



Papulopustular Rosacea: Where are we Now & What is New

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FORWARD-LOOKING STATEMENTS

This presentation contains “forward-looking statements” 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, but not limited to, statements regarding the commercial launch of EPSOLAY and statements regarding the benefits we expect to receive under our agreement with Galderma. These forward-looking statements include information about possible or assumed future results of our business, financial condition, results of operations, liquidity, plans and objectives. In some cases, you can identify forward-looking statements by terminology such as “believe,” “may,” “estimate,” “continue,” “anticipate,” “intend,” “should,” “plan,” “expect,” “predict,” “potential,” or the negative of these terms or other similar expressions. Forward-looking statements are based on information we have when those statements are made or our management’s current expectations and are subject to risks and uncertainties that could cause actual performance or results to differ materially from those expressed in or suggested by the forward-looking statements. Important factors that could cause such differences include, but are not limited to, the risk that we will not receive all of the anticipated benefits under our agreement with Galderma, the risk of a delay in the commercial availability of EPSOLAY and/or TWYNEO, the risk that EPSOLAY and TWYNEO will not provide treatment to the number of patients anticipated, risks relating to the effects of COVID 19 (coronavirus) as well as the following factors: (i) the adequacy of our financial and other resources, particularly in light of our history of recurring losses and the uncertainty regarding the adequacy of our liquidity to pursue our complete business objectives; (ii) our ability to complete the development of our product candidates; (iii) our ability to find suitable co-development partners; (iv) our ability to obtain and maintain regulatory approvals for our product candidates in our target markets, the potential delay in receiving such regulatory approvals and the possibility of adverse regulatory or legal actions relating to our product candidates even if regulatory approval is obtained; (v) our ability to commercialize our pharmaceutical product candidates; (vi) our ability to obtain and maintain adequate protection of our intellectual property; (vii) our ability to manufacture our product candidates in commercial quantities, at an adequate quality or at an acceptable cost; (viii) our ability to establish adequate sales, marketing and distribution channels; (ix) acceptance of our product candidates by healthcare professionals and patients; (x) the possibility that we may face third-party claims of intellectual property infringement; (xi) the timing and results of clinical trials that we may conduct or that our competitors and others may conduct relating to our or their products; (xii) intense competition in our industry, with competitors having substantially greater financial, technological, research and development, regulatory and clinical, manufacturing, marketing and sales, distribution and personnel resources than we do; (xiii) potential product liability claims; (xiv) potential adverse federal, state and local government regulation in the United States, Europe or Israel; and (xv) loss or retirement of key executives and research scientists. These and other important factors discussed in the Company's Annual Report on Form 20-F filed with the Securities and Exchange Commission (“SEC”) on April 4, 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. Except as required by law, we undertake no obligation to update any forward-looking statements in this presentation.



ACNE VS. ROSACEA

What's the difference





THE DIFFERENCE BETWEEN ACNE AND ROSACEA





Subject 213-009, SGT 54-02

Most Common Symptoms of Rosacea

- 


Pimple-like breakouts
But no blackheads.
- 


Eye problems
Including bloodshot eyes, red and swollen eyelids, problems seeing and discomfort.
- 


Facial redness
Near the central part of your face—cheeks, forehead, nose or chin. Redness may come and go or be permanent.
- 


Visible blood vessels
Caused by broken capillaries in the cheeks.

Most Common Symptoms of Acne

- 

Presents as pimples
Including blackheads, whiteheads, pimples or deep, painful cysts.
- 

Redness
Occurs around breakouts only.
- 

Oily T-zone
Affecting the nose, chin and forehead.
- 

Uneven skin texture
Bumpy skin texture, due to blemishes and scars.



Subject 417-004, SGT 65-04



What causes

Acne (Acne vulgaris)*

Acne is caused when sebaceous glands begin to produce too much sebum. The excess sebum mixes with dead skin cells and both substances form a plug in the follicle

The plugged follicle can bulge outwards, creating a whitehead or be open to the skin, creating a blackhead

Normally harmless *c acnes* bacteria that live on the skin can then infect the plugged follicles, causing papules, pustules, nodules or cysts

Rosacea (papulopustular rosacea)**

The cause of rosacea is unknown. The literature provides several possible causes:

Abnormalities in the blood vessels - facial flushing and spider veins may form due to abnormalities in the blood vessels of the face

Demodex folliculorum - people with rosacea tend to have more of these mites than others

Other causes - skin flora microbes, family history, sensitivity to triggers such as alcoholic beverages spicy food and temperature extremes

*<https://www.aad.org/public/diseases/acne/causes/acne-causes>

**<https://www.aad.org/public/diseases/rosacea/what-is/causes>



How to treat

Acne

Unclog the pores

Reduce microbial burden

Control sebum production

Reduce sebaceous gland size

Rosacea

Vasoconstrictors

Anti mite agents

Anti bacterial agents

A stylized logo consisting of a blue and green 'S' shape next to a vertical blue bar.

COMMON MEDICATIONS

Acne

OTC topical: salicylic acid, adapalene, benzoyl peroxide (BPO), etc.

Rx topical: retinoids (tretinoin, tazarotene, trifarotene), antibiotics (clindamycin, minocycline) dapsone, clascoterone, azelaic acid, etc.

Rx topical combinations: BPO/clindamycin, BPO/adapalene, encapsulated BPO/encapsulated tretinoin, tretinoin/clindamycin

Rx oral: antibiotics (minocycline, doxycycline, sarecycline), isotretinoin, spironolactone

Rosacea

No OTC drugs are indicated for the treatment of rosacea

Rx topical: antibiotics (metronidazole, minocycline), azelaic acid, ivermectin, brimonidine, oxymethazoline

No topical combinations

Rx oral: doxycycline



CAN ANTI-ACNE DRUG TREAT ROSACEA

A randomized, double-blind, placebo-controlled, pilot study to assess the efficacy and safety of clindamycin 1.2% and tretinoin 0.025% combination gel for the treatment of acne rosacea over 12 weeks

Background: A combination topical clindamycin phosphate 1.2% and tretinoin 0.025% gel is efficacious for acne vulgaris, and may be helpful for rosacea, since acne vulgaris and rosacea shares many similar clinical and histologic features.

Objective: To assess the preliminary efficacy and safety of a combination gel consisting of clindamycin phosphate 1.2% and tretinoin 0.025% on papulopustular rosacea after 12 weeks of usage.

