EVELO

Harnessing the Small Intestinal Axis, SINTAX™, to Create Big Change

Evelo Corporate Presentation

January 2022

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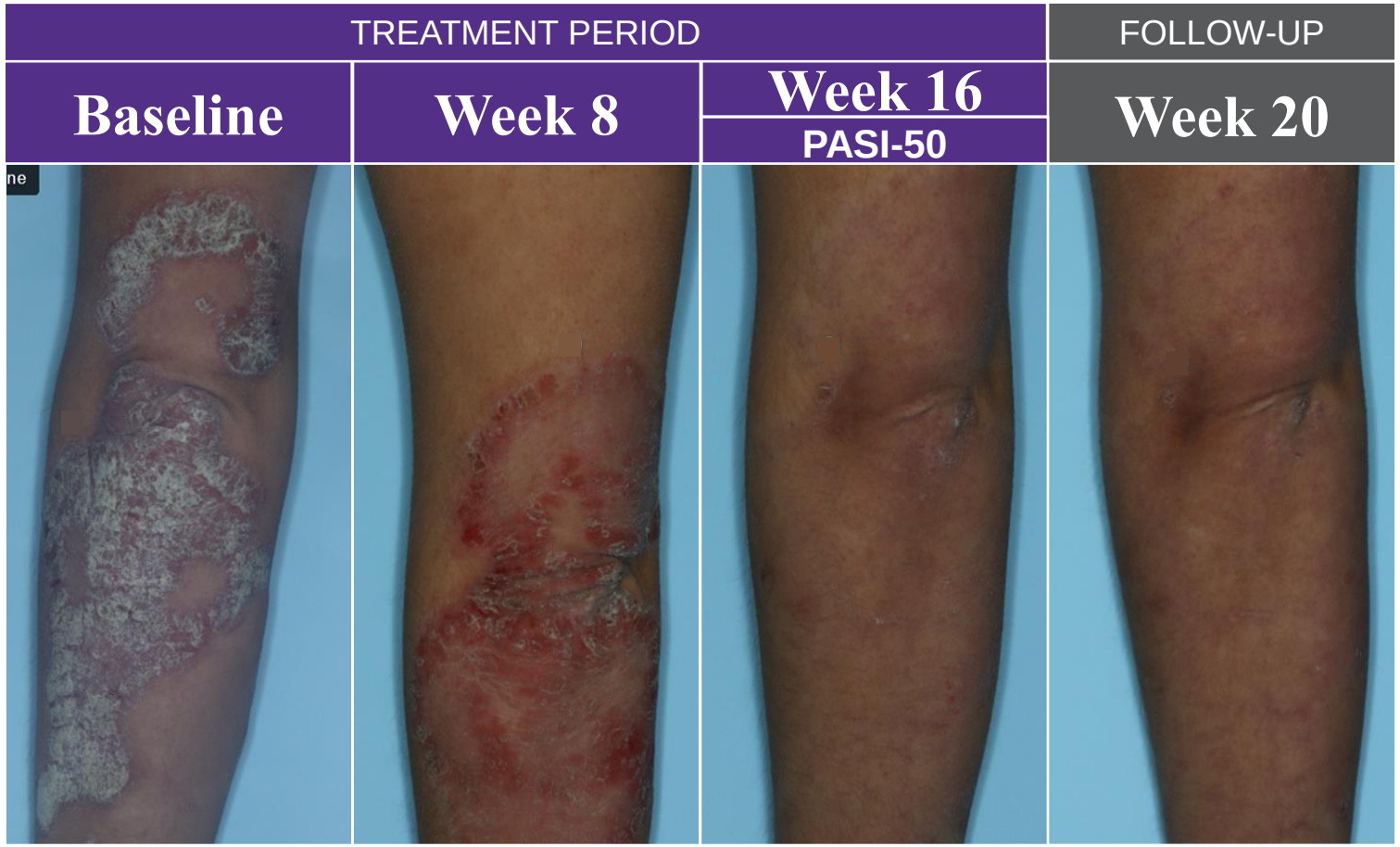
Positive EDP1815 Data Validates Platform, Supports Advancing Towards Phase 3

- Positive Phase 2 and Phase 1 results prove SINTAX platform
- Moving towards Phase 3
- EDP1815 had placebo-like safety and tolerability
- Potential utility across all stages of disease
- Potential use across broad spectrum of inflammatory diseases



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

2021 Achievements: Positive Clinical Data Validates Platform, Expanded and Advanced Pipeline

EDP1815 – Positive clinical data confirms ability to harness SINTAX

- Phase 2 clinical data in psoriasis showed placebo-like safety and tolerability
- Results support broad potential in inflammation
- Advancing towards Phase 3

Continued to advance pipeline

- Initiated clinical development of EDP1867, new microbe with broad therapeutic potential; bringing extracellular vesicle (EV) product candidate EDP2939 into clinic in 2022

Expanded platform

- Scaled manufacturing for microbes and EVs
- Furthered understanding of SINTAX mechanism of action
- Further developed formulations
- Expanded discovery pipeline

Development and commercial partnership

- Strategic collaboration with Abdul Latif Jameel Health to develop and commercialize EDP1815 in Middle East and Africa

1H 2022 Clinical Catalysts

Candidate	Catalyst
EDP1815 Psoriasis	**1Q 2022:** Part B data from Phase 2 trial
EDP1815 Atopic Dermatitis	**1Q 2022:** Initiation of dosing of patients in Phase 2 trial
EDP1815 –TACTIC-E COVID-19	**1H 2022:** Interim safety and futility analysis of 375 patients (125 patients on each arm)
EDP1867 Atopic Dermatitis	**1H 2022:** Phase 1b data

Further Catalysts –2H 2022 through 2023

2H 2022

EDP2939

- Initiation of clinical development in 2H

2023

EDP1815
Psoriasis

- Registration studies

EDP1815
Atopic Dermatitis

- Phase 2 data in 1H

EDP2939

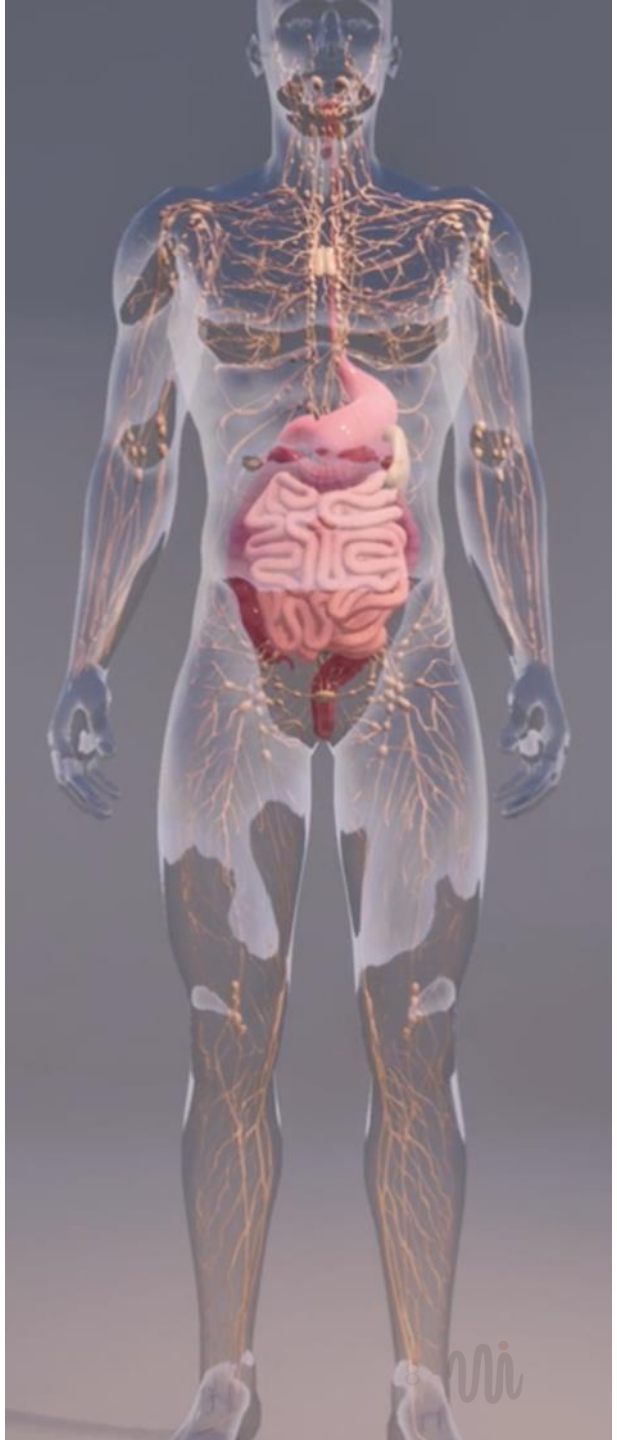
- Following feedback from regulatory agencies, initiate Phase 2 study

