EVELO

Harnessing the Small Intestinal Axis to Resolve Inflammation

Evelo Corporate Presentation

February 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 Quarterly Report on Form 10-Q for the period ended September 30, 2022, and our other reports filed with the SEC, could cause actual results to differ materially from those indicated by the forward-looking statements made in this presentation. Any such forward-looking statements represent management's estimates as of the date of this presentation. While we may elect to update such forward-looking statements at some point in the future, except as required by law, we disclaim any obligation to do so, even if subsequent events cause our views to change. These forward-looking statements should not be relied upon as representing our views as of any date subsequent to the date of this presentation.

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Positive Phase 2 Data of EDP1815 in Psoriasis Validates Potential of SINTAX Medicines

Advancing towards Phase 3 following feedback from FDA, EMA and MHRA

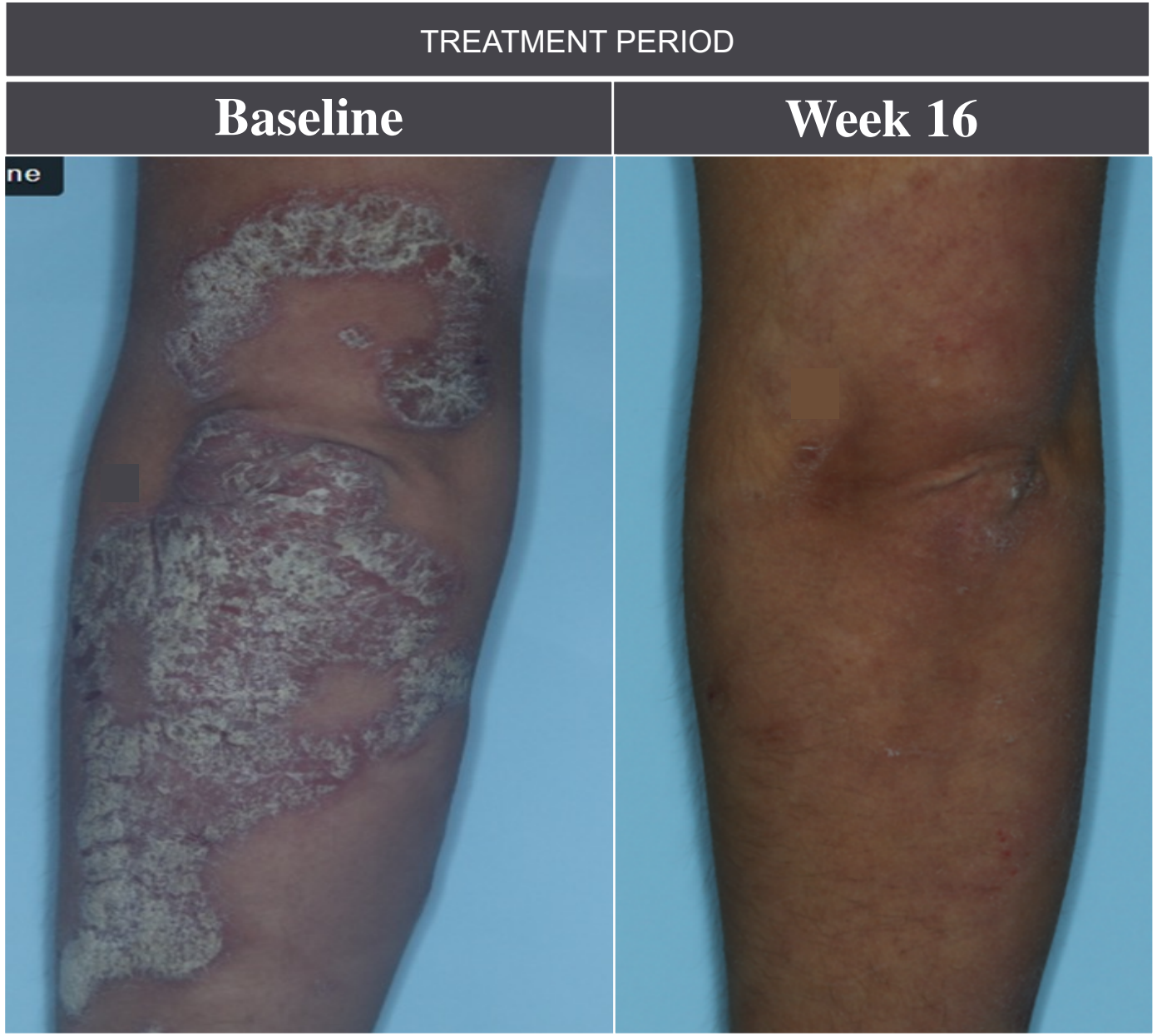


Photo is of a patient with moderate psoriasis enrolled in Phase 2 trial who achieved a PASI-50 response at week 16 on EDP1815.

A Potential Foundational Therapy for Inflammatory Disease

- SINTAX medicines could overcome limitations of current anti-inflammatory drugs and open up the potential to treat patients globally at all stages of disease.
    - In dermatology, SINTAX medicines could address the undertreated population of people with mild and moderate disease (the majority of patients) as well as maintenance therapy for those with severe disease.
- Favorable preliminary risk:benefit profile; efficacious, with safety and tolerability data in clinical trials to-date comparable to placebo, orally delivered and affordable.
- Novel mechanism of action and newly uncovered biology allows for potential treatment of multiple types of inflammation with a single drug.