Methods: Randomized, double-blind, placebo controlled two site study of 79 participants with moderate to severe papulopustular acne rosacea using both physician and subjects' validated assessment tools. Primary endpoint consisted of statistically significant reduction in absolute papule or pustule count after 12 weeks of usage.

Results: There was no significant difference in papule/pustule count between placebo and treated groups after 12 weeks ($P=0.10$).



CAN ANTI-ROSACEA DRUG TREAT ACNE

Evaluation of 0.75% metronidazole gel in acne - a double-blind study

Metronidazole, an imidazole, is an antibiotic with established efficacy against anaerobic bacteria. To date, however, there are no published data concerning the efficacy of topical metronidazole in the treatment of acne. This randomized, double-blind prospective clinical study of 96 patients was performed to investigate the efficacy and tolerability of 0.75% metronidazole gel vs. placebo in the treatment of mild to moderate acne. **The results of this study showed no significant benefit in using 0.75% metronidazole gel over placebo in reducing counts of inflamed and non-inflamed lesions of acne.** There was also no statistically significant difference between the two groups at any stage in the trial when skin tolerability was assessed



APIs USED IN BOTH INDICATIONS

Azelaic acid

Acne: 20% cream

Rosacea: 15% gel or foam

Minocycline

Acne: 4% foam, 50-100mg or 45-135mg ER capsules

Rosacea: 1.5% foam

Doxycycline

Acne: 50-150mg or 50-200mg DR capsules

Rosacea: 40mg capsule (Oracea)

Acne medications used off label in rosacea

Isotretinoin, dapson, sulfacetamide/sulfur, erythromycin, clindamycin, benzoyl peroxide

ER: extended release

DR: delayed release



EPSOLAY[®] (benzoyl peroxide, 5%, cream)

A novel, safe, fast and effective topical
treatment for papulopustular rosacea

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WHY BPO

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Benzoyl peroxide is a lipophilic agent with a rich 60-year history in the treatment of dermatologic disorders and is the most common OTC used to treat acne vulgaris

Broad and potent antimicrobial activity and comedolytic activity make BPO ideal for the management of acne

Skin irritation has thus far limited the utility of BPO in rosacea

Microencapsulation technology has the potential to extend the therapeutic reach of BPO by controlling the rate of exposure to optimize skin contact, improve local tolerability, and retain high efficacy

BPO=benzoyl peroxide.



BPO ENCAPSULATION PROCESS

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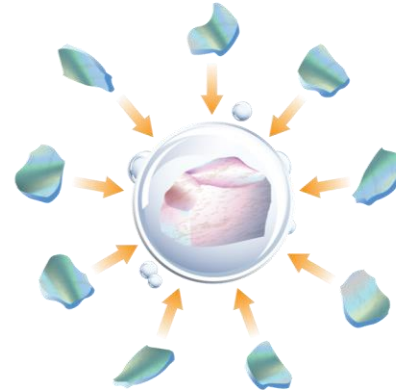
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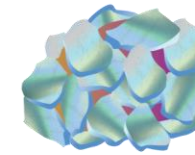
**BPO
Crystal**



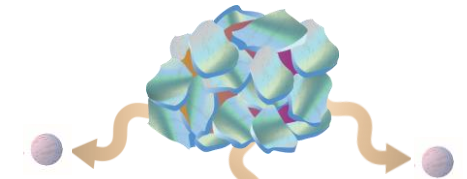
**BPO Crystal
Coated
With Surfactant**



**Silica
Monomers
Approaching**



**Silica Shell
Formation**



**Release of BPO
Through
Microchannels
in Silica**

BPO is dispersed in water with a positively charged surfactant



Silica solution is added in cycles to build up the silica shell around the BPO. This creates a permeable barrier between the active ingredient and skin



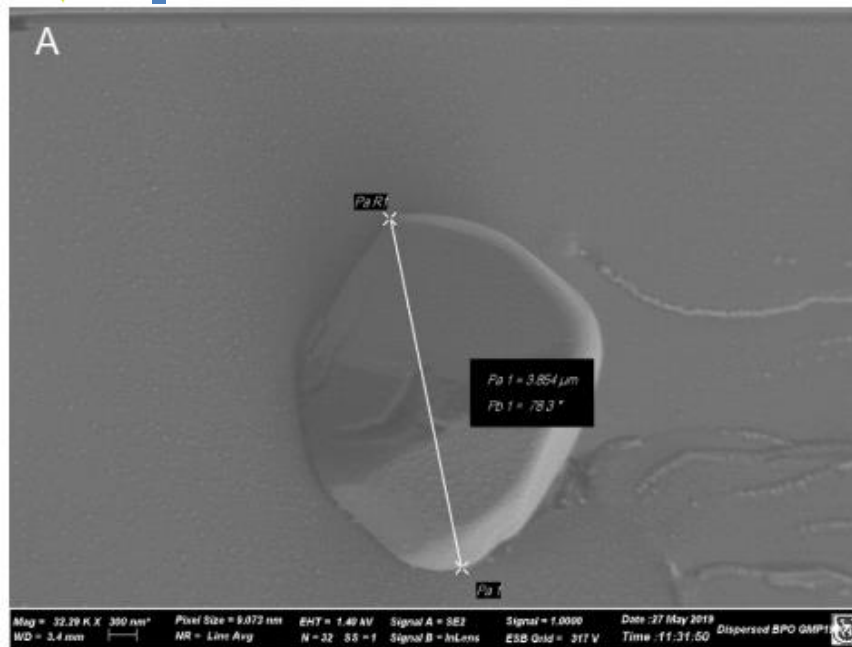
BPO is released gradually from the silica shell when it contacts the skin