Other indications

- Expand into psoriatic arthritis, asthma, neuroinflammation, pediatric populations, etc.

Harnessing SINTAX to Transform Medicine

- SINTAX medicines are a new class of orally delivered therapies that act on cells in the small intestine with systemic therapeutic effects.
- These cells play a central role in governing the immune, metabolic, and neurological systems.
- Profile of SINTAX medicines could allow Evelo to achieve its vision of providing a new class of:
  - Effective, safe, convenient, and affordable medicines
  - Benefitting billions of people at all stages of inflammatory disease



What are Evelo's Investigational Medicines?

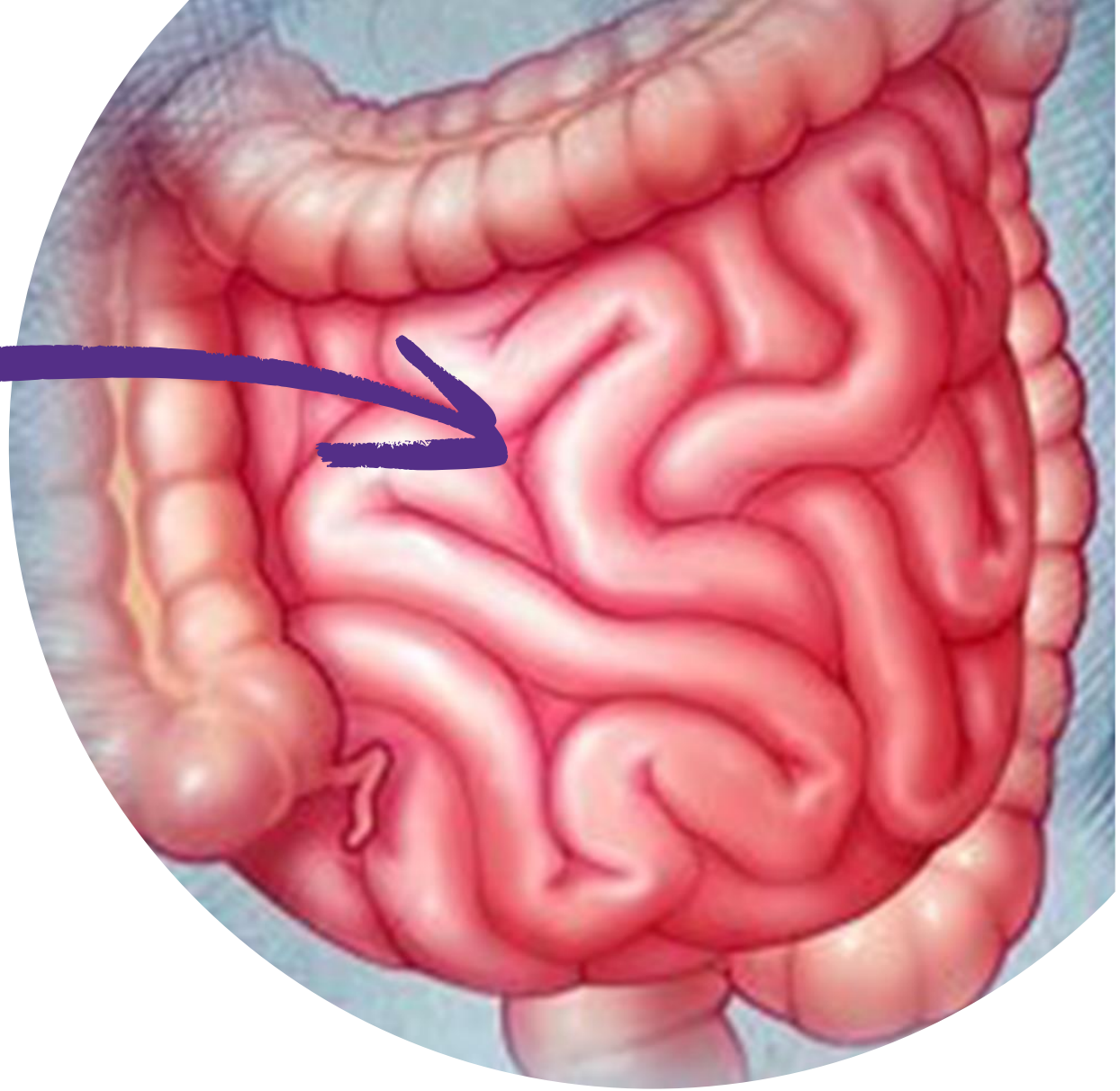
Evelo's potential medicines target SINTAX with oral microbial therapies

- Sourced from the gut mucosa
- Selected for a particular immune profile

SINTAX medicines are non-living pharmaceutical preparations of either single strains of bacteria or their extracellular vesicles

- Affects systemic immunity through interactions with immune cells in the gut
- No modification of the microbiome

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 governing of physiology throughout the body
- Very low level of resident gut microbes

