

Once-Daily Oral Sarecycline 1.5 mg/kg/day Is Effective for Moderate to Severe Acne Vulgaris: Results from Two Identically Designed, Phase 3, Randomized, Double-Blind Clinical Trials

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ABSTRACT

Background: Side effects may limit the use of current tetracycline-class antibiotics for acne.

Objective: Evaluate the efficacy and safety of once-daily sarecycline, a novel, narrow-spectrum tetracycline-class antibiotic, in moderate to severe acne.

Methods: Patients 9–45 years with moderate to severe facial acne (Investigator's Global Assessment [IGA] score ≥3, 20–50 inflammatory and ≤100 noninflammatory lesions, and ≤2 nodules) were randomized 1:1 to sarecycline 1.5 mg/kg/day or placebo for 12 weeks in identically designed phase 3 studies (SC1401 and SC1402).

Results: In SC1401 (sarecycline n=483, placebo n=485) and SC1402 (sarecycline n=519, placebo n=515), at week 12, IGA success (≥2-grade improvement and score 0 [clear] or 1 [almost clear]) rates were 21.9% and 22.6% (sarecycline), respectively, versus 10.5% and 15.3% (placebo; $P<0.0001$ and $P=0.0038$). Onset of efficacy in inflammatory lesions occurred by the first visit (week 3), with mean percentage reduction in inflammatory lesions at week 12 in SC1401 and SC1402 of −51.8% and −49.9% (sarecycline), respectively, versus −35.1% and −35.4% (placebo; $P<0.0001$). Onset of efficacy for absolute reduction of noninflammatory lesion count occurred at week 6 in SC1401 ($P<0.05$) and week 9 in SC1402 ($P<0.01$). In SC1401, the most common TEAEs (in ≥2% of either sarecycline or

placebo group) were nausea (4.6% [sarecycline]; 2.5% [placebo]), nasopharyngitis (3.1%; 1.7%), headache (2.7%; 2.7%), and vomiting (2.1%; 1.4%) and, in SC1402, nasopharyngitis (2.5%; 2.9%) and headache (2.9%; 4.9%). Most were not considered treatment-related. Vestibular (dizziness, tinnitus, vertigo) and phototoxic (sunburn, photosensitivity) TEAEs both occurred in ≤1% of sarecycline patients. Gastrointestinal TEAE rates for sarecycline were low. Among females, vulvovaginal candidiasis (SC1401: 1.1% [sarecycline] and 0 [placebo]; SC1402: 0.3% and 0) and mycotic infection (0.7% and 0; 1.0% and 0) rates were low.

Conclusion: The narrow-spectrum antibiotic sarecycline was safe, well tolerated, and effective for moderate to severe acne, with low rates of side effects common with tetracycline antibiotics.

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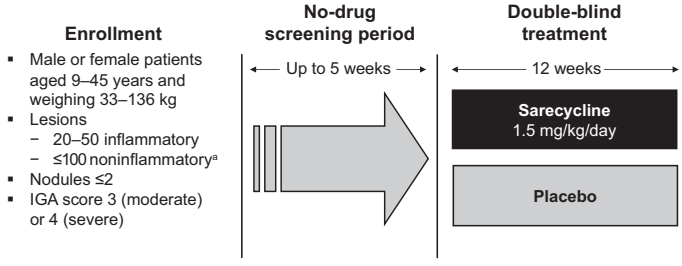
INTRODUCTION

Broad-spectrum tetracycline-class antibiotics, such as minocycline and doxycycline, are considered first-line therapy in the management of moderate to severe acne.[1] In addition to their antimicrobial activity, tetracycline-class antibiotics have anti-inflammatory properties.[2] However, currently available agents may be associated with gastrointestinal (GI) side effects, including nausea, diarrhea, and vomiting; other potential side effects include skin photosensitivity with doxycycline and vestibular events (eg, dizziness, vertigo) with minocycline.[1,3] Additionally, given their broad spectrum of antibacterial activity, oral tetracycline therapies for acne may negatively impact the microbiome, potentially leading to antimicrobial resistance, which may limit the efficacy of tetracycline antibiotics for the treatment of infectious diseases and, more broadly, promote multidrug resistant bacteria.[3-8] These limitations demonstrate a need for tetracycline-class antibiotics for acne with improved safety profiles and a targeted, narrow spectrum of antibacterial activity.[1,3]

Sarecycline is a once-daily, novel, tetracycline-class antibiotic for the treatment of moderate to severe acne. Sarecycline has a narrow antibacterial spectrum with limited activity against enteric gram-negative bacteria compared with minocycline, doxycycline, and tetracycline, which may confer less disruption of the GI microbiome at doses recommended for acne treatment. A 12-week, phase 2, dose-ranging trial demonstrated that sarecycline 1.5 mg/kg/day is well tolerated, safe, and effective in patients 12 to 45 years of age with moderate to severe facial acne.[9]

This report describes the results of 2 identically designed, phase 3 pivotal trials, SC1401 and SC1402, to evaluate the efficacy and safety of once-daily sarecycline 1.5 mg/kg for 12 weeks in patients aged 9 to 45 years with moderate to severe facial acne vulgaris.

FIGURE 1. Study design for SC1401 and SC1402. IGA, Investigator's Global Assessment. [a]After enrollment began, a protocol amendment removed the lower limit for noninflammatory lesion count at baseline.



