EVELO BIOSCIENCES

Harnessing SINTAX™, the small intestinal axis, to transform medicine

The small intestinal axis is the sensing system in the gut that governs inflammation and immunity throughout the body

Evelo is developing a new type of medicine that has the potential to be effective, safe, convenient, and affordable for billions of people

April 2021

Legal disclaimer

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this presentation that do not relate to matters of historical fact should be considered forward-looking statements, including statements concerning the development of EDP1815, EDP1867, EDP2939, and EDP1908, the promise and potential impact of our product candidates, the timing of and plans for clinical studies, the timing and results of clinical trial readouts, and the scalability of manufacturing for EDP1815.

These forward-looking statements are based on management's current expectations. These statements are neither promises nor guarantees, but involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, but not limited to, the following: the impact of the COVID-19 pandemic on our operations, including our preclinical studies and clinical trials, and the continuity of our business; we have incurred significant losses, are not currently profitable and may never become profitable; our need for additional funding; our cash runway; our limited operating history; our unproven approach to therapeutic intervention; the lengthy, expensive, and uncertain process of clinical drug development, including potential delays in regulatory approval; our reliance on third parties and collaborators to expand our microbial library, conduct our clinical trials, manufacture our product candidates, and develop and commercialize our product candidates, if approved; our lack of experience in manufacturing, selling, marketing, and distributing our product candidates; failure to compete successfully against other drug companies; protection of our proprietary technology and the confidentiality of our trade secrets; potential lawsuits for, or claims of, infringement of third-party intellectual property or challenges to the ownership of our intellectual property; our patents being found invalid or unenforceable; risks associated with international operations; our ability to retain key personnel and to manage our growth; the potential volatility of our common stock; our management and principal stockholders have the ability to control or significantly influence our business; costs and resources of operating as a public company; unfavorable or no analyst research or reports; and securities class action litigation against us.

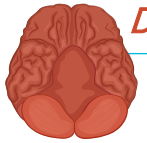
These and other important factors discussed under the caption "Risk Factors" in our Quarterly Report on Form 10-Q for the three months ended March31, 2021, and our other reports filed with the SEC could cause actual results to differ materially from those indicated by the forward-looking statements made in this presentation. Any such forward-looking statements represent management's estimates as of the date of this presentation. While we may elect to update such forward-looking statements at some point in the future, except as required by law, we disclaim any obligation to do so, even if subsequent events cause our views to change. These forward-looking statements should not be relied upon as representing our views as of any date subsequent to the date of this presentation.

Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and our own internal estimates and research. While we believe these third-party sources to be reliable as of the date of this presentation, we have not independently verified, and we make no representation as to the adequacy, fairness, accuracy or completeness of any information obtained from third-party sources. In addition, all of the market data included in this presentation involves a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions. Finally, while we believe our own internal research is reliable, such research has not been verified by any independent source.

Chronic inflammation is the driver of our most burdensome diseases

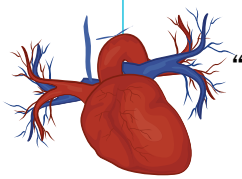
Neurological diseases; 7M US DALYs[1], 111M WW

"The contribution of inflammation in the pathogenesis of Alzheimer's Disease has been appreciated only recently" Nat Rev Neuro, 2015



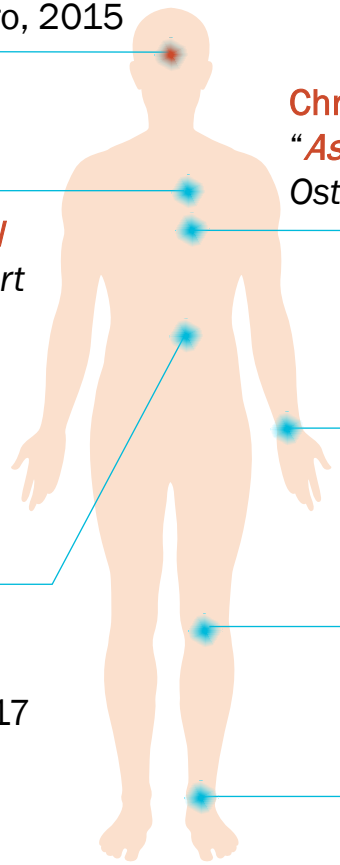
Cardiovascular disease; 16M US DALYs, 366M WW

"Chronic inflammation is a major contributor to heart disease" Johns Hopkins Medicine



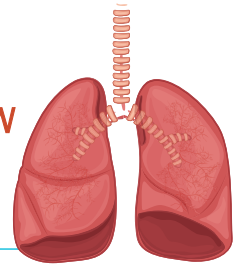
Diabetes; 4M US DALYs, 68M WW

"Inflammation is increasingly considered to be an established mediator [of diabetes]" J Clin Invest., 2017



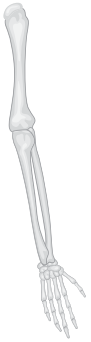
Chronic respiratory diseases; 6M US DALYs, 112M WW

"Asthma is a chronic inflammatory disease" J Amer Osteopathic Assc, 2011



Autoimmune diseases; 2M US DALYs, 18M WW

"Higher levels of systemic inflammation are associated with [cardiovascular decline in rheumatoid arthritis patients]" Ann Rheum Dis., 2015



Injuries; 10M US DALYs, 252M WW

"While inflammation is vital in clearing infection and debris, it can lead to tissue damage if prolonged, [causing chronic wounds]" Int J Mol Sci, 2016

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SOURCE: Scientific literature, Global Disease Burden 2017

[1] Disability-Adjusted Life Year (DALY)

5 Positive Sets of Clinical Data in EDP1815

- EDP1815 has shown positive preclinical and Phase 1b clinical results across Th1, Th2, and Th17 inflammation pathways
- Generally well tolerated, with no observed systemic exposure
- 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

SINTAX medicines are active preclinically and clinically

Preclinical mechanism of action

Efficacy

- Comparable with biologics and oral medication

Pharmacology

- Modulation of multiple inflammatory pathways
- Inflammation resolution without immunosuppression

Non-GLP Toxicology

- No clinical or histological adverse effects
- No observed systemic exposure

Clinical proof of principle and safety results

Human Experimental Model of Inflammation

- Observed >90% reduction in inflammation vs placebo
- Observed increased drug concentration resulted in increased effects

