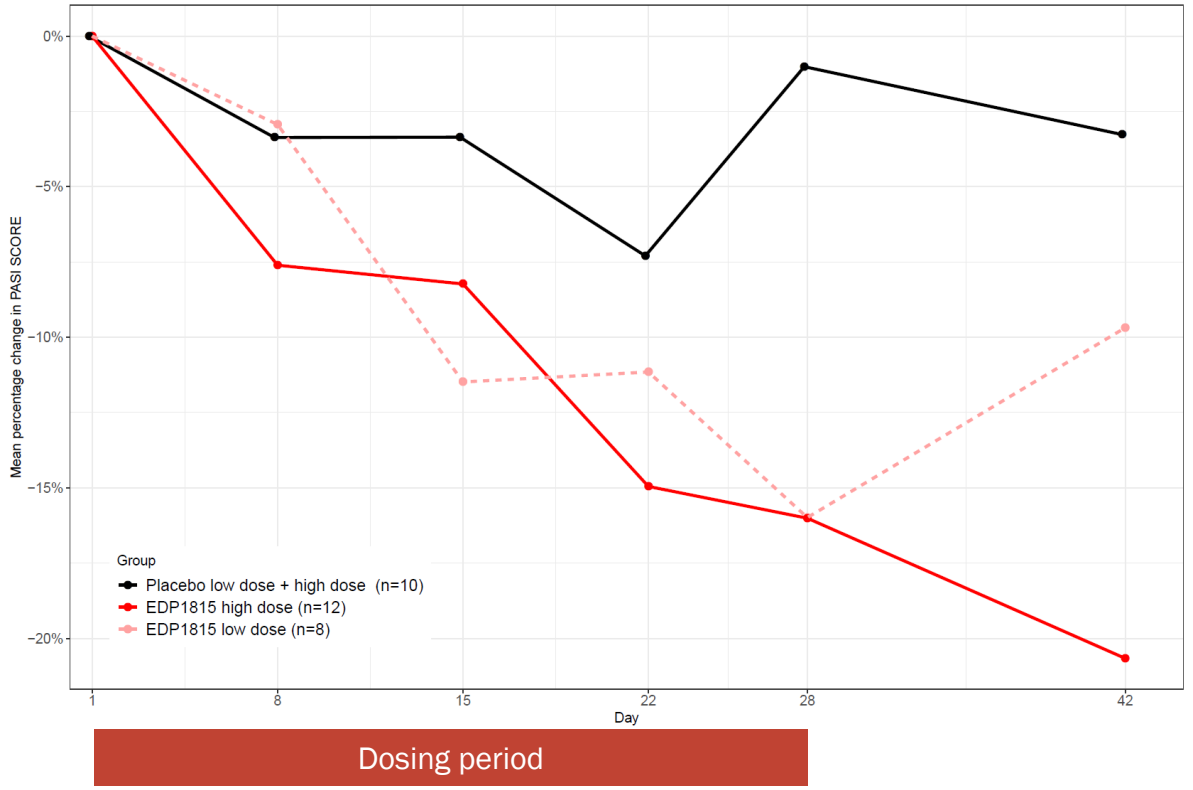
Positive Phase 1b Clinical Data with EDP1815 in Mild and Moderate Psoriasis

Double-blind, placebo-controlled Phase 1b trial with low (n=12) and high dose (n=18) cohorts, 28 days of oral administration of EDP1815 in a capsule, follow-up at day 42:

- Well tolerated with no overall difference vs. placebo
- Clinical activity observed, including:
  - Reduction in mean PASI scores vs. placebo
  - Reduction in Lesion Severity Score in-line with PASI
- Continued reduction observed in high dose cohort at day 42, two weeks after cessation of dosing, may be indicative of a sustained clinical effect and dose response

Clinically meaningful reduction in PASI at high dose

21% at day 42 versus placebo of 3%



EDP1815 Phase 2 Dose-Ranging Trial in Mild and Moderate Psoriasis

Trial Summary

- 16 week, double-blind, placebo-controlled, dose-ranging trial of ~225 patients
- Individuals with mild and moderate disease
- Evaluate three doses of enteric capsule formulation of EDP1815 vs. placebo
  - Randomized 2:1 (active:placebo) in each arm
- Follow-up at week 20

Summary of Endpoints

- Primary endpoint: mean reduction in PASI score at 16 weeks
- Key physician-reported secondary endpoints:
  - PGA (Physician's Global Assessment)
  - BSA (Body Surface Area)
  - PGA x BSA
  - Lesion Severity Score (LSS)
- Key patient-reported secondary endpoints:
  - DLQI (Dermatology Life Quality Index)
    - Includes itch and sleep
  - Psoriasis Symptom Inventory
  - Pain
  - Fatigue

Data expected 3Q 2021

Selection of Optimum Dose, Formulation, and Concentration

- In addition to Phase 2 dose-ranging trial, investigating different formulations and concentrations in multiple, parallel Phase 1b studies with EDP1815
- Formulation and concentration have potential to further improve efficacy
- Together with Phase 2 dose-ranging data, these Phase 1b studies will allow for selection of dose, concentration, and formulation
- Data from Phase 1b trials expected **3Q 2021**

