ACNE & ROSACEA SYMPOSIUM

SBS ~ February 8, 2020 ~ 8:45am

THERAPEUTIC ADVANCES

JAMES Q. DEL ROSSO, DO
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JDR Dermatology Research / Thomas Dermatology

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Disclosures

ACLARIS*^#
ALMIRALL*^#
ANAPTYS BIO*
ATHENEX*
BIOPHARMX*^
BOTANIX*
CARA THERAPEUTICS*
CELGENE*^#
DERMIRA*^
ENCORE^#
EPI HEALTH*^#
FERNDALE^#
FOAMIX*^
GALDERMA*^#
GENENTECH*#
GLENMARK^
INCYTE*
LEO PHARMA*^#
LA ROCHE POSAY^
MC2^
MENLO THERAPEUTICS*^
NOVAN*^
ORTHO DERMATOLOGY*^#
PFIZER^#
RALEXAR*
REGENERON*^#
SANOFI-GENZYME^#
SKINFIX^
SOLGEL*^
SONOMA (INTRADERM)^
SUN PHARMA*^#
VERRICA^

* Research Investigator
^ Consultant/Advisor
# Speaker

UPDATED 12-01-2019

ACNE VULGARIS

TOPICAL RETINOIDS

Tretinoin 0.05% Lotion in Acne Vulgaris
Once Daily – 12-Week Phase III Monotherapy Studies

≥9 Years of Age with Facial Acne (N=1640)

Moderate to Severe Acne at Baseline

Two Randomized (1:1) Controlled Studies

Greater Improvements in Skin Oiliness, Patient Satisfaction and QoL with active vs vehicle (Week 12 vs Baseline)

Figure 1: Percent Change in Mean Inflammatory Lesions from Baseline to Week 12 (ITT Population, LS Mean data). Study 301 in blue and 302 in red; vehicle data shown in corresponding dotted lines)

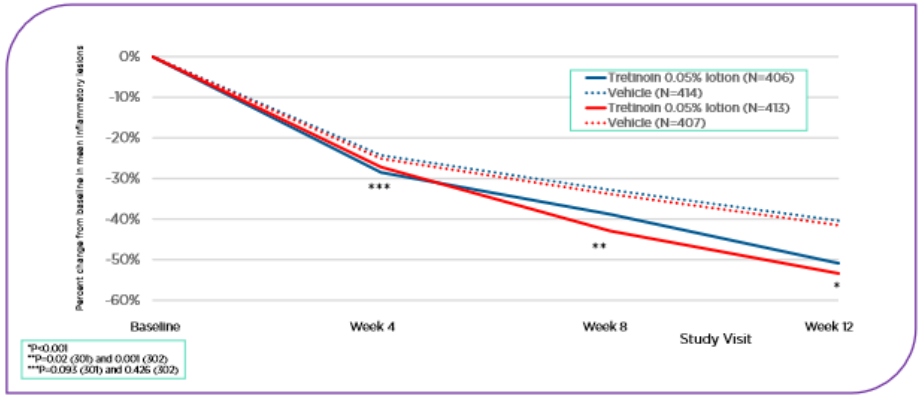
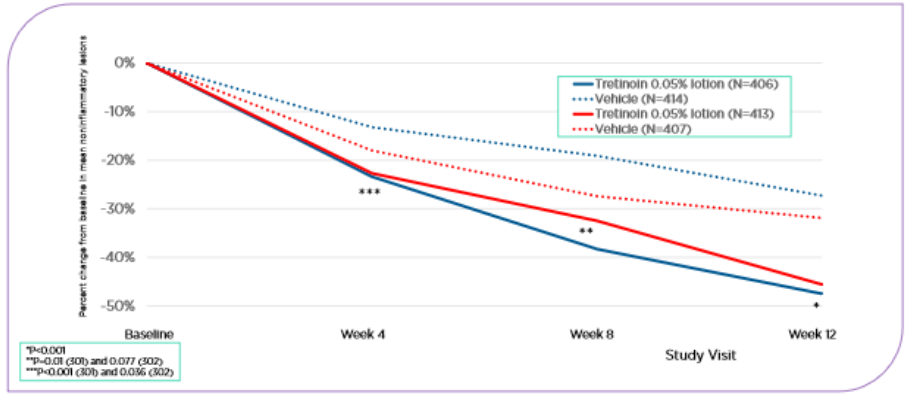


Figure 2: Percent Change in Mean Noninflammatory Lesions from Baseline to Week 12 (ITT Population, LS Mean data). Study 301 in blue and 302 in red; vehicle data shown in corresponding dotted lines)



WEEK 12

Mean % Reduction Inflammatory Lesions

50.9% - 53.4% (Tretinoin) vs

40.4% - 41.5% (Vehicle)

Mean % Reduction Comedonal Lesions

47.5% - 45.6% (Tretinoin) vs

27.3% - 31.9% (Vehicle)

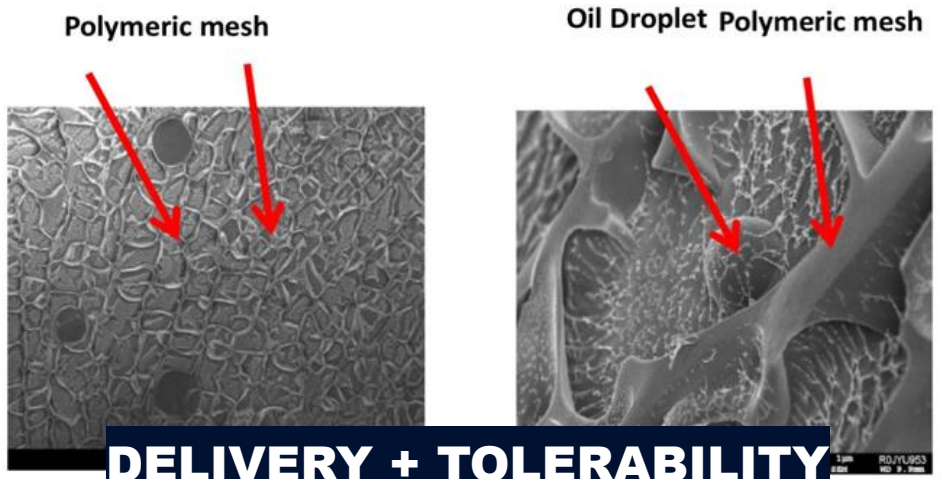
All Comparisons P<0.001

Del Rosso JQ, Pariser D, et al. Poster presentation, SCALE Meeting, Nashville, TN, May 2018

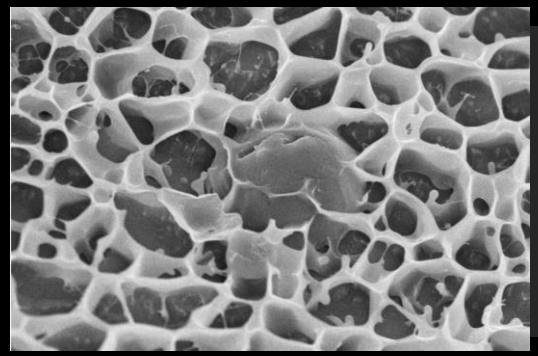
Harper JC, et al. J Dermatolog Treat. 2019 Apr 2:1-8.

Tretinoin 0.05% Lotion in Acne Vulgaris
Relevant Vehicle Characteristics

Figure 1: Cryo scanning electron microscopy (SEM) imaging of lotion formulation
A: 1000X magnification, B: 10,000X magnification



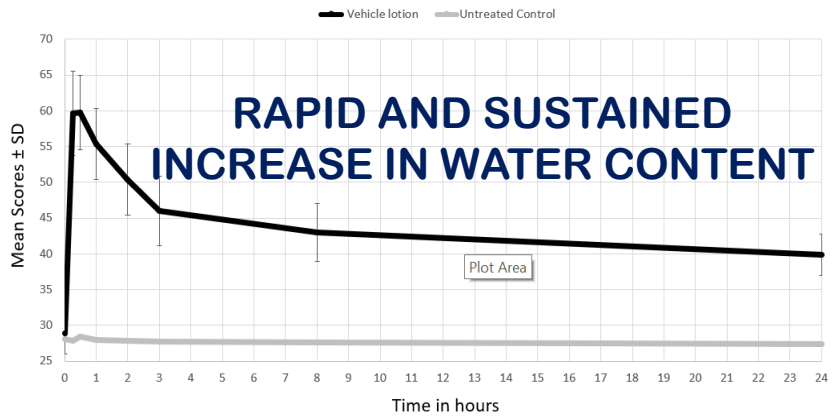
DELIVERY + TOLERABILITY



10,000X Magnification Honeycomb Mesh showing Emulsion or Oil Droplets

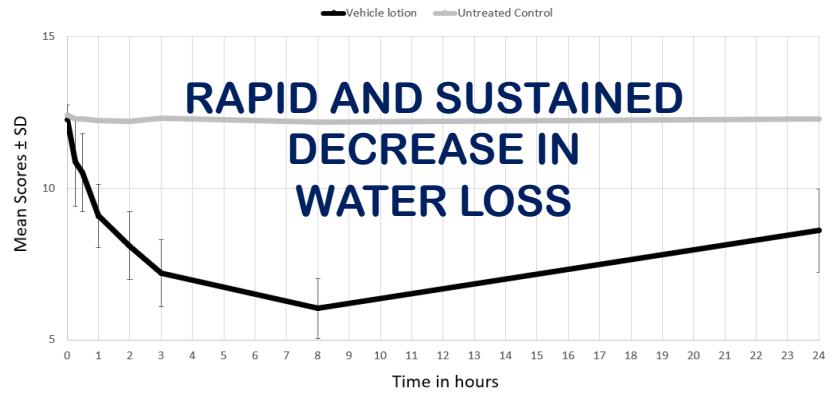
Kircik L, et al. Poster presentations. Fall Clinical Dermatology, Las Vegas, NV, October 2018.

Skin Moisturization Assessment over 24 Hours: Corneometry*



*All time points except baseline P<.001 versus untreated control

Skin Barrier Assessment over 24 Hours: Trans Epidermal Water Loss (TEWL)*



*All time points except baseline P<.001 versus untreated control

30 FEMALE VOLUNTEERS

BILATERAL TESTING ON VOLAR FOREARMS

TREATED AND UNTREATED SIDES

ASSESSMENT OVER 24 HOURS

NO ADVERSE REACTIONS

POST HOC ANALYSES FROM PIVOTAL TRIALS

ASIAN POPULATION (N=69)

AGE 12-48 YRS

EFFICACY AND TOLERABILITY CONFIRMED

Han G, et al. J Drugs Dermatol. 2019;18(9):910-916

PREADOLESCENT POPULATION (N=154)

AGE ≤13 YRS

EFFICACY AND TOLERABILITY CONFIRMED

Eichenfield L et al. Ped Dermatol. 2019;36(2): 193-199

ADULT AND ADOLESCENT FEMALE POPULATION (N=909)

AGE 9-58 YRS

EFFICACY AND TOLERABILITY CONFIRMED

Kircik L, et al. J Drugs Dermatol. 2019;18(2): 178-188

HISPANIC POPULATION (N=766)

AGE 11-50 YRS

EFFICACY AND TOLERABILITY CONFIRMED

Cook-Bolden F, et al. J Drugs Dermatol. 2019;18(1):32-38

Tazarotene 0.045% Lotion in Acne Vulgaris
Once Daily – 12-Week Phase 2 Comparative Study

≥12 Years of Age with Facial Acne (N=210)

Moderate to Severe Acne at Baseline

TAZAROTENE 0.045% LOTION (n=69)
vs
TAZAROTENE 0.1% CREAM (n=72)
vs
VEHICLES (n=69)

Tanghetti E, et al. J Drugs Dermatol. 1;18(6): 542-548

Figure 2: Percent Change in Mean Inflammatory Lesions from Baseline to Week 12 (ITT Population): Comparison of Tazarotene 0.045% lotion, Tazarotene 0.1% cream and Vehicle

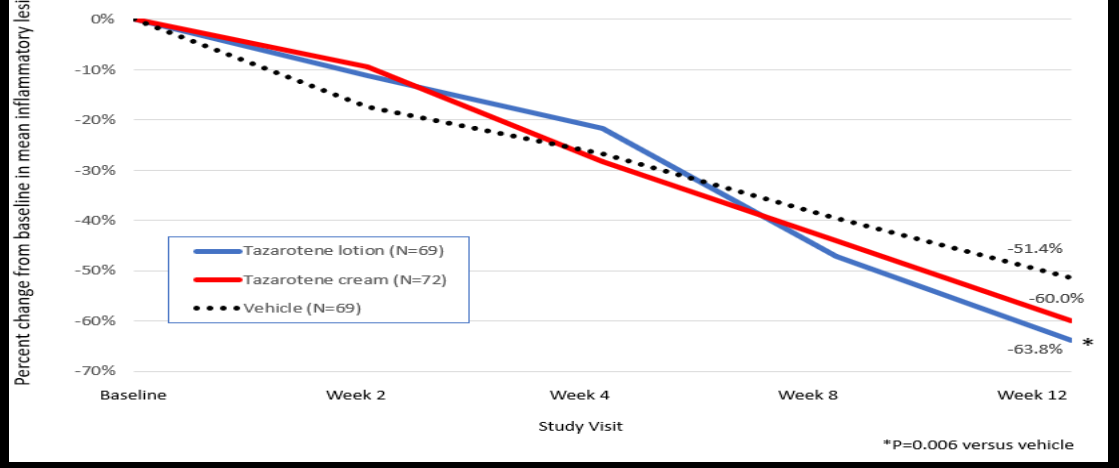
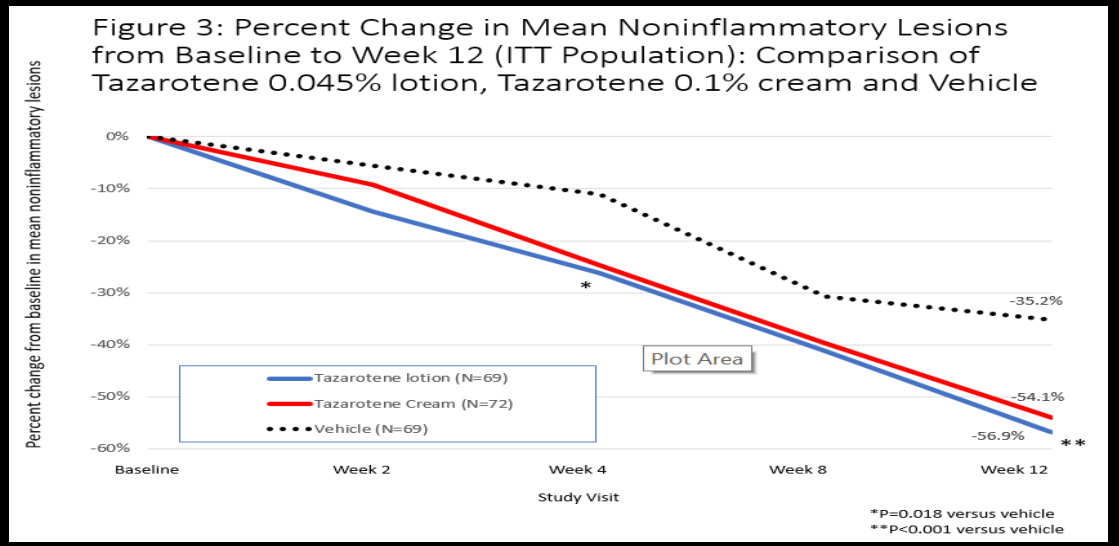


Figure 3: Percent Change in Mean Noninflammatory Lesions from Baseline to Week 12 (ITT Population): Comparison of Tazarotene 0.045% lotion, Tazarotene 0.1% cream and Vehicle



WEEK 12

Mean % Reduction Inflammatory Lesions
63.8%
(TAZ 0.045% LOTION) vs
60%
(TAZ 0.1% CREAM)

Mean % Reduction Comedonal Lesions
56.9%
(TAZ 0.045% LOTION) vs
54.1%
(TAZ 0.1% CREAM)

TREATMENT RELATED ADVERSE EFFECTS
5.6% (TAZ CREAM)
2.9% (TAZ LOTION)

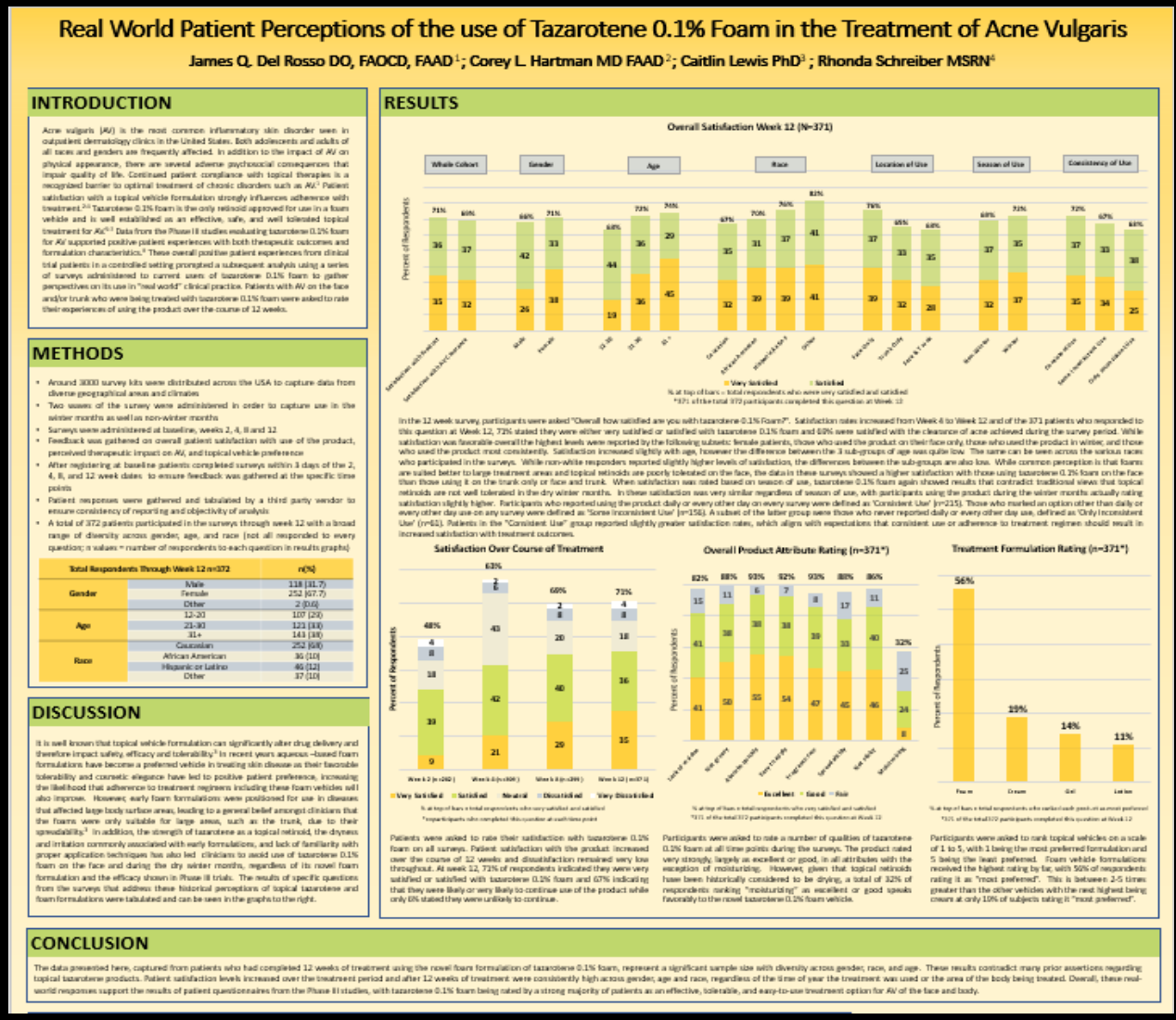
TAZAROTENE 0.1% FOAM EXPEPIENCE PROGRAM

PATIENT SAMPLE SIZE = 203
(WKS 2, 4, 8, 12)
57% FEMALE

82% TREATED FACE
(53% FACE ONLY / 29% BOTH)

4 WEEKS: 78% ACNE IMPROVED
64% VERY OR MODERATELY IMPROVED

12 WEEKS: 70% VERY SATISFIED OR SATISFIED
65% VERY LIKELY OR LIKELY TO CONTINUE USE



Real World Patient Perceptions of the use of Tazarotene 0.1% Foam in the Treatment of Acne Vulgaris

James Q. Del Rosso DO, FAOCD, FAAD[1]; Corey L. Hartman MD FAAD[2]; Caitlin Lewis PhD[3] ; Rhonda Schreiber MSRN[4]

INTRODUCTION

Acne vulgaris (AV) is the most common inflammatory skin disorder seen in outpatient dermatology clinics in the United States. Both adolescents and adults of all races and genders are frequently affected. In addition to the impact of AV on physical appearance, there are several adverse psychosocial consequences that impair quality of life. Continued patient compliance with topical therapies is a recognized barrier to optimal treatment of chronic disorders such as AV.[1] Patient satisfaction with a topical vehicle formulation strongly influences adherence with treatment.[2-5] Tazarotene 0.1% foam is the only retinoid approved for use in a foam vehicle and is well established as an effective, safe, and well tolerated topical treatment for AV.[6-9] Data from the Phase III studies evaluating tazarotene 0.1% foam for AV supported positive patient experiences with both therapeutic outcomes and formulation characteristics.[6] These overall positive patient experiences from clinical trial patients in a controlled setting prompted a subsequent analysis using a series of surveys administered to current users of tazarotene 0.1% foam to gather perspectives on its use in "real world" clinical practice. Patients with AV on the face and/or trunk who were being treated with tazarotene 0.1% foam were asked to rate their experiences of using the product over the course of 12 weeks.

