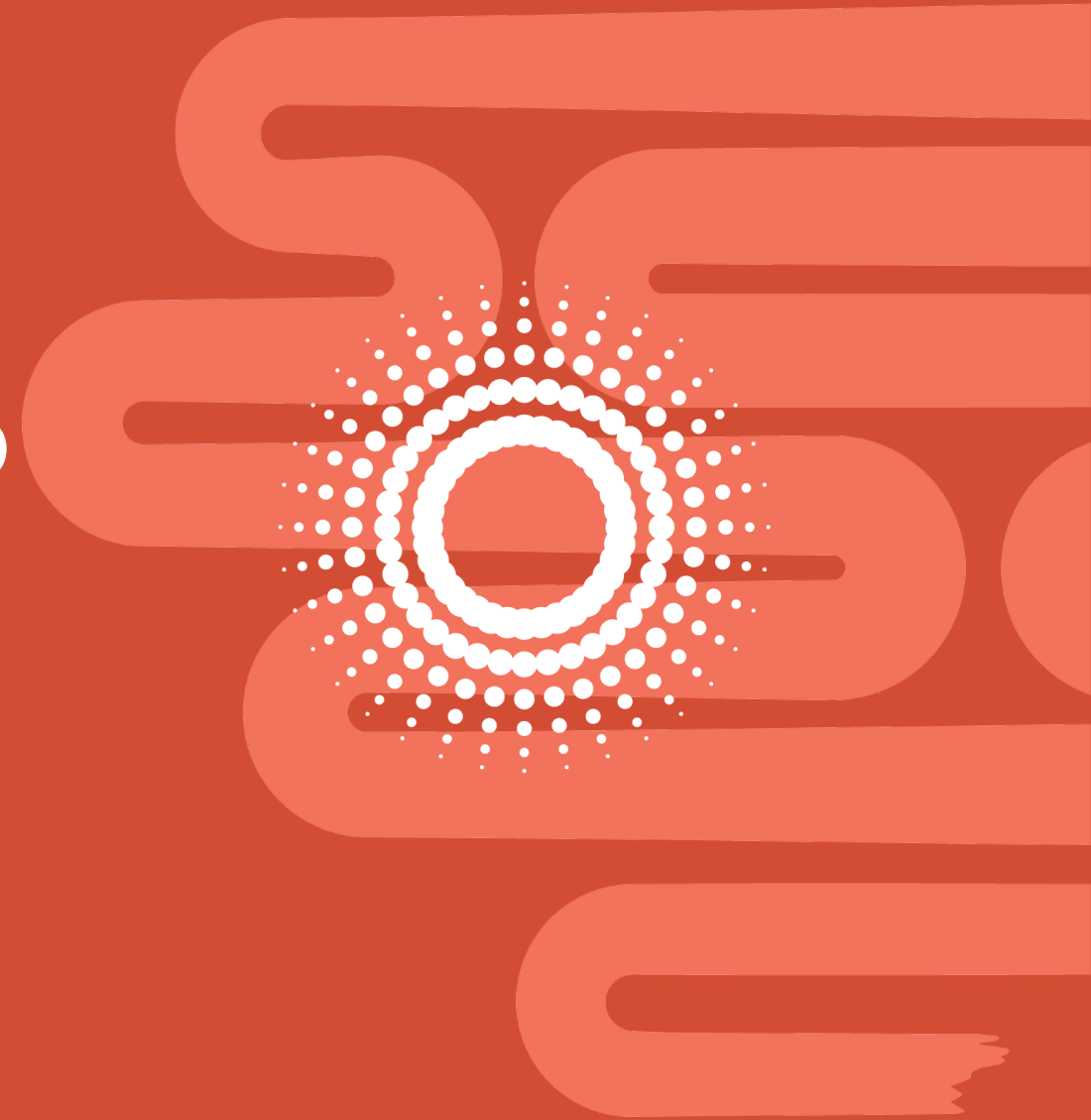




Harnessing the Small Intestinal Axis to Resolve Inflammation

Evelo Corporate Presentation

December 2022



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: the impact of the COVID-19 pandemic on our operations, including our preclinical studies and clinical trials, and the continuity of our business; that we have incurred significant losses, are not currently profitable and may never become profitable; our ability to continue as a going concern, and our need for additional funding; our cash runway; our limited operating history; our unproven approach to therapeutic intervention; 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; issues with the 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 retain key personnel and to manage our growth; the potential volatility of our common stock; our management and principal stockholders ability to control or significantly influence our business; costs and resources of operating as a public company; unfavorable or no analyst research or reports; 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.

Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and our own internal estimates and research. While we believe these third-party sources to be reliable as of the date of this presentation, we have not independently verified, and we make no representation as to the adequacy, fairness, accuracy or completeness of any information obtained from third-party sources. In addition, all of the market data included in this presentation involves a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions. Finally, while we believe our own internal research is reliable, such research has not been verified by any independent source.

EDP1815 is Advancing Towards Phase 3 in Psoriasis; Planning for Phase 3 in Atopic Dermatitis in 2H 2023



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 in atopic dermatitis expected in 1Q and 2Q 2023
- Data from EDP2939 in psoriasis expected in 2H 2023

Best in Class Leadership



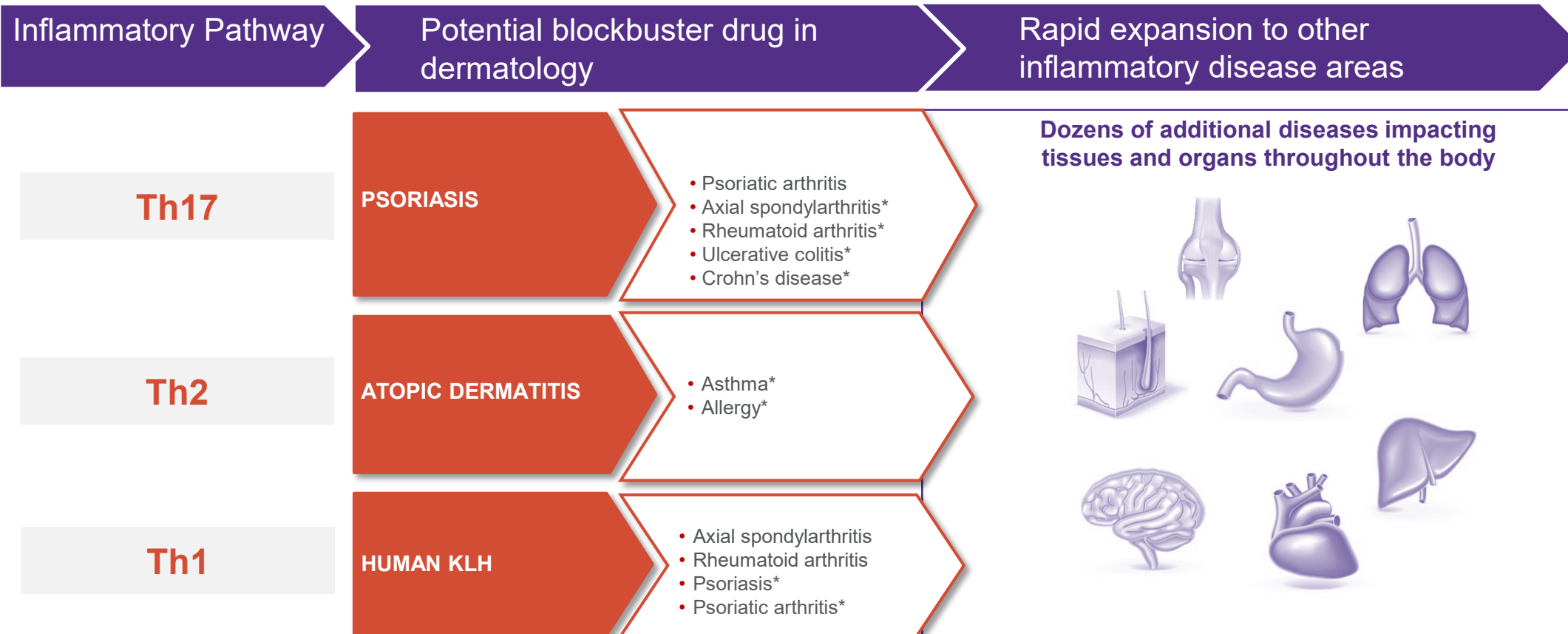
- Founded by Flagship Pioneering
- Leadership Team with decades of experience building innovative platforms, developing and commercializing therapeutics

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.