Phase 1b Atopic Dermatitis

- Improved atopic dermatitis measures vs placebo

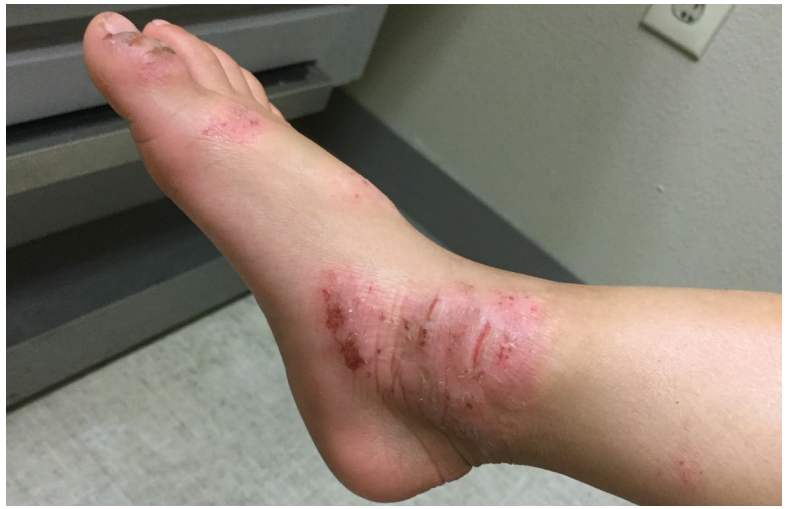
Phase 1b Psoriasis

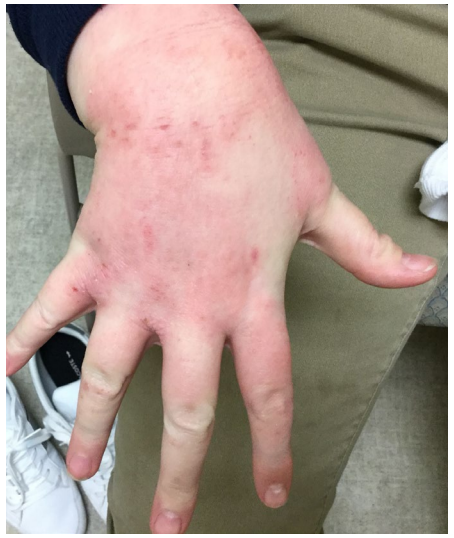
- Reduced skin lesions vs placebo in 2 cohorts
- Inhibited multiple systemic inflammatory cytokines

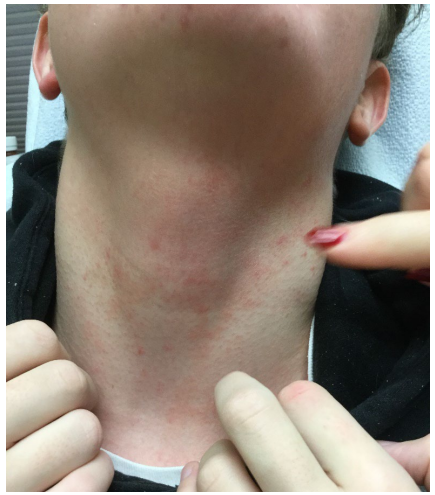
Safety and tolerability

- Generally well tolerated
- No observed systemic exposure

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

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[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.