SINTAX medicines

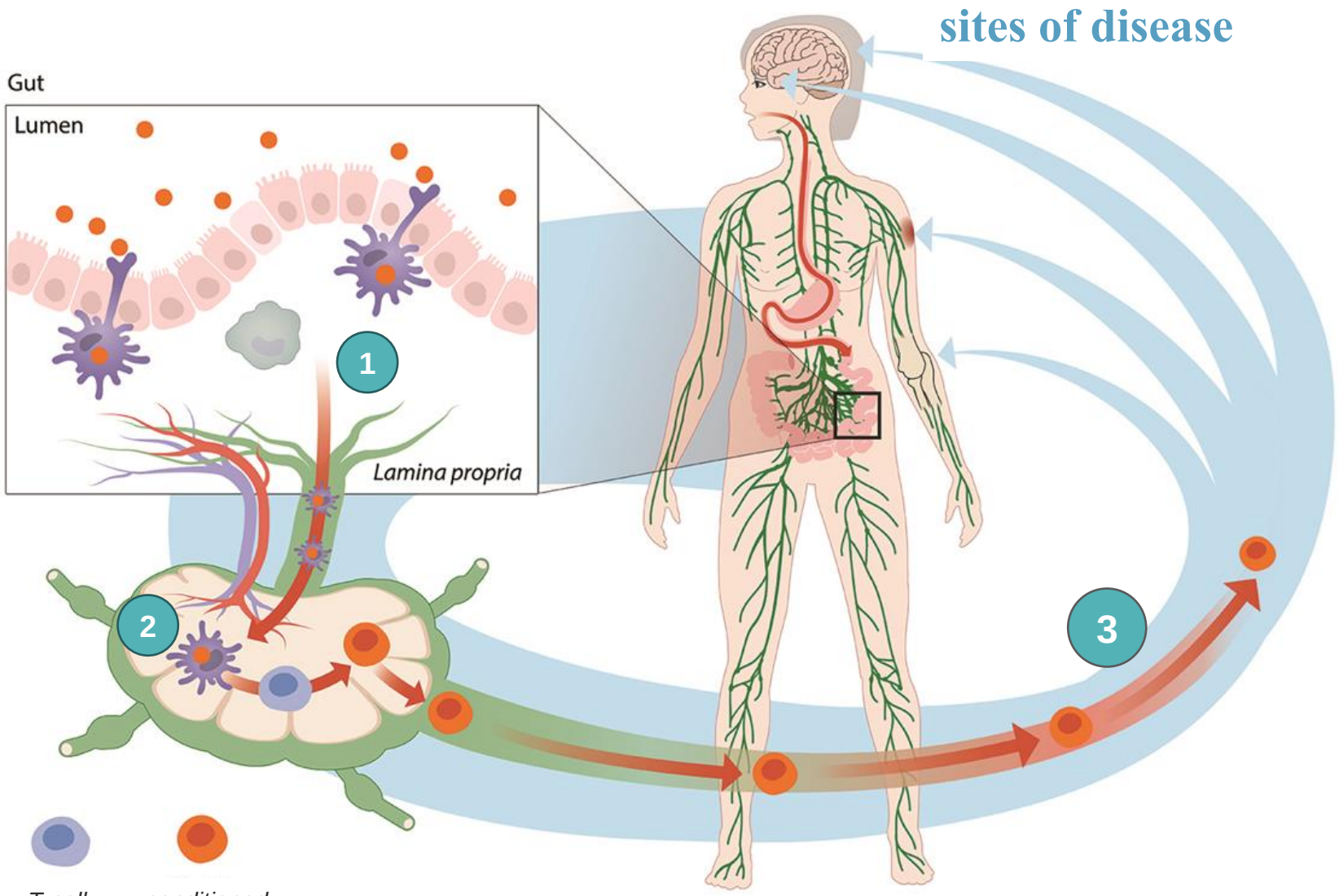
- SINTAX medicines target the small intestine
- Targeting SINTAX allows for remote control of systemic immunity

Mechanism of Action of SINTAX Medicines

1. **Sensing of SINTAX medicines by receptors and cells in the small intestine**

2. **Conditioning of T cells by dendritic cells and macrophages in lymph nodes**

3. **Migration of conditioned T-cells throughout the body**



macrophage *dendritic cell* *T-cell* *conditioned T-cell*

Extracellular Vesicles (EVs) are the Next Wave of SINTAX Medicines

- EVs are natural lipoprotein nanoparticles
- EV products potentially enable greater SINTAX activation for greater efficacy given small size and diffusion properties
- Compared to microbes, EVs are:
  - ~1/1000th volume of microbes - potential for higher dosing

Stokes-Einstein Equation

$$D = \frac{k_B T}{C \pi \eta a}$$

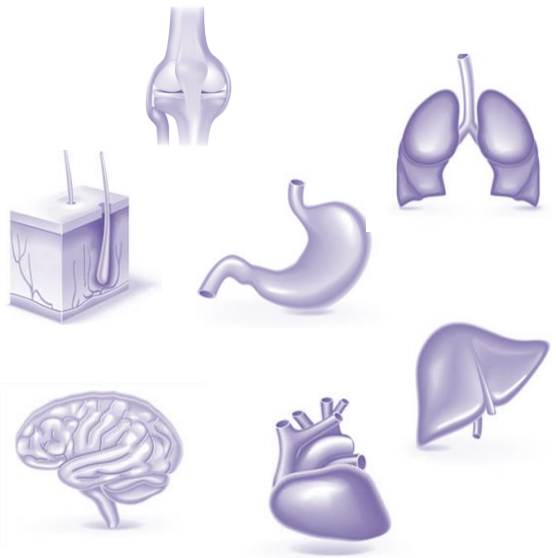
Fick's Laws of Diffusion

$$J \propto \frac{d\varphi}{dx} \quad \text{or} \quad J = -D \frac{d\varphi}{dx}$$

SINTAX Medicines Have Potential Use Across Spectrum of Inflammatory Diseases with Opportunity to Impact 1 Billion People

	Initial indications	Expansion indications
Th17 focused	PSORIASIS	• Psoriatic arthritis • Axial spondylarthritis* • Rheumatoid arthritis* • Ulcerative colitis* • Crohn's disease*
Th2 focused	ATOPIC DERMATITIS	• Asthma • Allergy
Th1 focused	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.

Majority of Psoriasis and Atopic Dermatitis Patients Have Mild or Moderate Disease

***93%** of PsO patients*

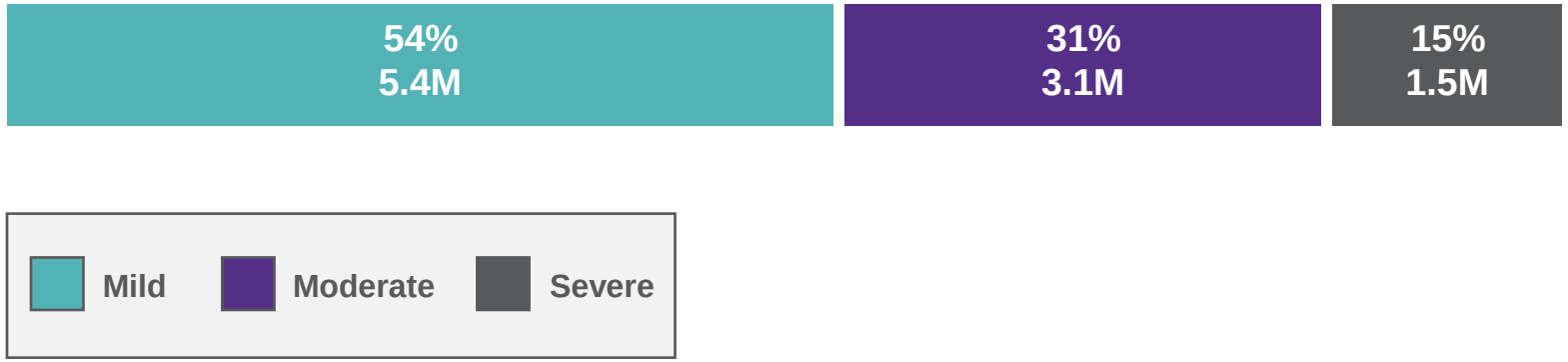
***85%** of AD patients*

Psoriasis

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

Atopic Dermatitis

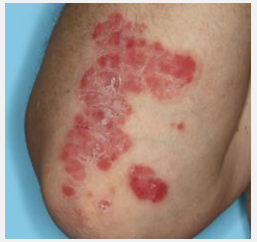
201M Worldwide prevalence
21.3M U.S. prevalence
10M U.S. diagnosed

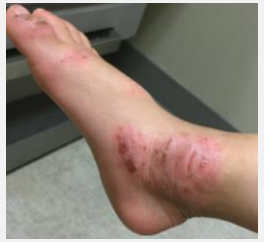


Source: Datamonitor Healthcare, Vanderpuyre-Orgle et al. J Am Acad Dermatol. 2015: 72:961–7

Mild Psoriasis and Atopic Dermatitis are Serious Conditions

Burdensome lesions





- **Painful, cracked skin**
- **Itchy and irritating**
- **Often highly visible**

Quality of life impacts

- **65%** of “mild” PsO sufferers report moderate - extremely high impact on daily life[1]
- Mild AD sufferers report **greater impact to quality of life** vs. people without AD[2]