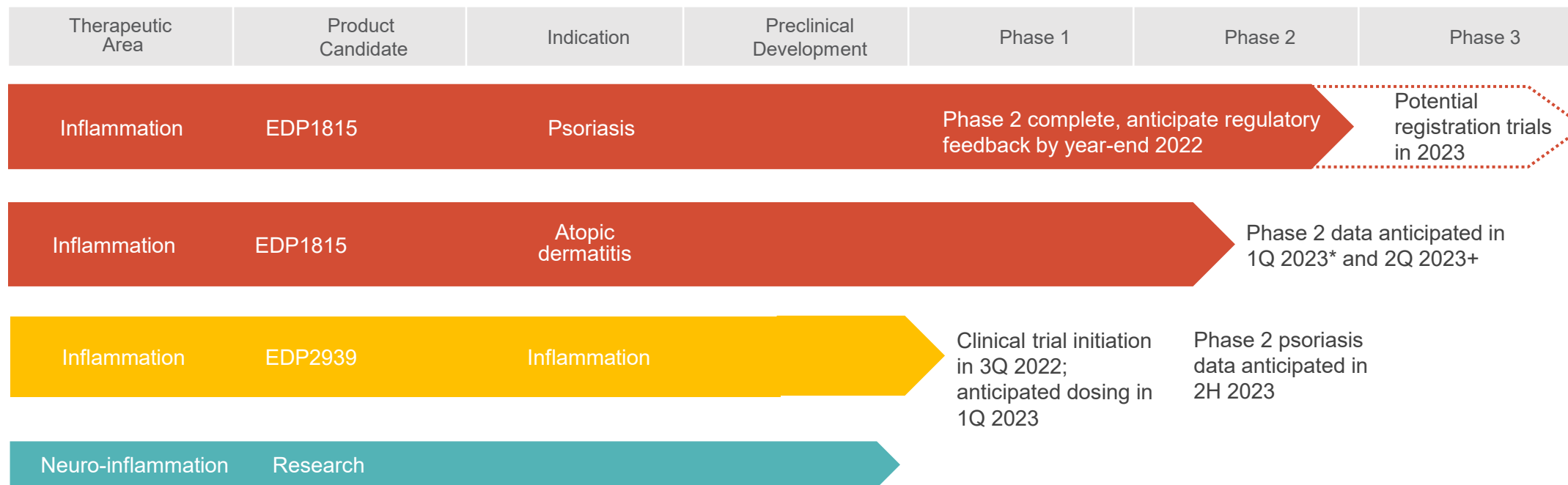


SINTAX Medicines Impact Multiple Inflammatory Pathways, Unlocking Potential Across Broad Range of Inflammatory Diseases



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

Late Stage Clinical Pipeline



*Data from first 3 cohorts in Phase 2 trial.

+ Data from 4th cohort in Phase 2 trial.

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

1Q 2023	2Q 2023	2H 2023	2023
<u>EDP1815</u> Phase 2 data expected from first 3 cohorts in atopic dermatitis	<u>EDP1815</u> Phase 2 data expected from 4 th cohort in atopic dermatitis	<u>EDP2939</u> Phase 2 data expected from cohort of patients with psoriasis	<u>EDP1815</u> Potential initiation of Phase 3 clinical trial in psoriasis



Opportunity in Inflammation

Evelo's Product Candidates

- EDP1815
- EDP2939

Appendix

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

 Mild  Moderate  Severe

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 systemics¹⁻⁶

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}

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

¹IQVIA and Symphony Health Data ²Datamonitor Healthcare, accessed June 2021. ³Armstrong A, et al., Dermatol Ther (Heidelb). 2017 Mar; 7(1). ⁴IQVIA Prescription data from Analyst Report, Oct 2020. ⁵DRG Epidemiology Database 2017 ⁶Lebwohl MG, et al., J Am Acad Dermatol. 2014 May;70(5):871-81.e1-30. ⁷Silverberg JI, et al., Allergy Asthma Immunol. 2018 Dec;121(6):729-734.e4. ⁸Armstrong, April W., et al. JAMA dermatology 149.10 (2013): 1180-1185. ⁹Regeneron 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 life¹
- Mild AD sufferers report **greater impact to quality of life** vs. people without AD²

