ORAL SARECYCLINE FOR TREATMENT OF PAPULOPUSTULAR ROSACEA: RESULTS OF A PILOT SUDY EVALUATION OF EFFECTIVENESS AND SAFETY

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Introduction

Cutaneous rosacea is a common inflammatory facial dermatosis characterized visibly by persistent central facial erythema, episodic dilation of vasculature (flushing), and telangiectasias, with or without papulopustular lesions and phymas.[1,2]

Beyond the signs and symptoms of rosacea, the disorder may be stigmatizing, can negatively influence workplace behavior, and has been associated with several adverse psychosocial sequelae.[3] Flushing episodes and papulopustular lesions have been reported by patients to be the most bothersome manifestations of rosacea across all severities.[4]

The second-generation broad spectrum tetracyclines—doxycycline and minocycline—have been commonly used as oral therapies for rosacea over the past several years.[5] In 2018, sarecycline (Seysara, Almirall), a third-generation oral tetracycline, was FDA-approved for treatment of acne. It exhibits a narrow spectrum of antibiotic activity and a low rate of adverse effects historically associated with oral tetracyclines, such as photosensitivity, GI side effects, vertigo, and vaginal yeast infections.[6]

Due to the well-established role for oral tetracyclines in rosacea and the desire to circumvent emergence of antibiotic resistant bacteria as much as possible, a pilot study was completed to evaluate oral sarecycline in adults with papulopustular rosacea.

Study Design

This was a prospective, parallel group, randomized, multicenter, investigator-blinded, IRB-approved clinical trial.

Study duration: 12 weeks; Scheduled visits/assessments: Screening, Baseline, Week 4, Week 8, Week 12 (end of study (EOS]).

Eligible subjects: Adults (≥18 years) of either gender with moderate or severe rosacea, based on Investigator Global Assessment rating with at least 15 and ≤50 facial papules and pustules but no more than 2 facial nodules.

Randomization: Subjects were randomized to 2 groups at a 3:1 ratio
Group A: Received the brand tablet formulation of oral sarecycline (Seysara) once daily based on weight-based dosing as described in the approved product labeling for acne vulgaris
Group B: Received one tablet daily of Centrum Adult Multivitamin

Efficacy Endpoints: *Primary:* Percent of subjects achieving clear or almost clear based on IGA grading scale;
Percent reduction of inflammatory lesions at week 12

Secondary: Percent of subjects achieving clear or almost clear based on the IGA rating and percent reduction of inflammatory lesions at week 4 and week 8;
Subject Global Assessment (SGA);
Tolerability, as measured by severity of erythema, dryness, peeling, oiliness, and pruritis

Statistical Analysis: Conducted on an intent-to-treat basis; all tests two-sided and interpreted at a 5% significance level. Comparisons between treatment groups performed using an ANCOVA technique; baseline values used as the covariate providing necessary assumptions for parametric test satisfaction. The Wilcoxon Rank-Sum test used if needed assumptions for parametric testing were not satisfied; comparative mean scores were also evaluated.

Study Evaluations

IGA GRADING SCALE

Table 1. Investigator Global Assessment

GRADE	DESCRIPTION
0=Clear	No inflammatory lesions present, no erythema
1=Almost Clear	Very few small papules/pustules, very mild erythema present
2=Mild	Few small or large papules/pustules, moderate erythema
3=Moderate	Several small or large papules/pustules, moderate erythema
4=Severe	Numerous small and/or large papules/pustules, severe erythema

INFLAMMATORY LESIONS (PAPULOPUSTULAR LESIONS)
• Number of facial papules/pustules at each study visit

SUBJECT GLOBAL ASSESSMENT (SGA)
• 5-point grading system:
Much worse, Slightly worse, Same, Slightly better, Much better

TOLERABILITY
• Current severity of erythema, dryness, peeling, and oiliness rated at each visit using a 5-point scale for each:
0=absent, 1=trace, 2=mild, 3=moderate, 4=severe

• Current severity of pruritus was documented from the subject at each visit using a 6-point scale:
0=absent, 1=trace, 2=mild, 3=moderate, 4=marked, 5=severe

Demographics

102 adult subjects with moderate-to-severe papulopustular rosacea were enrolled; 97 completed the study (72 in Group A, 25 in Centrum Group B).

Majority of subjects were female (n=80; 82%) and white (n=95; 98%)

Mean age was 52.4 years (SD = 14.5) and similar in both groups (age range 22 years to 81 years).

Baseline, IGA scores and inflammatory lesion counts were evenly distributed between treatments. Erythema, dryness, peeling, oiliness, and pruritus were evenly distributed at baseline; burning sensation was also not significantly different between groups (p=0.07).