EDP1815 Phase 1b in atopic dermatitis

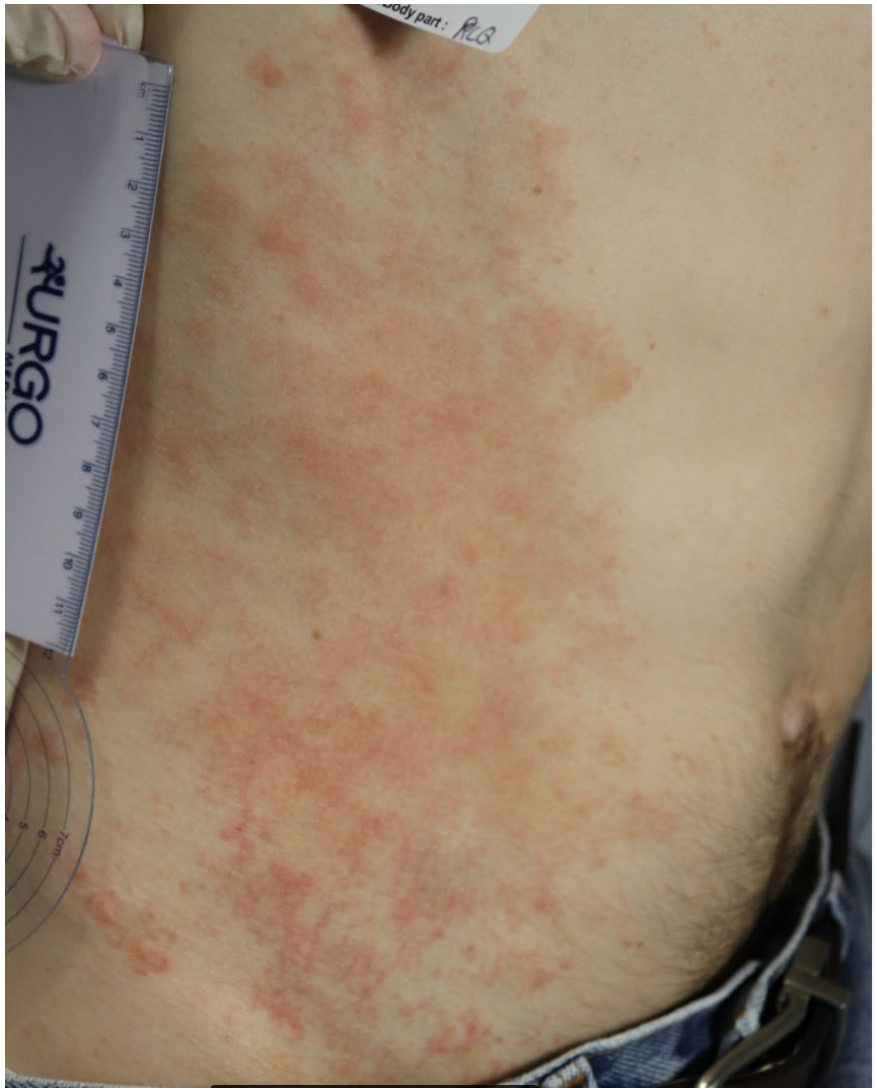
Trial Summary

- 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

Safety and Tolerability

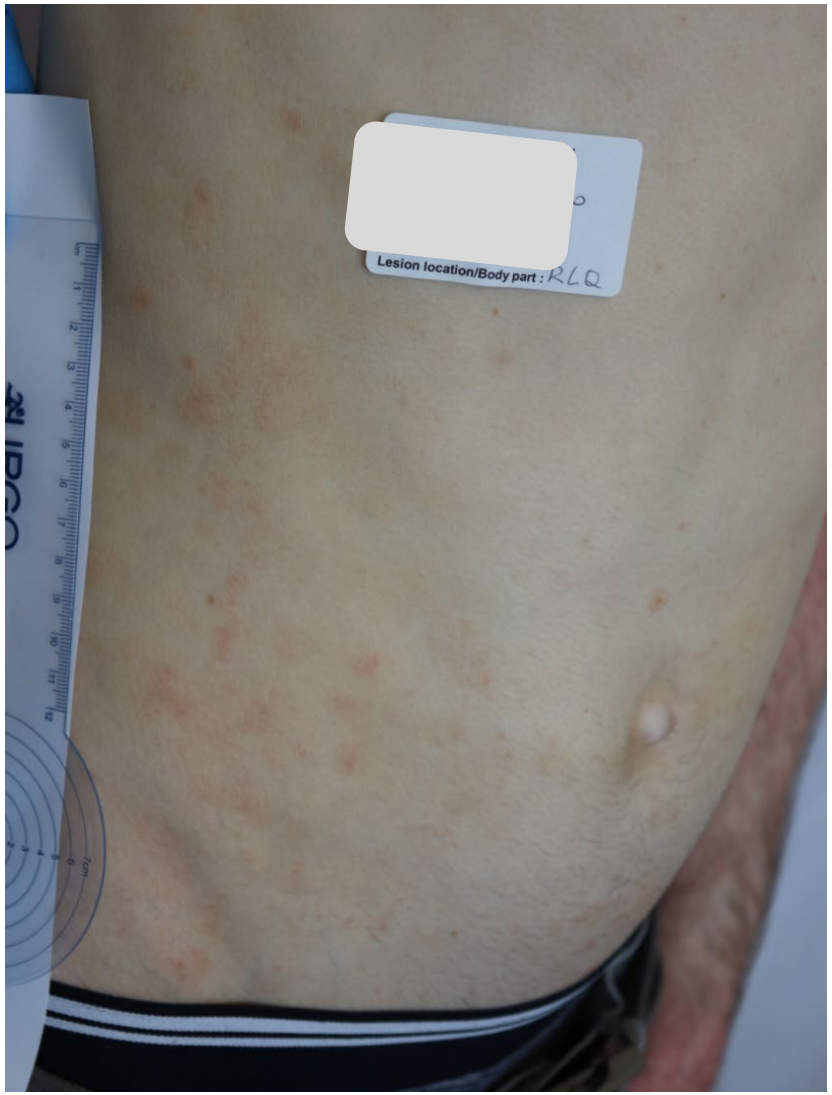
- EDP1815 was well tolerated with no treatment related adverse events of moderate or severe intensity, and no serious adverse events