METHODS

Study Design

Two identically designed, randomized, double-blind, placebo-controlled, parallel-group, phase 3 studies (Figure 1) were conducted in the United States: study SC1401 (Clinicaltrials.gov identifier NCT02320149), conducted at 56 centers, and study SC1402 (NCT02322866), conducted at 54 centers. After screening and baseline assessments, study visits occurred at weeks 3, 6, 9, and 12 of treatment.

The studies were conducted in compliance with Good Clinical Practice guidelines and approved by an Institutional Review Board. All patients provided written informed consent or assent.

Patients

Eligible patients were aged 9 to 45 years, weighed 33 to 136 kg, and had 20 to 50 inflammatory lesions, ≤100 noninflammatory lesions, ≤2 nodules, and a score of 3 (moderate) or 4 (severe) on the Investigator's Global Assessment (IGA) scale for inflammatory lesions of acne.

Individuals were excluded from the studies if they had a dermatologic condition or facial hair, any chronic illness interfering with study evaluations, allergy or resistance to tetracyclines, drug-induced acne, hormonal contraceptive initiation, systemic retinoids, systemic corticosteroids, androgens, or anti-androgens within 12 weeks prior to randomization.

All randomized patients composed the intent-to-treat (ITT) populations.

Treatment

Patients were randomized 1:1 to receive sarecycline (1.5 mg/kg) or placebo tablets administered orally once daily as 60 mg, 100 mg, or 150 mg of sarecycline or matching placebo tablets for 12 weeks.

Efficacy Assessments

At baseline and each study visit, facial acne was evaluated using the IGA and inflammatory and noninflammatory lesion counts. IGA scores ranged from 0 (clear) to 4 (severe) and reflected the investigator's overall general assessment of the quantity and quality of inflammatory lesions. Counts of inflammatory lesions (papules, pustules, and nodules) and noninflammatory lesions (open and closed comedones) on the forehead, cheeks, nose, and chin were recorded at each visit. Acne severity on the back and chest also was evaluated using IGA scores.

Efficacy analyses included IGA success for facial acne at week 12, defined as a ≥2-point decrease (improvement) from baseline and a score of 0 (clear) or 1 (almost clear), percentage change from baseline in facial inflammatory lesion counts at week 12, and absolute change from baseline in facial noninflammatory lesion counts at week 12. A post hoc analysis to determine the percentage change from baseline in noninflammatory lesion counts was also performed for each study in ITT patients who had ≥10 noninflammatory lesions at baseline. The percentages of patients in the ITT population with IGA success for back and chest acne (defined as a ≥2-point improvement in IGA score in those areas following a baseline IGA score ≥2) at week 12 were also assessed as post hoc analyses.

Patient-Reported Outcome Measure

The Skindex-16, a 16-item questionnaire measuring effects of skin disease on patients' quality of life using 3 scales (symptoms, emotions, and functioning), with scores standardized from 0 (never bothered) to 100 (always bothered),[10] was administered to patients at baseline and week 12.

Safety and Tolerability Assessments

Treatment-emergent adverse events (TEAEs) were assessed at every visit. Vital signs were recorded at screening, baseline, and each study visit. Clinical laboratory evaluations were conducted at screening, baseline, week 3, and week 12 visits. Electrocardiograms (ECGs) were conducted at screening and at week 12 visits, and physical examinations were conducted at screening, baseline, and week 12 visits.

Statistical Analyses

Efficacy analyses were conducted in the ITT populations. IGA success at week 12 was calculated using the Cochran-Mantel-Haenszel test, with adjustment for pooled site. The same methodology was used for nonfacial (chest and back) IGA assessments (≥2-point decrease in patients with IGA score ≥2 at baseline). An analysis of covariance model (ANCOVA), with baseline value as a covariate, treatment and pooled site effects as factors, and significance level set at $P \leq 0.05$, was used to calculate mean percentage changes from baseline in inflammatory lesion counts. This ANCOVA model was also used to calculate mean absolute changes from baseline in noninflammatory lesion counts in the entire ITT population and mean absolute and percentage changes from baseline in noninflammatory lesion counts in patients with ≥10 baseline noninflammatory lesions. Missing data were handled using a multiple imputation approach, except for nonfacial IGA assessments, which used observed data.

FIGURE 2. Patient disposition in SC1401 and SC1402. AEs, adverse events; ITT, intent-to-treat. [a]Safety population included all patients who received ≥1 dose of study medication after randomization.

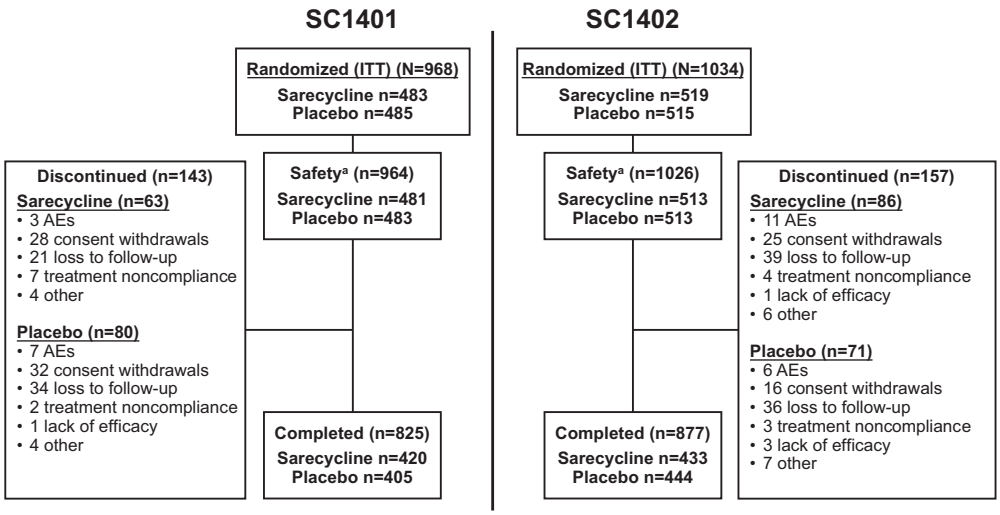


TABLE 1.