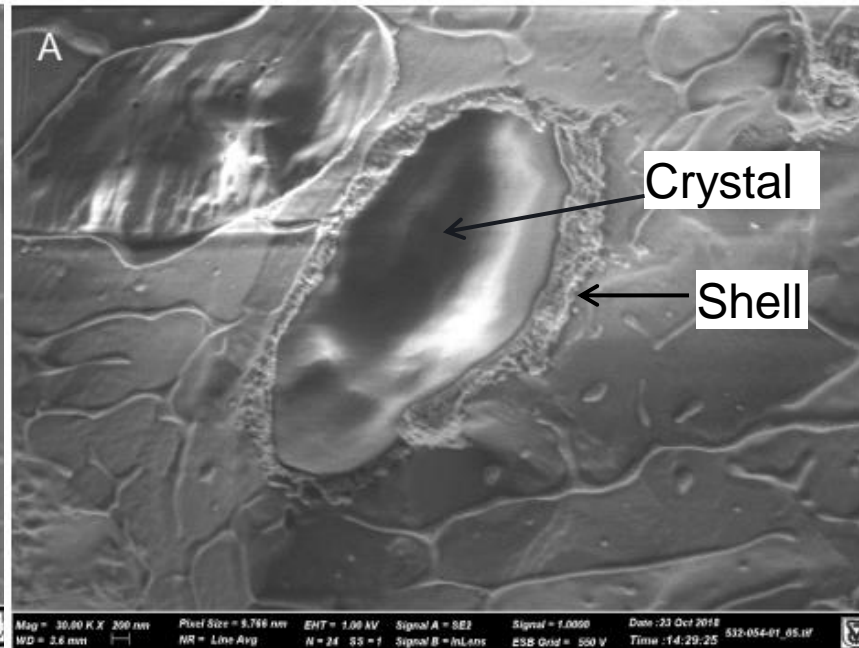
SEM PICTURES OF BPO AND E-BPO

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Non-encapsulated BPO crystals
dispersed in surfactant



E-BPO microcapsule



E-BPO microcapsule

E-BPO=encapsulated benzoyl peroxide.
SEM – scanning electron microscope

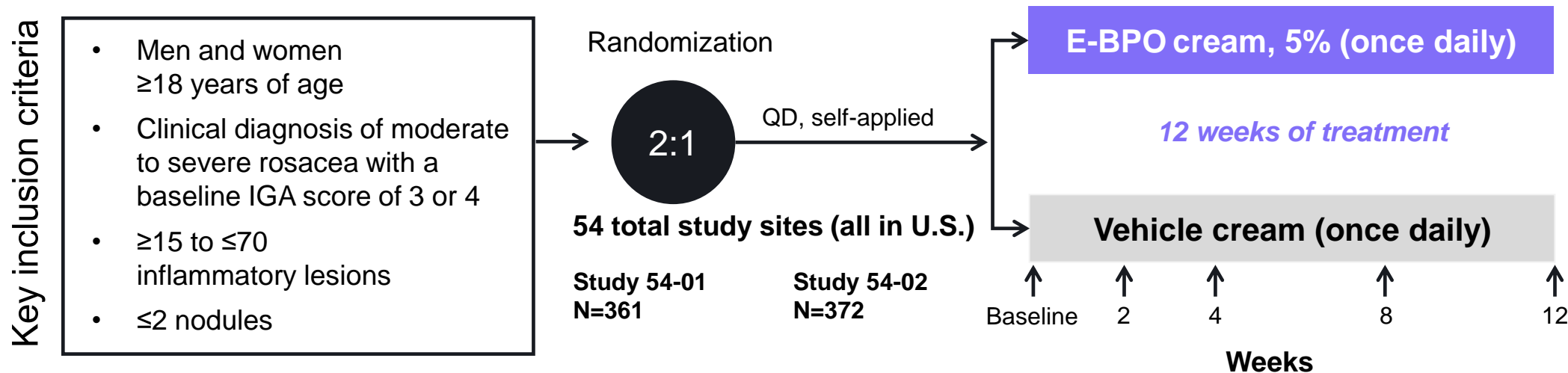


Summary of Two Phase 3 Multicenter, Double-blind, Randomized, Vehicle-controlled Studies of EPSOLAY in the Treatment of Papulopustular Rosacea

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Study Objective: Assess the efficacy and safety of E-BPO compared to vehicle when applied once daily for 12 weeks in patients with papulopustular rosacea



CO-PRIMARY ENDPOINTS:

- Proportion of subjects with the primary measure of success, “Clear” (0) or “Almost clear” (1), in the IGA relative to baseline at Week 12
 - The IGA scale ranged from “Clear” (0) to “Severe” (4) and included number of papules/pustules and erythema severity
- Absolute mean change in inflammatory lesion counts from baseline to Week 12

	Study 54-01		Study 54-02	
Randomized Subjects	EPSOLAY (n=243)	Vehicle (n=118)	EPSOLAY (n=250)	Vehicle (n=122)
Discontinued	21 (8.6%)	11 (9.3%)	15 (6.0%)	9 (7.4%)
Adverse events	5 (2.1%)	1 (0.8%)	4 (1.6%)	0
Lack of efficacy	0	0	0	0
Condition worsened	0	0	0	0
Lost to follow-up	6 (2.5%)	6 (5.1%)	1 (0.4%)	4 (3.3%)
Pregnancy	1 (0.4%)	1 (0.8%)	0	0
Protocol violation	0	0	1 (0.4%)	0
Withdrawal by subject	9 (3.7%)	3 (2.5%)	9 (3.6%)	4 (3.3%)
Physician decision	0	0	0	0
Other	0	0	0	1 (0.8%)
Completed	222 (91.4%)	107 (90.7%)	235 (94.0%)	113 (92.6%)



