EVELO

Harnessing the Small Intestinal Axis to Resolve Inflammation

Evelo Corporate Presentation

April 2023

Legal Disclaimer

This presentation contains forward-looking statements, including 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 without limitation statements concerning the development of EDP1815 and EDP2939, the promise and potential impact of our product candidates, the timing of and plans for clinical studies, and the timing and results of clinical trial readouts.

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: we have incurred significant losses, are not currently profitable and may never become profitable; our projected cash runway; our need for additional funding; our ability to meet our debt obligations (including restrictive and operational covenants and terms of refinanced debt); our ability to cure or satisfactorily resolve any default arising from our debt agreements; our limited operating history; our unproven approach to therapeutic intervention; our ability to address regulatory questions and the likelihood of regulatory filings and approvals; 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 operate with a reduced workforce, to manage potential growth and to retain key personnel, particularly following a significant downsizing; 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; the impact of the COVID-19 pandemic on our operations, including our preclinical studies and clinical trials, and the continuity of our business; and securities class action litigation against us.

These and other important factors discussed under the caption "Risk Factors" in our Annual Report on Form 10-K for the fiscal year ended December 31, 2022, and our other reports filed with the United States Securities and Exchange Commission, could cause actual results to differ materially from those indicated by the forward-looking statements made in this press release. Any such forward-looking statements represent management's estimates as of the date of this press release. 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.

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The primary immune role of the small intestine is to prevent inflammatory responses to the contents of the gut

This previously overlooked biology can be harnessed with a novel type of oral medicine to resolve inflammation broadly

Biology

The gut is an immune organ. The **small intestinal axis (SINTAX)** governs *systemic* inflammation

Modality

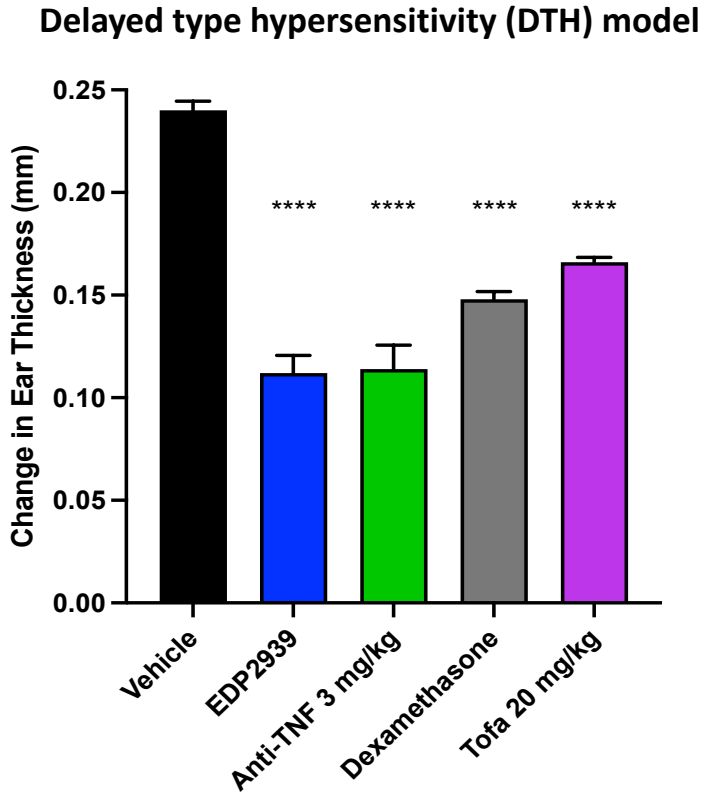
Extracellular vesicles (EVs) from microbes engage these mechanisms to modulate systemic immunity

Orally administered EVs are a simple and practical approach to **to resolve systemic inflammation via regulatory T cells**

Potential benefit across of all stages of multiple inflammatory diseases

Extracellular vesicles are a potential new class of oral medicine

- EVs are naturally shed by commensal microbes isolated from the mucosal surfaces of the small intestine
- When orally administered, EVs physically engage with immune cells in the small intestine, ultimately leading to the generation and mobilization of CD4+ regulatory T cells.
- These regulatory T cells circulate throughout the body and have the potential to drive inflammation resolution without immunosuppression, overcoming limitations of current anti-inflammatory drugs.

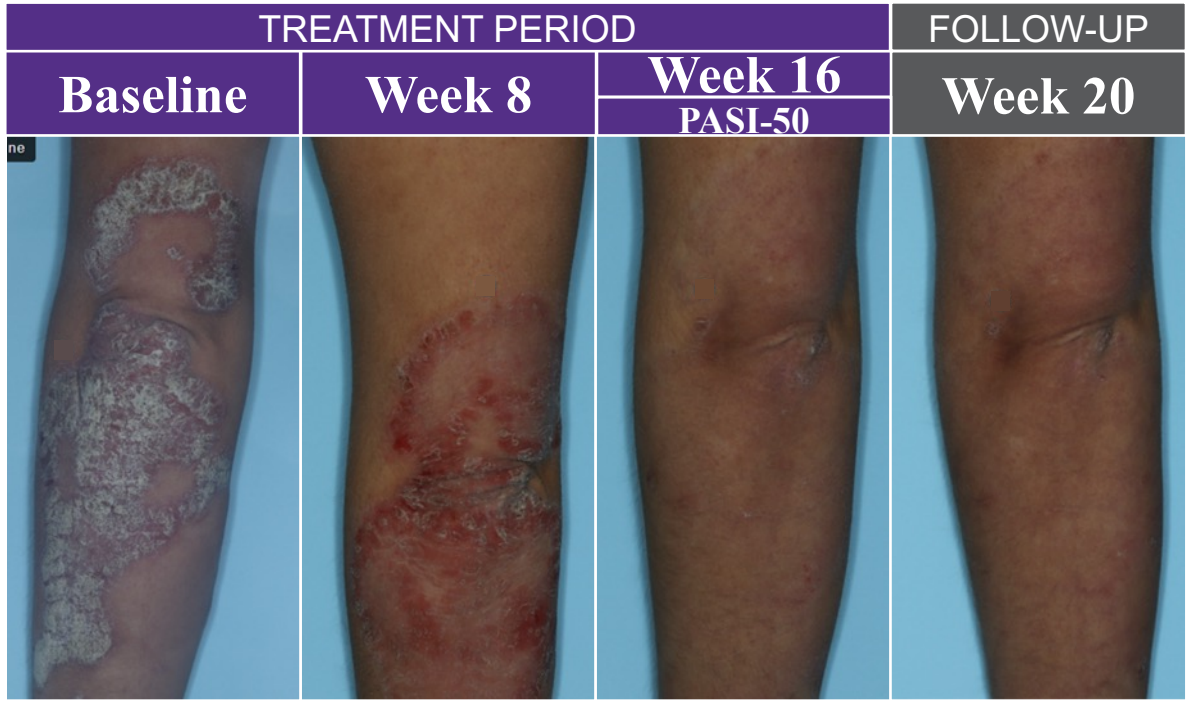


Lead EV candidate, EDP2939, demonstrated similar activity preclinically to standard anti-inflammatory medicines

Positive Phase 2 data with first generation candidate; potential for increased activity with 2nd generation EV candidate

Positive proof of concept Phase 2 data validate SINTAX and its therapeutic potential

