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Management of Truncal Acne With Oral Sarecycline: Pooled Results from Two Phase-3 Clinical Trials

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ABSTRACT

Background: Acne vulgaris is a common skin disease that affects the face, chest, and back. While truncal acne is present in at least 50% of patients, clinical studies have focused predominantly on facial acne.[1,2] Few treatments to date have been evaluated for truncal acne. Sarecycline is a narrow-spectrum, third-generation, tetracycline-class oral drug approved for the treatment of acne. Pivotal phase-3 studies show that sarecycline is safe, well-tolerated, and effective treatment for moderate to severe acne vulgaris.

Method: Pooled analysis was performed for truncal acne results with sarecycline from the two phase 3 studies. Investigator Global Assessment (IGA) success was evaluated at weeks 3, 6, 9, and 12.

Results: Chest IGA success rate were significantly greater with sarecycline versus placebo at weeks 3 (11.84% vs 7.71%, respectively; P=0.0192), 6 (18.81% vs 14.03%, respectively; P=0.0390), and 12 (33.42% vs 20.77%, respectively; P<0.0001). Back IGA success rate was also significantly greater with sarecycline versus placebo group at weeks 3 (12.13% vs 7.04%, respectively; P=0.0023), 6 (18.42% vs 14.34%, respectively; P=0.0412), 9 (29.05% vs 19.88%, respectively; P=0.0004) and 12 (33.07% vs 21.91%, respectively; P<0.0001).

Conclusion: Sarecycline efficacy for truncal acne was observed within 3 weeks after treatment, supporting sarecycline as an optimal choice for oral treatment of moderate to severe truncal acne.

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INTRODUCTION

Acne vulgaris is a chronic inflammatory disease that commonly affects the face, chest, and back. It is the most common inflammatory skin disease treated in ambulatory dermatology practice. Oral treatment for acne includes oral antibiotics, with second-generation broad-spectrum tetracyclines (doxycycline, minocycline) frequently prescribed by dermatologists for moderate to severe acne.1-4 Given that acne may result in permanent scarring and can lead to negative psychosocial impacts, including low self-esteem and emotional distress, suitable treatment options very important in clinical practice.[1,5-8]

Truncal acne, which affects the chest, back, and/or shoulders, has been shown to affect at least 50% of patients with acne, with 70% of patients desiring treatment even if they did not voluntarily report their truncal acne.[1,2,9] Despite its prevalence, truncal acne does not have specific treatment guidelines and is often managed based on data used to support the treatment of facial acne. Given that outcomes from clinical studies on facial acne may not accurately reflect efficacy in truncal acne, studies in truncal acne are vital to providing suitable recommendations for management.

Current approaches for mild to moderate truncal acne include topical therapies such as topical retinoids alone or with benzoyl peroxide (BP) and/or topical antibiotics, azelaic acid, and dapsone.[9] Oral antibiotics have been recommended for use in combination with topical therapies or combined oral

contraceptives (COCs) for moderate to severe acne.[9] Lastly, oral isotretinoin is optimal treatment when truncal acne is severe and refractory to other therapies and associated with marked scarring.[9]

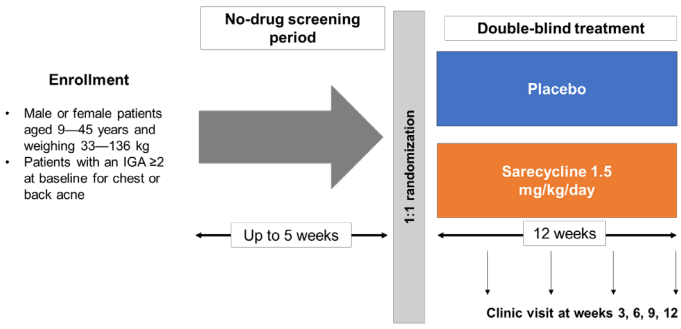
Sarecycline is a narrow-spectrum, 3rd generation, oral tetracycline-class antibiotic and the first new FDA-approved antibiotic specifically developed for acne treatment in approximately 5 decades.[10] Unlike other tetracyclines, sarecycline has a stable modification at the C7 hydrocarbon ring position that allows for direct interaction with the A site codon on messenger RNA (mRNA).[11,12] Structural modifications unique to sarecycline support its designation as a narrow-spectrum antibiotic, exhibiting high activity against *Cutibacterium acnes*, staphylococci, and streptococci, coupled with negligible activity against Gram-negative bacteria and several anaerobic organisms.[11-13] In addition to antibiotic activity, sarecycline has shown additional characteristics relevant to acne treatment, including anti-inflammatory properties.[13] Pivotal phase-3 studies demonstrate that sarecycline is safe, well-tolerated, and effective for moderate to severe facial acne, with low rates of adverse events (AEs) that are commonly associated with broad-spectrum tetracyclines, including "pill esophagitis"/abdominal pain, phototoxicity, vertigo, vaginal candidiasis, and hyperpigmentation.[14] Within these phase 3 studies, efficacy for truncal acne was captured in affected subjects based on IGA assessments. This article reports the efficacy of weight-based dosing of sarecycline (1.5 mg/kg/day) administered once daily for 12 weeks in this patient population.