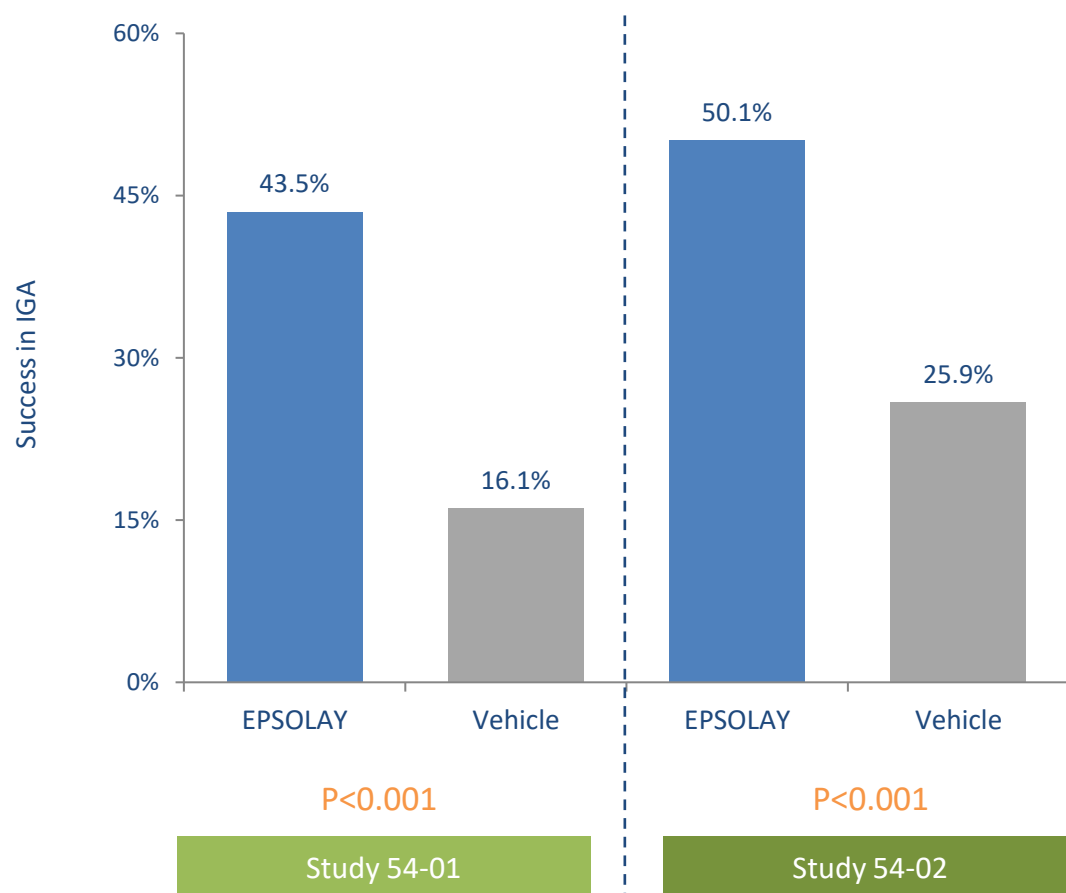
PHASE III RESULTS

SUCCESS IN PRIMARY ENDPOINTS

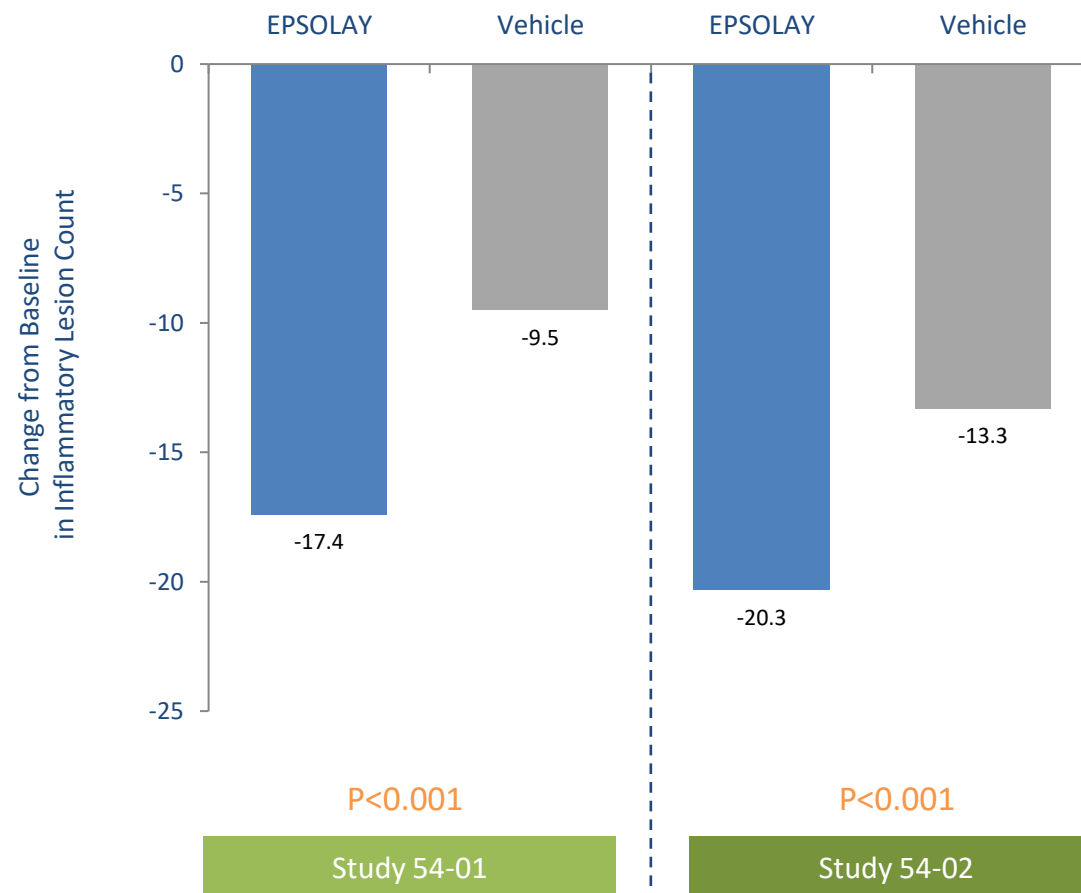
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Week 12
Success in IGA (ITT)



Week 12
Inflammatory Lesion Count
Change from Baseline (ITT)