METHODS

- Around 3000 survey kits were distributed across the USA to capture data from diverse geographical areas and climates
- Two waves of the survey were administered in order to capture use in the winter months as well as non-winter months
- Surveys were administered at baseline, weeks 2, 4, 8 and 12
- Feedback was gathered on overall patient satisfaction with use of the product, perceived therapeutic impact on AV, and topical vehicle preference
- After registering at baseline patients completed surveys within 3 days of the 2, 4, 8, and 12 week dates to ensure feedback was gathered at the specific time points
- Patient responses were gathered and tabulated by a third party vendor to ensure consistency of reporting and objectivity of analysis
- A total of 372 patients participated in the surveys through week 12 with a broad range of diversity across gender, age, and race (not all responded to every question; n values = number of respondents to each question in results graphs)

Total Respondents Through Week 12 n=372		n(%)
Gender	Male	118 (31.7)
	Female	252 (67.7)
	Other	2 (0.6)
Age	12-20	107 (29)
	21-30	121 (33)
	31+	143 (39)
Race	Caucasian	252 (68)
	African American	36 (10)
	Hispanic or Latino	46 (12)
	Other	37 (10)

DISCUSSION

It is well known that topical vehicle formulation can significantly alter drug delivery and therefore impact safety, efficacy and tolerability.[1] In recent years aqueous –based foam formulations have become a preferred vehicle in treating skin disease as their favorable tolerability and cosmetic elegance have led to positive patient preference, increasing the likelihood that adherence to treatment regimens including these foam vehicles will also improve. However, early foam formulations were positioned for use in diseases that affected large body surface areas, leading to a general belief amongst clinicians that the foams were only suitable for large areas, such as the trunk, due to their spreadability.[1] In addition, the strength of tazarotene as a topical retinoid, the dryness and irritation commonly associated with early formulations, and lack of familiarity with proper application techniques has also led clinicians to avoid use of tazarotene 0.1% foam on the face and during the dry winter months, regardless of its novel foam formulation and the efficacy shown in Phase III trials. The results of specific questions from the surveys that address these historical perceptions of topical tazarotene and foam formulations were tabulated and can be seen in the graphs to the right.

RESULTS

Overall Satisfaction Week 12 (N=371)

% at top of bars = total respondents who were very satisfied and satisfied
*371 of the total 372 participants completed this question at Week 12

In the 12 week survey, participants were asked "Overall how satisfied are you with tazarotene 0.1% Foam?". Satisfaction rates increased from Week 4 to Week 12 and of the 371 patients who responded to this question at Week 12, 72% stated they were either very satisfied or satisfied with tazarotene 0.1% foam and 88% were satisfied with the clearance of acne achieved during the survey period. While satisfaction was favorable overall the highest levels were reported by the following subsets: female patients, those who used the product on their face only, those who used the product in winter, and those who used the product most consistently. Satisfaction increased slightly with age, however the difference between the 3 sub-groups of age was quite low. The same can be seen across the various races who participated in the surveys. While non-white responders reported slightly higher levels of satisfaction, the differences between the sub-groups are also low. While common perception is that foams are suited better to large treatment areas and topical retinoids are poorly tolerated on the face, the data in these surveys showed a higher satisfaction with those using tazarotene 0.1% foam on the face than those using it on the trunk only or face and trunk. When satisfaction was rated based on season of use, tazarotene 0.1% foam again showed results that contradict traditional views that topical retinoids are not well tolerated in the dry winter months. In these satisfaction was very similar regardless of season of use, with participants using the product during the winter months actually rating satisfaction slightly higher. Participants who reported using the product daily or every other day on every survey were defined as 'Consistent Use' (n=215). Those who marked an option other than daily or every other day use on any survey were defined as 'Some Inconsistent Use' (n=156). A subset of the latter group were those who never reported daily or every other day use, defined as 'Only Inconsistent Use' (n=61). Patients in the "Consistent Use" group reported slightly greater satisfaction rates, which aligns with expectations that consistent use or adherence to treatment regimen should result in increased satisfaction with treatment outcomes.

Satisfaction Over Course of Treatment

Patients were asked to rate their satisfaction with tazarotene 0.1% foam on all surveys. Patient satisfaction with the product increased over the course of 12 weeks and dissatisfaction remained very low throughout. At week 12, 71% of respondents indicated they were very satisfied or satisfied with tazarotene 0.1% foam and 67% indicating that they were likely or very likely to continue use of the product while only 6% stated they were unlikely to continue.

Overall Product Attribute Rating (n=371*)

Participants were asked to rate a number of qualities of tazarotene 0.1% foam at all time points during the surveys. The product rated very strongly, largely as excellent or good, in all attributes with the exception of moisturizing. However, given that topical retinoids have been historically considered to be drying, a total of 32% of respondents ranking "moisturizing" an excellent or good speaks favorably to the novel tazarotene 0.1% foam vehicle.

Treatment Formulation Rating (n=371*)

Participants were asked to rank topical vehicles on a scale of 1 to 5, with 1 being the most preferred formulation and 5 being the least preferred. Foam vehicle formulations received the highest rating by far, with 56% of respondents rating it as "most preferred". This is between 2-5 times greater than the other vehicles with the next highest being cream at only 19% of subjects rating it "most preferred".

CONCLUSION

The data presented here, captured from patients who had completed 12 weeks of treatment using the novel foam formulation of tazarotene 0.1% foam, represent a significant sample size with diversity across gender, race, and age. These results contradict many prior assertions regarding topical tazarotene products. Patient satisfaction levels increased over the treatment period and after 12 weeks of treatment were consistently high across gender, age and race, regardless of the time of year the treatment was used or the area of the body being treated. Overall, these real-world responses support the results of patient questionnaires from the Phase III studies, with tazarotene 0.1% foam being rated by a strong majority of patients as an effective, tolerable, and easy-to-use treatment option for AV of the face and body.

Del Rosso JQ, et al. Poster presentation. Fall Clinical Dermatology, Las Vegas, Nevada, October 2019.

Trifarotene Cream

Phase 3 Studies in Moderate Facial AND Truncal Acne

- Trifarotene is a RARγ-selective topical retinoid in a cream (50 µg/g)
- Development program evaluated efficacy and safety in both FACIAL and TRUNCAL ACNE
- Two 12-week, double-blinded, multicenter, vehicle controlled studies
  - Once daily trifarotene cream (n=1209) or vehicle cream (n=1183)
  - Randomization pattern 1:1
- **TRUNCAL ACNE (Data at 12 Weeks)**

	Study 1	Study 2
Mean % Change Inflammatory Lesions	57.4% vs 50.0%	65.4% vs 51.1%
Mean % Change Non-Inflammatory Lesions	49.1% vs 40.3%	55.2% vs 45.1%

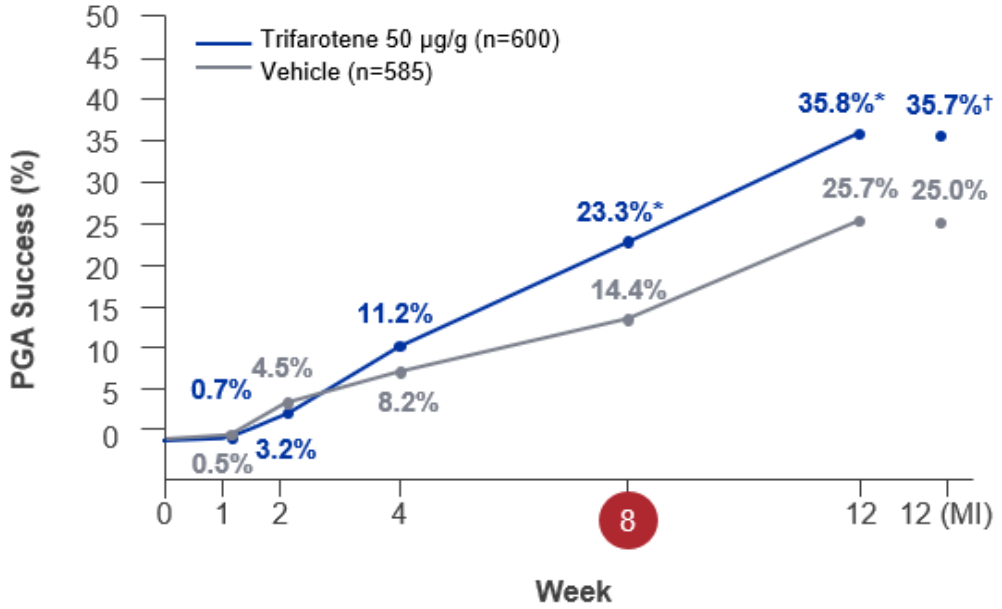
- Majority of adverse events local tolerability reactions early in therapy
  - Consistent with topical retinoid therapy – managed with proper skin care
  - Fewer reactions on trunk

Tan J, Thiboutot D, Popp G, et al. J Am Acad Dermatol. 2019;80(6):1691-1699.

Trifarotene Cream PGA* Success

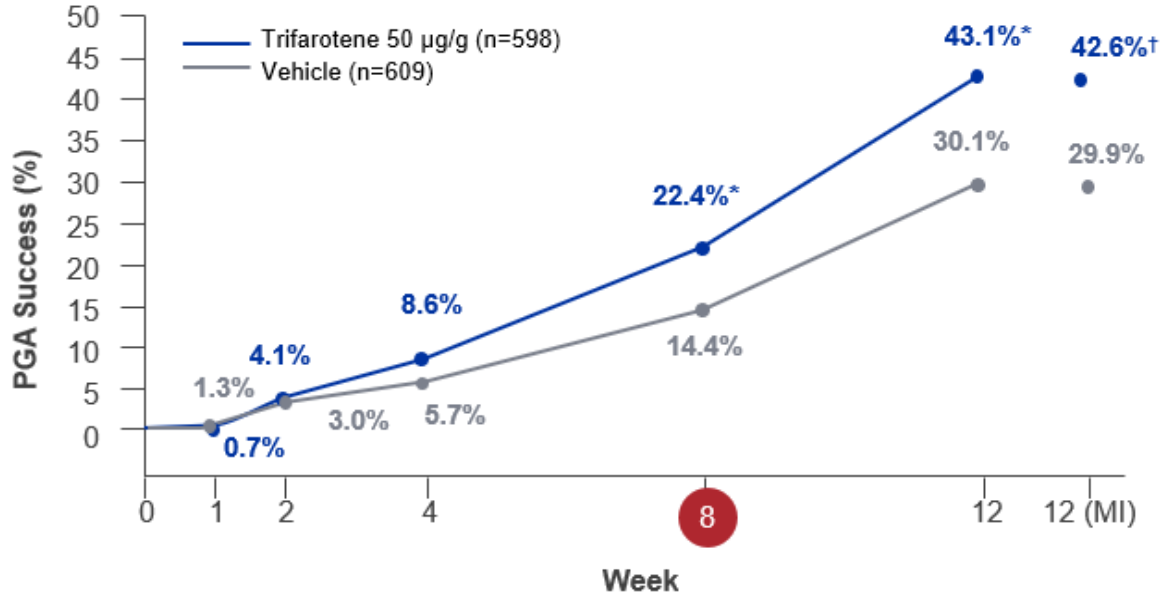
Phase 3 Randomized Controlled Studies: Moderate Truncal Acne

Study 1



* $P < 0.05$; 95% CI (4.6, 13.7)
† Treatment difference (95% CI) 10.7% (5.4, 16.1); $P < 0.001$

Study 2



* $P < 0.05$; 95% CI (3.5, 12.3)
† Treatment difference (95% CI) 12.7% (7.2, 18.2); $P < 0.001$

The coloured circle on the x-axis indicates time of first significant difference between treatment arms.
CI, confidence interval; MI, multiple imputation; PGA, Physician Global Assessment.

*PGA = Physician Global Assessment

Tan J, Thiboutot D, Popp G, et al. J Am Acad Dermatol. 2019;80(6):1691-1699.

J Eur Acad Dermatol Venereol. 2019 Jul 15. doi: 10.1111/jdv.15794. [Epub ahead of print]

Long-term safety and efficacy of trifarotene 50 μg/g cream, a first-in-class RAR-γ selective topical retinoid, in patients with moderate facial and truncal acne.

Blume-Peytavi U[1], Fowler J[2], Kemény L[3], Draelos Z[4], Cook-Bolden F[5], Dirschka T[6], Eichenfield L[7], Graeber M[8], Ahmad F[8], Alió Saenz A[8], Rich P[9], Tanghetti E[10].

Abstract

BACKGROUND: Treatment for both facial and truncal acne has not sufficiently been studied.

OBJECTIVES: To evaluate the long-term safety and efficacy of trifarotene in both facial and truncal acne.

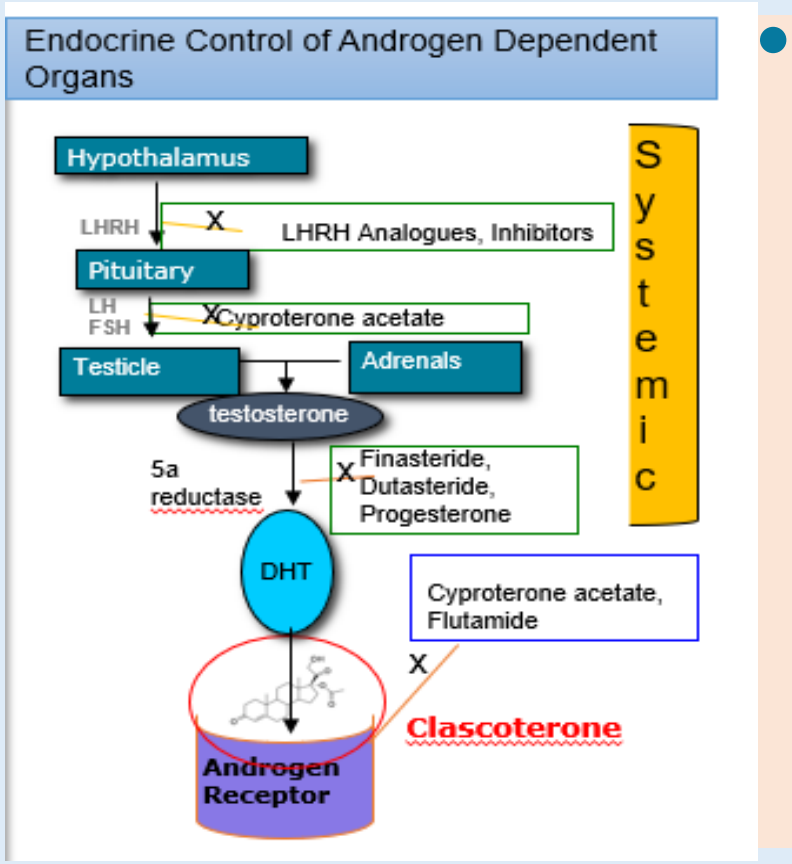
METHODS: In a multicentre, open-label, 52-week study, patients with moderate facial and truncal acne received trifarotene 50 μg/g cream (trifarotene). Assessments included local tolerability, safety, investigator and physician's global assessments (IGA, PGA) and quality of life (QOL). A validated QOL questionnaire was completed by the patient at Baseline, Week 12, 26 and 52/ET.

RESULTS: Of 453 patients enrolled, 342 (75.5%) completed the study. Trifarotene-related treatment-emergent adverse events (TEAEs) were reported in 12.6% of patients, and none was serious. Most related TEAEs were cutaneous and occurred during the first 3 months. Signs and symptoms of local tolerability were mostly mild or moderate and severe signs, and symptoms were reported for 2.2% to 7.1% of patients for the face and 2.5% to 5.4% for the trunk. Local irritation increased during the first week of treatment on the face and up to Weeks 2 to 4 on the trunk with both decreasing thereafter. At Week 12, IGA and PGA success rates were 26.6% and 38.6%, respectively. Success rates increased to 65.1% and 66.9%, respectively at Week 52. Overall success (both IGA and PGA success in the same patient) was 57.9% at Week 52. At Week 52 visit, 92/171 (53.8%) patients who had completed their assessments had scores from 0 to 1 (i.e. no effect of acne on their QOL) vs. 47/208 (22.6%) patients at Baseline visit.

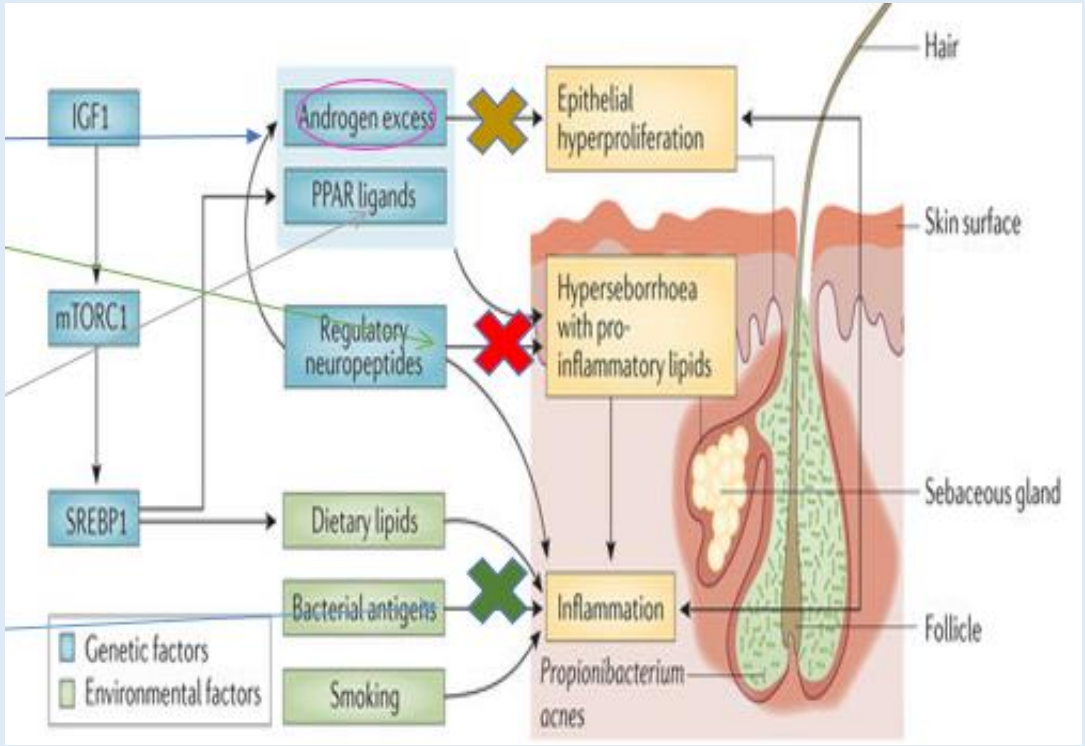
CONCLUSION: In this 52-week study, trifarotene was safe, well tolerated and effective in moderate facial and truncal acne.

