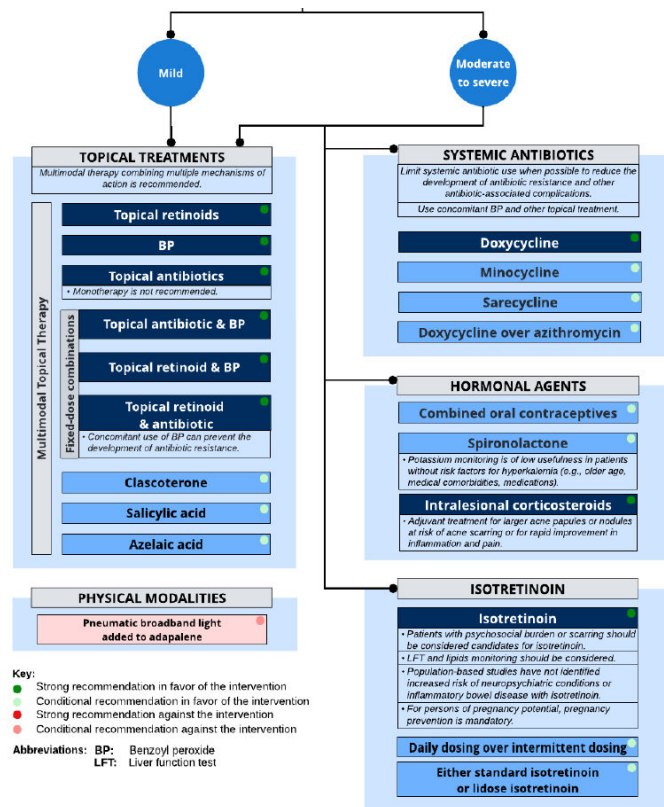
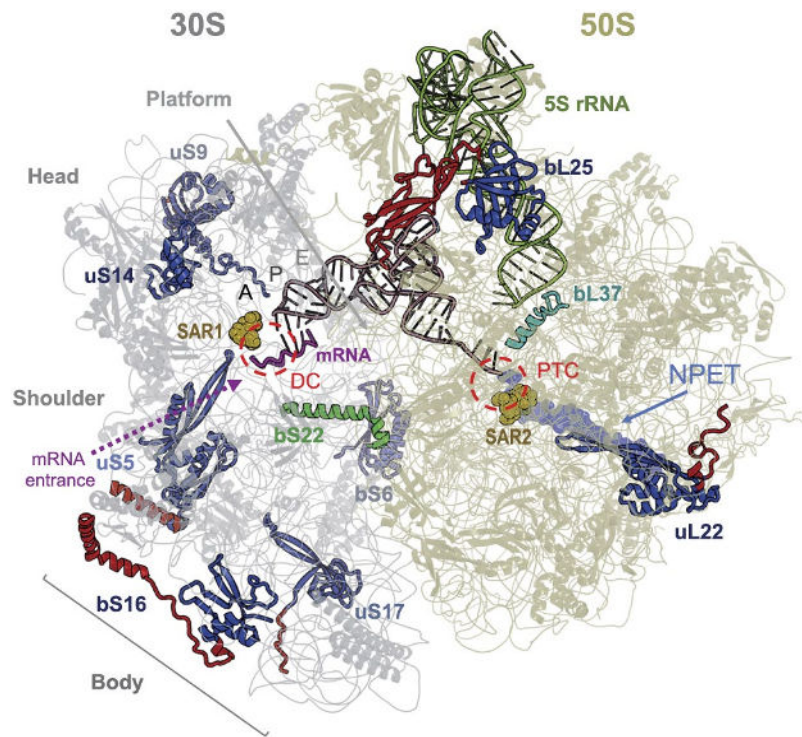
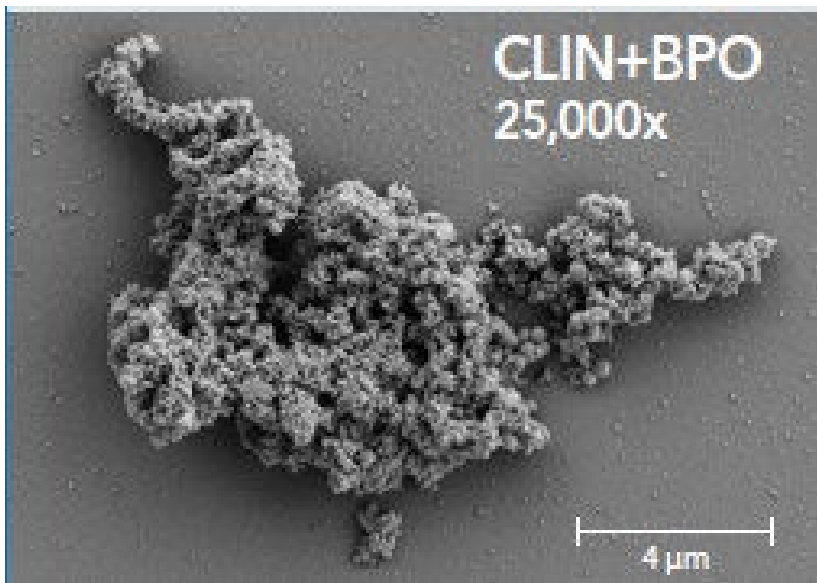


What's New in Acne?



Christopher G. Bunick, MD, PhD

Associate Professor of Dermatology & Program in Translational Biomedicine
Yale University



BRIDGING

MEDICAL AND AESTHETIC DERMATOLOGY

South Beach Symposium

FEB 8-11, 2024

MIAMI BEACH, FL

EARN 15.5 CME/CE CREDITS

Christopher G. Bunick, MD, PhD

What's New in Acne

**DISCLOSURE OF
RELATIONSHIPS
WITH INDUSTRY**

Abbvie: Consultant

Almirall: Investigator, Consultant

Arcutis: Consultant

EPI Health: Consultant

LEO Pharma: Consultant and Speaker

Novartis: Consultant




Ortho Dermatologics: Consultant, Investigator

Pfizer: Consultant

Sanofi-Regeneron: Consultant

UCB Pharma: Consultant

2016 AAD guidelines for treatment of acne vulgaris

	 <p>Mild Acne</p>	 <p>Moderate Acne</p>	 <p>Severe Acne</p>
1st-Line Treatment	<p>Benzoyl Peroxide (BP) or Topical Retinoid -or- Topical Combination Therapy* BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic</p>	<p>Topical Combination Therapy* BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic -or- Oral Antibiotic + Topical Retinoid + BP -or- Oral Antibiotic + Topical Retinoid + BP + Topical Antibiotic</p>	<p>Oral Antibiotic + Topical Combination Therapy* BP + Antibiotic or Retinoid + BP -or- Retinoid + BP + Antibiotic -or- Oral Isotretinoin</p>
Alternative Treatment	<p>Add Topical Retinoid or BP (if not on already) -or- Consider Alternate Retinoid -or- Consider Topical Dapsone</p>	<p>Consider Alternate Combination Therapy -or- Consider Change in Oral Antibiotic -or- Add Combined Oral Contraceptive or Oral Spironolactone (Females) -or- Consider Oral Isotretinoin</p>	<p>Consider Change in Oral Antibiotic -or- Add Combined Oral Contraceptive or Oral Spironolactone (Females) -or- Consider Oral Isotretinoin</p>

Pending Update to AAD Acne Guidelines

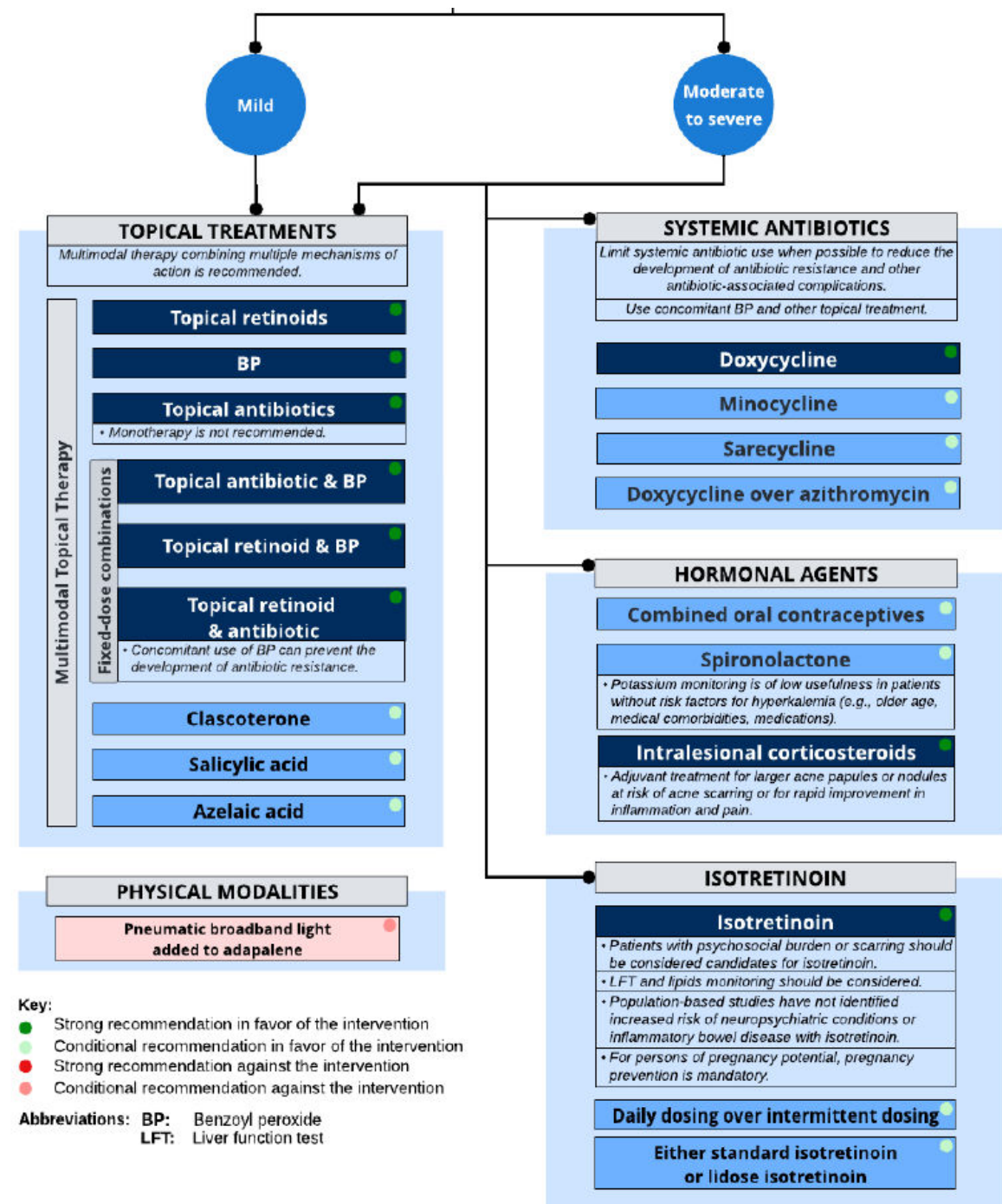
Management of Acne Vulgaris

Adults, adolescents, and preadolescents (≥ 9 years) with acne vulgaris

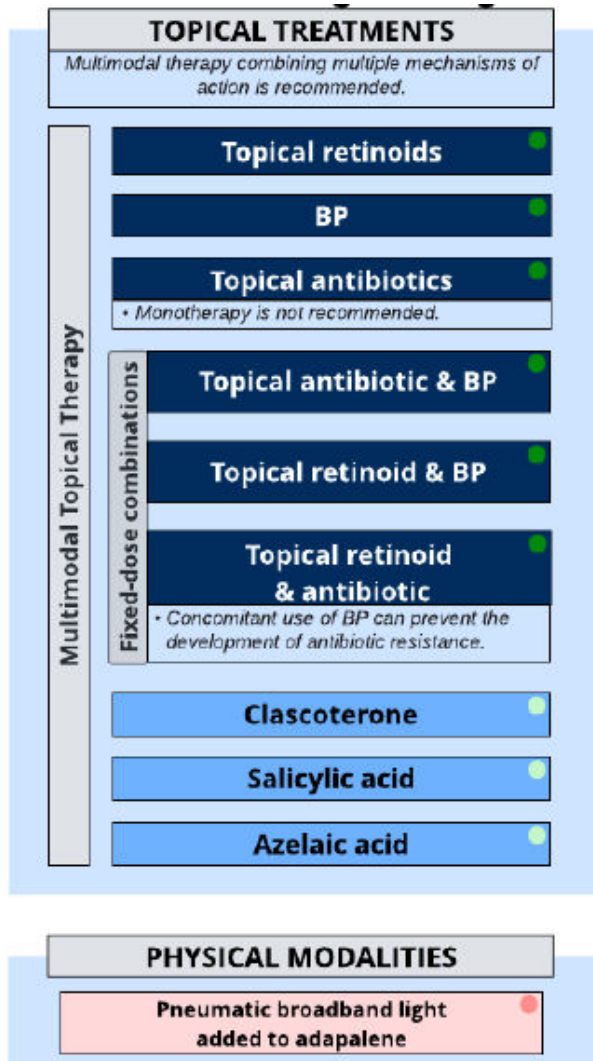
SEVERITY ASSESSMENT:

- Consistent use of an acne grading and classification system may help facilitate therapeutic decision-making and assess treatment response.
- Assess satisfaction with appearance, extent of scar / dark marks, treatment satisfaction, long-term acne control, and impact on quality of life.

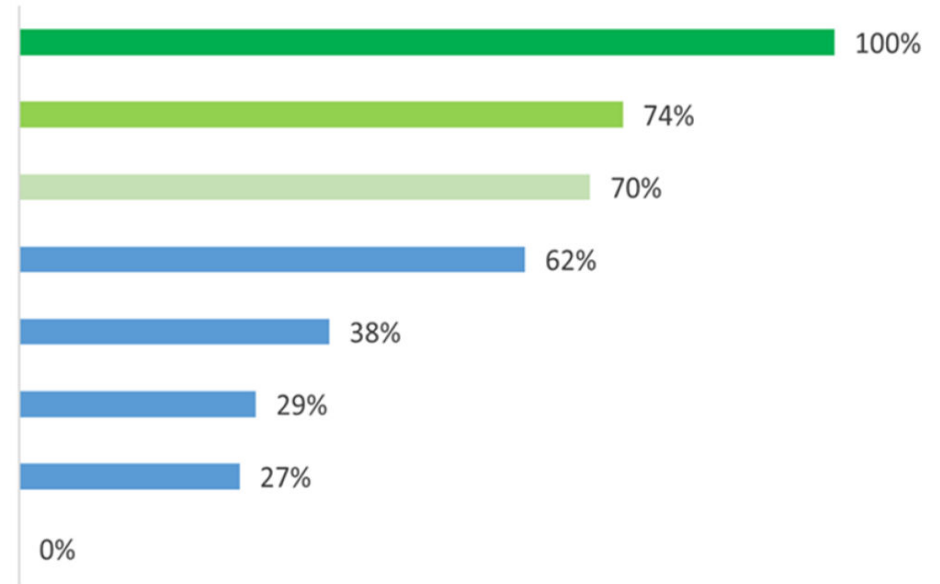
Routine microbiological and endocrine testing are not indicated.



