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REVIEW

Sarecycline: A Review of Preclinical and Clinical Evidence

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Abstract: Sarecycline is a tetracycline-derived oral antibiotic, specifically designed for acne, and is approved by the Food and Drug Administration (FDA) in 2018 for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris (AV) in patients 9 years of age and older. It has been decades since a novel systemic antibiotic was approved to treat AV, a disease that affects up to 90% of teenagers and young adults worldwide and lasts well into adulthood. Sarecycline holds promise to yield fewer side effects than other commonly used broad-spectrum tetracyclines, including minocycline and doxycycline. The narrower spectrum of antibacterial activity of sarecycline, which specifically targets *C. acnes* and some Gram-positive bacteria with little or no activity against Gram-negative bacteria, suggests not only the potential for reduced emergence of antibiotic-resistant bacterial strains but also less disruption of the human gut microflora. Here, we review the key preclinical and clinical evidence on sarecycline.

Keywords: acne vulgaris, antibiotic, narrow spectrum, tetracycline, sarecycline

Introduction

Acne vulgaris (AV) affects nearly everyone, particularly during teenage and young adult years. Over 40% of individuals still suffer from AV well into adulthood. Therefore, much effort continues to be made to identify the most effective and well-tolerated treatments.[1,2] Tetracyclines have been prescribed to treat moderate to severe AV since the 1970s. The antibacterial mechanism of action of tetracyclines occurs via inhibition of protein synthesis by preventing the association of aminoacyl-tRNA with the bacterial ribosome of susceptible organisms.[3] The therapeutic success of tetracyclines for AV, a disease of the pilosebaceous unit, is believed to correlate directly with both their anti-inflammatory and antimicrobial properties. The anti-inflammatory activity of tetracycline-class drugs is based on multiple reported biologic properties, including inhibition of matrix metalloproteinases (MMPs), suppression of IL-8, TNFα, and IL-6 gene expression from neutrophils and macrophages, suppression of hydrolases such as α-amylases and phospholipase A2, and scavenging of reactive oxygen species.[4,5]

Tetracyclines, including doxycycline and minocycline, are frequently prescribed for AV when topical treatment alone is deemed unsuccessful or unpractical, in patients that present with moderate-to-severe inflammatory AV.

Because of the increasing problem of antibiotic resistance, strategies to limit antibiotic overuse have emerged. These strategies include limiting the duration of broad-spectrum oral antibiotics and the preferential use of narrow-spectrum or

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targeted antibiotics when the causative organism is known.[6–10] Side effect profiles have also limited the use of oral tetracyclines in some patients, including gastrointestinal (GI) complications, phototoxicity, dizziness, vertigo, benign intracranial hypertension (pseudotumor cerebri), lupus-like syndrome, changes in pigmentation, and urticaria.[11–14]

Sarecycline is a novel tetracycline-derived drug, specifically designed for acne, with a narrow antibacterial spectrum when compared to previously available broad-spectrum tetracycline-class antibiotics; it was FDA-approved in October 2018 for once-daily treatment of inflammatory lesions of non-nodular moderate to severe AV in patients ≥9 years of age.[15] Here, we will review the pharmacology and clinical characteristics of sarecycline that are believed to relate to its therapeutic potential.

In vitro Antibacterial Activity

Tetracyclines exhibit a broad-spectrum of antibacterial activity, targeting a wide range of both Gram-positive and Gram-negative bacteria, including activity against normal bacterial microflora commonly found in the human GI tract.[3,16-19] These normal microbiota include *Enterobacteriaceae, Enterococcus*, and *Escherichia* species, of which disruption (dysbiosis) could potentially lead to sequelae associated with gastrointestinal disease,[20–22] but also the emergence of antibiotic-resistant strains.[23,24] Below, we summarize the main findings of the microbiological profile of sarecycline compared to other tetracyclines.