Efficacy of oral EDP1815 in atopic dermatitis



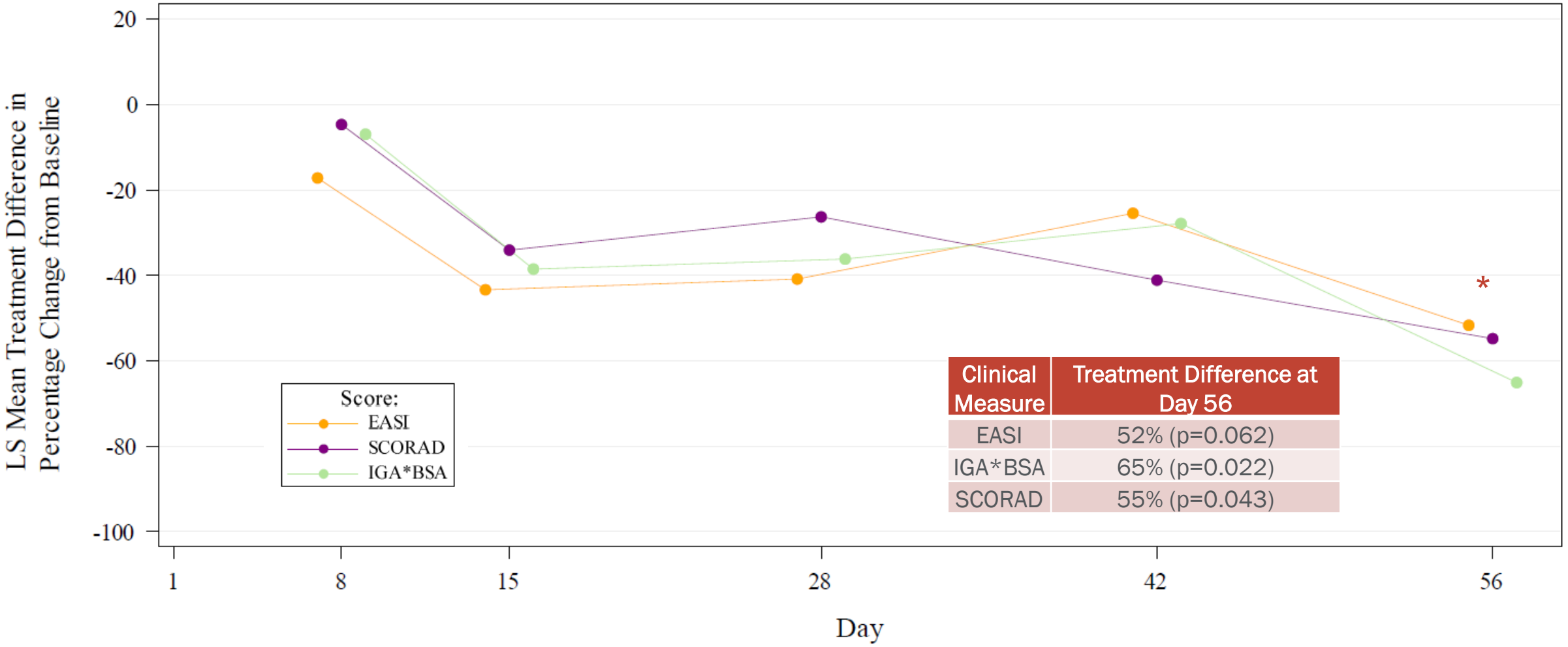
Before, day 0

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



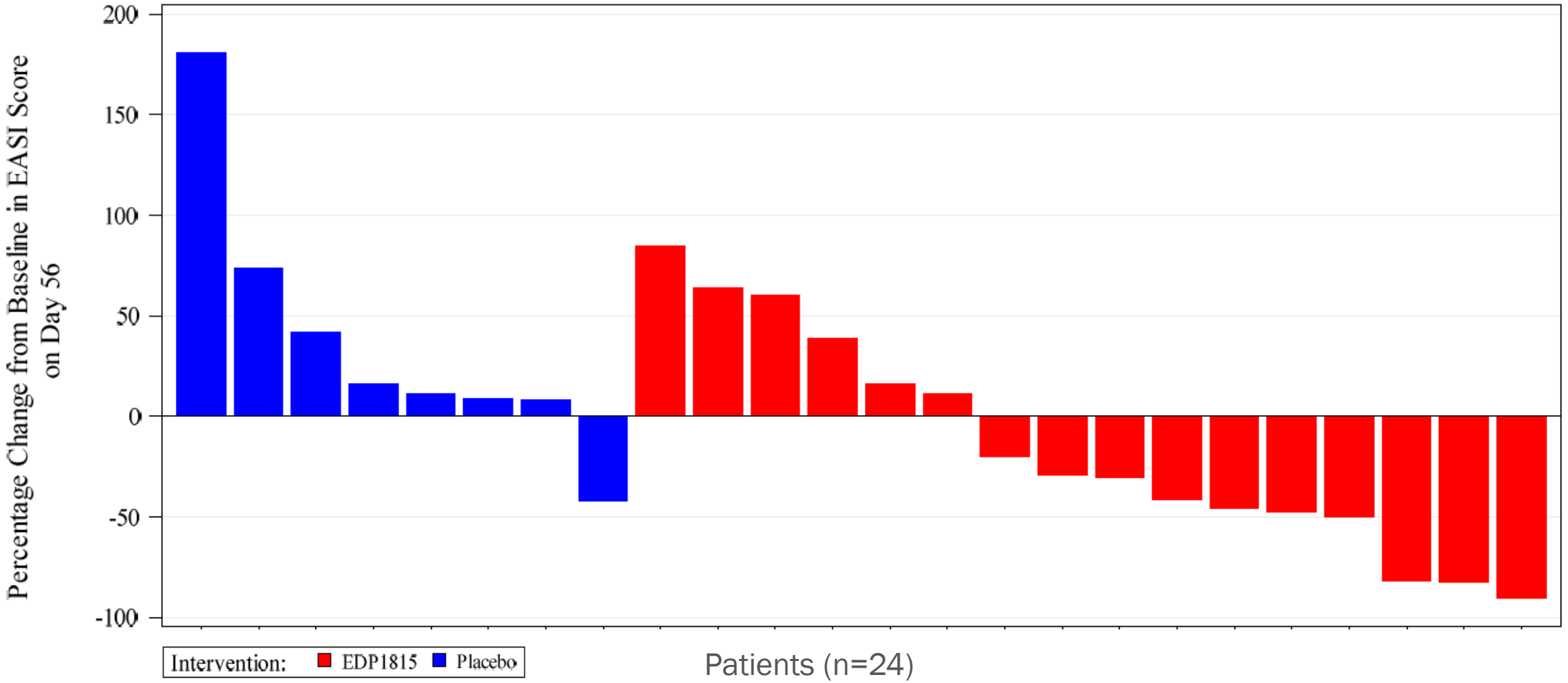
After, day 56

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.

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"

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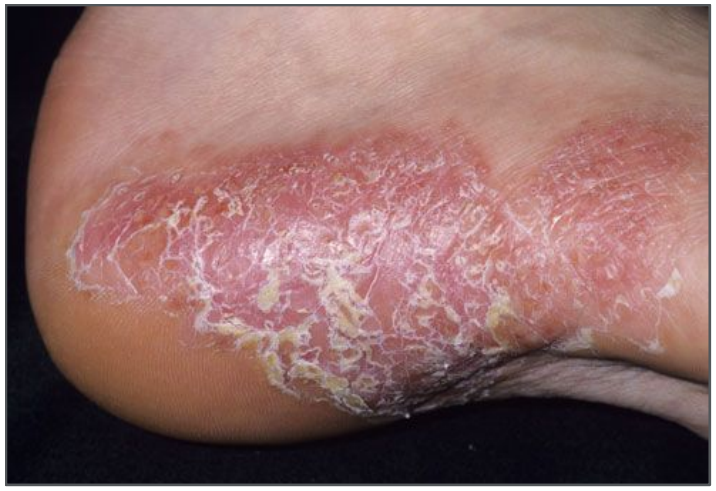
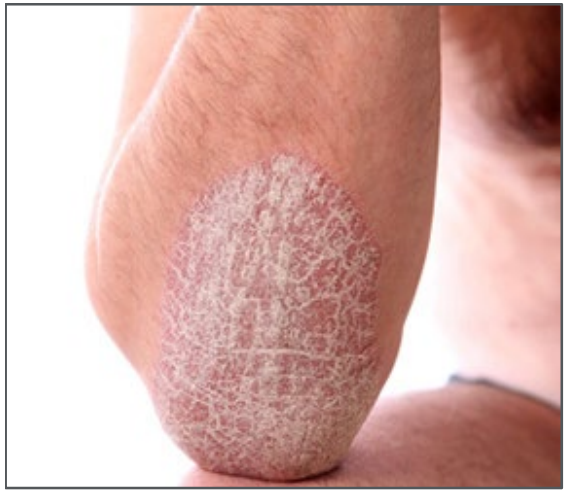
[1] Datamonitor Healthcare; DaVeiga, 2012; GBD, 2018; Nutten, 2015, National Eczema Foundation
[2] Evaluate Pharma, accessed Jul 2018

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

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[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

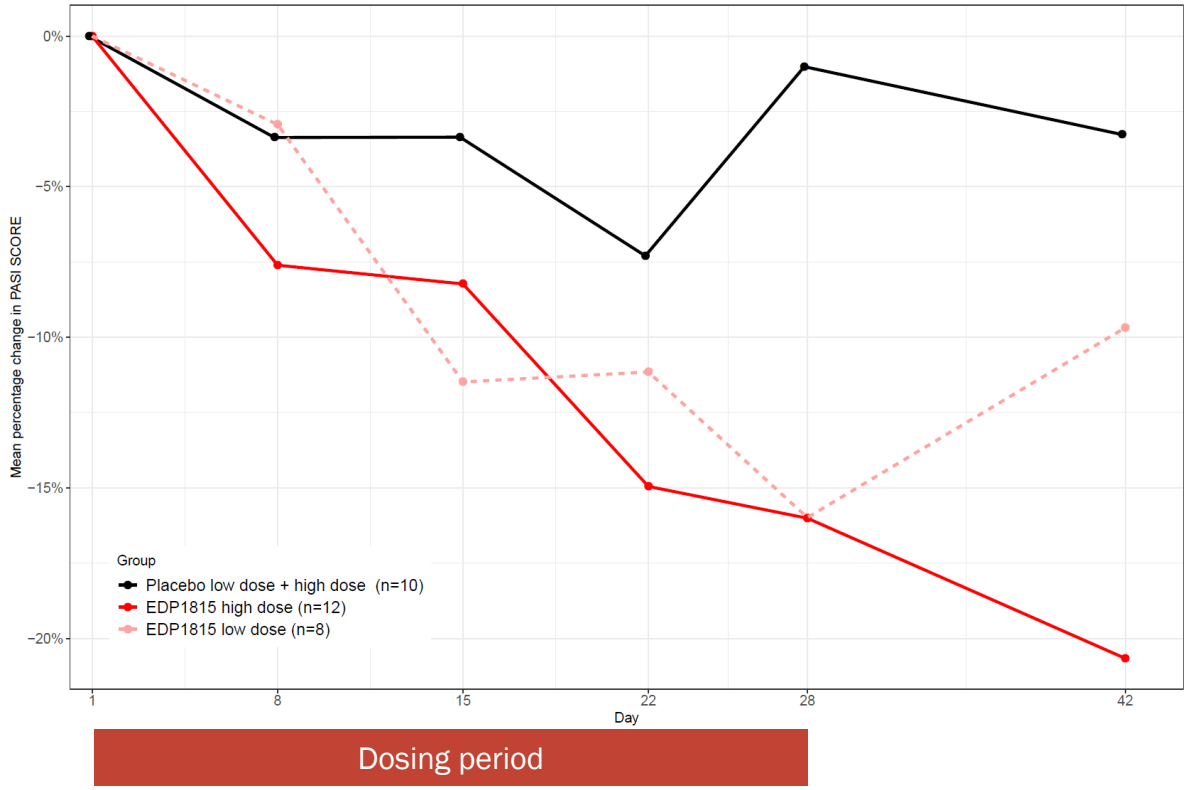
Positive Phase 1b clinical data with EDP1815 in mild and moderate psoriasis