Investment Highlights

Broad, Disruptive Platform

- Potential to treat spectrum of inflammatory diseases at varying stages of severity
- Favorable preliminary risk:benefit profile; efficacious, with safety and tolerability data in clinical trials to-date comparable to placebo, orally delivered and affordable

EDP1815 is a Pipeline in a Product

- EDP1815 is a potential blockbuster drug; opportunity to serve significant unmet need in mild and moderate disease
- May also address inflammatory diseases beyond dermatology: arthritides, IBD, asthma, and more

Multiple Upcoming Clinical Catalysts

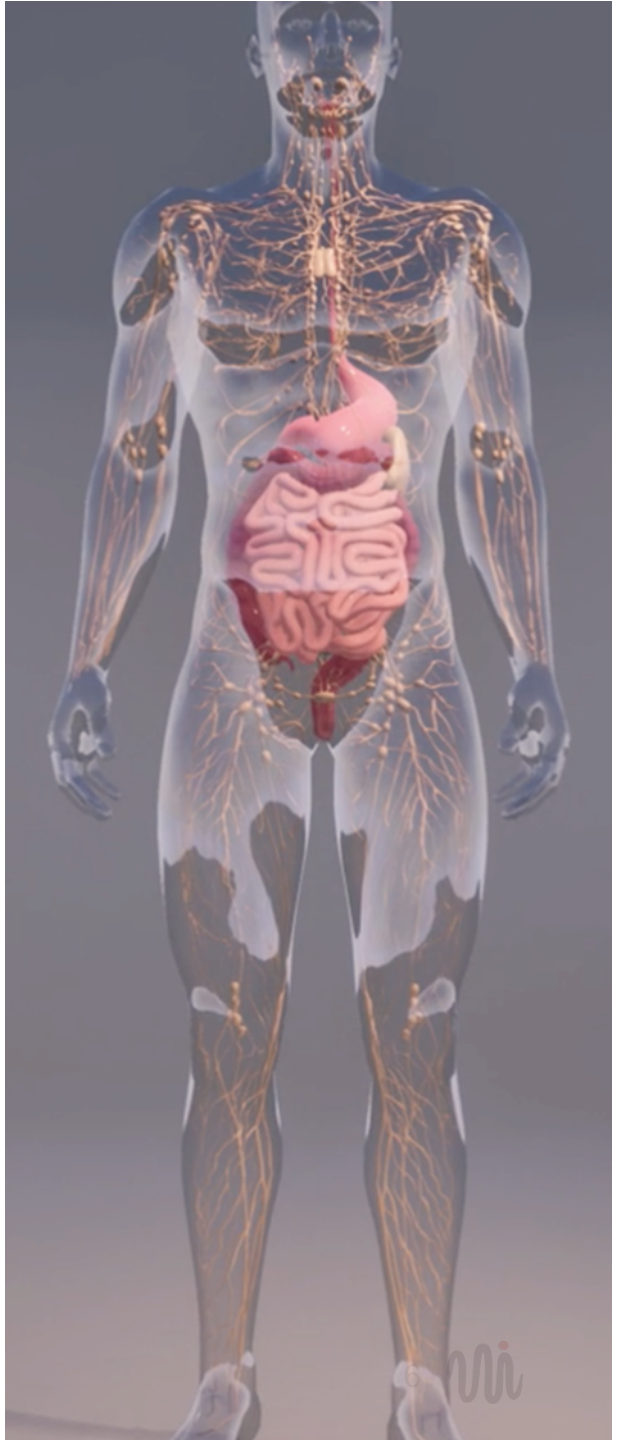
- EDP1815 in psoriasis expected to move to registration trials
- Data for EDP1815 faster release capsule in atopic derm expected in 2Q 2023
- Data from EDP2939 in psoriasis expected in 2H 2023

Best in Class Leadership

- Founded by Flagship Pioneering
- Leadership Team with decades of experience building innovative platforms, developing and commercializing therapeutics

Harnessing SINTAX to Transform Medicine

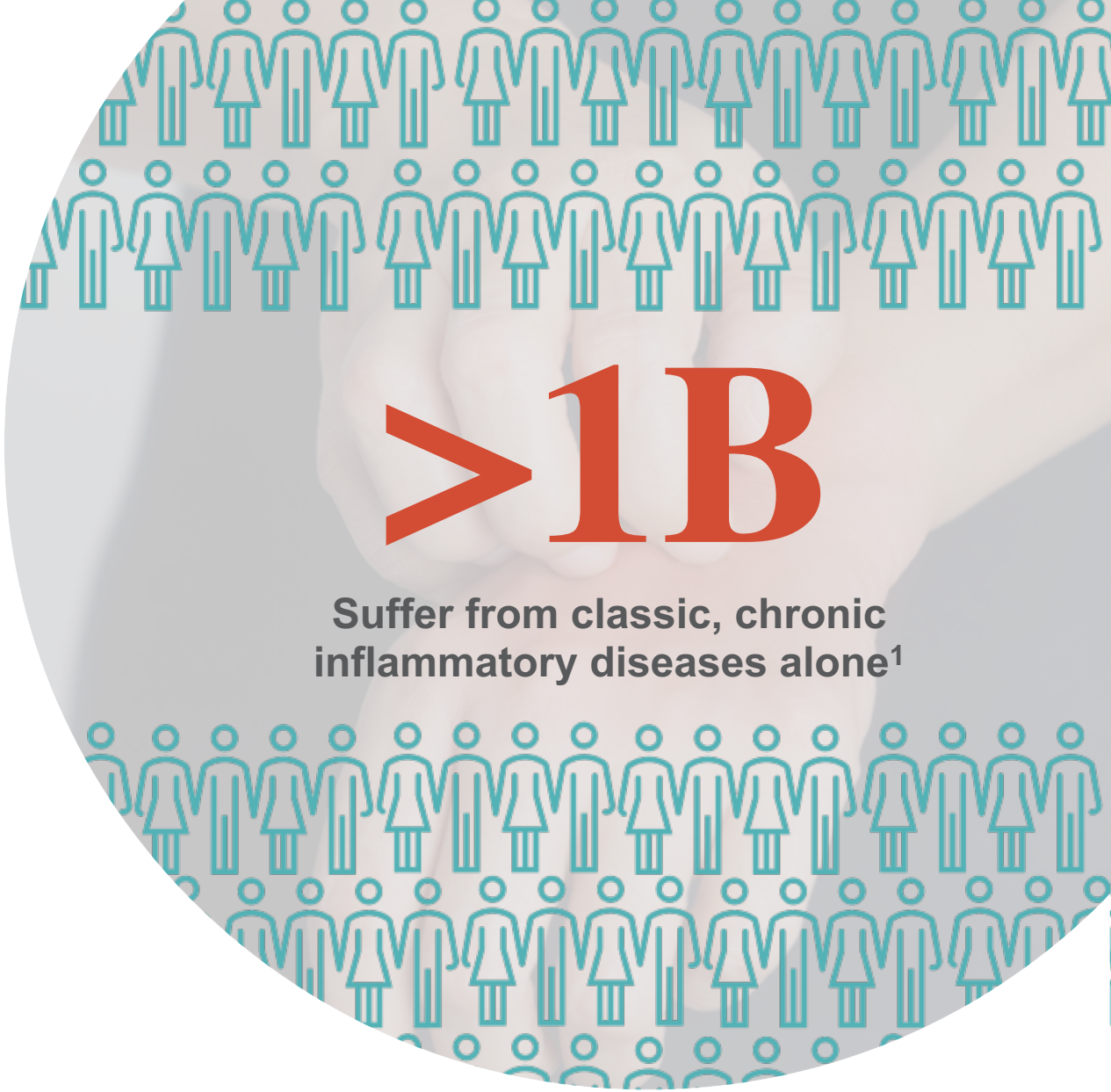
- **S**mall **INT**estinal **AX**is – SINTAX – the immune system of the small intestine, connected to the rest of the body via mesenteric lymph nodes.
- SINTAX medicines are a new type of orally delivered therapies that act on cells in the small intestine for systemic therapeutic effects.
- SINTAX-based medicines have been observed to resolve inflammation throughout the body via local action in the gut.