Next generation extracellular vesicles (EVs) show increased preclinical potency



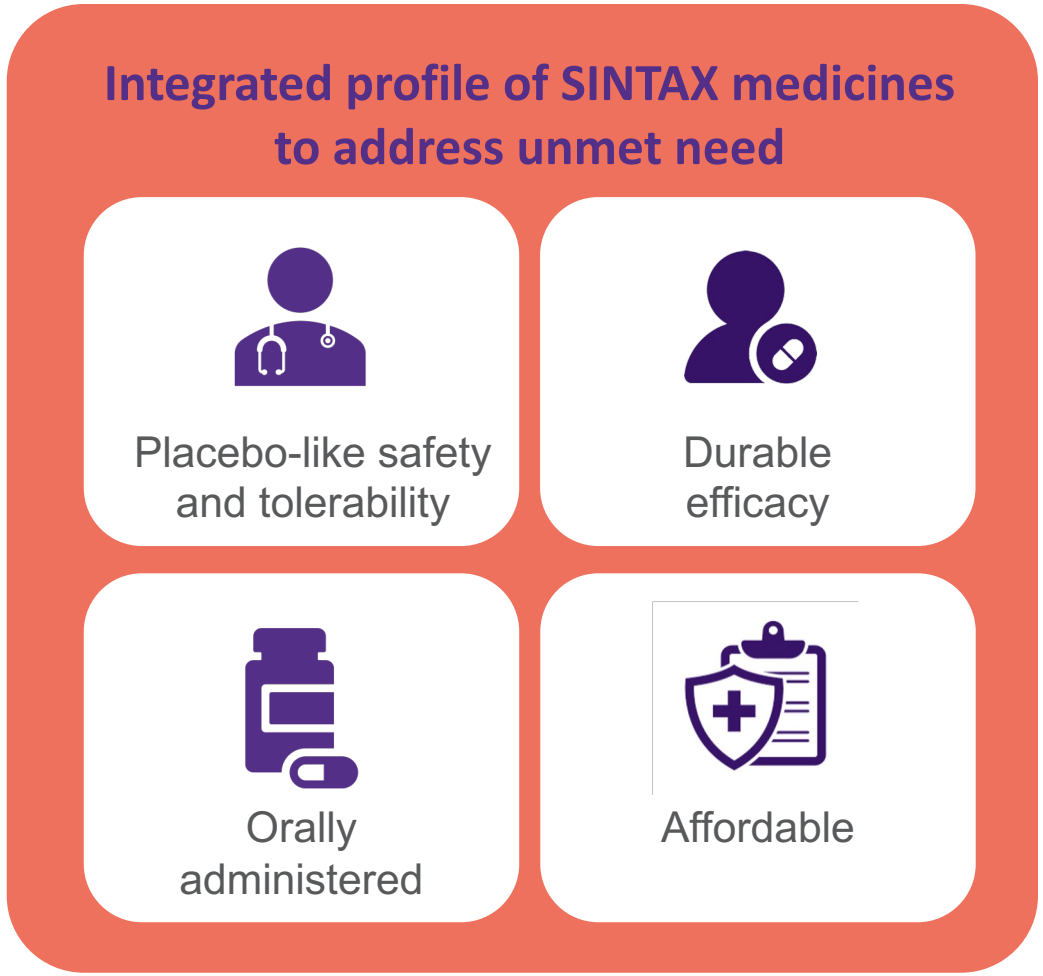
Patient with moderate psoriasis enrolled in Phase 2 trial who achieved PASI-50 response at week 16 on EDP1815 – skin lesions improved further at week 20

- The ability to isolate and deliver pharmaceutically active EVs in a more efficient and concentrated form enables a new type of highly potent SINTAX medicine.
- EDP2939 is a 2nd generation product candidate that is a pharmaceutical composition of EVs produced by the same strain of bacteria as in EDP1815.
- EDP2939 has potential for increased clinical activity to enable use across severity spectrum.

EDP2939 is in a Phase 2a study in moderate psoriasis with readout expected in early 4Q 2023

Unique profile may enable foundational use across the spectrum of disease severity, beginning in psoriasis

- Most patients suffering from inflammatory diseases are undertreated or not treated at all due to the limitations of treatments that are currently available
  - These include safety and tolerability concerns, route of administration, and high price.
- Clinicians view anticipated potential integrated profile of SINTAX medicines – effective, safe and well tolerated, orally administered, and affordable – as attractive and supportive of broad use if approved.
- This profile could address one of the largest unmet needs in global healthcare: the ability to treat all stages of many inflammatory diseases.

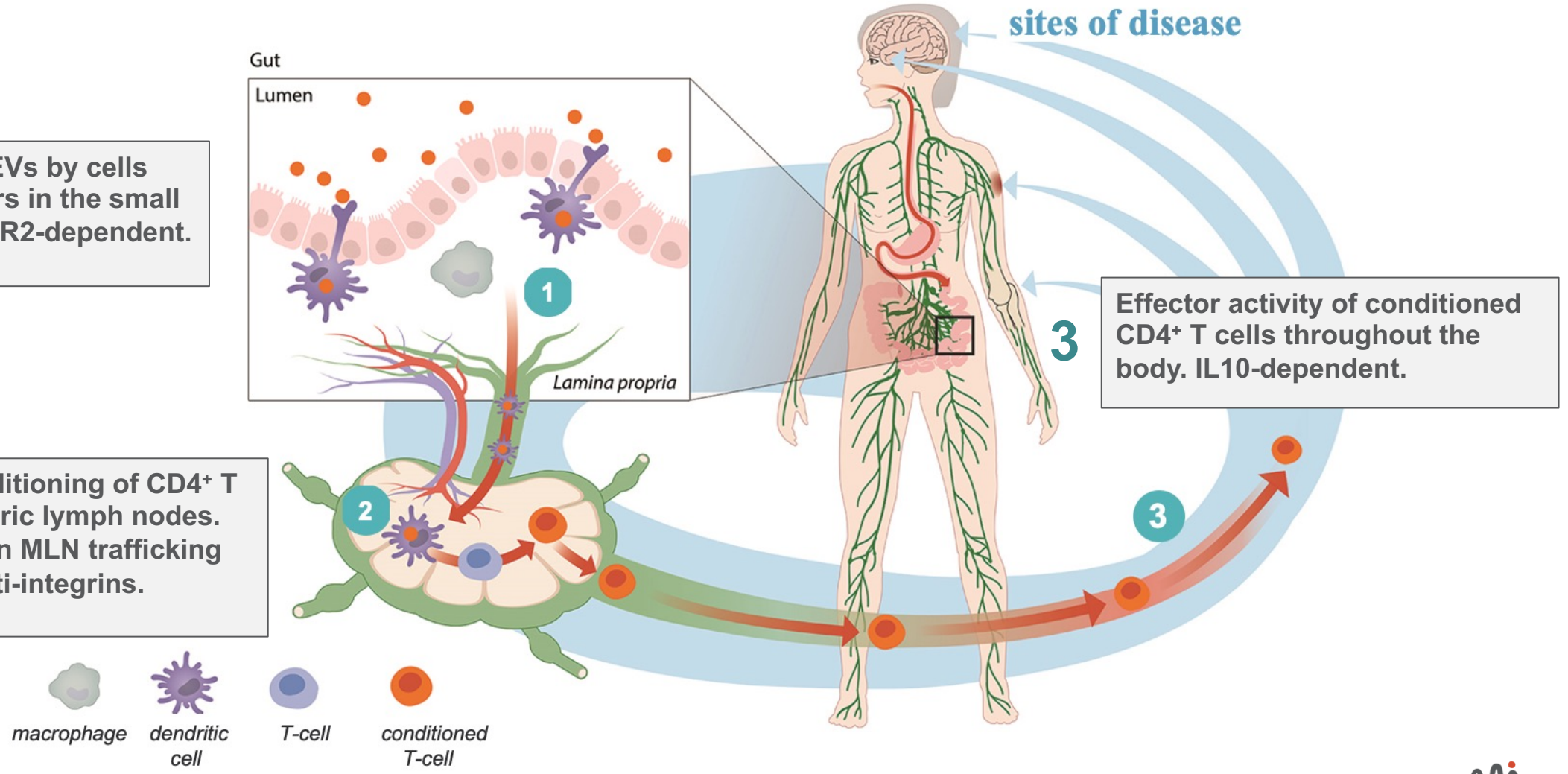


Three step model of regulatory T cell induction by EVs

1 Sensing of EVs by cells and receptors in the small intestine. TLR2-dependent.

2 Regulatory conditioning of CD4⁺ T cells in mesenteric lymph nodes. No efficacy when MLN trafficking blocked with anti-integrins.