Pending Update to AAD Acne Guidelines: Topical Therapy



Topical antibiotic/BPO/retinoid fixed-dose combinations
Topical retinoid/BPO fixed-dose combinations
Topical antibiotic/BPO fixed-dose combinations
Topical antibiotic/retinoid fixed-dose combinations
Topical antibiotic - monotherapy
Topical BPO - monotherapy
Topical retinoid - monotherapy
Vehicle



Key: Benzoyl peroxide (BPO)

- A Surface Under the Cumulative Ranking (SUCRA) value of 100% indicates that the topical triple-agent FDC has the highest probability of being the most effective among all the comparators in the NMA

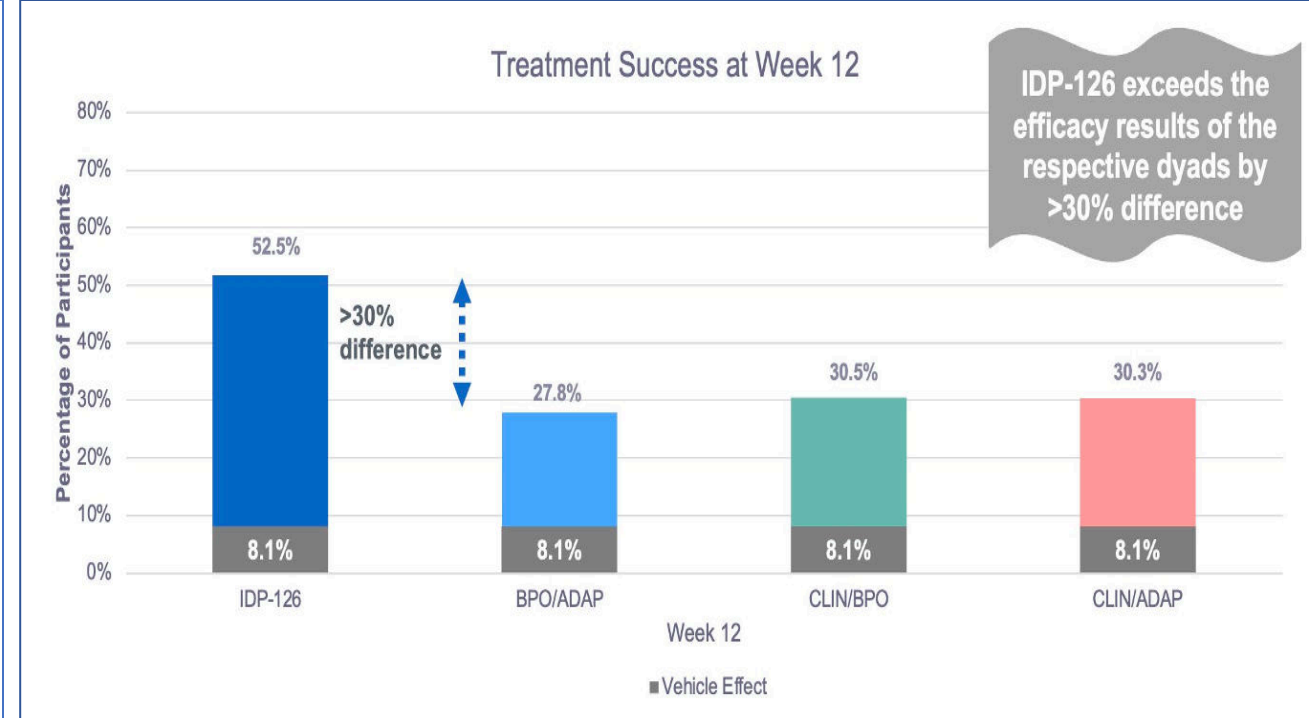
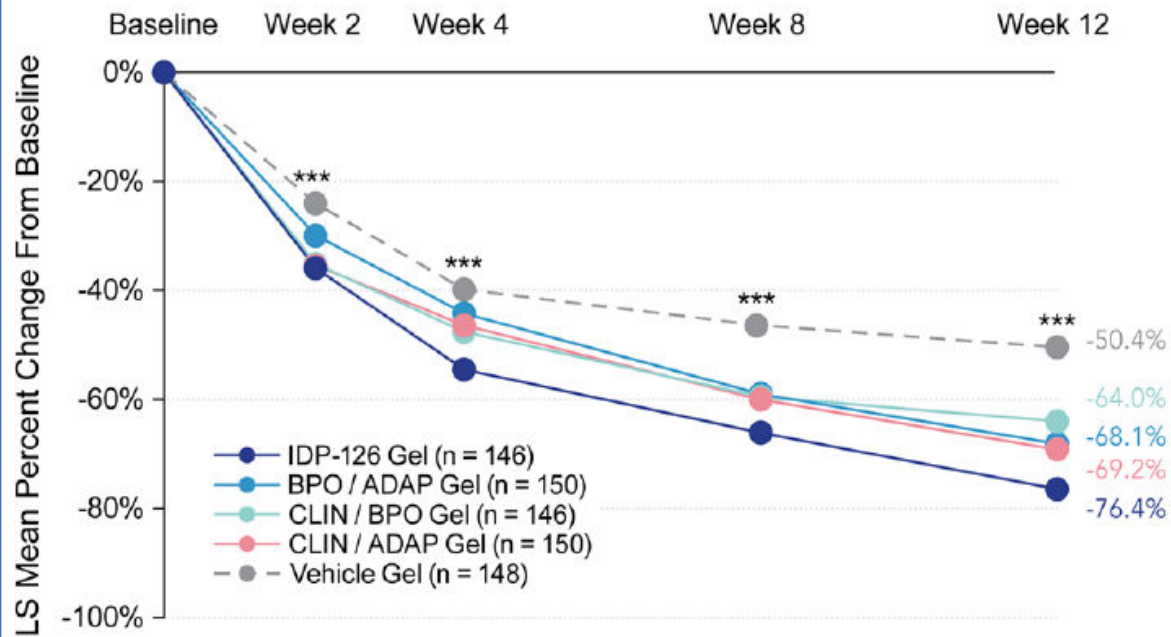
Harper J, et al. A systematic literature review and network meta-analysis of comparative efficacy of topical fixed-dose combination treatments for moderate to severe acne vulgaris. Bausch Health, Poster, Fall Clinical 2023.

Key:

- Strong recommendation in favor of the intervention
- Conditional recommendation in favor of the intervention
- Strong recommendation against the intervention
- Conditional recommendation against the intervention

Now FDA-Approved: triple combination topical IDP-126 enhances efficacy and may increase patient compliance

A. Inflammatory Lesions



Stein Gold L, et al.

Efficacy and Safety of a Fixed-Dose Clindamycin Phosphate 1.2%, Benzoyl Peroxide 3.1%, and Adapalene 0.15% Gel for Moderate-to-Severe Acne: A Randomized Phase II Study of the First Triple-Combination Drug.

Am J Clin Dermatol. 2022 Jan;23(1):93-104.

Clindamycin Phosphate 1.2%, Benzoyl Peroxide 3.1%, and Adapalene 0.15% Gel for Moderate-to-Severe Acne

13-Year-Old Female - Black

Baseline: EGSS 3

Week 12: EGSS 1



14-Year-Old Male - Asian

Baseline: EGSS 3

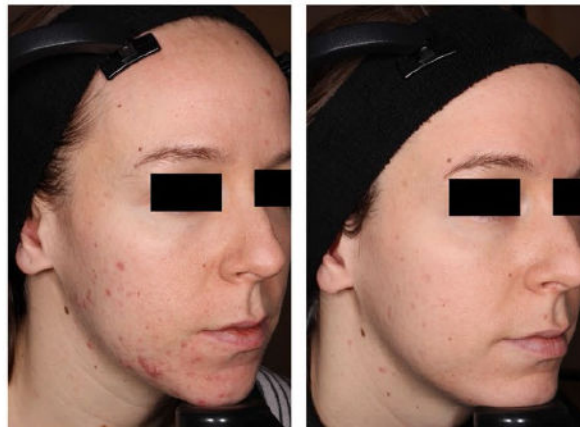
Week 12: EGSS 0



26-Year-Old Female - White

Baseline: EGSS 3

Week 12: EGSS 1



27-Year-Old Female - Black/White

Baseline: EGSS 3

Week 12: EGSS 1



Stein Gold L, et al. Efficacy and Safety of a Fixed-Dose Clindamycin Phosphate 1.2%, Benzoyl Peroxide 3.1%, and Adapalene 0.15% Gel for Moderate-to-Severe Acne: A Randomized Phase II Study of the First Triple-Combination Drug. Am J Clin Dermatol. 2022 Jan;23(1):93-104.

Acne improvements with clindamycin phosphate 1.2%/benzoyl peroxide 3.1%/adapalene 0.15% (IDP-126). Individual results may vary.
EGSS Evaluator's Global Severity Score (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe)

Benefits of clindamycin in triple-combination acne topical

Anti-inflammatory Properties of Clindamycin					
Proinflammatory Factors and Components	Study Type		Inhibits		Enhances ^a
	Acne ^b	Other	Yes	No	Yes No
<i>Propionibacterium acnes</i> growth	X ⁷²		X ⁷²		
<i>P. acnes</i> protein synthesis (50S ribosomal subunit binding)		X ^{26,70}	X ^{26,70}		
<i>P. acnes</i> lipase production	X ⁷³		X ⁷³		
<i>P. acnes</i> and the release of follicular free fatty acids	X ^{15,74}		X ^{15,74}		
Proinflammatory Chemokines (Attractants)					
<i>P. acnes</i> release of leukocyte chemotactic components	X ^{23,56,75,76}		X ^{23,56,75,76}		
IL-8	X ^{46,c}			X ^{46,c}	
Phagocytosis					
Opsonization of bacteria for enhanced phagocytosis		X ⁷⁷⁻⁸⁰			X ⁷⁷⁻⁸⁰
Enhances and potentiates phagocytosis		X ^{77,81,82}			X ^{77,81,82}
Respiratory burst (ROS as O ₂ ⁻ , H ₂ O ₂)		X ^{83,84}		X ^{83,84}	
iNOS enzymes		X ⁸⁵		X ⁸⁵	
Protein kinase C enzyme/granuloma formation	X ⁸⁶			X ⁸⁶	
Proinflammatory Cytokines (Primarily Monocytes)					
IL-1α	X ^{46,c}			X ^{46,c}	
IL-1β	X ^{46,d}	X ⁸⁷⁻⁸⁹		X ^{46,87-89,d}	
IL-6	X ^{46,c,e}			X ^{46,c,e}	
IL-12p70	X ^{46,d}			X ^{46,d}	
IFN-γ	X ^{46,d}			X ^{46,d}	
TNF-α	X ^{46,d}	X ^{85,87-90}		X ^{85,87-90}	X ^{46,d}
Keratinocyte Cytokines (Stimulants)					
GM-CSF	X ^{46,c,e}			X ^{46,c,e}	

Abbreviations: ROS, reactive oxygen species; O₂⁻, superoxide; H₂O₂, hydrogen peroxide; iNOS, inducible nitric oxide synthase; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor α; GM-CSF, granulocyte-macrophage colony-stimulating factor.

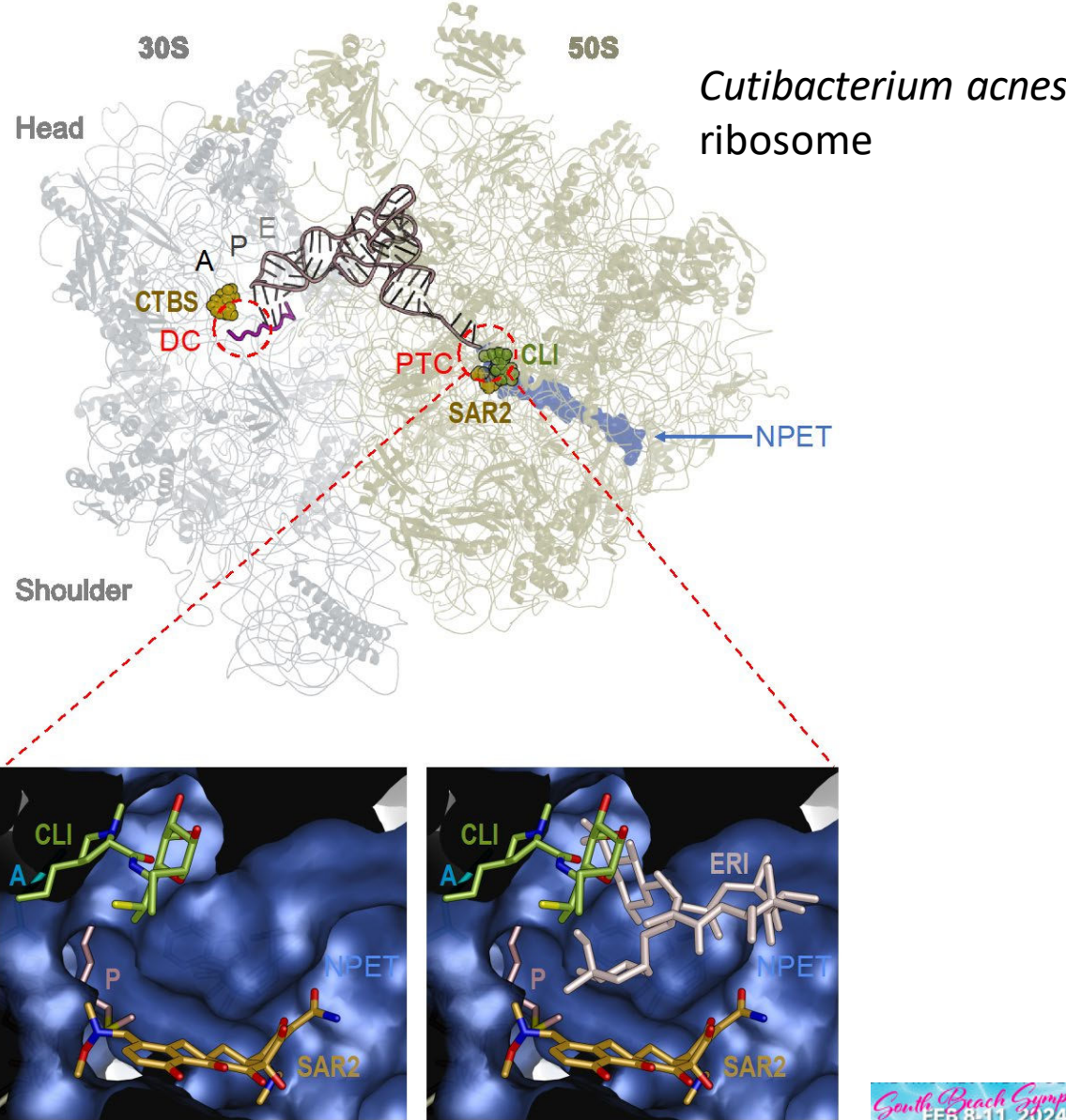
^aIn several instances, clindamycin can actually enhance rather than inhibit a process associated with inflammation. These enhancements can actually be beneficial therapeutically and therefore can be ranked as anti-inflammatory in nature.