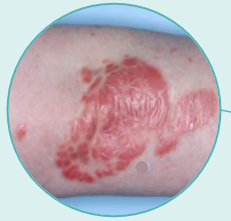
Psycho-social impacts

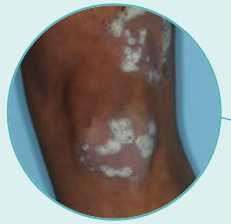
- **34%** of “mild” PsO sufferers have depression; **27%** suffer sleep disturbance[3]
- **50%** higher risk of depression for mild-moderate AD sufferers vs. people without AD[4]

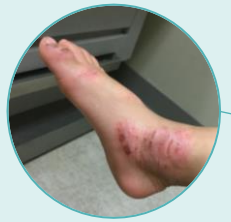
[1] Martin G., et al., J Clin Aesthet Dermatol. 2019:12(4):13-26. [2] Chiesa Fuxench, Z., et al., J Investigative Dermatol. 2019:139:583-590. [3] Luca M, Musumeci ML, D'Agata E, Micali G. Int J Psychiatry Clin Pract. 2020 Mar;24(1):102-104. [4] Toron, F., Neary, M.P., Smith, T.W. et al. Dermatol Ther (Heidelb) 11, 907–928 (2021).

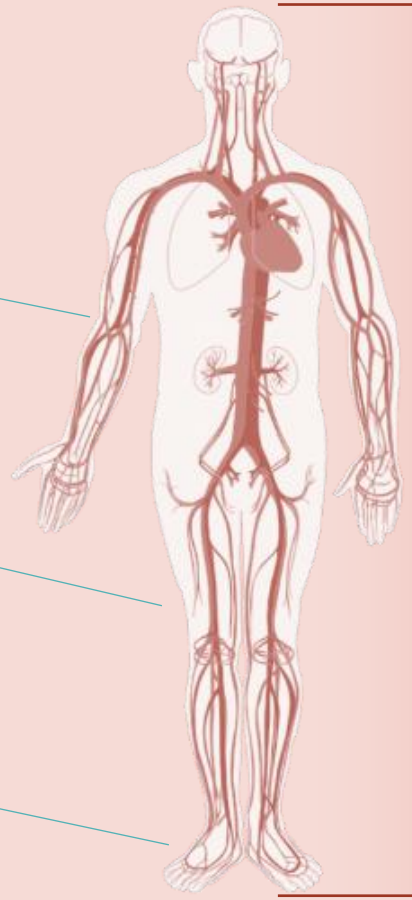
Psoriasis and Atopic Dermatitis are Diseases of Systemic Inflammation and are Associated with Multiple Comorbidities

SKIN INFLAMMATION



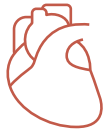




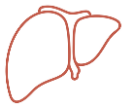


SYSTEMIC INFLAMMATION

PET scans of people suffering from PsO[1] and AD[2] confirm systemic inflammation, including in:



Heart



Liver

Joints and tendons

Comorbidities include: psoriatic arthritis, cardiac events, and inflammatory bowel disease for PsO[3,4]; Asthma, allergies, and cardiac events for AD[5-7]

[1] Mehta, Nehal N., et al. Archives of dermatology 147.9 (2011): 1031-1039. [2] Ungar, Benjamin, et al, The Journal of Allergy and Clinical Immunology: In Practice 8.10 (2020): 3500-3506. [3] Oliveira Mde F, Rocha Bde O, Duarte GV. An Bras Dermatol. 2015 Jan-Feb;90(1):9-20. [4] Addressing NCD Psoriasis and its Comorbidities – Shared Opportunities for Action." International Federation of Psoriasis Associations and NCD Alliance. 2017. [5] Silverberg et al. J Allergy Clin Immunol; 2013;132(5):1132-1138. [6] Silverberg JI. Ann Allergy Asthma Immunol; 2019;123(2):144-151. [7] Silverwood R J, Forbes H J, Abuabara K, Ascott A, Schmidt M, Schmidt S A J et al. BMJ 2018; 361 :k1786.

Few Patients with Psoriasis or Atopic Dermatitis Receive Therapies That Address Their Systemic Disease

Psoriasis

LESS THAN

8%

in the US receive injectable antibody therapies or oral systemics[1-6]

Atopic dermatitis

LESS THAN

2%

in the US receive dupilumab (no oral systemics approved)[2,9]

as many as 50% of PsO and AD sufferers in the US are not on any Rx treatment[2,7,8]

[1] IQVIA and Symphony Health Data [2] Datamonitor Healthcare, accessed June 2021. [3] Armstrong A, et al., Dermatol Ther (Heidelb). 2017 Mar; 7(1). [4] IQVIA Prescription data from Analyst Report, Oct 2020. [5] DRG Epidemiology Database 2017 [6] Lebwohl MG, et al., J Am Acad Dermatol. 2014 May;70(5):871-81.e1-30. [7] Silverberg JI, et al., Allergy Asthma Immunol. 2018 Dec;121(6):729-734.e4. [8] Armstrong, April W., et al. JAMA dermatology 149.10 (2013): 1180-1185. [9] Regeneron 2020 4th quarter earnings call.

Therapies for Psoriasis and Atopic Dermatitis Have Limitations Related to Safety, Tolerability, Convenience, and Price

>50% of PsO and **>90%** of AD sufferers are dissatisfied with current treatment options[1,2]

Topicals

PsO/AD

- Steroids, calcineurin inhibitors, others
- Not convenient
- Low compliance
- No systemic impact

Old-school Systemics

PsO

- Safety concerns
- Monitoring requirement
- Immunosuppressant

Oral Immunosuppressant

PsO

- Apremilast:
  - Safety and tolerability issues
  - High price

Injectable Biologics

PsO/AD

- Not convenient & needle fear
- Immunosuppressant
- High price

[1] Florek, Aleksandra G., et al., Archives of dermatological research 310.4 (2018): 271-319. [2] National Eczema Association report, 2020.

Majority of Psoriasis and Atopic Dermatitis Patients Could Benefit From a More Affordable Systemic Therapy

Traditional Pharma High-Price Model

Antibody therapies and innovative oral therapies for PsO and AD are priced high and used by a small portion of moderate – severe sufferers

~$40-80K
per person per year (US)
Injected antibody and novel oral therapies

New Affordable Volume-Based Model

An effective, safe, well tolerated, oral, and affordable therapy could expand the addressable patient population

EDP1815

- Advancing towards Phase 3 trial in psoriasis
- Initiating dosing in Phase 2 trial in atopic dermatitis
- Interim data readout in Phase 2/3 trial in COVID-19
- Multiple opportunities in inflammatory diseases with single microbe

Psoriasis

EDP1815 Phase 2 Trial in Mild and Moderate Psoriasis

Trial Summary

- 16 week, double-blind, placebo-controlled, dose-ranging trial in 249 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
- Limited use of emollients and topical therapies

Summary of Endpoints

Primary Endpoint

Mean reduction in PASI score at week 16 vs. placebo

- **Analysis**
  - Bayesian probability (%) that EDP1815 is superior to placebo
- **Result**
  - 80-90% probability that EDP1815 is superior to placebo at week 16 based on mean change in PASI

