EVELO

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

Evelo Corporate Presentation

June 2022

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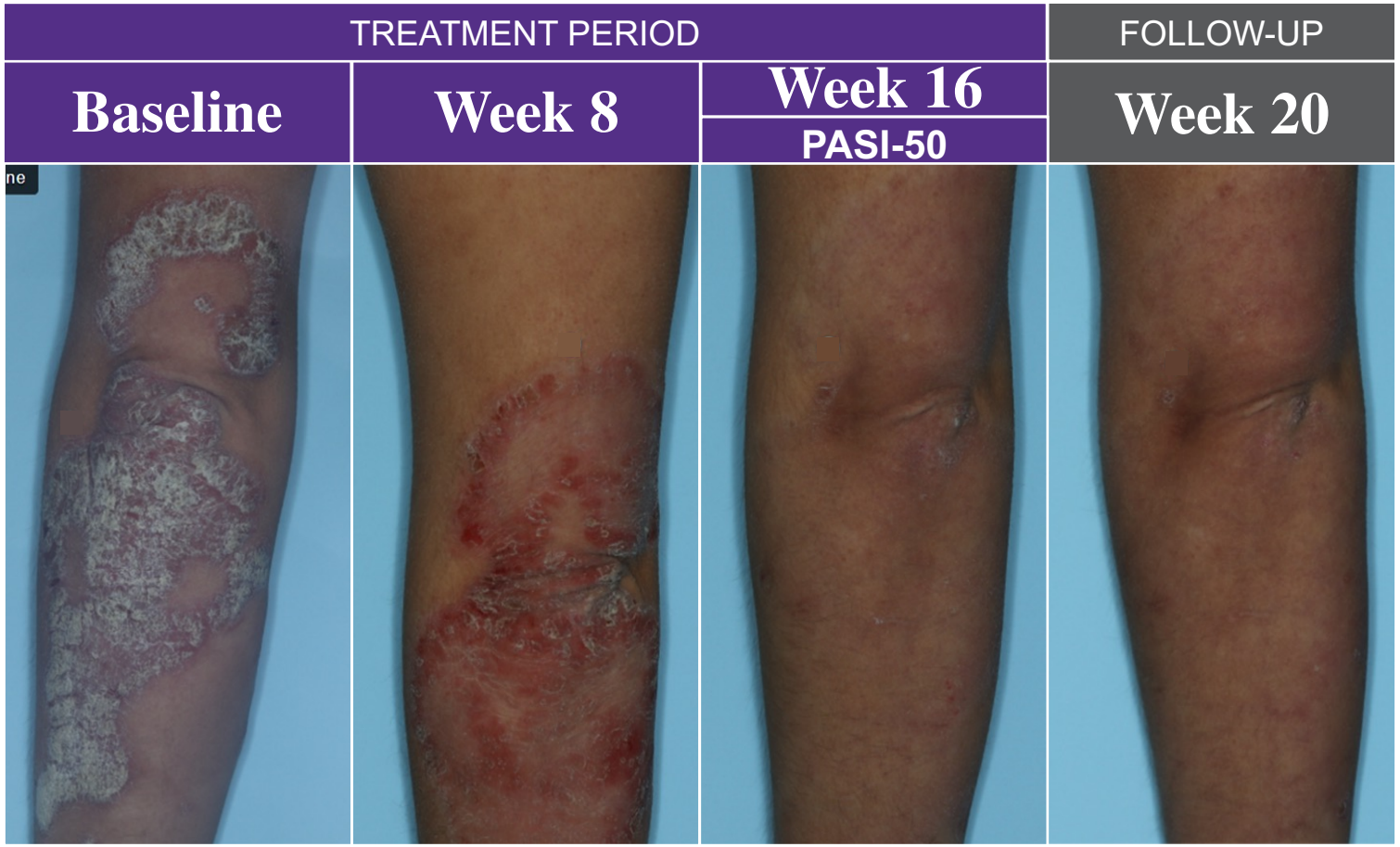
Positive EDP1815 Data Validates Platform, Supports Advancing Towards Registration Trials

- Positive Phase 2 and Phase 1 results prove SINTAX platform
- Moving towards registration trials
- 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

Upcoming Clinical Catalysts

1H 2022

Candidate	Catalyst
EDP1815 Psoriasis	**1Q 2022:** Cytokine data from Phase 2 trial ☑ Part B data from Phase 2 trial ☑ Formulation data ☑
EDP1815 Atopic Dermatitis	**1Q 2022:** Initiation of dosing of patients in Phase 2 trial ☑

2H 2022 / 2023

Candidate	Catalyst
EDP2939 Inflammation	**3Q 2022:** Initiation of clinical development **2H 2023:** Phase 2 data from cohort of patients with psoriasis
EDP1815 Psoriasis	**2023:** Potential registration trials
EDP1815 Atopic Dermatitis	**1Q 2023:** Data from first 3 cohorts in Phase 2 trial **2Q 2023:** Data from 4th cohort in Phase 2 trial

Other indications

- Potential to expand into psoriatic arthritis, asthma, neuroinflammation, pediatric populations, etc.

Section 1. SINTAX Platform

Section 2. Unmet Need in Inflammation

Section 3. Evelo's Product Candidates

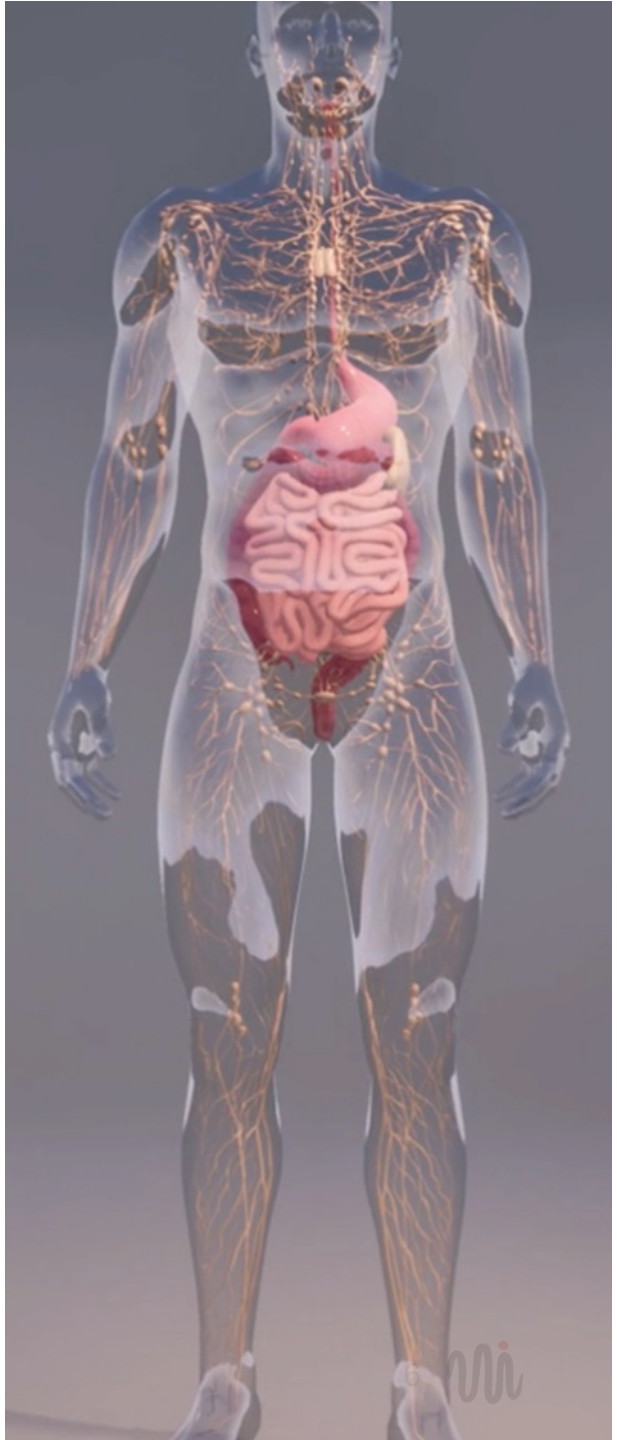
- EDP1815
- EDP2939

Section 4. Pipeline and Inflection Points

Appendix

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.
- SINTAX medicines could allow Evelo to achieve its vision of providing a new class of:
  - Effective, safe and well tolerated, oral and convenient, affordable medicines.
  - Benefitting billions of people at all stages of inflammatory disease



What are Evelo's Investigational Medicines?