^bAcne related based on available understanding of inflammatory mechanisms involved in pathogenesis.

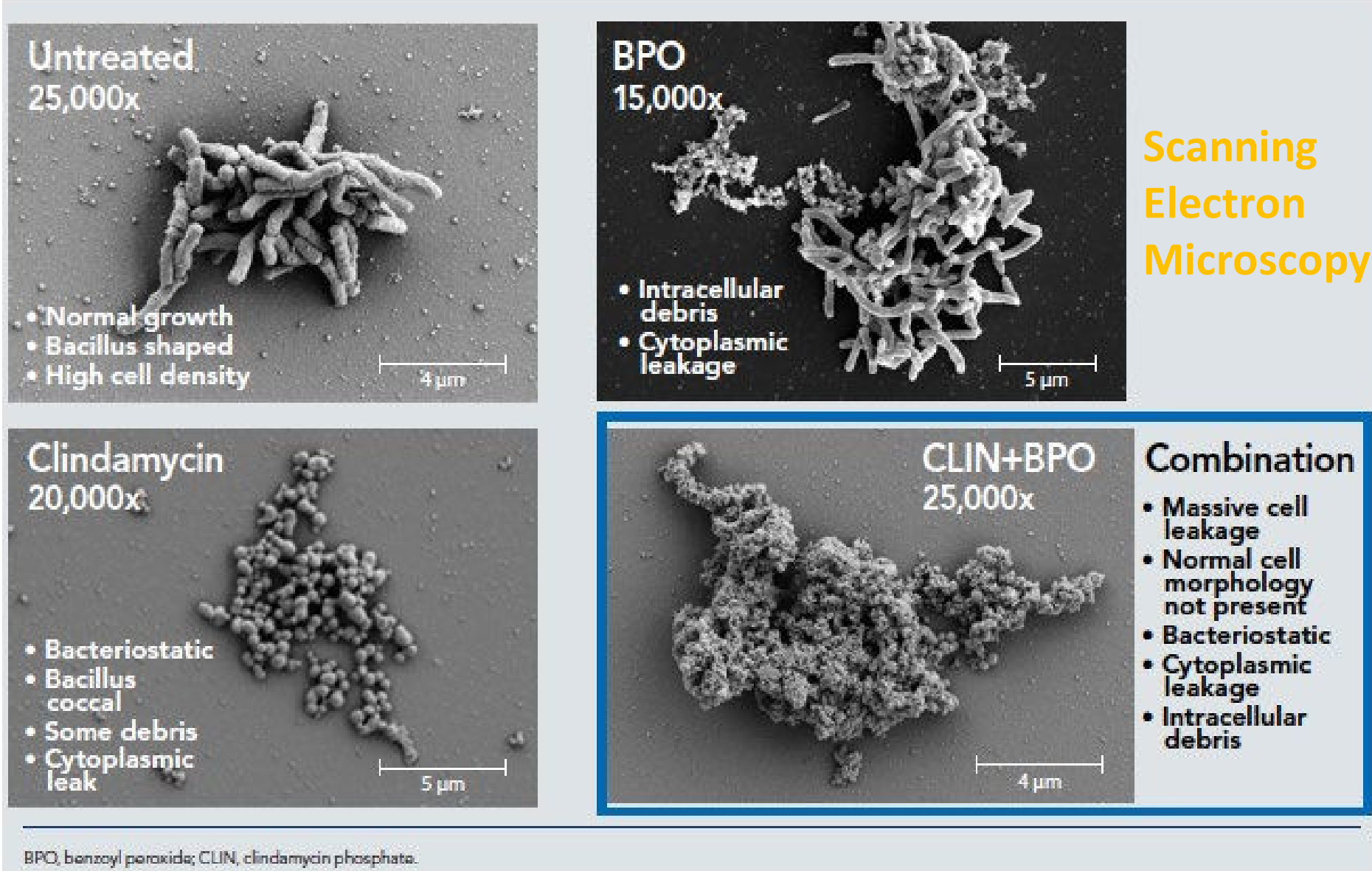
^cFrom human keratinocytes activated by heat-killed *P. acnes*.

^dFrom human monocytes activated by heat-killed *P. acnes*.

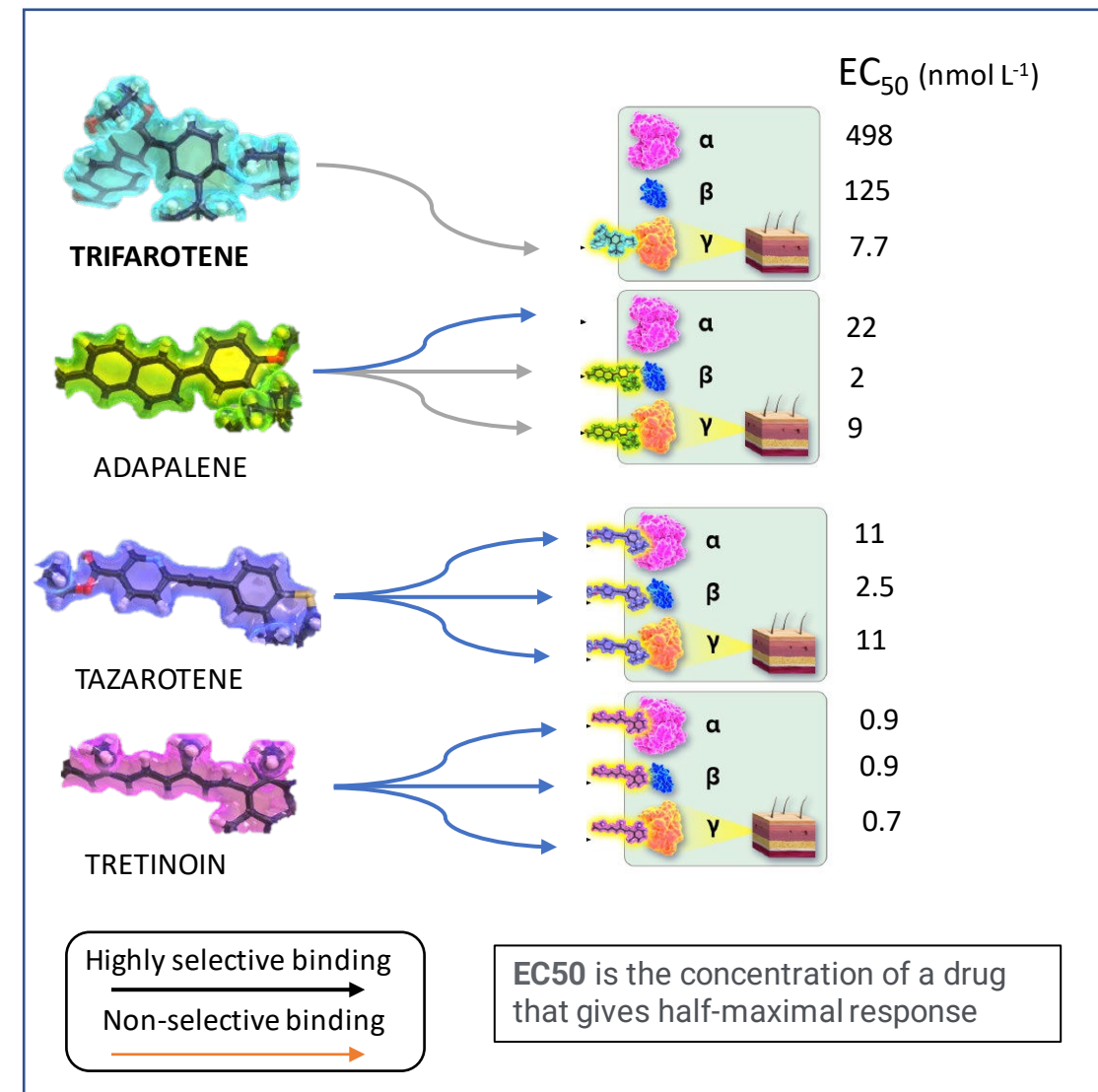
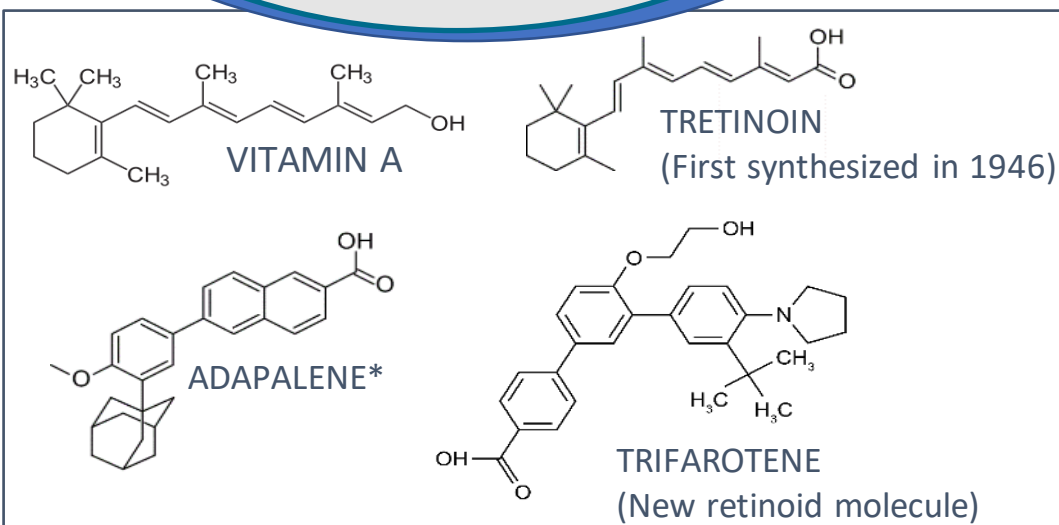
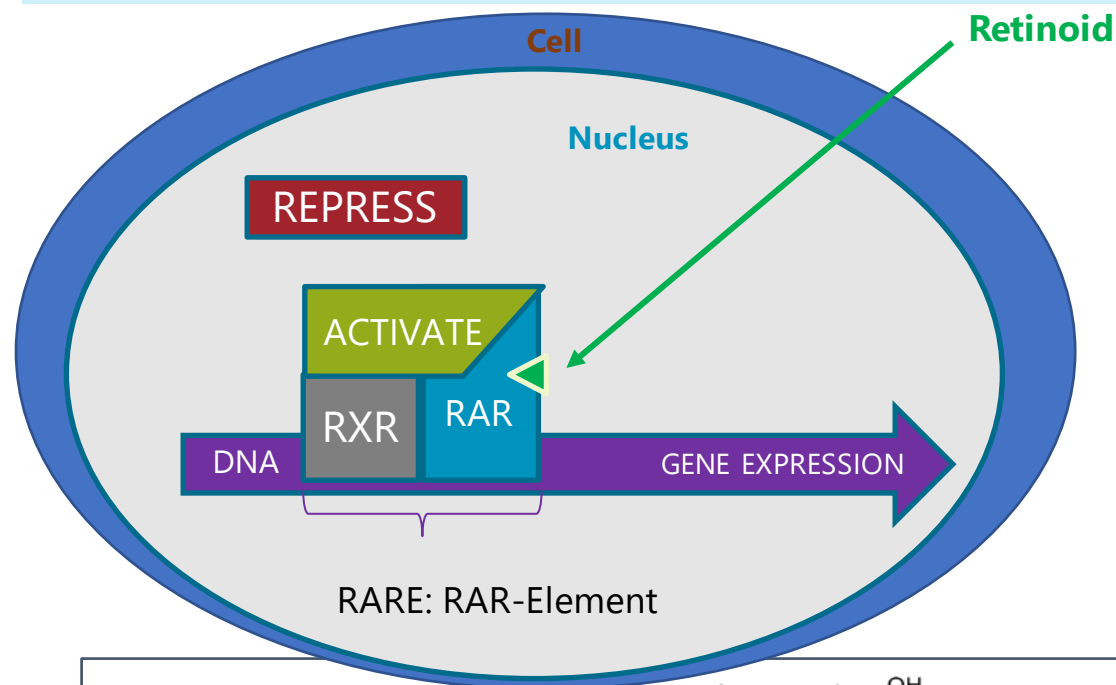
^eInhibits at high concentration; however, the investigators suggest that the high concentration of clindamycin used "may be achievable in acne lesions after single topical application . . ."⁴⁶



Clindamycin and BPO damages *C. acnes*



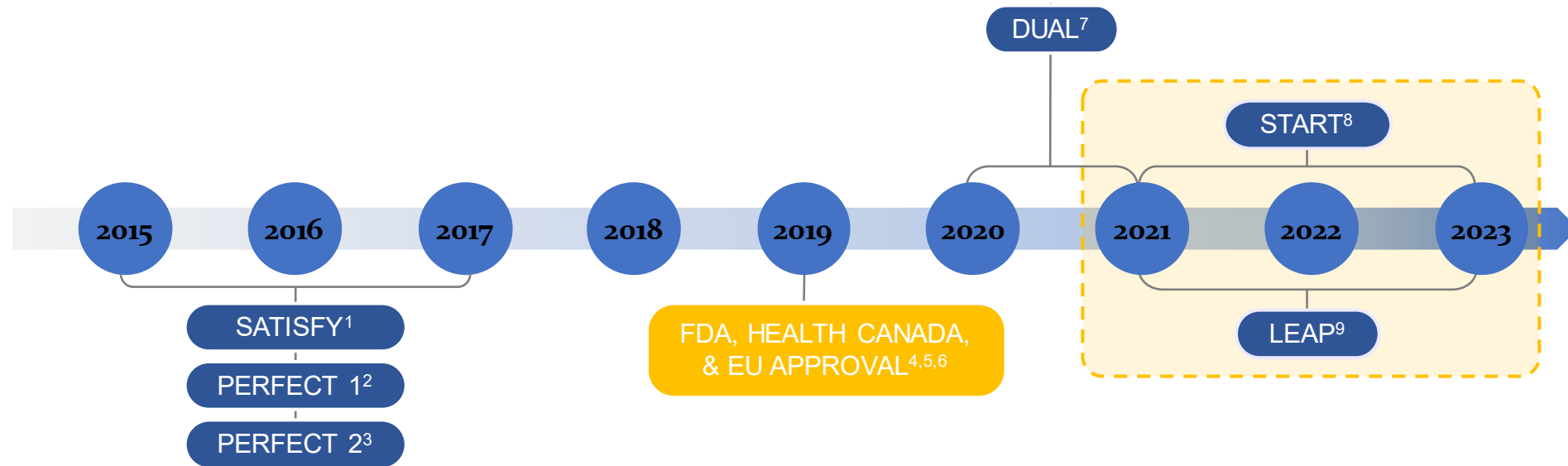
Retinoids: update on trifarotene



Trifarotene is a potent agonist of RAR, binding specifically to the γ subtype of RAR receptors, which is the predominant receptor type in the skin (~90%)