Patient Demographics and Baseline Characteristics (ITT population)

Characteristic	SC1401		SC1402	
	Sarecycline (n=483)	Placebo (n=485)	Sarecycline (n=519)	Placebo (n=515)
Age, years	-	-	-	-
Mean	19.6	19.8	20.4	19.7
Range	10, 45	10, 45	9, 44	10, 44
Sex, % male	44.5	44.1	39.3	43.3
Race, n (%)	-	-	-	-
White	377 (78.1)	377 (77.7)	407 (78.4)	391 (75.9)
Black	80 (16.6)	79 (16.3)	66 (12.7)	76 (14.8)
Other	26 (5.4)	29 (6.0)	45 (8.7)	48 (9.3)
Mean BMI, kg/m^2	25.5 (5.8)	25.3 (5.5)	25.9 (6.4)	25.4 (6.2)
Facial	-	-	-	-
Mean facial inflammatory lesions, n	29.7	30.2	30.3	30.2
Mean facial noninflammatory lesions, n	42.4	43.7	42.3	43.9
Mean IGA score (SD)	3.1 (0.4)	3.2 (0.4)	3.2 (0.4)	3.1 (0.4)
IGA score, n (%)				
3 (moderate)	413 (85.5)	410 (84.5)	440 (84.8)	439 (85.2)
4 (severe)	70 (14.5)	75 (15.5)	79 (15.2)	76 (14.8)
Back	-	-	-	-
Mean IGA score (SD)	1.6 (1.2)	1.6 (1.1)	1.8 (1.1)	1.8 (1.2)
IGA score, n (%)	-	-	-	-
0 (clear)	116 (24.0)	103 (21.2)	91 (17.5)	101 (19.6)
1 (almost clear)	96 (19.9)	121 (24.9)	103 (19.8)	97 (18.8)
2 (mild)	152 (31.5)	148 (30.5)	177 (34.1)	154 (29.9)
3 (moderate)	100 (20.7)	92 (19.0)	136 (26.2)	132 (25.6)
4 (severe)	19 (3.9)	21 (4.3)	12 (2.3)	31 (6.0)
Chest	-	-	-	-
Mean IGA score (SD)	1.2 (1.1)	1.2 (1.1)	1.4 (1.1)	1.4 (1.1)
IGA score, n (%)	-	-	-	-
0 (clear)[a]	178 (36.9)	152 (31.3)	140 (27.0)	141 (27.4)
1 (almost clear)[b]	115 (23.8)	145 (29.9)	132 (25.4)	128 (24.9)
2 (mild)[c]	137 (28.4)	126 (26.0)	156 (30.1)	150 (29.1)
3 (moderate)[d]	44 (9.1)	46 (9.5)	86 (16.6)	87 (16.9)
4 (severe)[e]	9 (1.9)	16 (3.3)	5 (1.0)	9 (1.7)

BMI, body mass index; IGA, Investigator's Global Assessment; ITT, intent-to-treat; SD, standard deviation.
[a]No evidence of papules or pustules.
[b]Rare inflammatory papules (must be resolving and may be hyperpigmented, though not pink-red).
[c]Few inflammatory lesions (papules/pustules only; no nodulocytic lesions).
[d]Multiple inflammatory lesions present; many papules/pustules; there may or may not be a few nodulocytic lesions.
[e]Inflammatory lesions more apparent; many papules/pustules; there may or may not be a few nodulocytic lesions.

Skindex-16 questionnaire scale scores and total scores were summarized by treatment and visit in the ITT population. Change from baseline in these scores was calculated for each treatment and analyzed using the ANCOVA model. Adjusted least squares means with associated 95% confidence intervals (CIs) from the ANCOVA model were analyzed for each treatment and difference between treatments.

Safety evaluations were conducted in all patients who received ≥1 dose of study drug. TEAEs were summarized by the number and percentage of patients reporting a TEAE by treatment.

RESULTS

Patient Demographics and Baseline Disease Characteristics

Demographic variables were similar across treatment groups in both studies (Table 1). Baseline disease characteristics, including facial inflammatory and noninflammatory lesion counts and facial IGA scores, were similar across treatment groups in both studies.

The majority of patients (SC1401: 85.2%; SC1402: 84.8%) completed the studies (Figure 2).

Efficacy

IGA success rate was significantly greater in the sarecycline group than in the placebo group in the ITT population beginning at week 6 in study SC1402 and at week 9 in study SC1401 and continuing through week 12 in both studies. In study SC1401, 21.9% of the sarecycline group versus 10.5% of the placebo group achieved IGA success at week 12 (P<0.0001; Figure 3). In study SC1402, the IGA success rate at week 12 was 22.6% for sarecycline versus 15.3% for placebo (P=0.0038).

Mean percentage change from baseline in inflammatory lesion count was significantly greater in the sarecycline group than the placebo group at the first follow-up visit at week 3 and continued through week 12 in both studies (Figure 4). In study SC1401, the mean percentage change from baseline in inflammatory lesion count at week 12 was –51.8% in the sarecycline group versus –35.1% in the placebo group (P<0.0001). In study SC1402, the mean percentage change from baseline in inflammatory lesion count at week 12 was –49.9% for sarecycline versus –35.4% for placebo (P<0.0001).