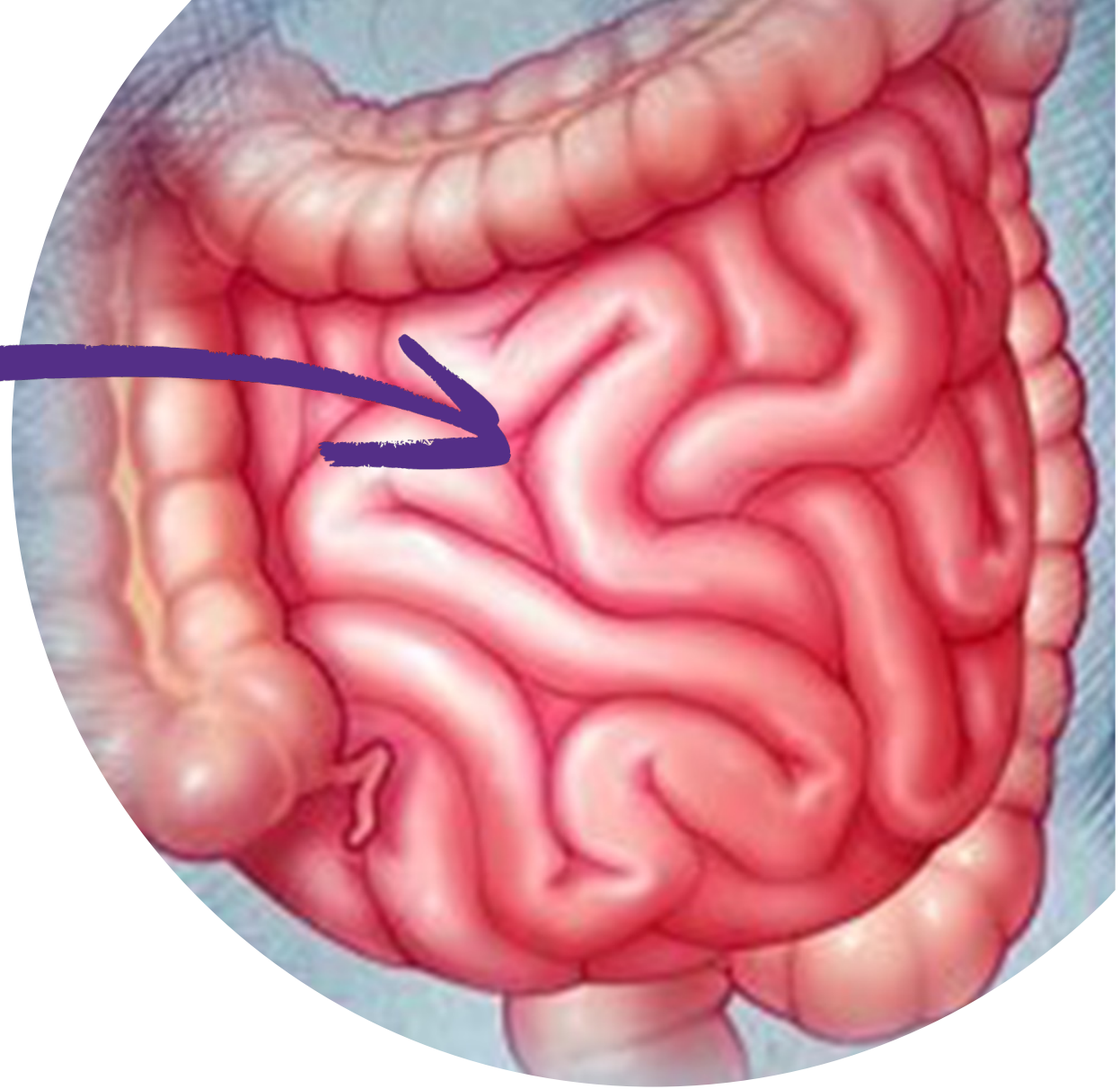
Evelo's potential medicines target SINTAX with oral microbial therapies

- 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

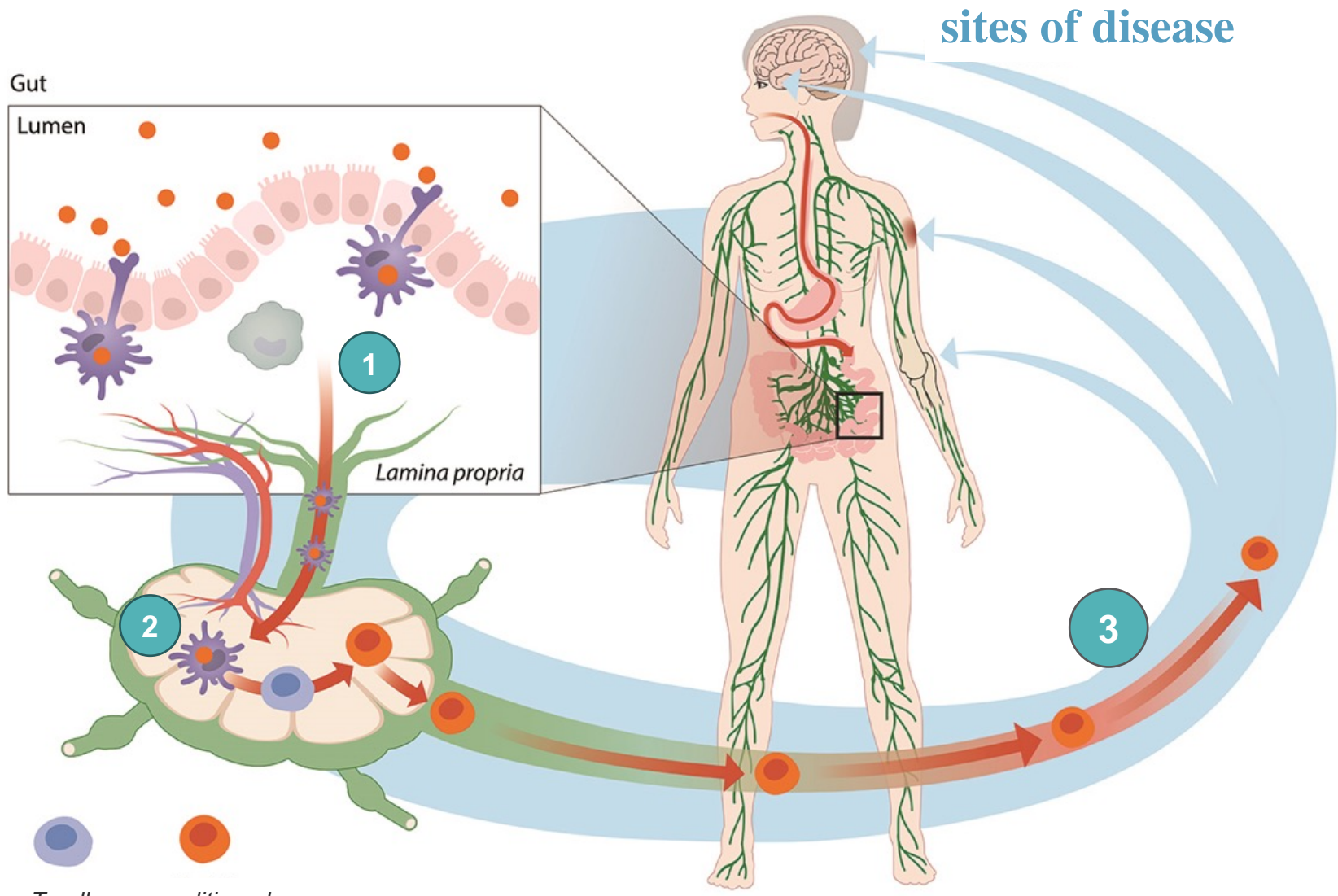
- 80-90% of the gut surface area
- Epithelium includes specialized cells
  - *Immune, endocrine, neural*
- Sensing of signals and governing of physiology throughout the body
- Very low level of resident gut microbes