Chronic Inflammation Impacts Billions of People Worldwide

SINTAX Medicines Impact Multiple Inflammatory Pathways, Unlocking Potential Across 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

Late Stage Clinical Pipeline

Therapeutic Area	Product Candidate	Indication	Preclinical Development	Phase 1	Phase 2	Phase 3
Inflammation	EDP1815	Psoriasis		Phase 2 complete, regulatory feedback received from FDA, EMA and MHRA		Potential registration trials in 2023
Inflammation	EDP1815	Atopic dermatitis			Phase 2 data with faster release capsule anticipated in 2Q 2023*	
Inflammation	EDP2939	Psoriasis			Phase 2 psoriasis data anticipated in 2H 2023	

** Data from 4th cohort in Phase 2 trial; data from first 3 cohorts in Phase 2 trial did not meet primary endpoint*

Two Phase 2 Clinical Readouts and Phase 3 Initiation Expected in 2023

2Q 2023	2H 2023	2023
EDP1815 Phase 2 data expected from 4th cohort with faster release capsule in atopic dermatitis*	**EDP2939** Phase 2 data expected from cohort of patients with psoriasis	**EDP1815** Potential initiation of Phase 3 clinical trial in psoriasis

** Data from 4th cohort in Phase 2 trial; data from first 3 cohorts in Phase 2 trial did not meet primary endpoint*

Opportunity in Inflammation

Evelo's Product Candidates

- EDP1815
- EDP2939

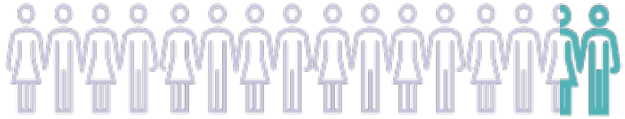
Majority of Psoriasis and Atopic Dermatitis Patients Have Mild or Moderate Disease

93% of Psoriasis patients
85% of Atopic dermatitis patients*

Most Patients Lack Treatment Options That Address Systemic Disease

Psoriasis

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



LESS THAN 8% in the US receive injectable antibody therapies or oral systemics[1-6]

Atopic Dermatitis

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

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

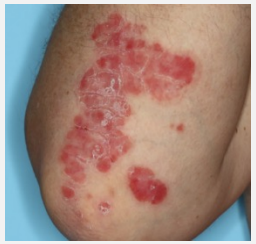
as many as 50% of PsO and AD sufferers in the US are not on any Rx treatment[2,7,8]

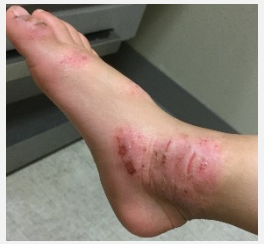
Mild Moderate Severe

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

Mild/Moderate 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).

SINTAX Medicines Could Be Superior to Existing Treatments

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

Current anti-inflammatory drugs

- **Corticosteroids & old school systemics:** immunosuppressant, safety concerns, require monitoring
- **Injectable biologics:** not convenient, immunosuppressant, mostly approved for severe disease only, high price
- **Oral immunosuppressants:** safety and tolerability issues, monitoring, high price
- **Topicals**: convenience and compliance issues, short-term use, non-systemic

Potential of SINTAX Medicines

- **Efficacy:** clinically meaningful impact on chronic inflammatory disease
- **Safety and tolerability:** placebo-like safety and tolerability profile
- **Oral delivery:** convenient
- **Novel MOA:** inflammation resolution across multiple pathways without immunosuppression
- **Affordable:** potential to treat all stages of disease; globally accessible

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

Opportunity in Inflammation

Evelo's Product Candidates

- EDP1815
- EDP2939

EDP1815

- Lead product candidate with blockbuster potential
- Advancing towards registration trials in psoriasis; regulatory feedback from FDA, EMA and MHRA supports path to registration studies
- Phase 2 trial in atopic dermatitis underway; data from faster release cohort anticipated 2Q 2023*
- Potential to expand broadly across inflammatory diseases beyond dermatology, including arthritides, inflammatory bowel disease, and chronic inflammatory respiratory diseases

** Data from 4th cohort in Phase 2 trial; data from first 3 cohorts in Phase 2 trial did not meet primary endpoint*

Psoriasis

EDP1815 Phase 2 Trial in Mild and Moderate Psoriasis

16-WEEK TREATMENT PERIOD

SCREENING PERIOD (up to 4 weeks)	TREATMENT PERIOD (16 weeks)

Randomized 2:1 in each arm (active:placebo)

- **Cohort 1: 1 capsule**
- **Cohort 2: 4 capsules**
- **Cohort 3: 10 capsules**

Key Inclusion Criteria:

- BSA of ≥3% and ≤10%
- PASI score of ≥6 and ≤15
- PGA score of 2 or 3

24-WEEK POST-TREATMENT PERIOD

POST-TREATMENT FOLLOW-UP (up to 4 weeks)	OPTIONAL FOLLOW-UP PERIOD (up to 20 weeks)

Week 20 | **Week 24** | **Week 28** | **Week 40**

Evaluation of Treatment Responses

- Following the 16-week treatment period all patients were followed for 4 weeks to week 20 (Part A)
- Patients on drug who achieved PASI-50 or greater at week 16 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

Summary of Endpoints

Primary Endpoint

Mean reduction in PASI score at week 16 vs. placebo using Bayesian probability

Result

80-90% probability that EDP1815 is superior to placebo at week 16 based on mean change in PASI

Responder Endpoint

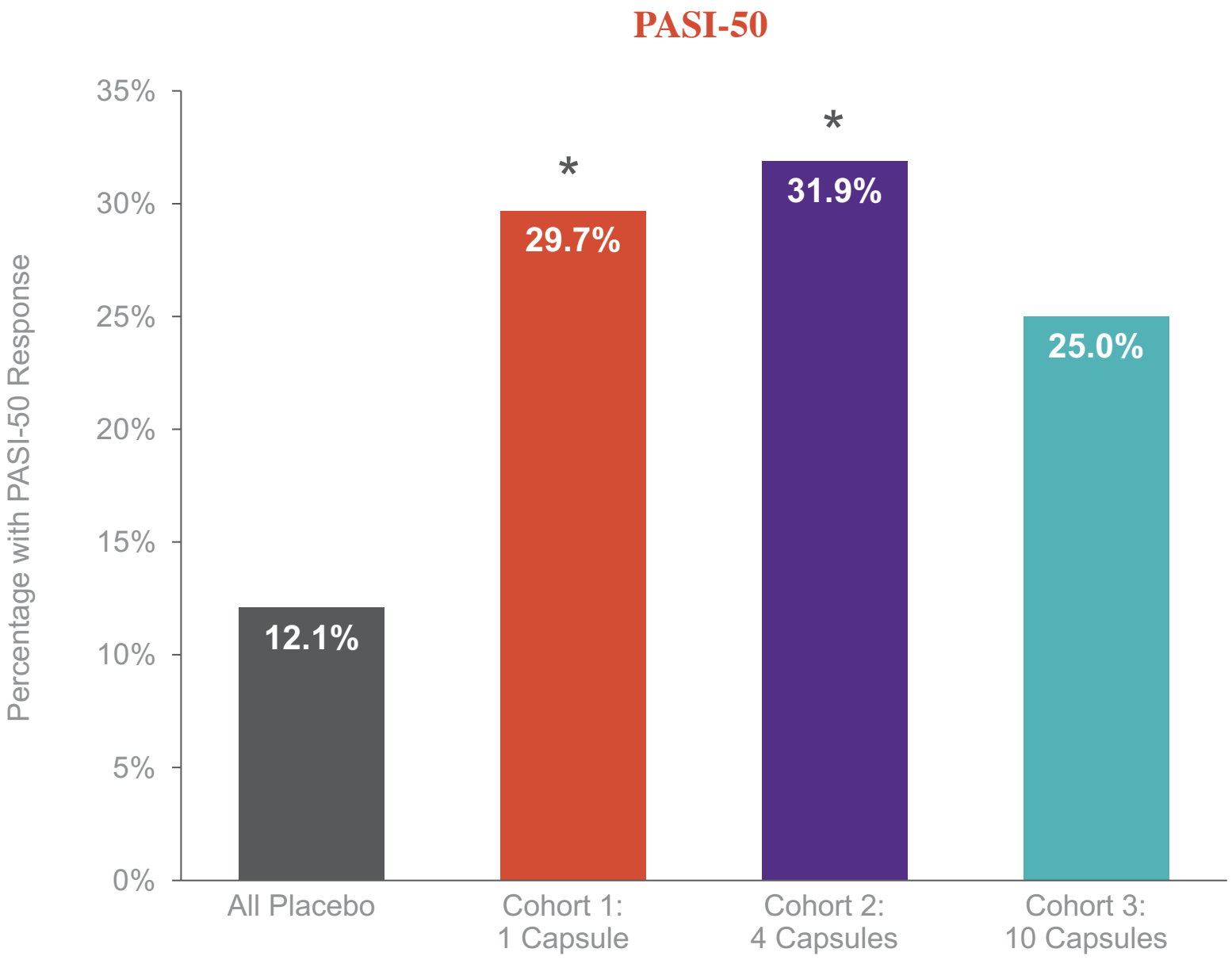
Percentage of patients achieving at least a PASI-50 by week 16

Result

Statistically significant p-value for 2 of the 3 individual dose cohorts, and directionally similar for the third