Psycho-social impacts



- **34%** of “mild” PsO sufferers have depression; **27%** suffer sleep disturbance³
- **50%** higher risk of depression for mild-moderate AD sufferers vs. people without AD⁴

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

Appendix

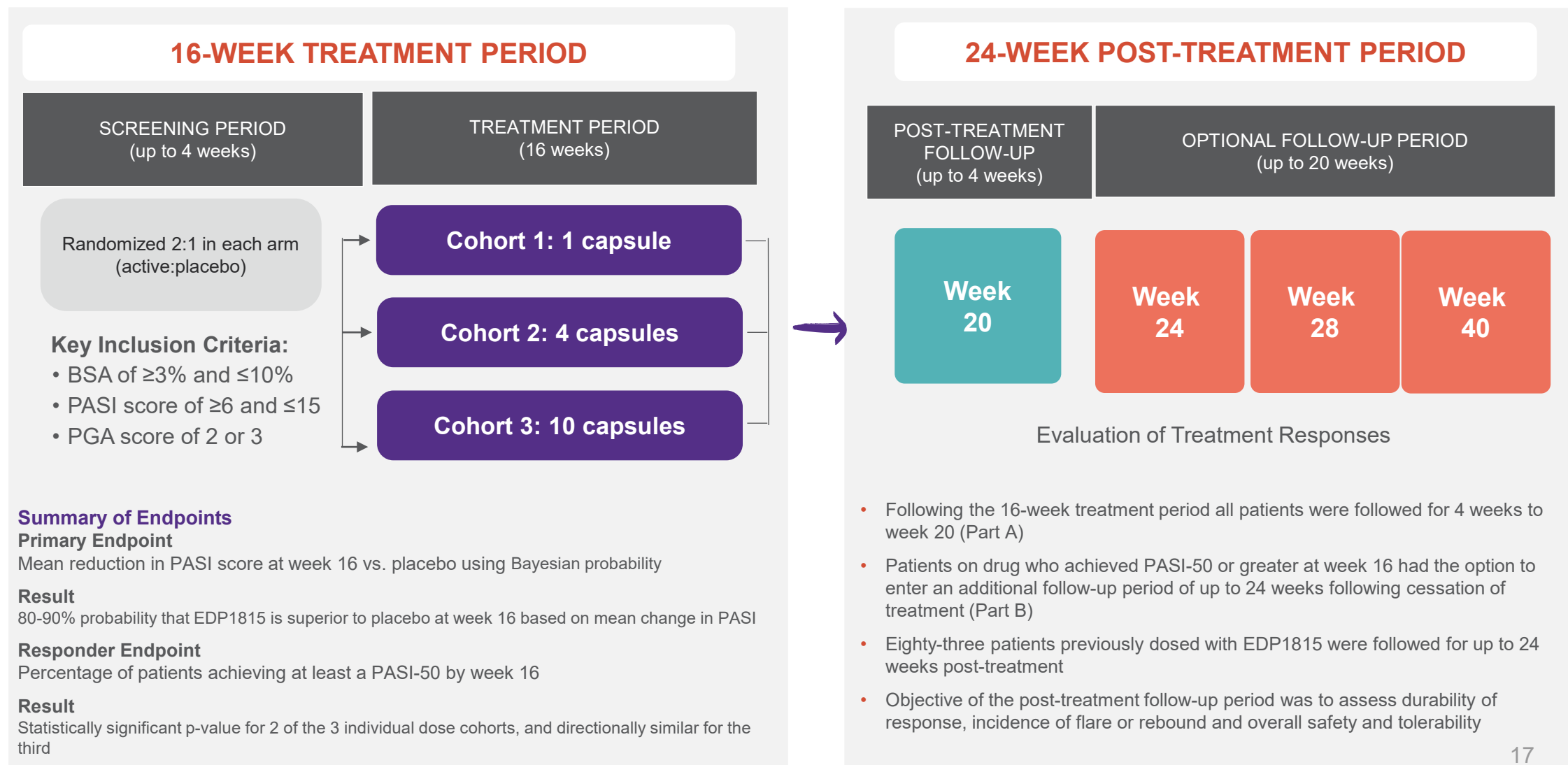
EDP1815

- Lead product candidate with blockbuster potential
- Advancing towards registration trials in psoriasis; regulatory feedback anticipated by year-end 2022
- Phase 2 trial in atopic dermatitis underway; data anticipated in 1Q and 2Q 2023
- Potential to expand broadly across inflammatory diseases beyond dermatology, including arthritides, inflammatory bowel disease, and chronic inflammatory respiratory diseases