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**



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

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

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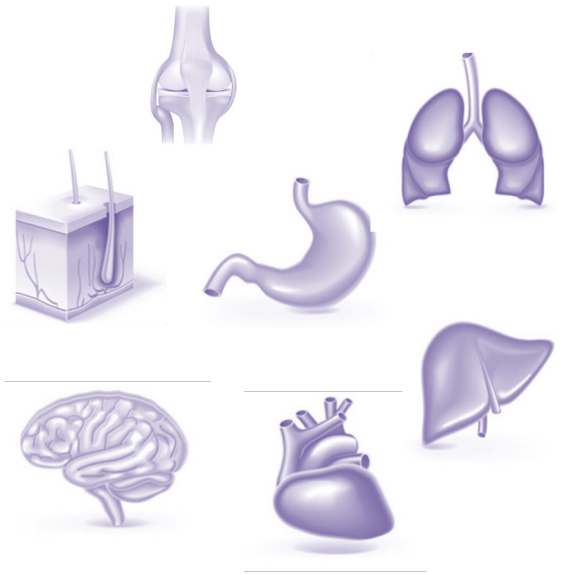
SINTAX Medicines Have Potential Use Across Spectrum of Inflammatory Diseases with Opportunity to Impact One Billion People

	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

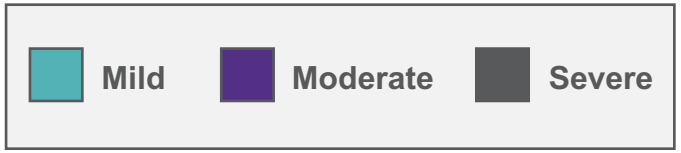
***93%** of PsO patients*
***85%** of AD patients*

Psoriasis

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

Atopic Dermatitis

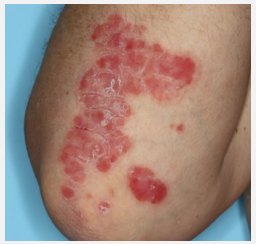
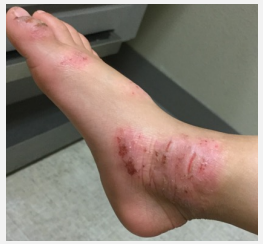
201M Worldwide prevalence
21.3M U.S. prevalence
10M U.S. diagnosed



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]

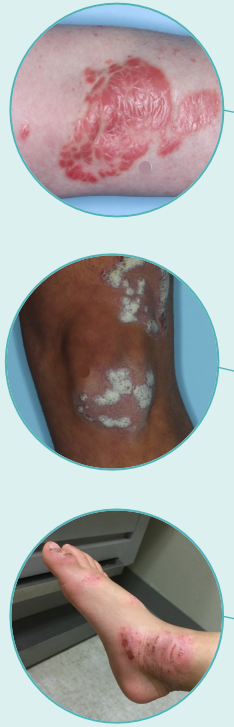
Psycho-social impacts

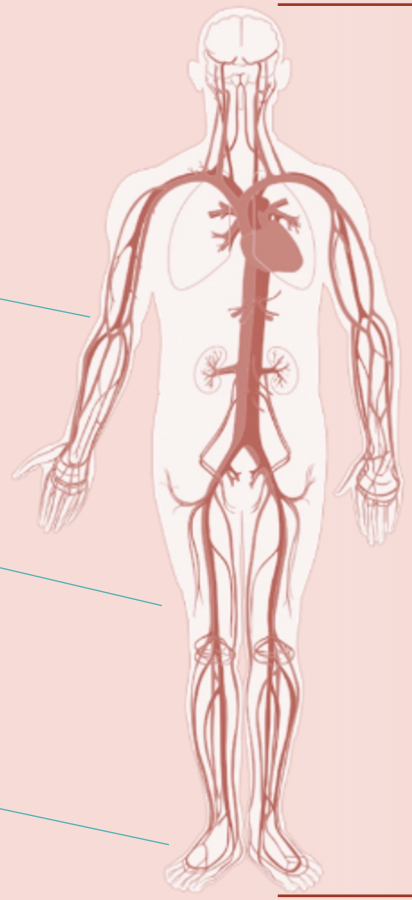
- **34%** of “mild” PsO sufferers have depression; **27%** suffer sleep disturbance[3]
- **50%** higher risk of depression for mild-moderate AD sufferers vs. people without AD[4]

[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

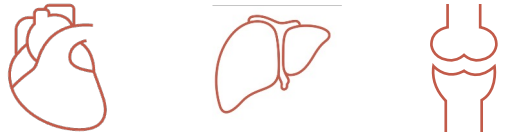
SKIN INFLAMMATION





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 and well tolerated, oral and convenient, affordable therapy could expand the addressable patient population

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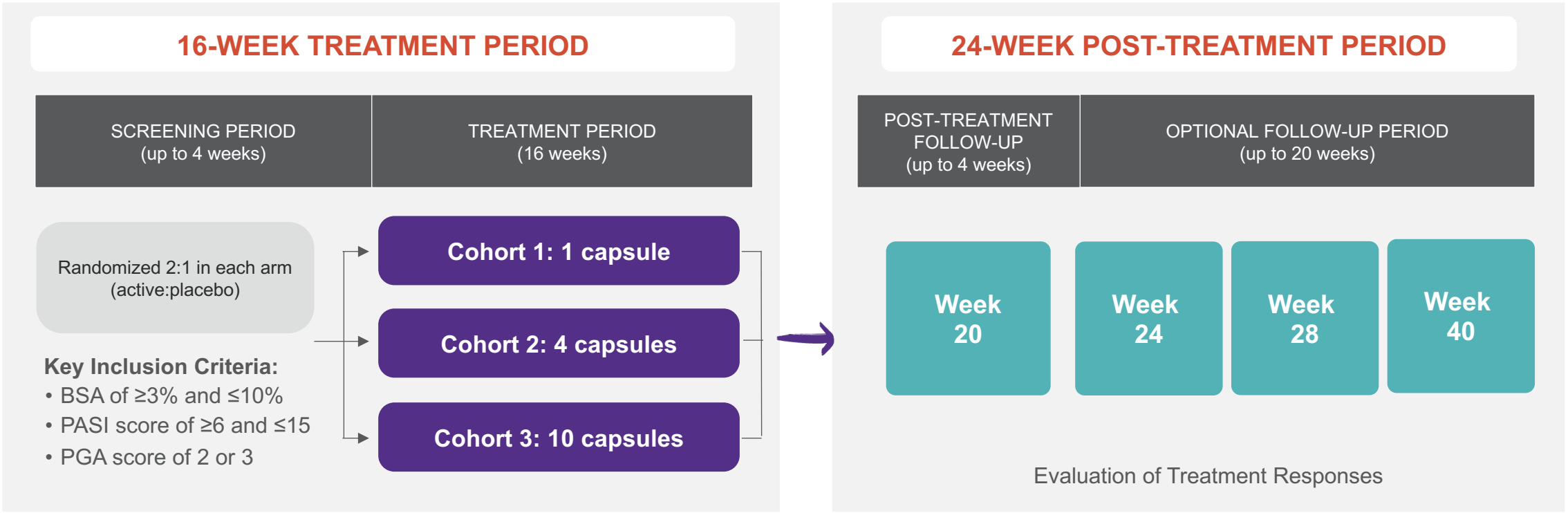
EDP1815

- Advancing towards registration trials in psoriasis
- Phase 2 trial in atopic dermatitis underway
- Multiple opportunities in inflammatory diseases with single microbe