Mean absolute change from baseline in noninflammatory lesion count was significantly greater in the sarecycline group than the placebo group beginning at week 6 in study SC1401 and at week 9 in study SC1402 and continuing through week 12 in both studies (Figure 5). In study SC1401, sarecycline-treated patients had a mean absolute change from baseline in nonin-

FIGURE 3. Percentage of patients with facial IGA success at week 12 (ITT population). Facial IGA success was defined as a ≥2-point decrease (improvement) in facial IGA score from baseline and a score of clear/almost clear. IGA, Investigator's Global Assessment; ITT, intent-to-treat. *P<0.0001 vs placebo; †P=0.0038 vs placebo.

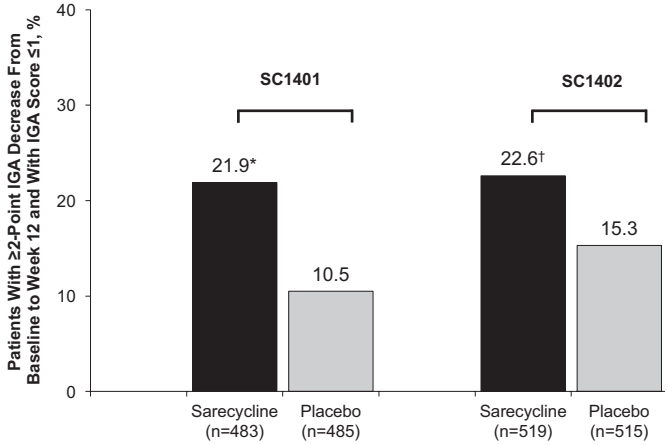


FIGURE 4. Mean percentage change from baseline through week 12 in inflammatory lesion counts for patients taking sarecycline compared with placebo (ITT population). ITT, intent-to-treat; LS, least squares.*P=0.0003 vs placebo; †P<0.0001 vs placebo.

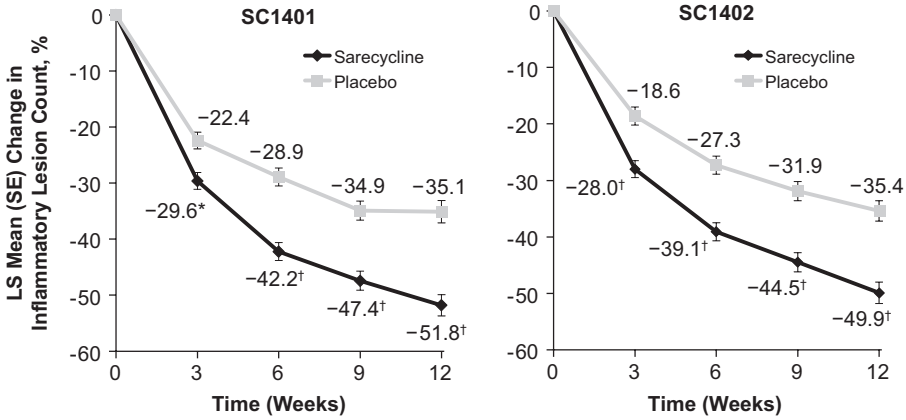
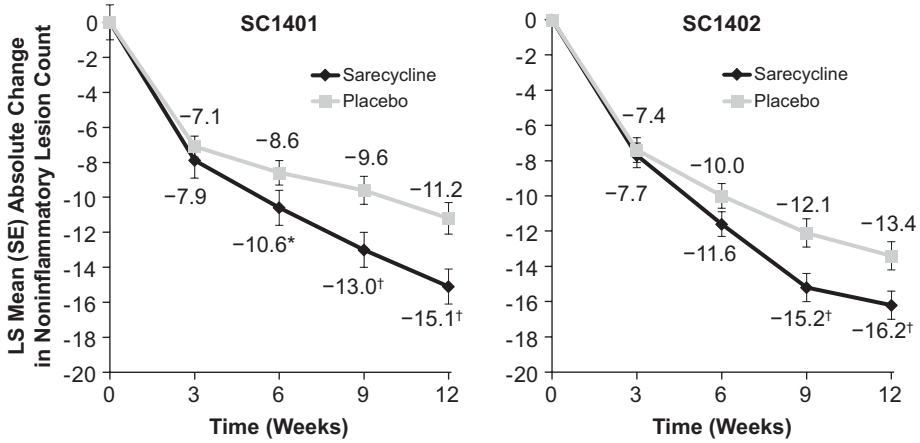


FIGURE 5. Mean absolute change from baseline through week 12 in noninflammatory lesion counts for patients taking sarecycline compared with placebo (ITT population). ITT, intent-to-treat; LS, least squares. *P<0.05 vs placebo; †P<0.01 vs placebo.



flammatory lesion count at week 12 of –15.1 versus –11.2 in the placebo group (P<0.01). In study SC1402, the mean absolute change was –16.2 for sarecycline versus –13.4 for placebo (P<0.01) at week 12.

Among patients who had ≥10 baseline noninflammatory lesions in study SC1401, the mean percentage change from baseline in noninflammatory lesion count was significantly greater for sarecycline than placebo starting at week 6 and continuing through week 12 (–34.5% vs –26.0%; P<0.05; Figure 6). In study SC1402, the mean percentage change from baseline in noninflammatory lesion count for patients with ≥10 baseline noninflammatory lesions was significantly greater for sarecycline than for placebo starting at week 9 and continuing through week 12 (–35.6% vs –28.2%; P<0.01). Figure 7 shows photographs depicting response to sarecycline treatment at week 12 in representative patients in studies SC1401 and SC1402.