Gram-Positive Bacteria

Studies have been conducted to determine the antibacterial spectrum of activity of sarecycline compared to other tetracycline-class compounds.[19] Similar to other tetracyclines, sarecycline exerts its antibacterial effect mainly as a ribosomal protein inhibitor.[19,25] Sarecycline has shown activity against *C. acnes* that is comparable to doxycycline and minocycline (Table 1). Importantly, the minimum inhibitory concentration (MIC_{90}) for sarecycline was 0.5 µg/mL against both methicillin-susceptible (MSSA) and methicillin-resistant (MRSA) strains of *S. aureus* and 2 µg/mL against both methicillin-susceptible and -resistant *S. epidermidis*, only twofold less active than doxycycline and minocycline. Sarecycline was more active than tetracycline and doxycycline against *S. haemolyticus*. Sarecycline MIC_{90} was 8–32 µg/mL against *S. pyogenes, S. agalactiae, E. faecalis*, and *E. faecium* (both vancomycin susceptible and resistant (Table 2)).

Table 1 Activity of Sarecycline and Comparator Agents Against 55 Clinical Isolates of *C. acnes*

Agent	MIC (µg/mL)		
	Range	50%	90%
Sarecycline	0.5 to 16	0.5	4
Tetracycline	0.5 to 32	1	2
Doxycycline	0.25 to 16	0.5	2
Minocycline	0.12 to 8	0.25	1
Clindamycin	≤ 0.06 to 64	≤0.06	4
Erythromycin	≤0.06 to >128	≤0.06	>128

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Gram-Negative Bacteria

Sarecycline demonstrated very low activity (MIC_{90} >64 µg/mL) against aerobic Gram-negative bacilli *E. cloacae, E. coli, K. pneumoniae, P. mirabilis*, and *Salmonella* spp (Table 3). Sarecycline was least active (2 to 32 fold reduced MIC_{90} potency compared to minocycline and doxycycline) against isolates of *Enterobacteriaceae* and other clinically relevant Gram-negative microflora commonly found in the human GI tract.[19]

In vivo Antibacterial Activity

A murine thigh infection model was used to represent a tissue-based in vivo infection. Sarecycline demonstrated in vivo efficacy against systemic infection caused by *S. aureus* and achieved a 2-log_{10} reduction in the bacterial burden in the thigh at a dose comparable to doxycycline.[19]

Available data support that sarecycline is a narrow-spectrum antibiotic, which targets *C. acnes*, the bacterium involved in AV pathophysiology, while having lower antibacterial activity than conventional tetracyclines against normal microflora, including *Enterobacteriaceae, Enterococcus*, and *Escherichia* species.

Resistance Profile and Mutation Rates of Different Bacteria

The same report that tested activity against various bacteria also looked at spontaneous mutation rates of bacteria (*C. acnes, S. aureus*, and *S. epidermidis*) cultured in the presence of sarecycline, vancomycin or minocycline.[19] Sarecycline showed a very low propensity to induce bacterial resistance with spontaneous mutation frequencies ranging from 10^{-9} to 10^{-11} for *C. acnes* at 4 and 8-fold the MIC, similar to vancomycin. The spontaneous

Table 2 Activity of Sarecycline and Comparator Agents Against Isolates of Gram-Positive Bacteria Except *C. acnes*