TOPICAL CLASTERONE

Clascoterone Targets Multiple Pathways Operative in Acne Pathophysiology



- **CLASCOTERONE Reduces**
  - **Sebum secretion[1]**
  - **Follicle cell keratinization[2]**
  - **Inflammation[1]**



1. Data on File. Clinical Study Report. Cassiopea SpA & Submitted manuscript to Investigative Derm.
2. Lai JJ et al. Arch Dermatol Res. 2012;304(7):499-510

Image from : Tuchayi SM et al. Acne Vulgaris. Nature Reviews: Disease Primers.2015; Sept. https://www.nature.com/articles/nrdp201529?WT.mc_id=TWT_NRDP

Topical Clascoterone Phase I/II Studies
Top Line Outcomes

- First topical anti-androgen + anti-inflammatory properties
  - New Chemical Entity ~ New Mode of Action
  - Previously referred to as CB-03-01 and/or cortexolone 17-α propionate
- Safety profile similar to vehicle (>1300 exposed in Phase I/II studies)
- Statistical significance in Phase II primary end-points
  - 35.7% Total Lesion Count reduction vs 13% with vehicle
- Clinically superior / better tolerated than topical tretinoin (Phase IIa trial)
  - 22% IGA improvement vs 11.5%, 66% Total Lesion Count reduction vs 52%
- Anticipate use in combination with other acne therapies

Clascoterone 1% Cream Baseline Data
Two Phase III Studies in Acne Vulgaris (N = 1440)

	Study 025		Study 026	
	Clascoterone 1% (N = 353)	Vehicle (N = 355)	Clascoterone 1% (N = 369)	Vehicle (N = 363)
BASELINE INFLAMMATORY LESIONS COUNTS				
Mean (SD)	42.4 (11.8)	42.9 (12.3)	42.9 (12.2)	41.3 (11.0)
BASELINE NON-INFLAMMATORY (COMEDONAL) LESION COUNTS				
Mean (SD)	59.1 (22.2)	60.7 (22.1)	62.8 (21.4)	63.3 (20.5)
BASELINE TOTAL LESION COUNTS				
Mean (SD)	101.5 (25.1)	103.6 (26.1)	105.7 (25.8)	104.6 (24.2)
BASELINE IGA SCORE, N (%)				
3 – Moderate	292 (82.7)	291 (82.0)	305 (82.7)	313 (86.2)
4 – Severe	61(17.3)	64 (18.0)	64 (17.3)	50 (13.8)

MEAN AGE
19 – 20 YEARS

~60% FEMALE

MODERATE SEVERITY
~82 – 86%

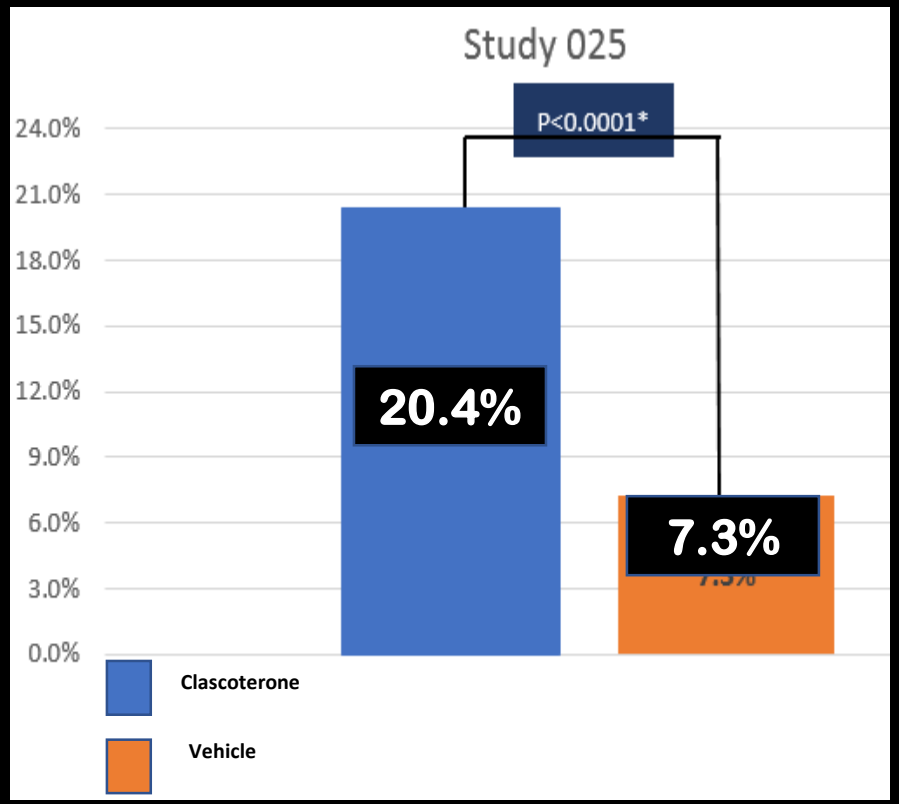
TOTAL LESIONS COUNTS
101 - 105

Baseline Inflammatory, Non-Inflammatory, Total Lesion Counts similar in treated and vehicle groups within each study and between the 2 studies

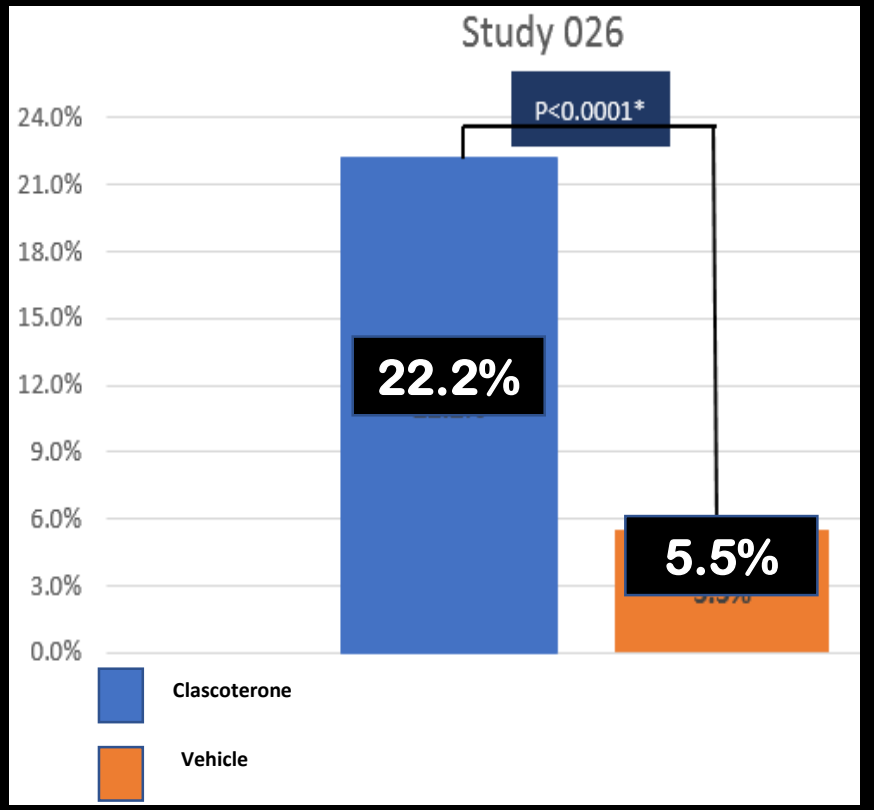
Baseline Investigator's Global Assessment (IGA) Scores similar with most rated as Moderate (3)

IGA: Investigator's Global Assessment ; SD: Standard Deviation Source: http://www.cassiopea.com/investor-relations/presentations/yr-2018.aspx

Clascoterone 1% Cream Efficacy Data
Two Phase III Studies in Acne Vulgaris (N = 1440)
ENDPOINT SUCCESS



N=531



N=560

MEAN AGE
19 – 20 YEARS

~60% FEMALE

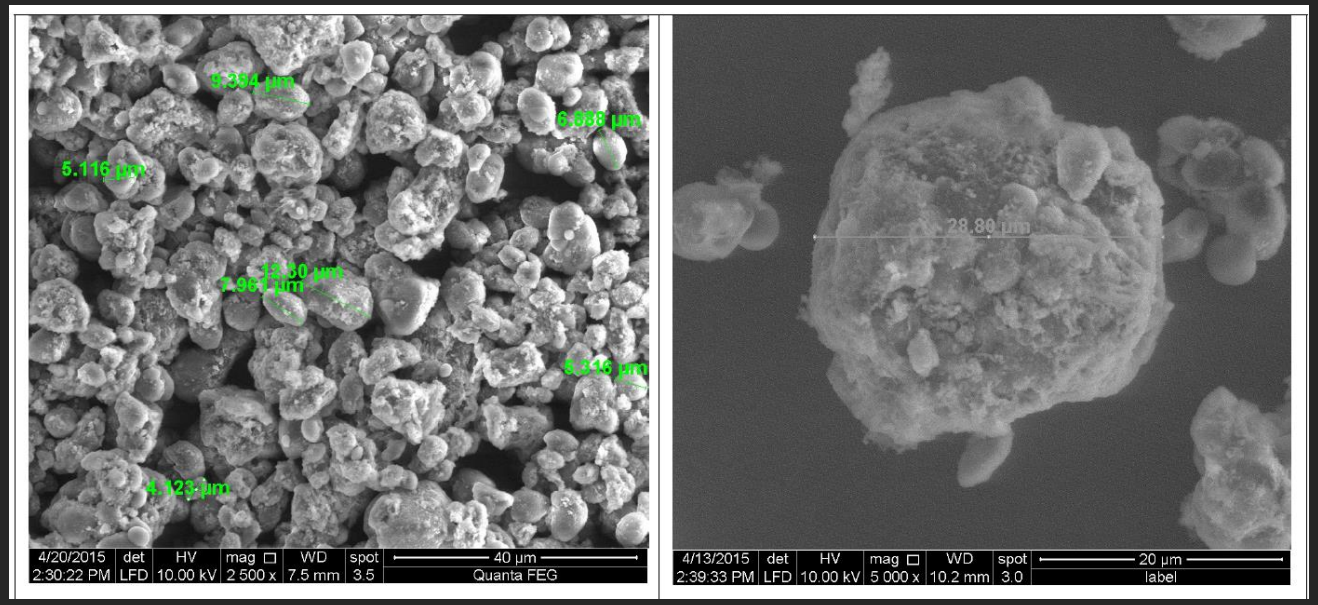
MODERATE SEVERITY
~82 – 86%

TOTAL LESIONS COUNTS
101 - 105

In Study 25, IGA Treatment Success for Clascoterone, 1% treatment group = 20.4% versus 7.3% in vehicle (p<0.0001)
In Study 26, IGA Treatment Success for Clascoterone, 1% treatment group = 22.2% versus 5.5% in vehicle (p<0.0001)

PP: Per Protocol
IGA: Investigator's Global Assessment Source: http://www.cassiopea.com/investor-relations/presentations/yr-2018.aspx

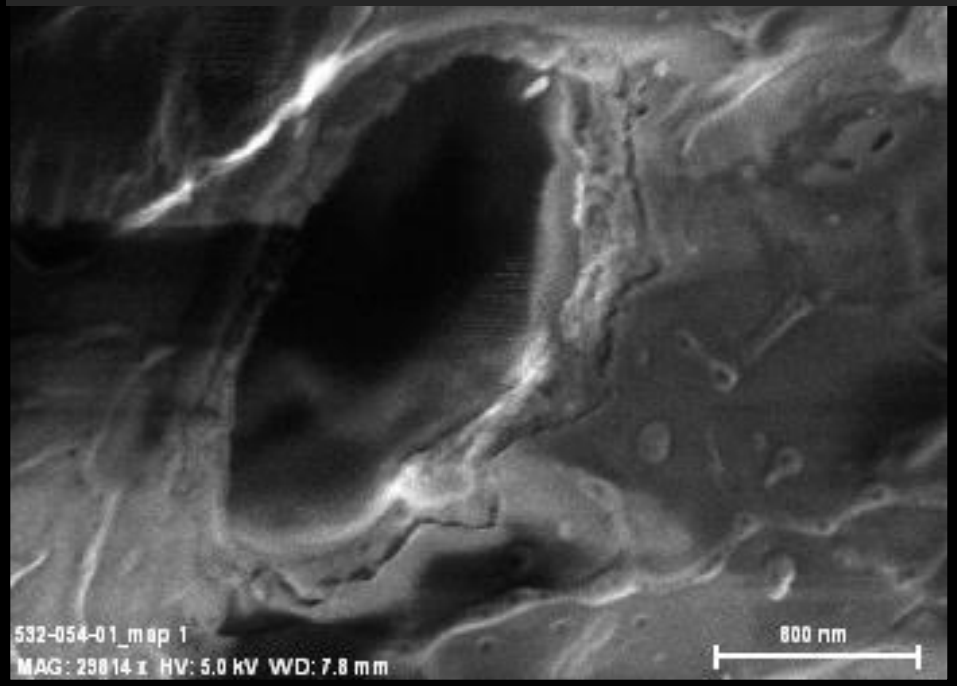
ENCAPSULATED BENZOYLPEROXIDE



TWIN **acne vulgaris**	▪ **A cream containing a fixed-dose combination of encapsulated tretinoin and encapsulated benzoyl peroxide** ▪ Major challenges were the instability of tretinoin in the presence of benzoyl peroxide and irritation ▪ Encapsulation allows stabilization and is also expected to contribute to patient compliance ▪ Opportunity exists for shift from prescribing tretinoin and existing combinations to prescribing TWIN
SIRS-T **acne vulgaris**	▪ **A topical formulation containing encapsulated tretinoin** ▪ Common side effects of tretinoin include itching, redness, swelling, dryness, peeling and scaling ▪ Encapsulation was designed to reduce irritation and is therefore expected to contribute to patient compliance ▪ Potential to be the 1st FDA-approved encapsulated tretinoin and more tolerable than currently available tretinoin drugs
Epsolay® **papulopustular rosacea**	▪ **A cream containing encapsulated benzoyl peroxide, 5%** ▪ Encapsulation was designed to reduce irritation caused by benzoyl peroxide ▪ Potential to be the 1st FDA-approved single-active benzoyl peroxide prescription drug product

ENCAPSULATED BENZOYL PEROXIDE (BP)
TOPICAL DELIVERY TECHNOLOGY

Encapsulated Benzoyl Peroxide



CRYO-SEM PICTURE

ENERGY-DISPERSIVE X-RAY SPECTROSCOPY MAPPING

Silica shell wraps BP crystals and serves as a barrier between benzoyl peroxide crystals and skin or other Ingredients

ENHANCED SKIN TOLERABILITY

Skin lipids migrate through the silica shell to promote solubilization of BP. Dissolved BP then migrates to sebaceous follicles

TOPICAL CANNABIDIOL

Cannabidiol (CBD) [BTX 1503] Mechanism of Action in Acne

BTX 1503 (Cannabidiol) Effects on Acne Pathophysiologic Factors

PRIMARY FACTORS IN ACNE PATHOPHYSIOLOGY:

- Excess sebum production
- Follicular hyperkeratinization (microcomedo)
- *C. acnes* (formerly *P. acnes*) colonization
- Perifollicular inflammation

CBD SHOWN TO:

-Suppress sebocyte proliferation[1]

-Inhibit human keratinocyte proliferation, through a of the follicle non-CB1/CBs mechanism [2]

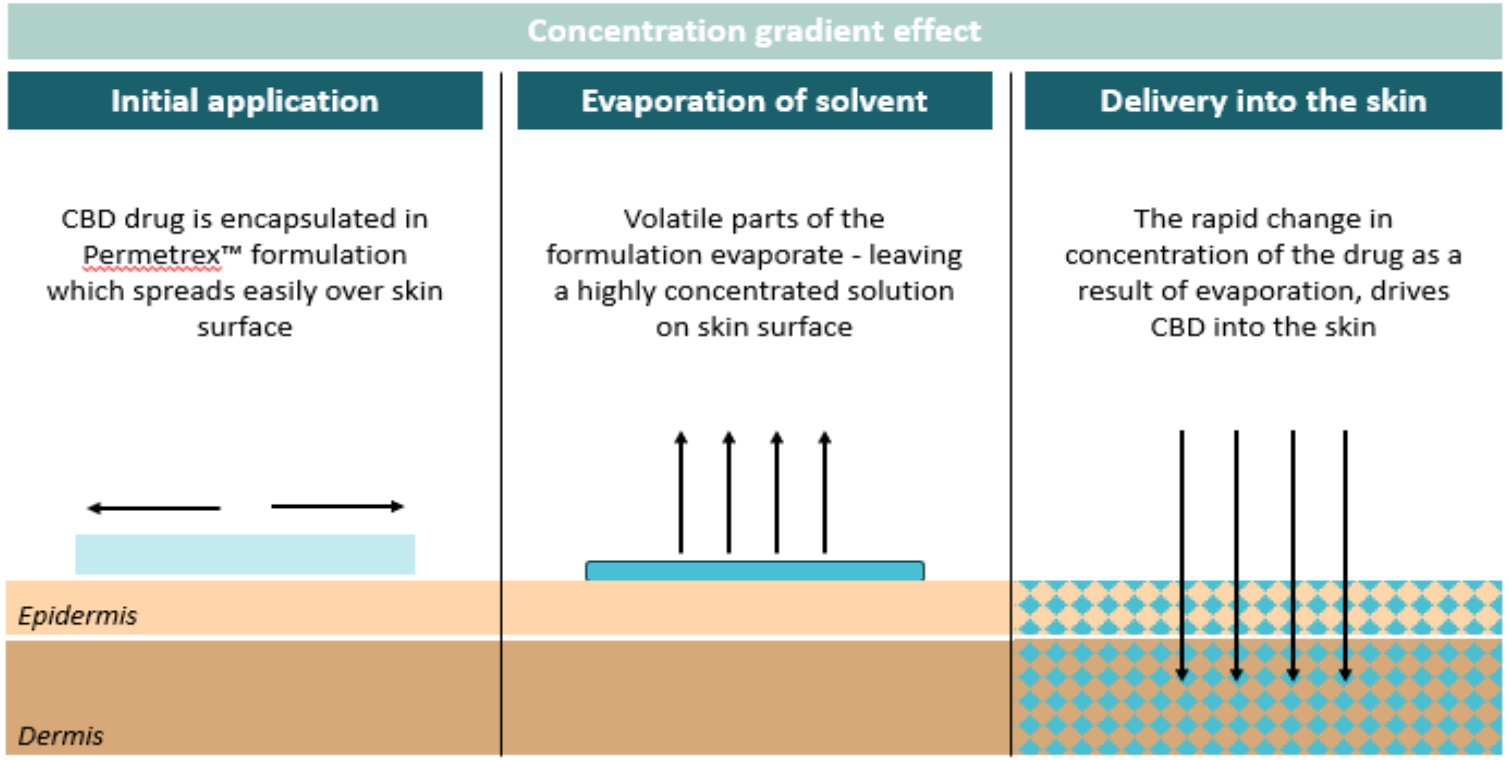
-Have potent anti-microbial activity against gram-positive bacteria[3]

-Have anti-inflammatory effects on human sebocytes [1]

1. Olah et al. *J Clin Invest*. 2014:124(9):3713-372;
2. Wilkinson & Williamson. *J Derm Sci*. 2007;45:87-92
3. Appendino et al. *J Natl Prod*. 2008;71:1427-1430;.