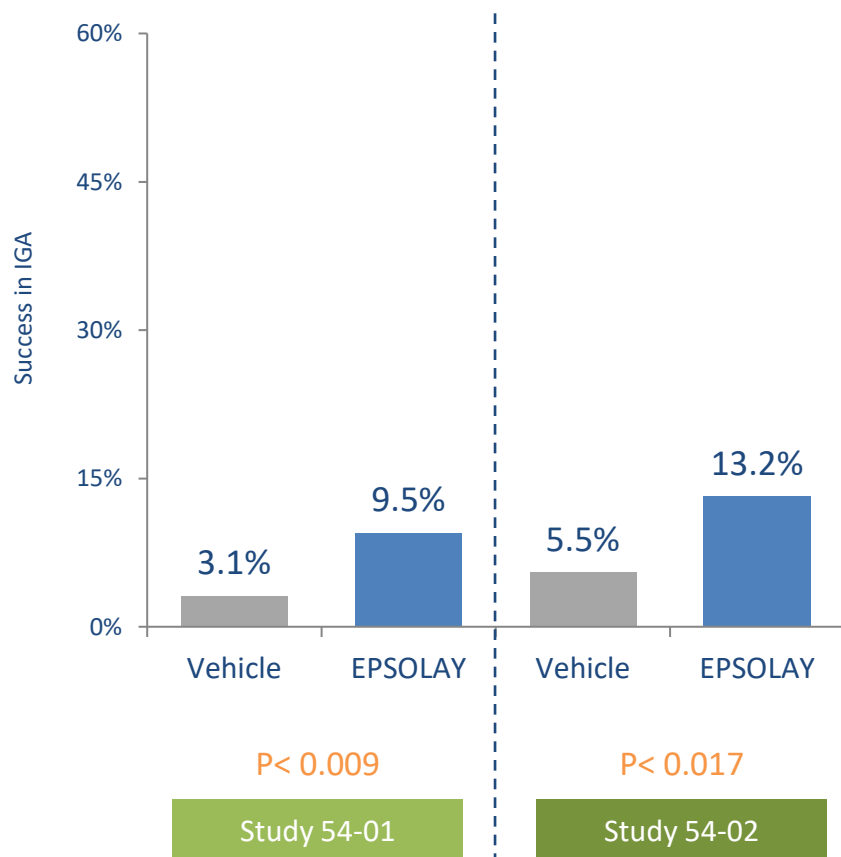
SUCCESS IN IGA

IMPROVEMENT AS OF WEEK 2

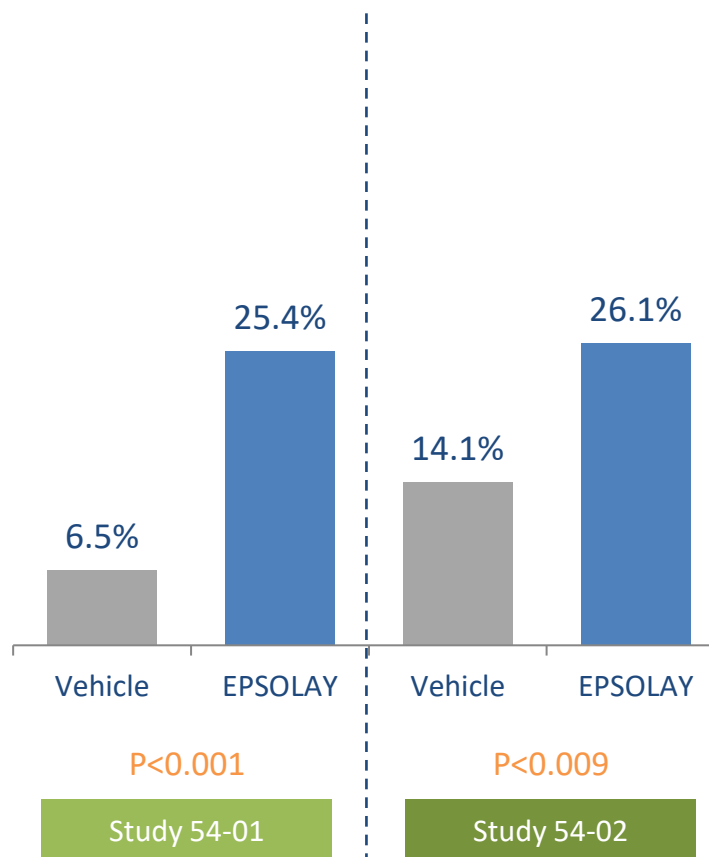
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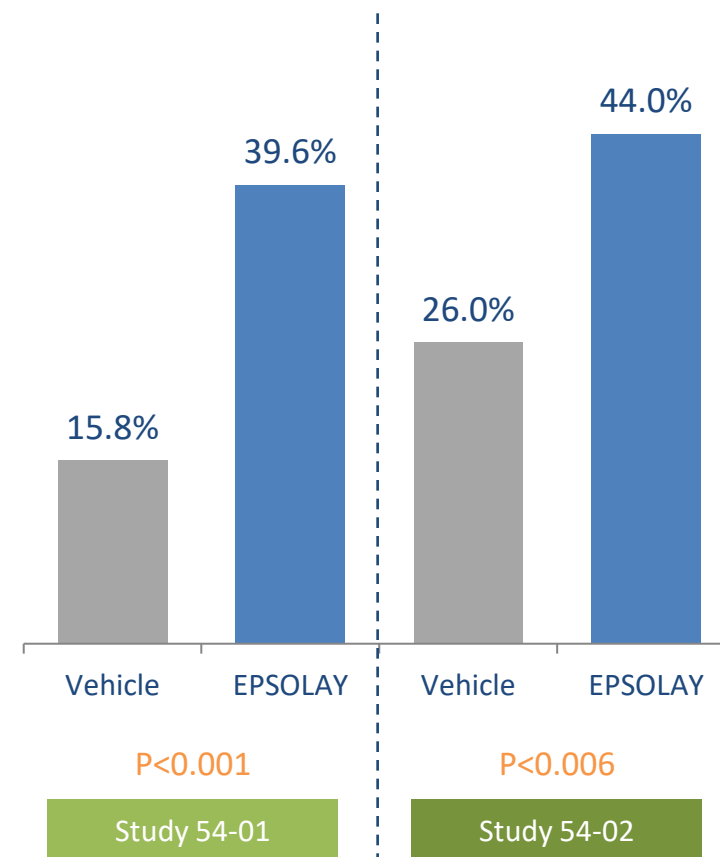
Week 2
Exploratory Endpoint (ITT)



Week 4
Secondary Endpoint (ITT)



Week 8
Secondary Endpoint (ITT)