Among patients who had baseline IGA scores of ≥2 for back or chest acne, the proportions achieving IGA success at these locations (≥2-point improvement in IGA score) at week 12 were significantly higher in the sarecycline than the placebo group in both studies (Figure 8). For back acne, this comparison was significant beginning at week 3 in study SC1401 and at week 9 in study SC1402. For chest acne, significance was noted at week 6 and week 12 in study SC1401, and at week 12 in study SC1402.

In study SC1401, significant mean differences for sarecycline over placebo (95% CI) were achieved in Skindex-16 scores for symptoms (–4.7 [–7.0, –2.4]), and emotion (–4.7 [–8.1, –1.4]) scales, and total score (–3.5 [–6.0, –1.1]). The mean difference for functioning (95% CI) was –1.5 (–4.3, 1.3). In study SC1402, the mean differences for sarecycline over placebo (95% CI) were significant for symptoms (–5.1 [–7.2, –2.9]), emotion (–7.7 [–11.0, –4.4]), functioning (–4.8 [–7.3, –2.2]), and total score (–5.9 [–8.1, –3.6]).

FIGURE 6. Mean percentage change from baseline through week 12 in noninflammatory lesion counts for patients with ≥10 noninflammatory lesions at baseline (ITT population); sarecycline group compared with placebo group. In SC1401, 97.7% of the ITT population had ≥10 baseline noninflammatory lesions; in SC1402, it was 95.8%. ITT, intent-to-treat; LS, least squares. *P<0.05 vs placebo; †P<0.01 vs placebo.

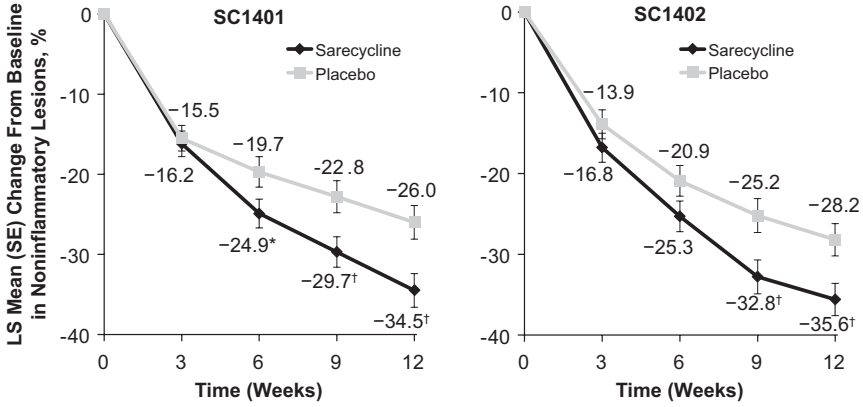
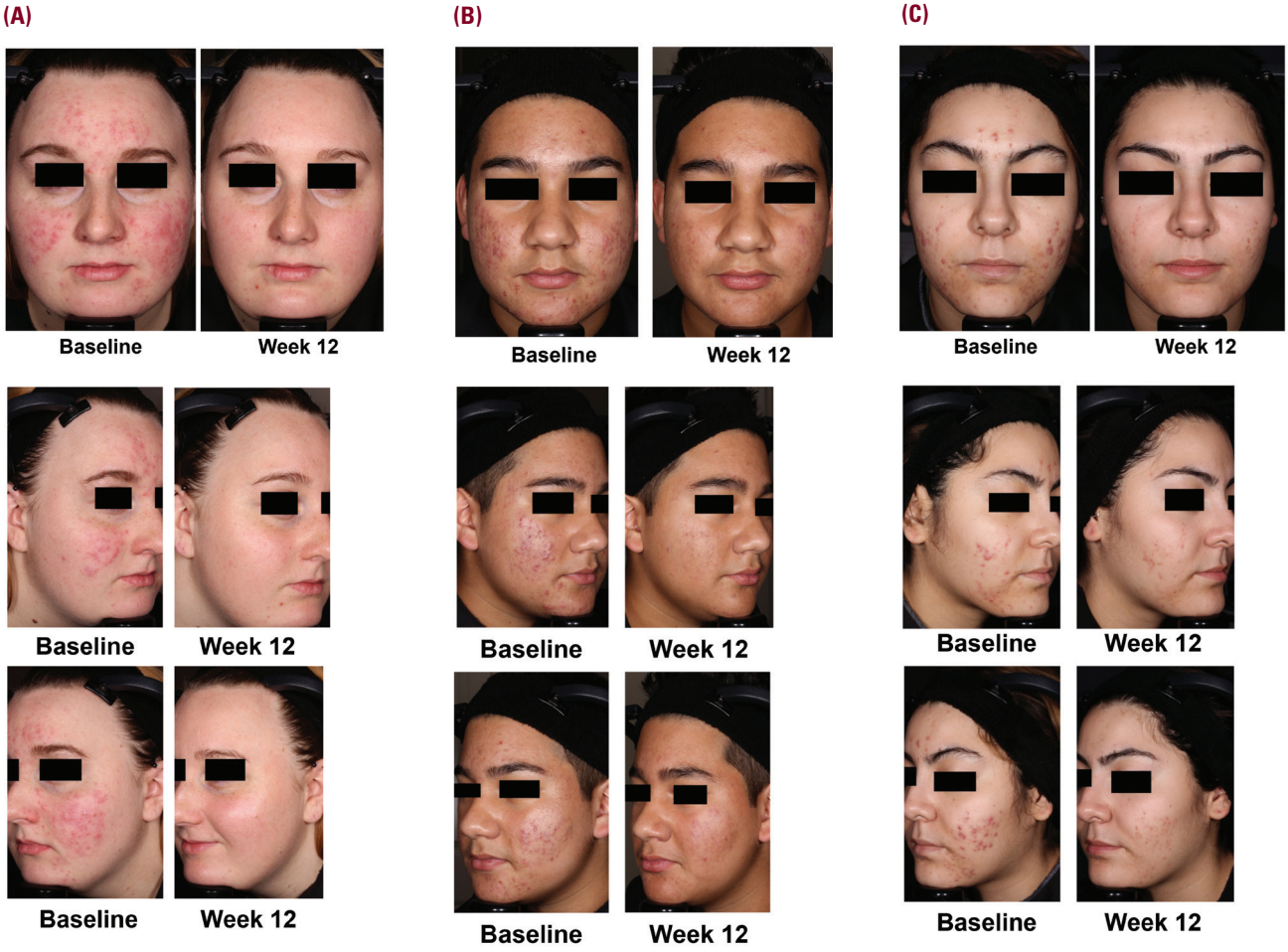