MATERIALS AND METHODS

Study Design

Two identically designed, randomized, double-blind, placebo-controlled, parallel-group, phase 3 studies in patients 9 years of age and older were conducted in the United States at multiple study centers.[10,14] Each study included a 35-day screening period followed by a 12-week treatment period (Figure 1). During the treatment period, patients were randomized 1:1 to receive daily oral doses of either 1.5 mg/kg sarecycline tablets or placebo tablets. Patients returned to the clinic following 3, 6, 9, and 12 weeks of treatment to determine Investigator's Global Assessment (IGA) scores. IGA scores for chest and back were reported as exploratory efficacy endpoints in both phase 3 studies. In the current analysis, pooled treatment efficacy was evaluated in truncal acne based on IGA scores of the chest and back following 3, 6, 9, and 12 weeks of treatment.

FIGURE 1. Design for two pivotal studies (SC1401, SC1402). Subjects with an IGA score of at least 1 at baseline for chest or back acne were analyzed for their respective population. IGA, Investigator's Global Assessment.



Enrollment Criteria

Eligibility criteria for the intent-to-treat (ITT) population in the phase 3 studies included patients who were 9 to 45 years, weighed between 33–136 kg, and had facial acne vulgaris with 20–50 inflammatory lesions (papules, pustules, and nodules), up to 100 non-inflammatory lesions (open and closed comedones), no more than 2 nodules, and an IGA score of moderate (IGA 3) or severe (IGA 4) at baseline.14 In the current analysis, patients who met the eligibility criteria in the pivotal phase 3 studies and with an IGA score ≥2 at baseline for chest or back acne were pooled and analyzed for study outcomes. Lesion count assessments were not used to evaluate therapeutic outcomes with truncal acne in these pivotal trials as evaluation of facial acne response was the primary objective.[14]

Patients were excluded from the phase 3 studies if they had any dermatological condition of the face that could interfere with clinical evaluations, any chronic illness interfering with study evaluations, allergy/hypersensitivity or resistance to tetracyclines, or drug-induced acne; designated washout periods were mandated for topical acne therapies, hormonal contraceptive use, systemic retinoids, systemic corticosteroids, androgens, or anti-androgens.[14]

Endpoints

Percentage of patients with IGA success, defined as ≥2-point decrease (improvement) in IGA score from baseline (IGA score ≥2) and a score of clear/almost clear, was evaluated for both the chest and back.[14]

Statistical Analyses

The treatment difference between sarecycline and placebo in the proportion of patients who achieved IGA success was analyzed using the Cochran-Mantel-Haenszel (CMH) test with integrated data from SC1401 and SC1402.[14] Pooled analysis for both studies were considered statistically significant if $P<0.05$ and when the corresponding analysis for both individual studies also achieved statistical significance.

RESULTS

Patient Demographics and Baseline Characteristics (Truncal Acne Population)

Of 2002 total patients, 839 patients with chest acne and 1134

TABLE 1.