Trifarotene Cream 0.005%: Phase 4 Studies of Acne Sequelae

LEAP: A Study of Acne-Induced Hyperpigmentation
START: A Study of Acne-Induced Scarring



Study Design

Design:

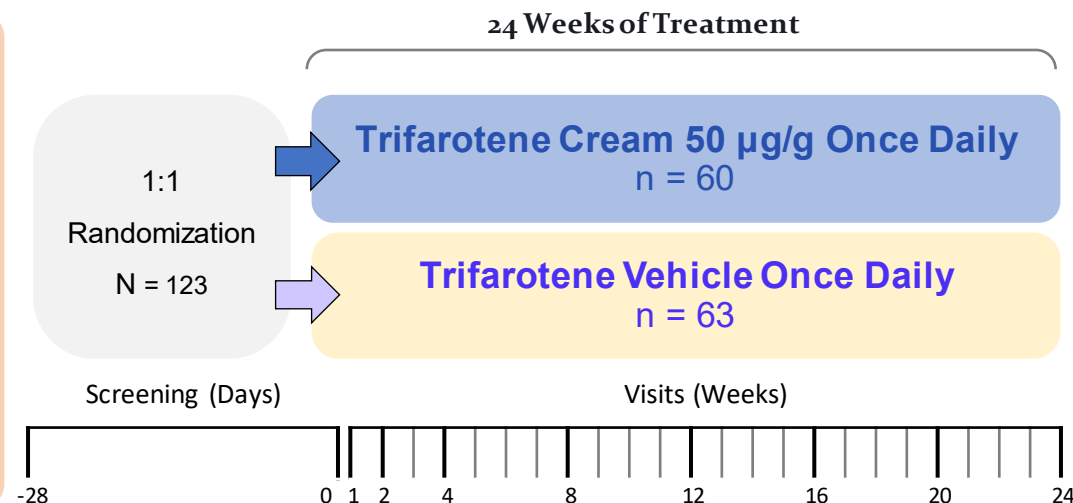
- 24-week, multicenter, randomized, double-blind, vehicle-controlled study
- Face only

Study Objective:

- Efficacy and safety of trifarotene cream in the treatment of acne-induced post-inflammatory hyperpigmentation

Key inclusion criteria

- Aged 13–35 years
- Clinical diagnosis of acne vulgaris defined by:
 - IGA score of 3 (Moderate Acne, 5 point scale)
 - ≥ 20 inflammatory lesions
 - ≥ 25 non-inflammatory lesions
 - ≤ 1 nodules or cysts (≥ 1 cm)
- ODS hyperpigmentation score 4 to 6 (Moderate to Marked on 9 point scale)
- Any Fitzpatrick skin type I to VI



Study Endpoints

Efficacy

Post-inflammatory Hyperpigmentation (PIH)

- Primary Endpoint: Absolute change from baseline in PIH overall disease severity (ODS) scores at Week 24
- Percent change from baseline in PIH ODS at Week 24
- Absolute and percent changes at Weeks 12, 16, and 20
- Post acne hyperpigmentation index (PAHPI) at Weeks 12, 16, 20, and 24

Acne

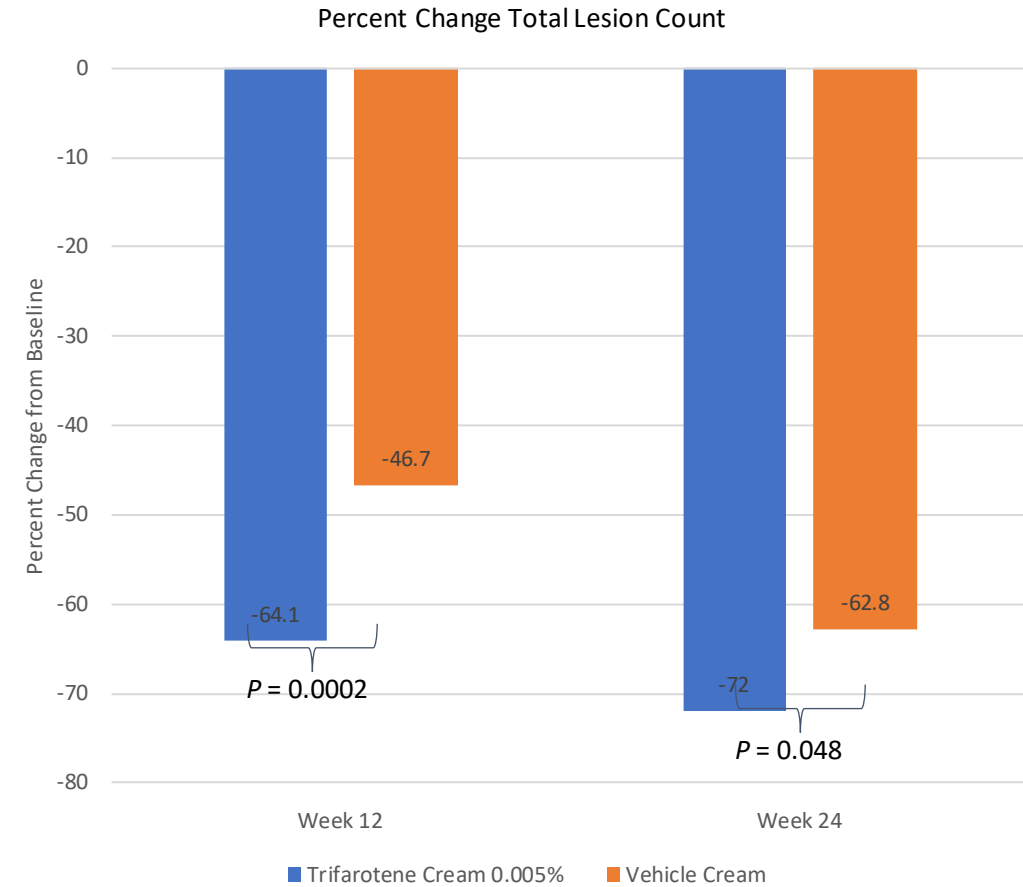
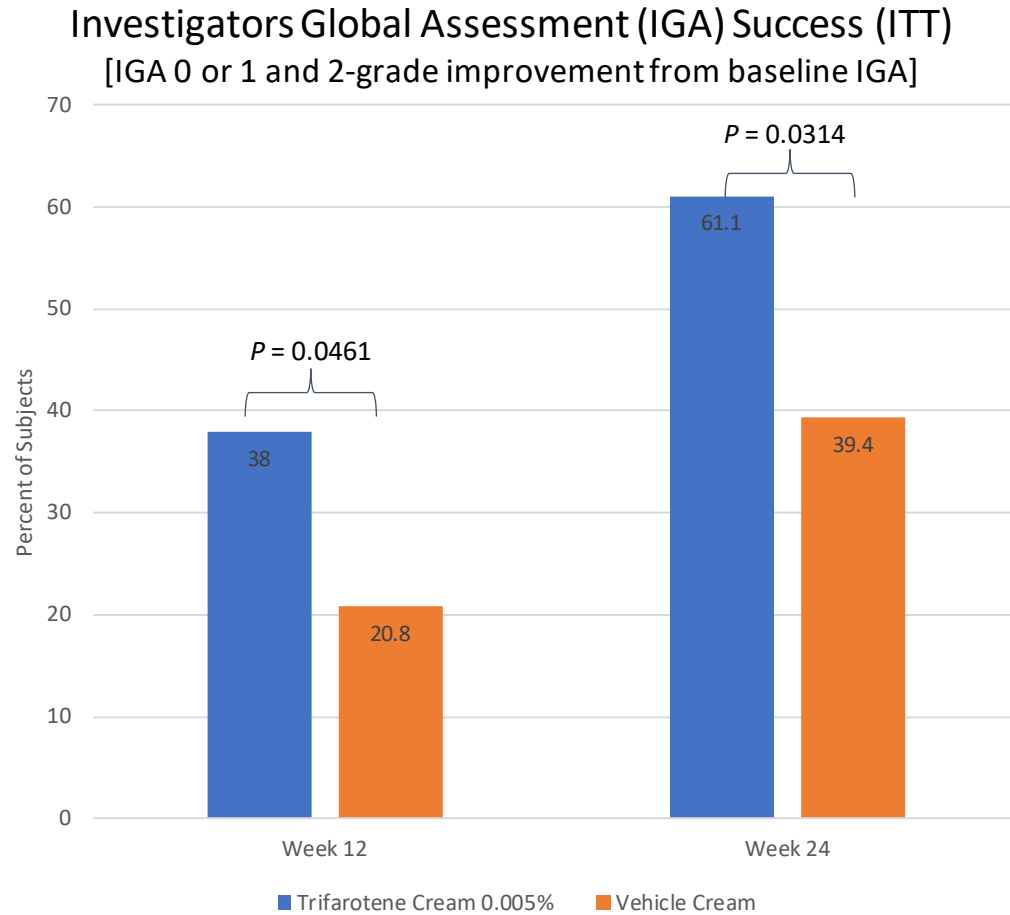
- Investigator's Global Assessment (IGA) success, absolute and percent change from BL in total lesion count (sum of NIL and IL), IL count, NIL count, at each post-BL visit

Safety

- Incidence of AEs
- Local tolerability (erythema, scaling, dryness and stinging/burning)

AE, adverse events; BL, baseline; HADS, Hospital and Anxiety Depression Scale; IGA, Investigator's Global Assessment; IL, inflammatory lesion; NIL, non-inflammatory lesion; QoL, quality of life; PAHPI, post acne hyperpigmentation index; PIH, post-inflammatory hyperpigmentation; PRO, patient-reported outcome; PSQ, Perceived Stigmatization Questionnaire.
Galderma Data on File RD.03.SPR.204245.

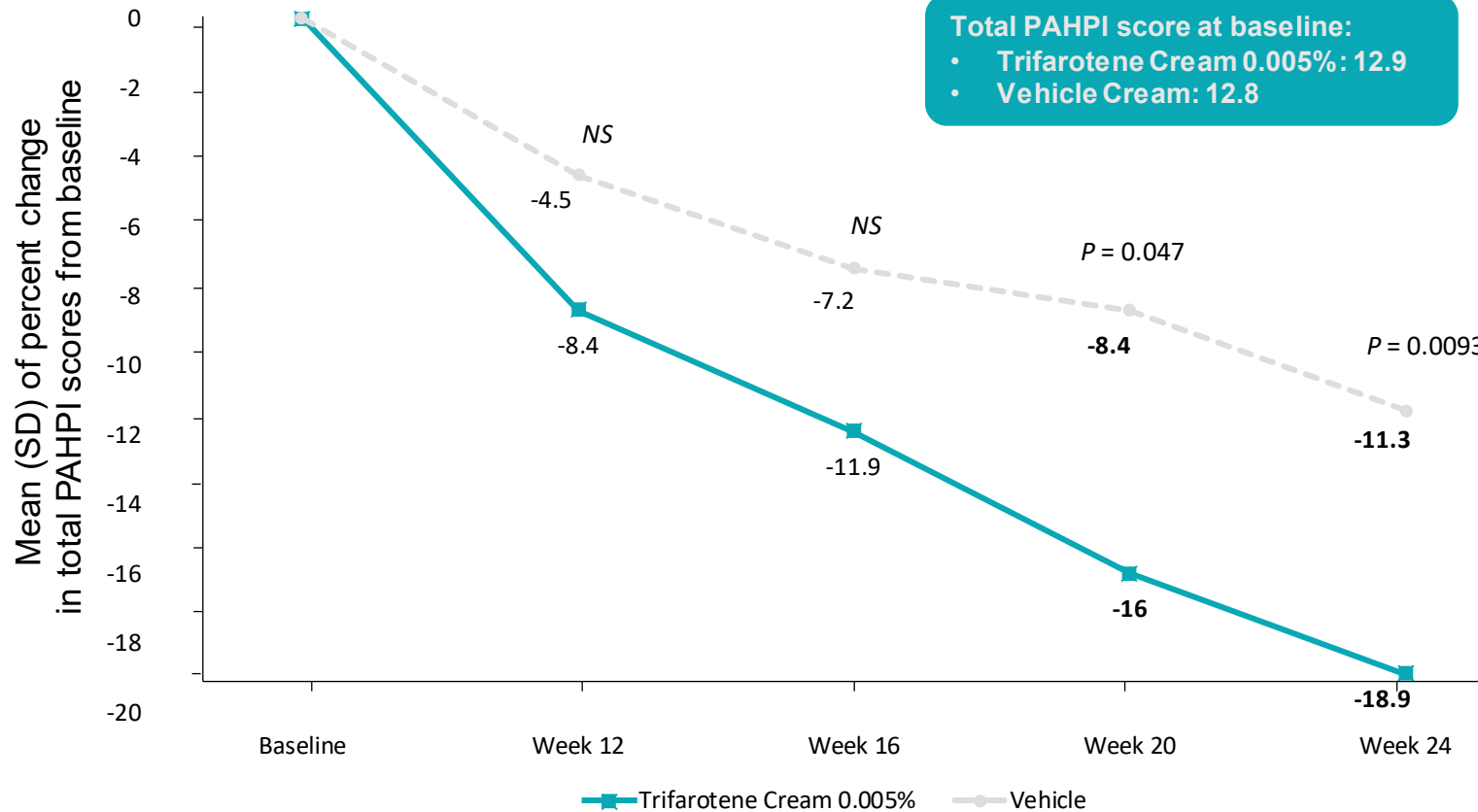
Acne Improvement



Missing data imputed using multiple imputation under the assumption of missing at random (ITT population).
BL, baseline; CI, confidence interval; IGA, investigators global assessment; ITT, intention-to-treat; MI, multiple imputation.
Galderma. Data on File RD.06.SPR.204245