Cannabidiol (CBD) [BTX 1503]
Proprietary Delivery Technology

Enables formulation of innovative topical products[1] that deliver very high doses of drug into the layers of skin without using permeation enhancers, preservatives or irritating levels of alcohol / petrol derivatives

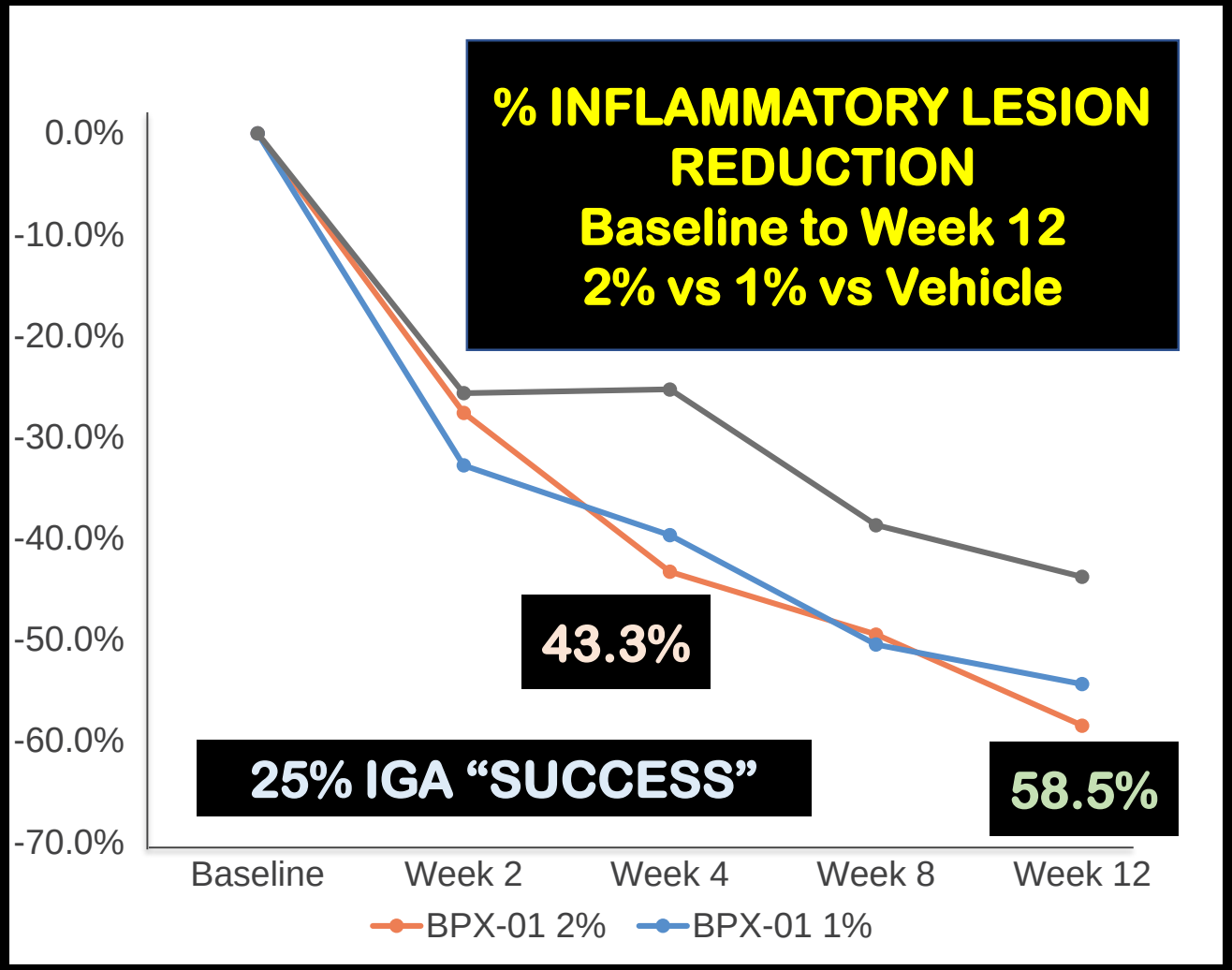


1. Data on File, Botanix Pharmaceuticals..

TOPICAL MINOCYCLINE FORMULATIONS

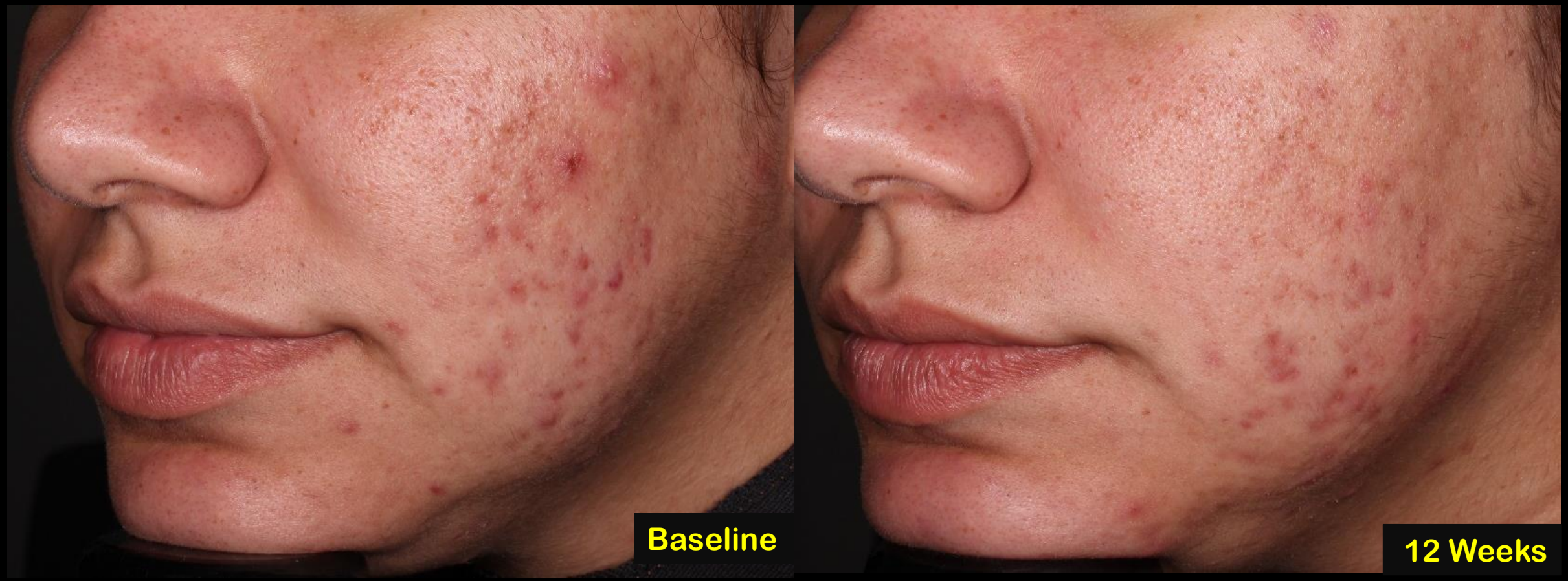
MINOCYCLINE GEL

Minocycline 2% Gel (BPX-01)
12-Week Phase 2b Study
Outcomes in Once Daily for Acne Treatment



- **58.5%** lesion reduction at Week 12 (2% dose)
- **43.3%** lesion reduction at Week 4 (2% dose)
- **25%** with ≥2-grade reduction in IGA + Clear or Almost Clear (2% dose)
- **25%** lesion reduction at Week 4 *(Time to Onset)*
- Statistically significant lesion reduction *(P=0.0256)*

Minocycline 2% Gel (BPX-01) Topical Gel for Acne Vulgaris



Poster presented at Alabama Dermatology Summer Symposium, June 22, 2017, Sandestin, Florida.

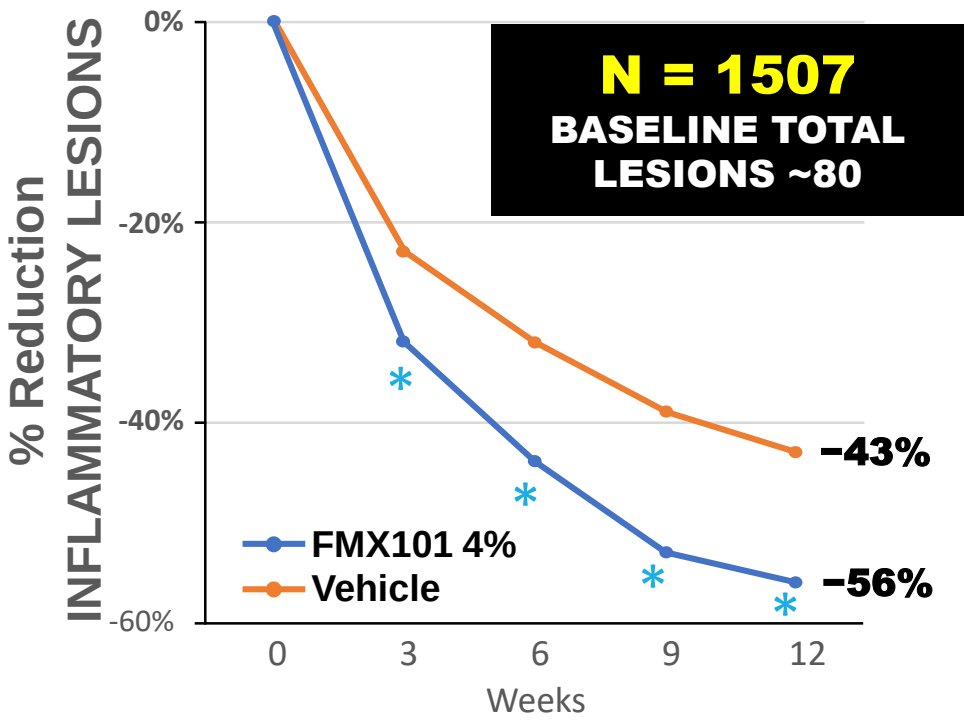
MINOCYCLINE FOAM

MINOCYCLINE 4% FOAM ONCE DAILY

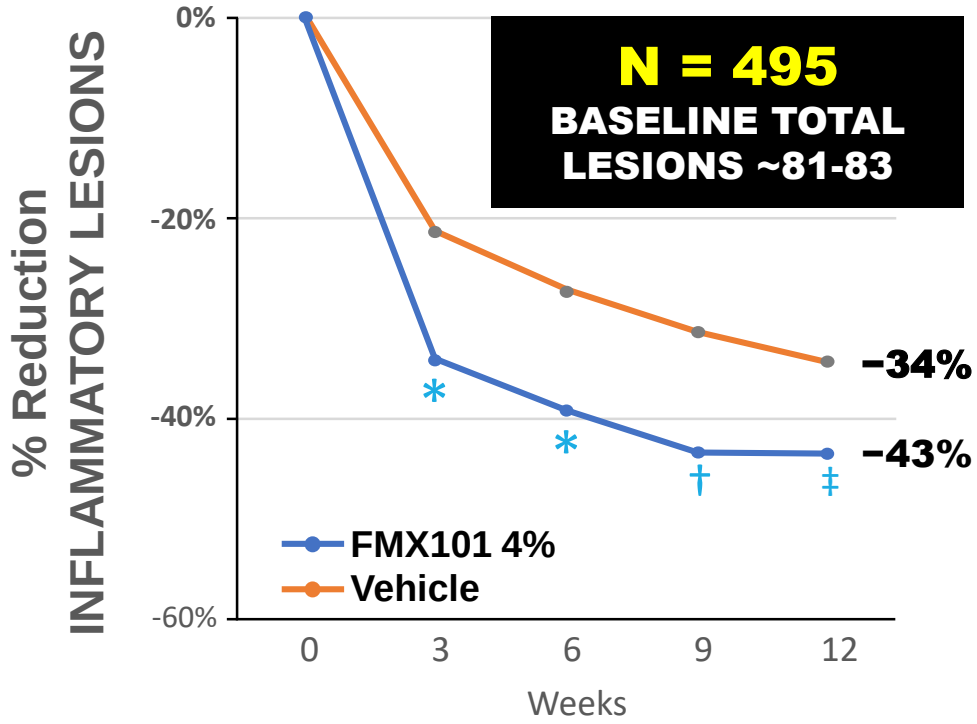
PHASE 3 12-WEEK STUDIES – MODERATE/SEVERE ACNE

≥9 YEARS OF AGE – CHANGE IN INFLAMMATORY LESIONS (ILs)

Study 22 - IL Count % Change



Study 05 - IL Count % Change

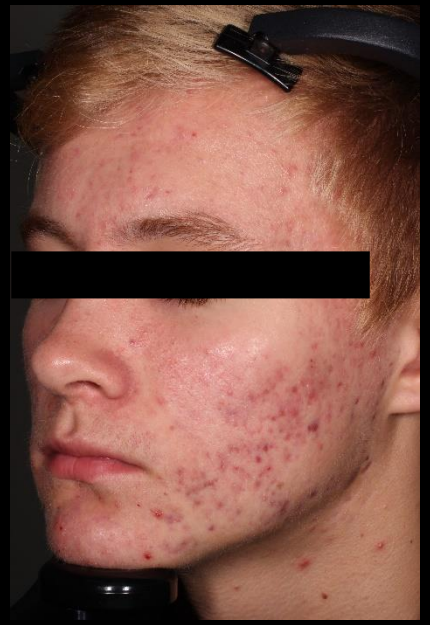
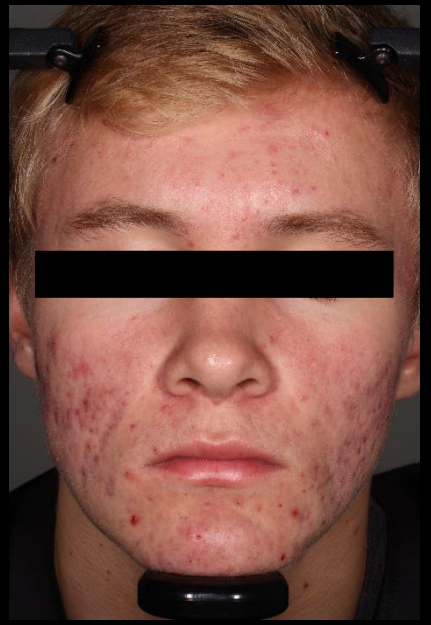
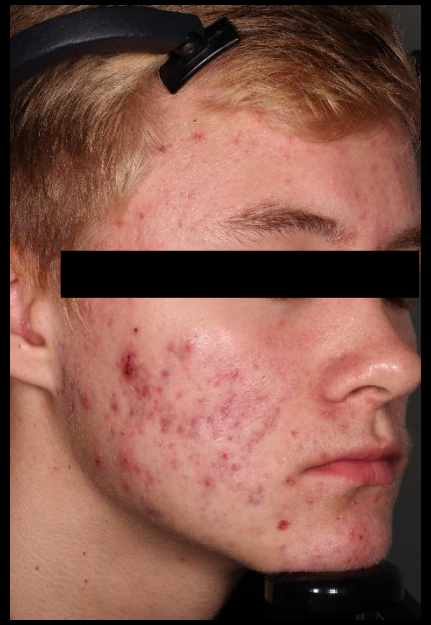


ANCOVA, Intent to Treat (ITT) Population, Observed Cases
*$P \leq .0001$; †$P \leq .001$; ‡$P \leq .01$.

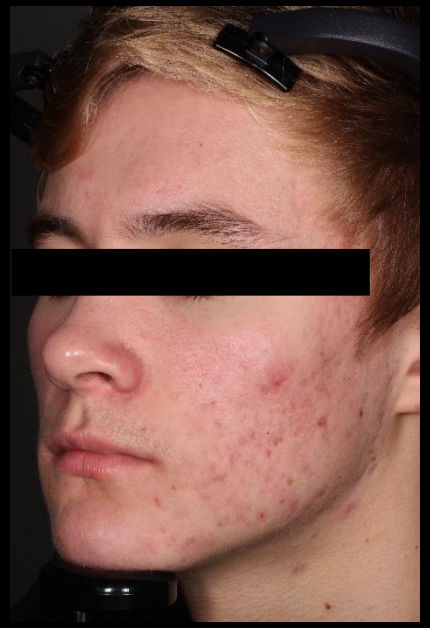
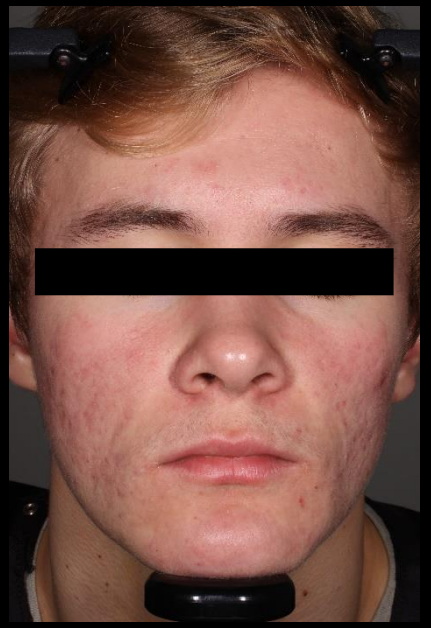
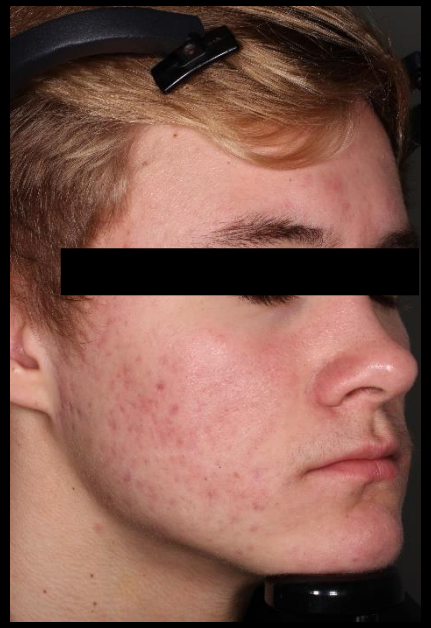
1. Raoof TJ et al. *J Am Acad Dermatol.* 2019; doi: 10.1016/j.jaad.2019.05.078. [Epub ahead of print]
2. Gold LS et al. *J Am Acad Dermatol*. 2019;80(1):168-177.

MINOCYCLINE 4%
FOAM
ONCE DAILY

BASELINE
IGA = 4
Lesion Count = 53

WEEK 12
IGA = 1
Lesion Count = 9

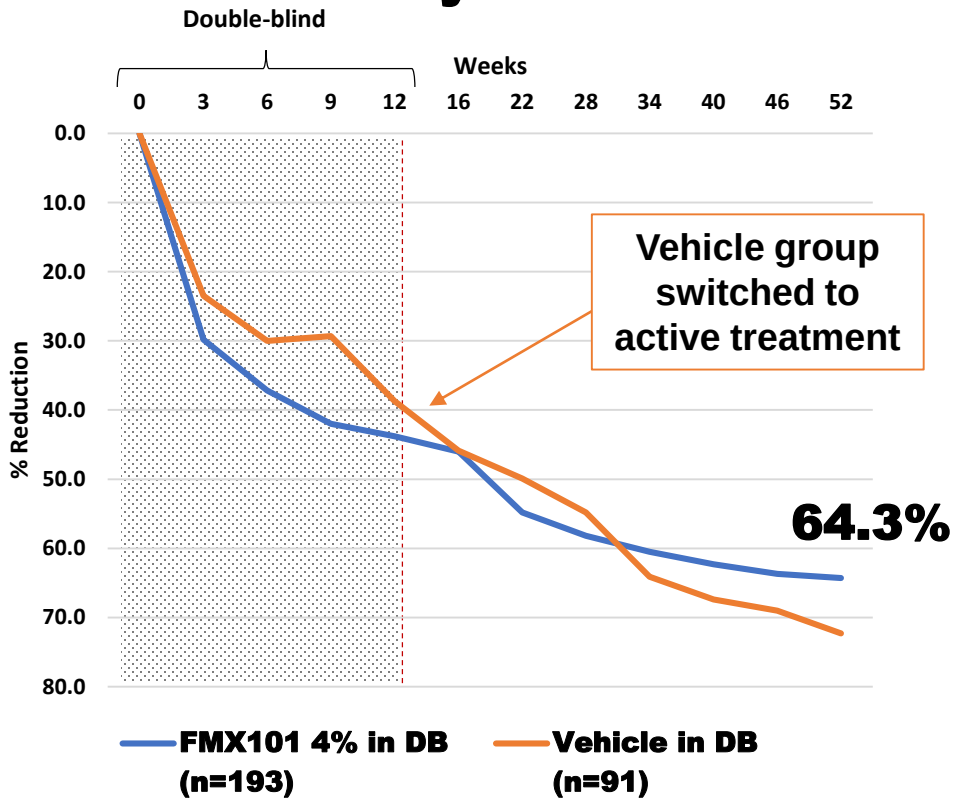
Study 22 Data on file. Foamix Pharmaceuticals Ltd.

