# EFFECT OF COMBINATION THERAPY ON VISIBLE/NON-VISIBLE SYMPTOMS, AND DISEASE BURDEN ASSOCIATED WITH SEVERE ROSACEA: **RESULTS FROM A POST-HOC ANALYSIS OF A RANDOMIZED CONTROLLED TRIAL**

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#### SYNOPSIS

- Rosacea affects over 16 million people in the US with symptoms in central areas of the face, causing flushing, stinging/burning, chronic erythema, and inflammatory lesions, with major negative impact on quality of life.<sup>1-3</sup>
- The disease is chronic and inflammatory in nature and burden typically extends beyond visible symptoms with impact on emotional, social, and psychological aspects of life.<sup>4</sup>
- In a global survey (N = 710) evaluating impact of symptoms associated with disease burden in rosacea, non-visible symptoms such as itching, burning/pain, and swelling were significantly associated with high disease burden.<sup>4</sup>

### OBJECTIVE

The objective of this post-hoc analysis was to extend beyond the Phase 4 study looking at the efficacy and safety of ivermectin 1% cream (IVM) and doxycycline 40 mg modified release (DMR) in severe rosacea subjects, and highlight the impact on the visible and nonvisible symptoms associated with rosacea.

The relationship between the following parameters was assessed:

- Impact of changes in the visible and nonvisible symptoms of rosacea on Dermatology Life Quality Index (DLQI)
- Impact of baseline lesion count, prior rosacea treatment, and disease duration on efficacy of combination therapy

### RESULTS

- Impact of stinging/burning and 'clear' vs 'almost clear' on DLQI
- A significant correlation was seen between change in stinging/burning over 12 weeks and change in DLQI score over 12 weeks (0.325; P=.000). [Figures 1a-b]
- Significant correlations between the reduction in stinging/burning and individual DLQI parameters were found for itchy, painful skin (0.338; P = .000), problems with partner/friends (0.247; P = .000), feeling embarrassed (0.243; P = .000), and social activities (0.237; P=.000). [Figure 1c]
- Significant correlations between 'clear' or 'almost clear' and individual DLQI parameters were found for feeling embarrassed (0.253; P=.000), interference with shopping/home garden (-0.161; P=.012), and social activities (-0.143; P=.026). [Figure 1d]
- Severity of flushing and impact on DLQI
- There was a significant correlation between change in flushing severity over 12 weeks and DLQI change over 12 weeks (0.222; *P*=.001). [Figure 2]
- Impact of baseline lesion count, previous oral and/or topical treatment, and disease duration on efficacy of combination therapy
- At week 12, there was a significant and strong correlation (-0.727; P=.000) between lesion counts at baseline and absolute change in lesion counts for the combined treatment arms. [Figures 3 a-c]
- In the combination therapy arm, the highest significant percent reduction in lesion count was observed for previous oral plus topical treatment (P=.016). [Figure 4]
- Disease duration for up to 9 years was significantly correlated with highest percent change in lesion counts from baseline to week 12 in the combination therapy arm (P=.006). [Figure 5]

## CONCLUSIONS

Combined IVM and DMR improved both visible (eg, inflammatory lesions, erythema, flushing) of rosacea. Correlations between symptom reduction and DLQI suggest improvements in different aspects of quality of life. Results from this Phase 4 study and this post-hoc analysis emphasize the importance of targeting both the visible and nonvisible signs and symptoms in patients with severe rosacea with combination therapy to create best outcomes.



- Combination therapy with multiple mechanisms of actions are often used to manage symptoms associated with rosacea. However, limited numbers of controlled studies have evaluated impact of combination therapy vs monotherapy on reducing the signs and symptoms associated with rosacea.<sup>5</sup>
- Ivermectin and doxycycline are two well-established molecules with proven efficacy and safety, targeting different and complementary pathological features of severe rosacea.<sup>5</sup>

#### METHODS

The study was a 12-week, multicenter, randomized, investigator-blinded, parallel-group comparative study in 273 adults with severe rosacea, as previously described (ClinicalTrials.gov number: NCT03075891).<sup>4</sup> Post-hoc analyses assessed the correlations between change in visible symptoms, stinging/burning, flushing severity, and Dermatology Life Quality Index (DLQI) and impact on disease burden using the Spearman's rank correlation coefficient, Mann–Whitney U test, Chi-square test, or Kruskal–Wallis test. Analyses were performed on the combined treatment arms.