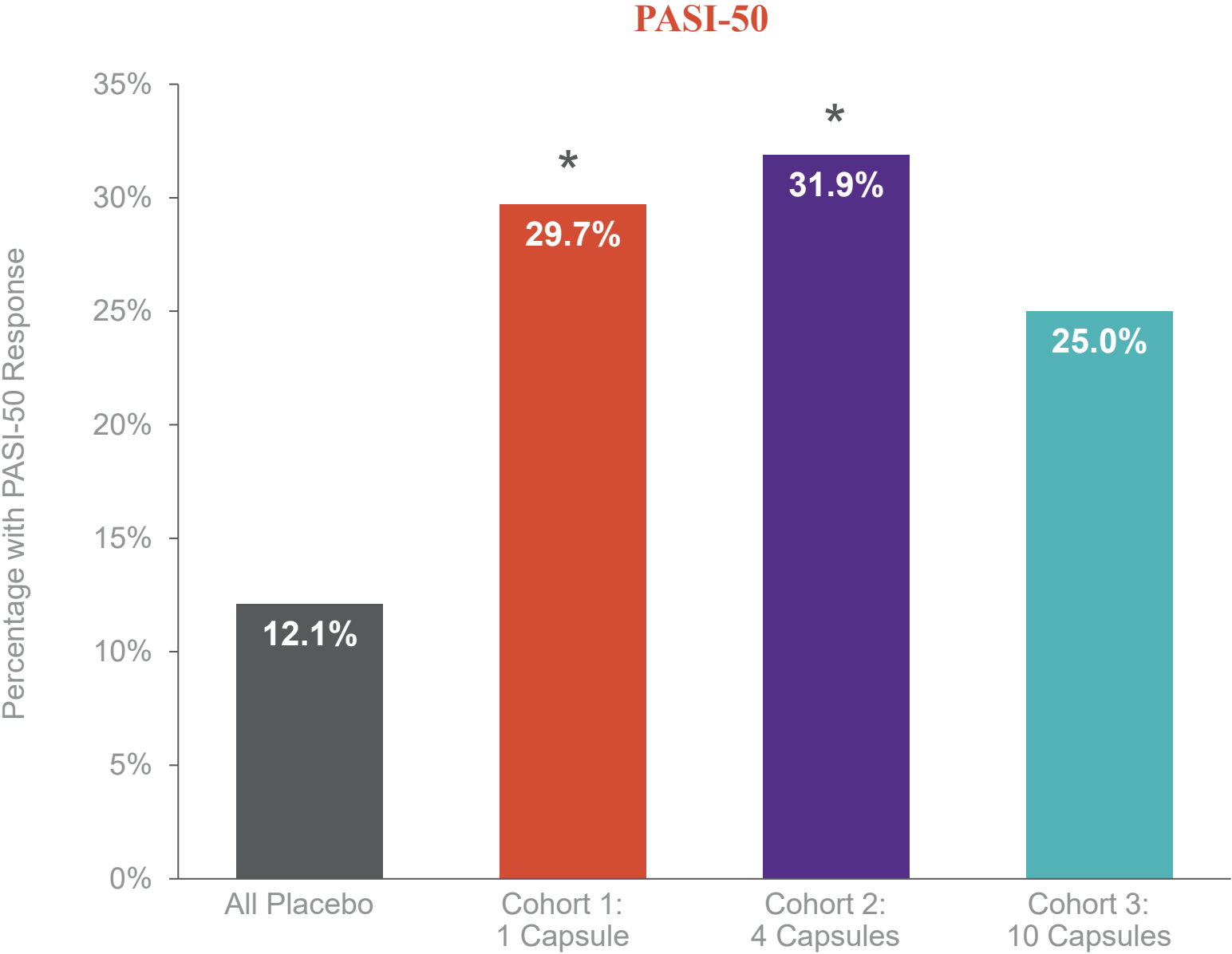
Psoriasis

EDP1815 Phase 2 Trial in Mild and Moderate Psoriasis



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

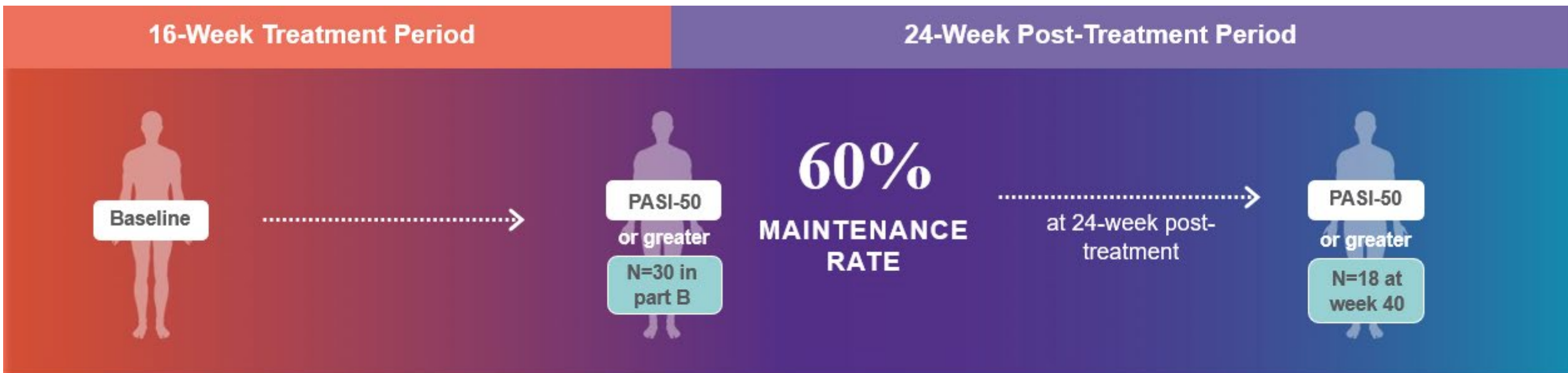
Deepening Response Over Time in Moderate Psoriasis Patients

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

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

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

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**

dotted arrow pointing from Week 16 to Week 24
during 24-weeks post-
treatment

PASI-75

or greater

N=9

BASELINE

WEEK 16

Week 24



PASI-100

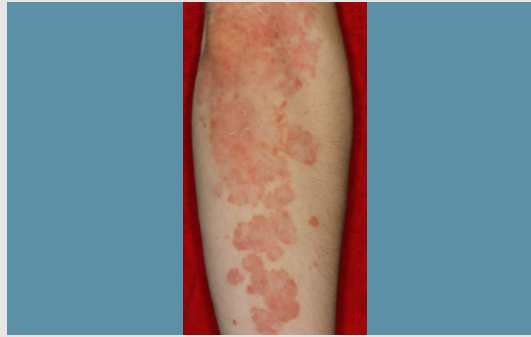
Deepening of Responses to PASI-75 or Greater During Post-Treatment Period