FIGURE 7. Response to sarecycline in (A) a 23-year-old female patient in SC1401[a]; (B) a 14-year-old male patient in SC1402[b]; (C) a19-year-old female patient in SC1401.[c] IGA, Investigator's Global Assessment. [a]IGA score: 4 at baseline, 1 at week 12. Inflammatory lesions: 50 at baseline, 4 at week 12. Noninflammatory lesions: 22 at baseline, 17 at week 12. [b]IGA score: 4 at baseline, 1 at week 12. Inflammatory lesions: 42 at baseline, 8 at week 12. Noninflammatory lesions: 74 at baseline, 31 at week 12. [c]IGA score: 4 at baseline, 1 at week 12. Inflammatory lesions: 33 at baseline, 8 at week 12. Noninflammatory lesions: 33 at baseline, 5 at week 12.



Safety

Overview

In study SC1401, TEAEs occurred in 29.3% (141/481) of patients in the sarecycline group and 29.8% (144/483) of patients in the placebo group. In study SC1402, TEAEs occurred in 25.0% (128/513) of patients in the sarecycline group and 26.7% (137/513) of patients in the placebo group (Table 2).

The most common TEAEs (in ≥2% of patients in either group) were nausea (4.6% sarecycline, 2.5% placebo), nasopharyngitis (3.1% and 1.7%), headache (2.7% in both groups), and vomiting (2.1% and 1.4%) in study SC1401, and nasopharyngitis (2.5% sarecycline and 2.9% placebo) and headache (2.9% and 4.9%) in study SC1402. Vulvovaginal candidiasis and vulvovaginal mycotic infection were rare in the sarecycline group, occurring in 1.1% and 0.7%, respectively, of female patients in SC1401 and 0.3% and 1.0% of female patients in SC1402, all of whom completed the study. They did not occur in the placebo group in either study.

TEAEs considered by the investigator to be related or possibly related to study treatment occurred in 1.9% (9/481) and 8.7% (42/481), respectively, of patients in the sarecycline group, and 0.4% (2/483) and 8.3% (40/483), respectively, of patients in the placebo group in study SC1401. TEAEs considered by the investigator to be related or possibly related to study treatment occurred in 1.6% (8/513) and 6.4% (33/513), respectively, of patients in the sarecycline group, and 0.6% (3/513) and 5.1% (26/513), respectively, of patients in the placebo group in study SC1402.

TABLE 2.

Overall Summary of Adverse Events (Safety Population)

Event	SC1401		SC1402	
	Sarecycline (n=481)	Placebo (n=483)	Sarecycline (n=513)	Placebo (n=513)
Overview of TEAEs				
Death	0	0	0	0
SAE	3 (0.6)[a]	5 (1.0)[b]	4 (0.8)[c]	1 (0.2)[d]
TEAEs leading to study discontinuation	3 (0.6)[e]	7 (1.4)[f]	11 (2.1)[g]	6 (1.2)[h]
Any TEAE	141 (29.3)	144 (29.8)	128 (25.0)	137 (26.7)
Any treatment-related TEAE[i]	51 (10.6)	42 (8.7)	41 (8.0)	29 (5.7)
TEAEs reported by ≥2% of patients in any group				
Headache	13 (2.7)	13 (2.7)	15 (2.9)	25 (4.9)
Nausea	22 (4.6)	12 (2.5)	10 (1.9)	5 (1.0)
Nasopharyngitis	15 (3.1)	8 (1.7)	13 (2.5)	15 (2.9)
Vomiting	10 (2.1)	7 (1.4)	3 (0.6)	2 (0.4)

