EVELO

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

Evelo Corporate Presentation

October 2021

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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, EDP1867, EDP1908, 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.

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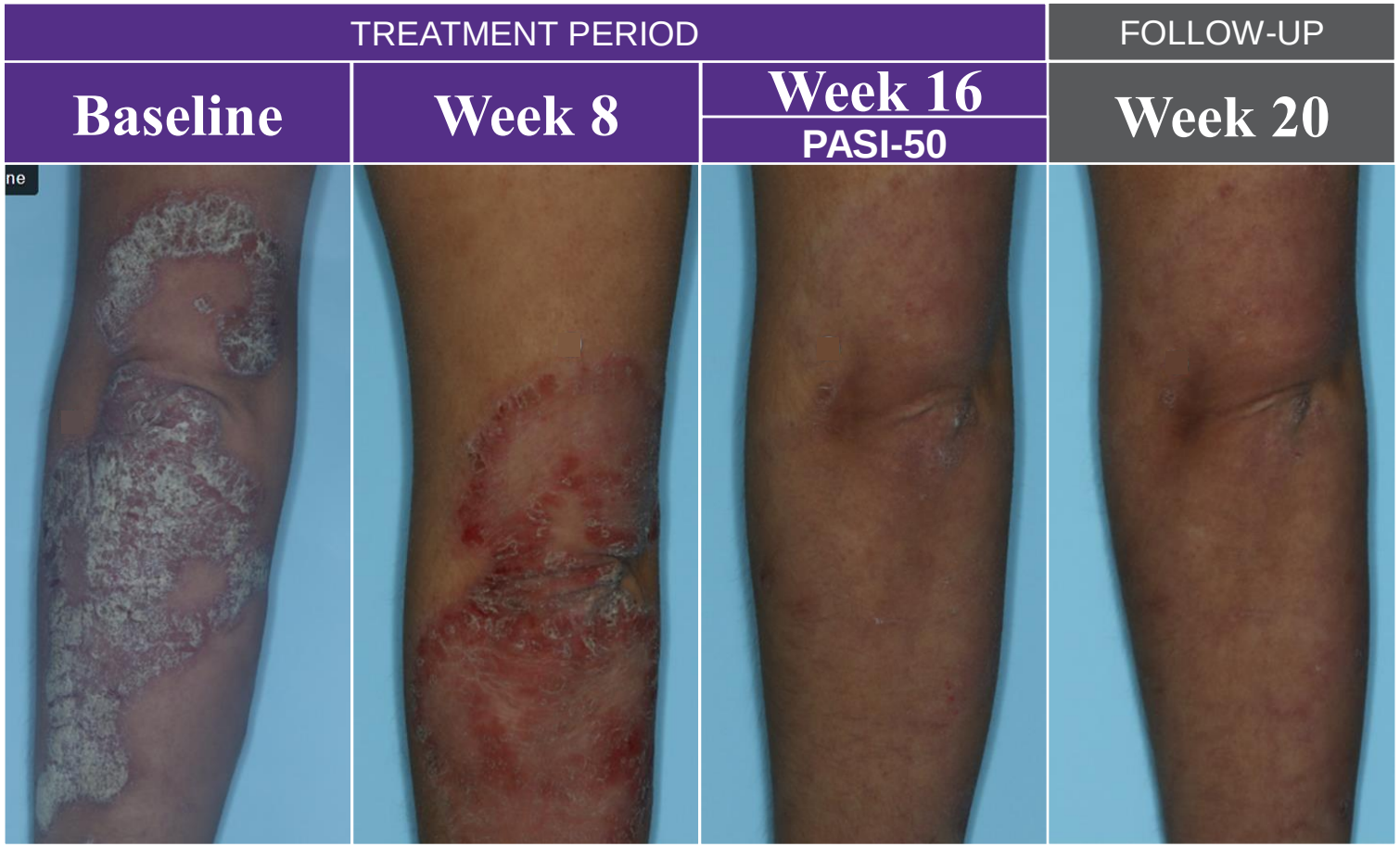
Positive Data from EDP1815 Confirms Ability to Harness SINTAX

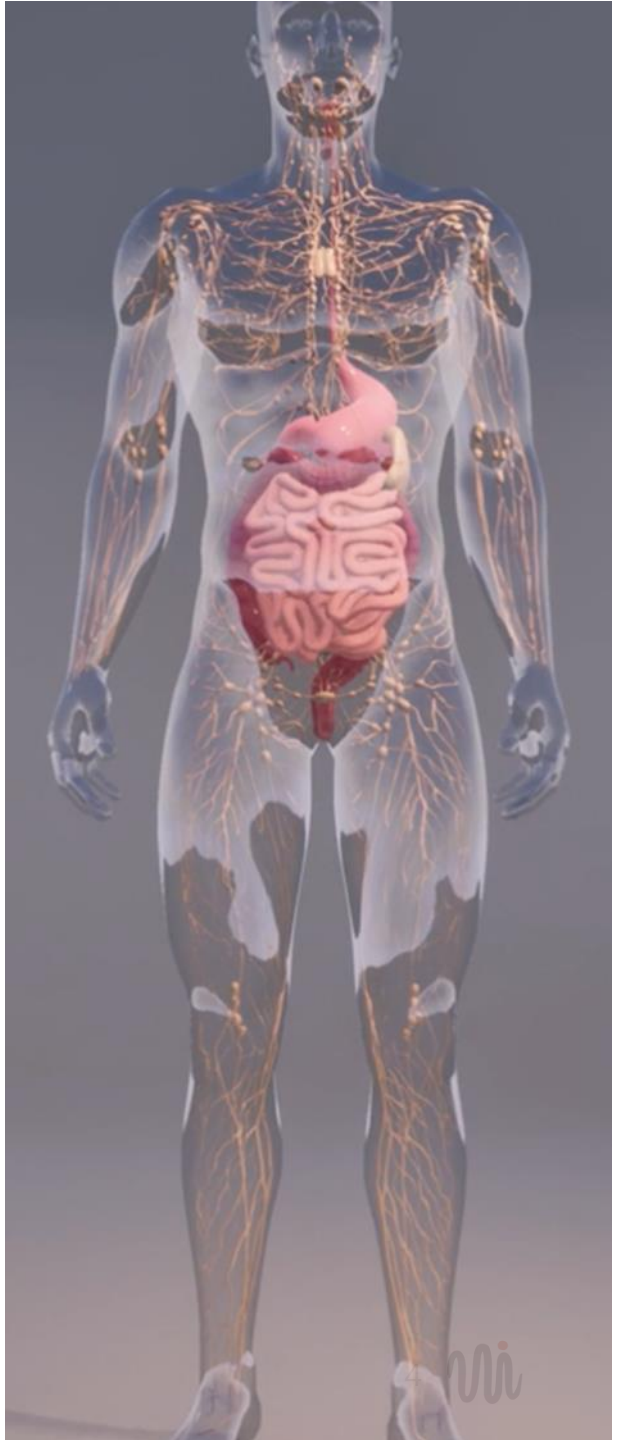
- Positive Phase 2 and Phase 1results prove SINTAX platform
- EDP1815 had placebo-like safety and tolerability
- Potential utility across all stages of disease: mild, moderate, and severe
- Potential to be used across broad spectrum of inflammatory diseases



Patient with moderate psoriasis achieved PASI-50 response at week 16 on EDP1815 – skin lesions improved further at week 20

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.
- Data prove that SINTAX-based medicines have meaningful clinical effects.
- Profile of SINTAX medicines allows 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?