Post-acne Hyperpigmentation Index (PAHPI; size, intensity, number)

Percent change from baseline in PAHPI of the face total score (ITT) ¹



Scoring the Post-Acne Hyperpigmentation Index (PAHPI)

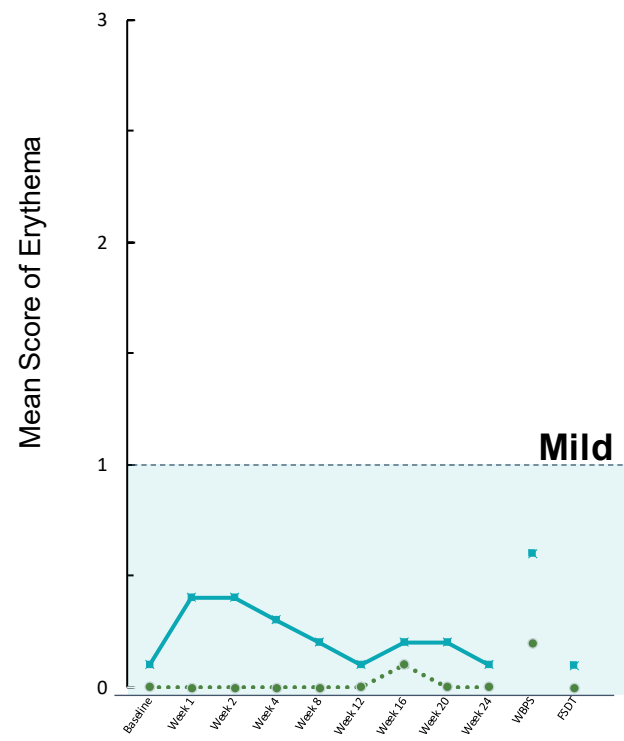
Weighted score (S)	Median lesion size
2	< 3 mm
4	3 – 6 mm
6	7 – 10 mm
8	> 10 mm

Weighted score (I)	Median lesion intensity
3	Slightly darker than surrounding skin
6	Moderately darker than surrounding skin
9	Significantly darker than surrounding skin

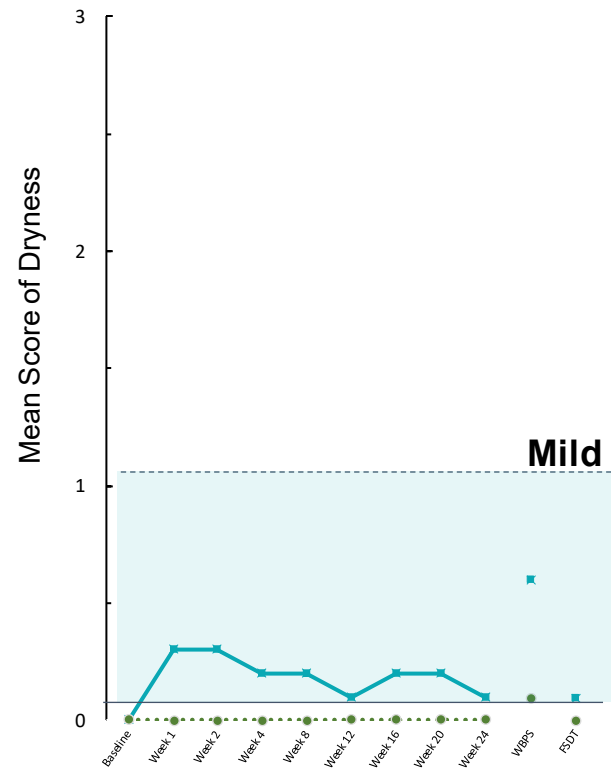
Weight score (N)	Number of lesions
1	1 – 15
2	16 – 30
3	31 – 45
4	46 – 60
5	> 60

Tolerability

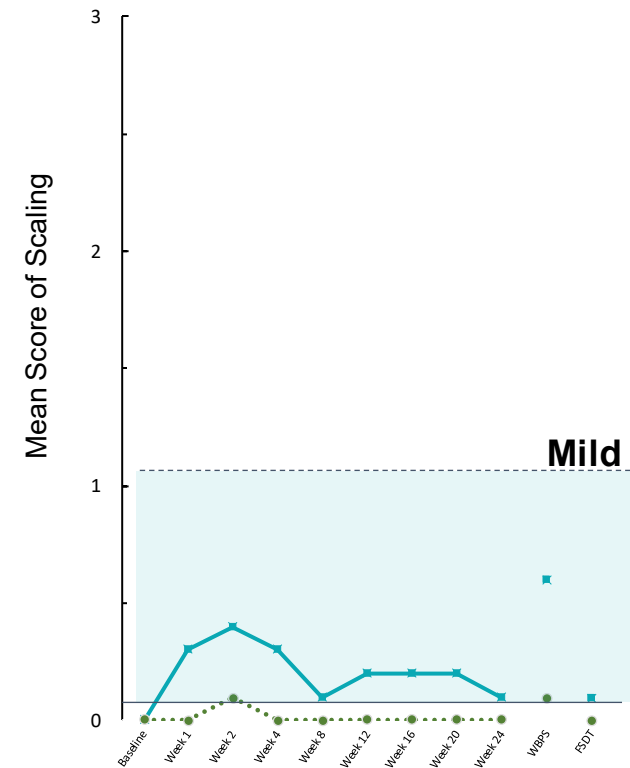
Erythema



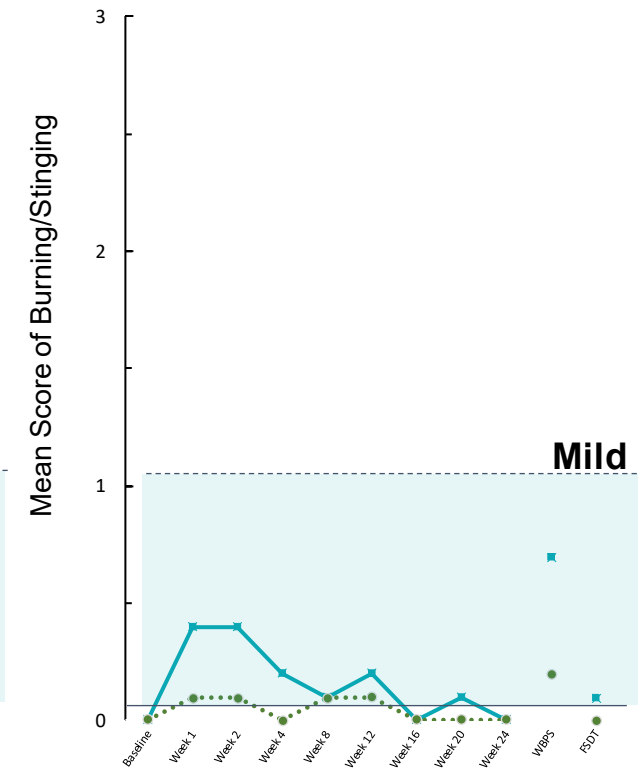
Dryness



Scaling



Burning/stinging



FSDT, final score during treatment; WPBS, worst post-baseline score
Scale 0 [none] through 3 [Severe]
Galderma RD.06.SPR.204245

—■— Trifarotene Cream 0.005% (n = 60)
····· Vehicle (n = 63)

Patient photographs

Vehicle group

Vehicle

Cross-Polarized



Baseline



Week 12



Week 24

Vehicle

Cross-Polarized



Patient Photographs

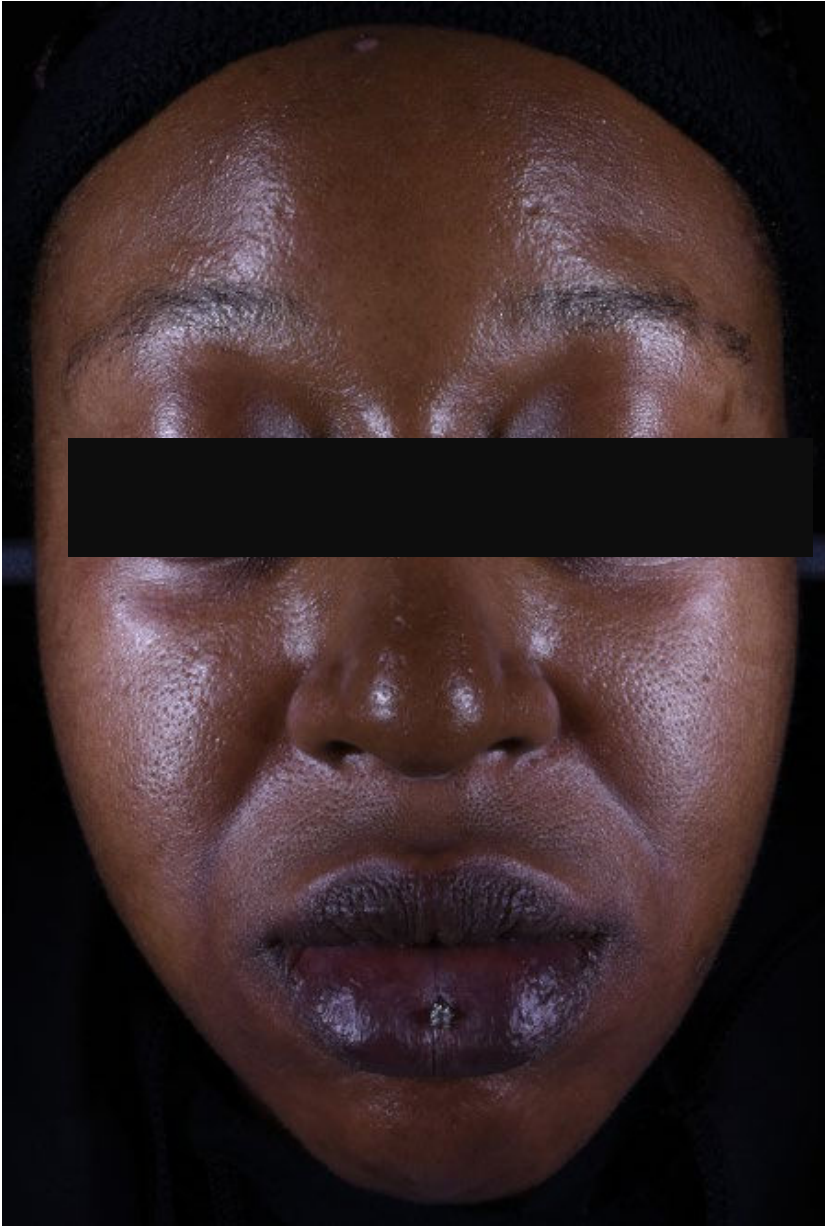
Trifarotene Group



Baseline



Week 12



Week 24



Baseline



Week 12



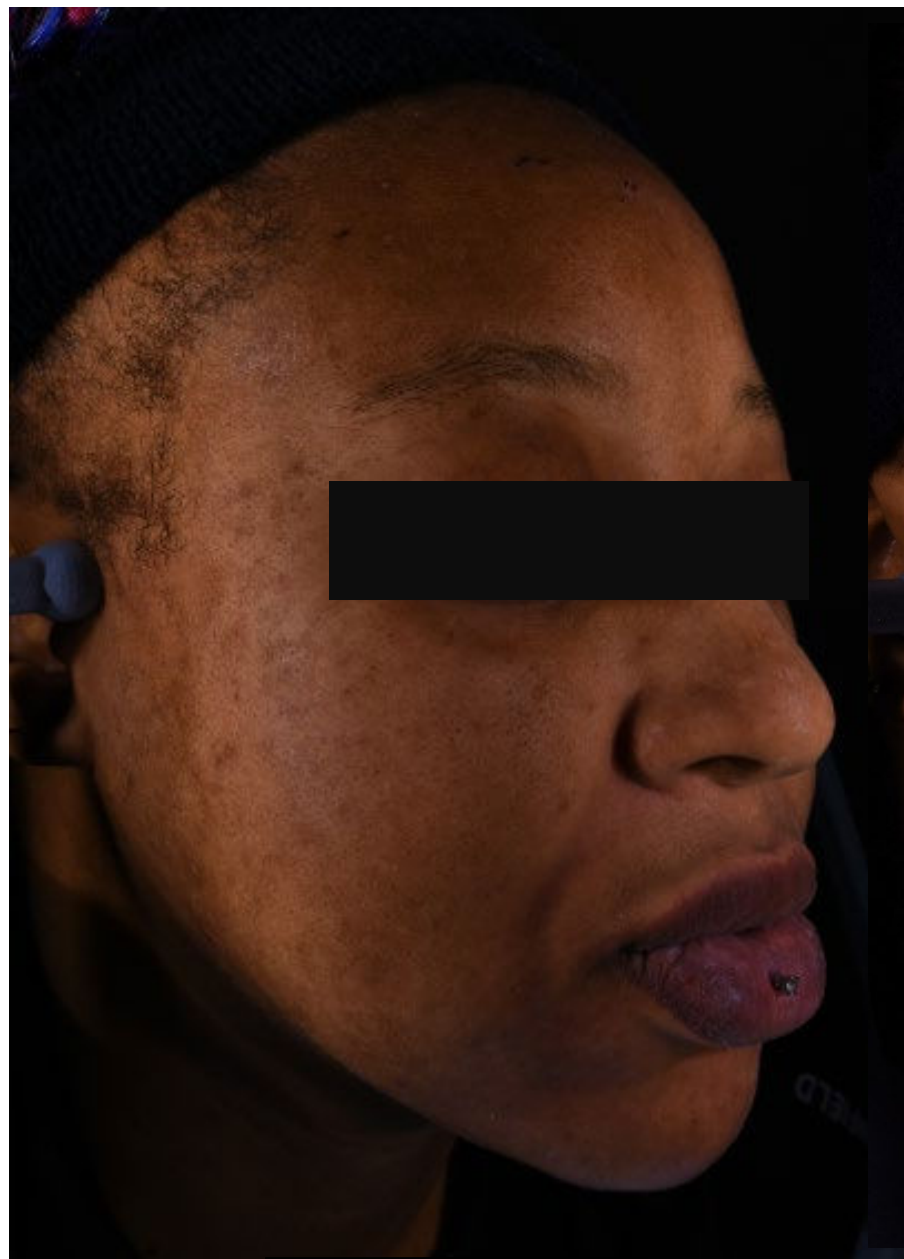
Week 24

Trifarotene

Cross-Polarized



Baseline



Week 12



Week 24

Trifarotene

Cross-Polarized



Baseline



Week 12



Week 24

Trifarotene

Cross-Polarized



Baseline



Week 12



Week 24



Baseline



Week 12



Week 24

Trifarotene

Cross-Polarized



Baseline



Week 12



Week 24





Trifarotene

Cross-Polarized



Baseline



Week 12



Week 24

Trifarotene

Cross-Polarized



Baseline



Week 12



Week 24

Study Design

Design:

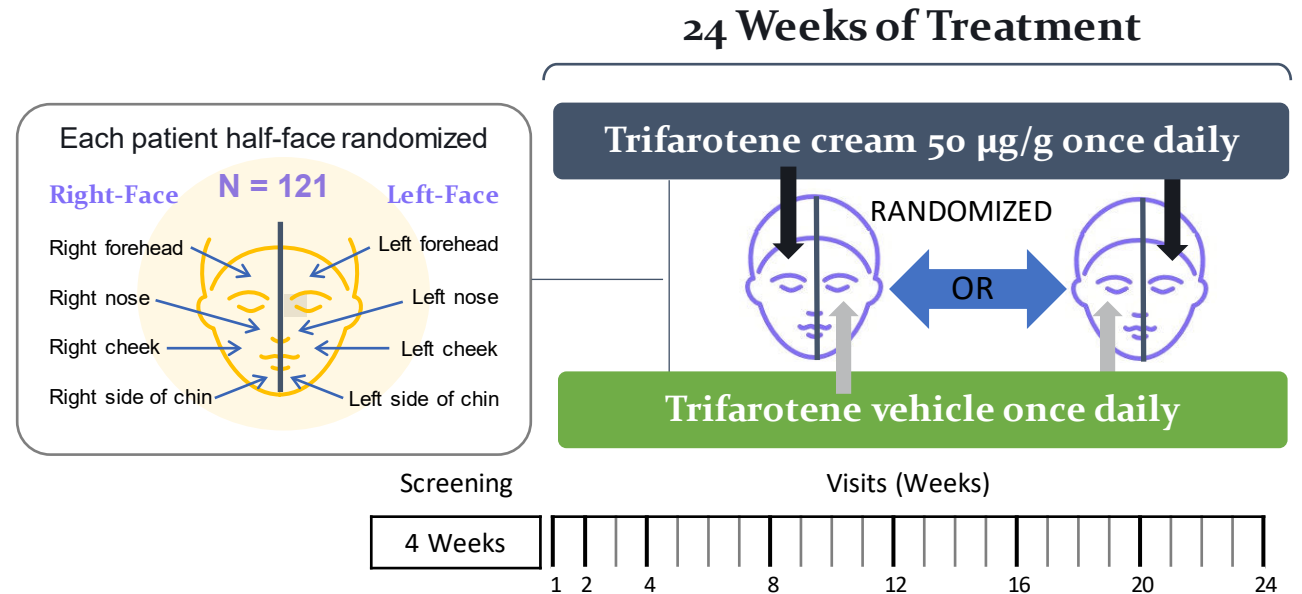
- Split-face, 24-week, multicenter, randomized, double-blind, vehicle-controlled study
- Face only

Study Objective:

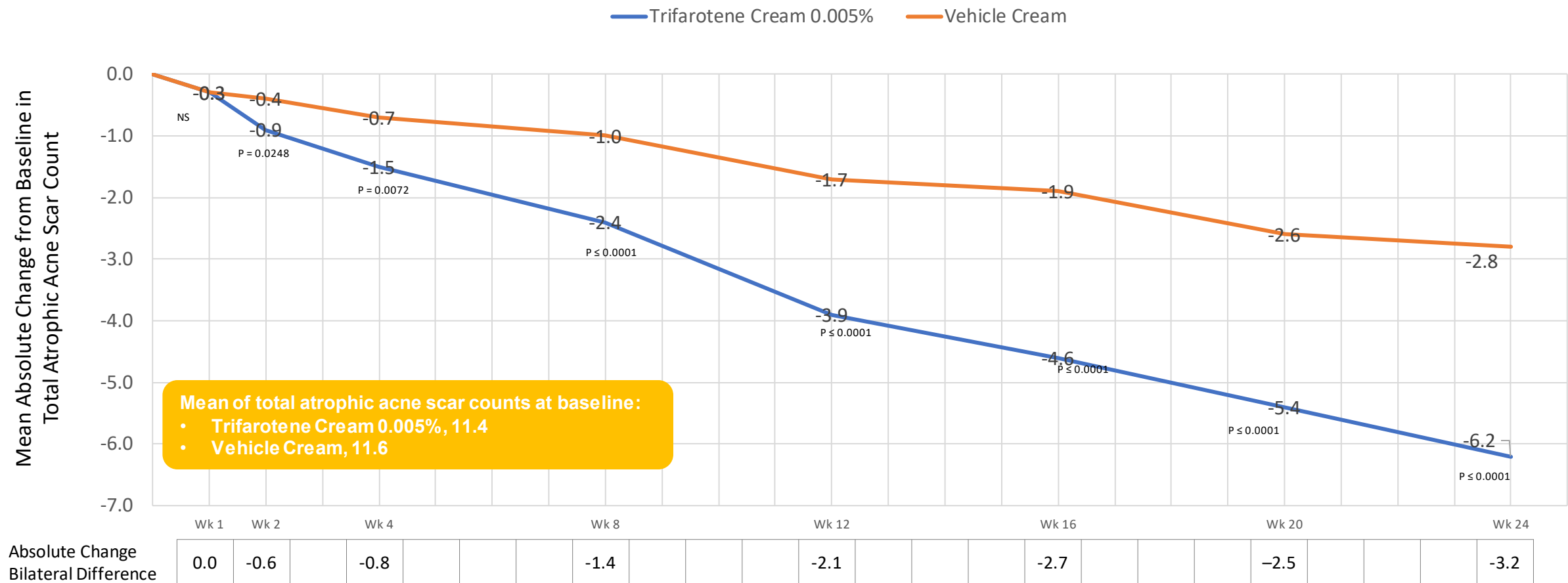
- Efficacy and safety of trifarotene cream in the treatment of acne-induced atrophic scarring

Key inclusion criteria

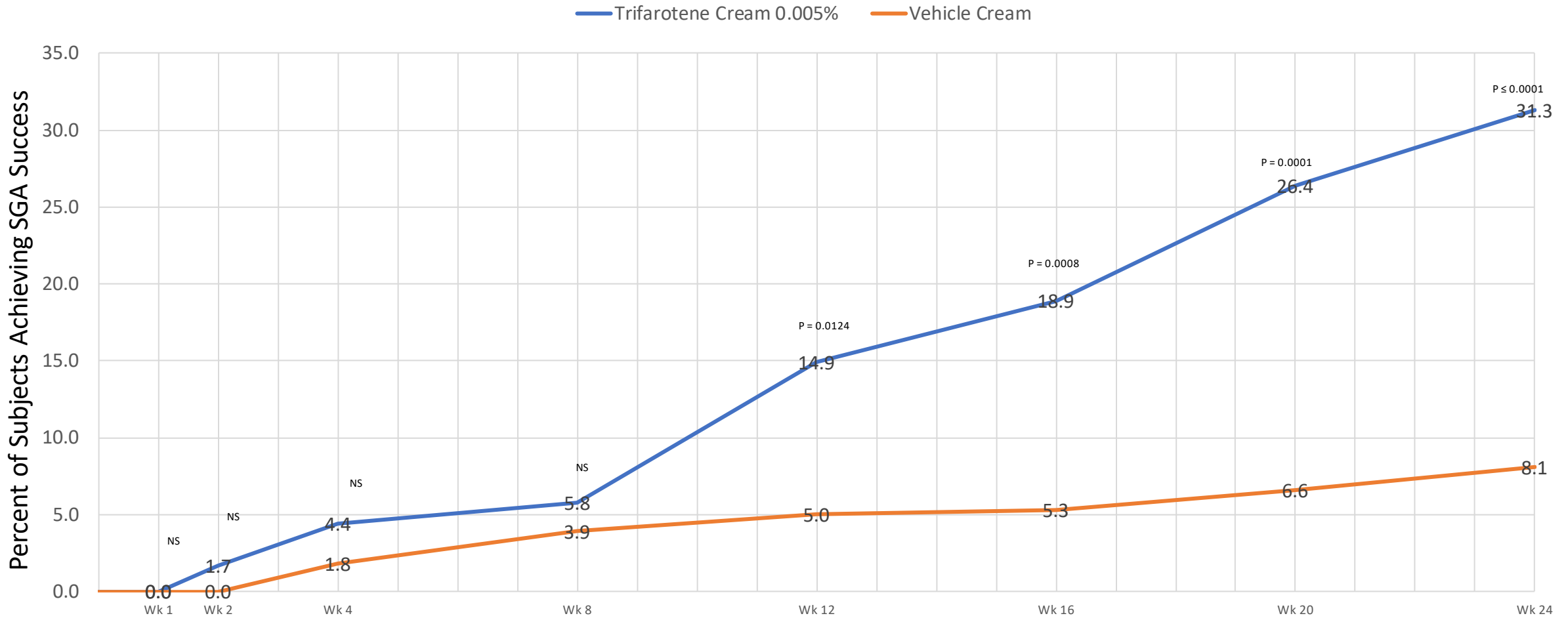
- Aged 17–35 years
- Clinical diagnosis of acne vulgaris defined by:
 - IGA score of 3 or 4 with same score on both sides of the face
 - ≥ 20 inflammatory lesions with ≥ 10 on each side
 - ≤ 2 nodules (≥ 1 cm in diameter)
 - ≥ 10 atrophic acne scars in total (> 2 mm)
- Symmetrical number of inflammatory and non-inflammatory lesions and atrophic acne scars (min 4 per half-face)



Absolute Change in Total Atrophic Acne Scar Count



Investigator Scar Global Assessment of Acne Scars

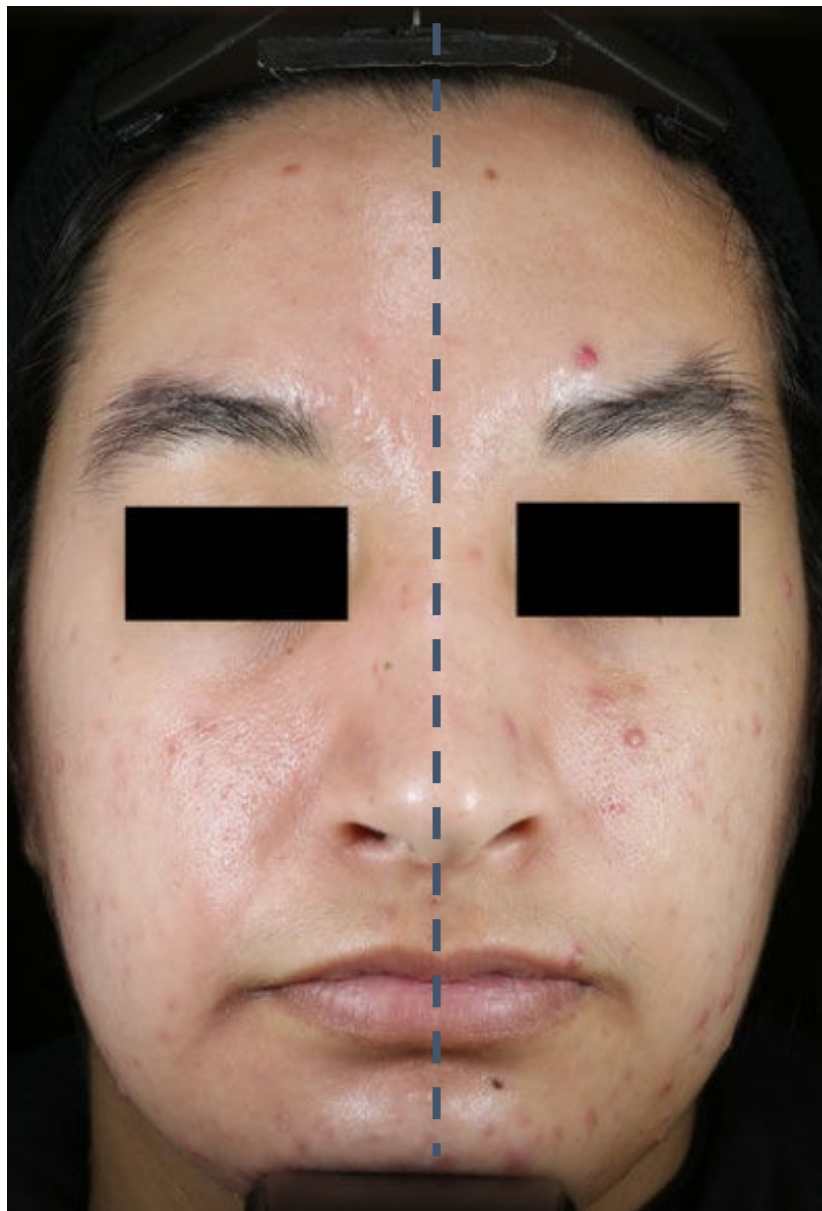


Missing data managed by imputing missing data using multiple imputation under the assumption of missing at random (ITT population)
Subjects are plotted according to the treatments their face halves were randomized to Investigator Scar Global Assessment
Success is defined as an SGA score of 1 - Almost Clear or 0 - Clear and at least a 2-grade improvement from Baseline
Baseline is defined as the last non-missing measurement prior to the first treatment
Proportions are based on the number of subjects in the ITT Population with data available at each visit
Galderma Data on File. RD.06.SPR.202395

Baseline



Week 12



Week 24



Baseline



Week 12



Week 24



Baseline



Week 12



Week 24

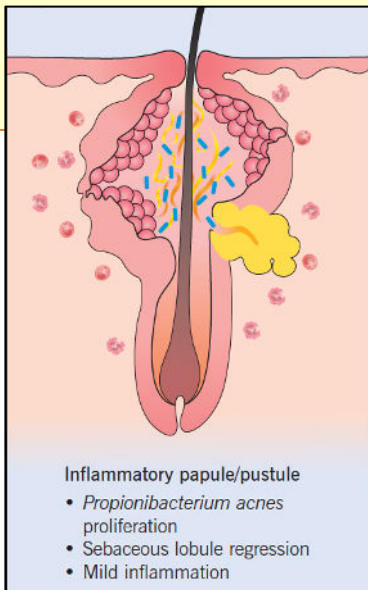


Why do we use oral antibiotics in acne?