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

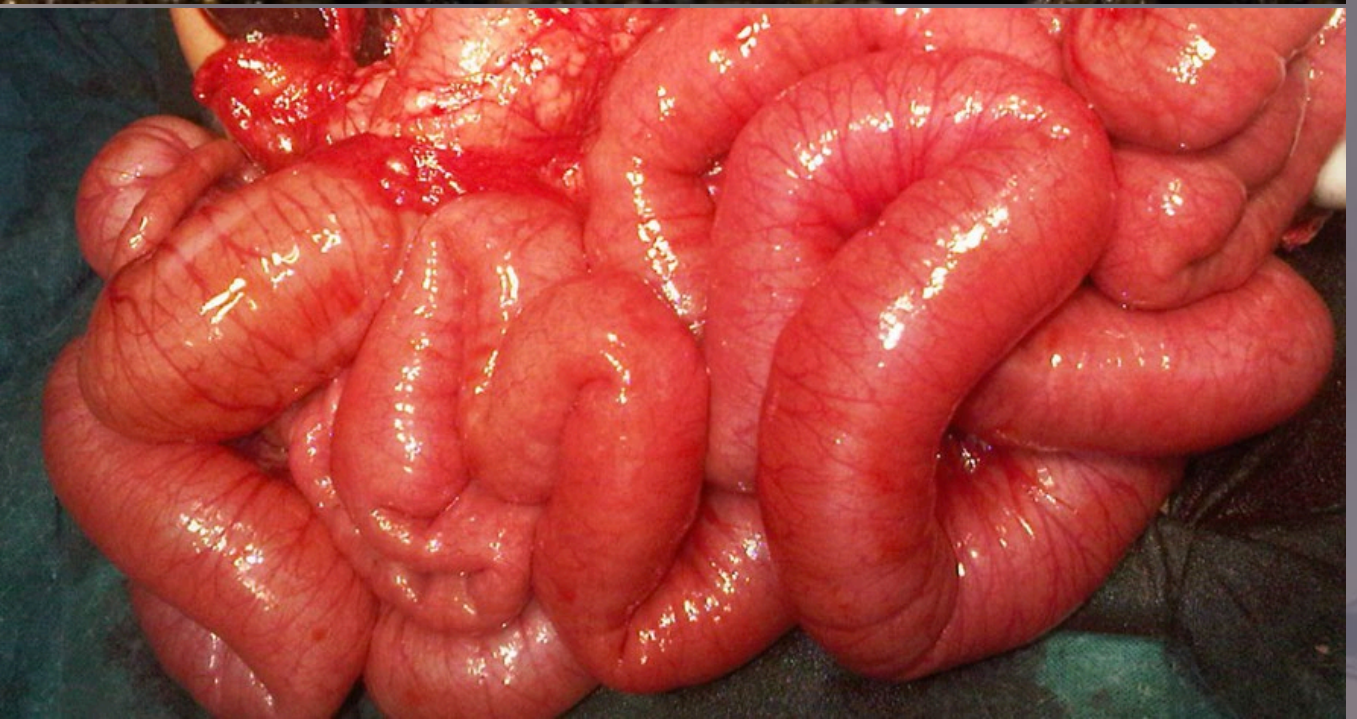
- Double-blind, placebo-controlled, dose-ranging trial ~225 patients
- Evaluate three doses of enteric capsule formulation of EDP1815 vs. placebo
- Individuals with more active disease scores than Phase 1b

Summary of Endpoints

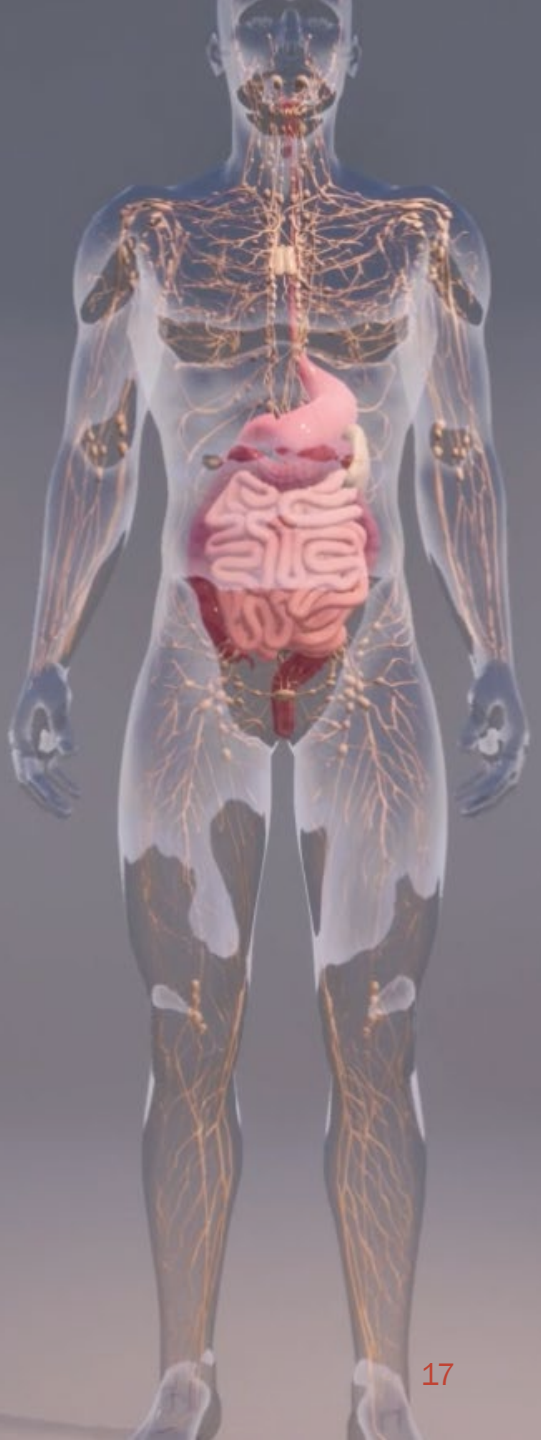
- Primary endpoint: Mean reduction in PASI score at 16 weeks
- Key secondary endpoints:
  - PGA (Physician's Global Assessment)
  - BSA (Body Surface Area)
  - PGA x BSA
  - DLQI (Dermatology Life Quality Index)
  - Lesion Severity Score (LSS)