MINOCYCLINE 4% FOAM ONCE DAILY

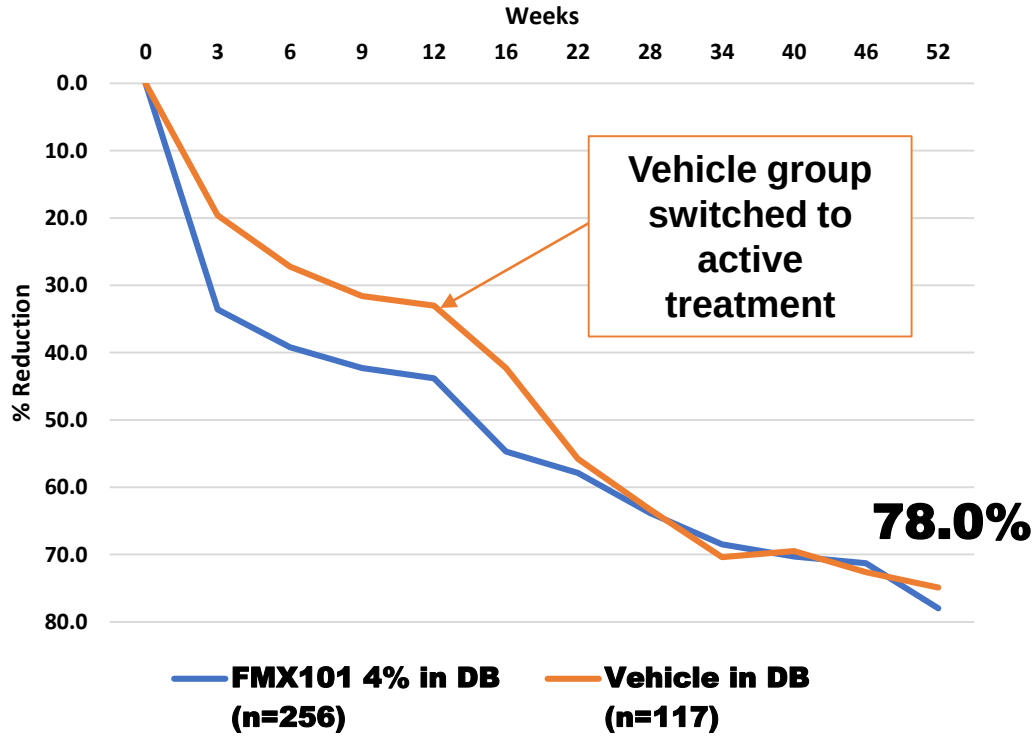
LONG TERM SAFETY DATA – MODERATE/SEVERE ACNE

≥9 YEARS OF AGE – CHANGE IN INFLAMMATORY LESIONS (ILs)

Study 04



Study 05



1. Raoof TJ et al. *J Am Acad Dermatol.* 2019; doi: 10.1016/j.jaad.2019.05.078. [Epub ahead of print]
2. Gold LS et al. *J Am Acad Dermatol*. 2019;80(1):168-177.
3. Data on File, Foamix Pharmaceuticals

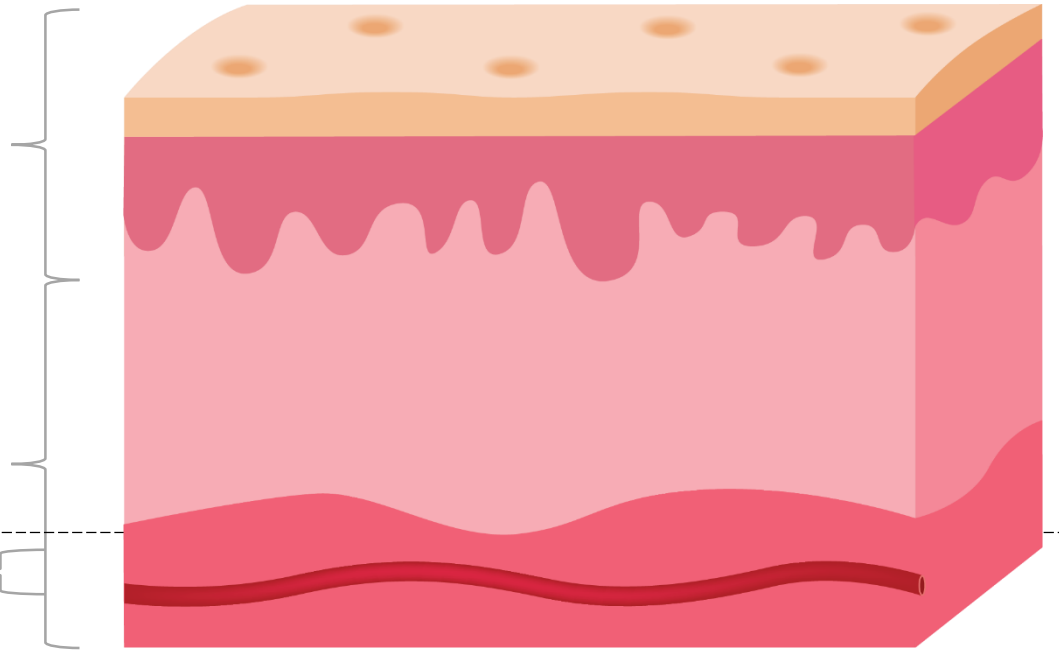
Minocycline Distribution
CONCENTRATIONS IN SKIN AND PLASMA

ORAL MINOCYCLINE (1mg/kg) at Day 21

EPIDERMIS[1]: 3.7 µg/mL

DERMIS[1]: 2.3 µg/mL

PLASMA[2] Mean C_{max} = 850 ng/mL



TOPICAL MINOCYCLINE 4% FOAM (10mg/cm²)

EPIDERMIS[3]: 560.21 µg/mL

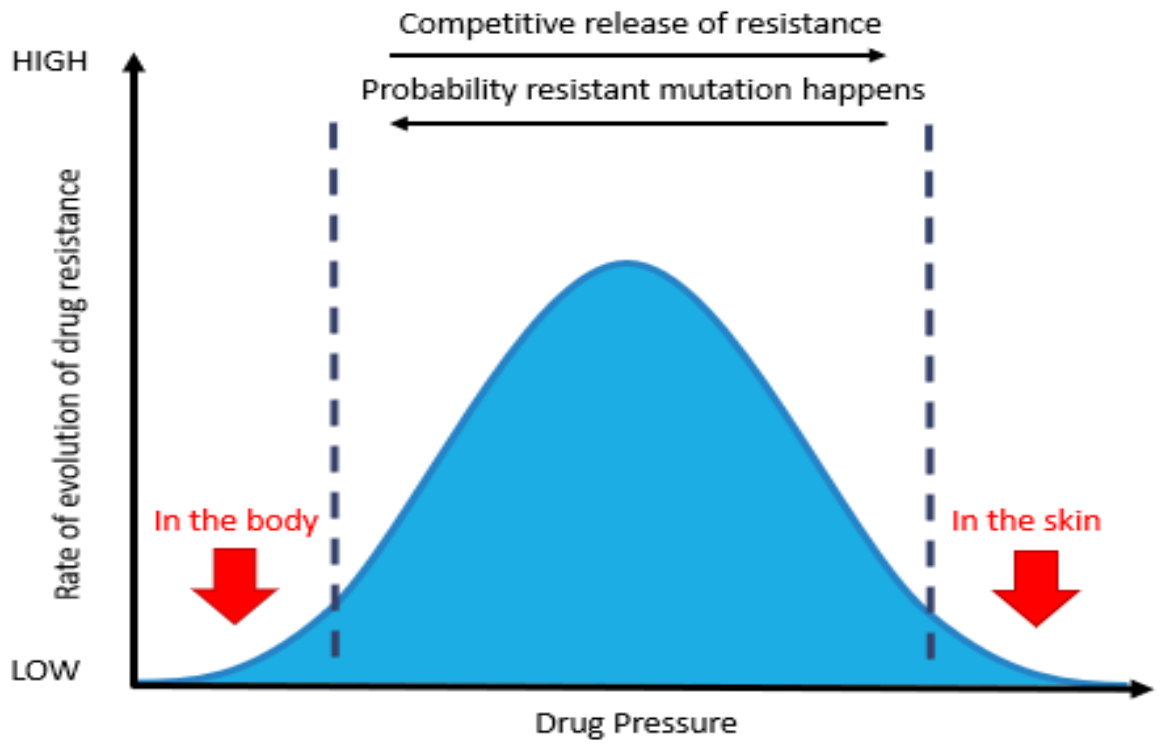
DERMIS[3]: 17.50 µg/mL

PLASMA[2] (4g/day for 21 days) Mean C_{max} = 1.3 ng/mL

Approximately half of minocycline delivered to the epidermis was recovered from the sebaceous appendages[1]

1 Macdonald H et al. *Clin Pharmacol Ther*. 1973;14(5):852-861 2 Jones TM. *J Drugs Dermatol*. 2017;16(10):1022-1028. 3 Data on file: MedPharm Study No. 474-1701-1702.

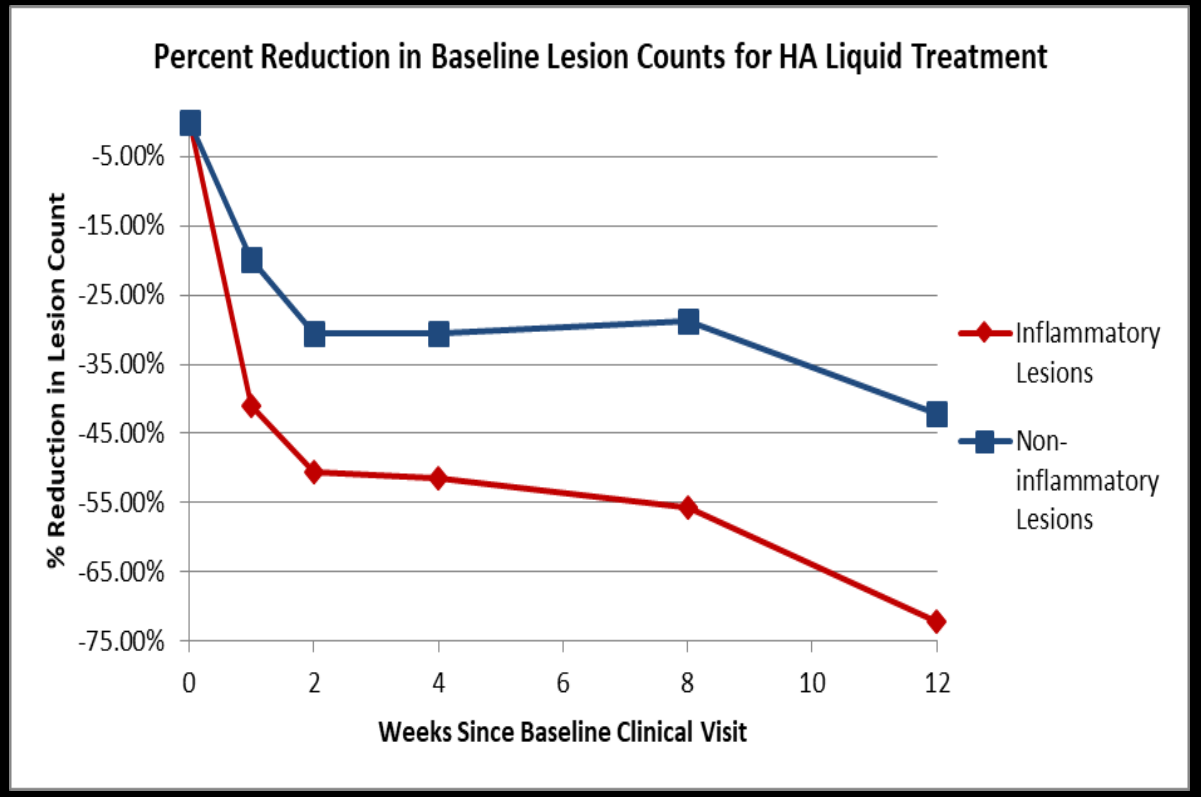
TOPICAL VS ORAL ANTIBIOTIC USE
IMPLICATIONS FOR MINOCYCLINE 4% FOAM

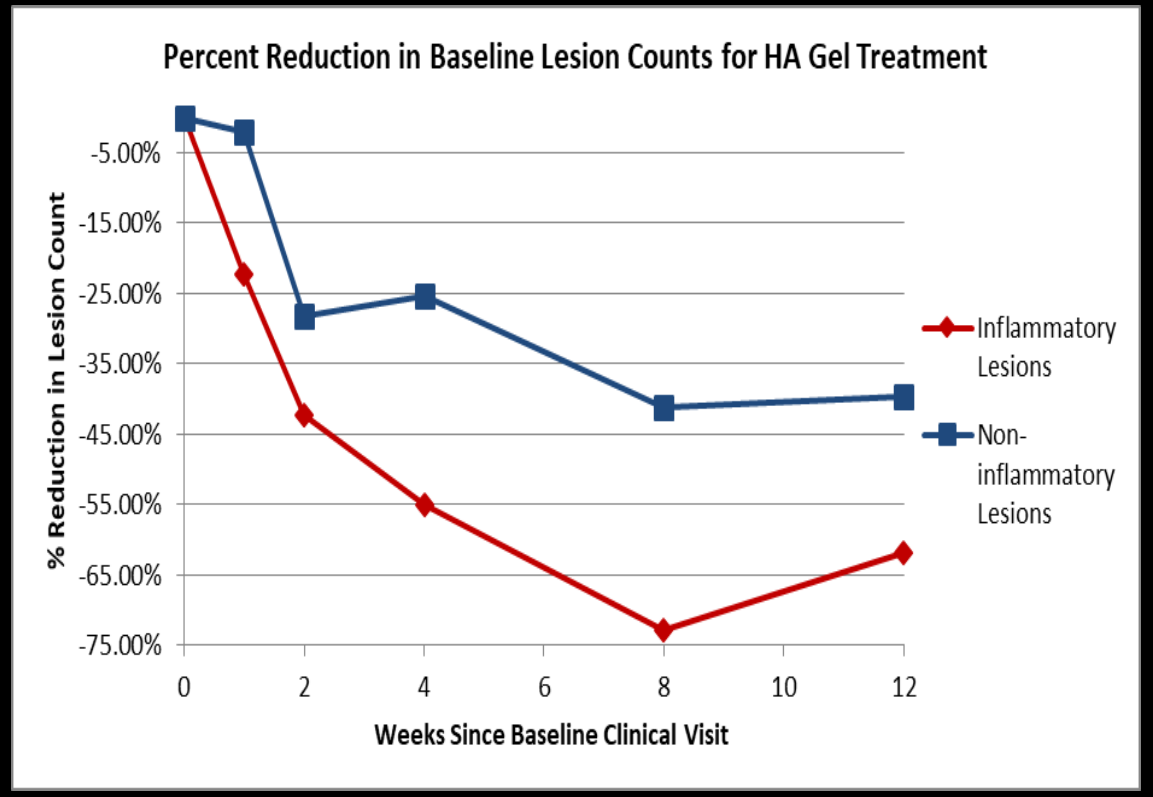


	Plasma C_{max}	Skin (epidermis) C_{max}	Skin/Plasma Ratio
FMX101 4%	1.3 ng/mL	560,000 ng/g	>400,000
Oral Minocycline	1000 ng/mL	8000 ng/g	8

Proprietary Stabilized pH Neutralized Hypochlorous Acid Gel or Liquid Applied in Acne Vulgaris

Pilot Study (N=20) / Mild to Moderate Severity / BID x 12 Weeks



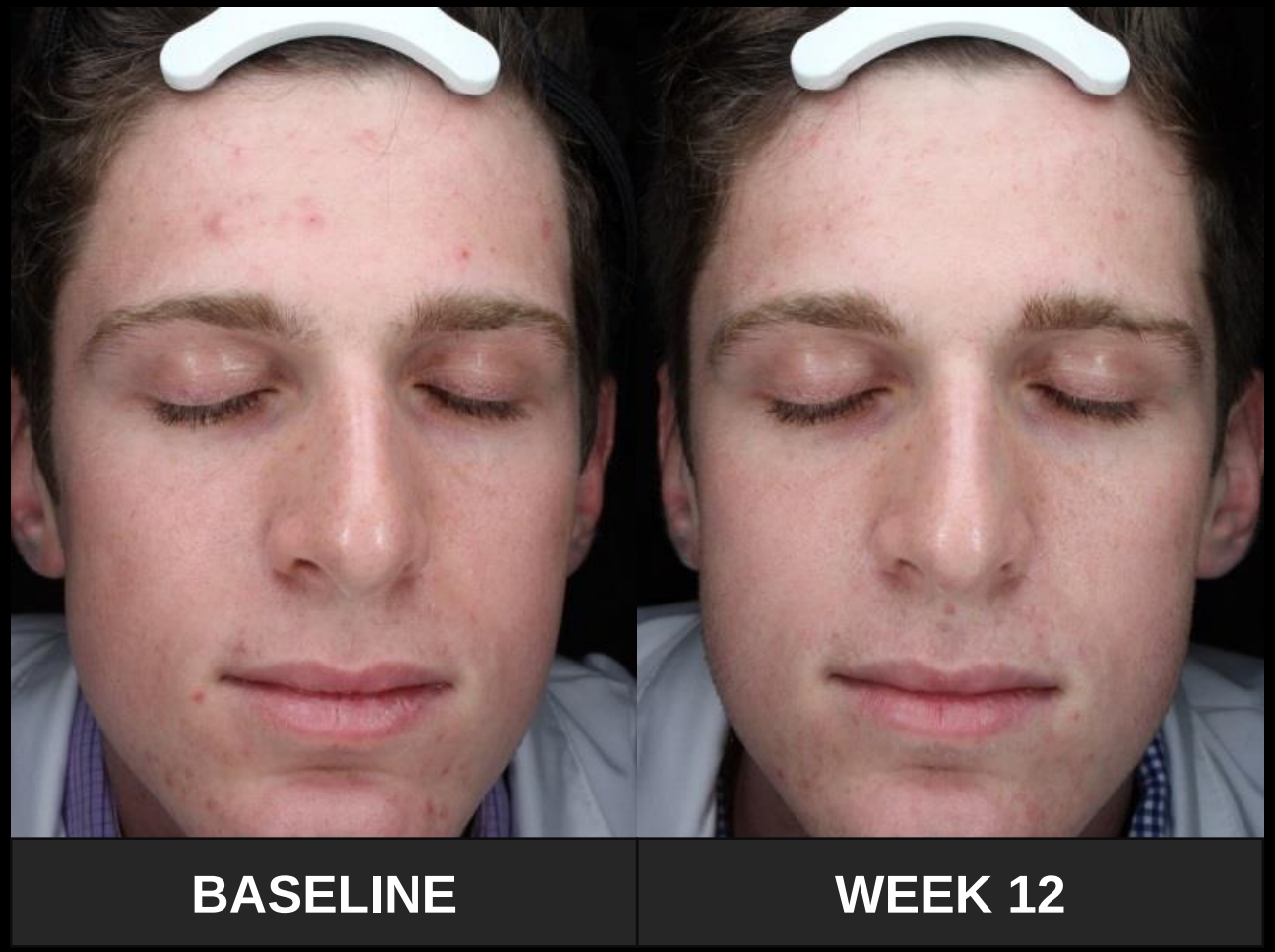


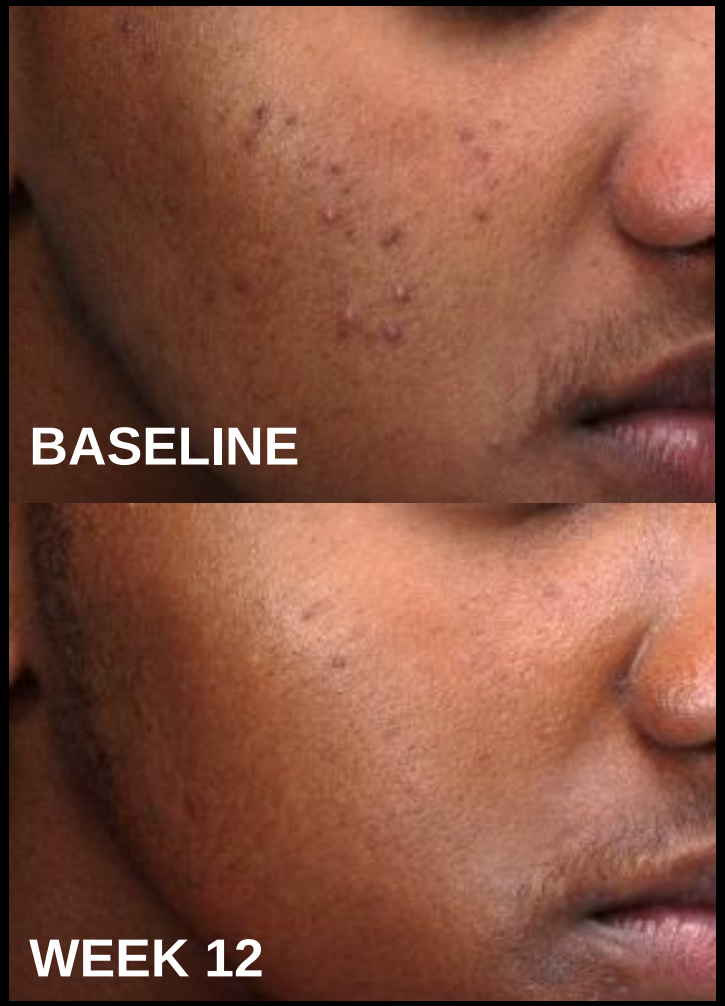
Subjective and Objective Local Skin Reactions Rated Extremely Mild
No Significant Adverse Events

Nestor M, et al. Presented in Vail Colorado, August 2018.