COVID-19

EDP1815 is a potentially differentiated treatment for COVID-19

- **Inflammation resolution without immunosuppression observed in Phase 1b clinical trial in psoriasis; "Goldilocks effect"**
  - Modulating multiple pathways associated with cytokine storm
  - Did not suppress type 1 interferons which are important for anti-viral immune response
- **Favorable safety and tolerability results in Phase 1b clinical trial in psoriasis and atopic dermatitis**
  - No systemic exposure observed, limiting risk of secondary infections or potential interaction with other medicines
  - Generally well tolerated with no treatment-related adverse events of moderate or severe intensity and no serious adverse events
- **Orally administered**, allowing for easy and flexible administration
- **Scalable manufacturing** for treatment of large populations

Potential to explore EDP1815 as treatment in other diseases in which hyperinflammation and cytokine storm may play a key role, such as influenza

Data from COVID-19 trial has potential to drive accelerated path

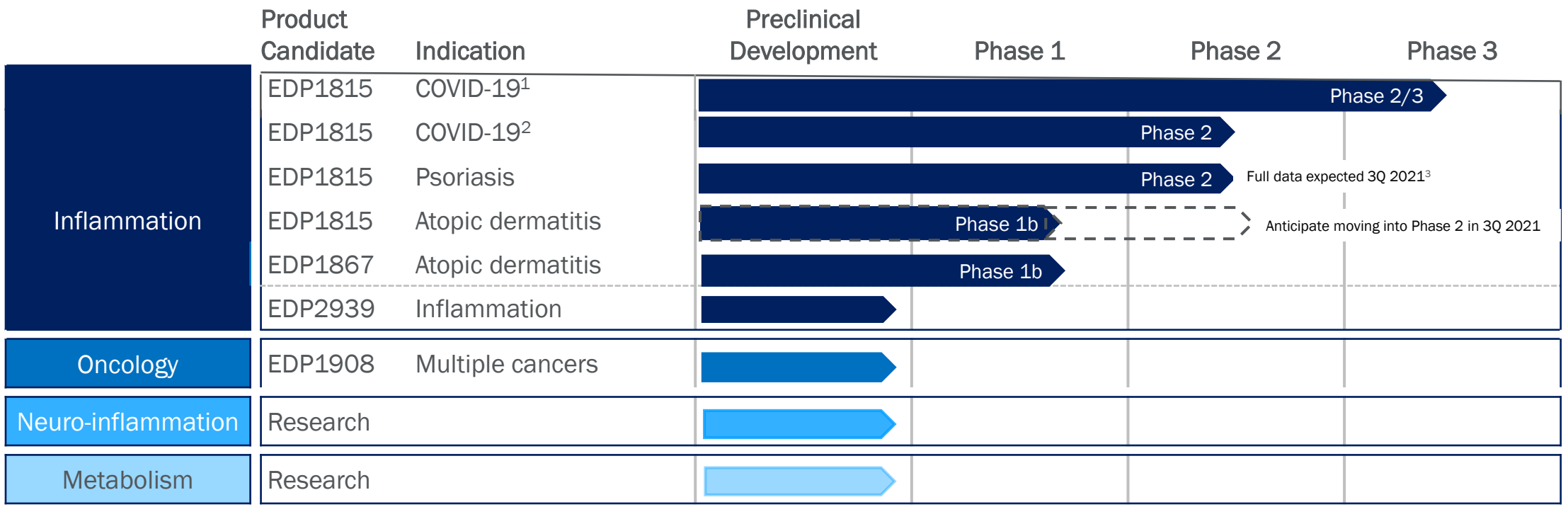
TACTIC-E: Phase 2/3 Platform Trial

- Phase 2/3 randomized platform trial across multiple UK centers, sponsored by Cambridge University Hospitals NHS Foundation Trust*
- Patients with identified risk factors who are at high risk of progression to ICU and/or death
- N=up to 469 per arm, 1:1:1 randomization
  - Arm 1: EDP1815 + standard of care
  - Arm 2: Ambrisentan and dapagliflozin + standard of care
  - Arm 3: Standard of care

*The investigators of the study are-expanding the trial to countries where COVID-19 remains prevalent, including Mexico and Brazil

Pipeline

Broad Clinical and Preclinical Pipeline with Multiple Upcoming Readouts



[1] The Phase 2/3 TACTIC-E study is an investigator-sponsored study being conducted by Cambridge University Hospitals NHS Foundation Trust
[2] The Phase 2 trial is in collaboration with Rutgers University and Robert Wood Johnson University Hospital
[3] Phase 1b data on different formulations and concentrations also expected in 3Q 2021

Appendix

Corporate Information

- ~110 employees
- Cash and cash equivalents of more than $120 million*
- $50 million ATM program with substantial capacity remaining
- Long-term debt outstanding of $30 million

*As of March 31, 2021