Responder Endpoint

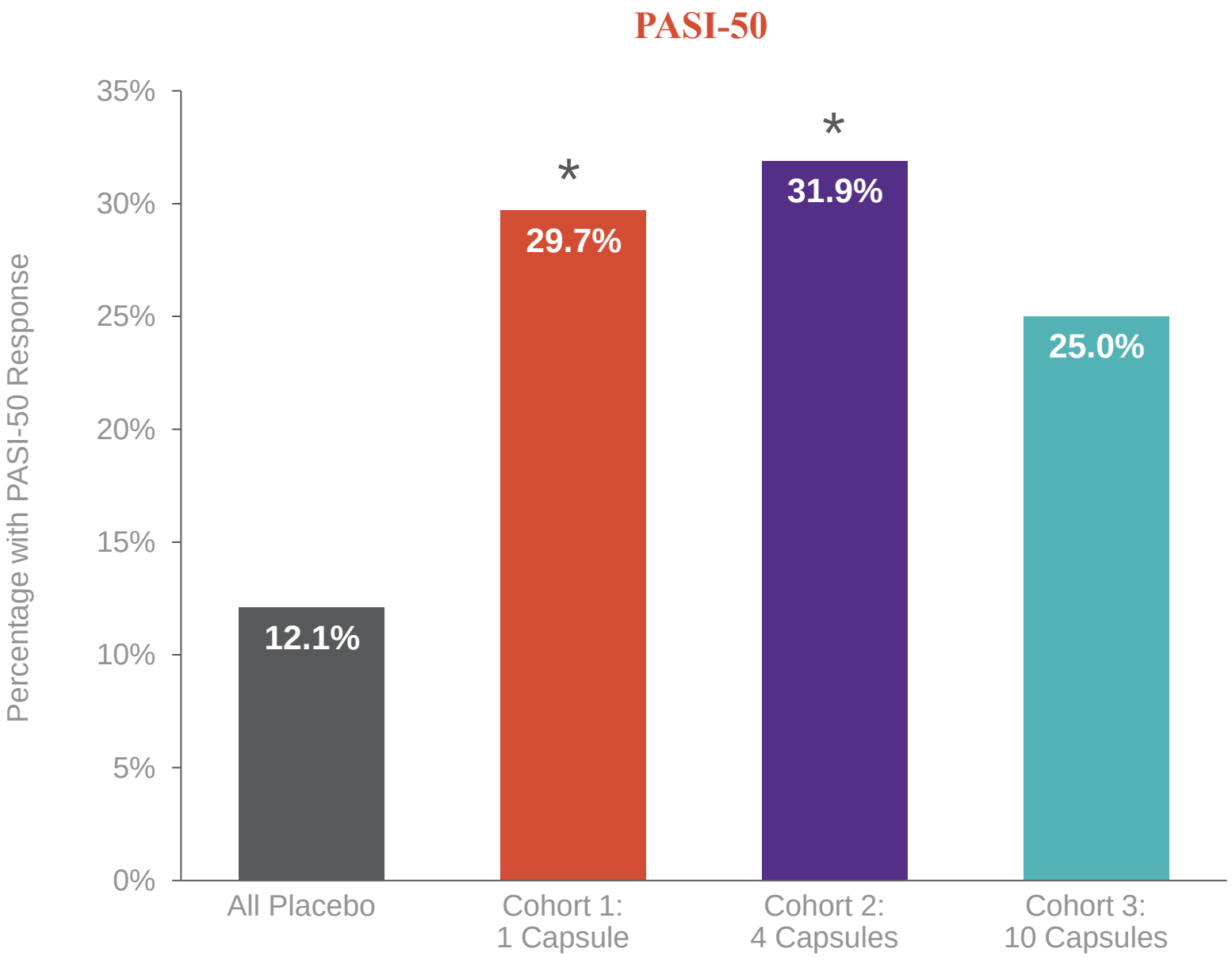
Percentage of patients achieving at least a PASI-50 by week 16

- **Analysis**
  - Statistical significance represented by $p<0.05$
- **Result**
  - Statistically significant p-value for 2 of the 3 individual dose cohorts, and directionally similar for the third

Robust PASI-50 Responses with EDP1815 at Week 16

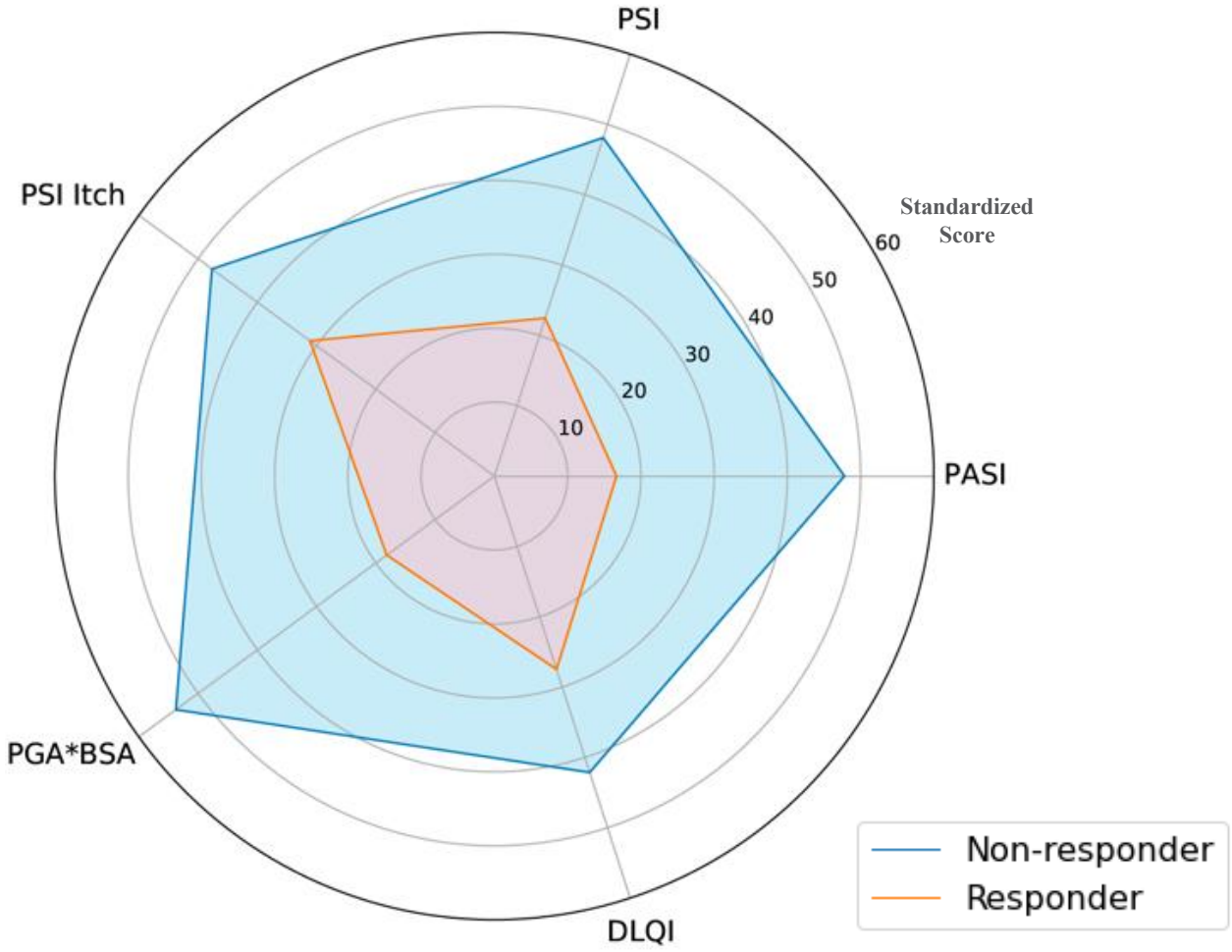
Statistically significant p-value (<0.05) for all 3 cohorts when pooled, and for 2 of the 3 individual dose cohorts

PASI-50 is a clinically meaningful response



*p<0.05

Responders* in Active Cohort Demonstrated Improvements Across Multiple Secondary Endpoints



Patients with PASI-50 or greater:

Mean PGA*BSA improvement

-63.6%

Active non-responders: **+9.8%**

Mean PSI itch improvement

-0.9

Active non-responders: **-0.15**

Mean PSI improvement

-6.9

Active non-responders: **-0.9**

Mean DLQI improvement

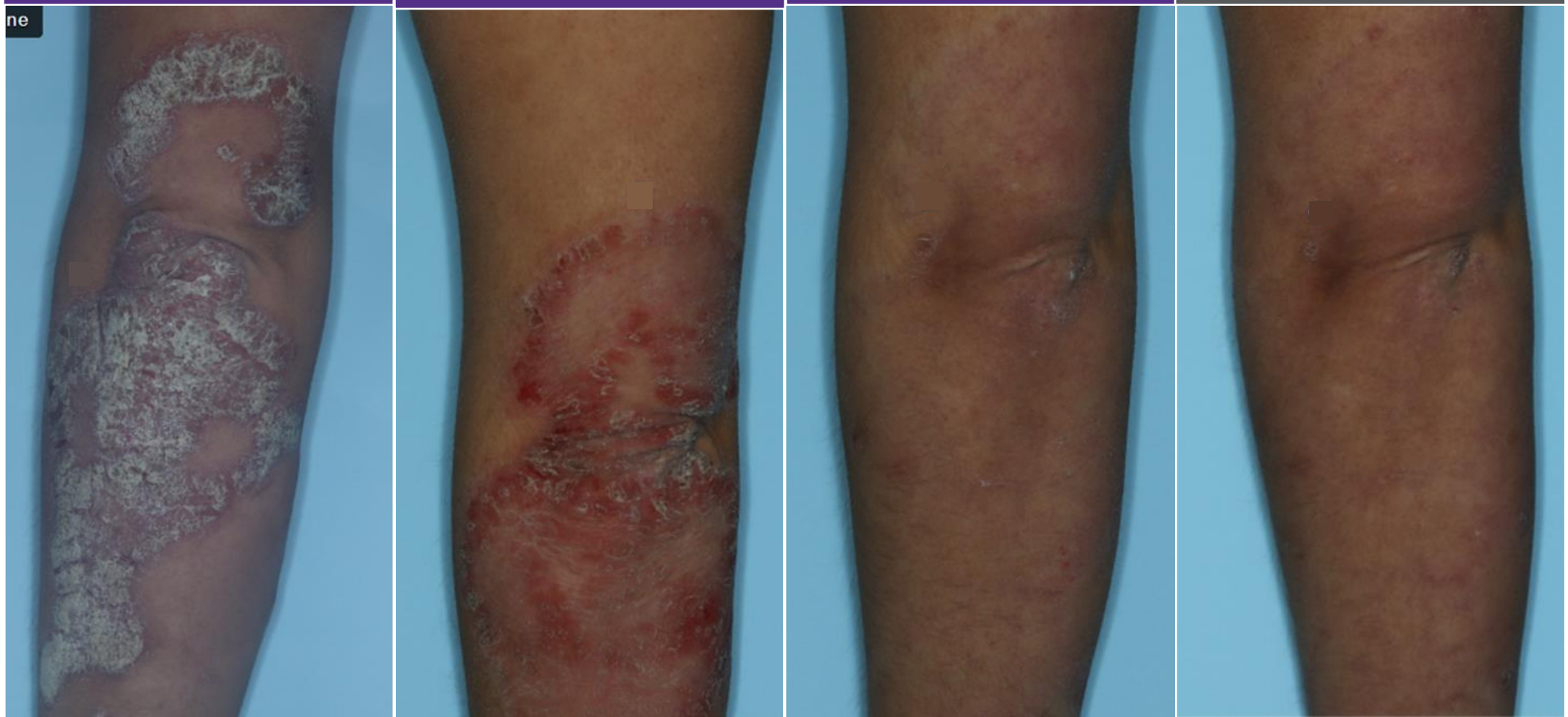
-3.5

Active non-responders: **-1.4**

*Responder = active patients who achieved PASI-50 or greater

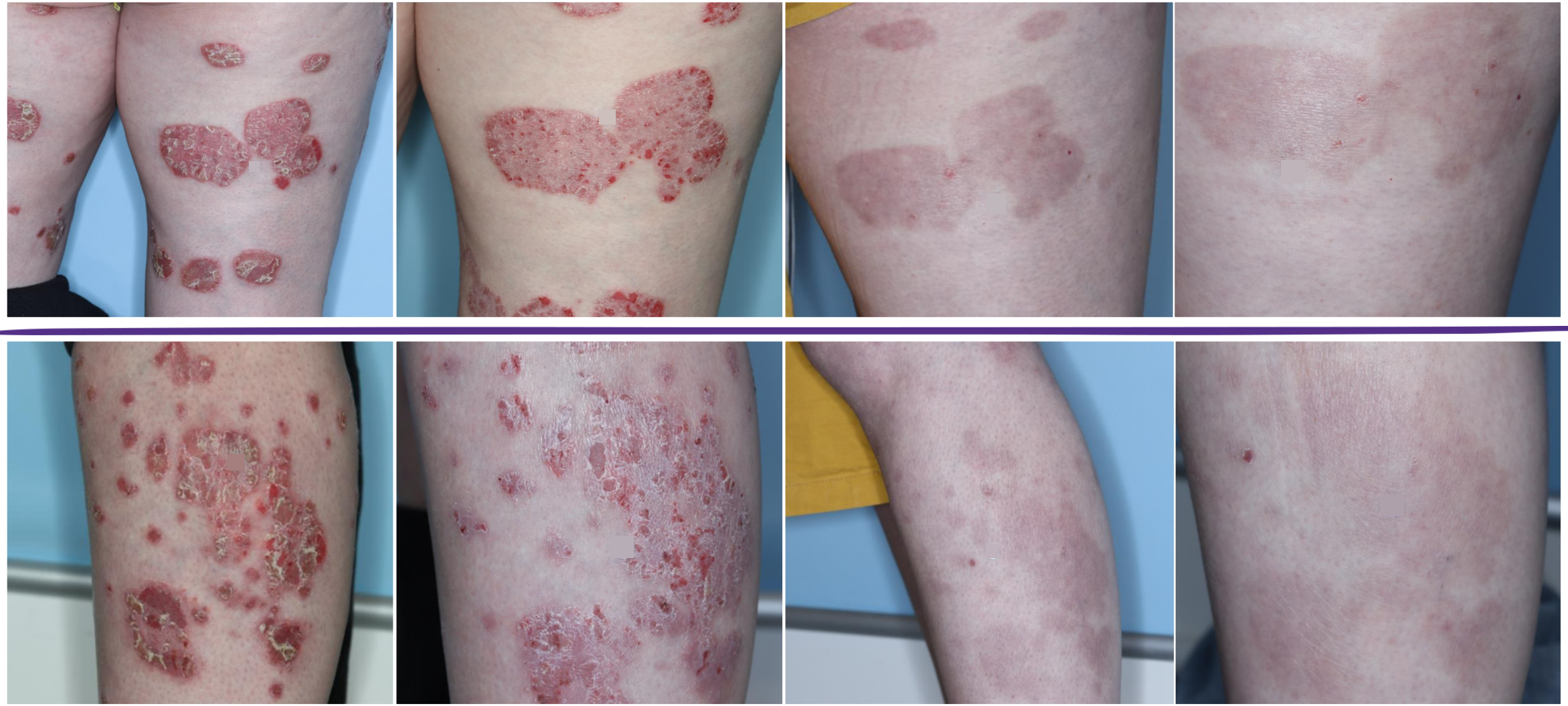
Patient with Moderate Psoriasis Achieved PASI-50 Response at Week 16 on EDP1815 – Skin Lesions Improved Further at Week 20