Proprietary Stabilized pH Neutralized Hypochlorous Acid Gel or Liquid Applied in Acne Vulgaris

Pilot Study (N=20) / Mild to Moderate Severity / BID x 12 Weeks

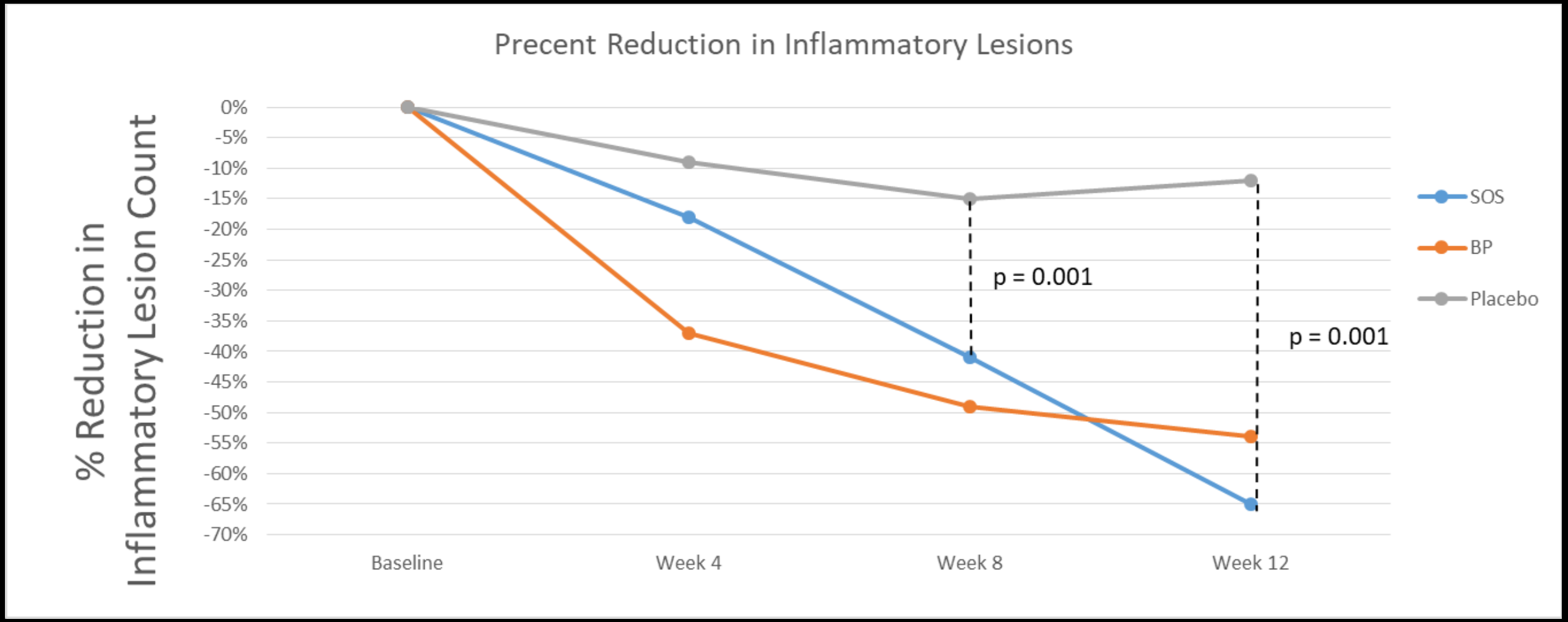




Nestor MS; Berman B; et al: A PILOT STUDY TO ASSESS THE EFFICACY AND TOLERABILITY OF TWO NEW PROPRIETARY, PURE HYPOCHLOROUS ACID-BASED (HOCL) TREATMENTS FOR MILD-TO-MODERATE ACNE VULGARIS. (Poster) Practical Symposium, Vail CO August 2018

Superoxidized Solution (HOCl) BID (n=39) vs Benzoyl Peroxide BID (n=24) vs Placebo BID (n=24) for Mild to Moderate Inflammatory Acne

Double-blinded, Placebo-controlled, Randomized Clinical Trial



Tirado-Sánchez A, Ponce-Olivera: Efficacy and Tolerance of Superoxidized Solution in the Treatment of Mild to Moderate Inflammatory Acne. A Double-Blinded, Placebo- Controlled, Parallel-Group, Randomized, Clinical Trial." *J Derm Treatment* 20, (5) 289–292, 2009.

ROSACEA

CONSENSUS

Update on the Management of Rosacea from the American Acne & Rosacea Society (AARS)

ABSTRACT

Importance: Previous consensus articles on rosacea from the American Acne and Rosacea Society (AARS) have focused on pathophysiology, clinical assessment based on phenotypic expressions of rosacea, management guidelines, discussions of individual medical therapies, and reviews of physical modalities. Pathophysiologic mechanisms believed to be operative in rosacea have been covered extensively in the literature.

by JAMES Q. DEL ROSSO, DO, FAOCD, FAAD; EMIL TANGHETTI, MD, FAAD; GUY WEBSTER, MD, PhD, FAAD; LINDA STEIN GOLD, MD, FAAD; DIANE THIBOUTOT, MD, FAAD; and RICHARD L. GALLO, MD, PhD, FAAD

Dr. Del Rosso is Adjunct Clinical Professor of Dermatology at Touro University, Nevada in Henderson, Nevada; and Research Director at JDR Dermatology Research, Clinical Dermatology, Thomas Dermatology in Las Vegas, Nevada. Dr. Tanghetti is with the Center for Dermatology and Laser Surgery in Sacramento, California. Dr. Webster is with Jefferson Medical College in Hockessin, Delaware. Dr. Stein Gold is the Director of Dermatology, Clinical Research, and Division Head of Dermatology at Henry Ford Health System in Detroit and West Bloomfield, Michigan. Dr. Thiboutot is Professor of Dermatology at Penn State University College of Medicine in Hershey, Pennsylvania. Dr. Gallo is Chief, Division of Dermatology, and Professor of Medicine and Pediatrics at the University of California, San Diego in San Diego, California.

Ivermectin 1% Cream

Dual Mode of Action in Rosacea: Anti-Inflammatory + Antiparasitic Properties

Ivermectin 1% Cream Appears to Modulate the Pathophysiology of Rosacea

Suppression of the Innate Immune Response[2]

Inhibition of the cathelicidin pathway[2]

DECREASE IN INNATE IMMUNE RESPONSE AND INFLAMMATION

REDUCTION IN ANGIOGENESIS

Reduction of *Demodex spp* Density *in vivo*[3]

>99% Decrease in mean Demodex mite count over 12 weeks

Baseline	99.9/cm^2*
≥ 6 weeks	3.8/cm^2*
≥ 12 weeks	0.8/cm^2*

Decreased expression of cutaneous inflammatory biomarkers[2,3]

Reduced interleukin-8, cathelicidin and Toll-like receptor 4 expression

REDUCED RESPONSE TO TRIGGERS

DECREASE NEUTOPHIL RECRUITMENT

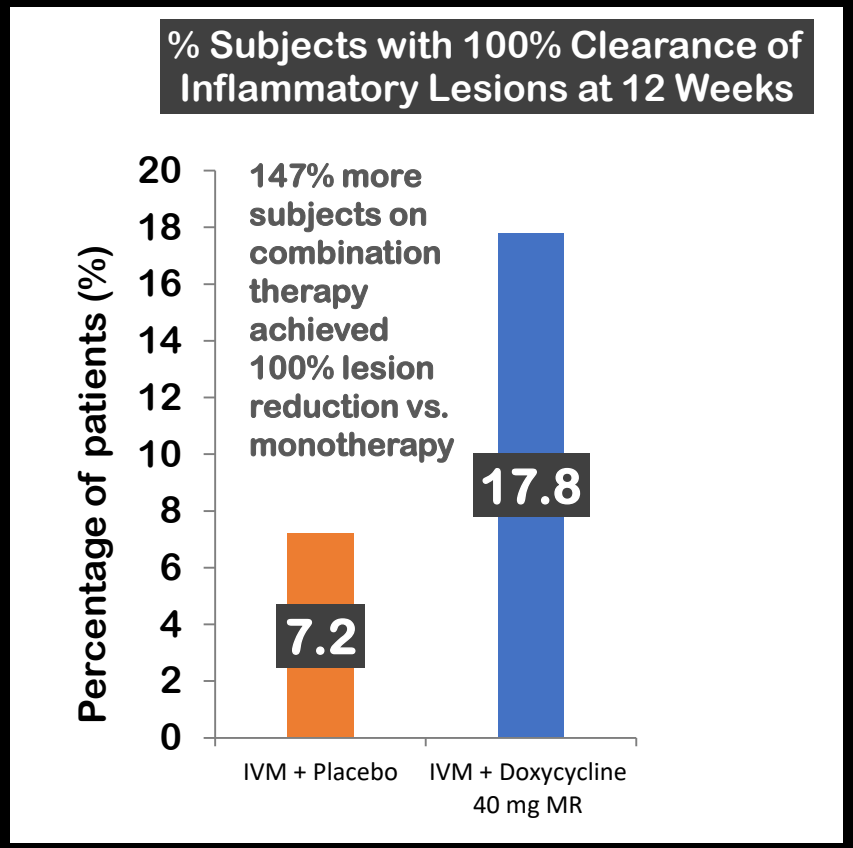
*P<0.001

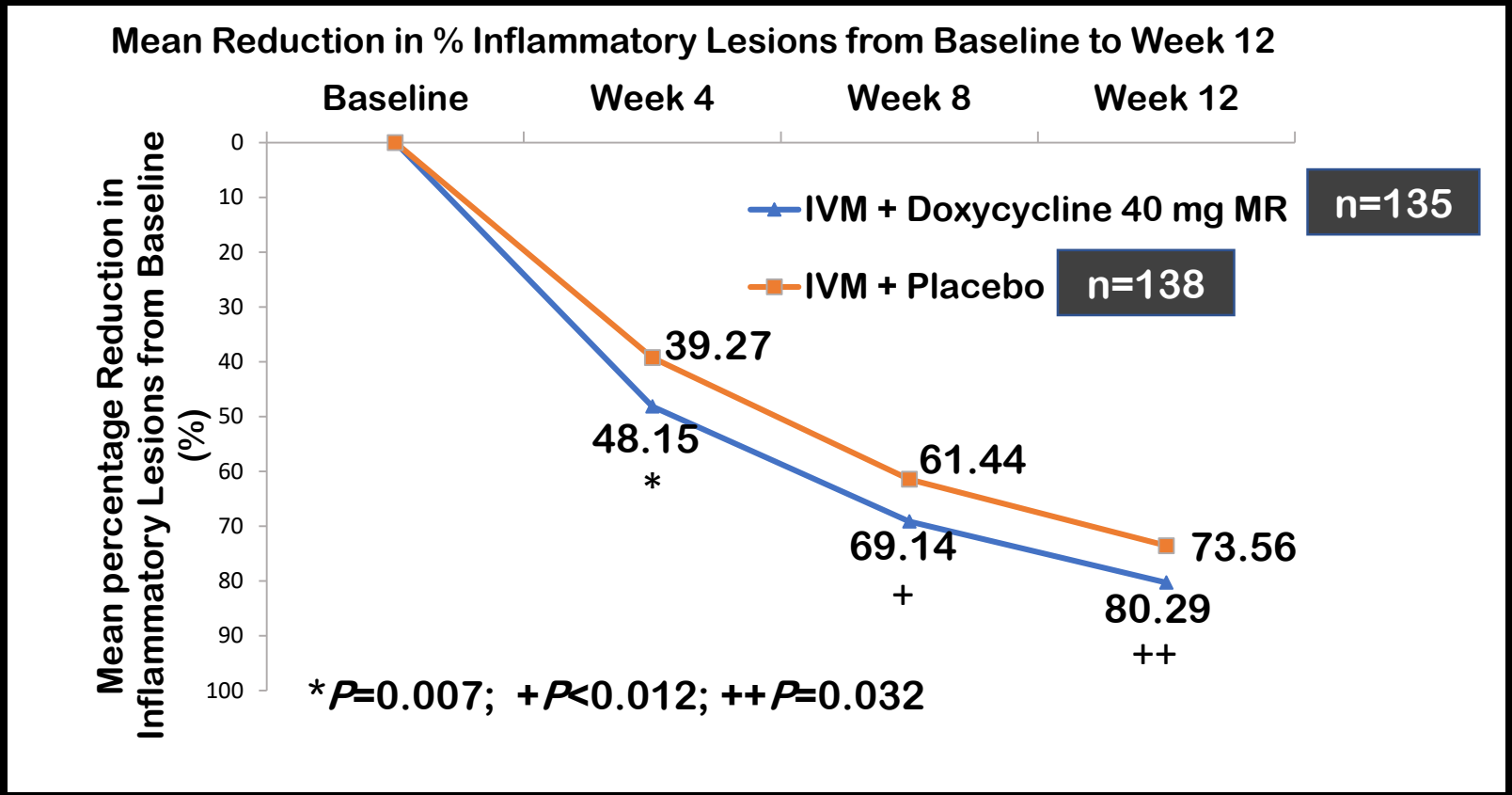
SPP, species.

1. Del Rosso JQ, *et al*. *J Clin Aesthet Dermatol* 2017;10(9):28–31. 2. Thibaut de Ménonville S, *et al*. *Dermatol Ther (Heidelb)* 2017;7(2):213–225.
3. Schaller M, *et al*. *JEADV* 2017;31(11):1907–1911. 4. Soolantra SPC.

Ivermectin (IVM) 1% Cream + Subantibiotic Dose Doxycycline(Doxy MR 40 mg/day) vs IVM 1% Cream Alone

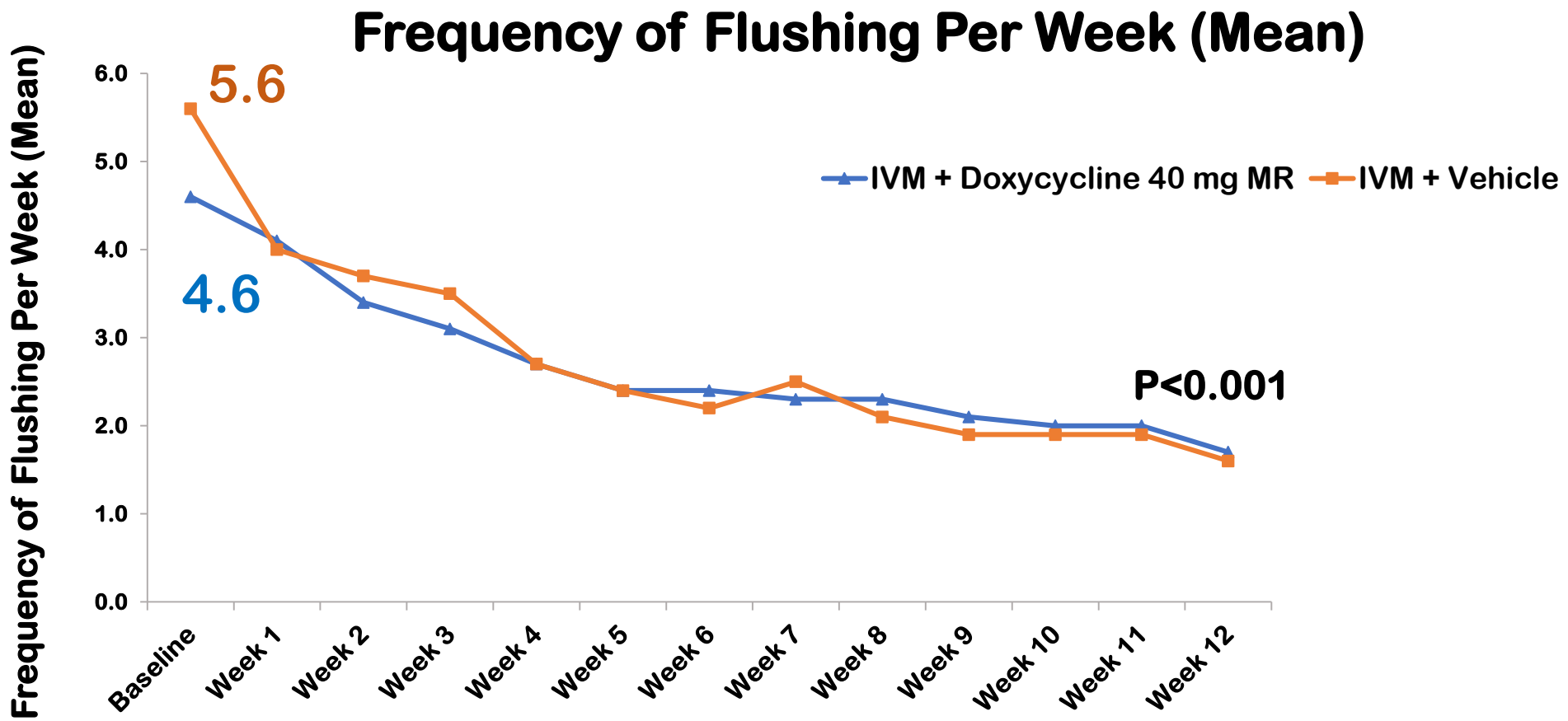
Severe Rosacea / Mean Lesion Count ~39 / Multiple Prior Therapies





ANSWER Study. Poster Presentation, Fall Clinical Dermatology, Las Vegas, NV, October 2018 / Soolantra Product Information, Galderma Laboratories, Fort Worth, TX.

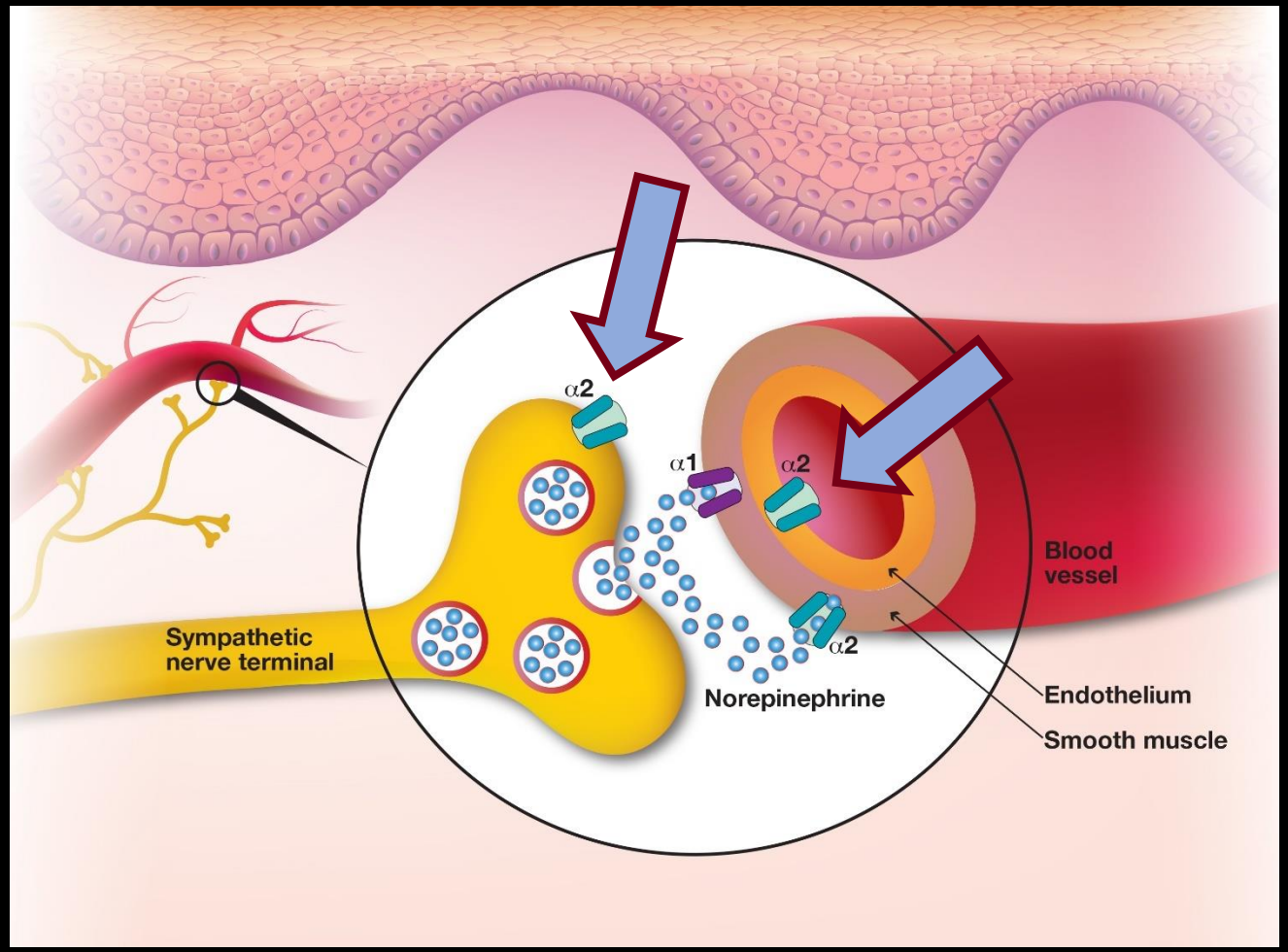
Reduction in Mean Frequency of Flushing Episodes vs Baseline
IVM 1% Cream vs IVM + Doxy-MR 40 mg/Day



Baseline: IVM + DMR n=135 IVM + PBO n=138; Week 12 IVM + DMR n=125 IVM + PBO n=124
DMR, doxycycline modified release; IVM, ivermectin; PBO, placebo
ANSWER Study. Poster Presentation, Fall Clinical Dermatology, Las Vegas, NV, October 2018

Oxymetazoline

α-1versus α-2 receptor agonism



PRESENCE OF PRESYNAPTIC α-2 RECEPTORS
→ INHIBITION OF NOREPINEPHRINE RELEASE
→ VASODILATION VIA A NEGATIVE FEEDBACK LOOP MECHANISM

PRESENCE OF α-2 RECEPTORS ON ENDOTHELIAL CELLS
→ MEDIATES RELEASE OF NITRIC OXIDE (NO)
→ STIMULATION CAUSES A VASODILATORY RESPONSE

Br J Dermatol. 2018 Nov 30. doi: 10.1111/bjd.17462. [Epub ahead of print]

Use of an Alternative Method to Evaluate Erythema Severity in a Clinical Trial: Difference in Vehicle Response With Evaluation of Baseline and Postdose Photographs for Effect of Oxymetazoline Cream 1.0% for Persistent Erythema of Rosacea in a Phase 4 Study.