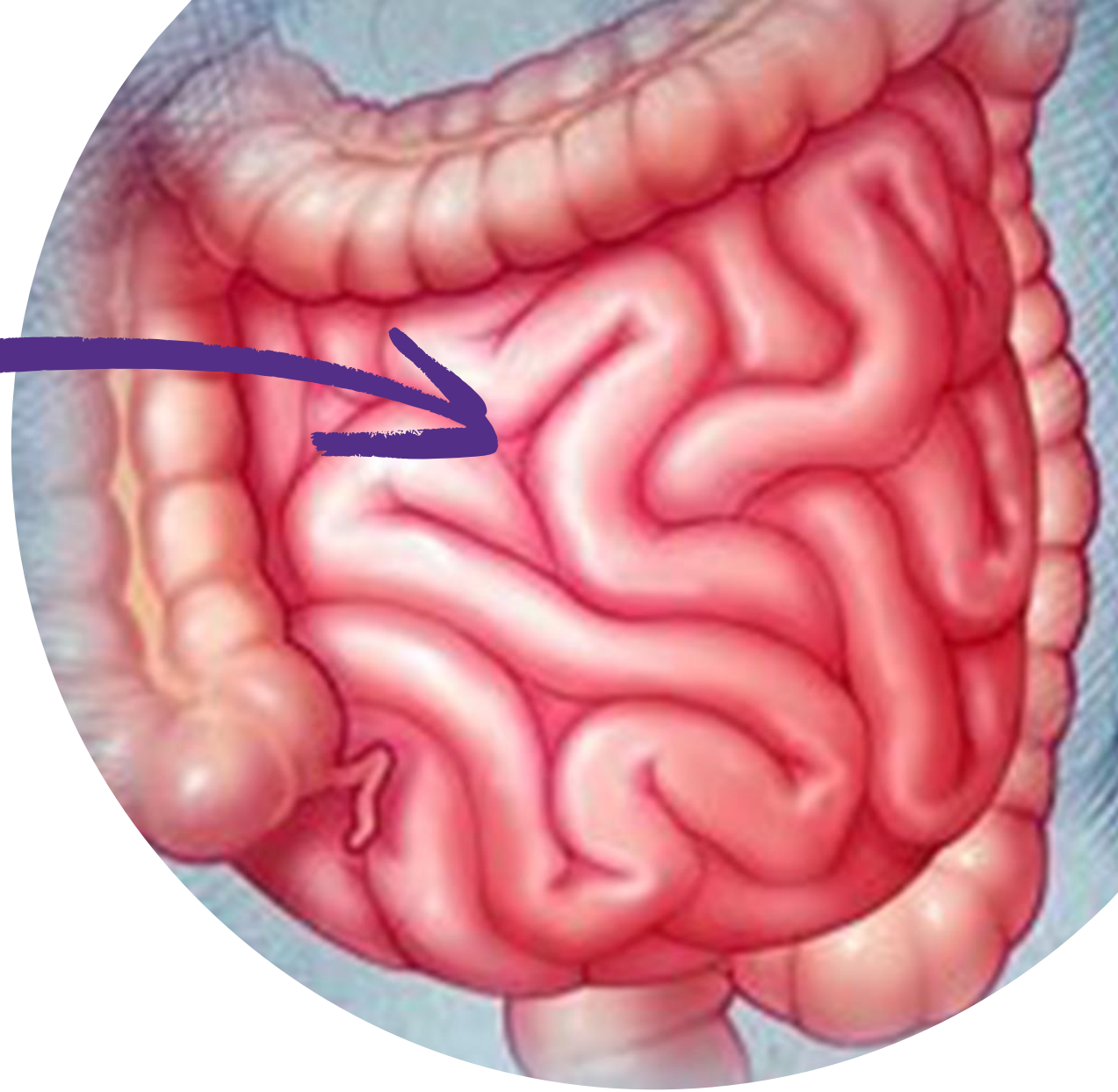
Evelo's potential medicines target SINTAX with oral microbial therapies

- 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

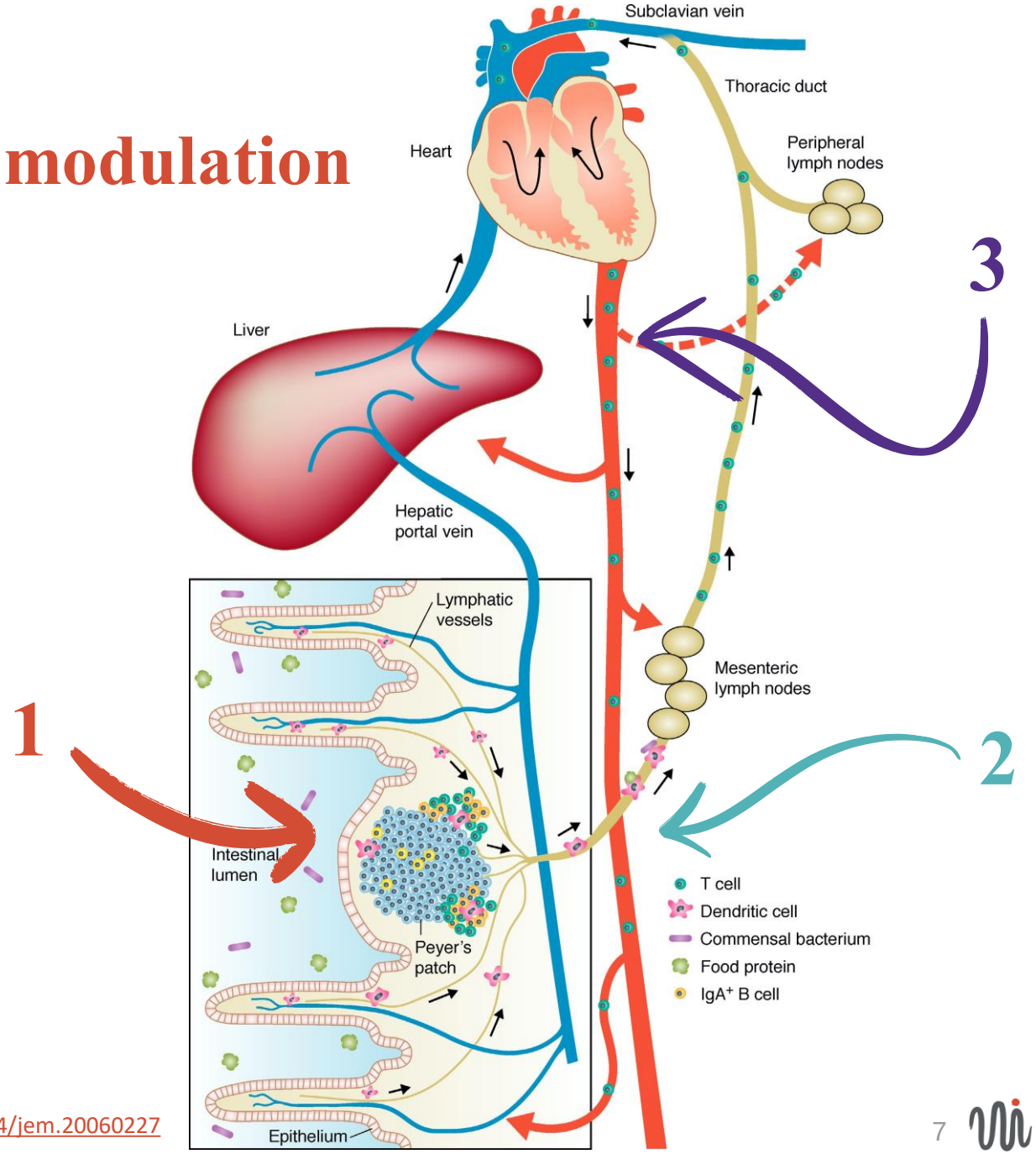
- SINTAX medicines target the small intestine
- Targeting SINTAX allows for remote control of systemic immunity

Three-Step Process for Immunomodulation by SINTAX Medicines

1. **Sampling of SINTAX medicines by cells in the small intestine**
   Effects driven by recognition of structural motifs

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

3. **Migration of effector T cells throughout the body via lymphatic circulation**
   Effects can be inflammation resolving or anti-tumor

