Safety and Tolerability of Sarecycline for the Treatment of Acne Vulgaris

Results from a Phase III, Multicenter, Open-label Extension Study and a Phase I Phototoxicity Study

David M. Pariser[1], Lawrence J. Green[2], Edward L. Lain[3], Carsten Schmitz[4]*, Amy S. Chinigo[4], Brian McNamee[5], David R. Berk[4]*, Jamison Hoffman[6], Ayman Grada[6]

[1]Eastern Virginia Medical School and Virginia Clinical Research, Inc., Norfolk, VA, USA; [2]George Washington University School of Medicine, Washington, DC, USA;
[3]Austin Institute for Clinical Research, Pflugerville, TX, USA; [4]Allergan plc, Irvine, CA, USA; [5]Allergan Biologics Ltd, Liverpool, UK; *Former employees; [6]Almirall LLC., Exton, PA, USA
Email: ayman.grada@Almirall.com

Background

- Sarecycline is a novel, narrow-spectrum, once-daily, oral tetracycline-class antibiotic indicated for the treatment of inflammatory lesions of non-nodular moderate-to-severe acne[1]
- Poor tolerability and bacterial resistance concerns may limit the use of broad-spectrum tetracycline antibiotics for the treatment of acne[1]

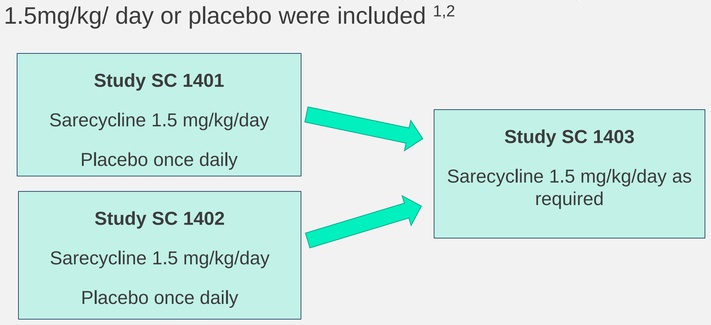
Objective

- To evaluate the long-term safety, tolerability, and patterns of use for the once-daily oral, narrow-spectrum antibiotic sarecycline in patients with moderate-to-severe acne vulgaris during a 40-week Phase III, multicenter, open-label extension study[1]
- Additionally, a Phase I, single-center, randomized, double-blind, placebo-controlled, crossover study conducted to evaluate the potential of sarecycline to cause phototoxicity[1]

Methods

Open-label Safety Evaluation

- Patients aged 9-years of age or older with moderate-to-severe acne who completed one of two prior Phase III, double-blind, placebo-controlled, 12-week trials in which they received sarecycline 1.5mg/kg/ day or placebo were included [1,2]



- Primary assessment was the safety of sarecycline treatment over one year as measured by adverse events (AEs), vital signs, electrocardiograms (ECGs), clinical laboratory tests, and physical examinations
- Study visits occurred at Weeks 2, 6, 12, 18, 24, 32, and 40

Phototoxicity Study

- 19 Subjects (healthy; non-smoker, men, aged 18 to 45 years) received placebo or 240mg of sarecycline in a random order in each of the two treatment periods (not weight based)
- A two-treatment, two-period, two-sequence crossover design. Treatment periods were separated by at least nine days
- At three hours after administration of the study treatment, a previously unexposed area of each subject's back was irradiated with 16J/cm^2 of UVA, after which point, another area was irradiated with UVA/UVB at 50 percent of the subject's minimum erythemal dose (MED)
- UV-exposed skin was assessed visually at 24, 48, and 72 hours after irradiation, and UV-induced skin reaction was evaluated using dermal response score scale
- Mean and maximum numerical UV-induced dermal response scores were determined for sarecycline and placebo

Results

- The safety population included 483 patients; 354 patients (73.3%) completed the study [1]
- The most common TEAEs were nasopharyngitis (3.7%), upper-respiratory-tract infection (3.3%), headache (2.9%), and nausea (2.1%). Clinical laboratory evaluations suggested no clinically meaningful differences between the treatment sequences [1]
- Rates of TEAEs commonly associated with other tetracycline antibiotics were for **dizziness (0.4%) and sunburn (0.2%), and for gastrointestinal TEAEs, nausea (2.1%), vomiting (1.9%), and diarrhea (1.0%). Vulvovaginal mycotic infection (0.8%)** [1]
- Dermal response to UV exposure did not exceed mild erythema with either sarecycline or placebo at any time point, and the mean and maximum UV-induced dermal response scores for both sarecycline and placebo were low. No TEAEs or serious AEs were reported in the phototoxicity study

Table 1. Summary of subject demographics and baseline characteristics[1]