EDP1815 Clinical Response at Week 16

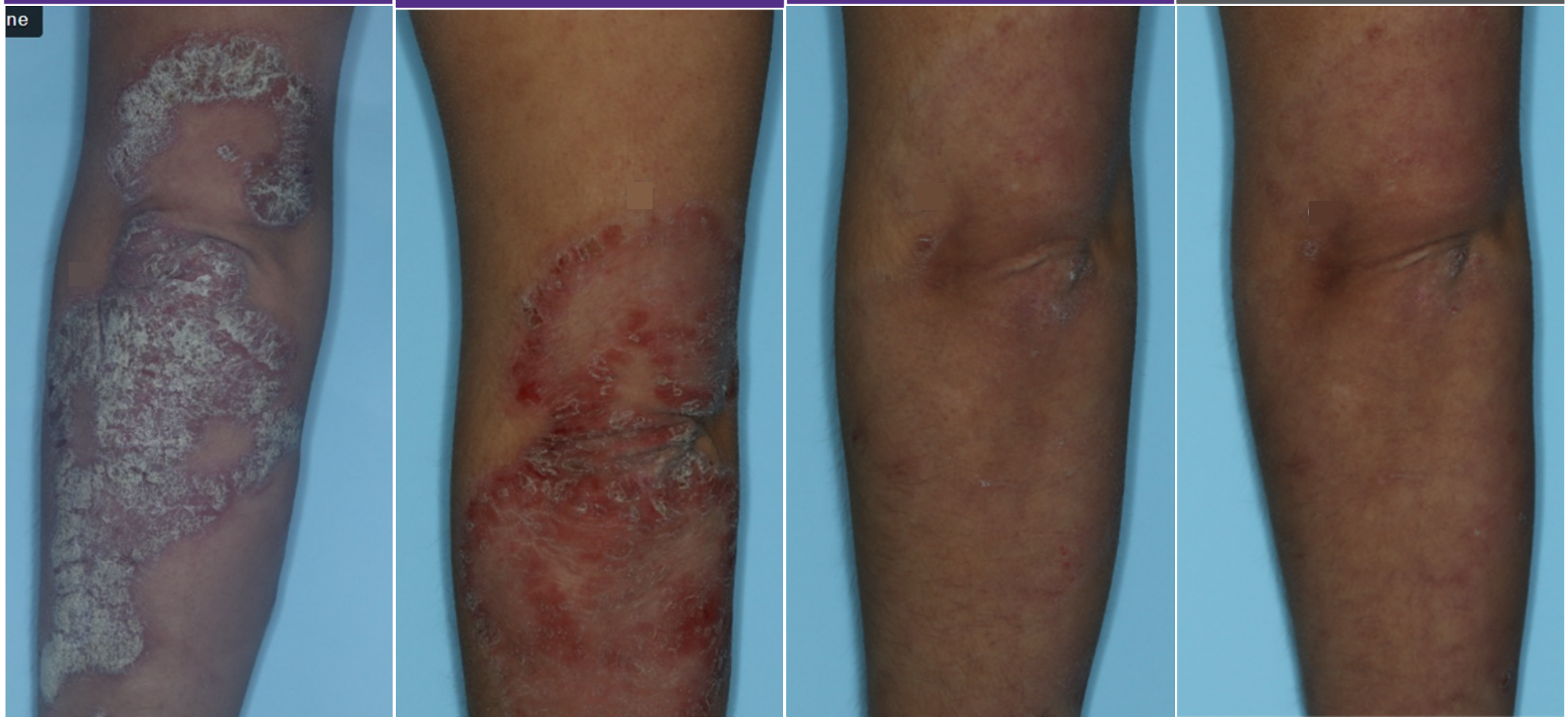
Statistically significant p-value (<0.05) for all 3 cohorts when pooled, and for 2 of the 3 individual dose cohorts



*p<0.05

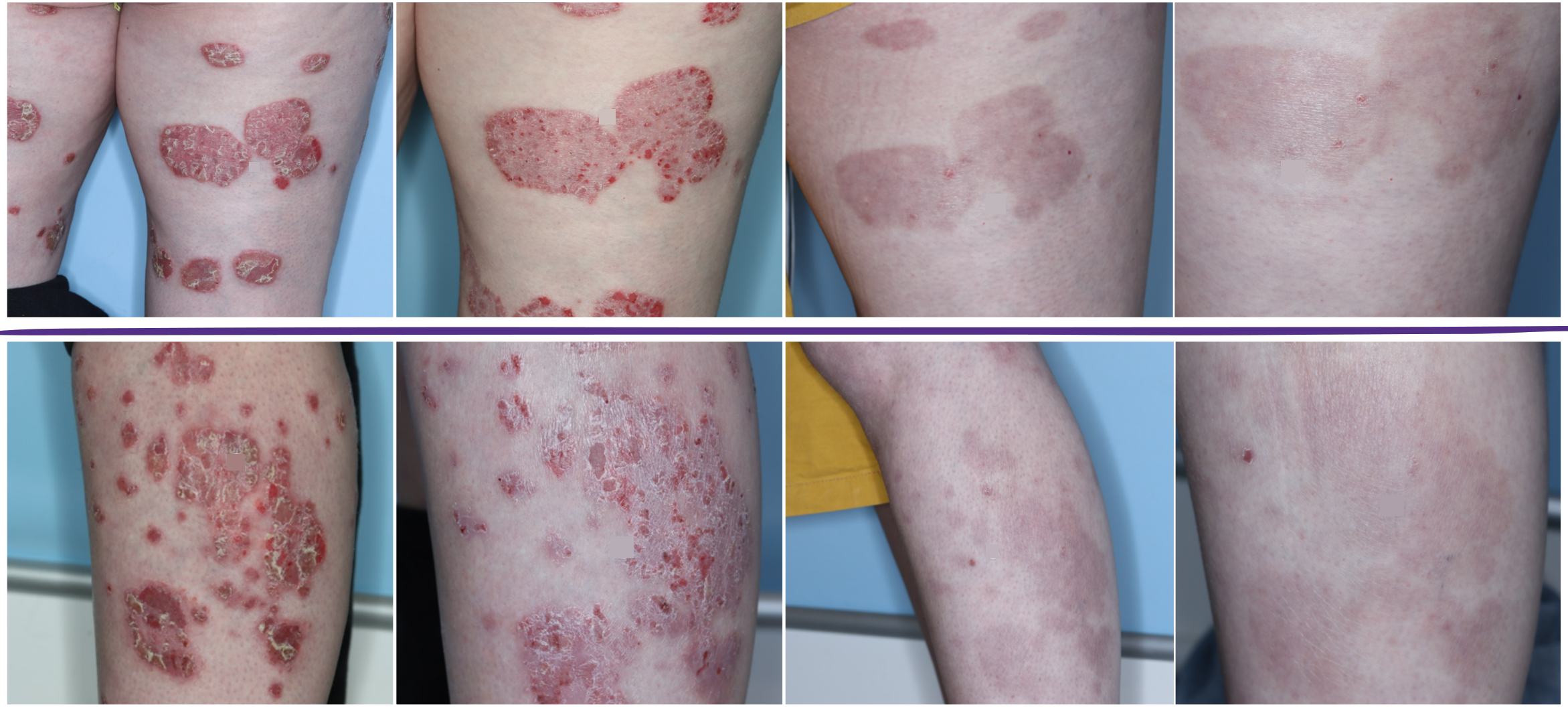
Deepening Response Over Time in Moderate Psoriasis Patients