Organism	Agent	MIC (μg/mL)		
		Range	50%	90%
S. aureus (methicillin susceptible)	Sarecycline	0.25 to 16	0.5	0.5
	Tetracycline	0.25 to >32	0.25	0.5
	Doxycycline	0.12 to 8	0.12	0.25
	Minocycline	0.06 to 8	0.12	0.12
S. aureus (methicillin resistant)	Sarecycline	0.25 to 4	0.25	0.5
	Tetracycline	0.25 to 2	0.25	0.5
	Doxycycline	0.12 to 2	0.12	0.25
	Minocycline	0.06 to 0.5	0.06	0.12
S. epidermidis (methicillin susceptible)	Sarecycline	0.12 to 2	0.25	2
	Tetracycline	0.12 to 2	0.25	2
	Doxycycline	0.06 to 1	0.12	1
	Minocycline	0.06 to 0.25	0.06	0.25
S.epidermidis (methicillin resistant)	Sarecycline	0.25 to 2	0.5	2
	Tetracycline	0.25 to >32	1	2
	Doxycycline	0.12 to 8	0.5	1
	Minocycline	0.06 to 0.5	0.12	0.25
S. haemolyticus	Sarecycline	0.12 to 2	0.12	2
	Tetracycline	0.12 to >32	1	>32
	Doxycycline	0.06 to 16	0.5	16
	Minocycline	≤0.03 to 0.5	0.06	0.5
S. pyogenes	Sarecycline	0.12 to 16	0.12	8
	Tetracycline	0.12 to 32	0.12	32
	Doxycycline	0.06 to 8	0.12	4
	Minocycline	0.03 to 8	0.06	0.5
S. agalactiae	Sarecycline	0.12 to 32	16	16
	Tetracycline	0.12 to >32	32	>32
	Doxycycline	0.06 to 16	8	16
	Minocycline	0.03 to 16	16	16
E. faecalis (vancomycin susceptible)	Sarecycline	0.5 to 32	32	32
	Tetracycline	0.25 to >64	32	64
	Doxycycline	0.12 to 16	8	8
	Minocycline	0.06 to 16	8	16
E. faecium (vancomycin resistant)	Sarecycline	0.12 to 32	2	32
	Tetracycline	0.12 to >64	2	>64
	Doxycycline	0.06 to 16	1	8
	Minocycline	≤0.03 to 16	0.25	16
E. faecium (vancomycin susceptible)	Sarecycline	0.12 to 32	0.5	32
	Tetracycline	0.12 to >64	1	>64
	Doxycycline	0.06 to 32	0.5	16
	Minocycline	≤0.03 to 16	0.12	16

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Table 3 Activity of Sarecycline and Comparator Agents Against Isolates of Gram-Negative Bacteria

Organism	Agent	MIC (μg/mL)		
		Range	50%	90%
E. cloacae	Sarecycline	0.25 to >64	32	>64
	Tetracycline	0.5 to >64	2	>64
	Doxycycline	0.96 to >32	2	32
	Minocycline	≤0.03 to >32	1	16
E. coli	Sarecycline	2 to >64	16	>64
	Tetracycline	1 to >64	2	>64
	Doxycycline	0.5 to >32	2	32
	Minocycline	0.25 to >32	1	8
K. pneumoniae	Sarecycline	16 to >64	>64	>64
	Tetracycline	1 to >64	8	>64
	Doxycycline	1 to >32	8	>32
	Minocycline	1 to >32	4	>32
P. mirabilis	Sarecycline	>64	>64	>64
	Tetracycline	16 to >64	32	64
	Doxycycline	32 to >32	>32	>32
	Minocycline	8 to >32	16	>32
Salmonella spp.	Sarecycline	8 to >64	16	>64
	Tetracycline	1 to >64	2	>64
	Doxycycline	2 to >32	2	32
	Minocycline	1 to >32	2	8

Note: Reproduced from Zhanel G, Critchley I, Lin LY, Alvandi N. Microbiological profile of sarecycline, a novel targeted spectrum tetracycline for the treatment of acne vulgaris. *Antimicrob Agents Chemother.* 2019;63:1. Creative Commons license and disclaimer available from: http://creativecommons.org/licenses/by/4.0/legalcode.[19]

mutation frequencies were 10^{-9} for *S. aureus* and 10^{-8} for *S. epidermidis* at 4- and 8-fold the MIC, similar to vancomycin. Sarecycline structural modification at C-7 has been attributed to overcoming tetracycline resistance mechanisms and to changing bacterial ribosome binding.[19,26] Possibly because of its unique structural properties and narrow spectrum of antibacterial activity, sarecycline may reduce the emergence of antibiotic-resistant bacterial strains.[19]

Dosage and Administration in Humans

Phase 2 dosage studies randomized patients to receive 0.75 mg/kg, 1.5 mg/kg, or 3 mg/kg sarecycline or placebo (1:1:1:1).[27] At week 12, sarecycline at 1.5 mg/kg and 3.0 mg/kg demonstrated significantly reduced inflammatory acne lesions compared to baseline (52.7% and 51.8%, respectively) vs placebo

(38.3%). Since the 3 mg/kg dose was not more effective than the 1.5 mg/kg dose, 1.5 mg/kg was identified as the therapeutic dose. The tablets come in 3 weight-based dosages – 60 mg (33–54 kg), 100 mg (55–84 kg), and 150 mg (>84 kg). Because clinical data did not show any difference in efficacy when sarecycline was taken with or without food, the FDA granted approval for sarecycline to be taken once daily with or without food.[15] Tetracyclines are not recommended for use during pregnancy.[28] Tetracyclines are not recommended for children below age 9 years due to the risk of tooth discoloration.[14]