1. Bacterial pathogenesis

Interaction of four main pathogenic factors

- Follicular hyperkeratinization
- Increased sebum production
- ***Cutibacterium acnes* (C. acnes)** an anaerobic G+ that is a normal component of skin flora
- Inflammation



2. AAD Acne Guidelines



1st-Line Treatment
Topical Combination Therapy*
BP + Antibiotic
or Retinoid + BP
or Retinoid + BP + Antibiotic
-or-
Oral Antibiotic + Topical Retinoid + BP
-or-
Oral Antibiotic + Topical Retinoid + BP + Topical Antibiotic

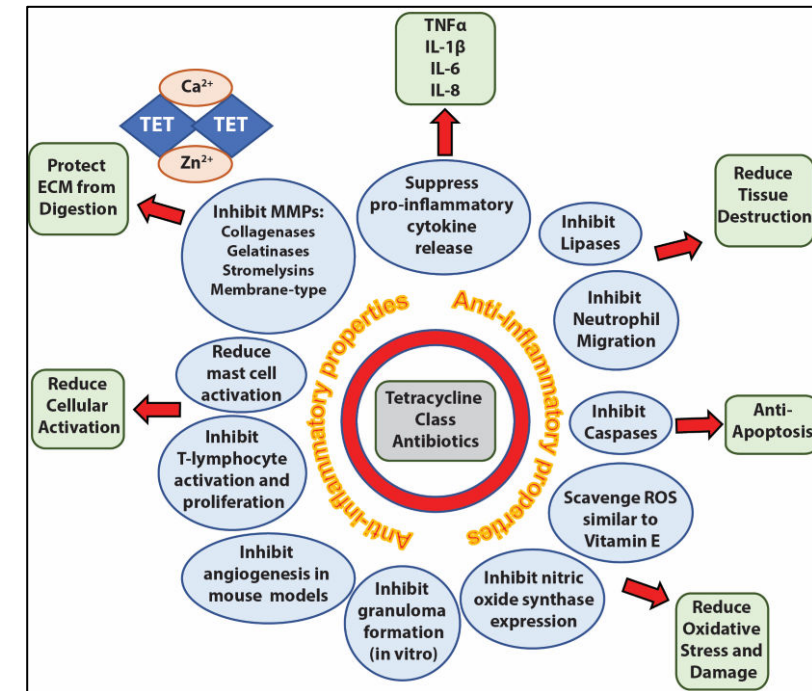
Alternative Treatment
Consider Alternate Combination Therapy
-or-
Consider Change in **Oral Antibiotic**
-or-
Add Combined Oral Contraceptive or Oral Spironolactone (Females)
-or-
Consider Oral Isotretinoin



1st-Line Treatment
Oral Antibiotic + Topical Combination Therapy*
BP + Antibiotic
or Retinoid + BP
-or-
Retinoid + BP + Antibiotic
-or-
Oral Isotretinoin

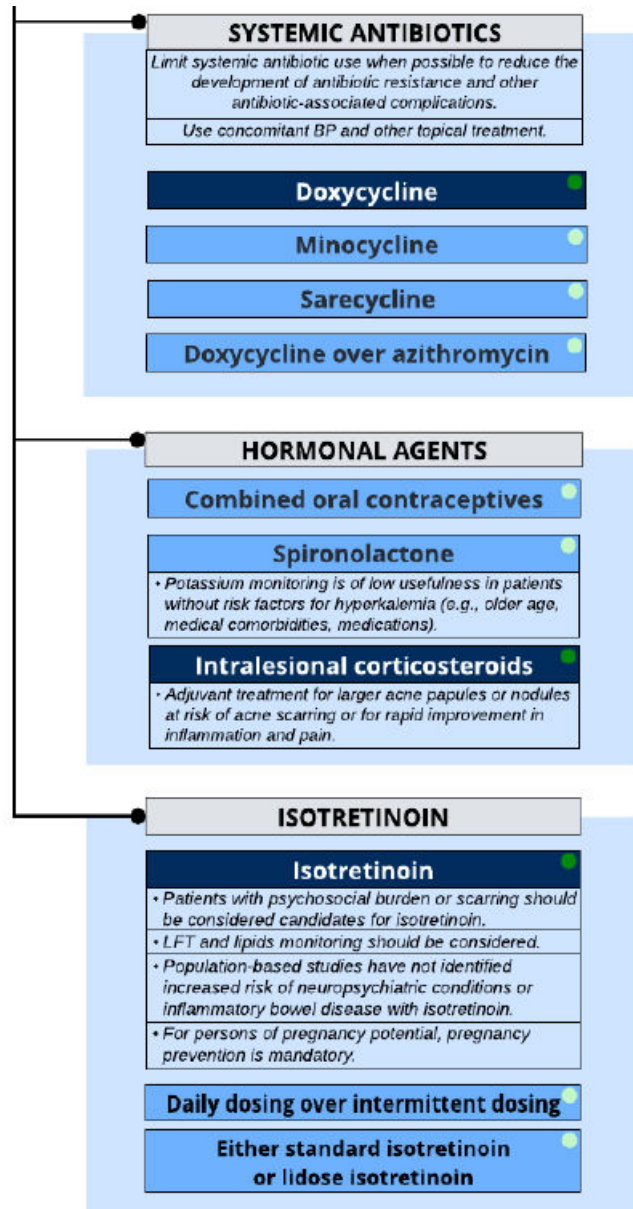
Alternative Treatment
Consider Change in **Oral Antibiotic**
-or-
Add Combined Oral Contraceptive or Oral Spironolactone (Females)
-or-
Consider Oral Isotretinoin

3. Anti-inflammatory



Grada et al. Antibiotics. 2022 May 27;11(6):722.

Pending Update to AAD Acne Guidelines: Oral Therapy

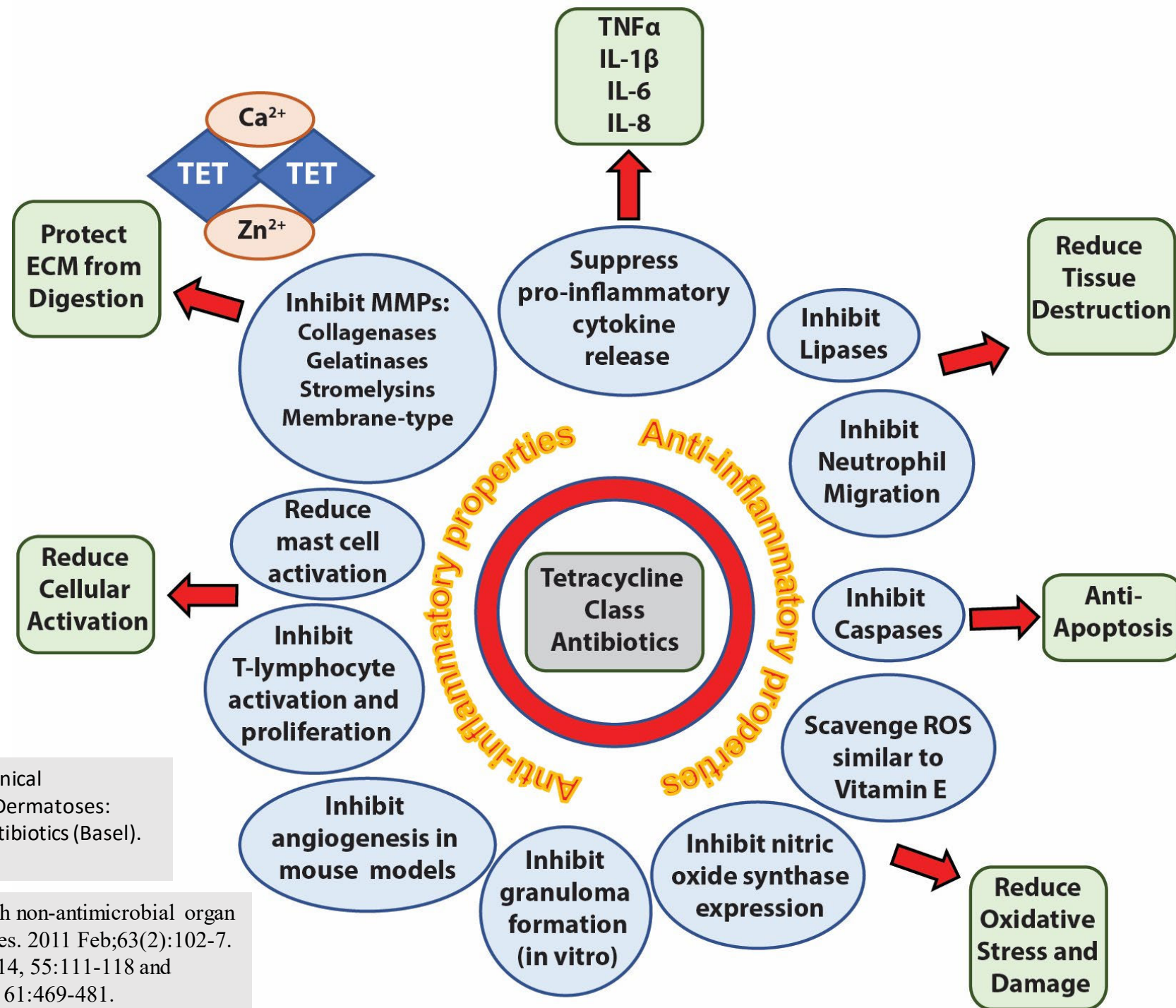


Oral Antibiotic Use 2014-2016

Tetracyclines	73.4%
Doxycycline	36.7%
Minocycline	36.5%
Tetracycline	0.2%
Penicillins	11.4%
Amoxicillin	
Cephalexin	
Macrolides	4.1%
Azithromycin	
Erythromycin	
Others	10.9%
Clindamycin	
Trimethoprim	
Trimethoprim-sulfamethoxazole	

Grada A, Armstrong A, **Bunick C**, Salem R, Feldman S. Trends in Oral Antibiotic Use for Acne Treatment: A Retrospective, Population-Based Study in the United States, 2014 to 2016. J Drugs Dermatol. 2023 Mar 1;22(3):265-270.

Anti-inflammatory properties of tetracycline-class antibiotics



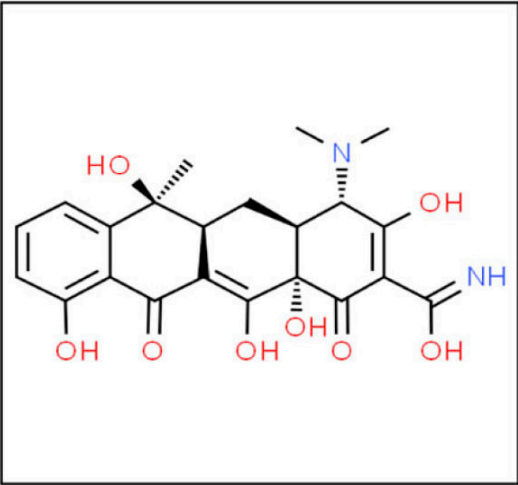
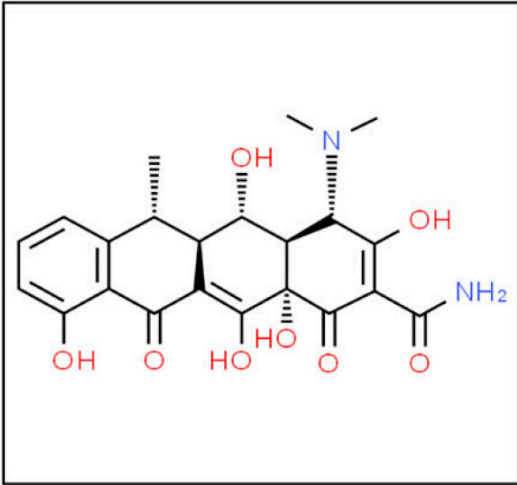
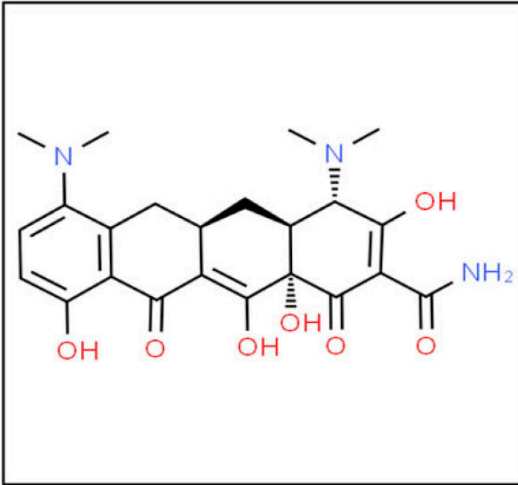
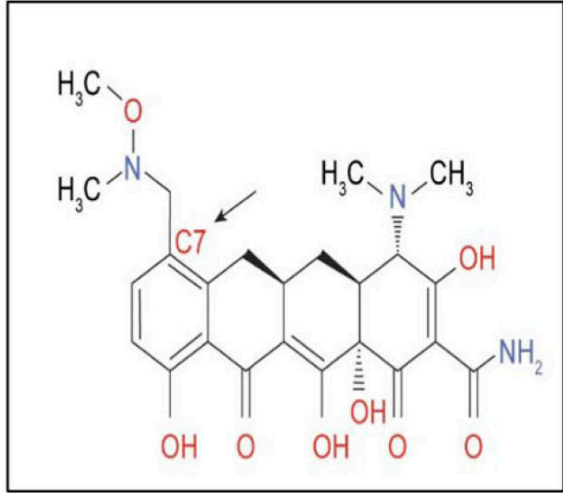
Grada A, Ghannoum MA, **Bunick CG**. Sarecycline Demonstrates Clinical Effectiveness against Staphylococcal Infections and Inflammatory Dermatoses: Evidence for Improving Antibiotic Stewardship in Dermatology. *Antibiotics* (Basel). 2022 May 27;11(6):722.

Griffin MO, Ceballos G, Villarreal FJ. Tetracycline compounds with non-antimicrobial organ protective properties: possible mechanisms of action. *Pharmacol Res*. 2011 Feb;63(2):102-7. Adapted from: Perret LJ, Tait CP, *The Australasian J Dermatol* 2014, 55:111-118 and Pradhan S, Madke B, Kabra P, Singh AL, *Indian J Dermatol* 2016, 61:469-481.

