



A randomized phase 3b/4 study to evaluate concomitant use of topical ivermectin 1% cream and doxycycline 40-mg modified-release capsules, versus topical ivermectin 1% cream and placebo in the treatment of severe rosacea

Martin Schaller, MD,^a Lajos Kemény, MD, PhD, DSc,^b Blanka Havlickova, MD, PhD,^c J. Mark Jackson, MD,^{d,e} Marcin Ambroziak, MD,^f Charles Lynde, MD,^g Melinda Gooderham, MD,^h Eva Remenyik, MD, PhD, DSc,ⁱ James Del Rosso, DO,^j Jolanta Weglowska, MD,^k Rajeev Chavda, MD,^l Nabil Kerrouche, MSc,^m Thomas Dirschka, MD,^{n,o} and Sandra Johnson, MD^p

Tübingen, Wuppertal, and Witten, Germany; Szeged and Debrecen, Hungary; Prague, Czech Republic; Louisville, Kentucky; Warsaw and Wrocław, Poland; Toronto and Peterborough, Ontario, Canada; Las Vegas, Nevada; Vevey, Switzerland; Sophia Antipolis, France; and Fort Smith, Arkansas

Background: Randomized controlled studies of combination therapies in rosacea are limited.

Objective: Evaluate the efficacy and safety of combining ivermectin 1% cream (IVM) and doxycycline 40-mg modified-release capsules (ie, 30-mg immediate-release and 10-mg delayed-release beads) (DMR) versus IVM and placebo for treatment of severe rosacea.

From the Department of Dermatology, Tübingen University Hospital^a; Department of Dermatology and Allergology, University of Szeged^b; Dermatology Center, Prague, Czech Republic^c; Division of Dermatology, University of Louisville^d; Forefront Dermatology, Louisville^e; Ambroziak Clinic, Warsaw^f; Department of Medicine, University of Toronto^g; SKiN Centre for Dermatology, Peterborough^h; Department of Dermatology, Faculty of Medicine, University of Debrecenⁱ; JDR Dermatology Research/Thomas Dermatology, Las Vegas^j; Niepubliczny Zakład Opieki Zdrowotnej multiMedica, Wrocław^k; Medical Evidence, Galderma S.A., Vevey^l; Galderma R&D, Sophia Antipolis^m; CentroDerm-Clinic, Wuppertalⁿ; and Faculty of Health, University of Witten-Herdecke, Witten^o; and Johnson Dermatology, Fort Smith.^p

Funding sources: Supported by Galderma.

Disclosure: Dr Schaller is a Galderma and Marpinion advisory board member; speaker for AbbVie, Bayer Healthcare, Galderma, and La Roche-Posay; recipient of research grants from Galderma and Bayer HealthCare; and investigator for GSK and Galderma. Dr Johnson is a Galderma advisory board member; Allermed/Greer/Nielsen, Regeneron and Sanofi Genzyme advisor; national speaker for Celgene, Allergan, and Candela Syneron; speaker for Galderma, Regeneron, and Sanofi Genzyme; and investigator for Galderma, Leo, Eli Lilly and Company, BMS, Foamix, and Gage. Dr Jackson is a Galderma investigator and advisor and Accutis advisor. Dr Kemény is an investigator for Galderma and a Janssen, Abbvie, Novartis, and Eli Lilly and Company advisory board member. Dr Remenyik is a Galderma investigator. Dr Del Rosso is a researcher for Galderma, BiopharmX, Foamix, and Leo Pharma (Bayer

Dermatology); Galderma advisory board member; speaker for Galderma, Leo Pharma (Bayer Dermatology), Mayne Pharma, and Almirall; and consultant for Leo Pharma (Bayer Dermatology), Mayne Pharma, Almirall, and Hovione. Dr Weglowska is an investigator for Galderma, Amgen, Sun Pharma, UCB, Regeneron, Leo Pharma, and Dermira and a Galderma advisory board member. Dr Gooderham is an investigator, speaker, and advisory board member for Galderma, Leo Pharma, and Valeant. Dr Ambroziak is an investigator for Galderma. Dr Lynde is an investigator, speaker, and advisory board member for Galderma, Leo Pharma, and Valeant/Bausch Health. Dr Havlickova is an investigator for Galderma. Dr Dirschka is an investigator for Galderma and has received research support from Almirall, Biofrontera, Galderma, Meda, and Schulze & Böhm GmbH. Dr Chavda is an employee of Galderma. Mr Kerrouche is a former employee of Galderma. No other conflicts of interest were declared.

Accepted for publication May 23, 2019.

Reprint requests: Martin Schaller, MD, Department of Dermatology, Eberhard Karls University Tübingen, Liebermeisterstrasse 25, 72076 Tübingen, Germany. E-mail: martin.schaller@med.uni-tuebingen.de.

Published online May 29, 2019.