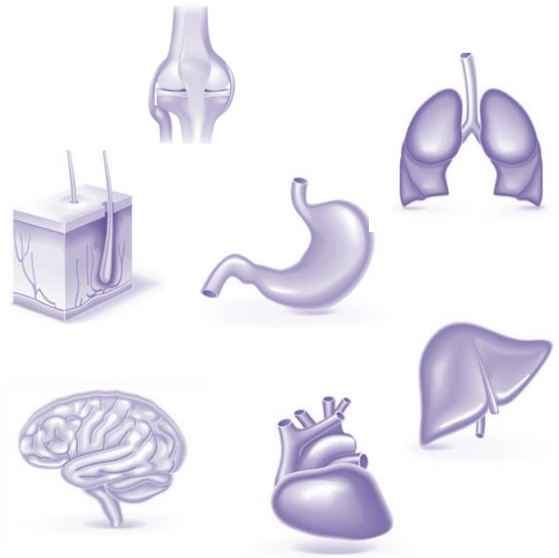


J Exp Med (2006) 203 (3): 497–500. https://doi.org/10.1084/jem.20060227

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*
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.*

Pipeline is Rich in Clinical Catalysts

2021

EDP1815

Psoriasis

- Positive Phase 2 data in 3Q; moving towards registration studies

2022

EDP1815

Psoriasis

- Part B of Phase 2 study 1Q
- Full data set during 2022

EDP1867

Atopic dermatitis

- Phase 1b data in 1H

EDP1815

Atopic Dermatitis

- Phase 2 data in 4Q

EDP2939

- Initiation of clinical development

2023

EDP1815

Psoriasis

- Registration studies

EDP1815

Atopic Dermatitis

- Registration studies

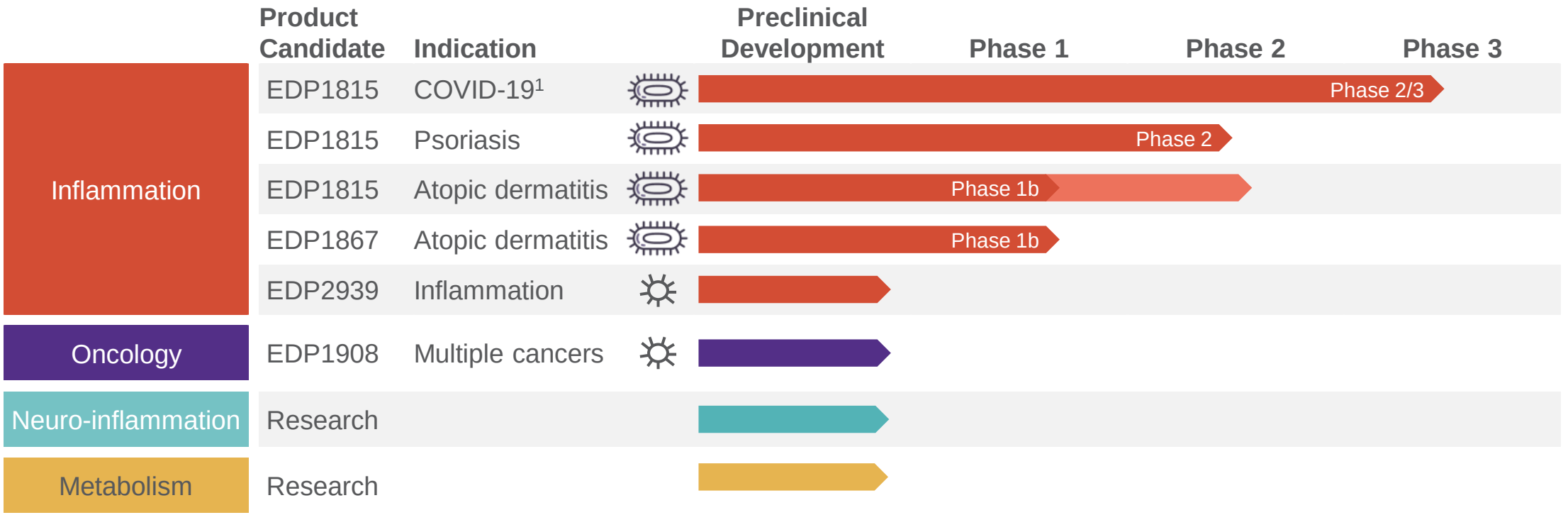
EDP2939

- Following feedback from regulatory agencies, initiate Phase 2 study

Other indications

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

Broad Clinical and Preclinical Pipeline Across Multiple Therapeutic Areas



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

EDP1815

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

***93%** of PsO patients*

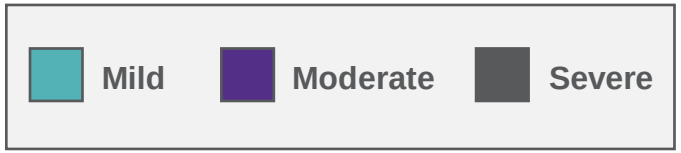
***85%** of AD patients*

Psoriasis

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

Atopic Dermatitis

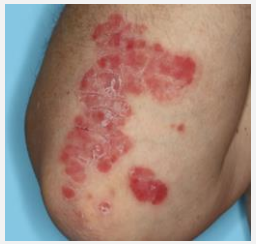
201M Worldwide prevalence
21.3M U.S. prevalence
10M U.S. diagnosed

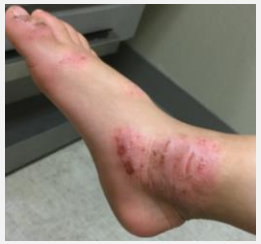


Source: Datamonitor Healthcare, Vanderpuyre-Orgle et al. J Am Acad Dermatol. 2015: 72:961–7

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]

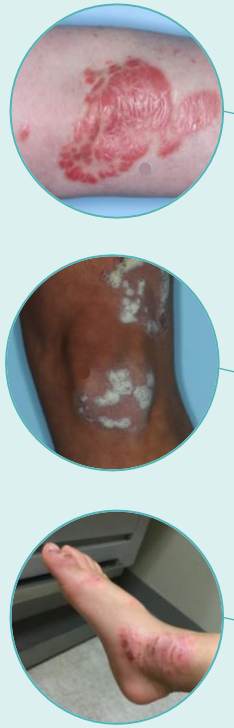
Psycho-social impacts

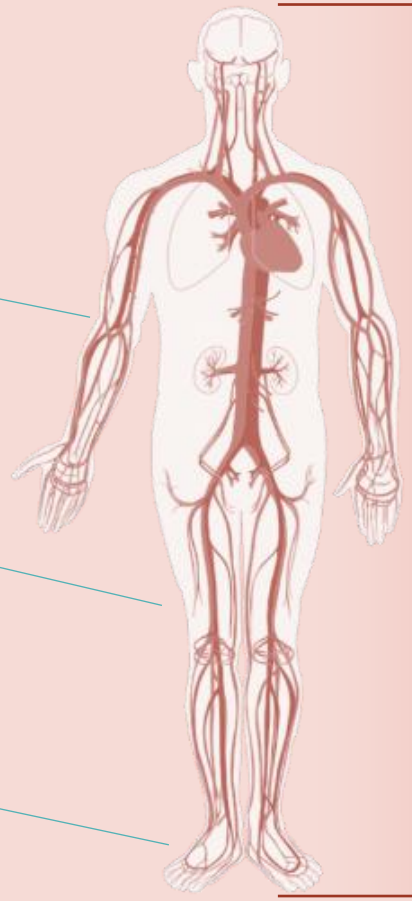
- **34%** of “mild” PsO sufferers have depression; **27%** suffer sleep disturbance[3]
- **50%** higher risk of depression for mild-moderate AD sufferers vs. people without AD[4]

[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

Psoriasis

EDP1815 Phase 2 Trial in Mild and Moderate Psoriasis

Trial Summary

- 16 week, double-blind, placebo-controlled, dose-ranging trial of 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