Pending Update to AAD Acne Guidelines: Oral Therapy

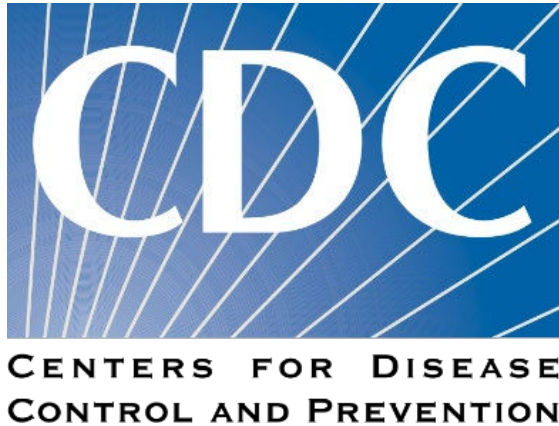
Broad Spectrum

Narrow Spectrum

First Generation	Second Generation		Third Generation
Tetracycline	Doxycycline	Minocycline	Sarecycline
FDA-approved 1953	FDA-approved 1967	FDA-approved 1971	FDA-approved 2018
			

Longest and largest C7 moiety gives Sarecycline unique properties

Antibiotic Stewardship



"and facilitate use of narrow-spectrum antibiotics whenever possible" – CDC

Source: [Antibiotic Stewardship Statement for Antibiotic Guidelines – Recommendations of the HICPAC](#)

"Core principles of antibiotic stewardship include **selecting narrow-spectrum agents when feasible**, using antibiotics only when necessary, and prescribing antibiotics for the shortest effective duration,"

Source: <https://www.cidrap.umn.edu/news-perspective/2020/04/stewardship-resistance-scan-apr-09-2020>

Due to concerns regarding antimicrobial resistance, the Centers for Disease Control and Prevention (CDC) has **stressed antibiotic stewardship**. This is an initiative to promote the appropriate use of antibiotics where patients receive the **right dose** of the **right antibiotic** at the **right time** for the **right duration**

Source: Zaenglein AL, Pathy AL, Schlosser BJ, Alikhan A, Baldwin HE, Berson DS, Bowe WP, Graber EM, Harper JC, Kang S, Keri JE. [Guidelines of care for the management of acne vulgaris](#). Journal of the American Academy of Dermatology. 2016 May 1;74(5):945-73.



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DERMATOLOGY | ASSOCIATION

Antimicrobial Resistance in *C. acnes*

Percentages of antibiotic-resistant *C. acnes* isolated from acne patients

Country	Clindamycin	Erythromycin	Oxytetracycline	Doxycycline
United States (1983)	79	81	63	57

Dreno B, Thiboutot D, Gollnick H, Bettoli V, Kang S, Leyden JJ, Shalita A, Torres V. [Antibiotic stewardship in dermatology: limiting antibiotic use in acne](#). European Journal of Dermatology. 2014 May 1;24(3):330-4.

Antibiotic	Concentration (µg)	Sensitive n(%)	Resistant n(%)
Doxycycline	30	63 (63)	37 (37)
Tetracycline	30	64 (64)	36 (36)
Erythromycin	15	27 (27)	73 (73)
Clindamycin	2	41 (41)	59 (59)
Trimethoprim/Sulfamethoxazole	12/5/23.75	69 (69)	31 (31)
Levofloxacin	5	85 (85)	15 (15)
Minocycline	30	97 (97)	3 (3)

Alkhawaja E, Hammadi S, Abdelmalek M, Mahasneh N, Alkhawaja B, Abdelmalek SM. Antibiotic resistant Cutibacterium acnes among acne patients in **Jordan**: a cross sectional study. BMC dermatology. 2020 Dec;20(1):1-9.

Antibiotic	Resistant n(%)
Doxycycline	19.4
Tetracycline	8.3
Erythromycin	25
Clindamycin	16.7
Minocycline	11.1

Sheffer-Levi S, Rimon A, Lerer V, Shlomov T, Copenhagen-Glazer S, Rakov C, Zeiter T, Nir-Paz R, Hazan R, Molcho-Pessach V. Antibiotic Susceptibility of Cutibacterium acnes Strains Isolated from **Israeli** Acne Patients. Acta Dermato-venereologica. 2020 Oct 20;100(17):adv00295-.

Protecting the host microbiome

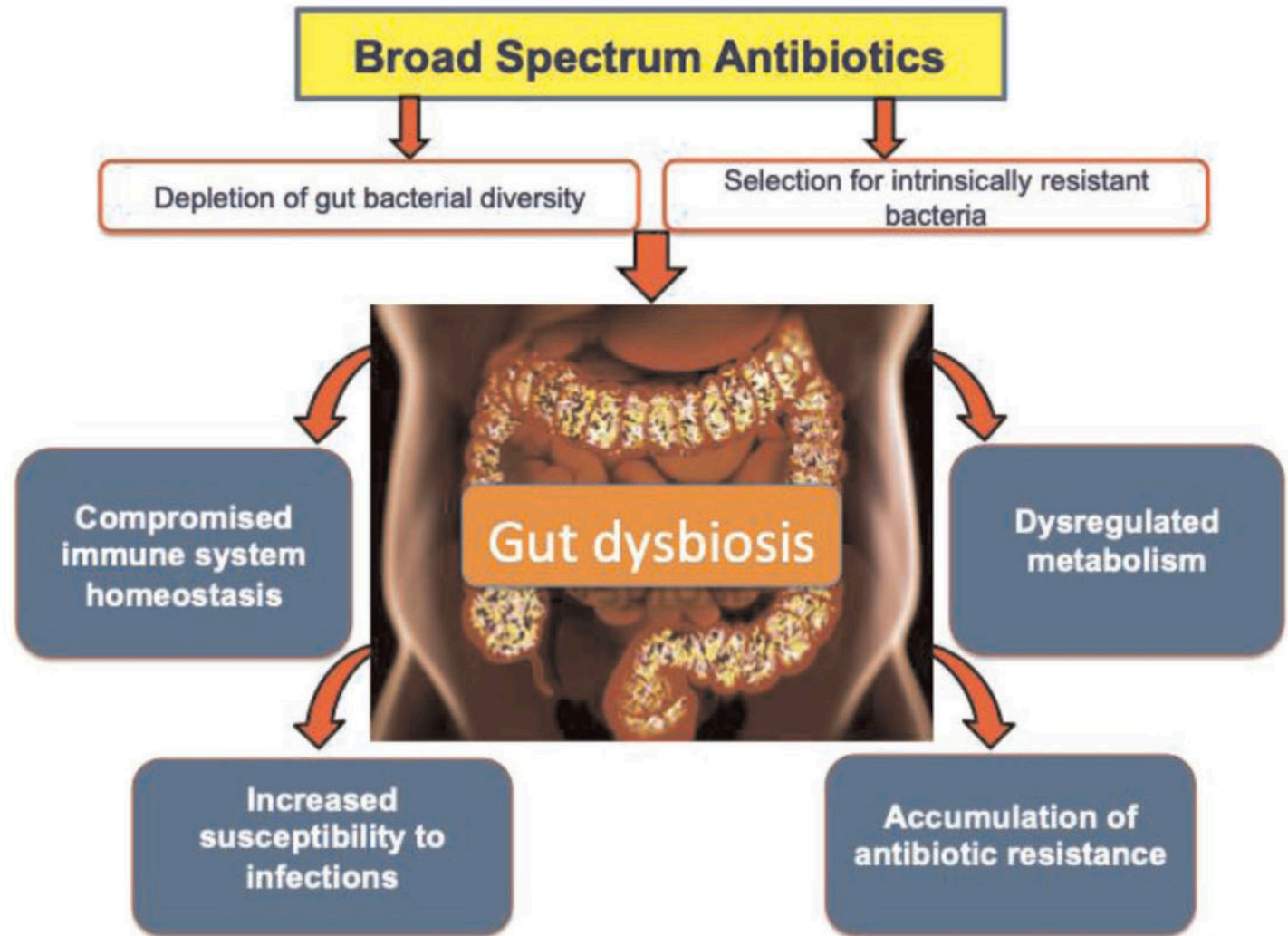
Narrow-spectrum Sarecycline protects the patient's gut microbiome

- Use of broad-spectrum antibiotics may cause depletion of gut bacterial diversity and selection for intrinsically resistant bacteria
- These changes are referred to as gut dysbiosis

Of the 100 trillion microbes that exist in our bodies, about **80% live in the gut**

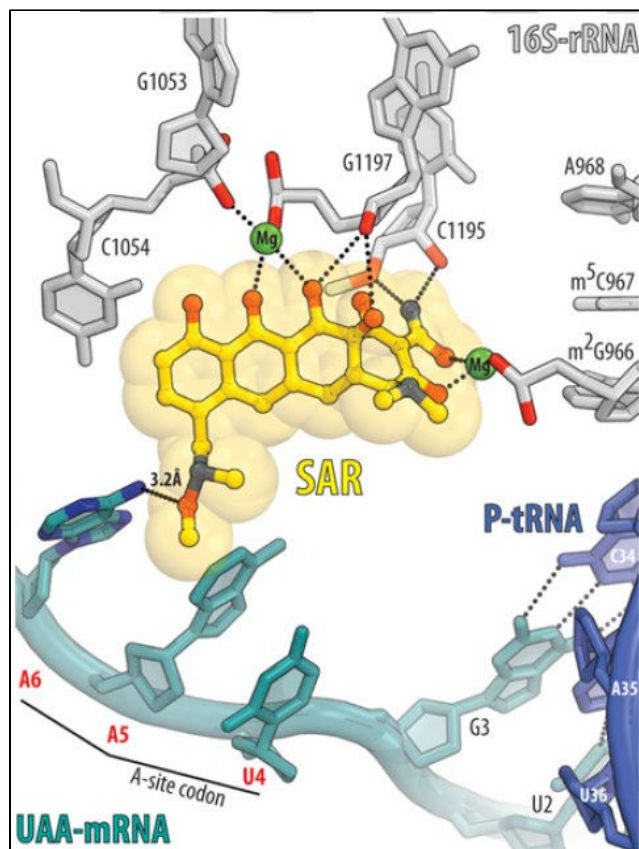
The gut microbiome is essential in the development/regulation of:

- ✓ Immunity, Nutrition, Digestion, Hormone secretion, Inflammation



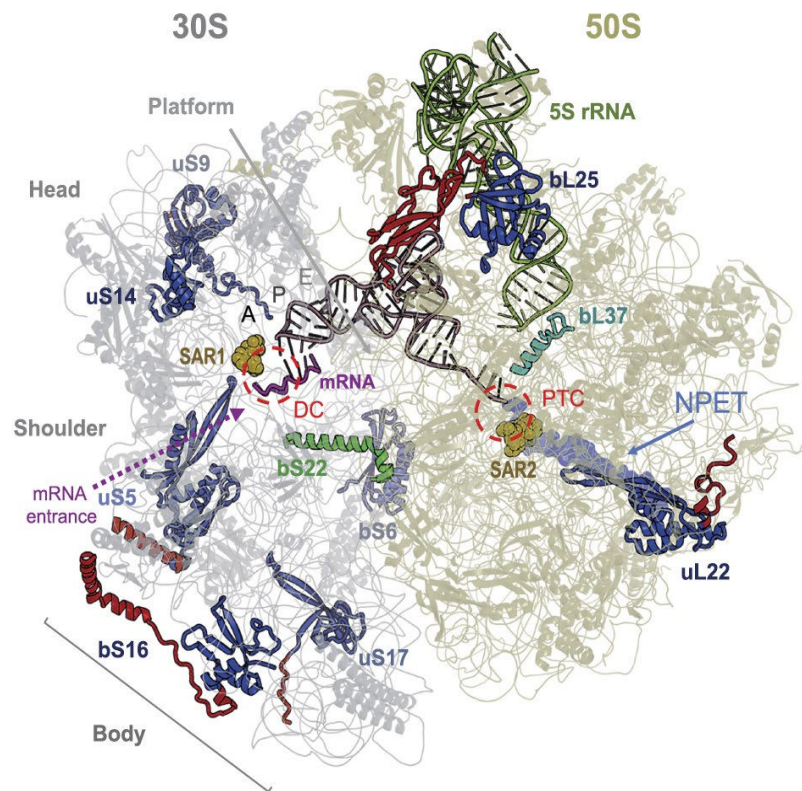
Narrow spectrum Sarecycline is molecularly distinct from Doxy and Mino

Sarecycline uniquely contacts mRNA in ribosome



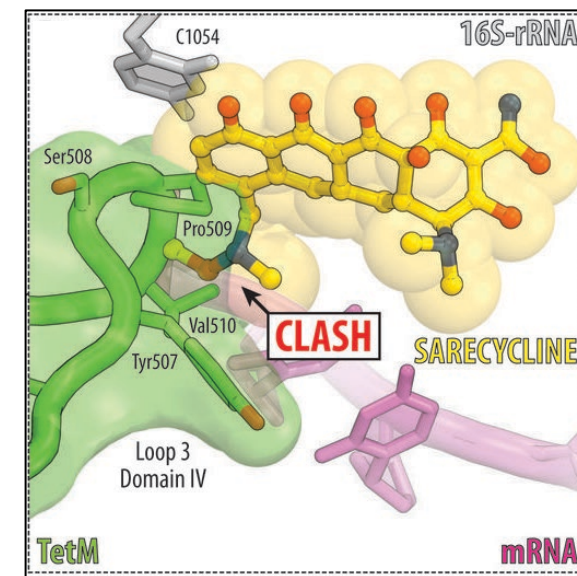
Batool Z, Lomakin IB, Polikanov YS, Bunick CG. Sarecycline interferes with tRNA accommodation and tethers mRNA to the 70S ribosome. *Proceedings of the National Academy of Sciences*. 2020 Aug 25;117(34):20530-7.

Sarecycline has novel 50S subunit exit tunnel binding site



Lomakin IB, Devarkar SC, Patel S, Grada A, Bunick CG. Sarecycline inhibits protein translation in *Cutibacterium acnes* 70S ribosome using a two-site mechanism. *Nucleic Acids Res*. 2023 Apr 11;51(6):2915-2930.

Sarecycline resists ribosomal protection proteins



P. acnes strains displayed a **low propensity for the development of resistance** to sarecycline, with spontaneous mutation frequencies being 10^{-10} at $4 - 8 \times \text{MIC}$

Acne accounts for an almost 2.5-fold higher proportion of dermatology visits among adult females compared to adult males in the United States: A study of the national ambulatory medical care survey from 2002–2016

Jungsoo Chang, Michael R. Nock, Jeffrey M. Cohen, Christopher G. Bunick

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Age groups	Total Dermatology Visits by Females	Diagnosis of Acne in Females	%	Total Dermatology Visits by Males	Diagnosis of Acne in Males	%	P value*
13–19	22,313,895	13,918,161	62.37	19,334,773	13,473,081	69.68	
20–29	24,561,556	10,899,975	44.38	13,942,660	3,637,344	26.09	<0.001
30–39	33,215,926	7,607,845	22.90	16,471,046	1,977,692	12.01	<0.001
40–49	39,504,477	4,890,284	12.38	22,461,687	1,128,227	5.02	<0.001
>50	163,191,246	2,875,150	1.76	145,500,032	1,306,024	0.90	<0.001
Total	282,877,917	40,191,415	14.21	217,710,198	21,522,368	9.88	<0.001

* Prevalence of dermatology visits related to acne were compared between males and females using χ^2 tests.

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