Pharmacokinetic Properties

The maximum plasma concentrations of sarecycline are reached in a median time of 1.5–2.0 hours and reach steady state by day 7 with a mean accumulation ratio of 1.5 to 1.6-fold with repeated dosing. Steady-state exposure increased slightly less than proportionally when the once-daily dose was increased from 60 to 150 mg. While sarecycline can be taken with or without food, taking the drug with a milk-containing meal high in fat and calories reduced drug C_{max} (maximum plasma concentration) by ~30% and delayed the T_{max} (time to maximum plasma concentration) by approximately half an hour.[15] However, these observed changes were not considered clinically relevant since efficacy was not impacted. No recommended adjustment in dosage of sarecycline is required for those with mild or moderate renal or hepatic impairment, as neither hepatic nor renal impairment impacted sarecycline pharmacokinetics.[29]

Blood–Brain Barrier

Minocycline is a lipophilic tetracycline capable of crossing the blood–brain barrier and is more lipophilic than doxycycline and tetracycline.[25,30] Sarecycline has demonstrated low potential for crossing the blood–brain barrier in an animal (rat) model study (Table 4).[29] It is believed that crossing of the blood–brain barrier contributes to an increased risk of vestibular side effects such as dizziness and vertigo, which are seen more commonly with minocycline as compared to other tetracyclines.[31]

Table 4 Reduced Blood–Brain Barrier Penetration of Sarecycline Relative to Minocycline in Rats

Time (hr)	Minocycline		Sarecycline	
	Plasma (ug/mL)	Brain (ug/g)	Plasma (ug/mL)	Brain (ug/g)
1	0.333	0.074	0.460	BLQ
3	0.174	0.139	0.217	BLQ
6	0.077	0.068	0.049	BLQ

Note: levels of sarecycline in the brain after IV administration of 1mg/kg to rats were below the level of quantification (BLQ) of the assay (below 0.05 μg/g).

Distribution, Metabolism, and Elimination

Sarecycline has a mean volume of distribution of 91.4–97.0 L at steady state and is minimally metabolized by liver microsome enzymes in vitro (<15%).[15] The drug is excreted through feces and urine with 42.6% and 44.1% of a single 100 mg oral dose being recovered via these respective routes. Sarecycline has a mean elimination half-life of 21–22 h and a mean oral clearance of around 3 L/hour at steady state.[15]

Clinical Efficacy

Two identically designed, well-controlled Phase 3, randomized, double-blind clinical trials (SC1401 and SC1402) enrolled n = 483 sarecycline, n = 485 placebo and n = 519

Table 5 Clinical Efficacy in Phase 3 Clinical Trials – 12 Weeks

Study	Number Participants		Age (Years)
	Sarecycline	Placebo	
SC1401	483	485	9–45
SC1402	519	515	9–45
Study	**Percent reduction in inflammatory lesion**		**P value**
	Sarecycline	**Placebo**	
SC1401	51.8	35.1	<0.0001
SC1402	49.9	35.4	<0.0001
Study	**Percentage of patients with facial IGA success**		**P value**
	Sarecycline	**Placebo**	
SC1401	21.9	10.5	<0.0001
SC1402	22.6	15.3	0.0038
Study	**Percentage of patients with truncal IGA success**		**P value**
	Sarecycline	**Placebo**	
SC1401 back	32.9	17.1	<0.001
SC1401 chest	29.6	19.6	<0.05
SC1402 back	33.2	25.7	<0.05
SC1402 chest	36.6	21.6	<0.001

Note: IGA success was defined as a >2-point decrease (improvement) in IGA score from baseline and a score of clear/almost clear.
Abbreviation: IGA, investigators global assessment score.

sarecycline, n = 515 placebo patients, respectively (Main findings summarized in Table 5).