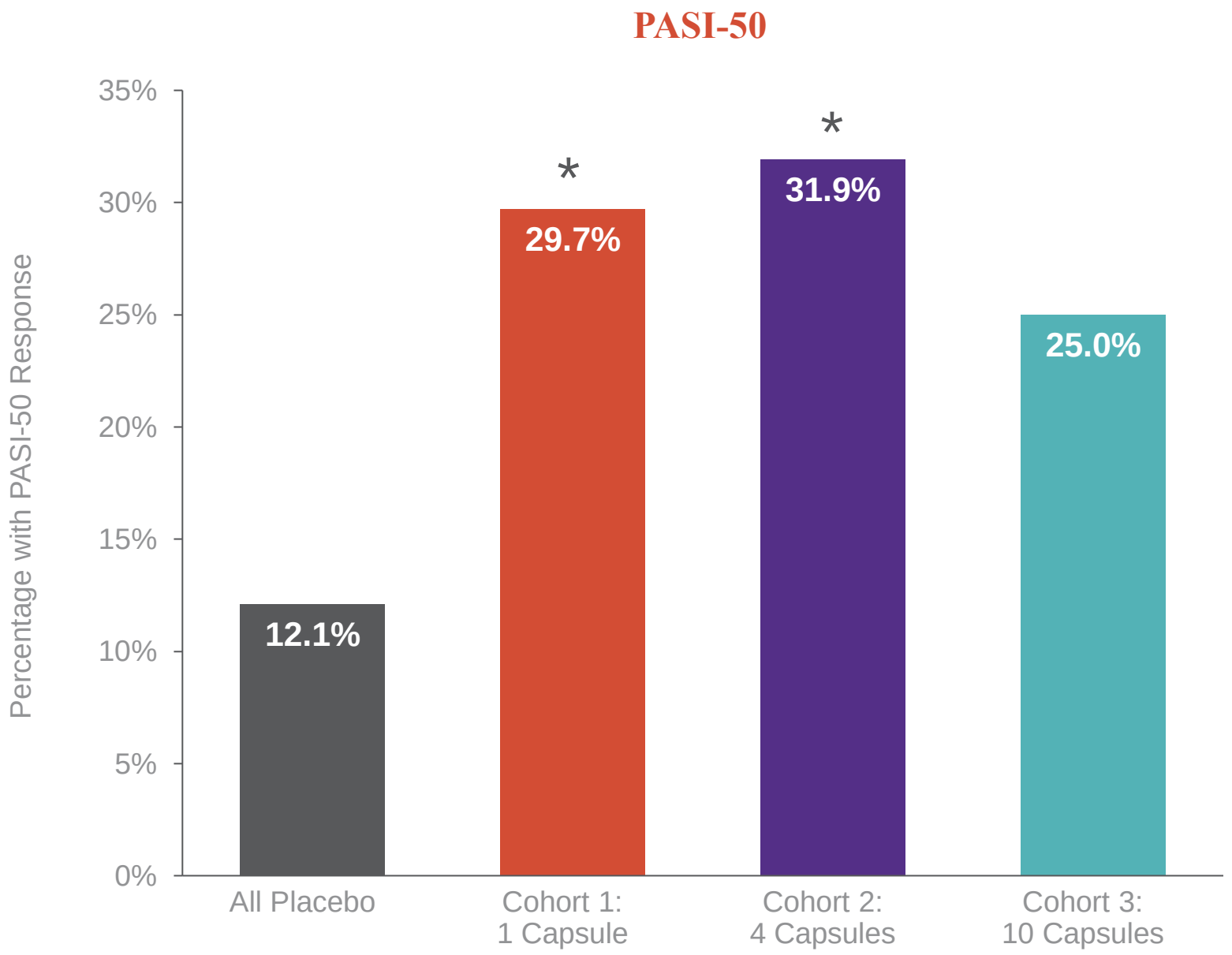
Percentage of patients achieving at least a PASI-50 by week 16

- **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

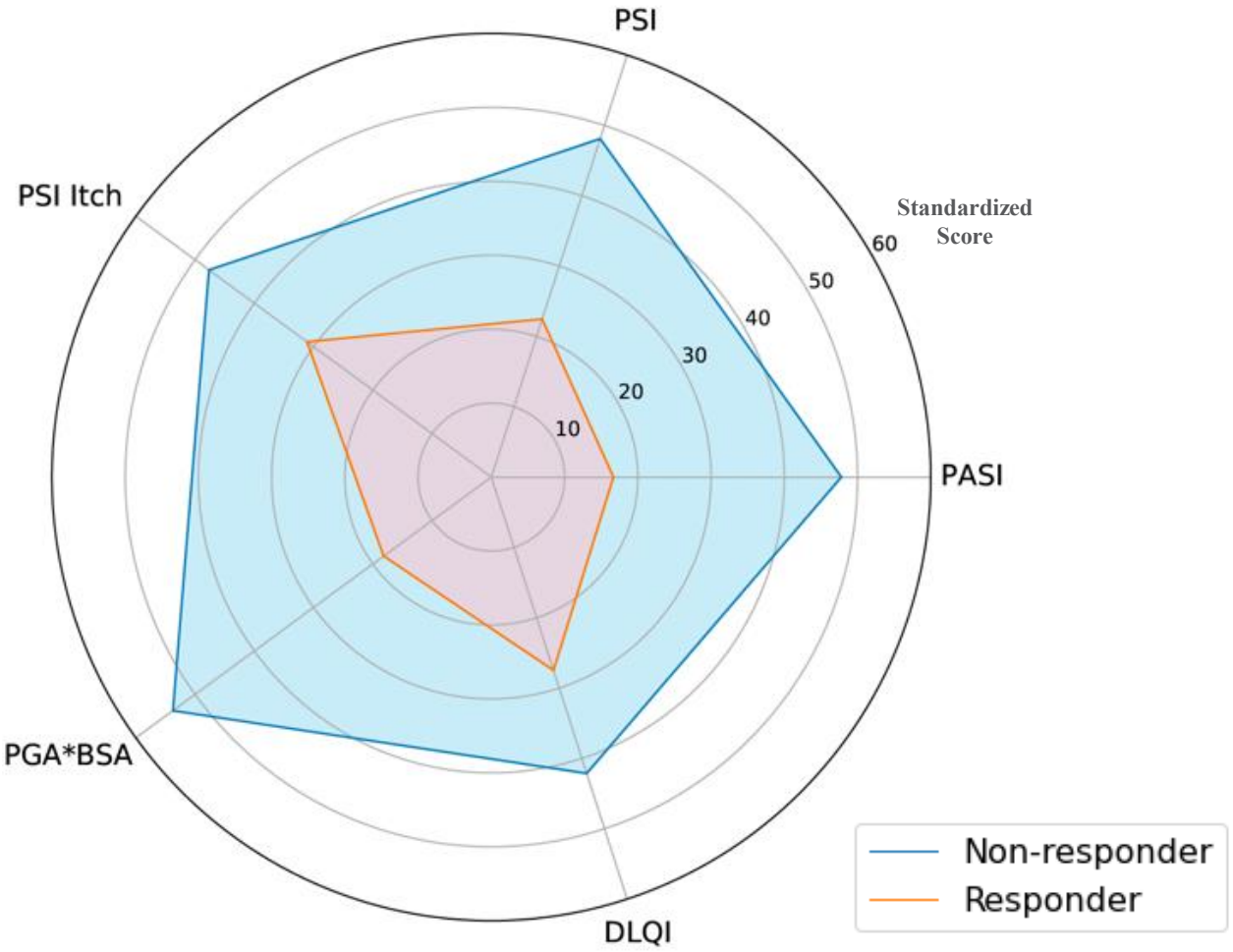
Statistically significant p-value (<0.05) for all 3 cohorts when pooled, and for 2 of the 3 individual dose cohorts