Eichenfield LF[1], Del Rosso JQ[2], Tan JKL[3], Hebert AA[4], Webster GF[5], Harper J[6], Baldwin HE[7], Kircik LH[8,9], Stein-Gold L[10], Kaoukhov A[11], Alvandi N[11].

Author information

Abstract

BACKGROUND: Once-daily topical oxymetazoline cream 1.0% significantly reduced persistent facial erythema of rosacea in trials requiring live, static patient assessments.

OBJECTIVE: To critically evaluate the methodology of clinical trials that require live, static patient assessments by determining whether assessment of erythema is different when reference to the baseline photograph is allowed.

METHODS: In two identically designed, randomised, phase 3 trials, adults with persistent facial erythema of rosacea applied oxymetazoline or vehicle once daily. This phase 4 study evaluated standardised digital facial photographs from the phase 3 trials to record ≥1-grade Clinician Erythema Assessment (CEA) improvement at 1, 3, 6, 9, and 12 hours postdose.

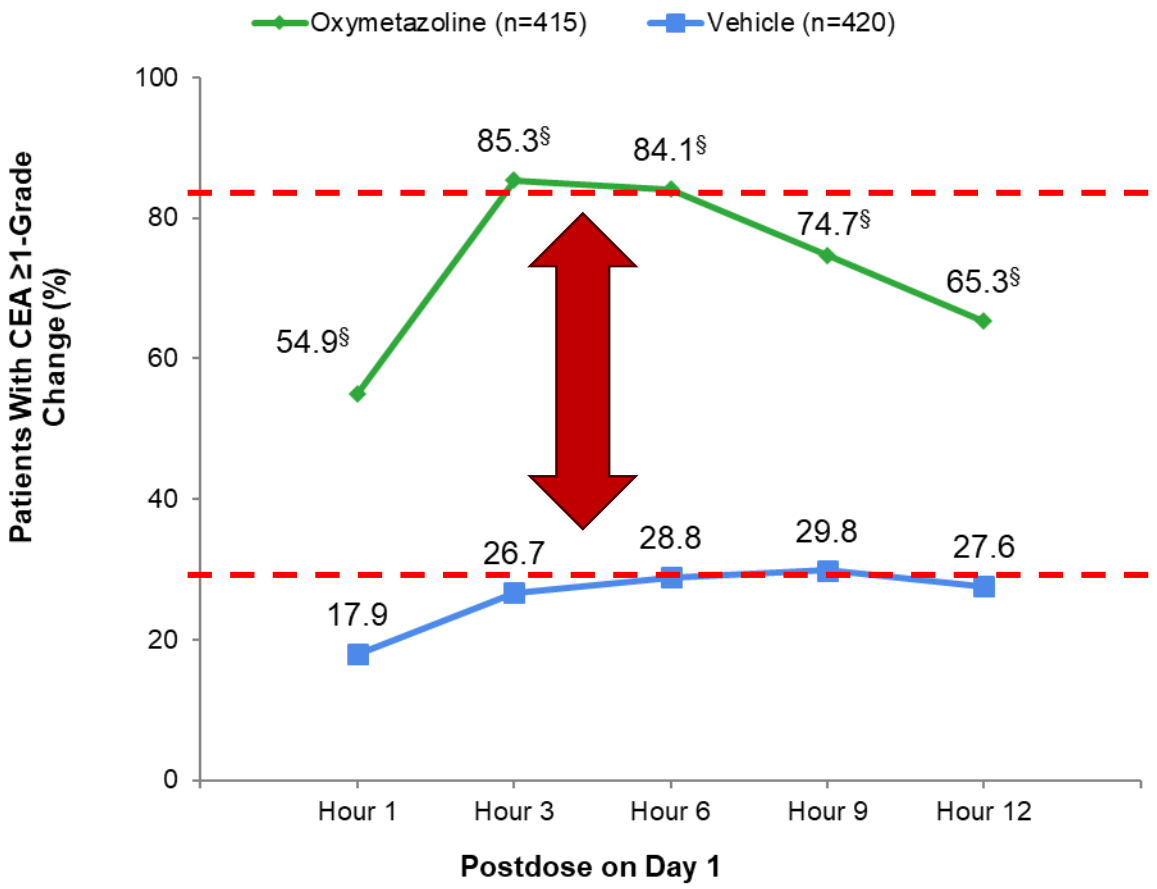
RESULTS: Among 835 patients (oxymetazoline n=415, vehicle n=420), significantly greater proportions of patients treated with oxymetazoline versus vehicle (P<0.0001) achieved ≥1-grade CEA improvement (up to 85.3% vs 29.8%). When reference to baseline photographs was allowed while evaluating posttreatment photographs, the results for oxymetazoline were similar to results of the phase 3 trials, but a significantly lower proportion of vehicle recipients achieved ≥1-grade CEA improvement (up to 52.3% vs 29.7%; P<0.001). Up to 80.2% of oxymetazoline patients achieved at least moderate erythema improvement, versus up to 22.9% of vehicle patients. The association between patients' satisfaction with facial skin redness and percentage of erythema improvement was statistically significant (Spearman rank correlation, 0.1824; P<0.0001 [oxymetazoline]; 0.0623; P=0.01 [vehicle]).

CONCLUSIONS: Assessment of study photographs, with comparison to baseline, confirmed significant erythema reduction with oxymetazoline on the first day of application. Compared to the phase 3 trials results, significantly fewer vehicle recipients attained ≥1-grade CEA improvement, inferring a mitigated vehicle effect. This methodology may improve the accuracy of clinical trials evaluating erythema severity. This article is protected by copyright. All rights reserved.

Oxymetazoline 1% Cream Phase 4 vs Phase 3 Outcomes

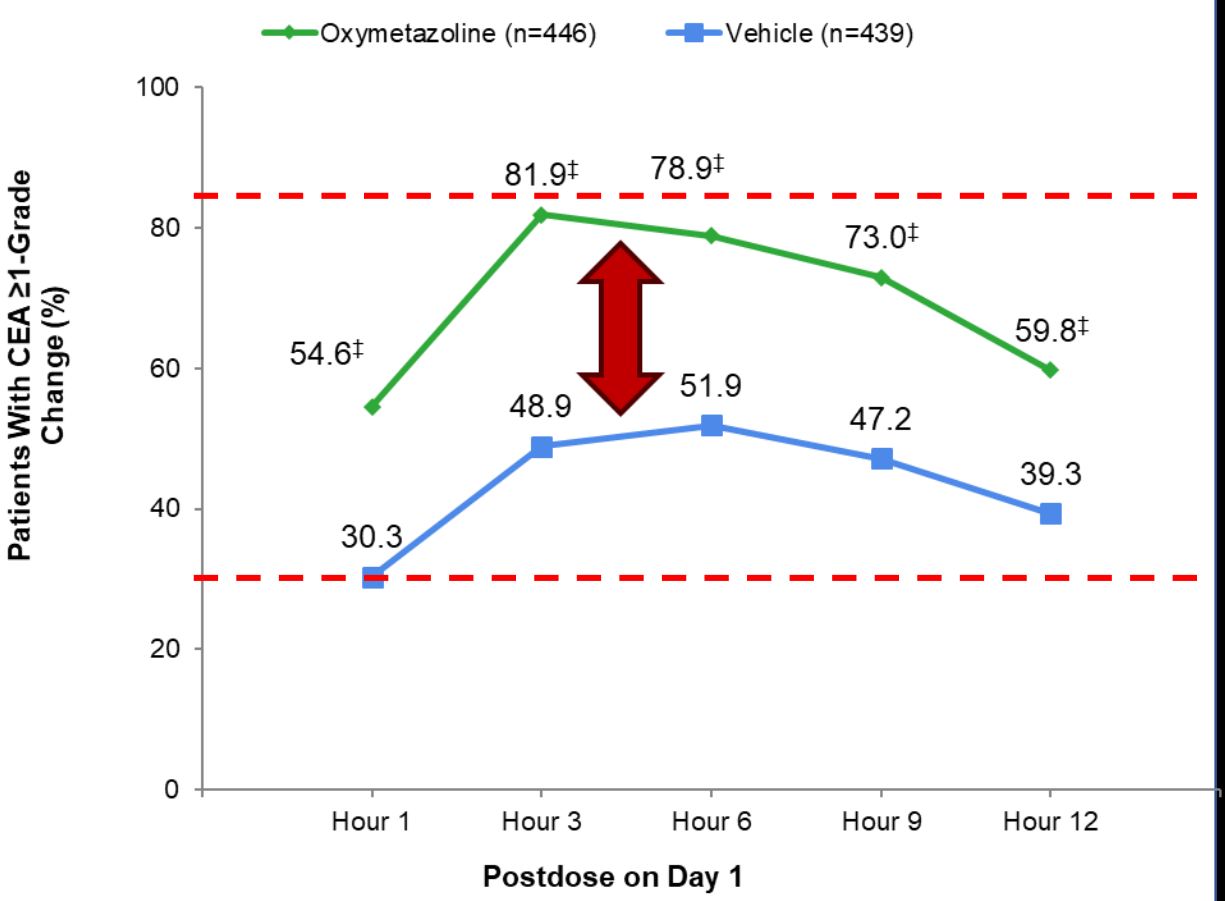
≥1-Grade Improvement in Clinician Erythema Assessment (CEA)

Phase 4 Trial



§*P*<0.0001 for the comparison to vehicle.

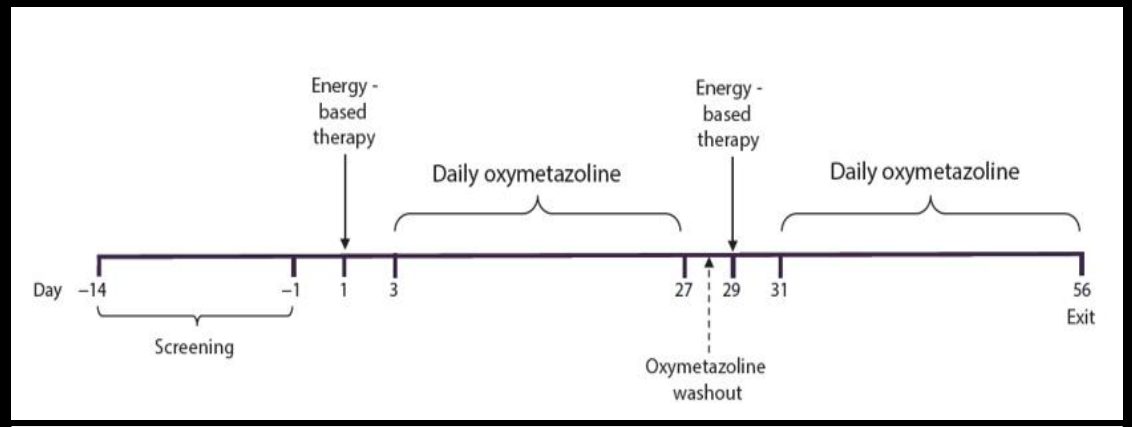
Phase 3 Pivotal Trials

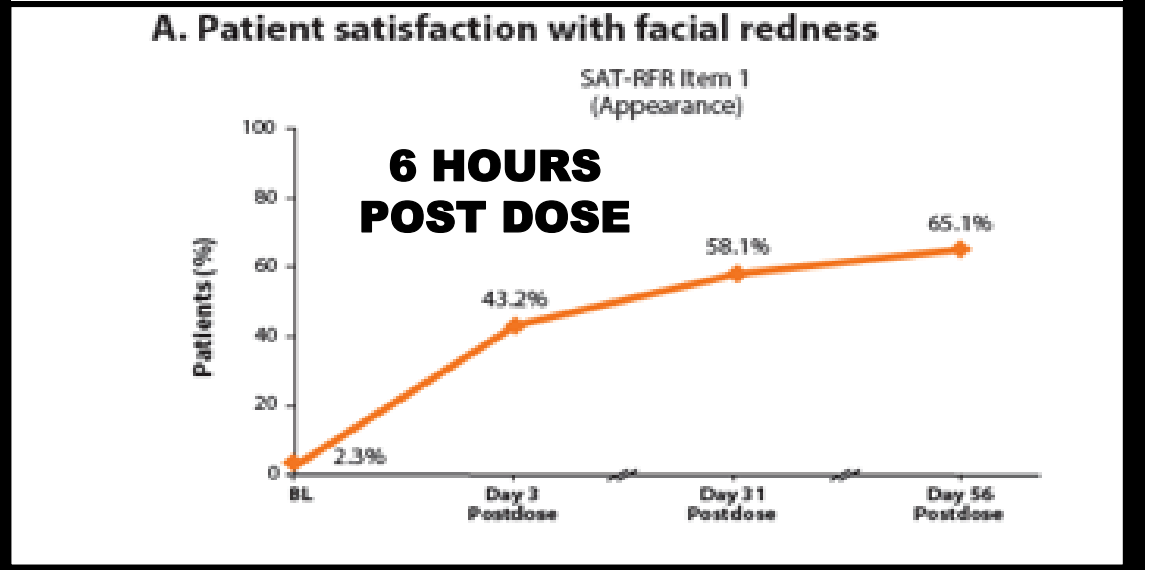


‡*P*<0.001 for the comparison to vehicle.

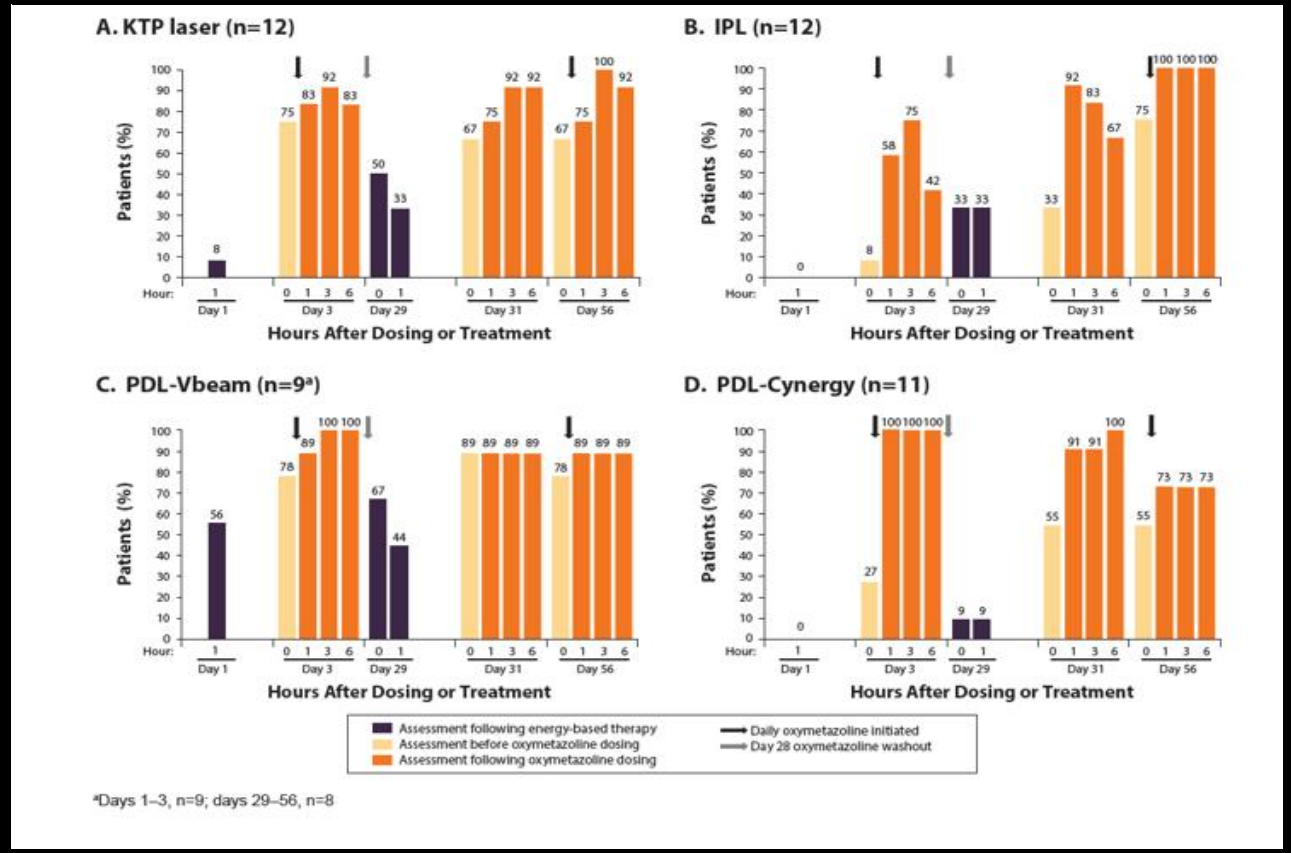
Submitted and accepted for publication by Br J Dermatol. 2019.

Oxymetazoline Hydrochloride 1% Cream with Energy-Based Therapy in Rosacea: Phase 4 Open-Label Study





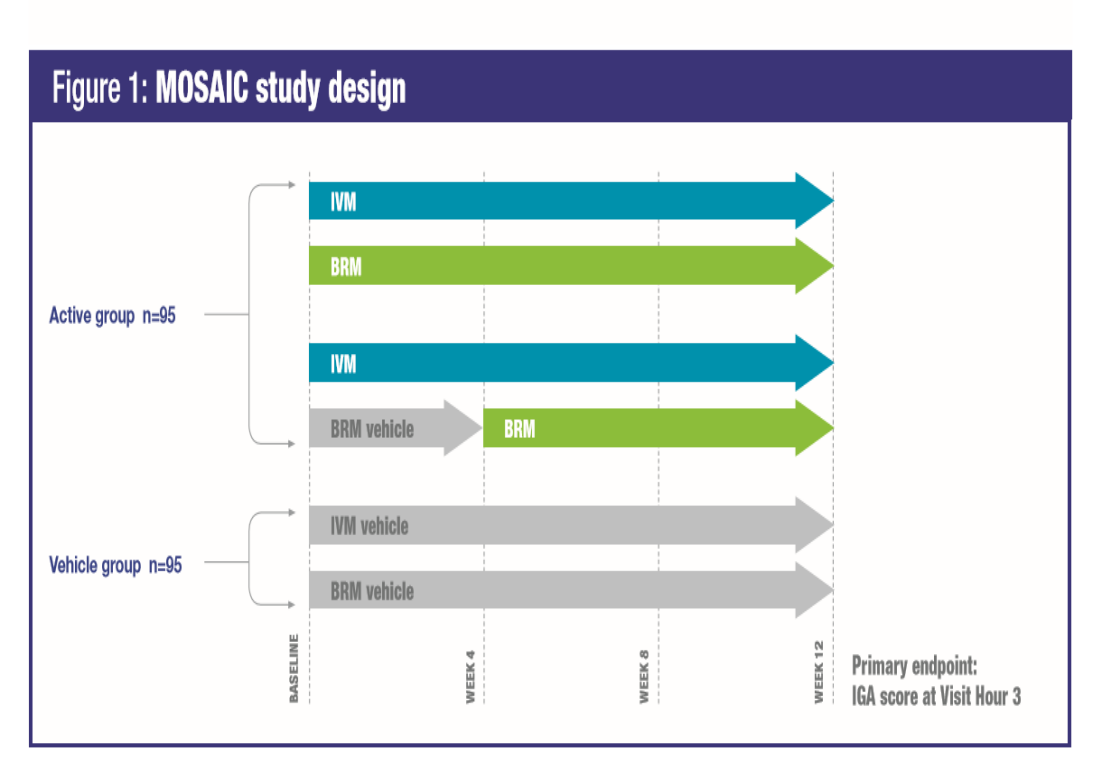
Patients (%) with ≥1-Grade Improvement in Clinician Erythema Assessment (days 1–3, n=44; days 29–56, n=43)



Goldberg D, et al. Poster. Fall Clinical Dermatology, Las Vegas, Nevada, October 2019.