Demographics and Baseline Characteristics of Study Subjects				
Characteristic	Chest		Back	
	Placebo (N = 421)	Sarecycline (N = 418)	Placebo (N = 561)	Sarecycline (N = 573)
Age, years, mean (range)	19.1 (10, 45)	19.5 (11, 44)	18.9 (10, 45)	19.2 (11, 43)
Sex – male, n (%)	214 (50.8)	182 (43.5)	273 (48.7)	262 (45.7)
Race, n (%)	421 (100)	417 (100)	561 (100)	572 (100)
White	350 (83.1)	338 (81.1)	456 (81.3)	474 (82.9)
Black	43 (10.2)	51 (12.2)	58 (10.3)	60 (10.5)
Other	28 (6.7)	29 (6.9)	47 (8.3)	38 (6.6)
Inflammatory lesion counts, mean (95% CI)	2.4 (2.4, 2.5)	2.4 (2.3, 2.4)	2.6 (2.5, 2.6)	2.5 (2.5, 2.6)
Noninflammatory lesion counts, mean (95% CI)	47.5 (45.4, 49.6)	44.4 (42.4, 46.4)	46.7 (44.9, 48.5)	43.1 (41.4, 44.8)
IGA score for face, n (%)	421 (100)	418 (100)	561 (100)	573 (100)
3	329 (78.2)	250 (83.7)	454 (80.9)	486 (84.8)
4	92 (21.9)	68 (16.3)	107 (19.1)	8 (15.2)
IGA score for chest or back, respectively, n (%)	214 (100)	418 (100)	561 (100)	573 (100)
2	272 (64.6)	281 (67.2)	296 (52.8)	318 (55.5)
3	127 (30.2)	123 (29.4)	217 (38.7)	225 (39.3)
4	22 (5.2)	14 (3.4)	48 (8.6)	30 (5.2)

patients with back acne were pooled and analyzed from both phase 3 studies. In the chest acne group, 421 patients received placebo and 418 patients received sarecycline. In the back-acne group, 561 patients received placebo and 573 patients received sarecycline. Demographic variables and baseline disease characteristics were similar across treatment groups for both chest and back populations (Table 1). Most patients in both chest and back populations had an IGA score of 2 (53–67%).

Pooled IGA Success in Chest Acne

In the individual studies, IGA success rate was significantly greater in the sarecycline group compared to the placebo group at weeks 6 (21.5% vs 14.6%, respectively; *P*=0.020) and 12 (29.6% vs 19.6%, respectively; *P*=0.006) for study SC1401 and at week 12 (21.6% vs 36.6%, respectively; *P*<0.001) for study SC1402 (Figure 2A-B). Pooled IGA success rate was significantly greater in the sarecycline group than in the placebo group at week 3 (11.84%

TABLE 2.

Pooled IGA Success in Chest Acne. Percentage of subjects ≥2 point decrease from baseline (IGA chest score ≥2). Data presented are n (%), unless otherwise stated.			
	Placebo (N = 421)	Sarecycline (N = 418)	Difference (Sarecycline – Placebo) (95% CI) *P*-value
Week 12			
Total	366 (100.00)	374 (100.00)	14.07 (8.62,19.52)
Successful Outcome	76 (20.77)	125 (33.42)	<0.0001
Week 9			
Total	376 (100.00)	367 (100.00)	5.36 (0.14,10.58)
Successful Outcome	76 (20.21)	92 (25.07)	0.0759
Week 6			
Total	392 (100.00)	388 (100.00)	5.43 (0.87,9.99)
Successful Outcome	55 (14.03)	73 (18.81)	0.0390
Week 3			
Total	415 (100.00)	414 (100.00)	4.84 (1.30,8.38)
Successful Outcome	32 (7.71)	49 (11.84)	0.0192

FIGURE 2. Percentage of subjects with IGA success (chest). IGA success in (A) SC1401 (B) SC1402 and (C) pooled SC1401 and SC1402. IGA success was defined as a ≥2-point decrease (improvement) in chest IGA score from baseline (IGA chest score ≥2) and a score of clear/almost clear. IGA, Investigator's Global Assessment. *P<0.05.