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

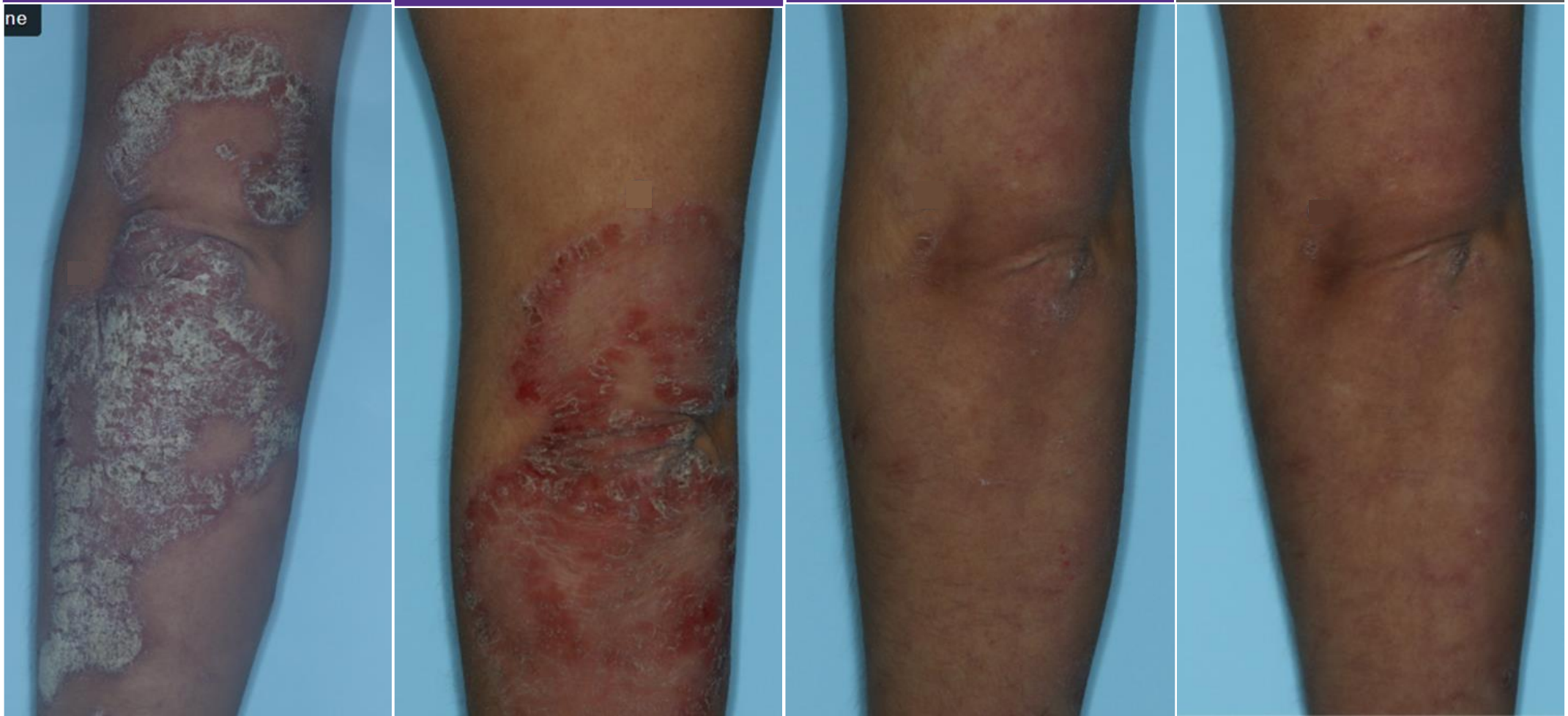
-3.5

Active non-responders: **-1.4**

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

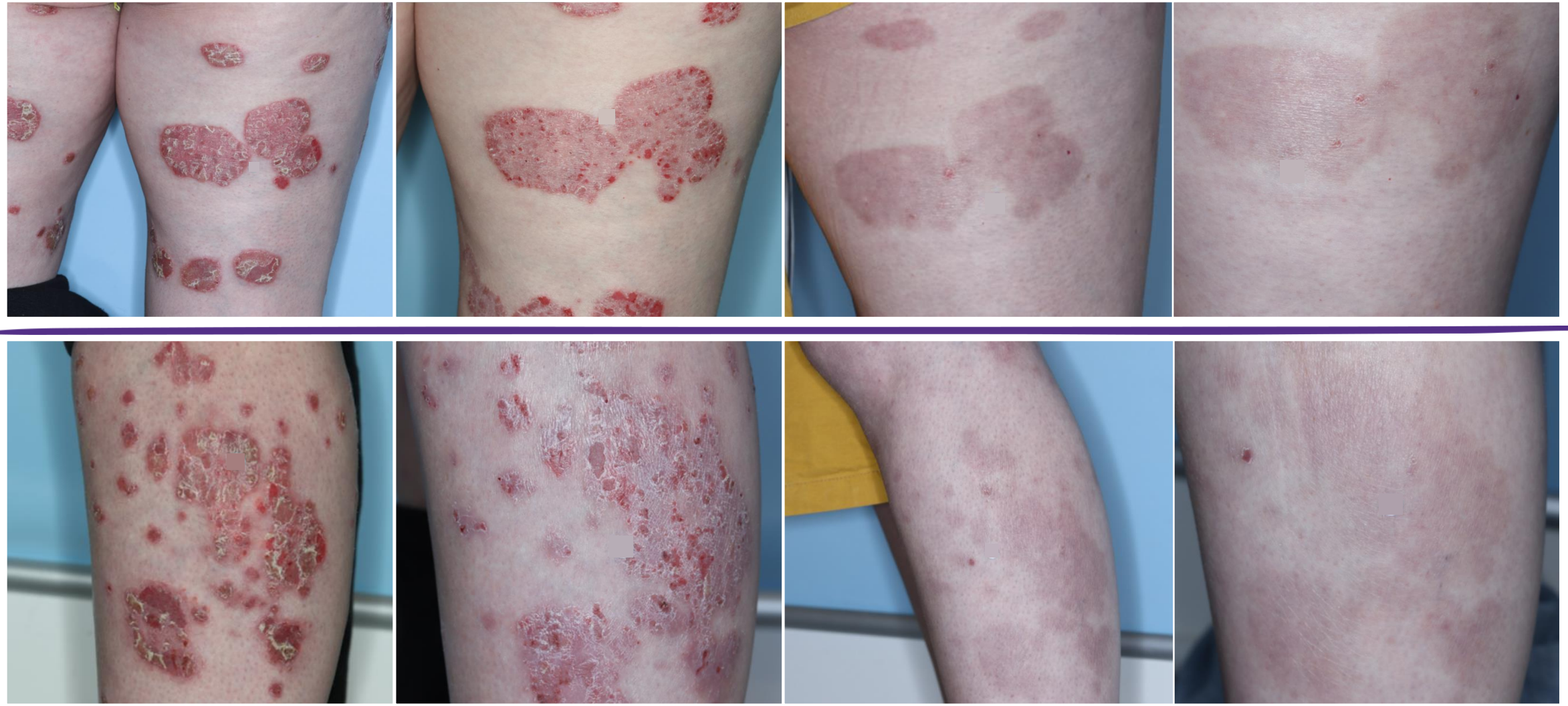
Patient with Moderate Psoriasis Achieved PASI-50 Response at Week 16 on EDP1815 – Skin Lesions Improved Further at Week 20