BASELINE

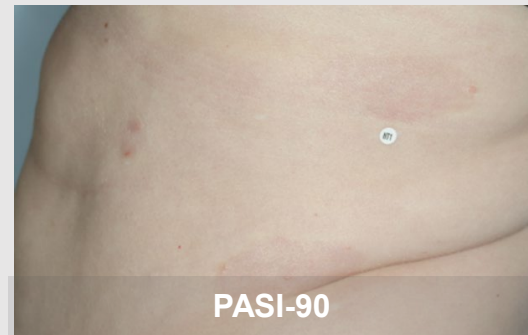
WEEK 16

PEAK RESPONSE

WEEK 16
RESPONDER*



Week 40:
>PASI-75



Week 24:
PASI-100

WEEK 16 NON-
RESPONDER



Week 28:
>PASI-75

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



Atopic Dermatitis

EDP1815 in Atopic Dermatitis

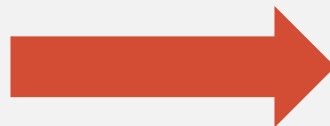


Before, day 0

Phase 1b trial

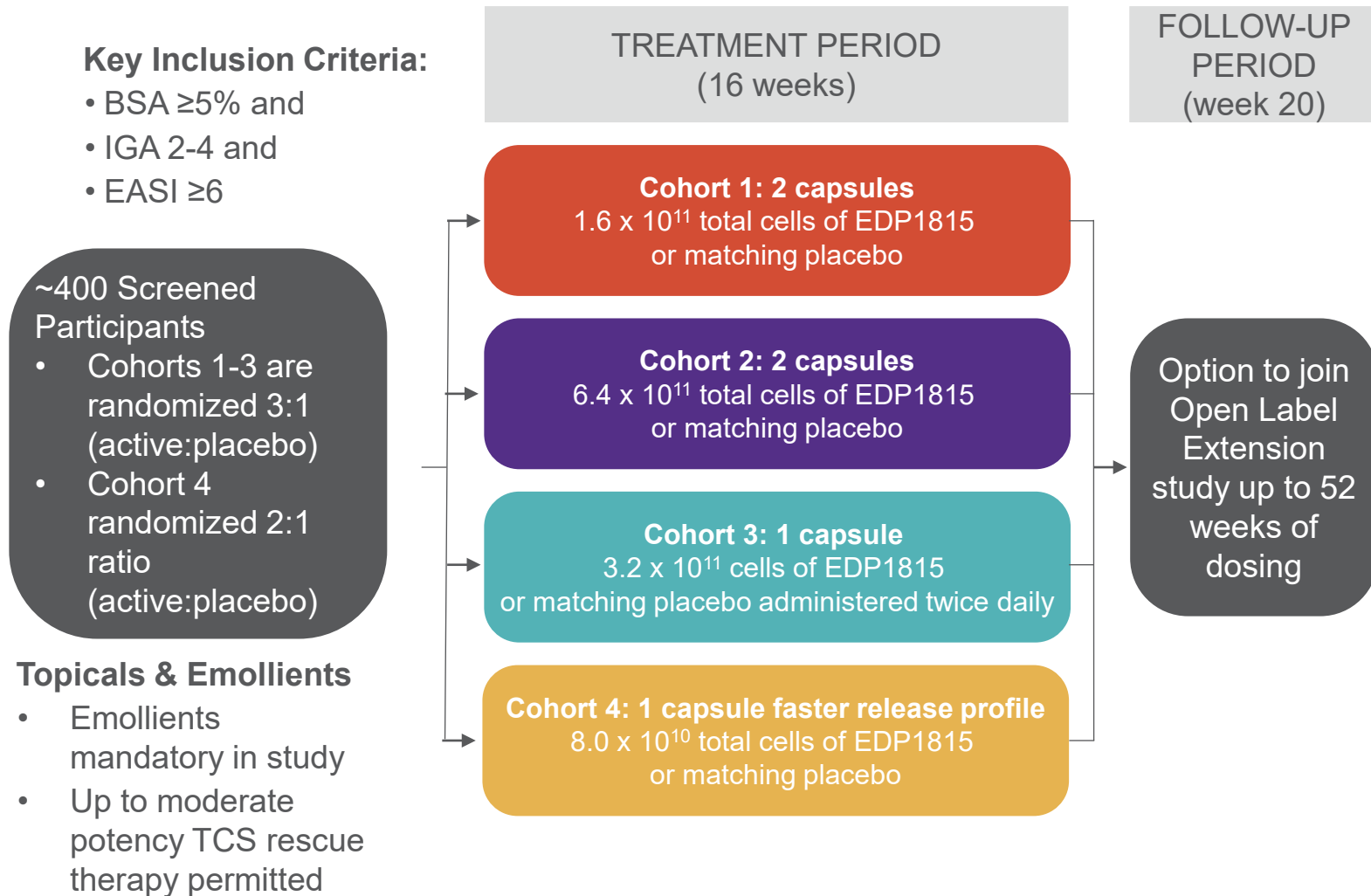
Patient on once daily EDP1815, no topical treatments.