Full data set expected 3Q 2021

Evelo Product Candidates & How They Work



600 million years

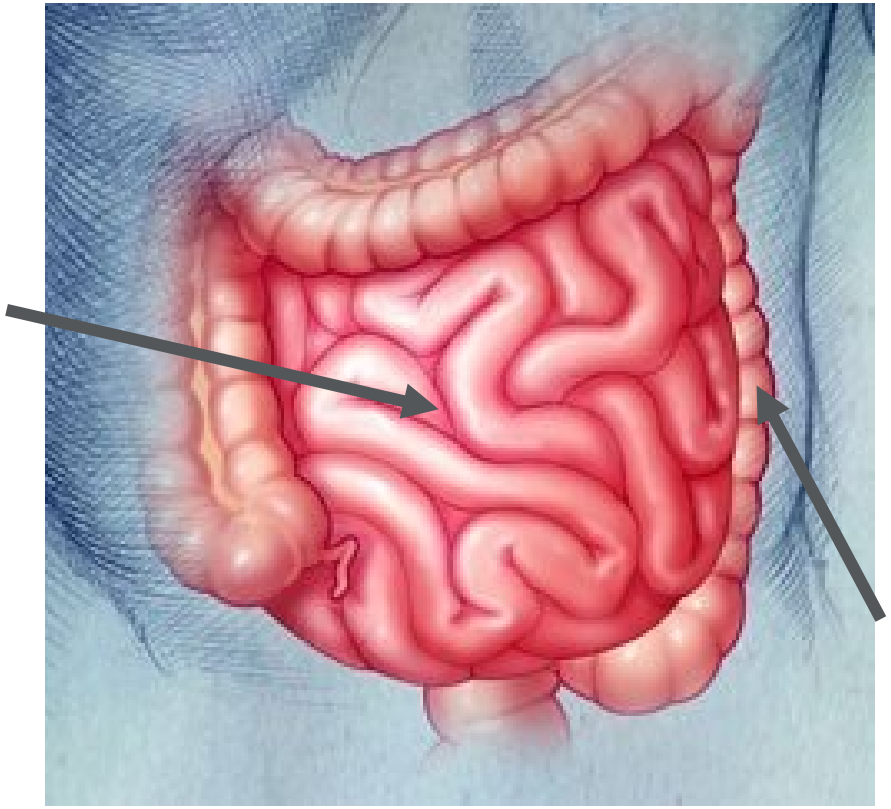


Cells in the small intestine are therapeutic targets for SINTAX medicines

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

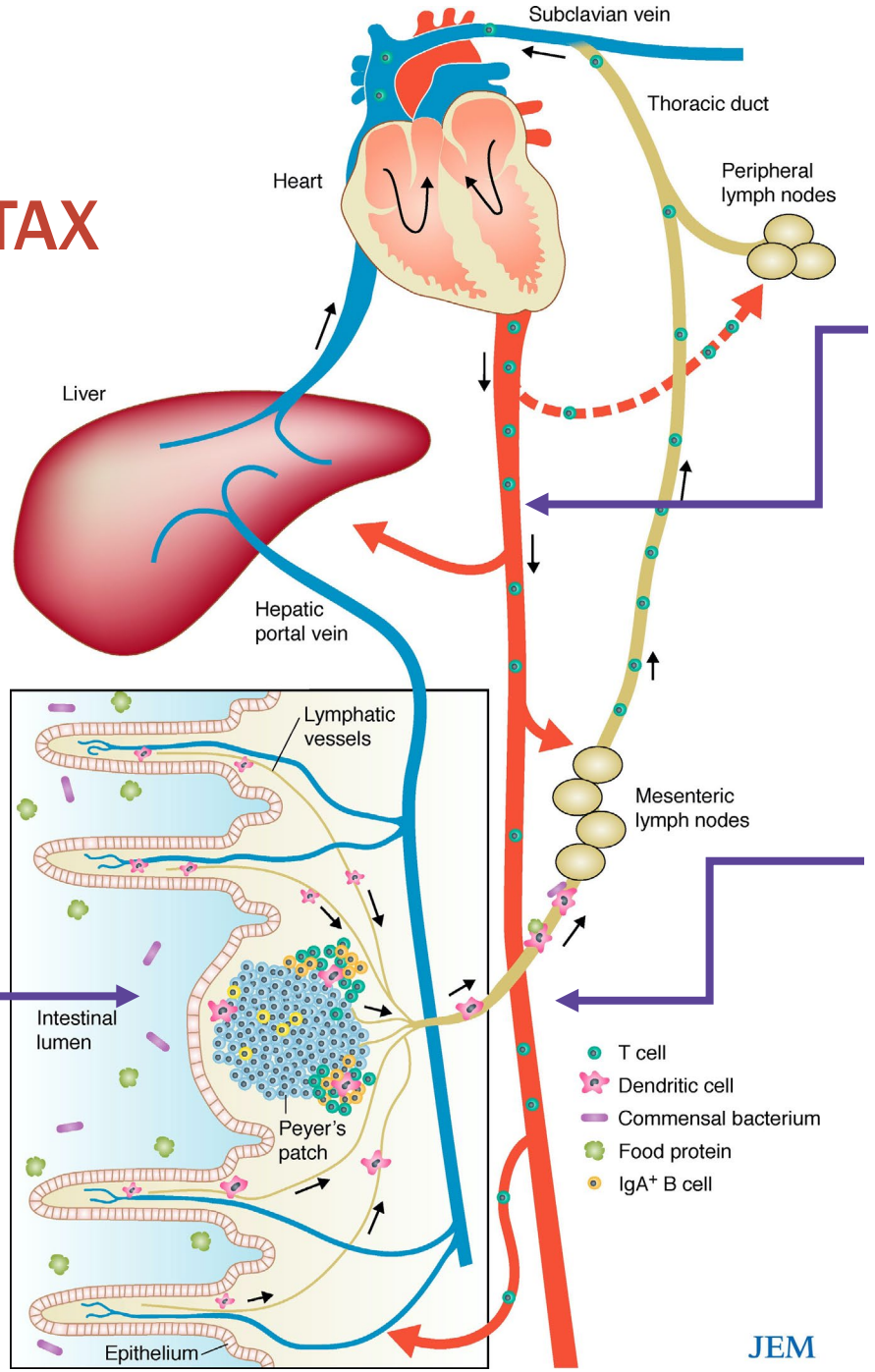
- 10-20% of the gut surface area
- Limited range of specialized cells
- Contains ~99.99% of the gut microbiome

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 the 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

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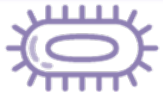
JEM

A new class of oral medicines which act in the small intestine with systemic effects

Evelo product candidates are composed of orally delivered, gut-restricted single strains of non-replicating and non-colonizing microbes and microbial extracellular vesicles. Effects are believed to be driven by recognition of structural motifs by host immune cells in the small intestine.