3 Effector activity of conditioned CD4⁺ T cells throughout the body. IL10-dependent.



1. Opportunity and unmet need

2. Clinical validation of SINTAX with EDP1815

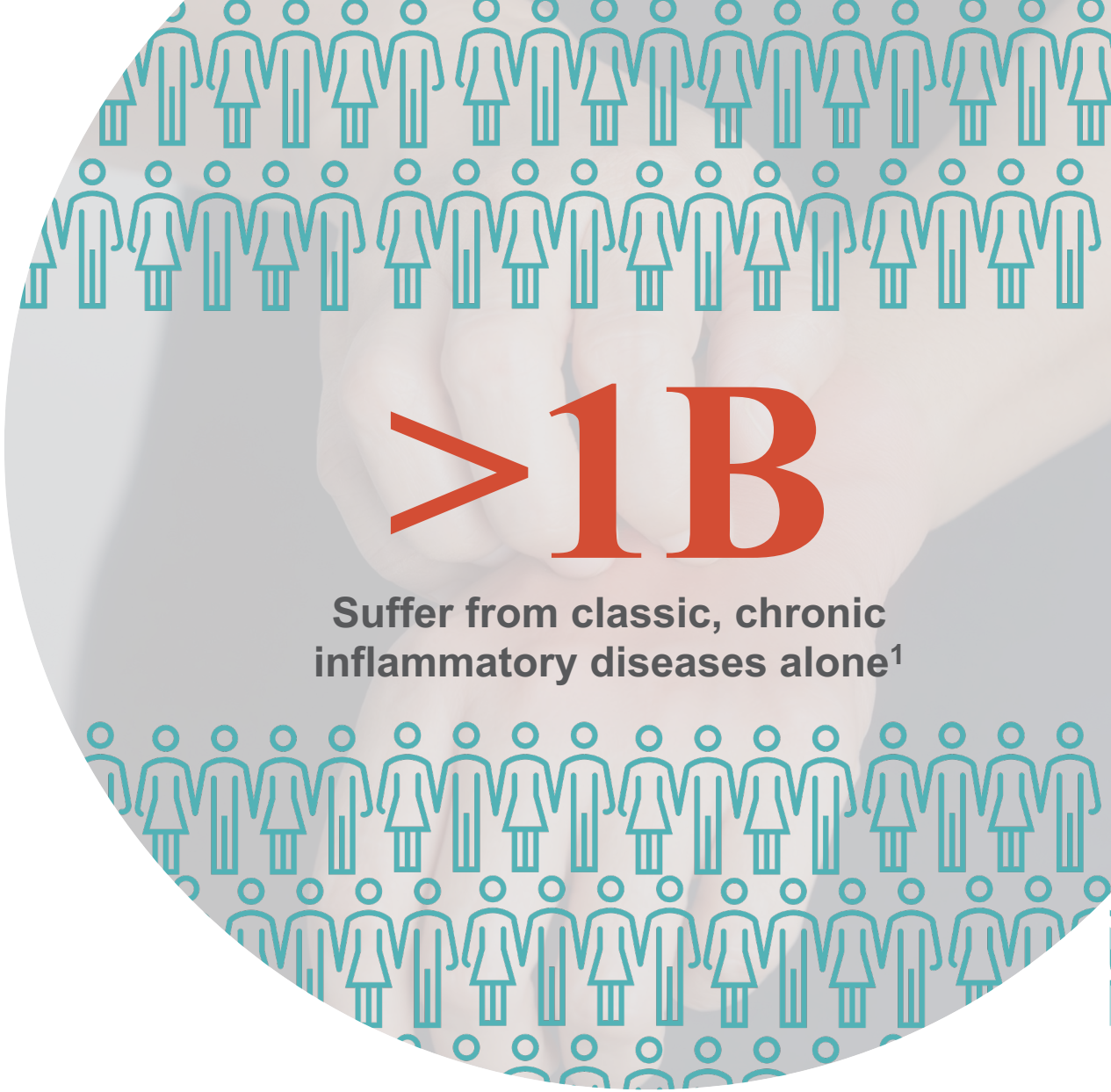
3. EDP2939 MOA and plan in psoriasis

4. Broad opportunity of EV platform

Chronic Inflammation Impacts Billions of People Worldwide

SINTAX Medicines Impact Multiple Inflammatory Pathways, Unlocking Potential Across A Broad Range of Inflammatory Diseases

- Psoriasis
- Psoriatic arthritis
- Atopic dermatitis
- Rheumatoid arthritis
- Asthma
- Food allergy
- Axial spondylarthritis
- Inflammatory bowel disease



[1] Datamonitor Healthcare, accessed Feb 2020

Major unmet need in psoriasis is in the majority population of mild and moderate patients

Majority (93%) of patients have mild or moderate disease[1]

55M Worldwide prevalence
8.6M U.S. prevalence
6.7M U.S. diagnosed

MORE THAN
92% in the US do not receive injectable antibody therapies or oral systemics[2-7]

[1]Datamonitor Healthcare, Vanderpuyre-Orgle et al. J Am Acad Dermatol. 2015: 72:961–7
[2]IQVIA and Symphony Health Data [3]Datamonitor Healthcare, accessed June 2021. [4]Armstrong A, et al., Dermatol Ther (Heidelb). 2017 Mar; 7(1). [5]IQVIA Prescription data from Analyst Report, Oct 2020. [6]DRG Epidemiology Database 2017 [7]Lebwohl MG, et al., J Am Acad Dermatol. 2014 May;70(5):871-81.e1-30.

No effective, safe, well-tolerated, oral, and affordable medicine for psoriasis patients

>50% of patients are dissatisfied with current treatment options[*]
Same challenges with newly approved or future PsO products

Topicals

- Topical corticosteroids, Topical calcineurin inhibitors
- New Topicals: JAKs, VTAMA (tapinarof) and ZORYVE (roflumilast)
- Not convenient
- Low compliance
- No impact on systemic inflammation

Old-School Systemics

- Methotrexate and cyclosporine:
  - Safety concers
  - Monitoring requirement
  - Immunosuppressant

Oral Immunosuppressant

- Otezla (apremilast):
  - GI tolerability issues
  - High price
- JAK inhibitor class
  - Negative safety halo w/ black box warning
  - High Price

Injectable Biologics

- Not convenient & needle fear
- Immunosuppressant
- High price

[*] Armstrong AW, et al.. National Psoriasis Foundation surveys, 2003-2011

KOLs, community dermatologists view integrated profile as attractive

Broad use expected based on proof-of-concept EDP1815 profile, with potential for EDP2939 to be even better

Novel mechanism of action has the potential to transform the treatment of inflammatory diseases
Bruce Strober

A product with such a benign safety/tolerability profile will get a lot of use
-US Community Derm

This could be an ideal 1st line, combination or maintenance therapy
Clive Liu

EDP1815 could be used on all psoriasis patients
-EU Derm KOL

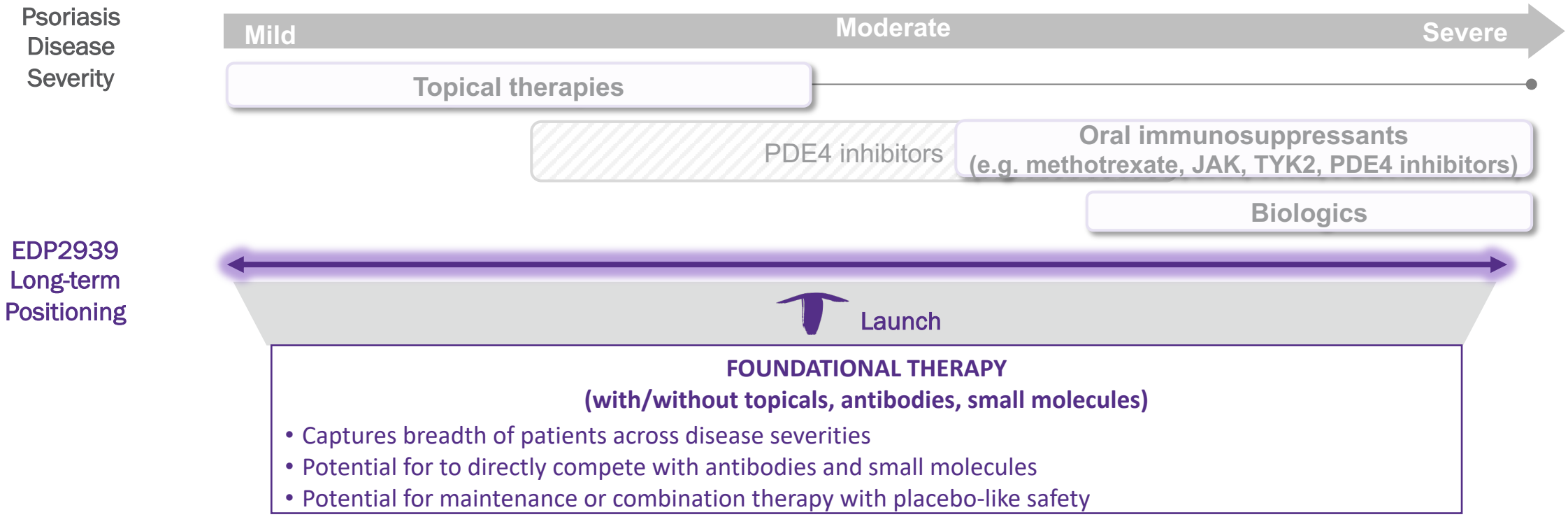
My patients have limited access to innovative therapies . . . affordability will drive use
-US Community Derm

I want everyone in the room to take a moment and realize that this is one of those moments and scientific breakthroughs to remember
Andy Blauvelt, AAD 2022 Late Breaker Session

The science is a game changer
-US Derm KOL

*Quotes from expert encounters at Dermatology congresses and those collaborating with Evelo based on EDP1815 Phase 2 data; EDP2939 has potential for significantly improved clinical efficacy

With even greater efficacy, EDP2939 could become a foundational therapy across the psoriasis spectrum if approved



1. Opportunity and unmet need

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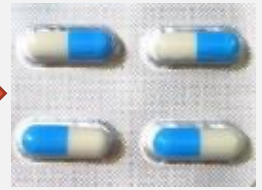
EDP1815 and EDP2939 are products of the same single strain of *Prevotella histicola* from the duodenum of a human donor