Efficacy was evaluated primarily in facial AV, but also in truncal AV involving the chest and back.[32] Marked improvement was observed in facial inflammatory AV lesions with sarecycline compared to placebo with statistically significant onset of efficacy as early as week 3 (P=0.0003 vs placebo in SC1401 and P<0.0001 vs placebo in SC1402). At the end of treatment (week 12), the clinical efficacy was 51.8% improvement sarecycline vs 35.1% placebo in SC1401, P<0.0001 and 49.9% improvement sarecycline vs 35.4% placebo in SC1402, P<0.0001 (Table 5). Furthermore, statistically significant improvement at week 12 was noticed in truncal acne (P<0.05). The percentage of patients with truncal acne investigator global assessment (IGA) success at week 12 in SC1401 was 32.9% sarecycline versus 17.1% placebo (P<0.001, back) and 29.6% sarecycline versus 19.6% placebo (P<0.05, chest). The percentage of patients with truncal acne IGA success at week 12 in SC1402 was 33.2% sarecycline versus 25.7% placebo (P<0.05, back) and 36.6% sarecycline versus 21.6% placebo (P<0.001, chest). Sarecycline also demonstrated a therapeutic effect on non-inflammatory (comedonal) lesions with greater mean absolute changes from baseline 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.[32] In study SC1401, sarecycline-treated patients had a mean absolute change from baseline in non-inflammatory lesions at week 12 of −15.1 versus −11.2 in placebo-treated patients (P<0.01), while in study SC1402 the mean absolute change was −16.2 for sarecycline-treated patients' non-inflammatory lesions versus −13.4 for placebo (P<0.01).

Safety

In the pivotal Phase 3 clinical trials (SC1401 and SC1402), treatment-emergent adverse events (TEAEs) occurred in 29.3% and 25% of patients in the sarecycline groups (SC1401 and SC1402, respectively) and in 29.8% and 26.7% of patients in the placebo groups. Adverse events included 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%) for SC1401, and nasopharyngitis (2.5% sarecycline and 2.9% placebo) and headache (2.9% and 4.9%) in SC1402, but most were not considered treatment-related.[32] There were nearly as many adverse events (AEs) in the placebo groups as in the treatment groups in these studies. In study SC1401, 3 of the 483 patients (0.6%) in the sarecycline group, and 7 of the 481 (1.4%) of patients in the placebo group discontinued the study due to AEs. In study SC1402 11/513 (2.1%) and 6/513 (1.2%) patients in the sarecycline and placebo groups, respectively, discontinued due to AEs. The majority of these discontinuations were judged by the investigator as possibly related or related to the study treatment. Vulvovaginal candidiasis and vulvovaginal mycotic infections were rare (1.1% and 0.7% of female patients, respectively, in SC1401 and 0.3% and 1.0% of female patients, respectively, in SC1402). No cases of these infections occurred in the placebo group in either study (Table 6).[32]

Long-Term safety

A Phase 3, multicenter, open-label extension study evaluated the long-term safety of sarecycline (1.5 mg/kg/day) in patients with moderate to severe acne vulgaris up to 1 year.[33] Patients who had completed 12 weeks of study in

Table 6 Selected Treatment-Emergent Adverse Events Common to Tetracycline-Class Antibiotics

Selected TEAE Safety Population n (%)	SC1401		SC1402		SC1403
	Placebo (n=483)	Sarecycline (n=481)	Placebo (n=513)	Sarecycline (n=513)	Sarecycline (n=483)
Sunburn	2 (0.4)	3 (0.6)	1 (0.2)	4(0.8)	1(0.2)
Urticaria	1 (0.2)	0	2 (0.4)	1(0.2)	2(0.4)
Vulvovaginal mycotic infection[a]	0	2 (0.7)	0	3 (1.0)	2(0.8)
Vulvovaginal candidiasis[a]	0	3(1.1)	0	1(0.3)	1(0.2)
Nausea	12(2.5)	22(4.6)	5(1.0)	10(1.9)	10(2.1)
Dizziness	7(1.4)	3(0.6)	4(0.8)	2(0.4)	2(0.4)
Vomiting	7(1.4)	10(2.1)	2(0.4)	3(0.6)	9(1.9)
Diarrhea	8(1.7)	5(1.0)	6(1.2)	6(1.2)	1(0.2)
Tinnitus	0	0	0	0	0

Note: [a]Percentages calculated from the number of female patients.