Psoriasis

EDP1815 Phase 2 Trial in Mild and Moderate Psoriasis



EDP1815 Phase 2 Trial in Mild and Moderate Psoriasis – Part A

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

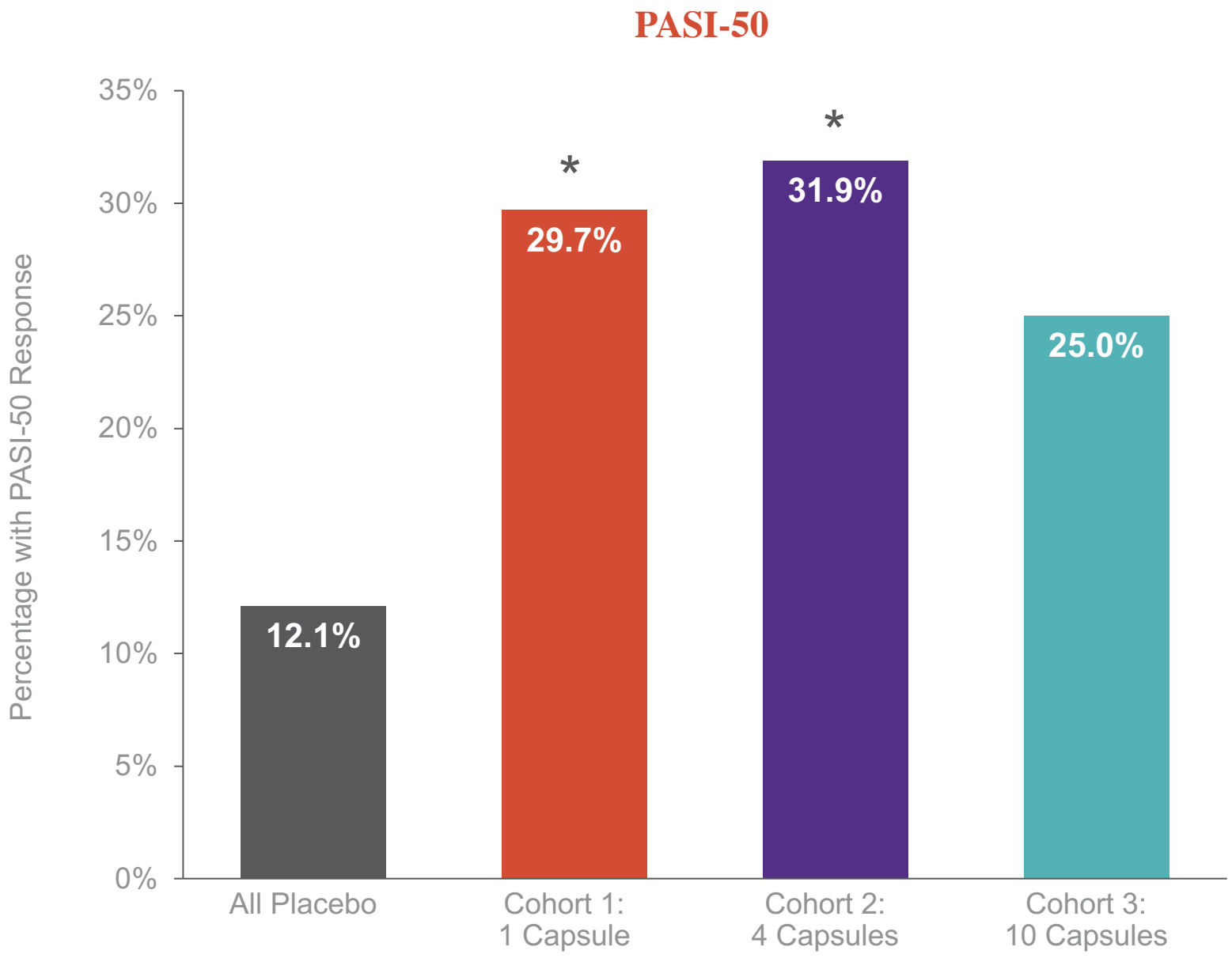
Percentage of patients achieving at least a PASI-50 by week 16

- **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

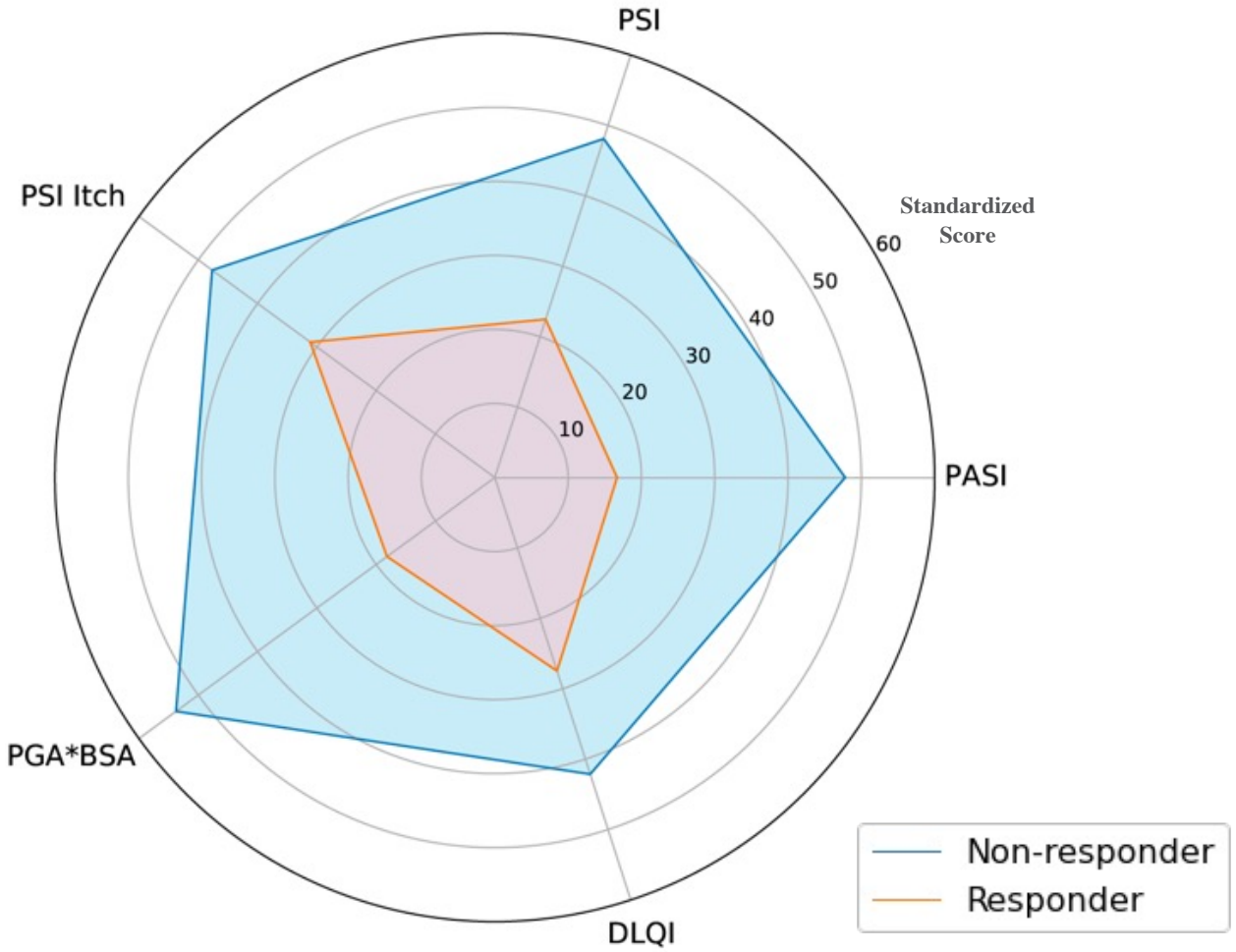
Statistically significant p-value (<0.05) for all 3 cohorts when pooled, and for 2 of the 3 individual dose cohorts