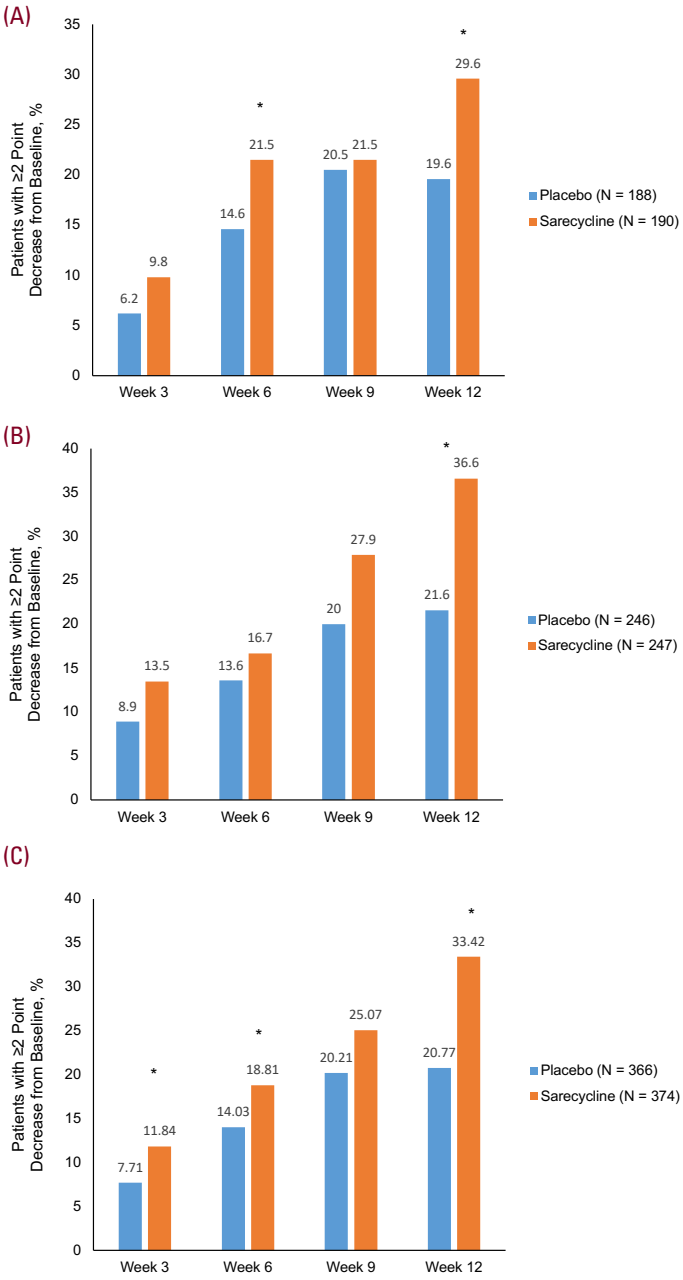
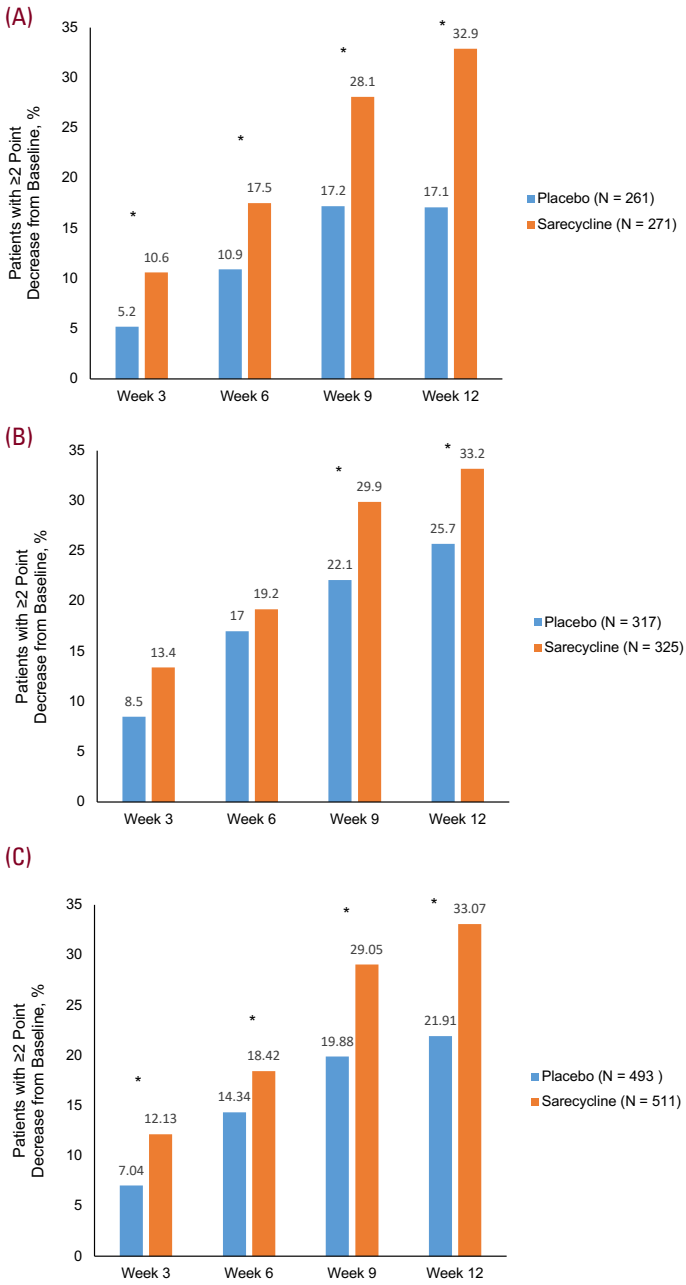