TREATMENT PERIOD			FOLLOW UP
Baseline	Week 8	Week 16 PASI-50	Week 20

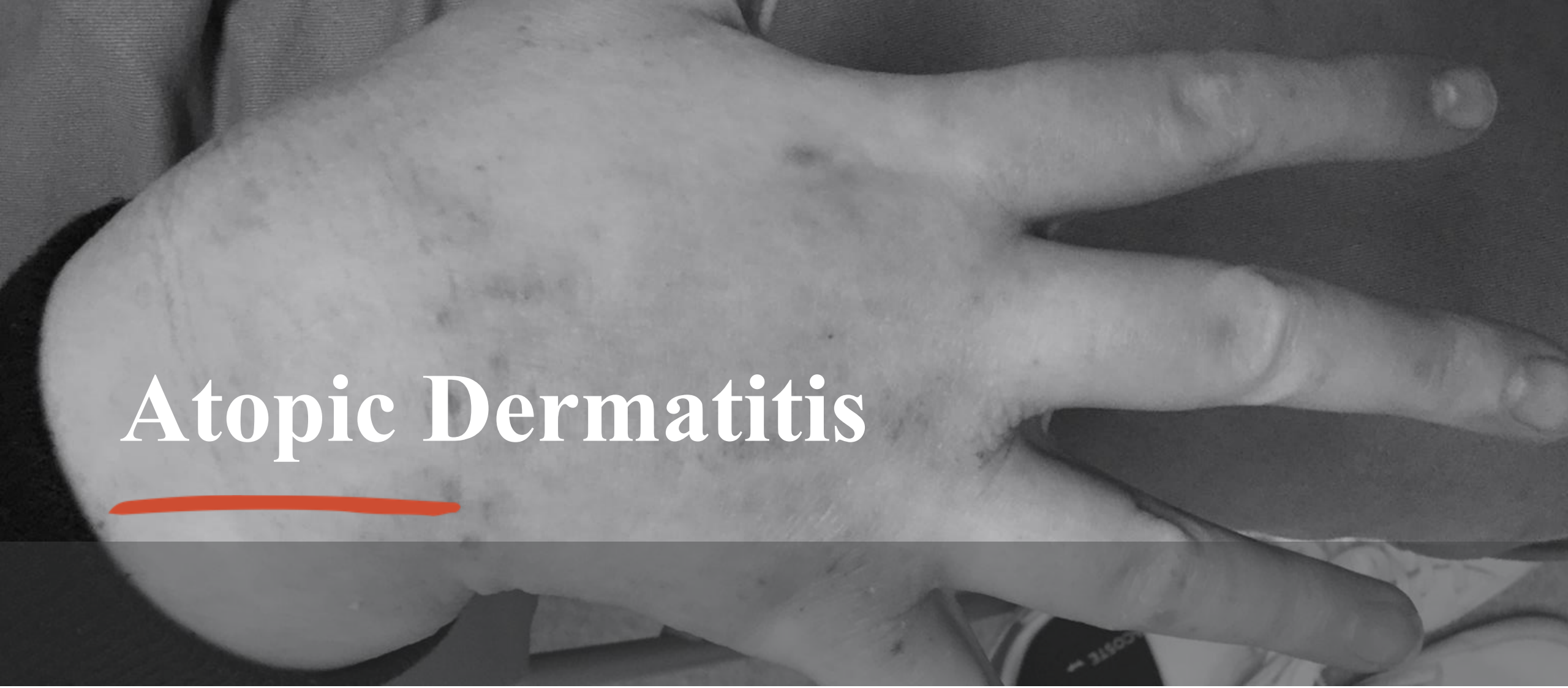


Patient with Moderate Psoriasis Achieved PASI-90 Response at Week 16 on EDP1815 – Skin Lesions Improved Further at Week 20

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



EDP1815 Advancing Towards Registration Studies in Psoriasis



Atopic Dermatitis

EDP1815 Phase 2 Study in Mild, Moderate and Severe Atopic Dermatitis

Trial Summary

- 16 week, double-blind, placebo-controlled trial in 300 patients
- Randomized into one of three cohorts – each cohort has ~100 patients randomized in a 3:1 ratio (75 to EDP1815 and 25 to placebo)
  - **Cohort 1**: Dose of 1.6 x 10^{11} total cells of EDP1815 or matching placebo administered as two capsules once daily
  - **Cohorts 2 & 3:** Dose of 6.4 x 10^{11} total cells of EDP1815 or matching placebo administered as two capsules once daily or one capsule twice daily, respectively
- Opportunity to join open-label study post dosing period, for up to 52 weeks

Summary of Endpoints

- Primary endpoint: % of patients achieving EASI-50 response at week 16
- Key physician-reported secondary endpoints:
  - IGA (Investigator Global Assessment)
  - BSA (Body Surface Area)
- Key patient-reported secondary endpoints:
  - DLQI (Dermatology Life Quality Index)
  - POEM (Patient-Oriented Eczema Measure)
  - Pruritus-NRS (Numerical Rating Scale)

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
  - No suppression of type 1 interferons critical for anti-viral immune response
- **Safety and tolerability results comparable to placebo in clinical trials to date**
  - No systemic exposure observed, limiting risk of secondary infections or potential drug interaction
- **Orally administered**
- **Scalable manufacturing** for treatment of large populations

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

Data from COVID-19 Trial has Potential to Drive Accelerated Path

TACTIC-E: Phase 2/3 Platform Trial; Futility Analysis Expected in 1H 2022

- Phase 2/3 randomized platform trial across multiple 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

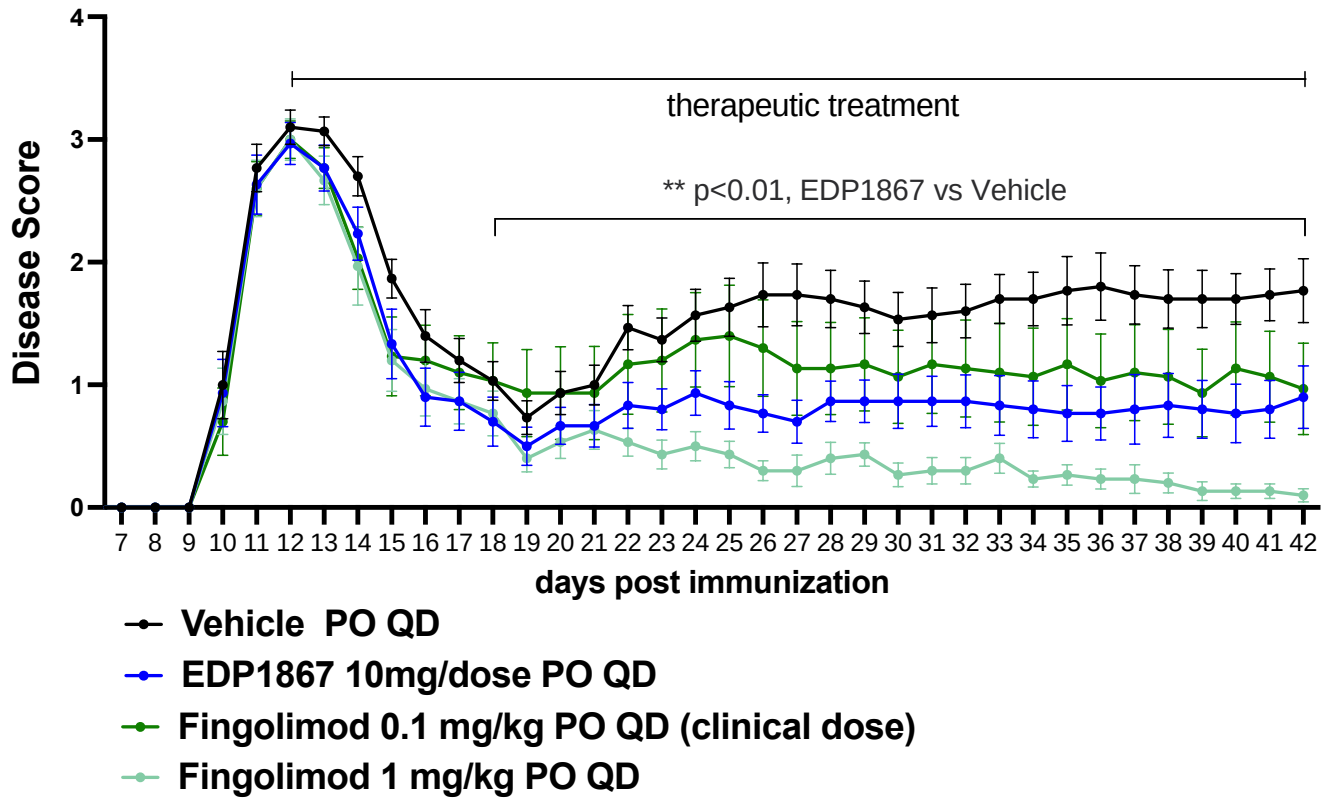
*The investigators of the study have expanded the trial to countries where COVID-19 remains prevalent, including Mexico, India, and Brazil