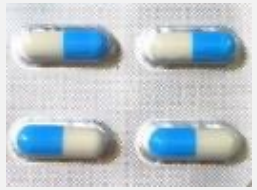
Fermenter

Centrifuge

EDP2939: Supernatant
P. histicola extracellular vesicles (EVs)

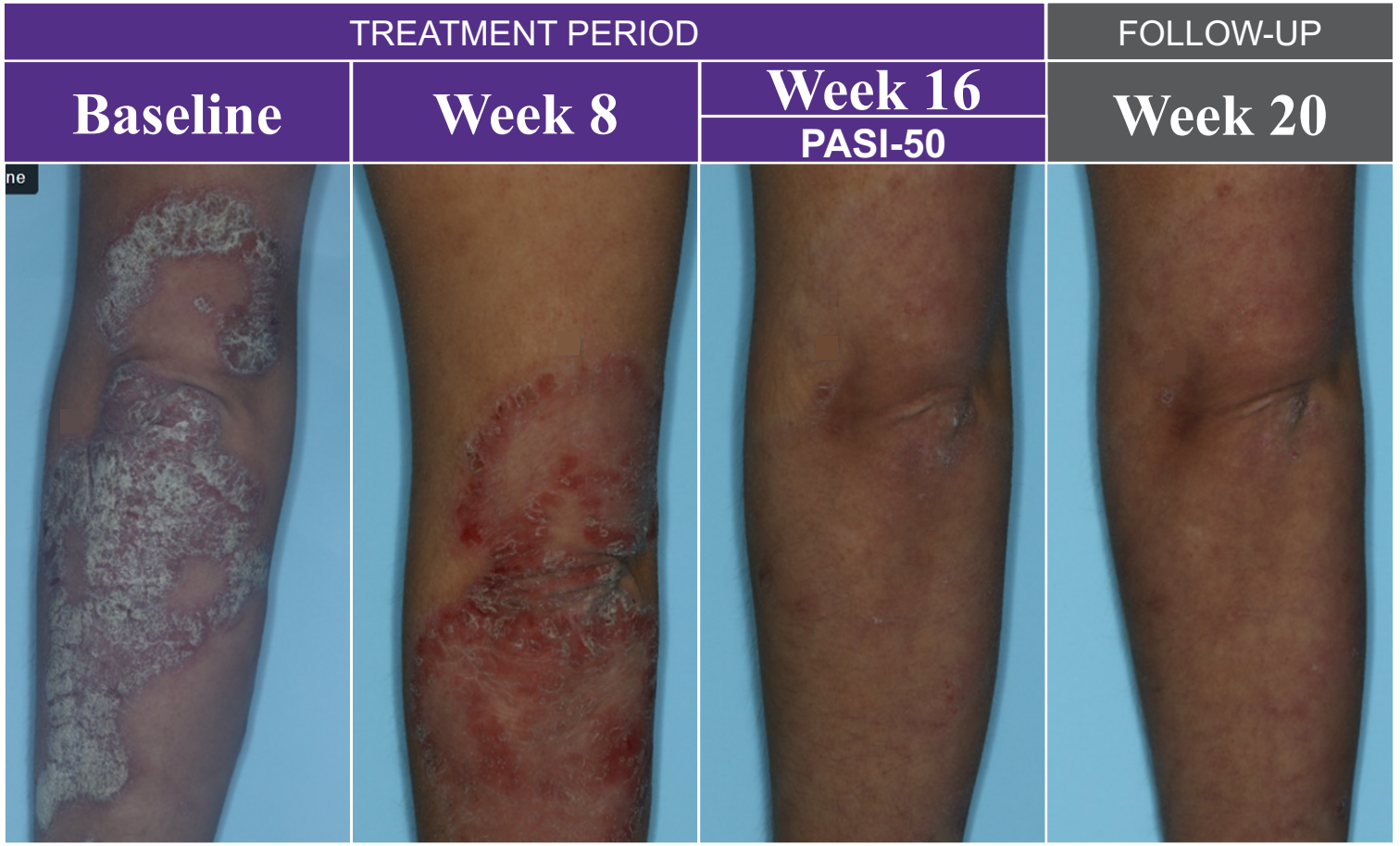


EDP1815: Pellet
Non-viable *P. histicola* cells and EVs



EDP1815 proof-of-concept Phase 2 data in psoriasis validates the systemic impact of SINTAX in humans

- EDP1815 was well-tolerated with durable, deepening clinical efficacy in post-treatment period
- EDP1815 drug substance contains high EV content
- EDP2939 has the potential to build upon this efficacy while maintaining the target integrated profile of an oral, safe and affordable product candidate



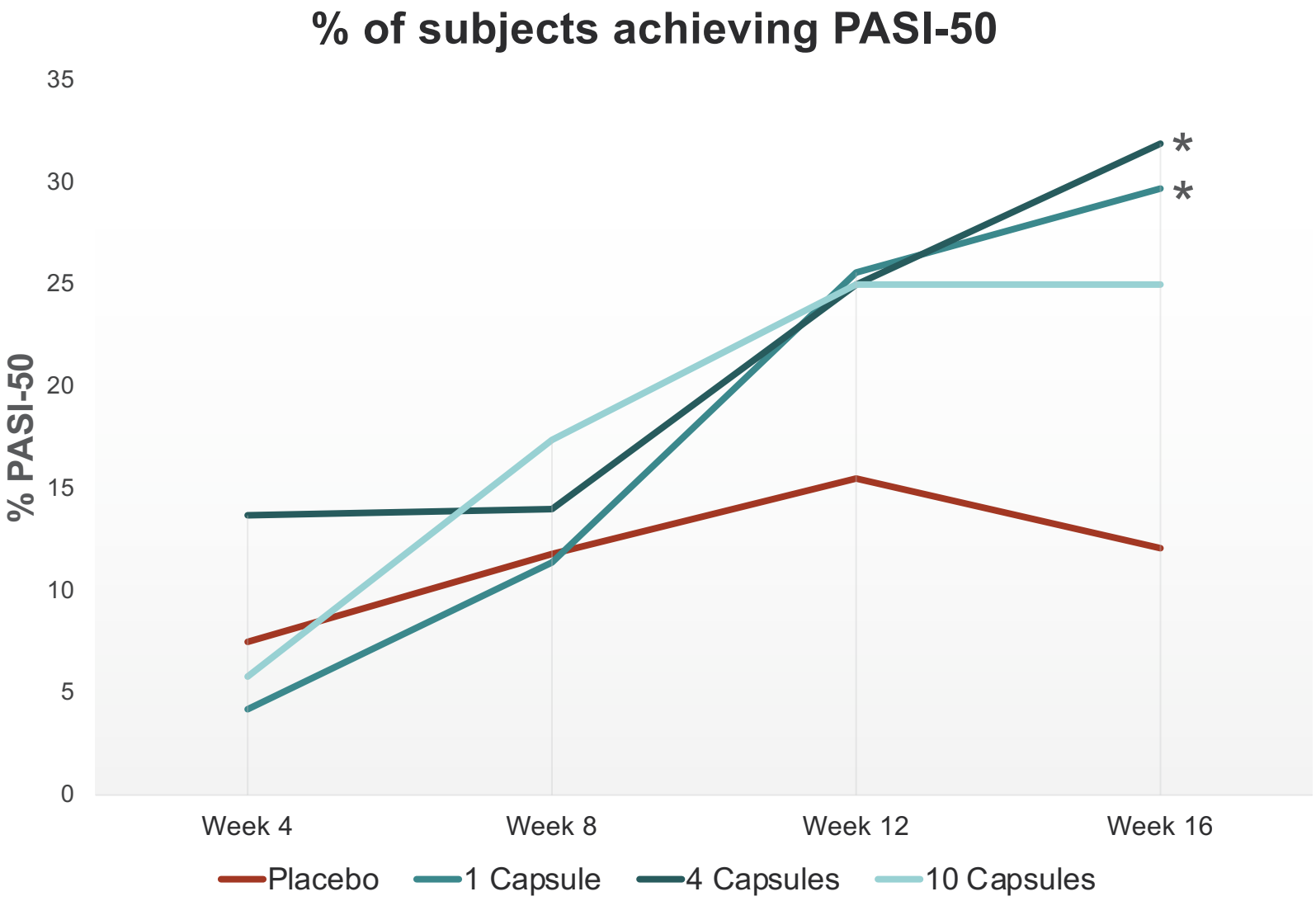
Patient with moderate psoriasis enrolled in Phase 2 trial who achieved PASI-50 response at week 16 on EDP1815 – skin lesions improved further at week 20

EDP2939 delivers the active substance of EDP1815 in a more concentrated form to enable potentially greater activity

Robust PASI-50 responses with EDP1815 at week 16

Statistically significant p-value (<0.05) for 2 of the 3 individual dose cohorts, and for all 3 cohorts when pooled