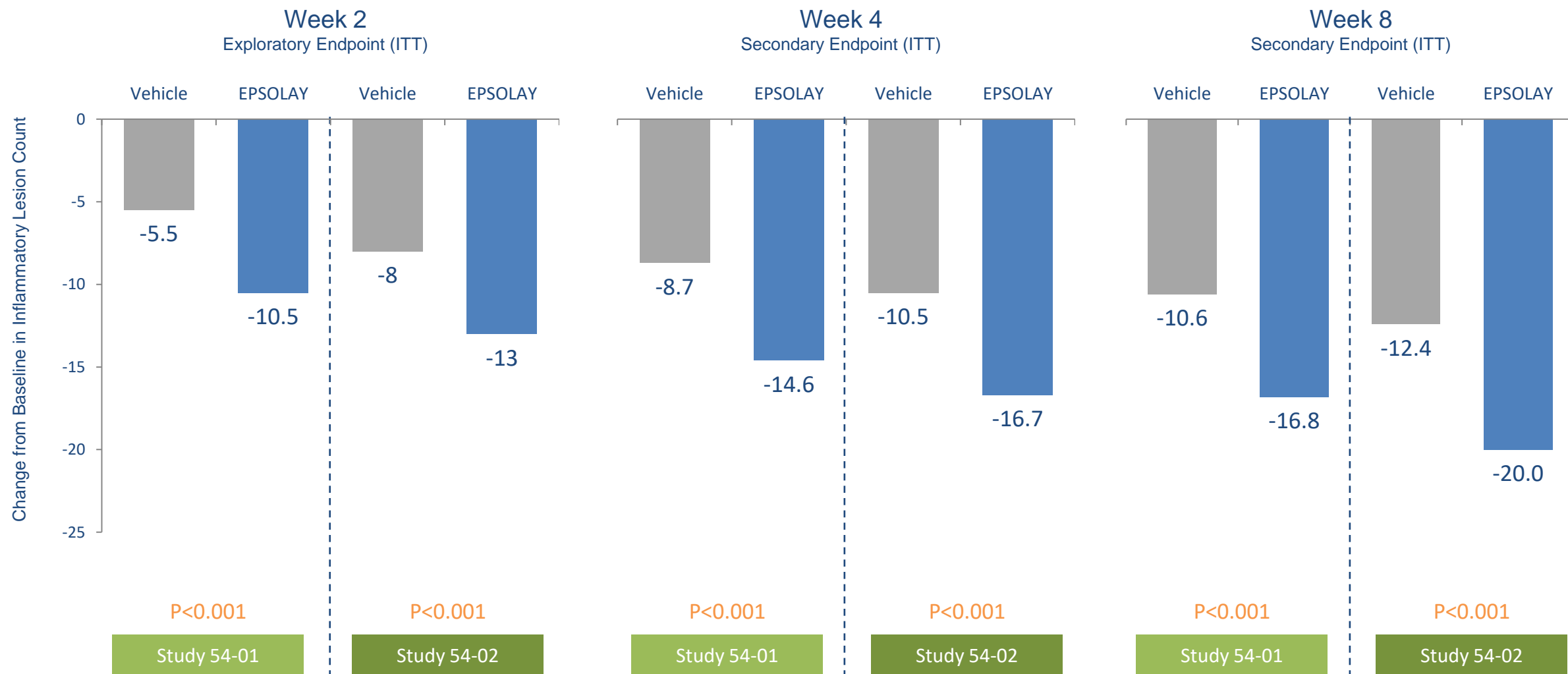



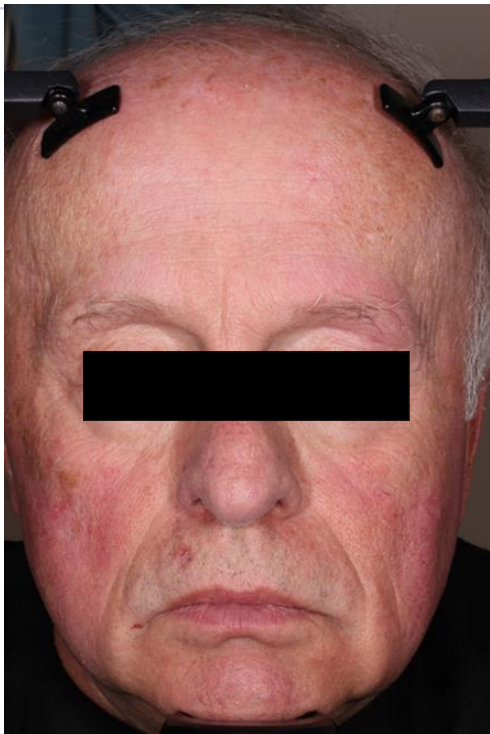
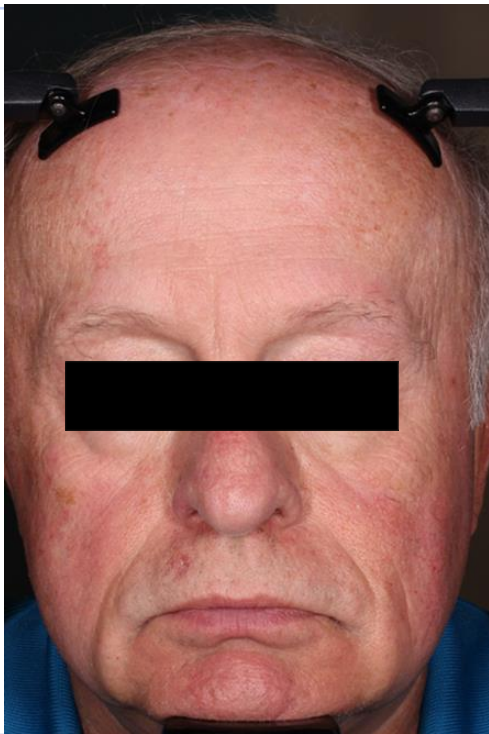
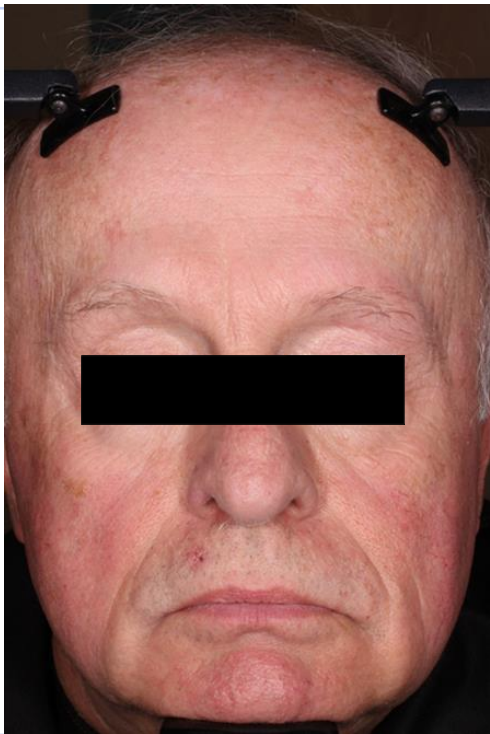
REDUCTION IN LESION COUNT



IMPROVEMENT AS OF WEEK 2






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Baseline/Screening	Week 4	Week 8	Week 12
			
IGA 4 Inflammatory 32	0 0	0 0	0 0

Baseline	Week 12
 	 
<p>IGA 4 Inflammatory 32 (31 papules/1 pustule)</p>	<p>0 0</p>

Baseline/Screening	Week 2	Week 4	Week 8	Week 12
				
IGA 4 Inflammatory 31 (26 papules/5 pustules)	1 2 (2 papules/0 pustules)	0 0	0 0	1 1 (1 papule/0 pustules)






Baseline/Screening	Week 2	Week 12
		
IGA 4 Inflammatory 31 (26 papules/5 pustules)	1 2 (2 papules/0 pustules)	1 1 (1 papule/0 pustules)

Baseline/Screening	Week 2	Week 4	Week 8	Week 12
				
IGA 4 Inflammatory 69 (48 papules/21 pustules)	3 36 (33 papules/3 pustules)	3 26 (23 papules/3 pustules)	3 31 (4 papules/27 pustules)	2 10 (10 papules/0 pustules)