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

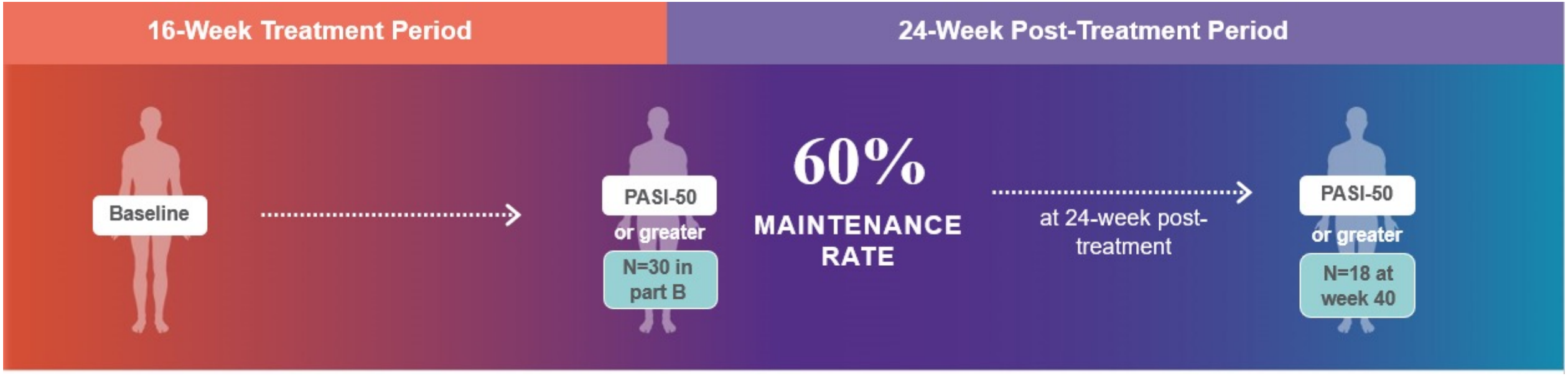


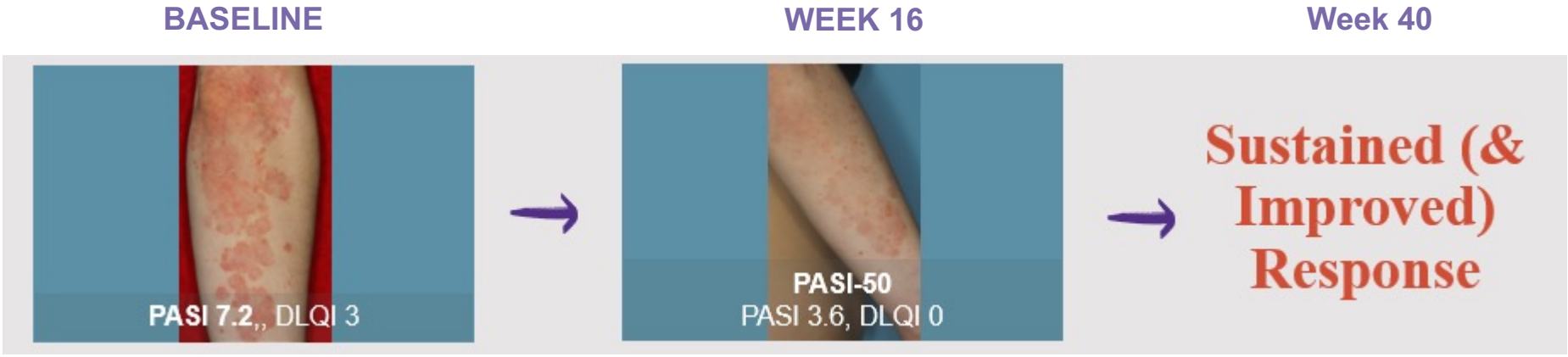
Some Patients Achieved PASI-90 at Week 16 With Further Improvement Post Treatment

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



Durability of Clinical Responses Seen 24-Weeks Post Treatment





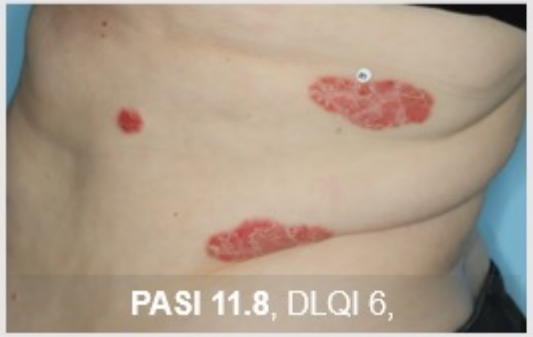
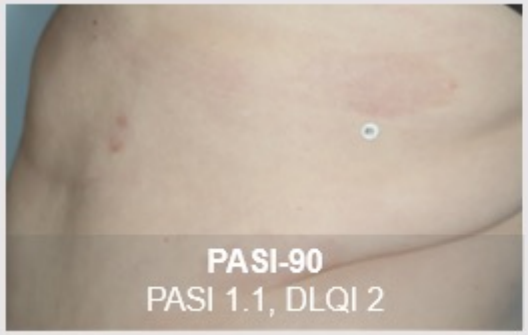
Deepening of Clinical Responses Seen 24-Weeks Post Treatment