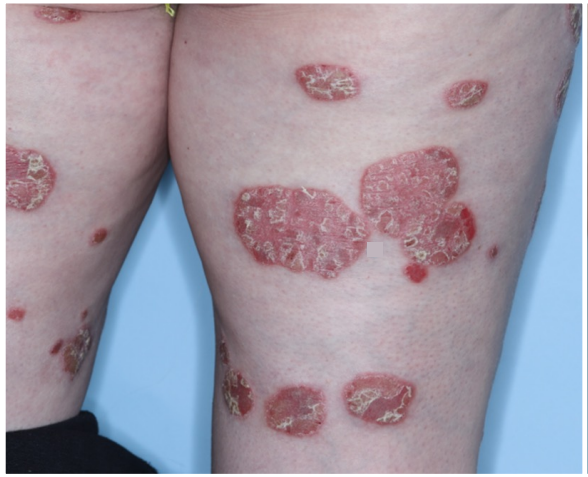
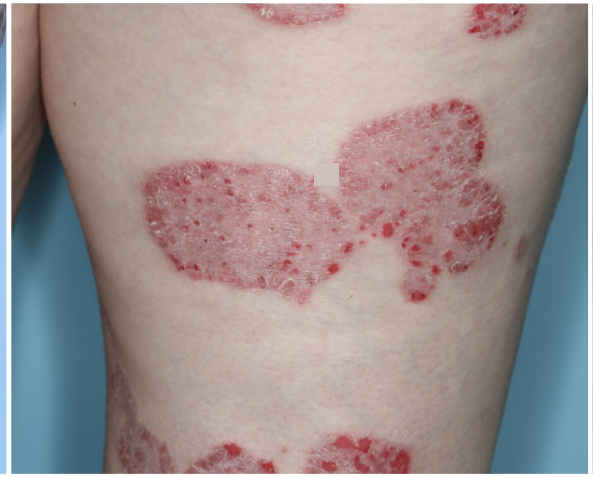
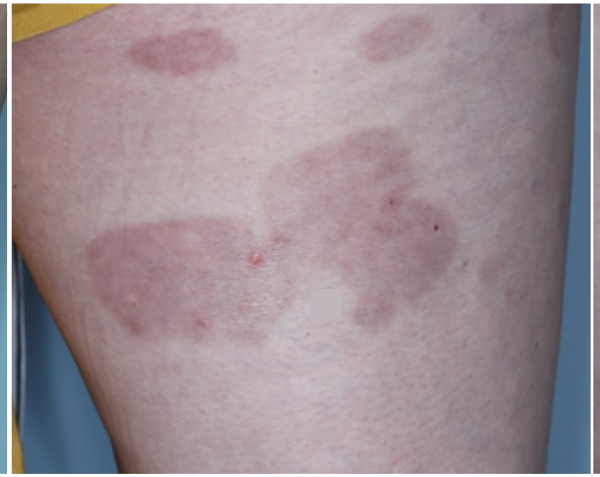
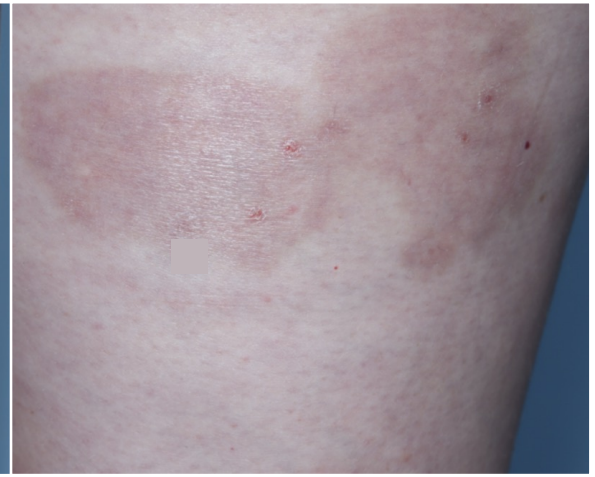
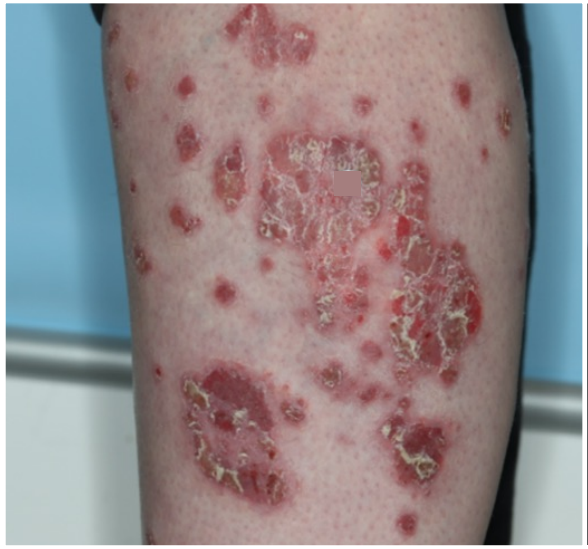
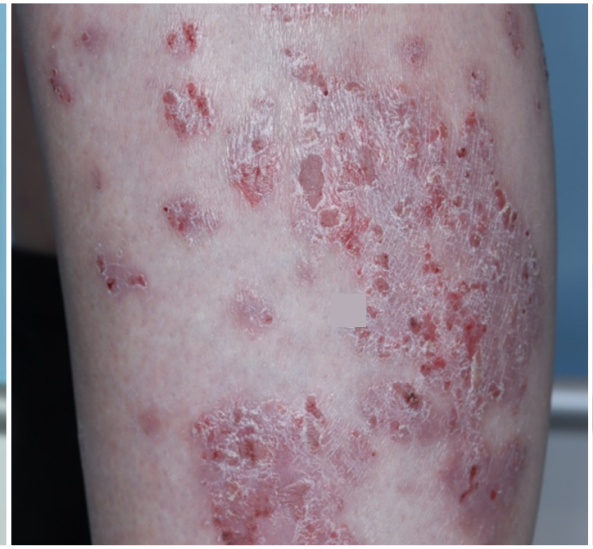
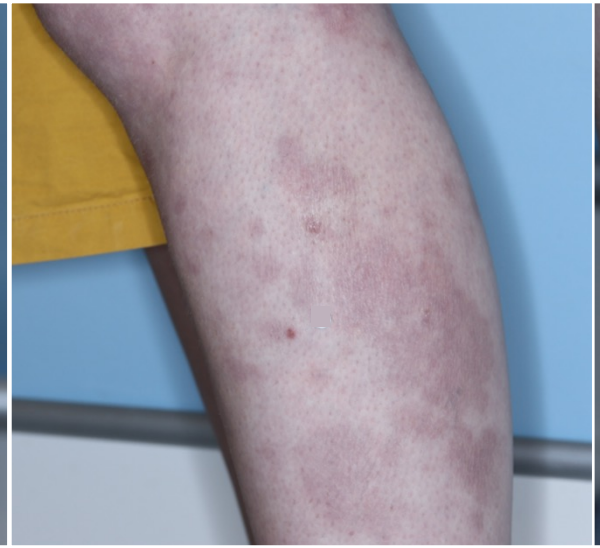
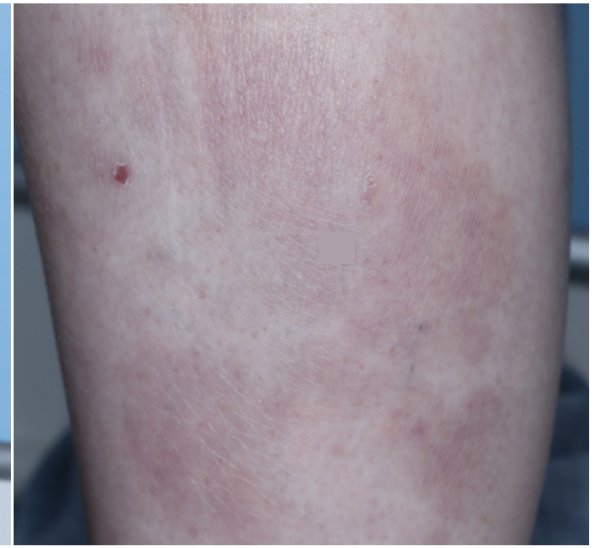
Durability and deepening of clinical responses observed in 24-week post-treatment period



***p<0.05**

Data from Phase 2 study on EDP1815 in mild-to-moderate psoriasis (n=249)

Some Patients Achieved PASI-90 at Week 16 With Further Improvement Post Treatment

TREATMENT PERIOD			FOLLOW UP
Baseline	Week 4	Week 16 PASI-90	Week 20
			
			

Safety and tolerability of EDP1815 comparable to placebo during 16-week treatment and 24-week post-treatment period

- ***No*** *related serious adverse events*
- ***No*** *evidence of drug-induced flares or disease rebound*
- ***No*** *meaningful difference in GI-related AEs compared to placebo*