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

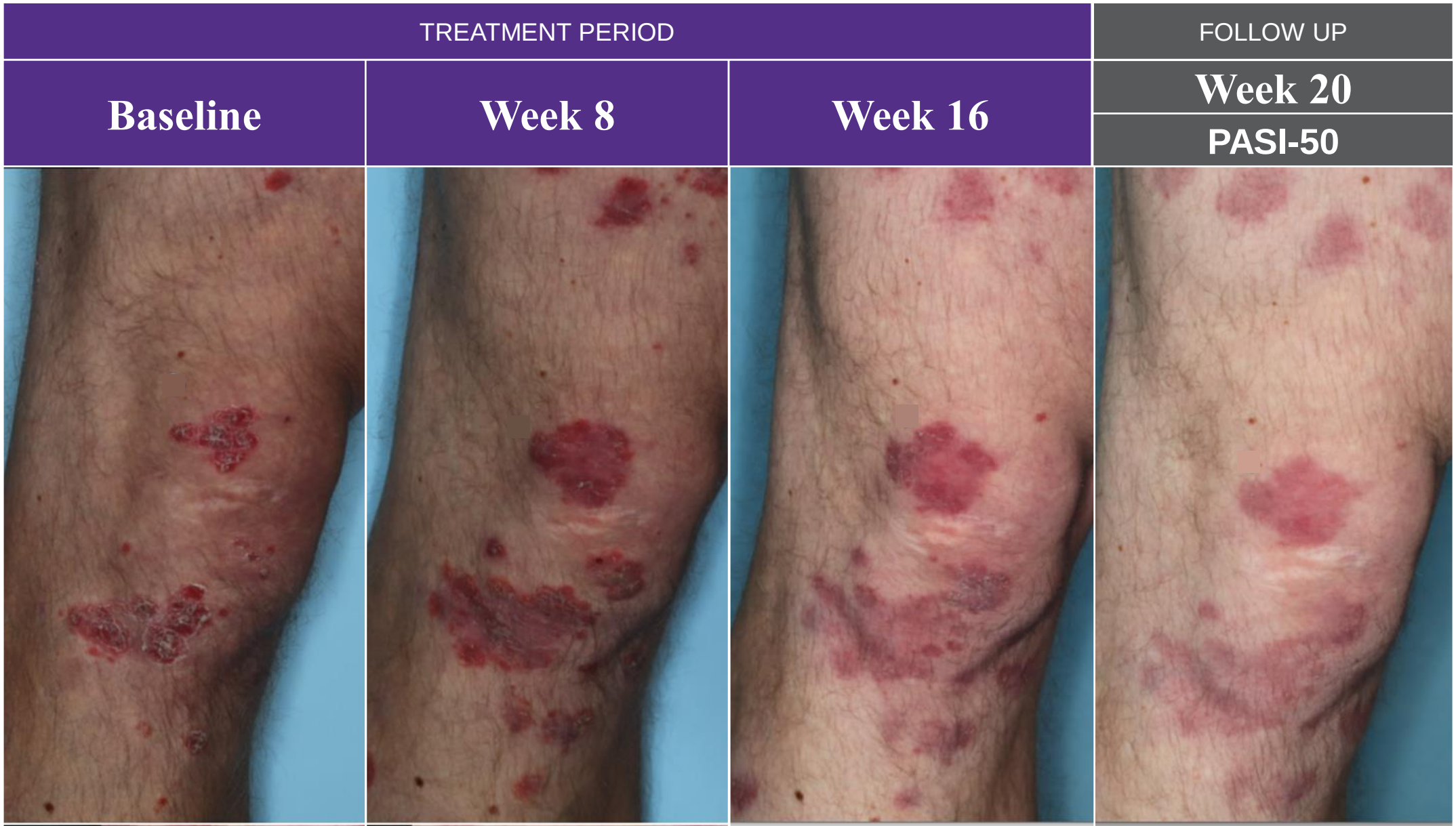


Patient with Moderate Psoriasis Achieved PASI-90 Response at Week 16 on EDP1815 – Skin Lesions Improved Further at Week 20

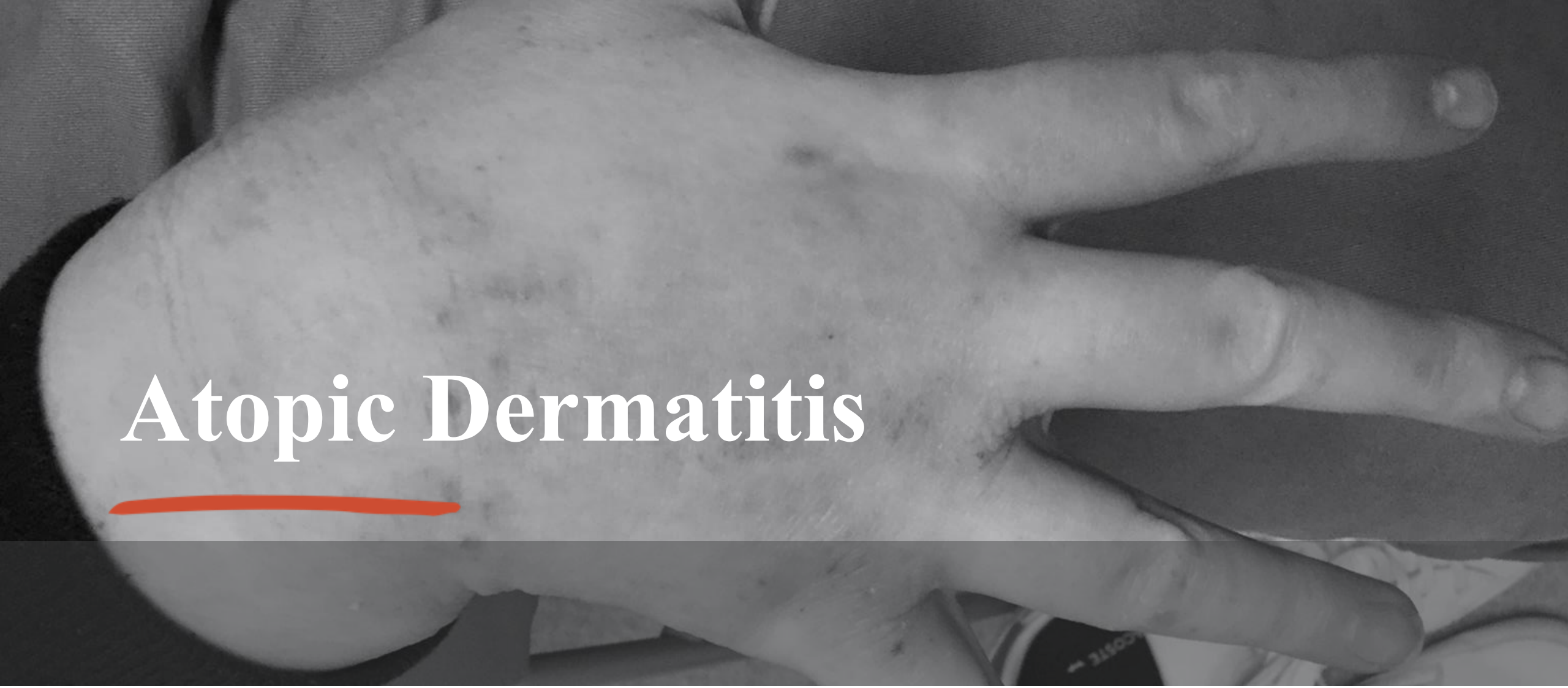
TREATMENT PERIOD			FOLLOW UP
Baseline	Week 4	Week 16 PASI-90	Week 20



Patient with Moderate Psoriasis Considered a Non-responder at Week 16, Achieved PASI-50 Response at Week 20 on EDP1815 – Suggests Deepening Response Over Time