Failure Subject - Wk 12 score ≠ 0/1

Baseline/Screening		Week 2		Week 12	
					
IGA 4 Inflammatory 69 (48 papules/21 pustules)		3 36 (33 papules/3 pustules)		2 10 (10 papules/0 pustules)	

Failure Subject - Wk 12 score \neq 0/1

Baseline/Screening	Week 2	Week 4	Week 8	Week 12
				
IGA 4 Inflammatory 38 (34 papules/4 pustules)	2 19 (17 papules/2 pustules)	3 11 (9 papules/2 pustules)	2 10 (10 papules/0 pustules)	2 5 (5 papules/0 pustules)

Failure Subject - Wk 12 score ≠ 0/1

Baseline/Screening		Week 2		Week 12	
					
IGA 4 Inflammatory 38 (34 papules/4 pustules)		2 19 (17 papules/2 pustules)		2 5 (5 papules/0 pustules)	

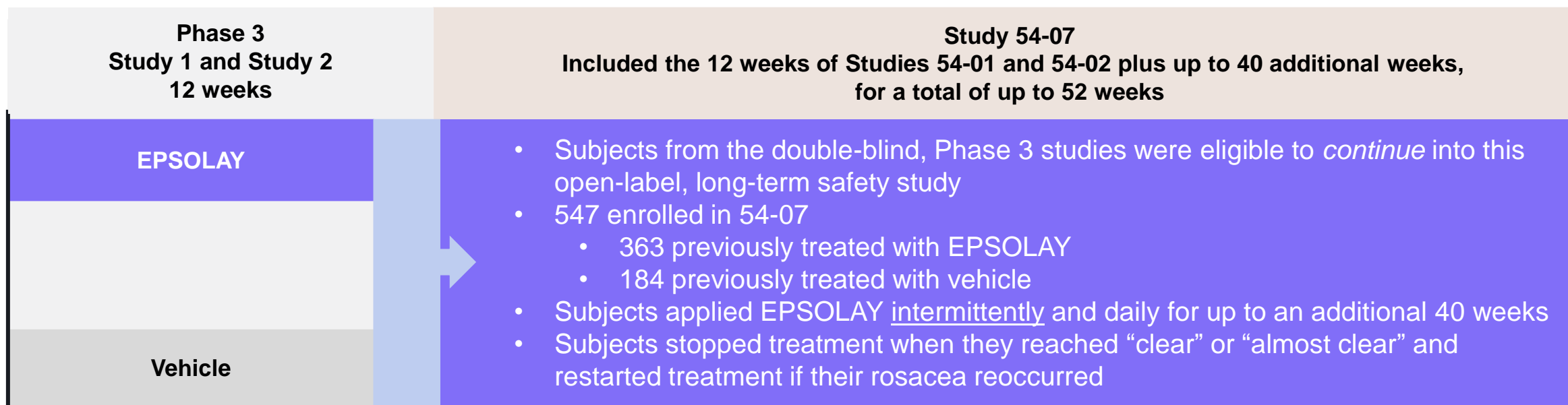
Failure Subject - Wk 12 score \neq 0/1



Multicenter, Open-label, Long-term Safety Study of EPSOLAY to Evaluate the Safety of EPSOLAY in Patients With Papulopustular Rosacea

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The safety endpoints assessed included

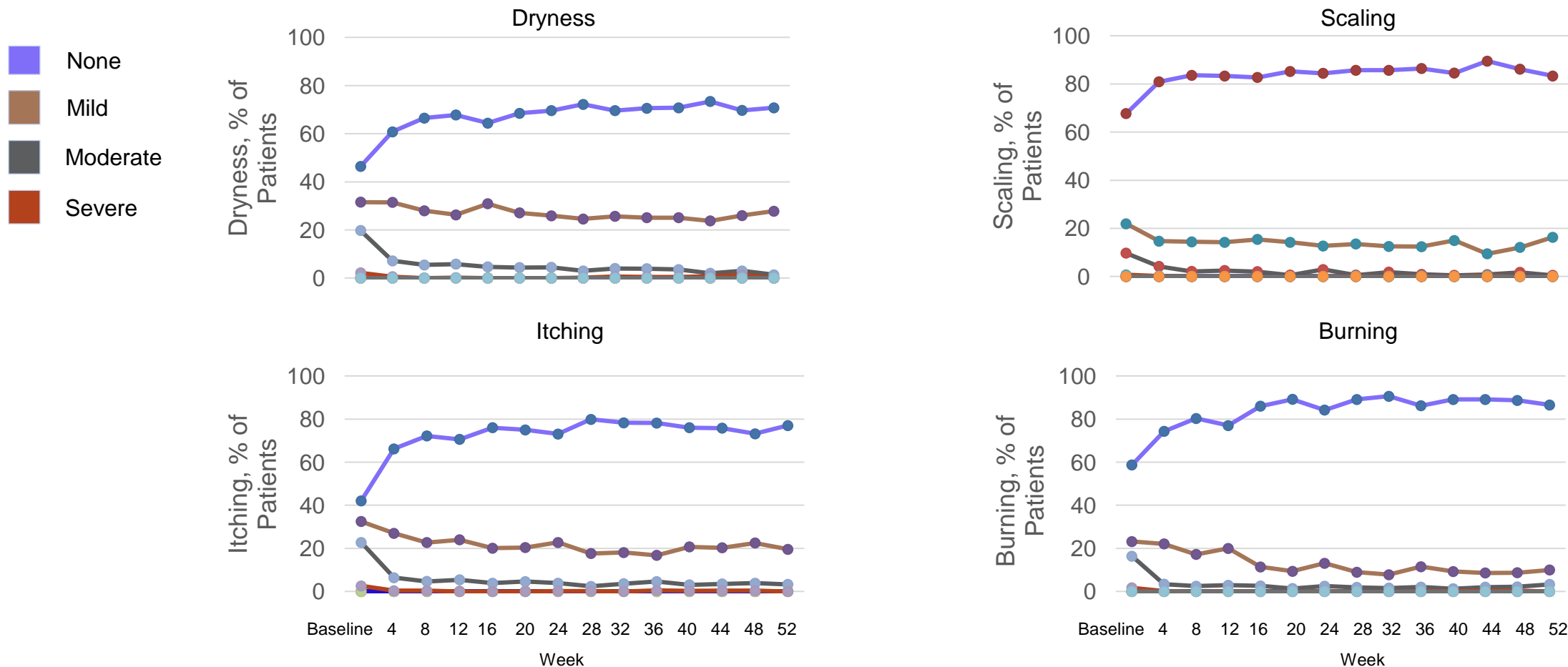
- The frequency of both local and systemic adverse events
- Investigator cutaneous safety assessment (dryness and scaling) and local tolerability assessment (itching and burning/stinging)

Termination: The study was **terminated early in accordance with the protocol**. Per the protocol, the Sponsor intended to follow a minimum of at least 300 subjects for 28 weeks and at least 100 subjects for 52 weeks, which was required to complete an adequate assessment of long-term safety as specified in the ICH E1A guidance.