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

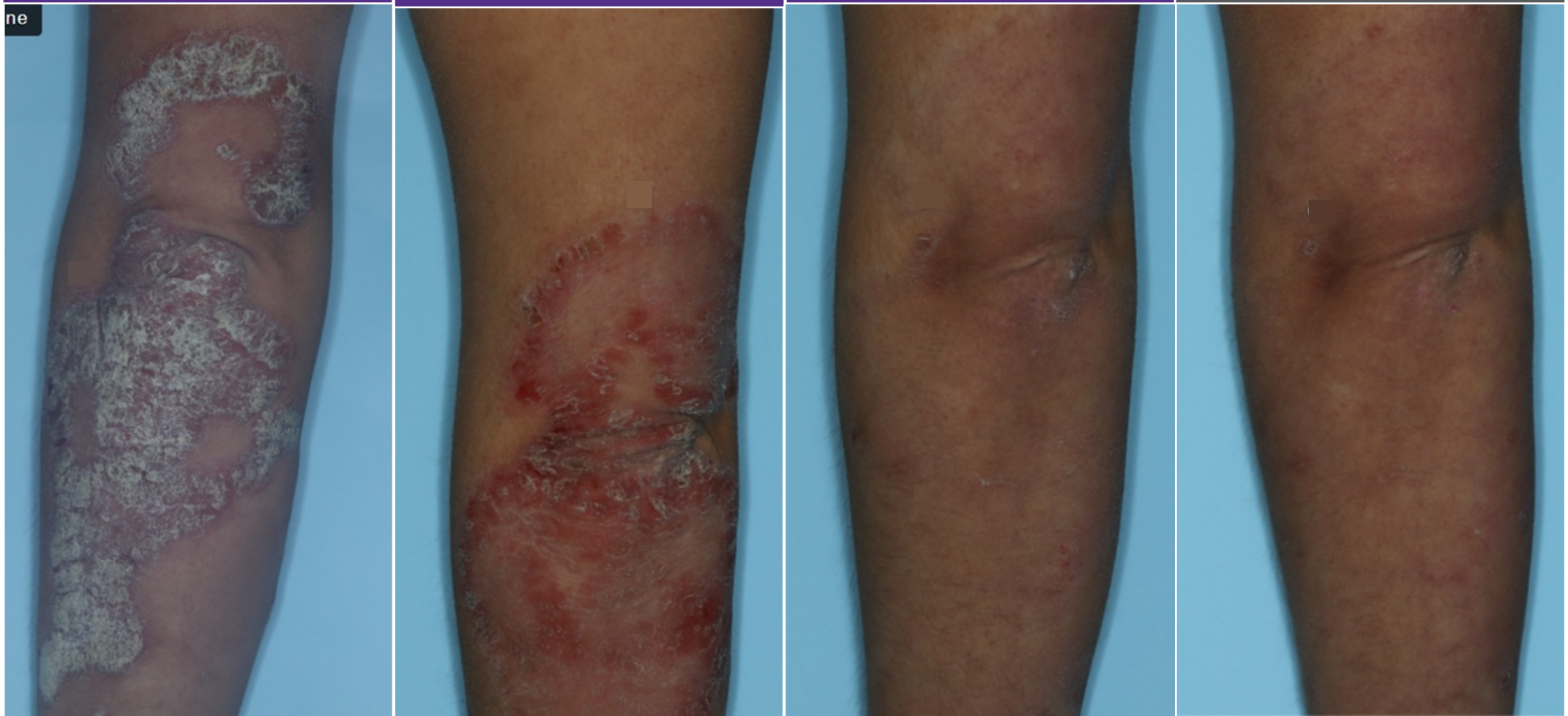
-3.5

Active non-responders: -**1.4**

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

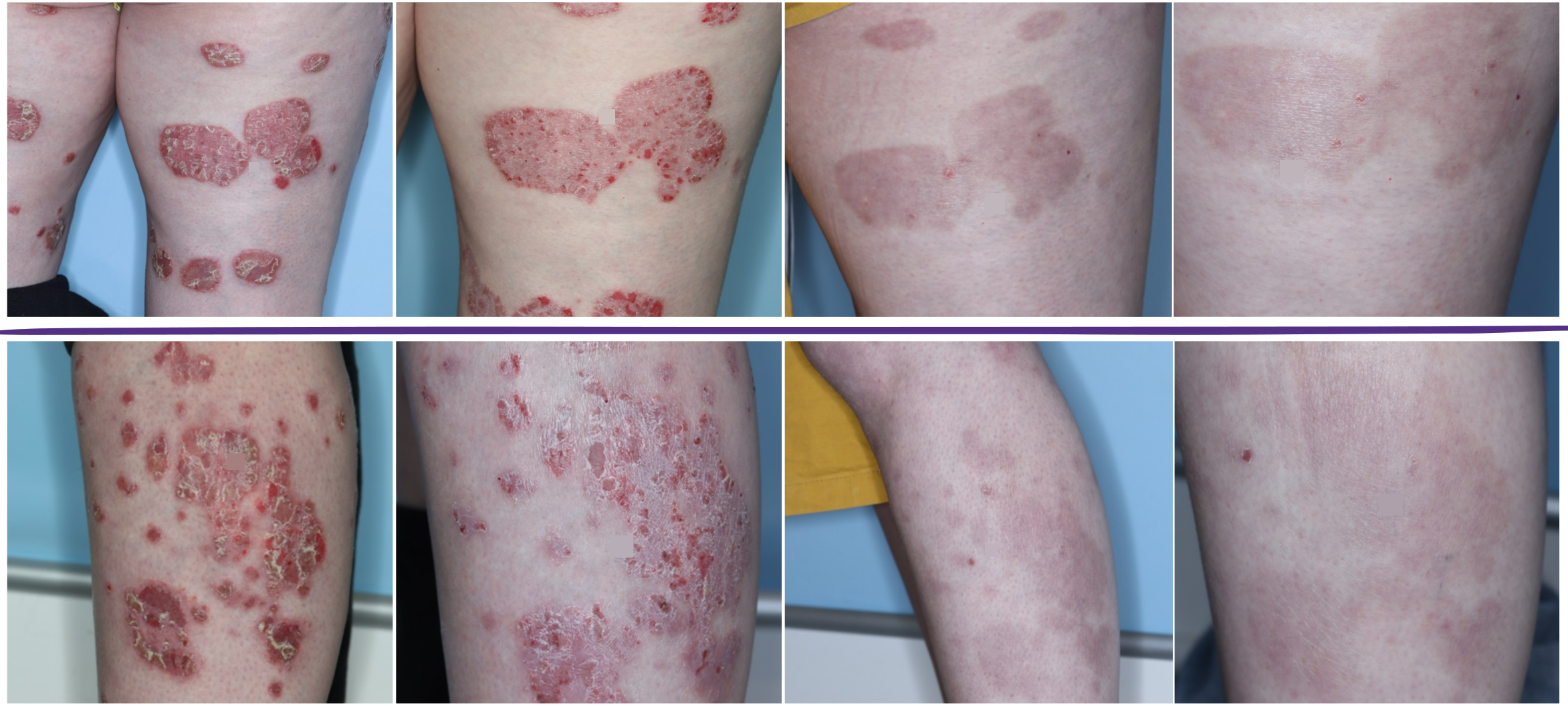
Patient with Moderate Psoriasis Achieved PASI-50 Response at Week 16 on EDP1815 – Skin Lesions Improved Further at Week 20

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

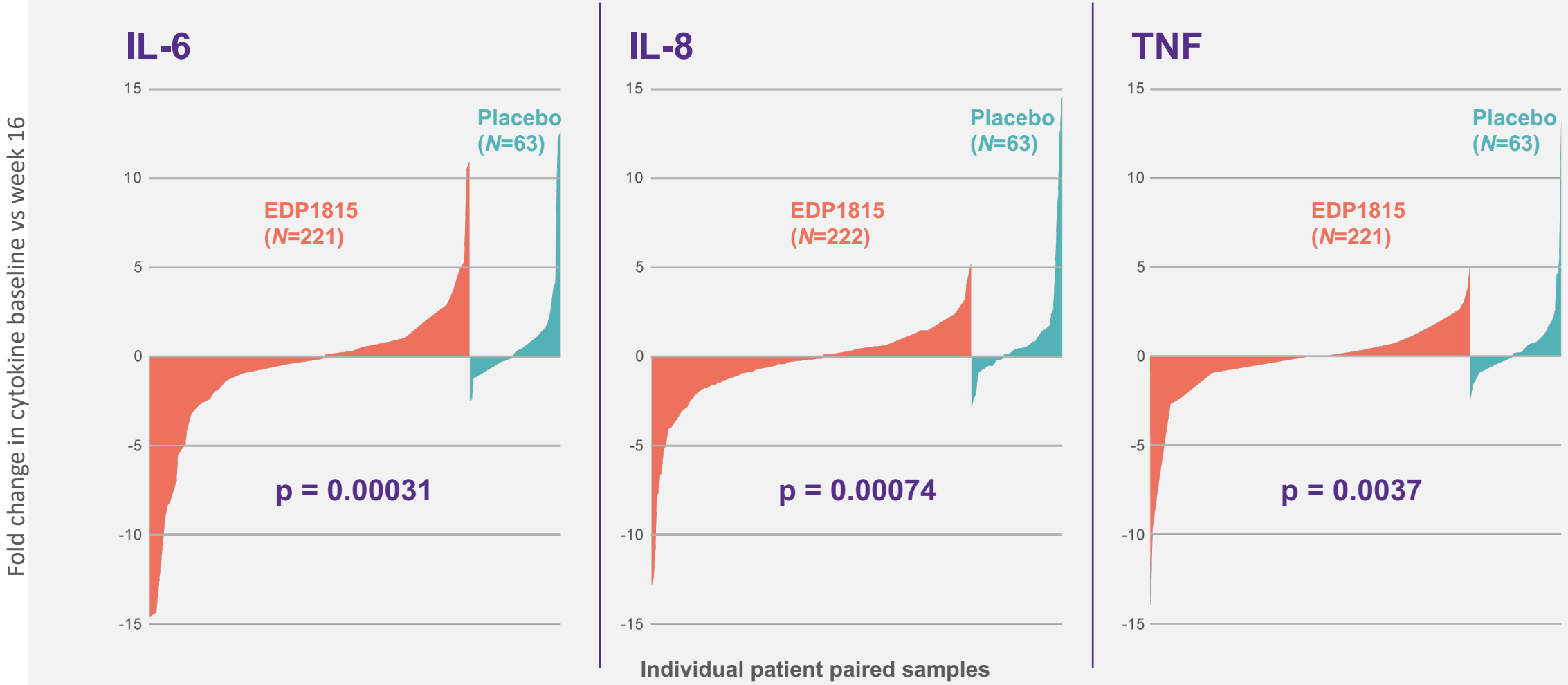
TREATMENT PERIOD			FOLLOW UP
Baseline	Week 4	Week 16 PASI-90	Week 20