0190-9622

© 2019 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jaad.2019.05.063>

Methods: This 12-week, multicenter, randomized, investigator-blinded, parallel-group comparative study randomized adult subjects with severe rosacea (Investigator's Global Assessment [IGA] score, 4) to receive either IVM and DMR (combination arm) or IVM and placebo (monotherapy).

Results: A total of 273 subjects participated. IVM and DMR displayed superior efficacy in reduction of inflammatory lesions (-80.3% vs -73.6% for monotherapy [$P = .032$]) and IGA score ($P = .032$). Combination therapy had a faster onset of action as of week 4; it significantly increased the number of subjects achieving an IGA score of 0 (11.9% vs 5.1% [$P = .043$]) and 100% lesion reduction (17.8% vs 7.2% [$P = .006$]) at week 12. Both treatments reduced the Clinician's Erythema Assessment score, stinging/burning, flushing episodes, Dermatology Life Quality Index score, and ocular signs/symptoms and were well tolerated.

Limitations: The duration of the study prevented evaluation of potential recurrences or further improvements.

Conclusion: Combining IVM and DMR can produce faster responses, improve response rates, and increase patient satisfaction in cases of severe rosacea. (J Am Acad Dermatol 2020;82:336-43.)

Key words: clear; combination therapy; concomitant use; doxycycline; individualized treatment; ivermectin; rosacea; rosacea treatment; severe rosacea.

Rosacea is a chronic inflammatory disease of the skin that displays a broad diversity of clinical manifestations¹ from erythema to inflammatory lesions and phymata, as well as ocular symptoms.² Combination therapy with topical and oral agents has become a common treatment option for patients with moderate or severe rosacea presenting with diverse signs and symptoms.^{3,4} By simultaneously treating different rosacea features, combination therapy might be preferable to monotherapies.³

Studies of combination therapy in rosacea are limited, with a lack of high-level evidence regarding the superiority of a combination therapy approach.⁵ The topical agents evaluated in previous combination therapy studies are metronidazole and azelaic acid, primarily with oral doxycycline.⁶ Concomitant use of ivermectin 1% cream (IVM) (Soolantra cream, Galderma Production Inc, Montreal, Canada) and brimonidine 0.33% gel (Mirvaso gel, Galderma Production Inc, Alby-sur-Chéran, France, and Düsseldorf, Germany) demonstrated superior efficacy regarding erythema and inflammatory lesions.⁷

CAPSULE SUMMARY

- Combination therapy may be complementary in the treatment of moderate to severe rosacea and better than monotherapy in many subjects.
- Adding doxycycline 40-mg modified-release capsules, to daily ivermectin 1% cream can produce faster responses, improve response rates, and increase patient satisfaction in cases of severe rosacea compared with 1% ivermectin alone.

Another study found that a combination of metronidazole 1% gel and doxycycline 40-mg modified-release capsules (DMR) (Oracea capsules, Catalent Pharma Solutions, LLC, Winchester, Kentucky), demonstrated a greater mean reduction in inflammatory lesion counts from baseline to week 12 than did metronidazole 1% gel (MetroGel gel, Galderma Production Inc, Quebec, Canada) alone.⁸ Additionally, IVM once daily showed superiority to metronidazole 0.75% cream twice

daily in terms of percentage reduction of inflammatory lesion counts and improvement in quality of life.⁹⁻¹¹ Because IVM and DMR may have both different and shared molecular targets in the inflammatory cascade of rosacea and because it is known that 2 agents may increase efficacy regardless of whether they act on different or common targets, their combined use may result in complementary action, superior efficacy, and an optimized clinical outcome.¹²

The main objective of the present study was to evaluate the efficacy of concomitant use of IVM and DMR versus that of IVM and placebo (PBO) in the treatment of severe rosacea.

Abbreviations used:

| | |
|-------|---|
| AE: | adverse event |
| CEA: | Clinician's Erythema Assessment |
| DLQI: | Dermatology Life Quality Index |
| DMR: | doxycycline 40-mg modified-release capsules |
| IGA: | Investigator's Global Assessment |
| ITT: | intent-to-treat |
| IVM: | ivermectin 1% cream |
| LOCF: | last observation carried forward |
| PBO: | placebo |
| SD: | standard deviation |

METHODS**Study design and randomization**

This was a multicenter, randomized, investigator-blinded, parallel-group comparison, 12-week, phase 3b/4 study. Subjects underwent 4 visits: a baseline/screening visit and visits at weeks 4, 8, and 12.

Before study initiation, a randomization list was generated by Galderma R&D. The RANUNI routine of the SAS software (SAS Institute Inc, Cary, NC) system was used to generate kit numbers, each of which was assigned to a subject by the investigator. The randomization list was accessible only to designated personnel responsible for labeling and handling the study treatments.

Subjects were randomized (1:1) to receive 12 weeks of combination therapy (IVM and DMR) or monotherapy (IVM and PBO). Treatment was allocated following the randomization list in chronological order of inclusion. Investigators were kept blinded by restricting their contact with the study treatments.