Whole, inactivated microbes 

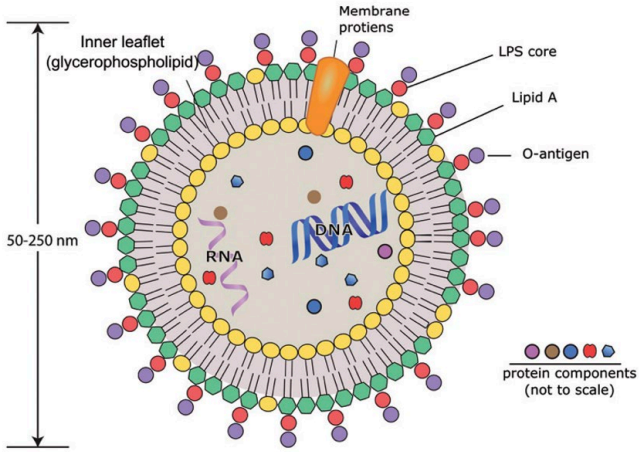
- Non-replicating, non-colonizing, and gut restricted
- Biomarkers show inflammation resolution without immunosuppression

Extracellular Vesicles 

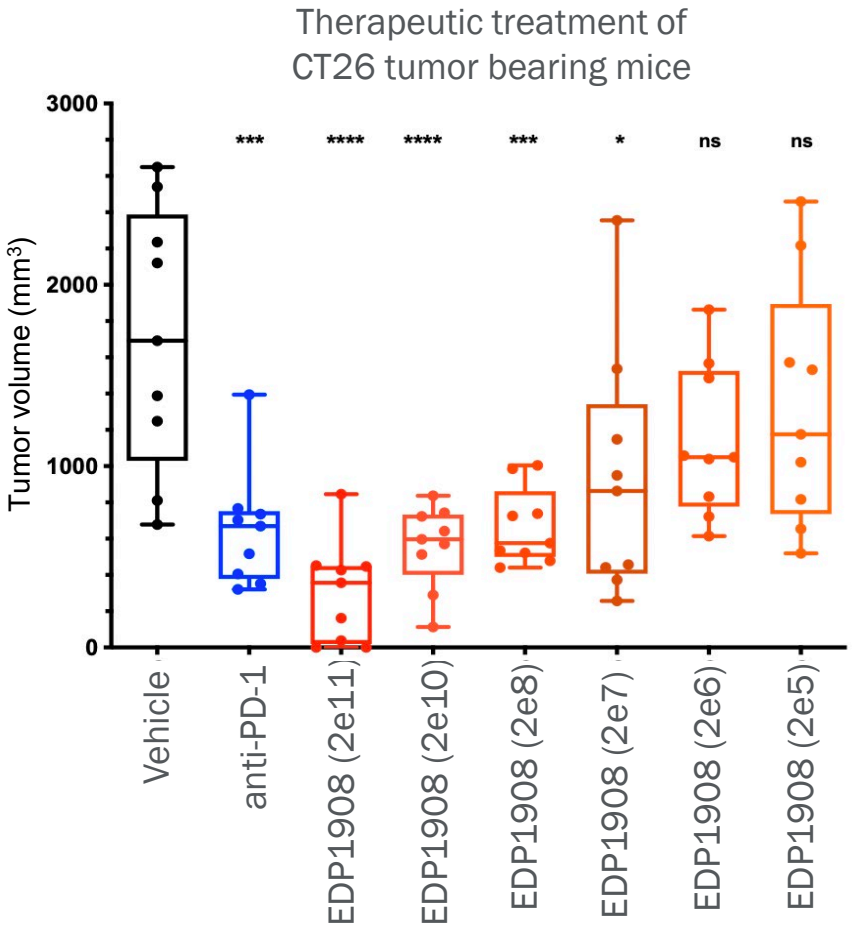
- Lipoprotein nanoparticles naturally produced by some bacteria- macromolecular content is a subset of the parent; non-viable
- 1/1,000th volume of whole microbes enabling increased target engagement
- Potent efficacy in oncology and inflammation pre-clinical models
- Initiation of clinical development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

EVs represent a potential new immuno-oncology treatment

EVs have potential in oncology across all stages of disease and may be well suited for synergistic combinations with checkpoints and therapies which augment neoantigen exposure



Anand et al 2017



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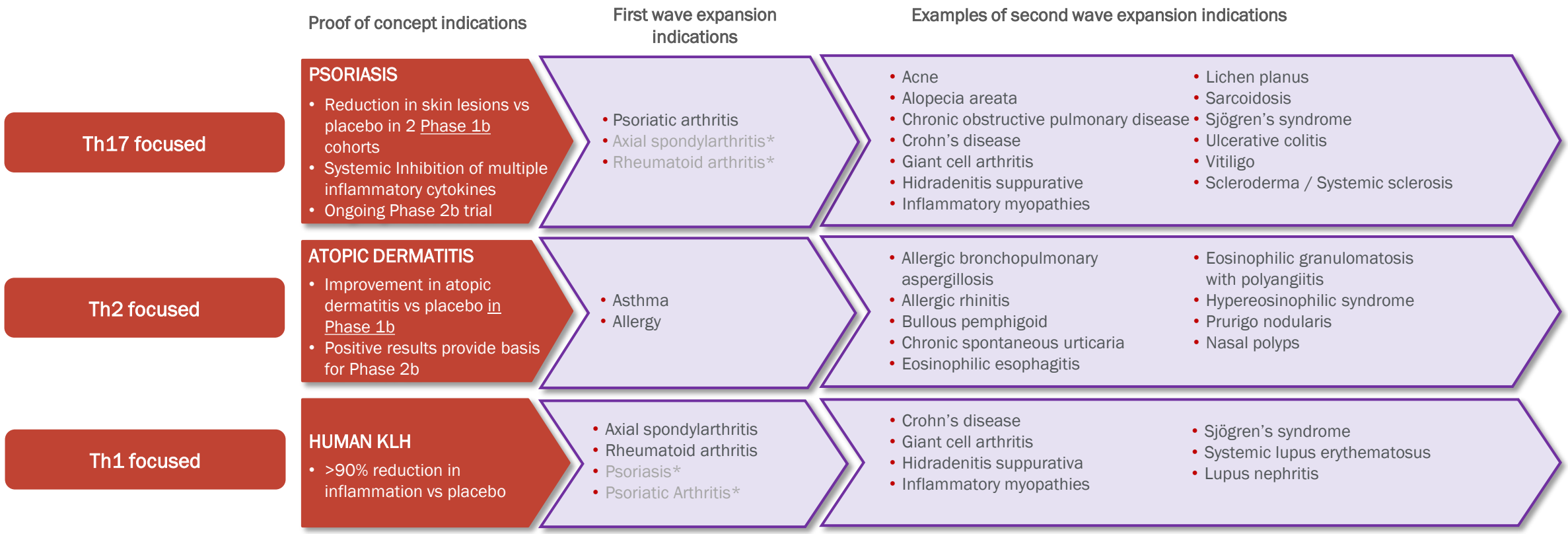
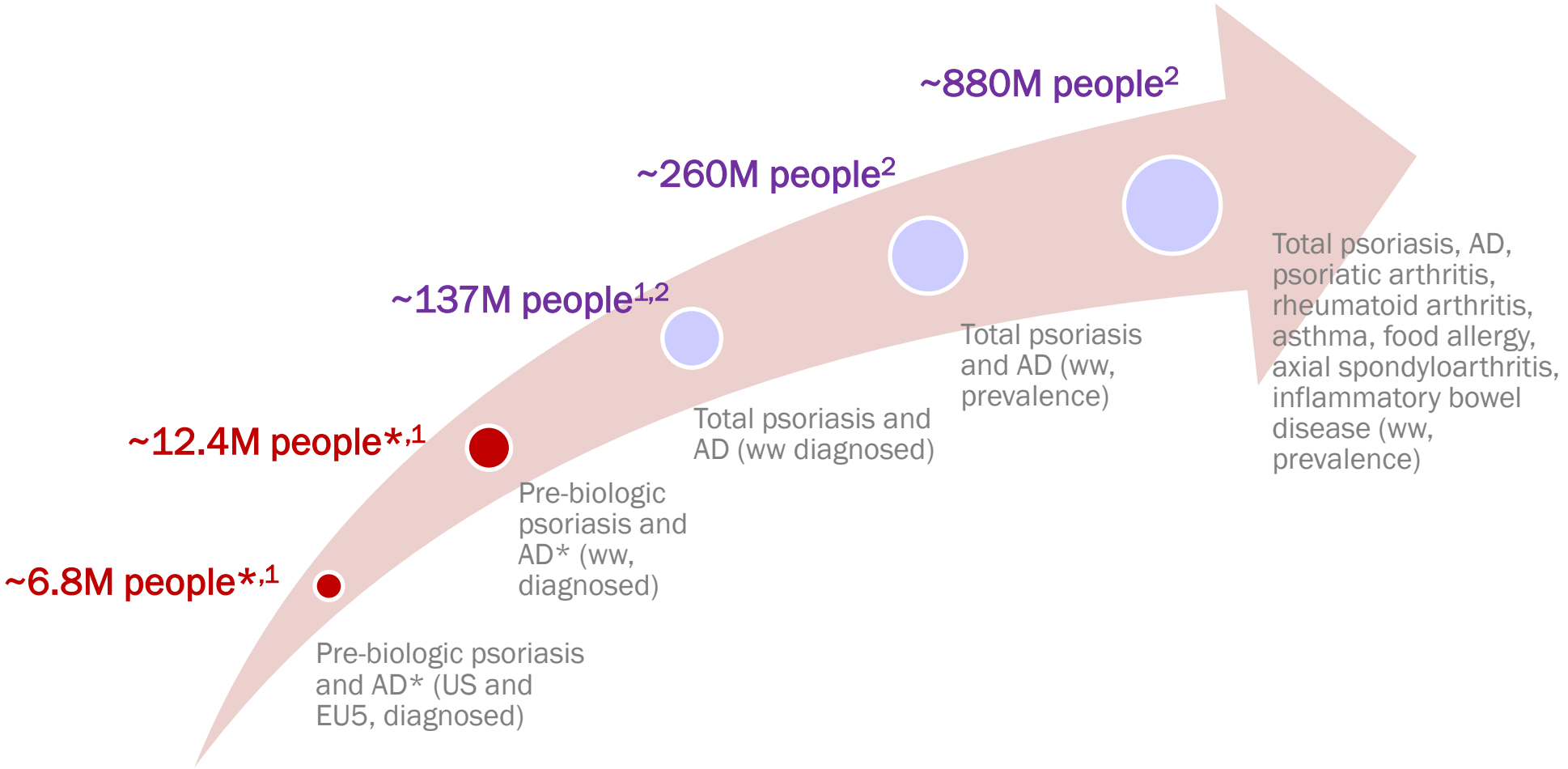
The Opportunity