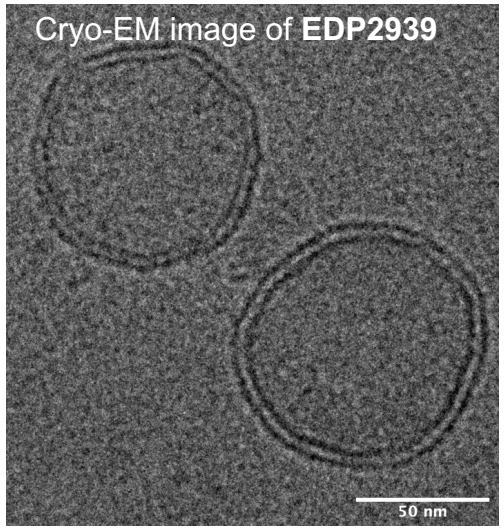
1. Opportunity and unmet need

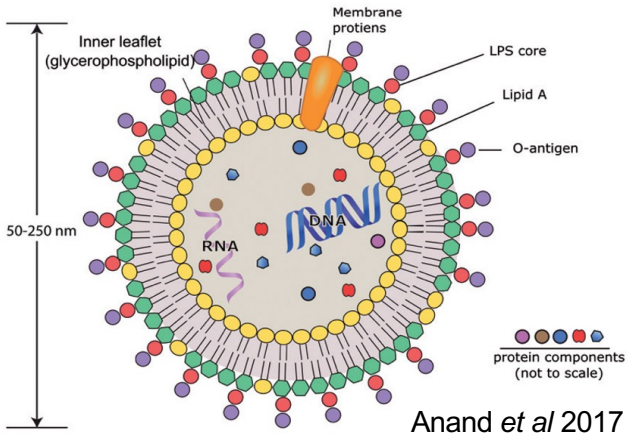
2. Clinical validation of SINTAX with EDP1815

3. EDP2939 MOA and plan in psoriasis

4. Broad opportunity of EV platform

Bacterial EVs are natural lipid nanoparticles which have evolved to modulate inflammation through interaction with host receptors





Anand *et al* 2017

EVs are natural lipid nanoparticles shed by most bacteria that enable cell-cell communication

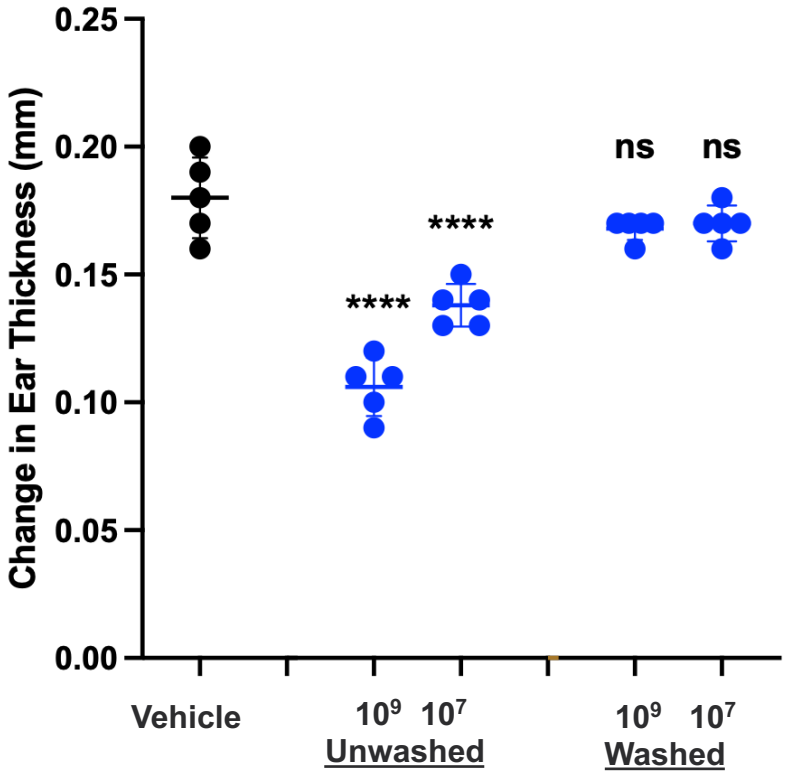
1/1000th volume of parent cell

Lipoprotein and glycoprotein displayed on the vesicle surface drive regulatory T cell induction by action in the small intestine

Small size and diffusion properties potentially enable greater SINTAX activation for greater efficacy

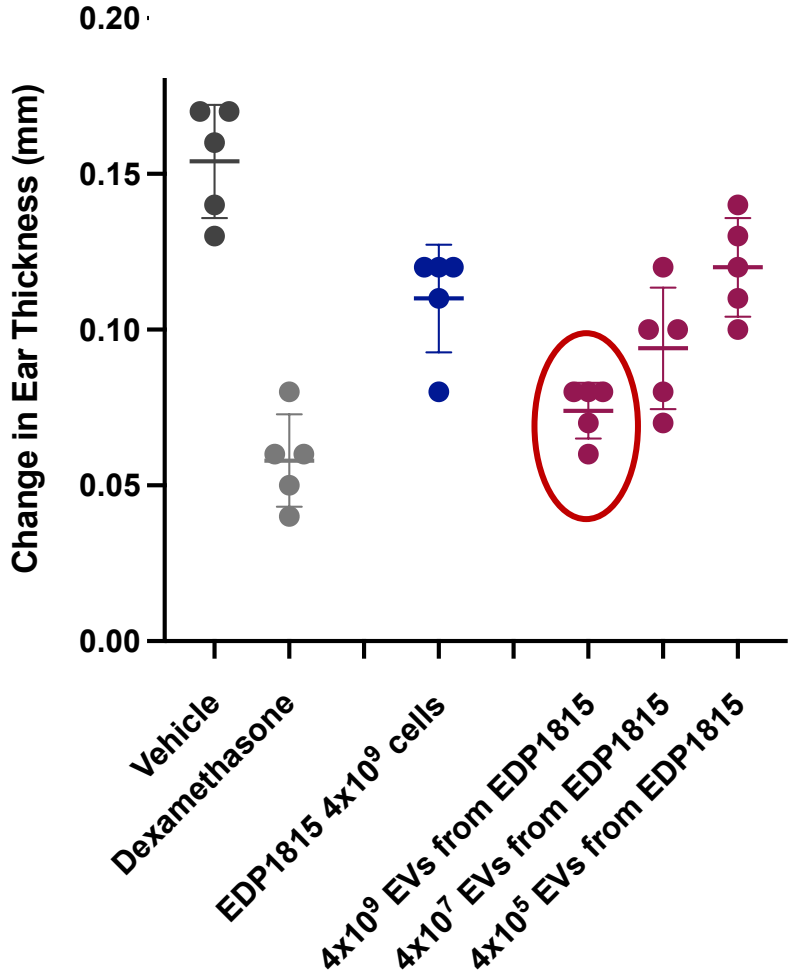
EDP1815 includes EVs - EVs showed more potent activity when isolated

Washing EDP1815 removed DTH efficacy from residual bacterial cells



EDP1815 cell number dose

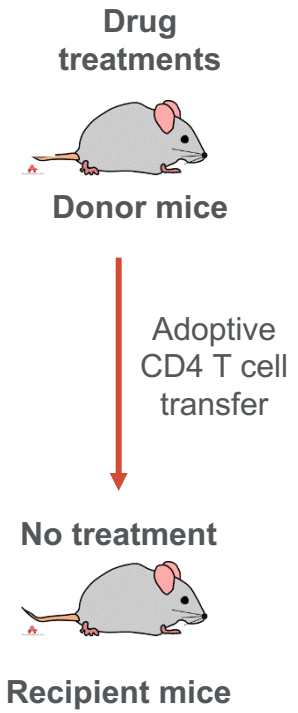
EVs recovered from EDP1815 were active in mouse DTH

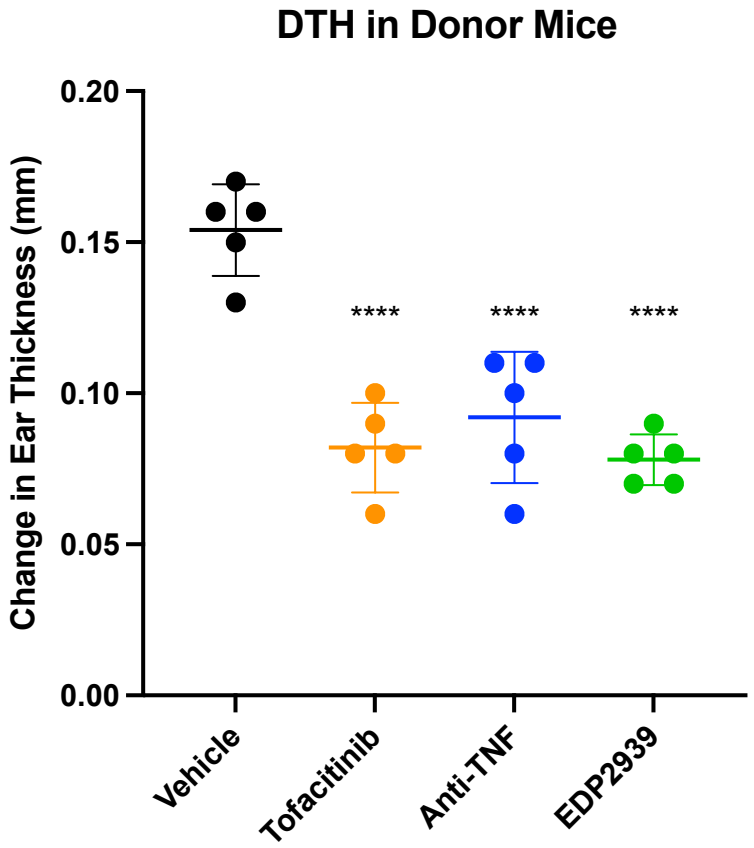


EDP1815 4 x 10^9 cells contains ~ 8 x 10^{10} EV particles.