FIGURE 3. Percentage of subjects with IGA success (back). IGA success in (A) SC1401 (B) SC1402 and (C) pooled SC1401 and SC1402. IGA success was defined as a ≥2-point decrease (improvement) in back IGA score from baseline (IGA back score ≥2) and a score of clear/almost clear. IGA, Investigator's Global Assessment. *P<0.05.



vs 7.71%, respectively; P=0.0192), week 6 (18.81% vs 14.03%, respectively; P=0.0390), and week 12 (33.42% vs 20.77%, respectively; P<0.0001) for chest acne (Table 2; Figure 2C). IGA success at week 9 was numerically higher, but not significantly different in the sarecycline group compared to the placebo group (25.07% vs 20.21%, respectively; P=0.0759).

Pooled IGA Success in Back Acne

In the individual studies, IGA success rate was significantly greater in the sarecycline group compared to the placebo group at weeks 3 (10.6% vs 5.2%, respectively; P=0.011), 6 (17.5% vs 10.9%, respectively; P=0.046), 9 (28.1% vs 17.2%, respectively; P=0.006) and 12 (32.9% vs 17.1%, respectively; P<0.001) for

TABLE 3.

Pooled IGA Success in Back Acne. Percentage of subjects ≥2 point decrease from baseline (IGA back score ≥2). Data presented are n (%), unless otherwise stated.

	Placebo N = 561	Sarecycline N = 573	Difference (Sarecycline – Placebo) (95% CI) *P*-value
Week 12			
Total	493 (100.00)	511 (100.00)	11.41 (6.41,16.40)
Successful Outcome	108 (21.91)	169 (33.07)	<0.0001
Week 9			
Total	503 (100.00)	506 (100.00)	9.62 (4.75,14.49)
Successful Outcome	100 (19.88)	147 (29.05)	0.0004
Week 6			
Total	523 (100.00)	532 (100.00)	4.58 (0.48,8.68)
Successful Outcome	75 (14.34)	98 (18.42)	0.0412
Week 3			
Total	554 (100.00)	569 (100.00)	5.29 (2.17,8.41)
Successful Outcome	39 (7.04)	69 (12.13)	0.0023

SC1401 and at weeks 9 (29.9% vs 22.1%, respectively; *P*=0.019) and 12 (33.2% vs 25.7%, respectively; *P*=0.024) for SC1402 (Figure 3A-B). IGA success rate was significantly greater in the sarecycline group than in the placebo group at weeks 3 (12.13% vs. 7.04%, respectively; *P*=0.0023), 6 (18.42% vs 14.34%, respectively; *P*=0.0412), 9 (29.05% vs 19.88%, respectively; *P*=0.0004) and 12 (33.07% vs 21.91%, respectively; *P*<0.0001) for back acne (Table 3; Figure 3C).

Pooled Safety

The safety data of these studies have previously been reported.[14] In brief, sarecycline was well tolerated with no serious AEs related or possibly related to study treatment and no deaths were reported.[14]

DISCUSSION

To date, there is a conspicuous absence of scientific data based on well-designed and controlled studies when it comes to the management of truncal acne. Current systemic treatment options are based on recommendations for facial acne, and very little is known about truncal acne regarding the effectiveness and optimal use of various treatment options.[1,2,9] In addition, using clinical studies on facial acne to provide recommendations for truncal acne can be problematic. For example, available data suggest that using benzoyl peroxide as a cleanser/wash or in low-to-moderate concentrations as a short-contact therapy are not effective in reducing *C. acnes* on the trunk, unlike results associated with BP use on the face.[15]