Data are (n) % of patients.
AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]Five SAEs occurred in 3 patients (increased alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase [all considered possibly related to treatment], n=1; diabetic ketoacidosis, n=1; and nephrolithiasis, n=1 [both considered not related to treatment]).
[b]Six SAEs occurred in 5 patients (spontaneous abortion, n=2; appendicitis, n=1; cellulitis and suicide attempt, n=1 [all considered not related to treatment]; and miscarriage of partner [considered possibly related to treatment], n=1).
[c]Four SAEs occurred in 4 patients (Crohn's disease, tonsillitis, depression, and abortion [all considered not related to treatment], n=1).
[d]Oppositional defiant disorder was reported in 1 patient (considered not related to treatment).
[e]One case each of increased gamma-glutamyl transferase, thyroid-stimulating hormone, and nausea.
[f]One case each of maculopapular rash, abdominal pain, diarrhea, nausea, acne, latent tuberculosis, headache, urticaria, and panic attack.
[g]Diarrhea, headache, and nausea (all in 1 patient), muscle spasms and photosensitivity reaction (both in 1 patient), 2 cases of acne, and 1 case each of dizziness, abdominal discomfort, upper abdominal pain, peripheral edema, urticaria, and increased hepatic enzyme, alanine aminotransferase, and aspartate aminotransferase (the latter two occurring in 1 patient).
[h]Peripheral edema and urticaria (both in 1 patient), 2 cases of headache, and 1 case each of abdominal pain, urticaria, and increased alanine aminotransferase and aspartate aminotransferase (the latter two occurring in 1 patient).
[i]Includes TEAEs considered "possibly related" or "related" by the investigator.

TABLE 3.

Treatment-Emergent Adverse Events Common to Tetracycline-Class Antibiotics (Safety Population)

Event, n (%)	SC1401		SC1402	
	Sarecycline (n=481)	Placebo (n=483)	Sarecycline (n=513)	Placebo (n=513)
Gastrointestinal effects in ≥1% of patients in any group				
Nausea	22 (4.6)	12 (2.5)	10 (1.9)	5 (1.0)
Vomiting	10 (2.1)	7 (1.4)	3 (0.6)	2 (0.4)
Abdominal pain	6 (1.2)	6 (1.2)	3 (0.6)	1 (0.2)
Abdominal discomfort	5 (1.0)	1 (0.2)	2 (0.4)	2 (0.4)
Diarrhea	5 (1.0)	8 (1.7)	6 (1.2)	6 (1.2)
Vestibular effects				
Dizziness	3 (0.6)	7 (1.4)	2 (0.4)	4 (0.8)
Motion sickness	0	0	1 (0.2)	1 (0.2)
Tinnitus	0	0	0	0
Vertigo	0	0	0	0
Phototoxic effects				
Photosensitivity	0	0	1 (0.2)	0
Sunburn	3 (0.6)	2 (0.4)	4 (0.8)	1 (0.2)
Vaginal yeast infections in females				
Vulvovaginal candidiasis[a]	3 (1.1)	0	1 (0.3)	0
Vulvovaginal mycotic infection[a]	2 (0.7)	0	3 (1.0)	0

[a]Percentages were calculated based on the number of female patients.

TEAE severity was mild or moderate in most patients in both studies; 95.9% (233/243) of TEAEs in the sarecycline group and 96.0% (238/248) in the placebo group in study SC1401 were mild or moderate, as were 97.8% (224/229) of TEAEs in the sarecycline group and 97.0% (226/233) in the placebo group in study SC1402.

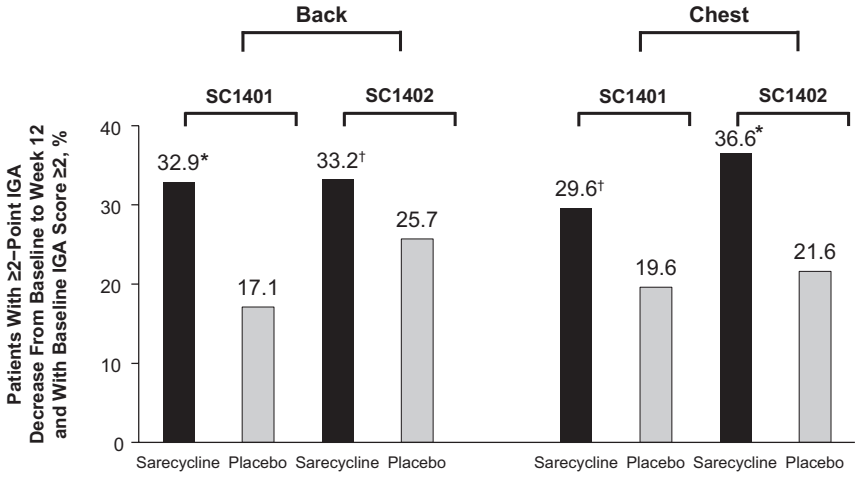
Serious adverse events were rare in both studies, and all were considered not related or possibly related to study treatment. There were no deaths during either study.

There were no clinically meaningful differences between the sarecycline and placebo groups in clinical laboratory, vital sign, and ECG measurements in either study.

Adverse Events Leading to Discontinuations

In study SC1401, TEAEs leading to study discontinuations occurred in 0.6% (3/481) and 1.4% (7/483) of patients in the sarecycline and placebo groups, respectively, but none were judged by the investigator as being related to study treatment; most were judged as possibly related (Table 2). In study SC1402, 2.1% (11/513) and 1.2% (6/513) of patients in the sarecycline and placebo groups, respectively, discontinued due to AEs, the majority of which were judged by the investigator as possibly related or related to study treatment.

FIGURE 8. Percentage of patients with nonfacial IGA success at week 12 (ITT population). Nonfacial IGA success was defined as a ≥2-point decrease (improvement) in nonfacial IGA score from baseline and a score of clear/almost clear. In SC1401, 39.0% and 55.0% of the ITT population had baseline IGA scores ≥2 for chest and back acne, respectively. In SC1402, 47.7% and 62.1% of the ITT population had baseline IGA scores ≥2 for chest and back acne, respectively. IGA, Investigator's Global Assessment; ITT, intent-to-treat. *P<0.001 vs placebo; †P<0.05 vs placebo.