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Study Results

Both study groups met the primary endpoint (Group A: p< .001, Group B: p = .0008), however, Group A (Sarecycline) had greater reductions in IGA scores (p < .0001). Sarecycline performed significantly better than the multivitamin (p < .0001). (Figure 1)

Sarecycline was associated with statistically superior total inflammatory lesion count reductions at week 12 (EOS), compared to multivitamin (p<.0001). Absolute and percent lesion count reductions were greater in the sarecycline group at all study visits (p < .001 for all). (Table 2).

A significant favorable change in SGA scores (Secondary endpoint) was seenin the sarecycline group (p<.001), but not in the multivitamin group (p=.68) from week 4 to week 12.

Sarecycline was well tolerated. At week 12, absent or trace ratings for erythema were significantly better in the sarecycline group (63%), compared to the multivitamin group (12%; p<.0001). By week 12, significant reductions in dryness (p = .01) and peeling (p=.02) were observed in the sarecycline group. Oiliness was not commonly observed among subjects in either treatment group. Sarecycline-treated subjects exhibited statistically significantly greater reduction in skin burning (p=0.01). Significant reductions in pruritus were seen only in the sarecycline group from baseline to week 12 (p<.001).

Twenty-six AEs occurred in 16 subjects in the sarecycline group. Nine were considered "definitely related," 3 were "probably related," and 3 were "possibly related" to study drug (7 were rated as mild, 17 as moderate, 2 as severe). None were determined to be serious AEs. The AEs of specific interest with a tetracycline derivative were nausea (n=2), headache (n=2), and facial sunburn (n=2). Sarecycline was discontinued in 3 subjects, with 2 AEs probably related to sarecycline (headache, gastroenteritis).

Figure 1.

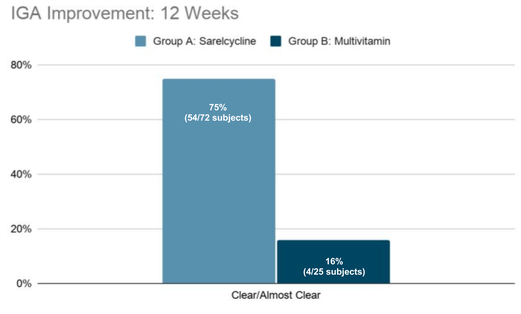

Table 2. Primary Efficacy Endpoint Data Based on Total Inflammatory Lesion Counts at Each Study Visit

		CENTRUM (C)			SARECYCLINE (S)			
Visit	Statistics	Inflammatory Lesions	Change from Visit 1	P-value	Inflammatory Lesions	Change from Visit 1	P-value	C vs. S P-value
Visit 1	Mean (SD)	19 (7)			21 (9)			0.13
(Baseline)	Median	17 (16, 20)			18 (16, 23)			
	Min, Max	15, 42			14, 48			
Visit 2	Mean (SD)	14 (10)	-5 (5)	.0003	11 (10)	-11 (6)	< .0001	< .0001
(Week 4)	Median	12 (9, 16)	-5 (-9, -2)		8 (4, 13)	-10 (-15, -7)		
	Min, Max	1, 49	-15, 7		0, 43	-28, 4		
	% Change from BL (SD)		-31 (30)	.0002		-56 (29)	< .0001	< .0001
Visit 3	Mean (SD)	12 (11)	-8 (7)	.0005	7 (8)	-14 (6)	< .0001	< .0001
(Week 8)	Median	8 (5, 12)	-10 (-14, -5)		4 (1, 10)	-15 (-16, -11)		
	Min, Max	1, 47	-16, 15		0, 32	-28, 4		
	% Change from BL (SD)		-44 (42)	.0005		-71 (27)	< .0001	.0002
Visit 4	Mean (SD)	9 (11)	-11 (7)	< .0001	5 (7)	-16 (6)	< .0001	< .0001
(Week 12)	Median	6 (4, 8)	-11 (-15, -7)		2 (0, 8)	-16, (-19, -13)		
	Min, Max	0, 45	-22, 4		0, 32	-31, 4		
	% Change from BL (SD)		-60 (32)	< .0001		-80 (24)	< .0001	< .0001

Key: BL, Baseline; SD, Standard Deviation

Conclusion

Results of this pilot study demonstrate that oral sarecycline is efficacious as early as 4 weeks and safe for the treatment of papulopustular rosacea in adults based on IGA assessments, total inflammatory lesion reductions, SGA outcomes, and safety evaluations.

Notably, this study assesses facial skin signs and symptoms at baseline and throughout the study, and evaluates results with oral therapy only; therefore the noted significant improvements in facial skin manifestations such erythema, dryness, peeling, burning, and pruritus are believed to be reflective of the therapeutic response of rosacea to oral sarecycline.

The type, frequency, and severity of AEs reported in this study are consistent with what has been reported with oral sarecycline in clinical trials completed to date for treatment of acne, including the pivotal studies performed for FDA approval.

The authors suggest additional studies be conducted to further evaluate the use of oral sarecycline for the treatment of rosacea.

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