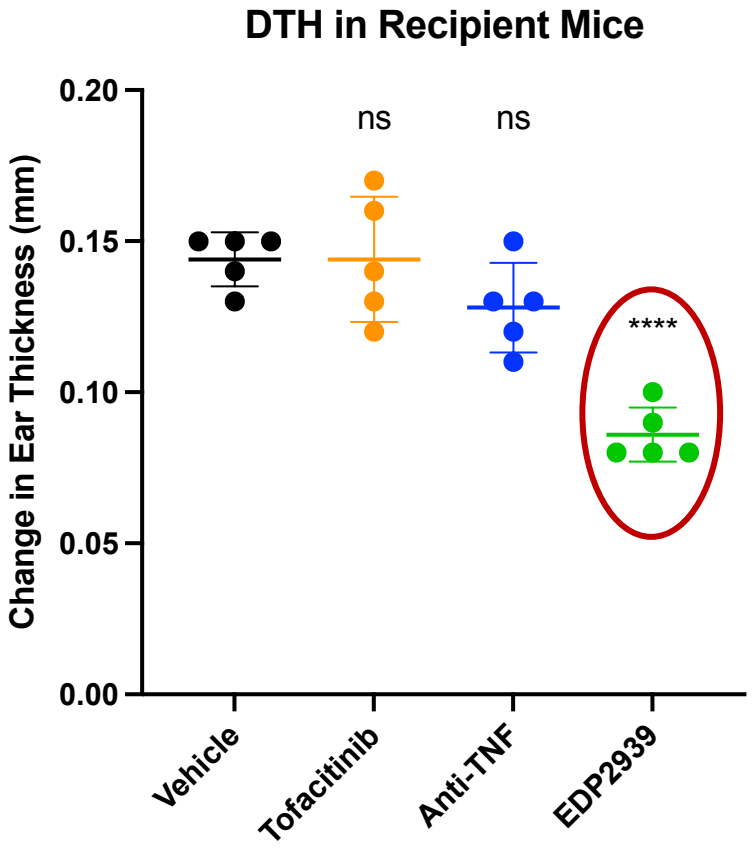
In this experiment the EVs re-isolated from EDP1815 drug substance had orders of magnitude higher specific activity and higher maximal anti-inflammatory effect.

EDP2939 showed similar results to standard anti-inflammatory medicines with its distinct regulatory T cell mechanism





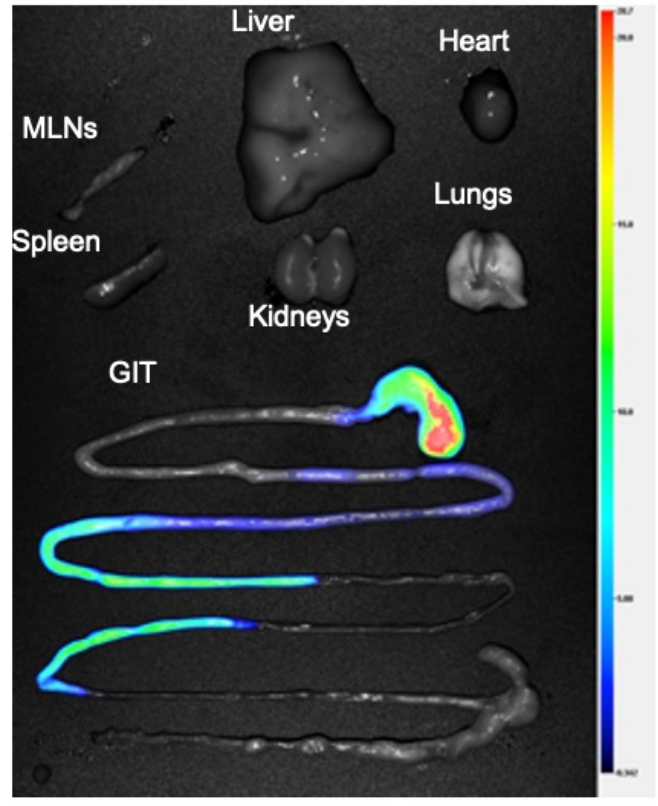
In donor mice EDP2939 matched standard of care anti-inflammatories



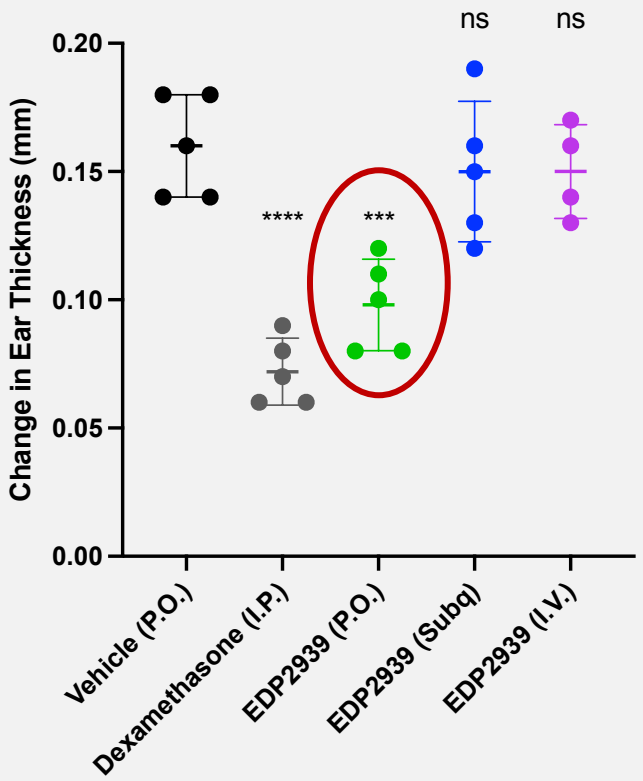
Only EDP2939 generated CD4⁺ T cells that inhibited inflammation in recipients

The systemic effect of EDP2939 is dependent on signaling in the gut

Biodistribution



Mouse DTH



- Orally delivered EDP2939 is not detected outside the GI tract
- Only oral administration is efficacious preclinically
- No effect of systemic exposure s.c. or i.v.

EVs represent a major potential clinical advance in treating inflammatory diseases

Regulatory T cell mechanism of oral bacterial EVs is distinct from and complementary to approved therapeutics

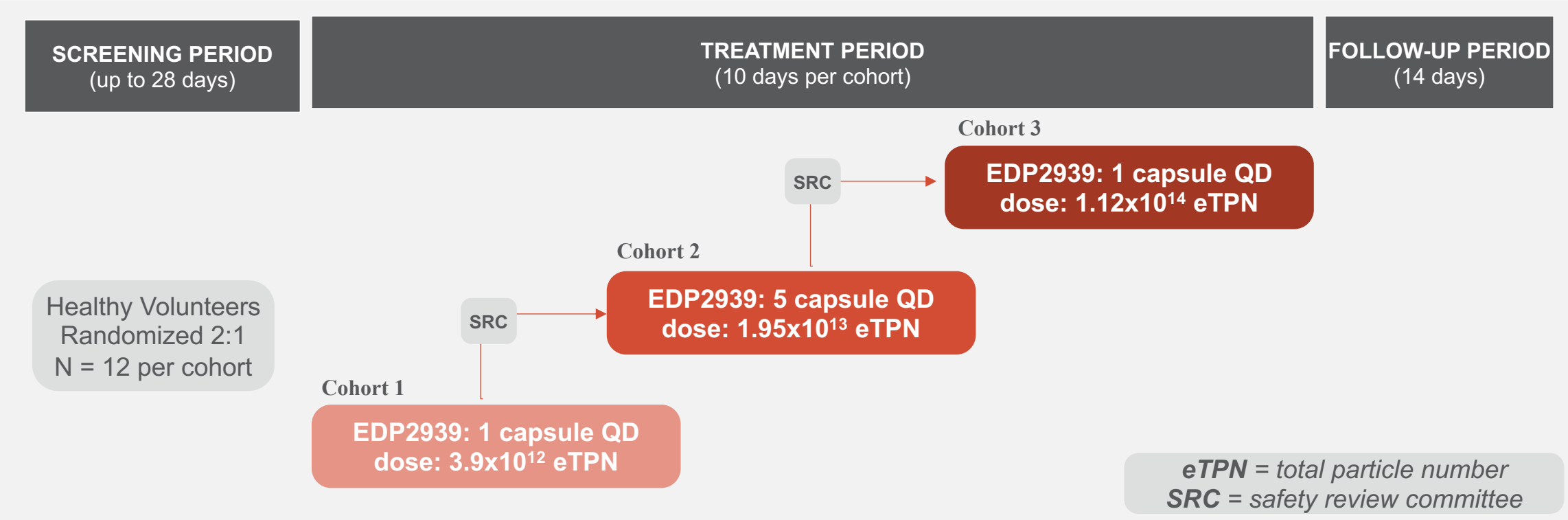
Clinical proof of concept with microbial precursor product, EDP1815