Overview of Phase 2 *Ex vivo* Stimulation Analysis Protocol

- Blood samples at baseline and after 16 weeks from EDP1815 (n=74) and placebo (n=22) patients
  - 54 patients from active and placebo groups who had ≥PASI-50 or PASI scores >150% worse than baseline at week 16
  - Further 41 patients from active and placebo groups drawn at random pro rata
- Whole blood was incubated with either lipopolysaccharide (LPS), antibodies to CD3 and CD28, or staphylococcal enterotoxin B (SEB)
- The following graph is the difference in *ex vivo* stimulated cytokine production between baseline and week 16
  - Each patient sample pair for each stimulus is plotted, giving the total N numbers shown in the figures

EDP1815 Led to Significantly Lower Production of IL-6, IL-8 and TNF



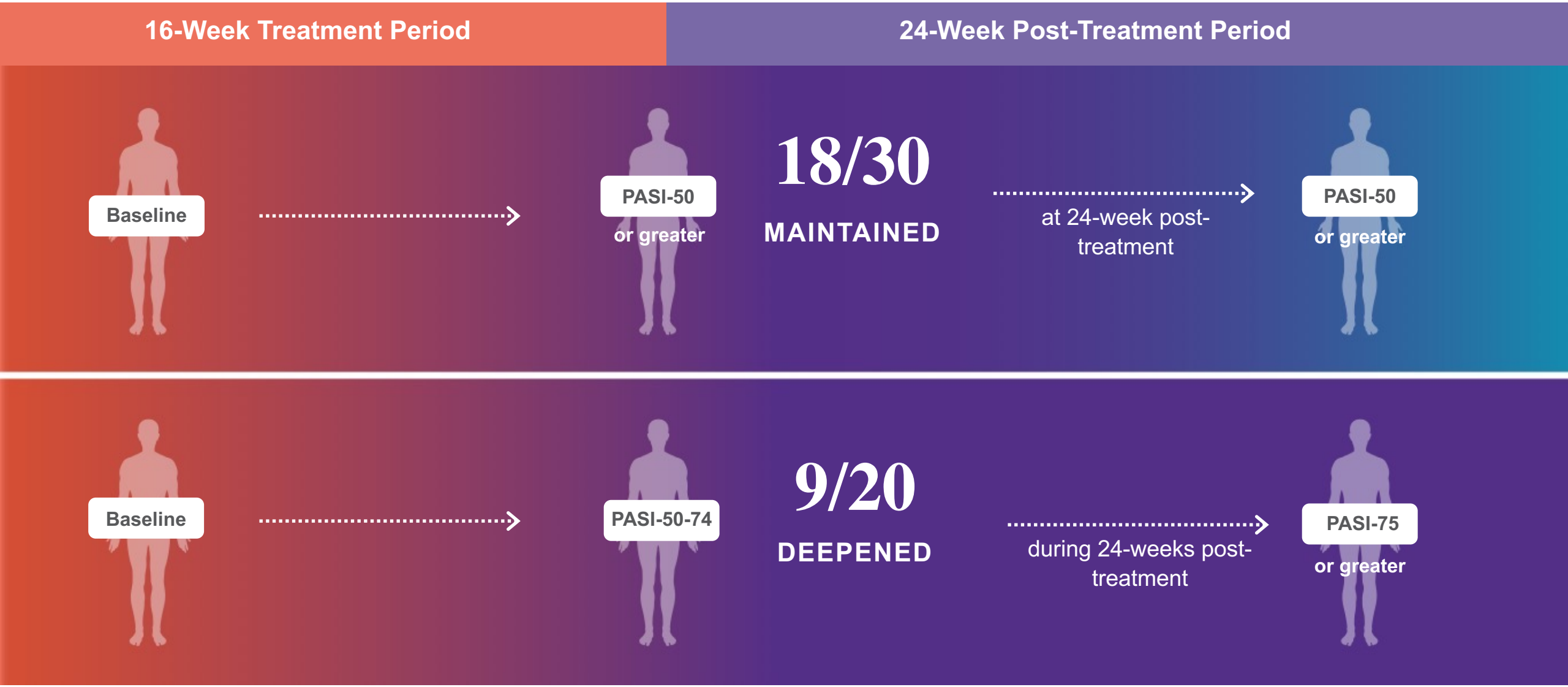
PASI-50+ Responders Showed Reduced Levels of Cytokine RNA in Skin After 16 Weeks of Treatment

- Skin biopsies of active lesions taken at baseline and week 16 from 6 patients who achieved at least a PASI-50 from baseline at week 16
- RNAseq analysis showed reductions in transcript levels for psoriasis-relevant cytokines in paired skin lesions:
  - IL-17
  - IL-23
  - IL-12b
- Data consistent with cytokine reductions in blood samples; suggests EDP1815 reduces inflammation in skin by modulating multiple proinflammatory cytokines systemically

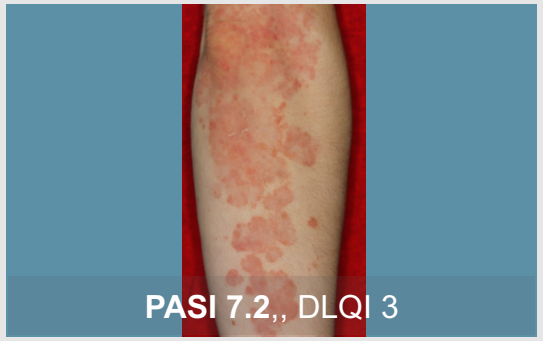
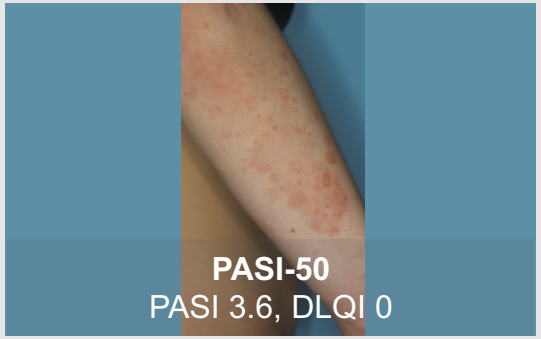
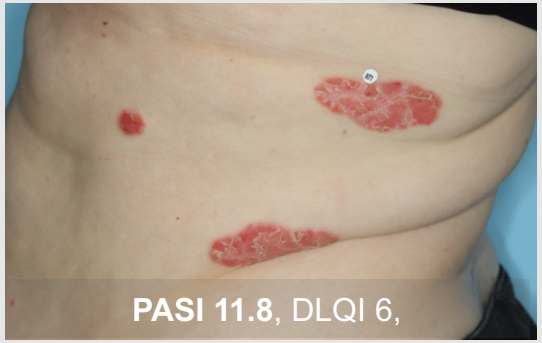
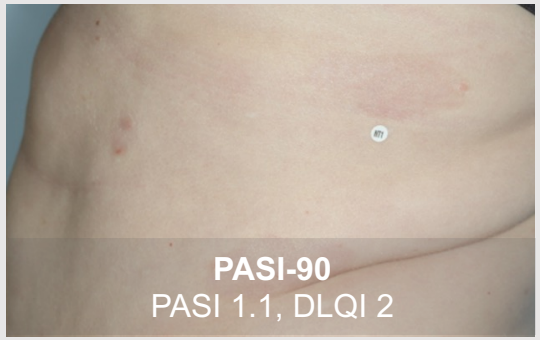
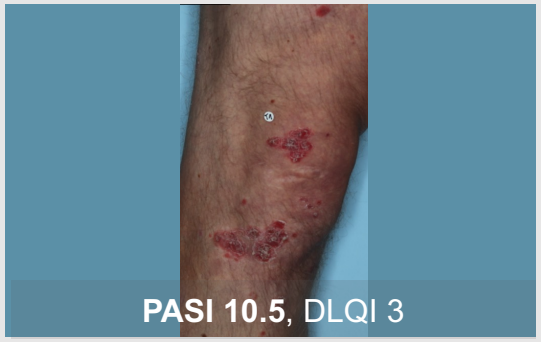
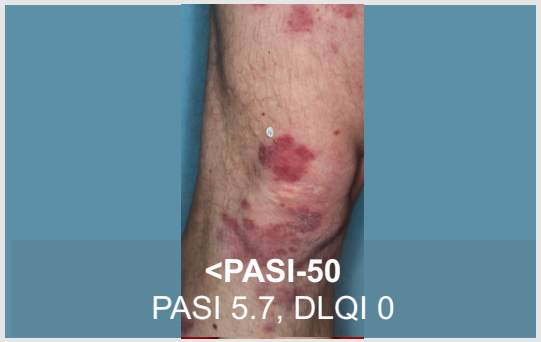
Phase 2 Post-Treatment Period of Up to 24 Weeks – Part B