16-Week Treatment Period | **24-Week Post-Treatment Period**

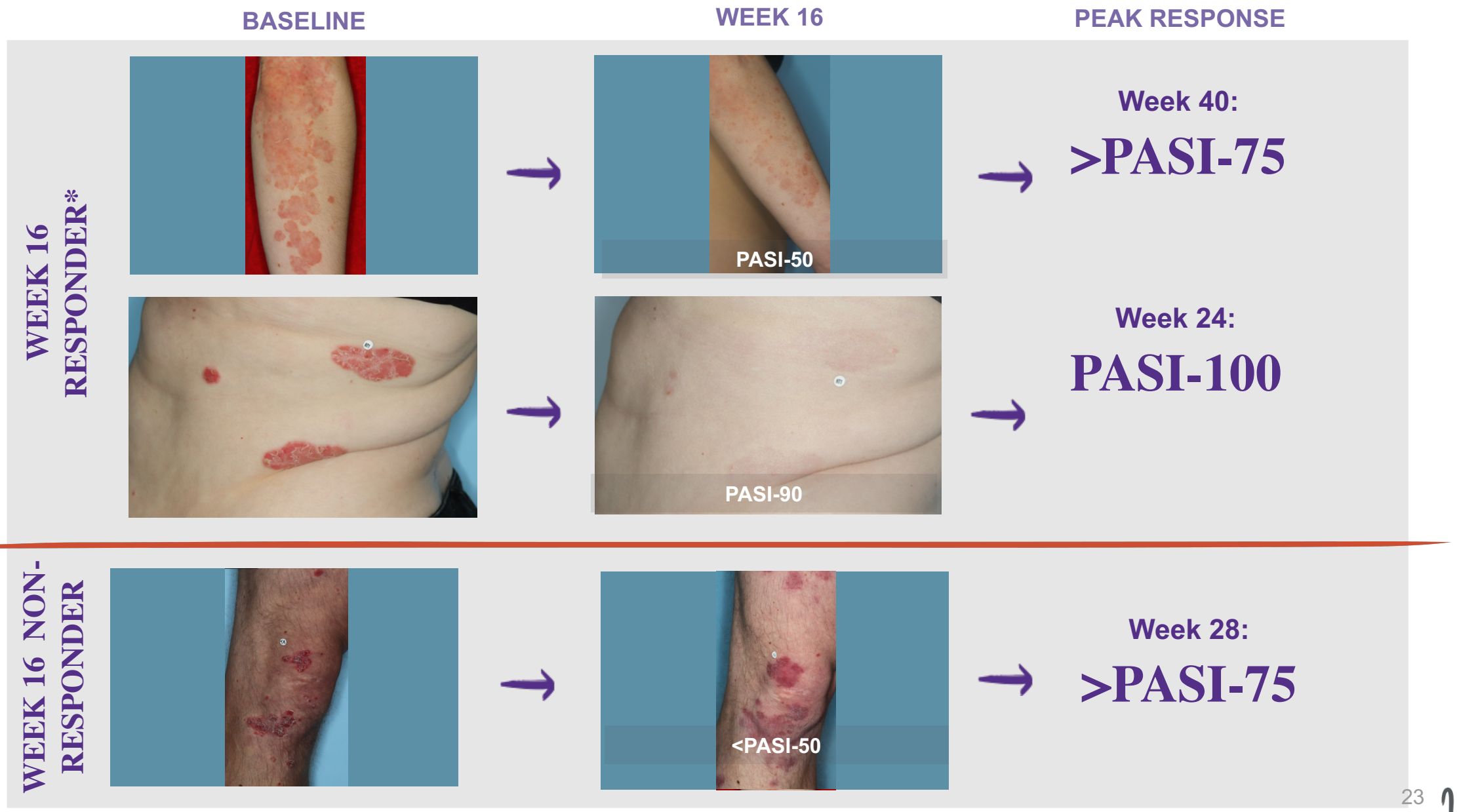
Baseline → PASI-50-74 (N=20 in part B)

45% IMPROVED FURTHER TO PASI75 OR BETTER

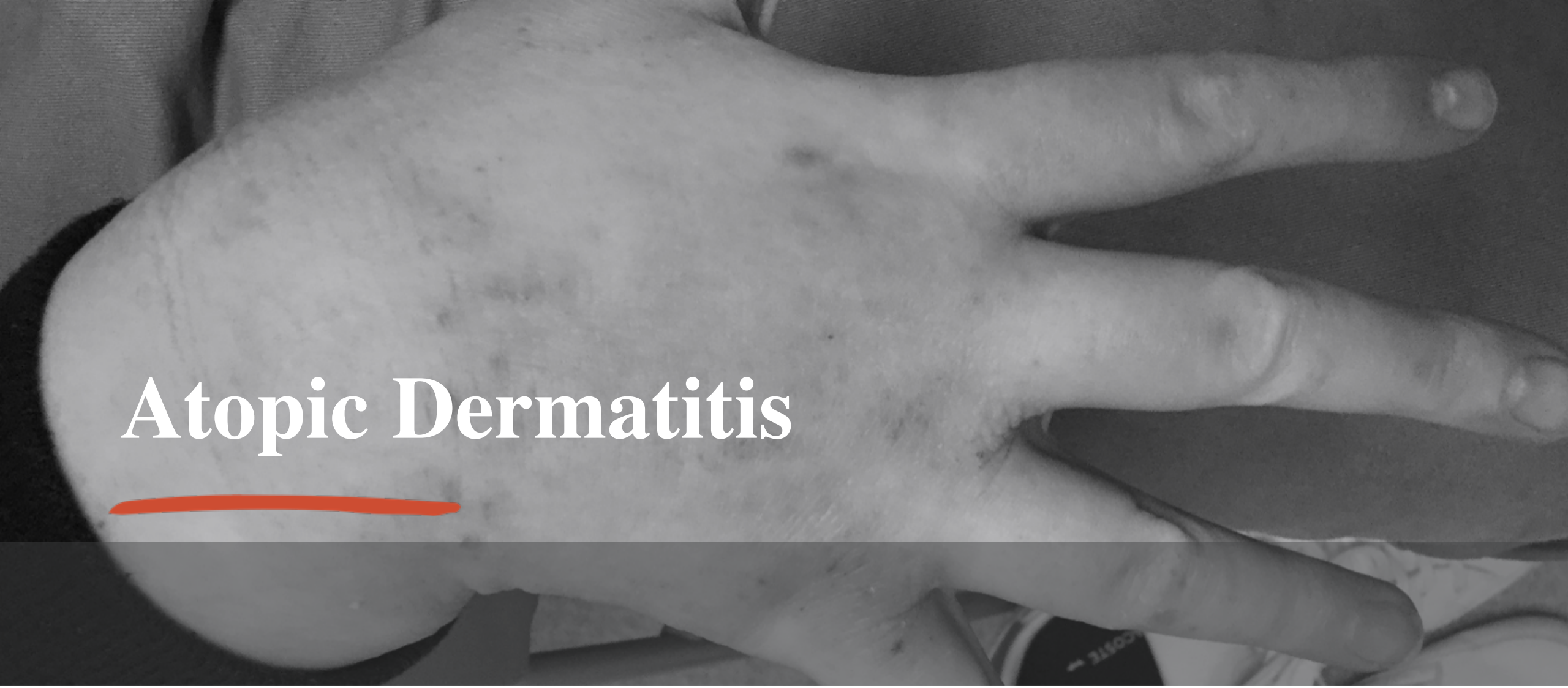
during 24-weeks post-treatment → PASI-75 or greater (N=9)