EDP1815 Advancing Towards Registration Studies in Psoriasis



Atopic Dermatitis

EDP1815 Phase 1b Trial in Atopic Dermatitis

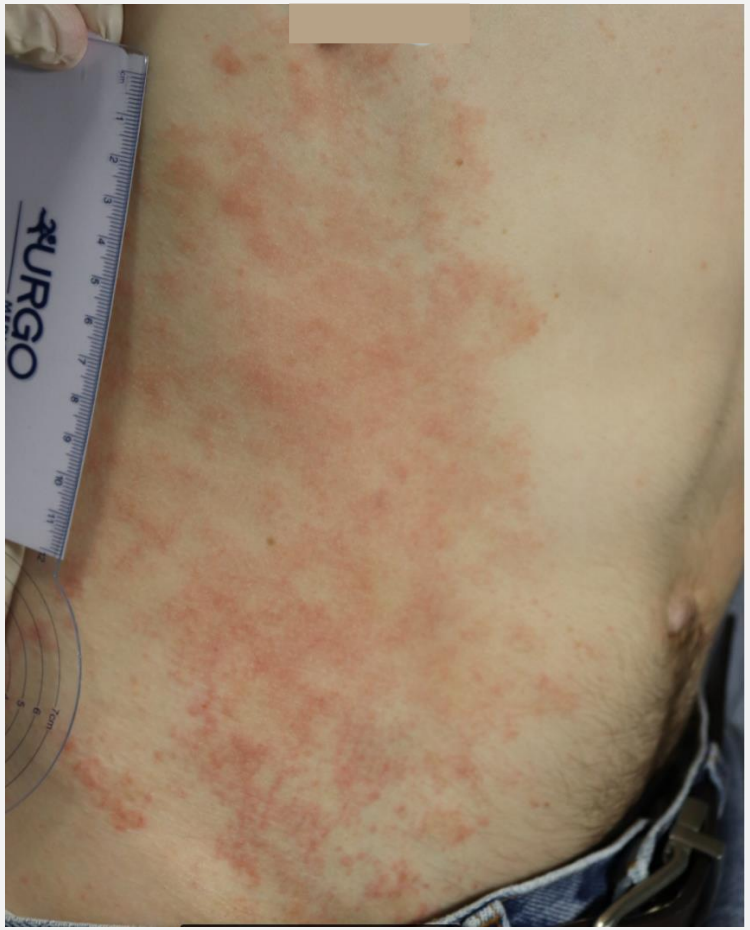
Trial Summary

- 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

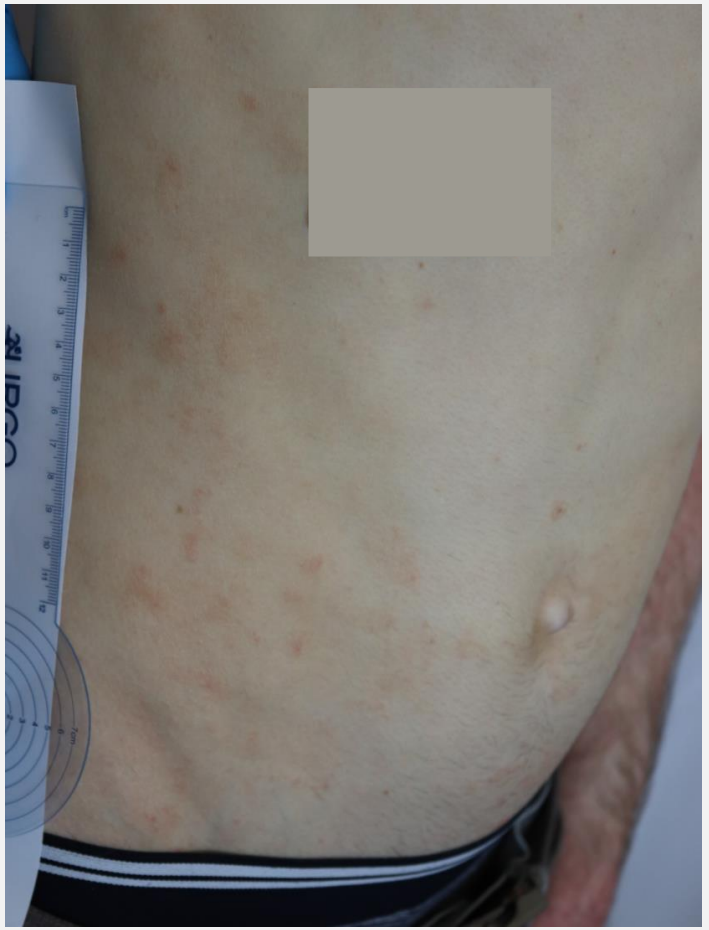
Summary of Endpoints

- 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



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



Before, day 0

After, day 56

Clinically Meaningful Improvements in Clinical Scores and Patient Reported Outcomes, Including Sleep and Itch

For EDP1815-treated patients at day 56:

Improvements in EASI, IGA*BSA, and SCORAD

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

Improvements in Patient-Reported Outcomes

DLQI (Dermatology Life Quality Index)
mean improvement exceeded clinically validated threshold[1]

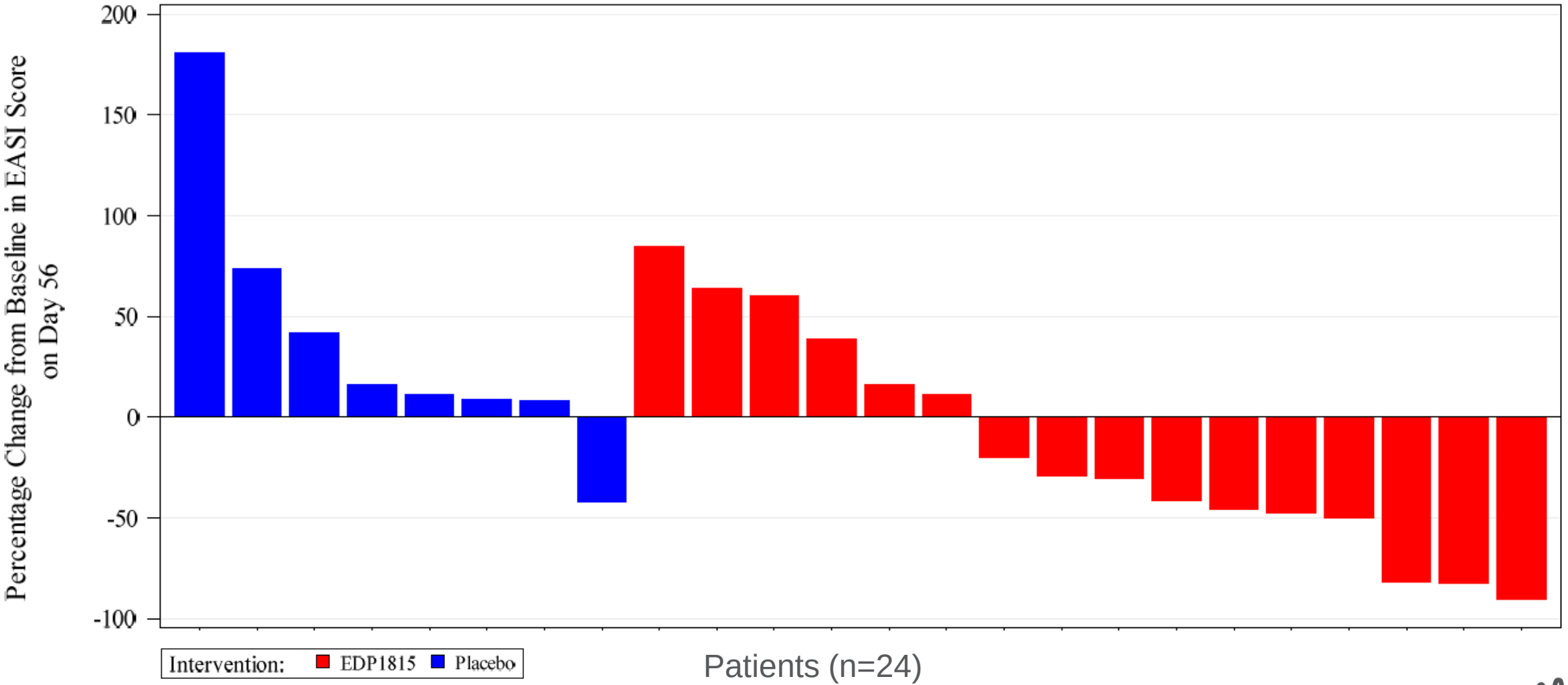
POEM (Patient-Oriented Eczema Measure)
mean improvement exceeded the clinically validated threshold[2]

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.