- Following the 16-week treatment period all patients were followed for 4 weeks to week 20 (Part A)
- All patients had the option to enter an additional follow-up period of up to 24 weeks following cessation of treatment (Part B)
  - Eighty-three patients previously dosed with EDP1815 were followed for up to 24 weeks post-treatment
- Objective of the post-treatment follow-up period was to assess durability of response, incidence of flare or rebound and overall safety and tolerability

Durability and Deepening of Clinical Responses Observed in 24-Week Post-Treatment Period



Deepening of Responses to PASI-75 or Greater During Post-Treatment Period

	BASELINE	WEEK 16	PEAK RESPONSE
WK 16 RESPONDER	 PASI 7.2,, DLQI 3	 PASI-50 PASI 3.6, DLQI 0	Week 40: PASI 1.2, DLQI 1 >PASI-75
	 PASI 11.8, DLQI 6,	 PASI-90 PASI 1.1, DLQI 2	Week 24: PASI 0, DLQI 2 PASI-100
WK 16 NON RESPONDER	 PASI 10.5, DLQI 3	 <PASI-50 PASI 5.7, DLQI 0	Week 28: PASI 1.6, DLQI 0 >PASI-75

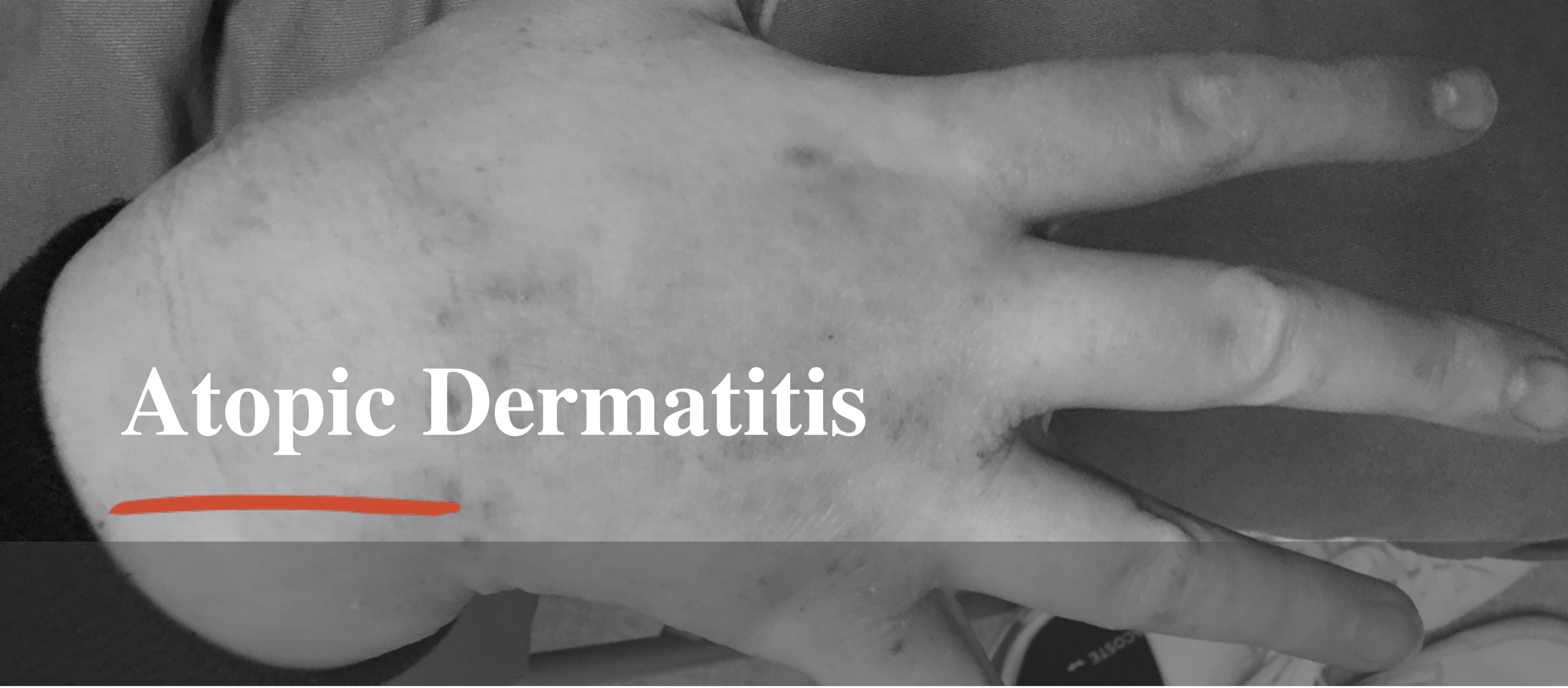
Safety and Tolerability Comparable to Placebo Over Duration of 24-Week Post-Treatment Period

- ***No*** *related serious adverse events*
- ***No*** *evidence of drug-induced flares or disease rebound*

EDP1815 Advancing Towards Registration Studies in Psoriasis

Potential Advantages of SINTAX Medicines for the Treatment of Psoriasis

Mechanism of Action	Novel MOA targeting underlying disease pathways through SINTAX, using gut-restricted agents with systemic effects
Safety & Tolerability	Safety and tolerability results in trials to-date comparable to placebo; monitoring not expected
Route of Administration	Orally delivered, convenient
Efficacy	Clinically meaningful responses observed in psoriasis Phase 2 trial



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 (1) – 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

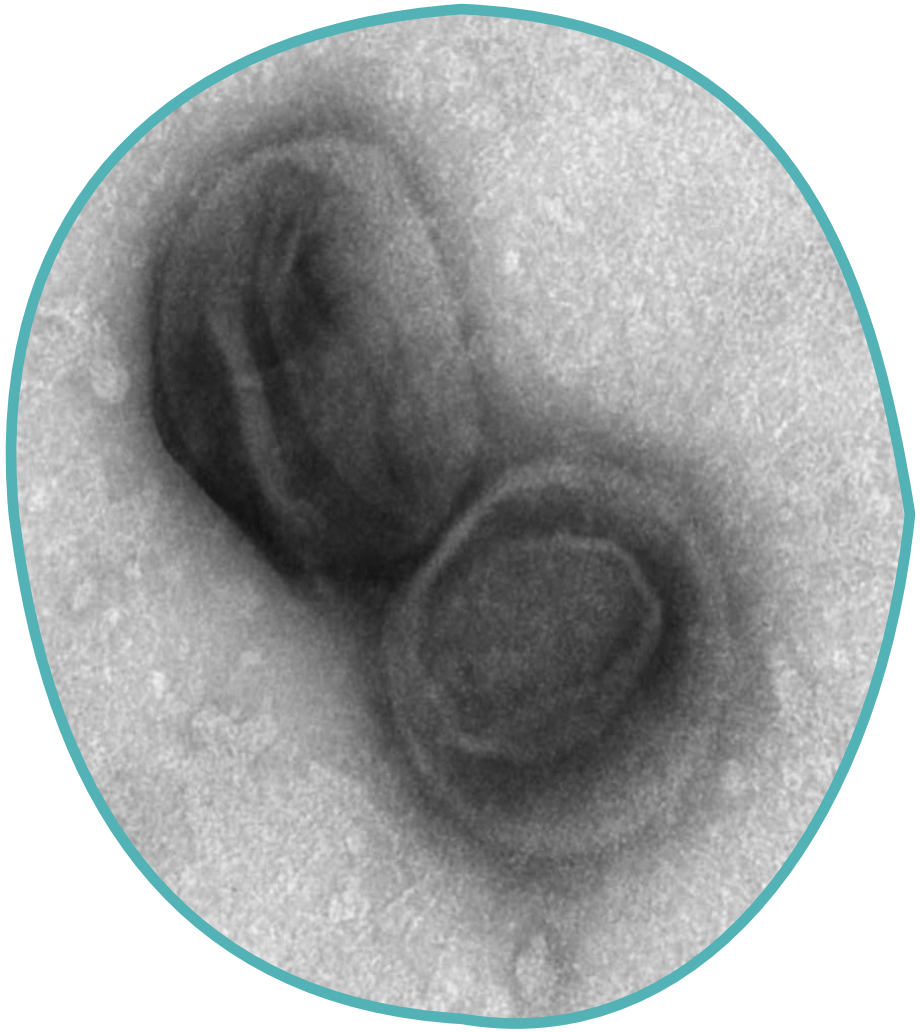
- Primary endpoint: % of patients achieving EASI-50 response at week 16
- Key physician-reported secondary endpoints:
  - IGA (Investigator Global Assessment)
  - BSA (Body Surface Area)
- Key patient-reported secondary endpoints:
  - DLQI (Dermatology Life Quality Index)
  - POEM (Patient-Oriented Eczema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