- In preclinical studies, EVs have shown substantially more potent activity than EDP1815, which we previously reported positive Phase 2 clinical data from in psoriasis
- Together, we believe this supports the potential of EDP2939, if approved, to become an attractive and unique foundational oral treatment to address all stages of psoriasis and other Th1/Th17 driven inflammatory diseases, including psoriatic arthritis, rheumatoid arthritis, axial spondyloarthritis and inflammatory bowel disease.

Lead EV product EDP2939 is in the clinic

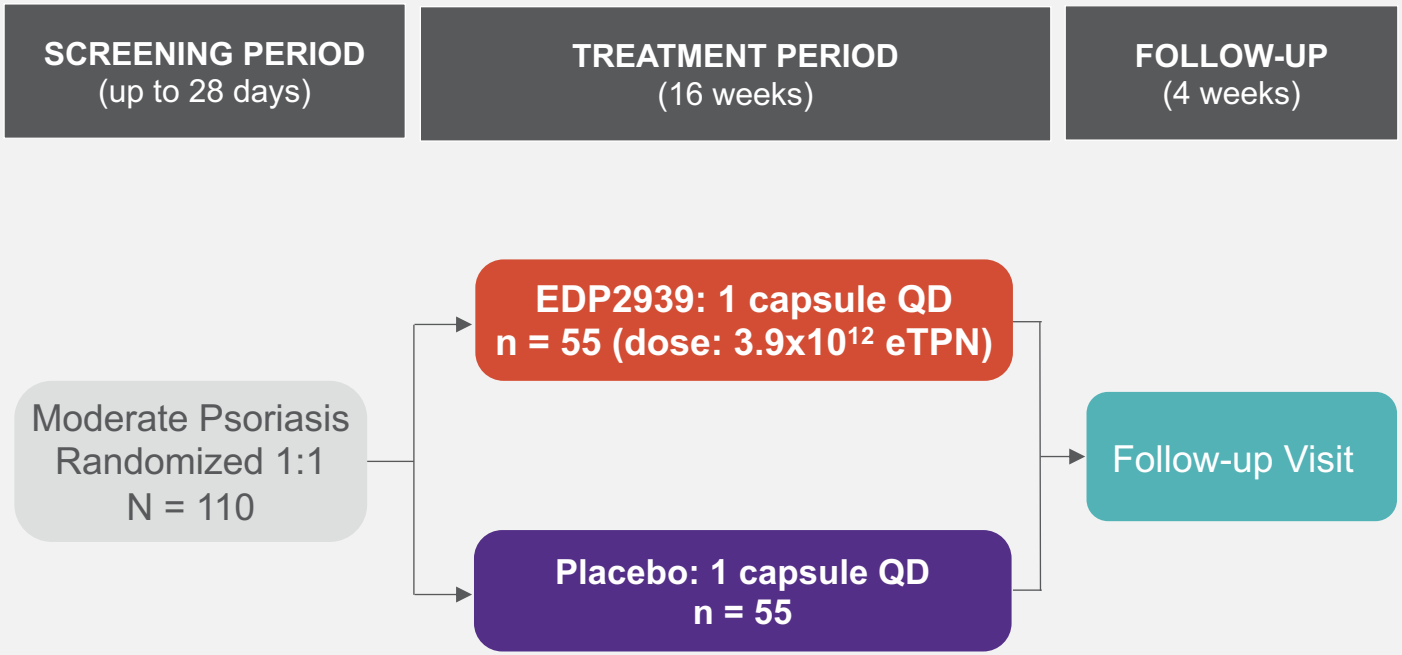
- GMP manufacturing and regulatory pathways for EVs established
- Safety in HVs has been demonstrated, Phase 2a psoriasis readout expected in 4Q 2023
- Positive Phase 2a data would enable advancement to Phase 2b in psoriasis and potentially additional indications

EDP2939-101 Part A: EV Safety and Tolerability in Healthy Volunteers



Primary Endpoint	• Evaluate the **safety and tolerability** of EDP2939 administered to healthy volunteers
Exploratory Endpoints	• Evaluate the effect of EDP2939 on blood-based biomarkers e.g. RNAseq, *ex vivo* stimulation of cytokines

EDP2939-101 Part B: EV Proof of Concept in Moderate Psoriasis



Primary Endpoint	• Proportion of participants achieving PASI-50 at week 16
Key Secondary Endpoints	• Proportion of participants achieving PASI-75 at week 16 • Proportion of participants achieving PGA-0/1 at week 16 • Safety and tolerability of EDP2939

A randomised, double-blind, placebo-controlled Phase 2a study evaluating EDP2939 in moderate psoriasis.

Key Inclusion Criteria:

- Plaque Psoriasis meeting all the severity criteria:

a. sPGA score of 3 (moderate), **and**
b. BSA of ≥5% and ≤20%, **and**
c. PASI of ≥5 and ≤20

Key Exclusion Criteria:

- Use of any systemic medications or phototherapy within 28 days
- Use of any topical medications (except emollients without active ingredients) within 14 days.
- No topical steroids or rescue therapy permitted throughout the study

1. Opportunity and unmet need

2. Clinical validation of SINTAX with EDP1815

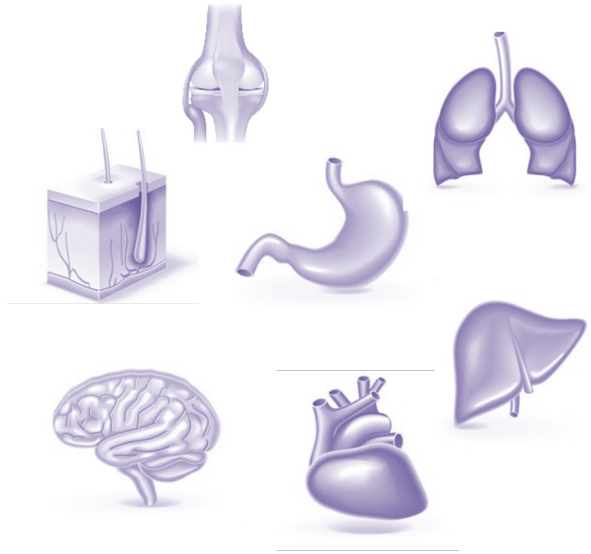
3. EDP2939 MOA and plan in psoriasis

4. Broad opportunity of EV platform

Product candidates targeting SINTAX have the potential to impact multiple inflammatory pathways and enable exploration beyond psoriasis

Inflammatory Pathway	Potential blockbuster drug in dermatology	Rapid expansion to other inflammatory disease areas
Th17	PSORIASIS	• Psoriatic arthritis • Axial spondylarthritis* • Rheumatoid arthritis* • Ulcerative colitis* • Crohn's disease*
Th2	ATOPIC DERMATITIS	• Asthma* • Allergy*
Th1	HUMAN KLH	• Axial spondylarthritis • Rheumatoid arthritis • Psoriasis* • Psoriatic arthritis*

Dozens of additional diseases impacting tissues and organs throughout the body



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

As the originator of oral bacterial EVs as potential medicines, Evelo has an established position in IP, manufacturing, regulatory, and talent

Patents and IP	30 families of global patent applications on EV medicines covering composition, use, manufacture, formulation
	First U.S. patent on compositions of oral EVs granted December 2022
Manufacturing	Evelo's manufacturing processes define the product candidate; captured in patents, trade secrets and know-how
Regulatory	Engaged with health authorities to establish regulatory path for EV medicines
People	Unique knowledge and insight of inventors of the platform