Impact of Reach	ning 'Clear' and 'Almost Clea	ir' on DLQI
d)		
		IGA score at 12 weeks (LOCF)
How embarrassed or	Correlation coefficient	-0.253
self-conscious have you been because of your skin?	<i>P</i> -value	0.000
	Ν	243
How much has your skin interfered with you going	Correlation coefficient	-0.161
shopping or looking after your home or garden?	<i>P</i> -value	0.012
	Ν	243
How much has your skin	Correlation coefficient	-0.143
affected any social or leisure activities?	ected any social or leisure <i>P</i> -value	0.026
	Ν	243

Analyses were performed on the combined treatment arms

Figure 1: d) Spearman's correlation between individual DLQI parameters and completely/almost clear by IGA (the three parameters with the strongest correlations are shown)





Figure 3: a) Box plot of number of lesions at baseline versus absolute change in lesion count from baseline to week 12 for the treatment arms combined. Association between number of lesions at baseline versus absolute change in lesion count from baseline to week 12 in the treatment arms combined examined by b) Kruskal–Wallis test and c) Spearman's correlation

Change in lesic

Asymp. sig. 0.000 12 weeks (LOCF)

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#### Reference

. Steinhoff M, Schmelz M, Schauber J. Facial erythema of rosacea - aetiology, different pathophysiologies and treatment options. Acta Derm Venereol. 2016;96(5):579–586.

- 2. Schaller M, Almeida LMC, Bewley A, et al. Recommendations for rosacea diagnosis, classification and management: Update from the global ROSacea COnsensus (ROSCO) 2019 panel. Br J Dermatol. August 2019. [Epub ahead of print]
- 3. National Rosacea Society Website. https://www.rosacea.org/rosacea-review/2010/winter/rosacea-now-estimated-to-affect-at-least-16-million-americans. Accessed November 21, 2019.
- 4. Tan J, Steinhoff M, Bewley A, Gieler U, Rives V. Characterizing high-burden rosacea subjects: a multivariate risk factor analysis from a global survey. J Dermatolog Treat. June 2019. [Epub ahead of print]
- 5. Schaller M, Kemeny L, Havlickova B, et al. A randomized phase 3b/4 study to evaluate concomitant use of topical ivermectin 1% cream and placebo in the treatment of severe rosacea. J Am Acad Dermatol. May 2019. [Epub ahead of print]

Impact	Impact of Prior Rosacea Treatment on Efficacy of Combination Therapy					
Per	Percentage change in lesion count from baseline to week 12 (LOCF)					
Treatment	Oral, topical or both	Mean	N	Standard deviation		
	Oral	-75.9	6	17.6		
	Topical	-70.2	31	25.1		
IVM – DMK	Oral + topical	-84.8	18	23.7		
	Total	-75.6	55	24.5		
Treatn	ient	Percento from bo	ige change in lesion iseline to week 12 (L	count OCF)		

Asymp. sig. week 12 investigated by Kruskal–Wallis test in the individual treatment arms and in the treatment arms co

IVM + DMI

Impact of Disease Duration on Efficacy of Combination Therapy

Percentage change in lesion count from baseline to week 12 (LOCF)					
Treatment	Duration of rosacea	Mean	N	Standard deviation	
IVM + DMR	0–4 years	-75.6	46	22.4	
	5–9 years	-86.5	39	17.8	
	$\geq$ 10 years	-79.8	50	22.9	
	Total	-80.3	135	21.7	
Treatn	1ent	Percentage chang from baseline to		n count (LOCF)	
IVM + DMR		Chi-square		10.266	
		df		2	
		Acymp cia		0.006	

Figure 5: Association between disease duration and percentage change in lesion count from baseline to week 12 investigated by Kruskal–Wallis test **IVM+DMR** Therapy Resulted in Notable **Reduction in Visible Symptoms** 



**Baseline** IGA=4; IL=55; CEA=2



IGA=1; IL=1; CEA=1

Fig 6. Subject Visual Symptom Improvement from Baseline to Week 12