With the exception of trifarotene cream, most clinical trials evaluate the use of topical therapies for truncal acne and are small in size.[9,16,17,18] Dapsone 7.5% gel was evaluated in a 16-week, open-label pilot study and improved IGA and lesion counts in moderate to severe truncal acne.[16] In addition, azelaic acid 15% foam has been effective in improving IGA and lesion counts on the trunk in a 16-week, open-label pilot study in moderate truncal acne.[17] Topical trifarotene cream applied once daily was evaluated in 12-week phase 3 studies for both facial and truncal acne and is FDA-approved for acne treatment.[18] Topical trifarotene significantly reduced Physician Global Assessment (PGA) scores reduced both inflammatory and noninflammatory lesions in truncal acne.[18] Importantly, unlike facial acne, truncal acne often affects a large body surface area, which can create difficulty with applying a topical treatment consistently in some patients; oral therapy is often utilized for management of truncal acne due to ease of use and the perception of clinicians that oral therapy is often needed to obtain efficacy, especially for moderate-to-severe acne.[1,9,19] Thus, oral antibiotics, isotretinoin, or spironolactone with or without COCs (in women) remain preferred treatment options, with treatment selection based on patient-specific factors; with an oral antibiotic such as sarecycline, or with spironolactone, combination treatment with topical therapy is often a rational approach.[2,9]

Current broad-spectrum oral antibiotics prescribed for moderate to severe acne may be limited by side effects and bacterial resistance to antibiotics.[3,4] By contrast, narrow-spectrum antibiotics, including sarecycline, exhibit less antibiotic selection pressure and have shown a low propensity to induce bacterial resistance.[10] While further studies are needed to further confirm the minimal impact of sarecycline on the microbiome, the use of broad-spectrum tetracycline-class drugs such as doxycycline

and minocycline have been associated with bacterial dysbiosis with alterations in both the gut and the skin.[20-23] In addition, some reports suggest a potential association between inflammatory bowel disease (IBD) and broad-spectrum antibiotics.[23-25]

Sarecycline is a narrow-spectrum tetracycline-class antibiotic; its narrow-spectrum is defined as negligible antibiotic activity against many Gram-negative and anaerobic bacteria, while retaining high activity against *C. acnes* and clinically relevant Gram-positive organisms such as streptococci and *Staphylococcus aureus*, including methicillin-resistant strains.[26] Sarecycline has been shown to more selectively inhibit *C. acnes* and several Gram-positive bacteria with minimal activity against enteric aerobic gram-negative bacteria, such as those commonly found in the gut.[11-13,26] Additionally, sarecycline is active against macrolide erythromycin-resistant *C. acnes*.[26]

Sarecycline has shown reduced potential for antibacterial resistance and is currently the only antibiotic approved for acne with a low bacterial resistance statement supported in FDA-approved prescribing information.[10,26] Available microbiologic data supports that sarecycline has a low propensity to induce bacterial resistance among many specific types of bacteria, including many Gram-negative bacteria and some anaerobes, which differentiates sarecycline from other tetracycline-class antibiotics that exhibit a broader spectrum of antibiotic activity.[26]

To date, sarecycline is the only oral antibiotic formally studied in truncal acne in pivotal trials, although evaluation of truncal acne was not the primary objective of the phase 3 studies. In pivotal phase 3 studies, sarecycline was shown to be effective for moderate to severe facial acne, with low rates of AEs, including GI side effects.[10,14] Analysis of IGA data in subjects with truncal acne enrolled in the phase 3 studies demonstrates the efficacy of sarecycline for acne affecting the chest and/or back, observed as early as 3 weeks after initiation of treatment, with continued improvement over the duration of the study. The narrower spectrum of antibiotic activity compared to other tetracyclines commonly used for acne, favorable safety and tolerability profile, convenience of once-daily administration with or without food, and decreased likelihood of antibiotic resistance based currently available data, collectively support sarecycline as an optimal choice for the oral treatment of moderate to severe acne affecting the face and/or trunk.

DISCLOSURES

James Del Rosso is a consultant and/or speaker (honoraria), and/or research investigator (grants) for Almirall, BioparmX, Bausch Health (Bausch Health), EPI Health, Galderma, JEM Health, LaRoche-Posay, Leo Pharma, Mayne Pharma, Sebacia, SolGel, Sun Pharma, and Vyne Therapeutics (Foamix).

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