Patient achieved EASI50 score



After, day 56

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



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

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

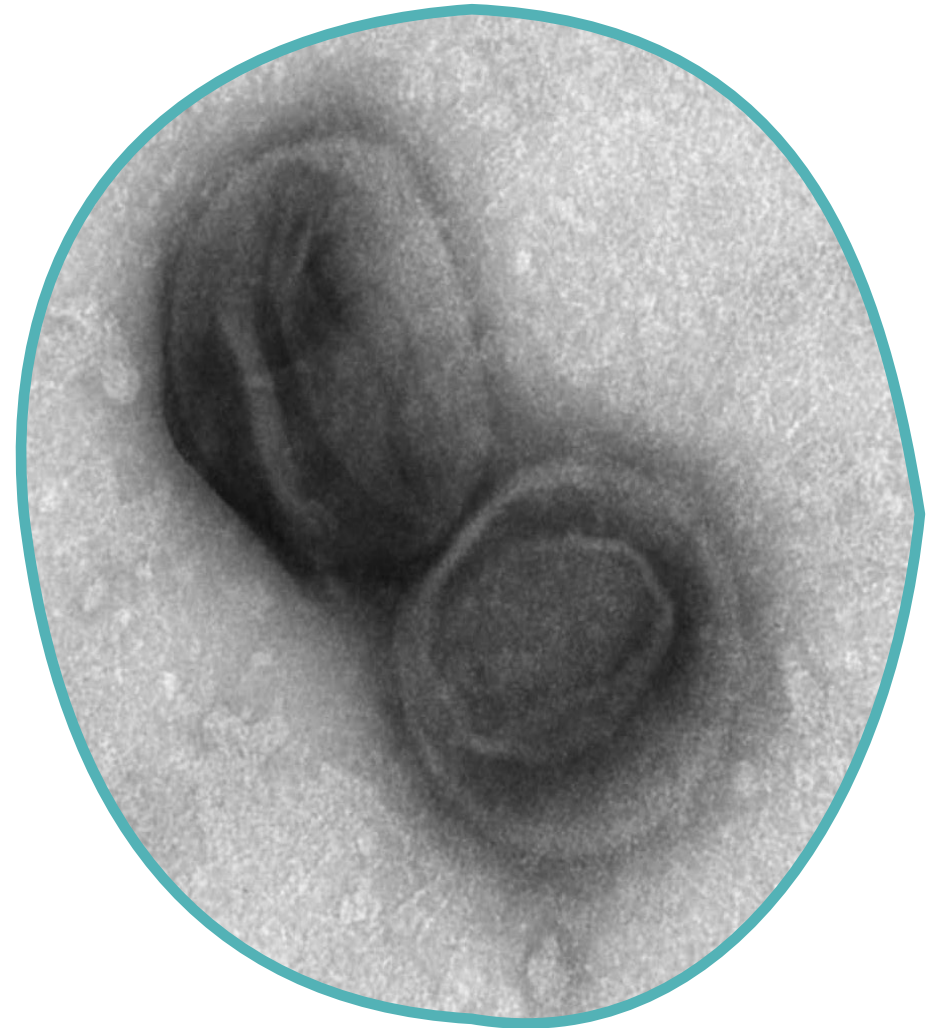
$$D = \frac{k_B T}{6\pi \eta r}$$

Fick's Laws of Diffusion

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

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
- Phase 2 data anticipated in 2H 2023





Opportunity in Inflammation

Evelo's Product Candidates

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Appendix

Corporate Information as of September 30, 2022

**119
employees**

**Cash and cash equivalents
of ~\$69.1 million**

**\$75 million ATM program
with capacity remaining**

Long-term debt \$45 million