EDP1867

EDP1867 Reduces CNS Inflammation in Animal Models; Phase 1b Data Expected 1H 2022

SINTAX medicine candidate with broad inflammation resolving potential

Data from EDP1867 in patients with atopic dermatitis expected 1H 2022

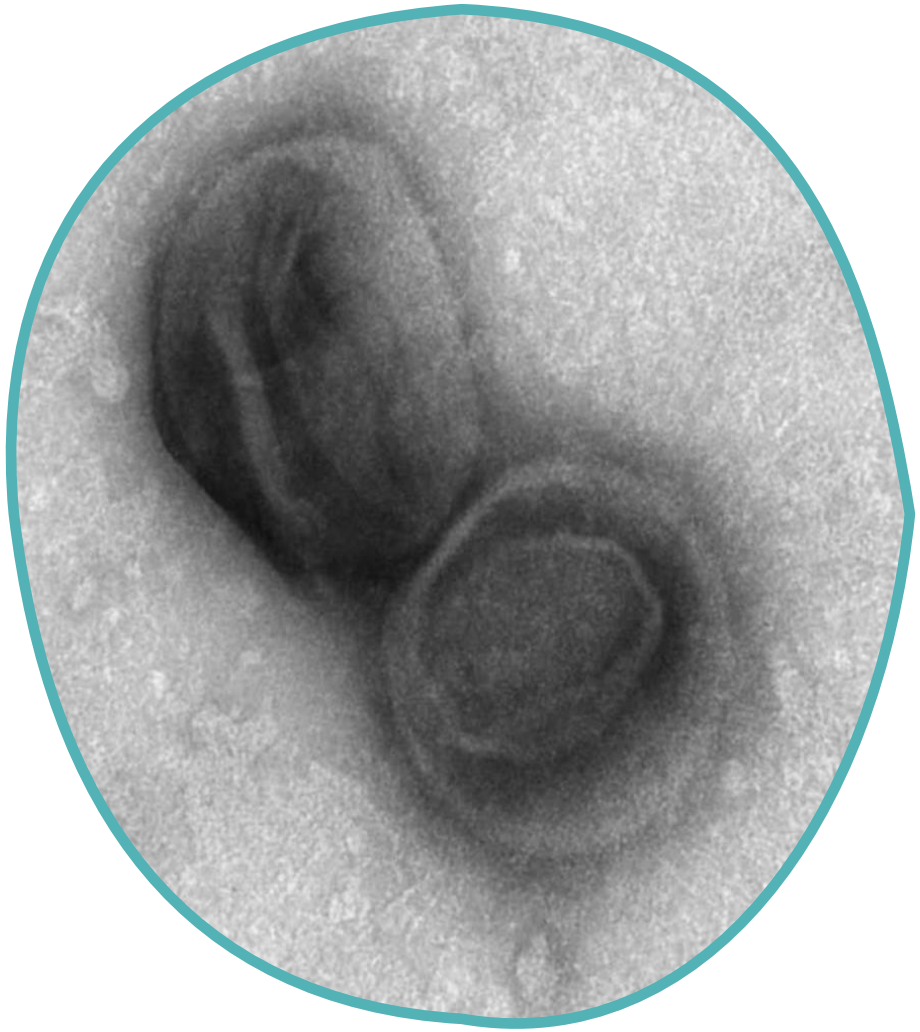


- EDP1867 reduced disease severity and relapse in EAE model of MS better than clinical dose of fingolimod
- EDP1867 reduced demyelination in the CNS

EDP2939 –First Anti-Inflammatory EV

EDP2939 in Inflammatory Diseases

- EDP2939 is Evelo's first EV clinical candidate
- Pre-clinical data show EDP2939 reduces inflammation in murine models of Th1 and Th17 inflammation
- It was observed that EDP2939 is gut-restricted, with no apparent safety or tolerability issues in animal models
- EDP2939 will enter the clinic in 2H 2022, with data anticipated in 2023



Pipeline Provides Multiple Diversified Non-Correlated Opportunities

EDP1815: Th17 Effects

Potential to expand into other Th17-mediated diseases

Psoriasis

- Phase 2 Part B data in **1Q 2022**

Other Potential Indications

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

EDP1815: Th1/Th2 Effects

Potential to expand in other Th1 and Th2-mediated diseases

Atopic Dermatitis

- Begin dosing of patients in Phase 2 trial in **1Q 2022**
- Phase 2 data expected in **1H 2023**

Other Potential Indications

- Asthma and allergy
- Neuroinflammation
- Numerous others

EDP1815: Integrated Effects

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

COVID-19

- Interim safety and futility analysis of 375 patients (125 in each arm) in Phase 2/3 TACTIC-E trial in **1H 2022**

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 **1H 2022**

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

- Anticipate initiation of clinical development in **2022**

Broad use across all inflammatory diseases

Multiple Diversified Non-Correlated Opportunities Across Form, Formulation, and Disease Application

MICROBE SELECTION

EDP1815
EDP1867
EDP2939
EDP1908

FORM

Whole microbes
Extracellular vesicles

FORMULATION

Capsule
Upper GI release

DISEASE APPLICATION

Th1
Th2
Th17
Viral

Broad Clinical and Preclinical Pipeline with Multiple Upcoming Readouts

	Product Candidate	Indication	Preclinical Development	Phase 1	Phase 2	Phase 3
Inflammation	EDP1815	COVID-19[1]			Phase 2/3	
	EDP1815	Psoriasis			Phase 2	
	EDP1815	Atopic dermatitis		Phase 1b		
	EDP1867	Atopic dermatitis		Phase 1b		
	EDP2939	Inflammation				
Oncology	EDP1908	Multiple cancers				
Neuro-inflammation	Research					
Metabolism	Research					

Whole, inactivated microbes

Non-replicating, non-colonizing, gut restricted and pharmacologically active single strains of microbes

Microbial Extracellular Vesicles (EVs)

Lipoprotein nanoparticles naturally produced by some bacteria - non-viable and 1/1,000th volume of whole microbes, potentially enabling increased target engagement and potency

[1] The Phase 2/3 TACTIC-E study is an investigator-sponsored study being conducted by Cambridge University Hospitals NHS Foundation Trust

Corporate Information

~120 employees	Cash and cash equivalents of ~$96 million*
~$50 million ATM program with capacity remaining	Long-term debt $45 million

*As of September 30, 2021