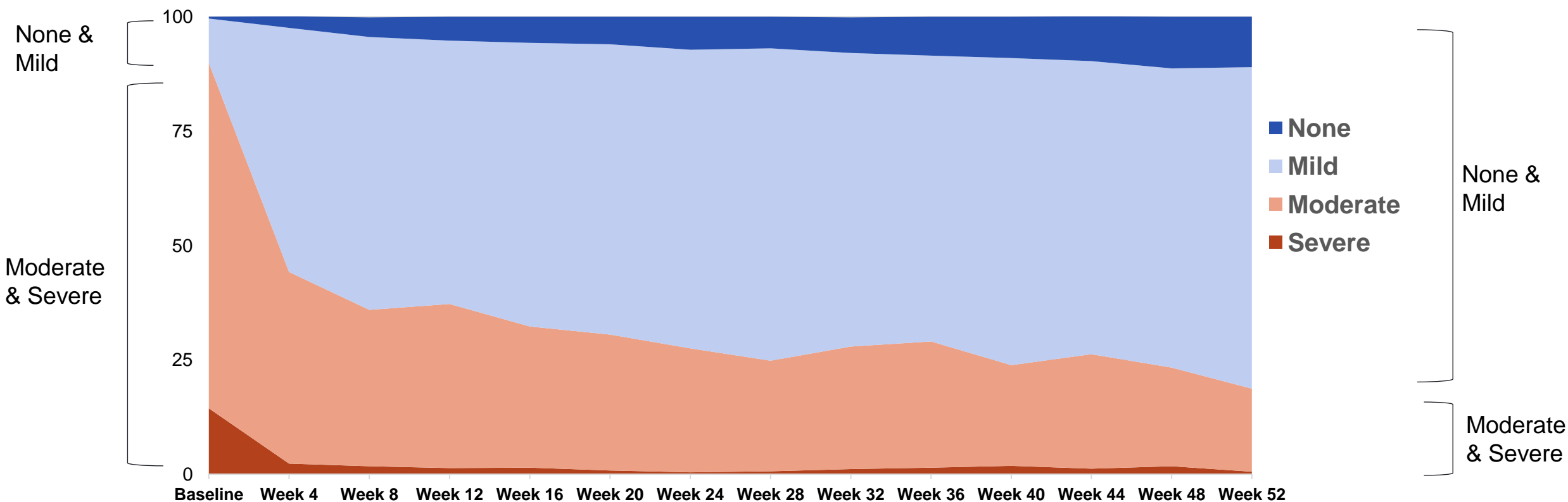


TOLERABILITY RESULTS, BASELINE TO WEEK 52

EPSOLAY remained well-tolerated over the course of 1 Year (52 Weeks)



Facial erythema generally improved during the study, n=535



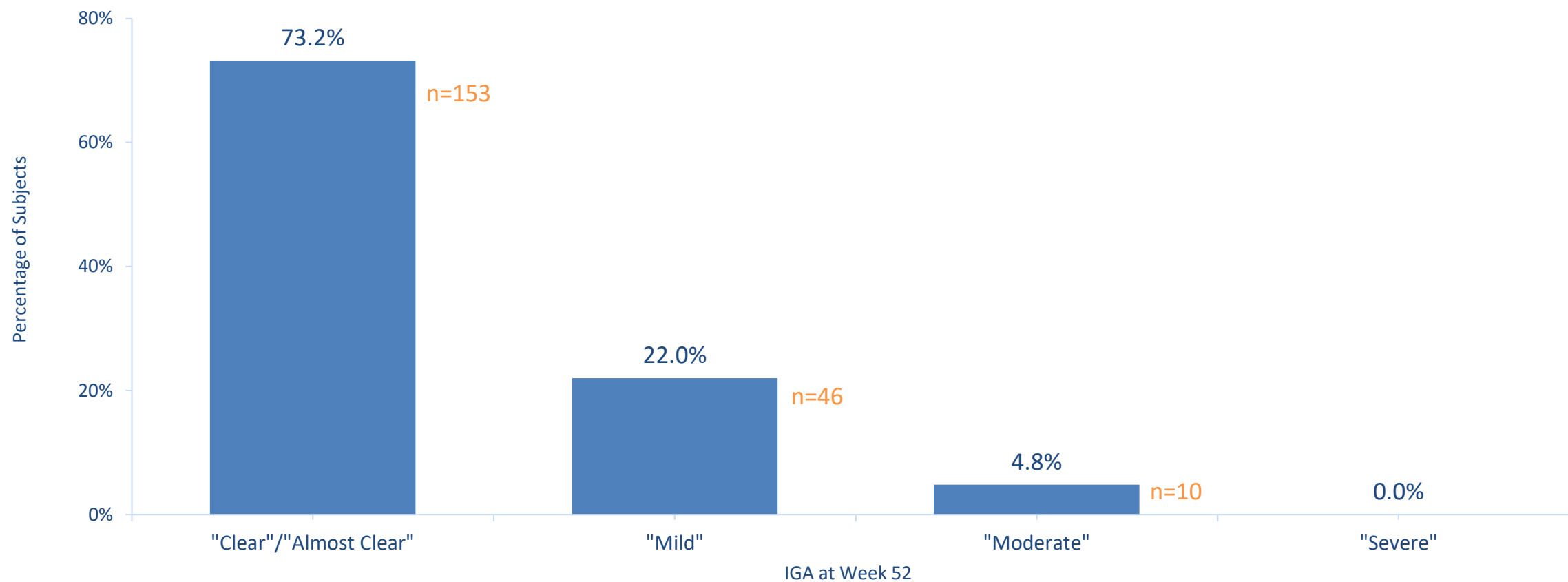


LONG-TERM SAFETY STUDY

IMPROVEMENT IN IGA

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This study was not intended to assess efficacy. Certain efficacy data and endpoints were, however, summarized



Thanks