(1) Plan to add an additional cohort of patients to assess the faster release capsules is being finalized. This cohort, if approved by regulatory agencies, will be dosed at 8.0 x 10^{11} total cells of EDP1815 or placebo as one capsule, once daily.

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 3Q 2022, with Phase 2 data anticipated in 2H 2023



Section 1. SINTAX Platform

Section 2. Unmet Need in Inflammation

Section 3. Evelo's Product Candidates

- EDP1815
- EDP2939

Section 4. Pipeline and Inflection Points

Appendix

Pipeline Provides Multiple Diversified Non-Correlated Opportunities

EDP1815: Th17 Effects

Potential to expand into other Th17-mediated diseases

Psoriasis

- Advancing towards registration trials

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

- Began dosing of patients in Phase 2 trial in **1Q 2022**
- Data from first 3 cohorts in Phase 2 trial in **1Q 2023**
- Data from 4th cohort in Phase 2 trial in **2Q 2023**

Other Potential Indications

- Asthma and allergy
- Neuroinflammation
- Numerous others

EDP2939: EV

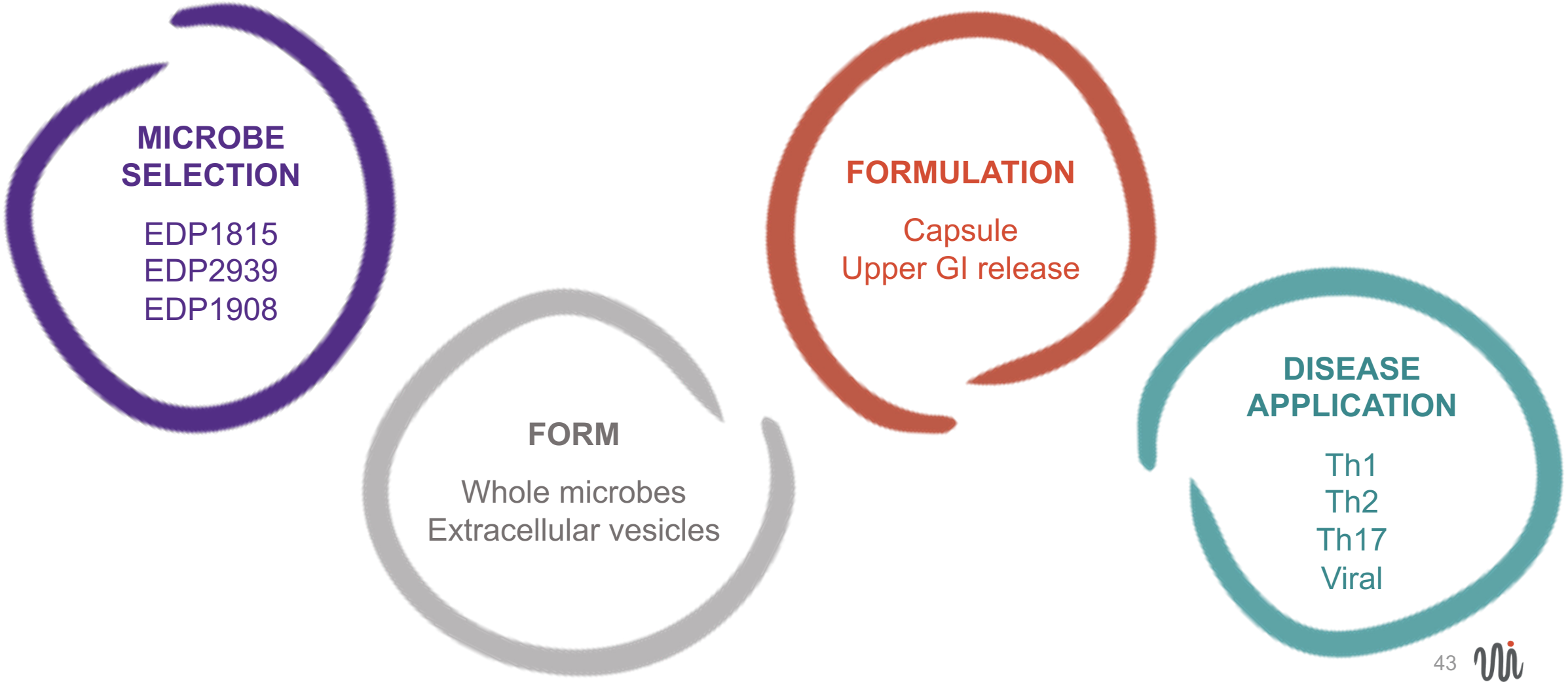
Preclinical data suggests broad use across inflammation

Inflammation

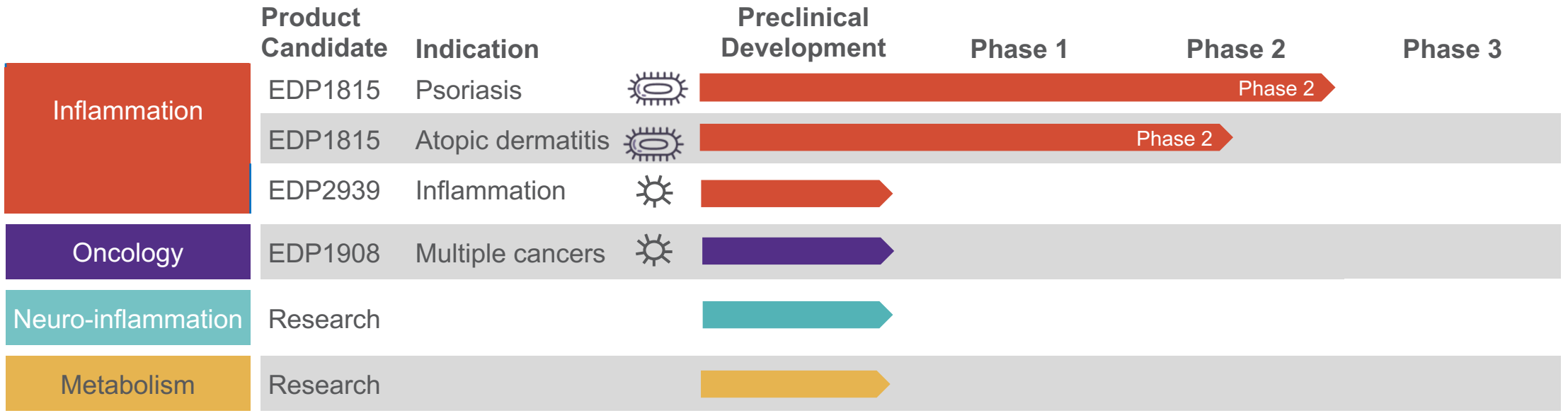
- Anticipate initiation of clinical development in **3Q 2022** with Phase 2 data in **2H 2023**

Broad use across all inflammatory diseases

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



Broad Clinical and Preclinical Pipeline



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

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Corporate Information

~130
employees

Cash and cash equivalents
of ~$40 million*

~$40 million ATM program
with capacity remaining

Long-term debt $45 million

*Does not include the $79.2 million raised in May 2022 financing