SINTAX medicines show potential application across spectrum of inflammatory diseases - plan to capture full breadth in staged manner



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

Significant opportunity for SINTAX medicines on a global basis across inflammatory diseases



** 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*

Pipeline & Catalysts

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

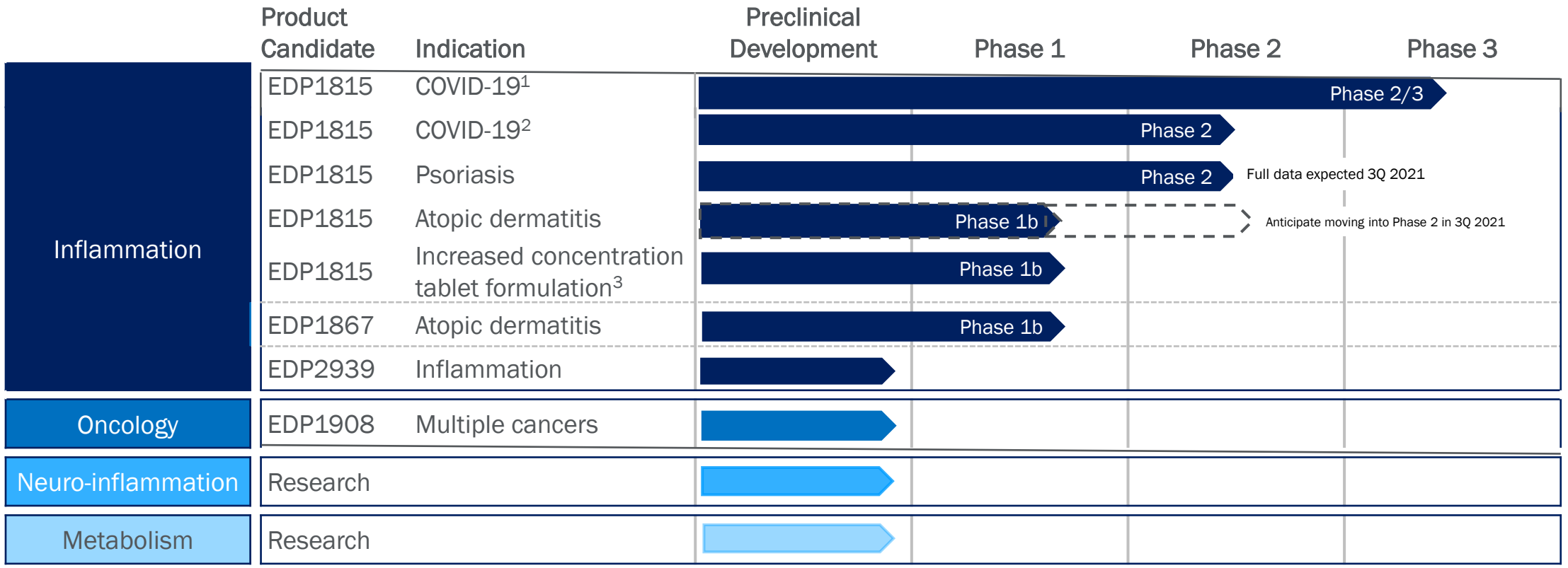
TACTIC-E: Phase 2/3 Platform Trial

- 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
- Interim safety data and completion of futility analysis expected in 2Q 2021

Manufacturing plans expedited; potential to rapidly scale production to supply drug at reasonable cost in 2021

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

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] Evelo is conducting Phase 1b studies on increased concentration and tablet formulations of EDP1815

Pipeline is rich in anticipated near-term clinical catalysts

Candidate	Catalyst
EDP1815 Psoriasis	3Q 2021: Full Phase 2b data 3Q 2021: Data from Phase 1b cohorts with tablets and capsules
EDP1815 Atopic dermatitis	3Q 2021: Phase 2 initiation 1Q 2022: Phase 2 interim data
EDP1867 Atopic dermatitis	4Q 2021: Phase 1b data
EDP2939 Inflammation	2022: Initiation of clinical development
EDP1908 Oncology	2022: Initiation of clinical development

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