BASELINE	WEEK 16	Week 24
		**PASI-100**

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



*Responder if defined as active patient who achieved PASI-50 or greater



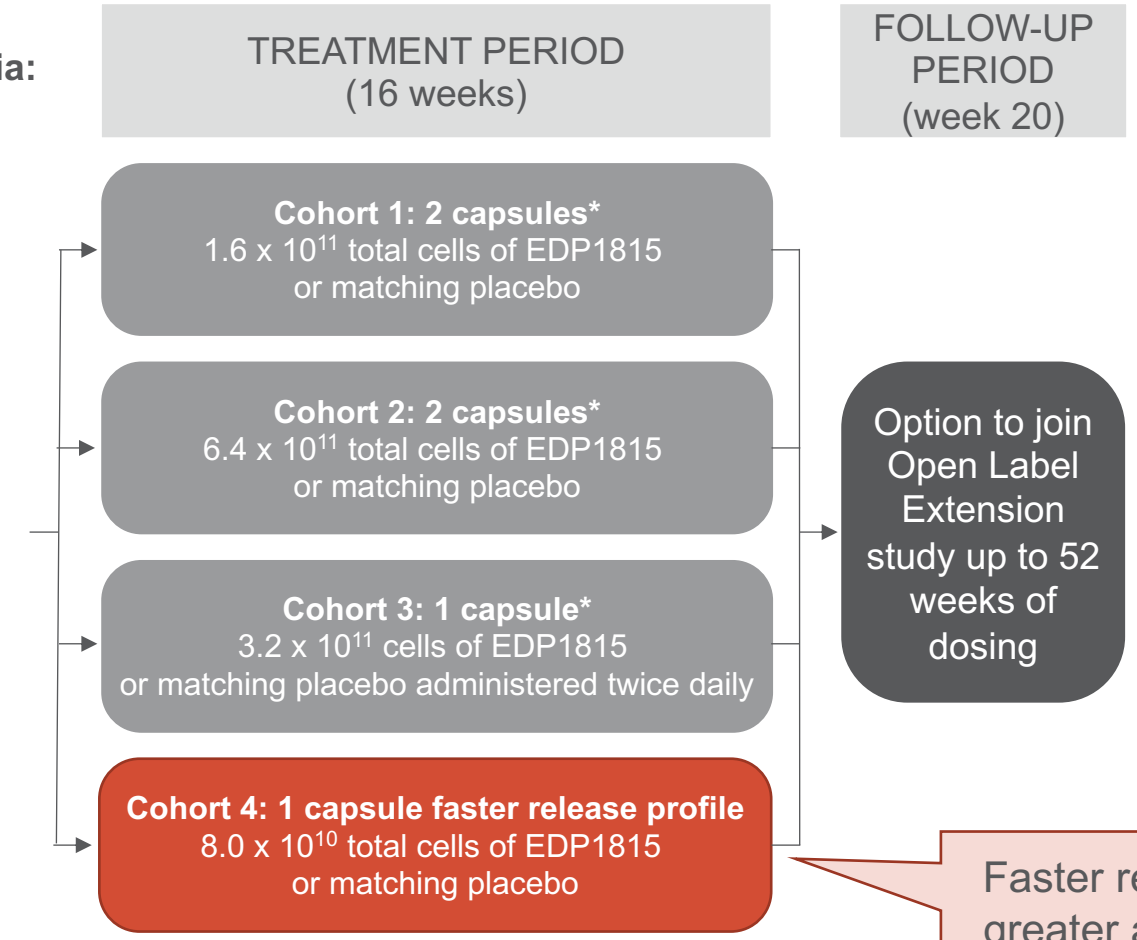
Atopic Dermatitis

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

Key Inclusion Criteria:
- BSA ≥5% and
- IGA 2-4 and
- EASI ≥6

~400 Screened Participants
- Cohorts 1-3 are randomized 3:1 (active:placebo)
- Cohort 4 randomized 2:1 ratio (active:placebo)

Topicals & Emollients
- Emollients mandatory in study
- Up to moderate potency TCS rescue therapy permitted



Primary endpoint:
- % of participants achieving EASI-50 response at week 16

Secondary endpoints:
- **Key physician-reported secondary endpoints:**
  - IGA
  - BSA
- **Key patient-reported secondary endpoints:**
  - DLQI
  - POEM
  - Pruritus-NRS

Faster release capsule potentially allows for greater activity by enabling increased target engagement in upper part of small intestine

** Data from first 3 cohorts in Phase 2 trial did not meet primary endpoint*

EDP2939 –First Anti-Inflammatory EV

EVs: The Next Wave of SINTAX Medicines

- EVs are natural lipoprotein nanoparticles
- Compared to microbes, EVs are:
  - ~1/1000th volume of microbes - potential for higher dosing via packaging at high concentrations in standard size capsules
- Potentially enable greater SINTAX activation for greater efficacy given small size and diffusion properties
- Pharmacologically active strains of gut mucosa-derived microbes naturally shed EVs
- Small size and diffusion properties enable target engagement in the gut

Stokes-Einstein Equation

$$D = \frac{k_B T}{6\pi \eta r}$$

Fick's Laws of Diffusion

$$J = -D\frac{d\varphi}{dx} \quad \text{and} \quad \frac{\partial \varphi}{\partial t} = D\frac{\partial^2 \varphi}{\partial x^2}$$

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 is currently in a Phase 1/2 clinical study in psoriasis – Phase 2 data is anticipated in 2H 2023