Together Out of the Shoot vs Staggered

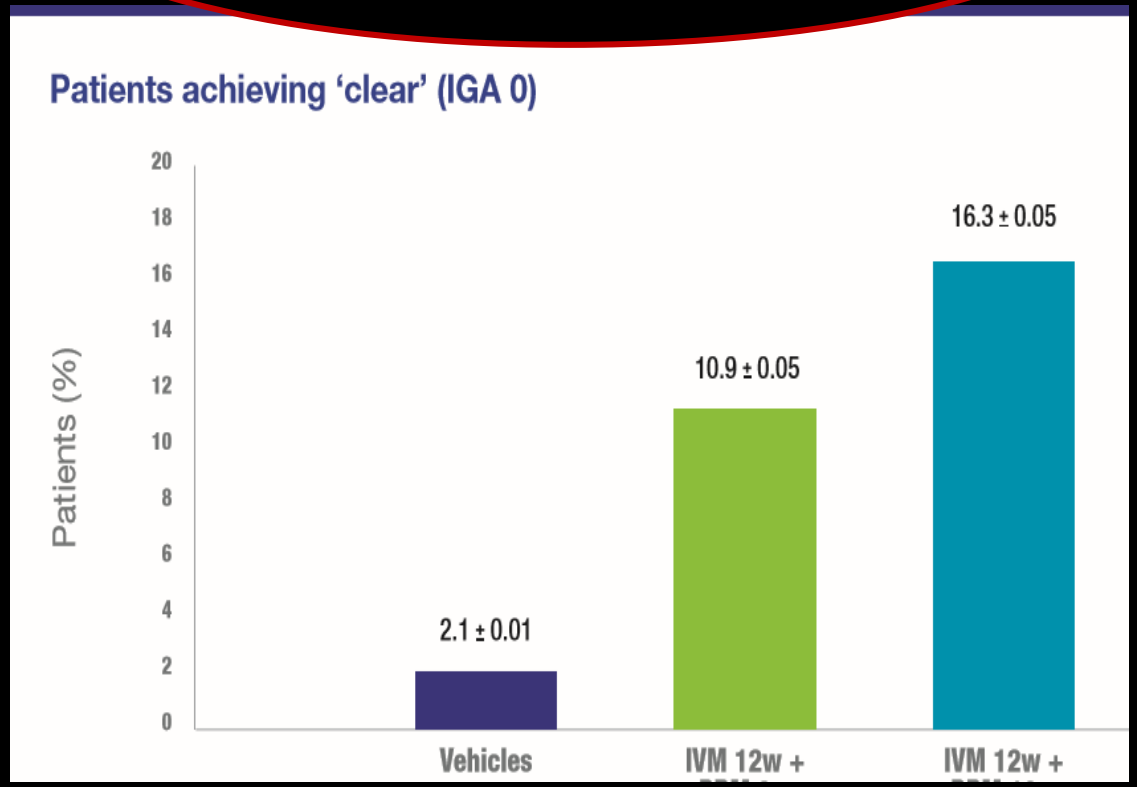
Combining Topical Agents in Papulopustular Rosacea (N=190)



12-Week Randomized Controlled Study
Moderate to Severe-Papulopustular Rosacea (N=190)
TOPICAL IVERMECTIN + BRIMONIDINE REGIMENS
CONTROLLED APPLICATION AND SKIN CARE

DEL ROSSO JQ, PAPP K, ET AL, EADV, 2016

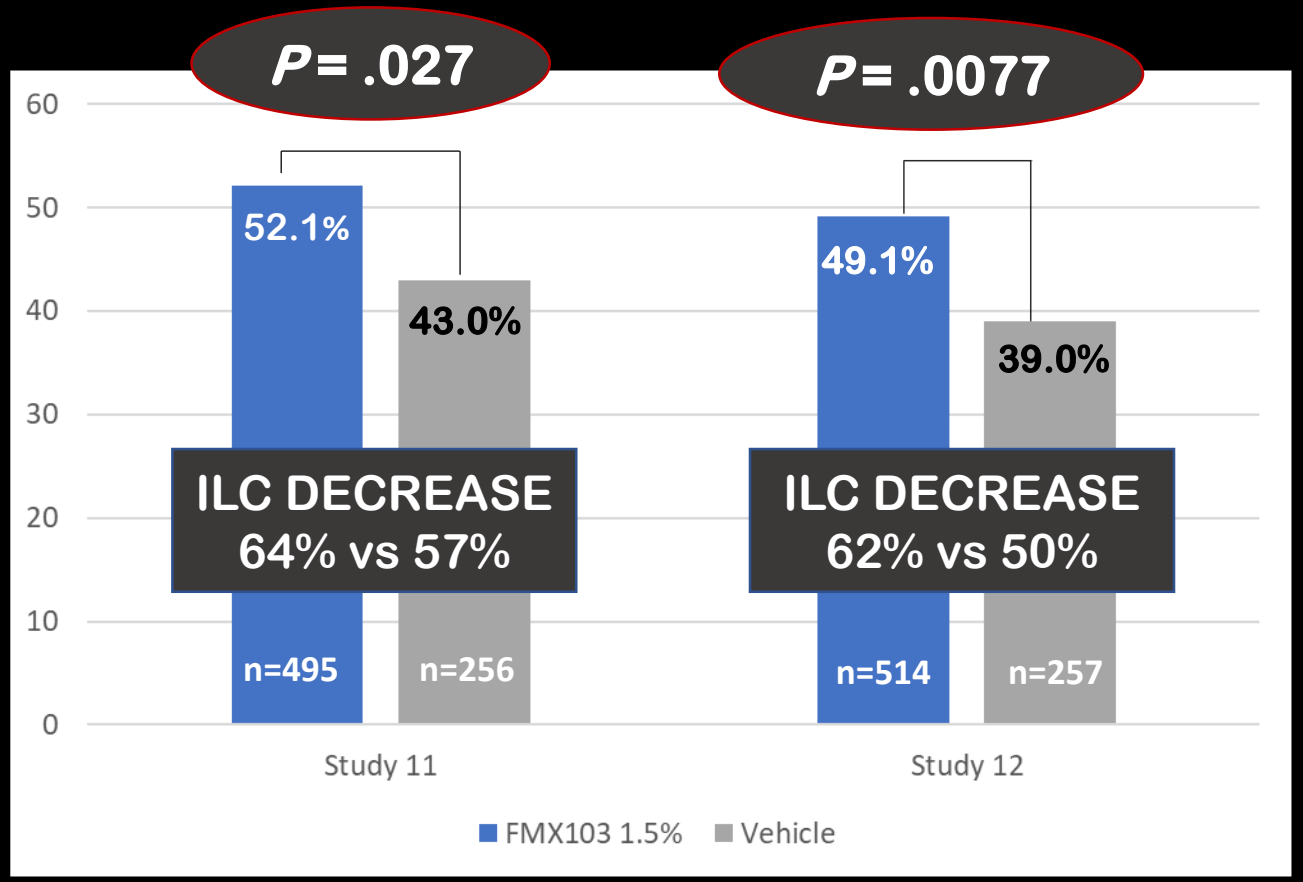
TOGETHER FROM START
=
BETTER RESULT



Minocycline Topical 1.5% Foam Once Daily

Phase 3 12-Week Studies in Moderate-to-Severe Papulopustular Rosacea (N=1522 / 2:1)

Subjects Achieving IGA SUCCESS (%) at WEEK 12



Co-Primary End Points

- ✓ Absolute change from Baseline in Inflammatory Lesion Count (ILC) Week 12
- ✓ IGA success at Week 12 (Clear" or Almost Clear) + ≥2-grade Decrease from Baseline

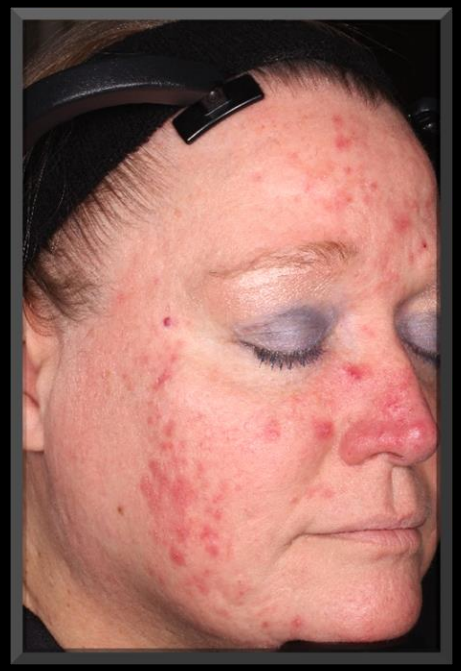
Stein Gold L, Del Rosso JQ, DO, Bhatia ND, et al. Phase 3 Studies, Foamix Pharmaceuticals, Data on File, 2019.

Minocycline Topical 1.5% Foam Once Daily

Moderate-to-Severe Papulopustular Rosacea (N=1522)

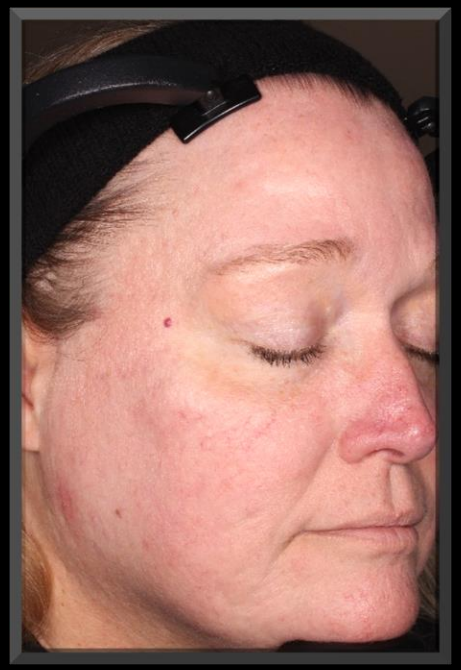
Phase 3 – 12 Weeks / Mean Lesions = 28.5-30.2

Baseline



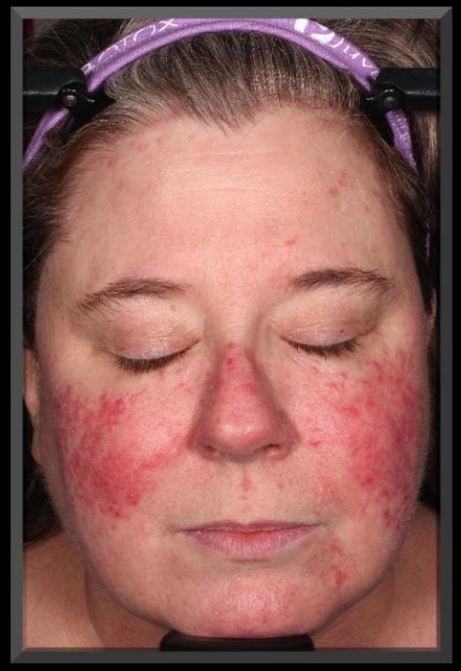
IGA=3

Week 12



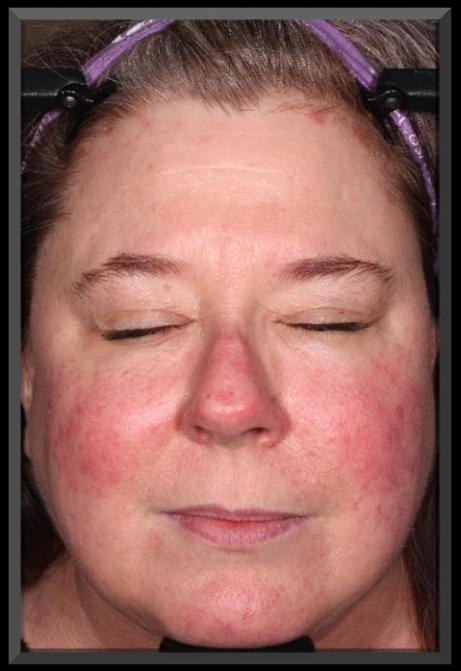
IGA=0

Baseline



IGA=3

Week 12

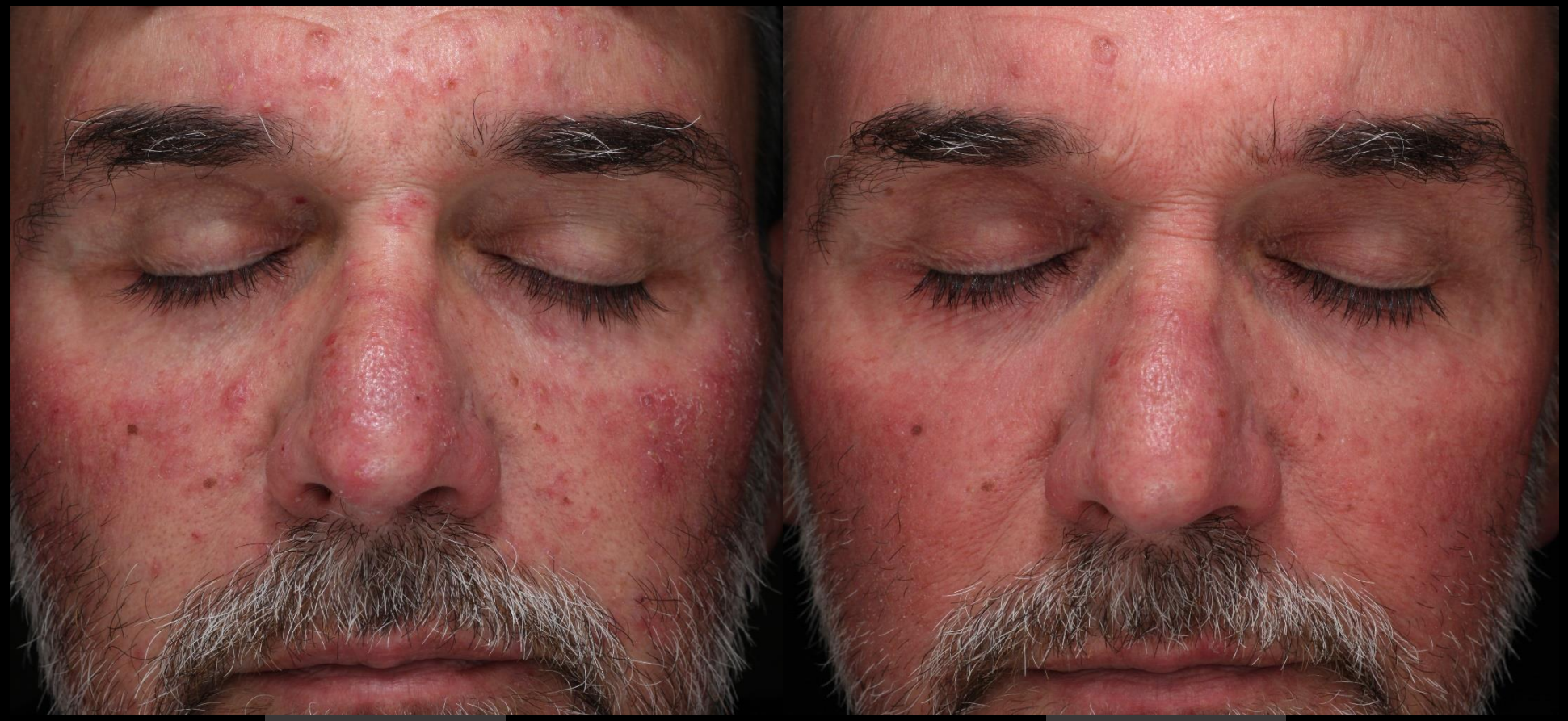


IGA=2

Stein Gold L, at al. SKIN, 2019.

Minocycline 2% Topical Gel

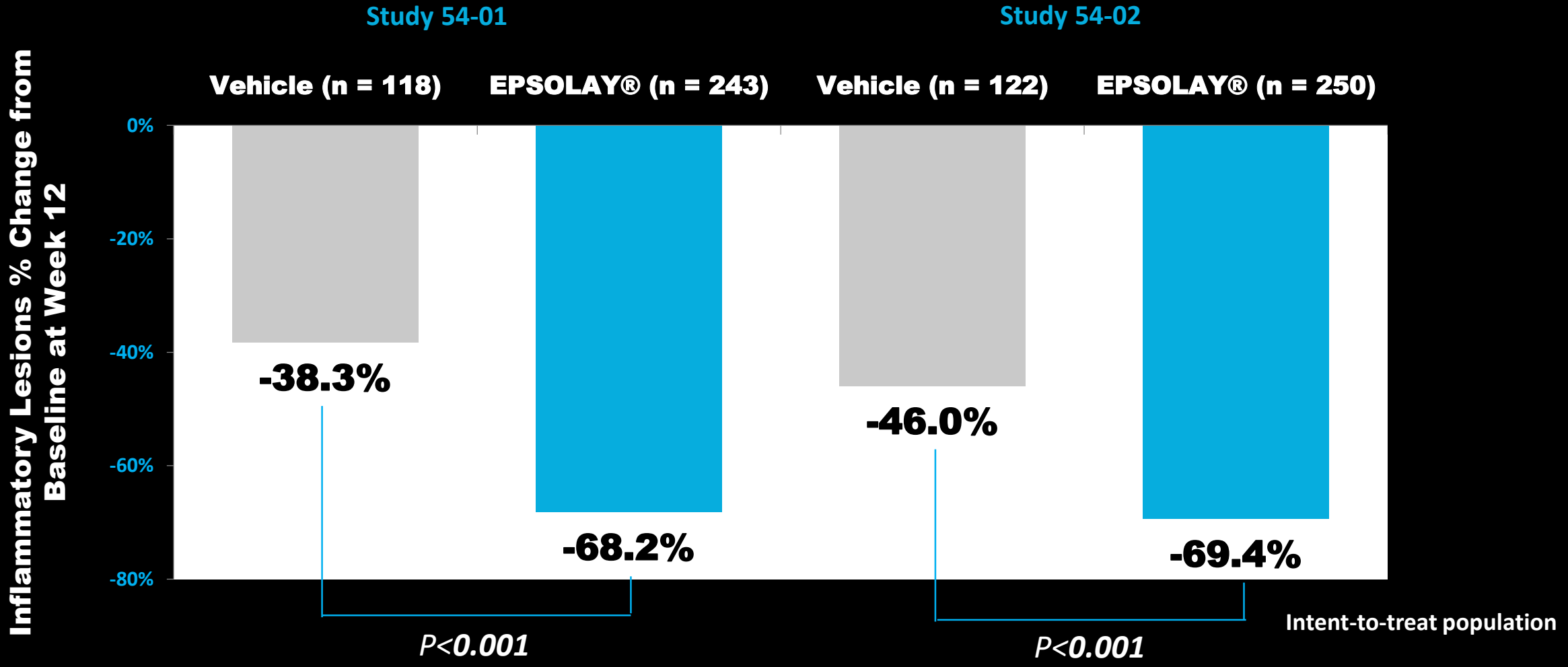
Pilot Study in Moderate-to-Severe Papulopustular Rosacea (N=19)



Bhatia ND, Del Rosso JQ. Poster presentation. Fall Clinical Dermatology, Las Vegas, NV, October 2018.
1% = n=10; 2% = n=9

ENCAPSULATED BENZOYL PEROXIDE 5% ONCE DAILY - PAPULOPUSTULAR ROSACEA

% CHANGE INFLAMMATORY LESIONS FROM BASELINE TO WEEK 12



INCIDENCE OF ADVERSE EVENTS (E-BP GROUPS): 5.9 (n=14) and 3.6% (n=9)

Sol-Gel, Data on file, http://ir.sol-gel.com/static-files/1ee0e842-1fab-4299-8332-ef9450983cc4, accessed 22 July 2019