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



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

Key Inclusion Criteria:

- IGA of 2, 3 or 4
- BSA of ≥ 5%
- EASI of ≥ 6

Data expected 4Q 2022

Screening Period: *up to 4 weeks*

Treatment Period: *16 weeks*

Follow-up Period: *4 weeks*
(or participant can proceed into Open Label Extension study)

Cohort 1: 1 capsule once daily EDP1815 or Placebo

Cohort 2: 2 capsules once daily EDP1815 or Placebo

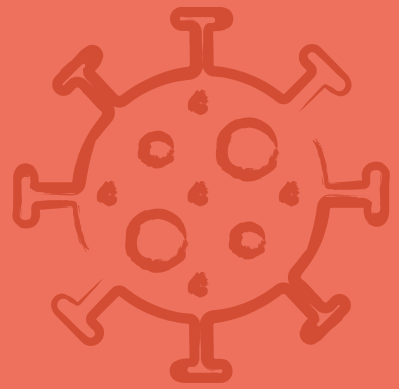
Cohort 3: 1 capsule twice daily EDP1815 or Placebo

N=300

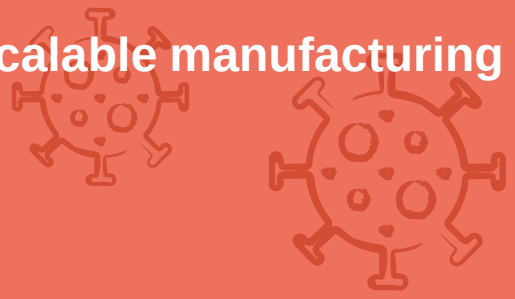
Primary Endpoint: *Achievement of an EASI-50 response at week 16*

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

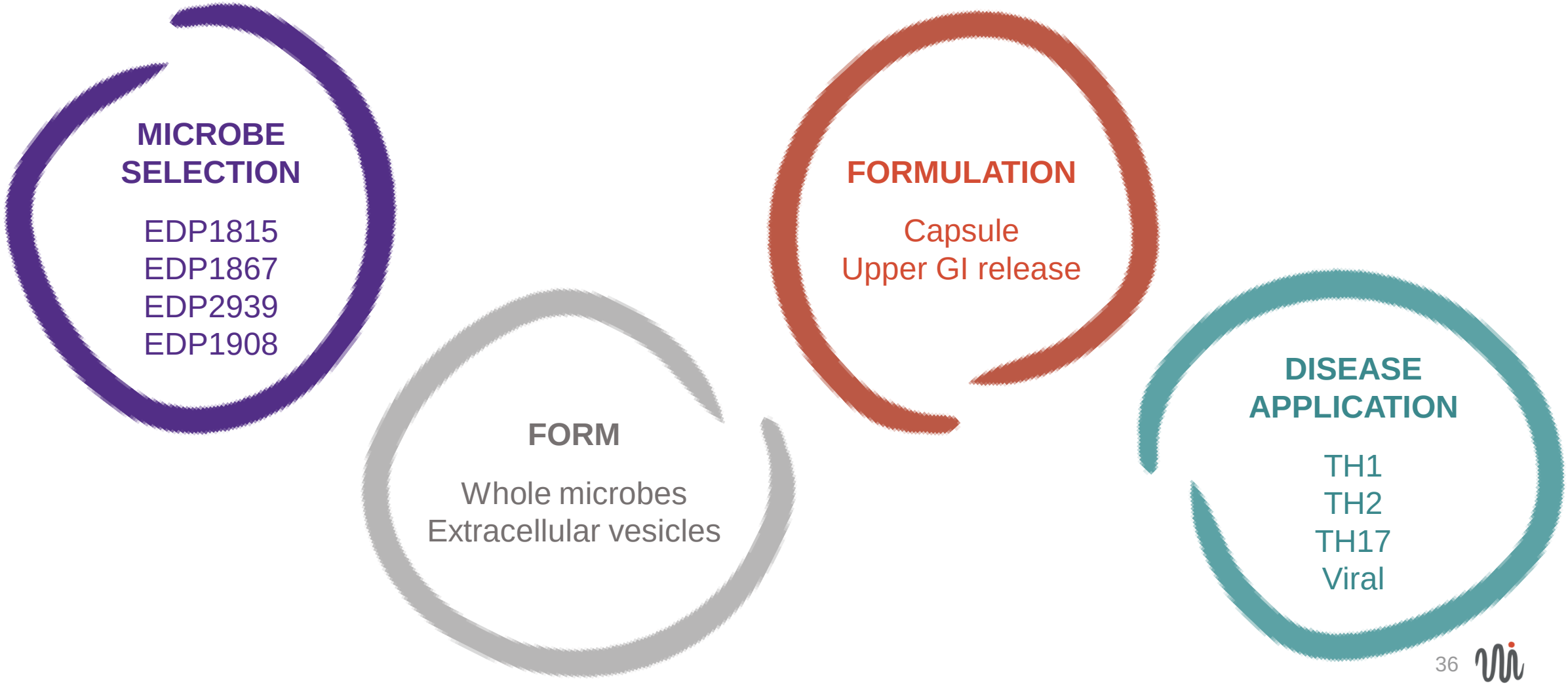
TACTIC-E: Phase 2/3 Platform Trial

- 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

Next Wave of SINTAX Medicines

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



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

- Pharmacologically active strains of gut mucosa-derived microbes naturally shed lipoprotein nanoparticles called EVs
  - Their molecular content is a subset of the parent
- Future 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
  - Non-live
  - Small size and diffusion properties enable potential target engagement in the gut
- Evelo has scaled manufacturing of EVs

Stokes-Einstein Equation

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

Fick's Laws of Diffusion

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

Pipeline

Pipeline Provides Multiple Diversified Non-Correlated Opportunities

EDP1815: Th17 Effects

Potential to expand into other Th17-mediated diseases

Psoriasis

- Positive topline Phase 2 clinical data; moving to registration studies
- Phase 2 Part B data **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

- Phase 2 data expected **4Q 2022**

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

- Phase 2/3 TACTIC-E 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 **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

EDP1908: EV

Preclinical data suggests broad use across oncology

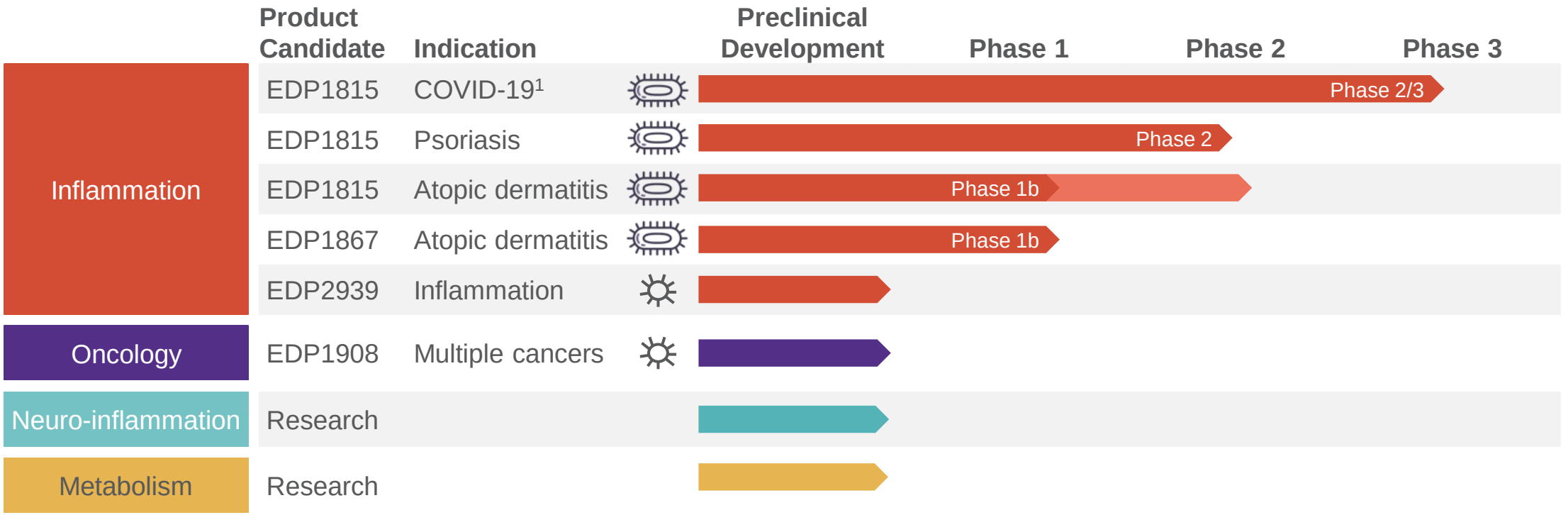
Oncology

- Anticipate 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

Broad Clinical and Preclinical Pipeline with Multiple Upcoming Readouts



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

Appendix

Corporate Information

~120 employees

Cash and cash equivalents of more than $120 million*

~$50 million ATM program with capacity remaining

Long-term debt $45 million

*As of June 30, 2021