Reduced Blood-brain Barrier Penetration of Sarecycline Relative to Minocycline in Rats Corresponds with Lipophilicity and Low Vestibular Side Effects

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Introduction

- Sarecycline is an FDA-approved narrow-spectrum tetracycline-class oral antibiotic specifically designed for the treatment of moderate-to-severe acne vulgaris.
- Doxycycline and minocycline have historically been reported with side effects of dizziness, vertigo, or tinnitus.
- Pooled data from 2 Phase III randomized controlled trials (n=2002) and a 40-week open-label extension study (n=483) for sarecycline reported low rates of vestibular events (dizziness (≤0.5%), vertigo (0%), and tinnitus (0%)).
- We sought to investigate penetration of the blood-brain barrier of sarecycline relative to minocycline in a rat model and the relative lipophilicity of sarecycline compared to minocycline and doxycycline.

Methods

Table 1. **Blood-brain barrier penetration**: Rats (pre-cannulated, jugular vein) were dosed with IV sarecycline or minocycline at a total dose of 1.0 mg/kg. Rats were fasted overnight (about 16 hours) prior to dosing and access to food was restored 2 hours after dosing. Animals were euthanized via CO_2 and whole blood (via heart puncture) and brain were collected from 2 rats at each of the following time points: 1, 3 and 6 hr post dosing.

Table 2. **Lipophilicity**: The octanol/water distribution coefficients (logD) of sarecycline, minocycline, and doxycycline were measured using the shake flask method at pH 5.5 and 7.4 at 25°C.

Results - Table 1. Unlike minocycline, sarecycline was not detectable in the brain in rats

Time (hours)	Mcn-pl µg/mL	Scn-pl µg/mL	Mcn-br µg/g	Scn-br µg/g
1	0.333	0.460	0.074	BLQ
3	0.174	0.217	0.139	BLQ
6	0.077	0.049	0.068	BLQ

Pl = plasma, Br = brain, Mcn = minocycline, Scn = sarecycline
Limit of quantitation (LOQ) (plasma) = 0.025 µg/mL, LOQ (brain) = 0.05 µg/g; BLQ – Below the limit of quantitation

Results - Table 2. Sarecycline has slightly lower lipophilicity than minocycline and doxycycline

Compound	pH 5.5	pH 7.4
Sarecycline HCl	-0.16 ± 0.01	-0.26 ± 0.01
Doxycycline HCl	-0.00 ± 0.02	-0.18 ± 0.03
Minocycline HCl	0.09 ± 0.02	0.12 ± 0.02

Octanol/water distribution coefficients of sarecycline HCl, minocycline HCl, and doxycycline HCl at 25°C. The numbers after ± represent standard deviations obtained from triplicate samples.

Discussion - Table 3. Vestibular adverse events were low in Phase 3 efficacy and safety studies for sarecycline

Vestibular effects	Sarecycline (n=994)	Placebo (n=996)
Dizziness	5 (0.5)	11 (1.1)
Vertigo	0	0
Tinnitus	0	0

- Pooled safety data from 2 identical Phase 3 studies (SC1401, SC1402).
- 12 week double-blind treatment with study visits at 3, 6, 9, and 12 weeks

Reference: Moore A, Green LJ, Bruce S, et al. 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.

Discussion - Table 4. Vestibular adverse events were low in an open-label long-term safety study for sarecycline

Vestibular effects	Placebo/ Sarecycline (n=236)	Sarecycline/ Sarecycline (n=247)	Total (n=483)
Dizziness	1 (0.4)	1 (0.4)	2 (0.4)
Vertigo	0	0	0
Tinnitus	0	0	0

- Patients from previous 12 week Phase 3 studies received once daily sarecycline for up to 40 weeks.

Reference: Pariser DM, Green LJ, Lain EL, et al. 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. *Journal of Clinical and Aesthetic Dermatology.* 2019;12(11):E53-E62.

Conclusions

- Sarecycline's inability to cross the blood-brain barrier compared to minocycline corresponds with sarecycline's lower lipophilicity and may explain the low rate of vestibular adverse events observed in sarecycline's clinical trials.

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