Adverse Events Reported with Other Tetracycline-Class Antibiotics

Among AEs reported with other tetracycline-class antibiotics, vestibular TEAEs (specifically dizziness, vertigo, tinnitus) and phototoxic TEAEs (photosensitivity, sunburn) were rare in sarecycline-treated patients, occurring in ≤1% of patients, and rates of GI TEAEs for sarecycline were low (Table 3). In each study, there were no cases of vertigo or tinnitus, and fewer cases of dizziness in sarecycline-treated patients than in placebo-treated patients. The most common GI TEAEs were nausea, vomiting, diarrhea, abdominal pain, abdominal discomfort, and constipation.

DISCUSSION

Sarecycline is the first narrow-spectrum tetracycline-class antibiotic for the treatment of moderate to severe acne. These pivotal phase 3 studies demonstrated that oral sarecycline 1.5 mg/kg per day for 12 weeks was effective in the treatment of moderate to severe acne vulgaris, with an onset of efficacy for inflammatory lesions observed as early as the first follow-up visit at week 3, and an overall safety profile generally similar to that of placebo. In addition, sarecycline showed a significant effect on acne severity in nonfacial sites.

Interestingly, sarecycline showed a statistically significantly greater improvement than placebo in noninflammatory lesion counts beginning at week 6 in study SC1401 and week 9 in study SC1402, with continued improvement through week 12. The analyses in patients with at least 10 noninflammatory lesions at baseline provided further evidence of the therapeutic effect on noninflammatory lesions. Although the exact effect of sarecycline on noninflammatory lesions is unknown, a possible explanation may be that sarecycline exerts anti-inflammatory effects on an early inflammatory process that is postulated to occur during the development of comedones.[11,12]

Antibiotic resistance is a concern with oral antibiotic treatments for acne.[3-7] Agents that unnecessarily target a broad spectrum of bacteria are associated with greater potential for antibiotic resistance,[13] and the American Academy of Dermatology recommends responsible usage of systemic antibiotics for acne.[1] The current first-line antibiotics for moderate to severe acne are broad-spectrum tetracycline-class antibiotics, such as minocycline and doxycycline,[1] highlighting the need for a narrow-spectrum antibiotic that can be used as first-line treatment for moderate to severe acne. In vitro studies have demonstrated the narrow antibacterial spectrum of sarecycline and its limited activity against enteric gram-negative bacteria (Data on file; Allergan plc, Dublin, Ireland).

The antibacterial profile of sarecycline, particularly its targeted activity against *P. acnes*, may reduce its potential for disrupting the human gut microbiome. In contrast, administration of the tetracycline-class antibiotics doxycycline, minocycline, and tetracycline has been associated with disruption of the gut microbiome.[14-16] The favorable safety profile of sarecycline in these studies represents an important finding for a tetracycline-class antibiotic. Tetracycline-class antibiotics may be associated with GI side effects and phototoxicity (typically seen with doxycycline) or vestibular side effects (observed with minocycline),[3] yet low rates of such side effects were reported in these studies with sarecycline. In the current phase 3 studies, the incidence of AEs related to the GI tract, including nausea, vomiting, diarrhea, and abdominal pain, was low.

The patient-reported outcomes for Skindex-16 symptoms, emotion, and functioning indicate that patient quality of life improved with the use of sarecycline over 12 weeks. They are also similar to Skindex-16 outcomes in patients with moderate to severe acne who were treated with minocycline.[17]

Limitations

Monotherapy with oral antibiotics, as evaluated in the trials here, is not standard in clinical practice[1]; the concomitant use of topical treatments could augment the benefit demonstrated here. The studies did not include microbiological testing of cultures obtained from patients, which may have yielded additional valuable insights into the antibacterial activity of sarecycline and impact on the human microbiome.[1] Additionally, the studies were originally designed to evaluate the effect of sarecycline on noninflammatory lesion counts from a safety standpoint; thus no lower limit on baseline noninflammatory lesion counts was established to assess changes from baseline as an efficacy measure. The studies also were not powered to evaluate the effect of sarecycline on nonfacial acne. Nevertheless, sarecycline demonstrated a statistically significant benefit for noninflammatory lesions and nonfacial acne.

CONCLUSIONS

Sarecycline is a novel, tetracycline-class antibiotic representing the first narrow-spectrum, targeted therapy for acne. Oral sarecycline 1.5 mg/kg per day was effective for improving acne severity and inflammatory and noninflammatory lesion counts, with onset of efficacy for inflammatory lesions observed as early as week 3, and onset of efficacy for absolute reduction in noninflammatory lesion count observed at week 6 for study SC1401 and at week 9 for study SC1402. A benefit was also seen for nonfacial acne at week 12. Sarecycline was well tolerated and associated with low rates of vestibular side effects, phototoxicity, and GI side effects, all of which are commonly observed with use of currently available first-line oral tetracycline-class antibiotics for moderate to severe acne.

DISCLOSURES

S. Bruce, F. E. Cook-Bolden, S. S. Dhawan, D. Forsha, M. H. Gold, L. J. Green, S. Guenthner, S. E. Kempers, L. H. Kircik, A. Moore, A. Nasir, J. L. Parish, M. I. Rendon, P. Rich, N. Sadick, L. Stein-Gold, E. Tschen, S. K. Tyring, R. A. Weiss, and W. P. Werschler are investigators for Allergan plc. T. I. Boodhoo and D. R. Berk are employees of Allergan plc, and C. Schmitz and A. Kaoukhov were employees of Allergan plc at the time the studies were conducted; all may own stock/stock options in that company.

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