	Placebo / Sarecycline[a] (N=236)	Sarecycline / Sarecycline[b] (N=247)	Total[c] (N=483)
Mean (SD) age, years	18.7 (6.0)	18.4 (5.9)	18.5 (6.0)
≥9 and <12 years	2	3	5
≥12 and <18 years	138	152	290
≥18 years	96	92	188
Gender, n (%)	48.3	49.4	48.9
Female	122 (51.7)	125 (50.6)	247 (51.1)
Male	114 (48.3)	122 (49.4)	236 (48.9)
BMI, mean (SD), kg/m2	25.07 (5.4)	25.36 (6.1)	25.22 (5.8)
Race, n (%)			
White	198 (83.9)	201 (81.4)	399 (82.6)
Black or African American	28 (11.9)	29 (11.7)	57 (11.8)
Other	10 (4.2)	16 (6.5)	26 (5.4)
Investigator's Global Assessment, n (%)			
3 (moderate)	191 (80.9)	207 (83.8)	398 (82.4)
4 (severe)	45 (19.1)	40 (16.2)	85 (17.6)

[a]The Placebo/Sarecycline population contained patients who received placebo in the placebo-controlled, double-blind lead-in trials.
[b] The Sarecycline/Sarecycline populations contained patients who received sarecycline in the placebo-controlled, double-blind lead-in trials.
[c] Safety Population included all participants among the screened population who were exposed to study treatment (sarecycline) in either the double-blind lead-in study or this open-label extension study.
SD, standard deviation

Table 2. Summary of subject demographics and baseline characteristics [1] (Phase-I Phototoxicity Study)

	TOTAL (n = 19)
Age, mean (SD), years	30.7 (9.0)
White, n (%)	19 (100)
Hispanic/Latino, n (%)	6 (31.6)
Body mass index, mean (SD), kg/m^2	26.1 (2.5)
Fitzpatrick Skin Phototype, n (%)	
I	3 (15.8)
II	7 (36.8)
III	9 (47.4)

SD: standard deviation.
[a]Number enrolled and randomized; one subject was lost to follow-up and excluded from phototoxicity analysis.

Table 3. Common TEAEs (≥2% of patients in either group; safety population)

Patients, n (%)	Placebo / Sarecycline[a] (N=236)	Sarecycline / Sarecycline[b] (N=247)	Total[c] (N=483)
Nasopharyngitis	13 (5.5)	5 (2.0)	18 (3.7)
Upper-respiratory-tract infection	7 (3.0)	9 (3.6)	16 (3.3)
Headache	9 (3.8)	5 (2.0)[b]	14 (2.9)[b]
Nausea	4 (1.7)[b]	6 (2.4)	10 (2.1)[b]
Vomiting	3 (1.3)[b]	6 (2.4)	9 (1.9)[b]
Urinary tract infection	2 (0.8)	5 (2.0)	7 (1.4)

[a]One patient in each treatment group had an AE that occurred more than 30 days after the dose of sarecycline.
[b]One of these TEAEs was an AE that occurred more than 30 days after the last dose of sarecycline but before study completion.
AE: adverse event; TEAE: treatment-emergent adverse event.

Table 4. Overall summary of patients with adverse events (safety population)

Paitents, n (%)	Placebo / Sarecycline[a] (N=236)	Sarecycline / Sarecycline[b] (N=247)	Total[c] (N=483)
Any TEAE	94 (39.8)	94 (38.1)	188 (38.9)
Any severe TEAE	3 (1.3)	2 (0.8)	5 (1.0)
SAEs	2 (0.8)	2 (0.8)	4 (0.8)
Abdominal pain	0	1 (0.4)	1 (0.2)
Anemia	1 (0.4)	0	1 (0.2)
Dehydration	0	1 (0.4)	1 (0.2)
Headache[a]	1 (0.4)	0	1 (0.2)
Peptic Ulcer[b]	1 (0.4)	0	1 (0.2)

[a]Considered possibly related to study treatment according to the investigator's assessment
[b]Experienced by the same patient with anemia
SAE: serious adverse event; TEAE: treatment-emergent adverse event

Conclusion

- Sarecycline was associated with low rates of TEAEs, with nasopharyngitis, upper-respiratory-tract infection, headache, and nausea being the only TEAEs reported by two percent or more of patients with moderate-to-severe acne vulgaris aged nine years or older treated with sarecycline once daily for up to 40 weeks.
- Adverse events commonly associated with other tetracycline antibiotics such as dizziness, sunburn, nausea, vomiting, and diarrhea were low
- No clinically meaningful safety findings were noted

References

1. Pariser, David M., Lawrence J. Green, Carsten Schmitz, Amy Chinigo, Brian McNamee, and David R. Berk. "Safety and Tolerability of Sarecycline for the Treatment of Acne Vulgaris: Results from a Phase III, Multicenter, Open-Label Study and a Phase I Phototoxicity Study : JCAD: The Journal of Clinical and Aesthetic Dermatology." JCAD, November 1, 2019. http://jcadonline.com/sarecycline-acne/. **ClinicalTrials.gov Registration: NCT02413346**
2. Moore A, Green LJ, Bruce S, Sadick N, Tschen E, Werschler P, Cook-Bolden FE, Dhawan SS, Forsha D, Gold MH, Guenthner S. 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. Journal of drugs in dermatology: JDD. 2018 Sep;17(9):987-96.

Disclosures

Financial Support: This study was funded and sponsored by Allergan. Sarecycline is owned and marketed by Almirall, LLC.