SC1401 or SC1402 were followed at 52 centers in the United States for 9 months with study visits occurring at weeks 2, 6, 12, 18, 24, 32, and 40, or at early termination. A total of 483 patients were enrolled in the study, with 354 patients (73.3%) completing the study (Table 6). Overall, 38.9% of patients reported at least 1 TEAE. Only 2.5% withdrew from the study due to an AE. The most common adverse events (>2%) were nasopharyngitis (3.7%), upper respiratory tract infection (3.3%), headache (2.9%), and nausea (2.1%).[33]

Rates of TEAEs of special interest due to commonly reported association with other tetracyclines were evaluated in study subjects treated with sarecycline. The outcomes showed dizziness in 0.4%, sunburn in 0.2%, nausea in 2.1%, vomiting in 1.9%, and diarrhea in 0.2%.[33] There were no clinically meaningful safety findings new to tetracyclines in the pivotal trials with sarecycline, and no treatment-emergent serious AEs were considered related to study treatment. In the Phase 3 clinical studies of sarecycline, vestibular AEs were low (0.5% in the sarecycline group and 1.1% in the placebo group).

Regarding phototoxicity, in a Phase I study, one patient (0.2%) in the sarecycline group had a mild non-treatment-related sunburn. Another patient (0.2%) reported hyperpigmentation on his upper forehead, but this was thought to be due to excessive sun exposure and not related to study treatment. The patient went on to complete the study.[33]

Side Effects Among Broad-Spectrum Tetracyclines

Sarecycline has not been compared head to head with other tetracyclines, including either doxycycline or minocycline, in any clinical studies. However, historical reports of commonly recognized AEs often associated with tetracycline-class antibiotics show rates that are generally higher for both doxycycline and minocycline than those reported in the recent clinical trials for sarecycline (Table 6). The use of doxycycline has been associated with an increased risk of developing irritable bowel diseases (IBS) and inflammatory bowel diseases (IBD).[34–36] In a large retrospective study, patients who were prescribed doxycycline for their acne had a 2.25-fold greater risk of developing Crohn's disease.[35] Rare but significant systemic AEs have occurred primarily with the use of minocycline.[31,37] English literature was analyzed on doxycycline and minocycline adverse drug reactions (ADRs) between 1966 and 2003 by Smith and Leyden who found that minocycline was associated with 333 ADRs compared to 130 doxycycline-associated ADRs.[14] The ranges in incidence of AEs were 0% to 61% for doxycycline (24 clinical trials, n = 3833) and 11.7% to 83.3% for minocycline (11 clinical trials, n = 788). Extended-release formulations of minocycline that incorporate weight-based dosing have been shown to exhibit lower rates of acute vestibular side effects compared to immediate-release formulations of minocycline.[38,39]

Conclusion

Sarecycline is an oral antibiotic, specifically designed for acne, and approved by the FDA in 2018 for the treatment of AV in patients 9 years old and above. It has demonstrated clinical efficacy in moderate to severe AV, as early as 3 weeks. It has been studied in both inflammatory (face and trunk) and non-inflammatory (comedonal) acne lesions with few adverse events and a safety profile established for up to 1 year.[32,33] Its narrow-spectrum antibacterial activity, demonstrated by reduced in-vitro activity against Gram-negative bacteria commonly found in the human gut microbiota, along with lower penetration of the blood-brain barrier may have contributed to not only the fewer adverse events observed in clinical trials but also the low potential for inducing bacterial resistance. Further studies are needed to continue monitoring adverse events. Altogether, sarecycline holds great promise as a new treatment for acne and the first novel tetracycline-class drug to be approved for acne treatment in several decades.

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Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

JLJ is an employee of DerMEDit and reports personal fees from Almirall, during the conduct of the study. AYM receives funds as consultant (C), clinical study investigator (I), and speaker (SP) from Almirall (C,I,SP), Foamix (I,SP), Galderma (I), Mayne Pharma (C,I), and Naked Biome (I). JDR has served as a consultant, researcher and speaker for Almirall and Bausch Health and as a consultant and speaker

for Mayne Pharma and EPI Health. AG is serving as the Director of R&D and Medical Affairs at Almirall (US). The authors report no other conflicts of interest in this work.

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