Study participants

Subjects were recruited from 39 sites in the United States, Canada, Germany, Czech Republic, Hungary, and Poland. Eligible subjects had severe rosacea (Investigator's Global Assessment [IGA] score of 4), were at least 18 years old, and had 20 to 70 inflammatory lesions (papules and pustules) and no more than 2 nodules on the face. The ethical principles of the Declaration of Helsinki (1964) and subsequent amendments and applicable regulatory requirements were followed. All subjects provided written consent.

Treatment

Subjects were instructed to apply IVM once daily in the evening, avoiding the eyes, eyelids, inner nose, mouth, and lips, and to take DMR or PBO once daily (preferably while fasting in the morning). Subjects were provided with and instructed to use controlled, rosacea-specific, noninvestigational skin

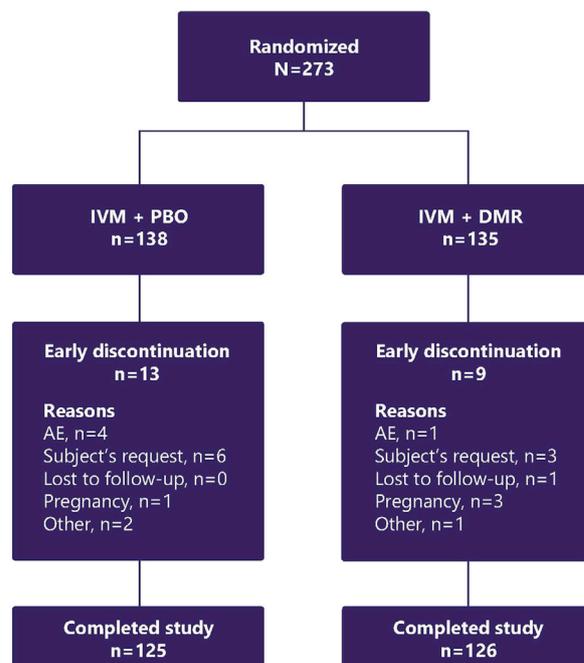


Fig 1. Rosacea. Subject disposition. *AE*, Adverse event; *DMR*, doxycycline 40-mg modified-release capsules; *IVM*, ivermectin 1% cream; *PBO*, placebo.

care products: gentle skin cleanser (Cetaphil Redness Relieving Foaming Face Wash [Galderma] before application of the study treatment) and facial moisturizer (Cetaphil Redness Relieving Facial Moisturizer [Galderma], sun protection factor 30 [20 in the United States], within 1 hour after application of the study treatment).

Study end points

The primary end point was the percentage change from baseline in inflammatory lesion count at week 12.

Secondary end points included percentage change from baseline in inflammatory lesion count at each intermediate visit; Clinician's Erythema Assessment (CEA), IGA, and stinging and burning at each postbaseline visit; global improvement in rosacea at the last visit; and percentage change from baseline in terms of flushing count per week over 12 weeks (medical history based on diaries kept beginning a week before starting treatment).

Other end points included global assessment of ocular signs and symptoms, if present at baseline, at each postbaseline visit (0-4 scale: 0, no ocular sign/symptom; 1, mild blepharitis with lid margin telangiectasia; 2, blepharoconjunctivitis; 3, blepharokeratoconjunctivitis; and 4, sclerokeratitis, anterior uveitis); Dermatology Life Quality Index (DLQI) questionnaire results at baseline and last visit; and subject satisfaction questionnaire at last visit.

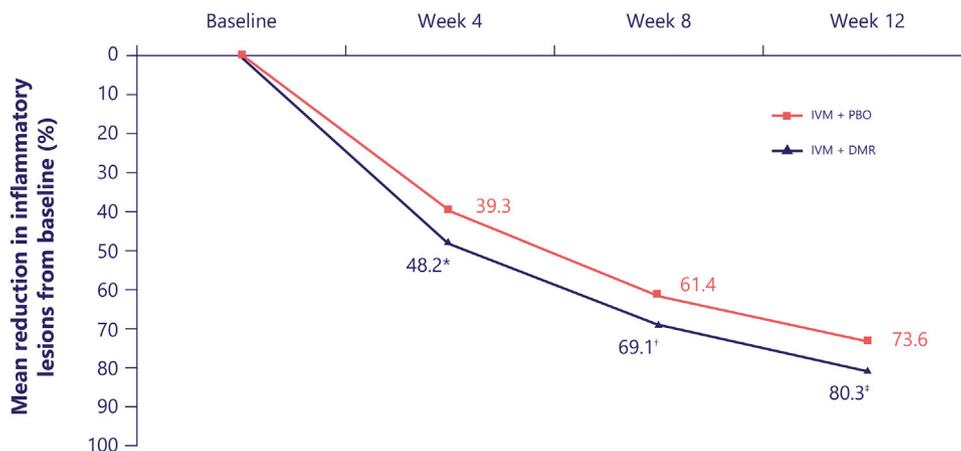


Fig 2. Rosacea. Mean percentage reduction of inflammatory lesions from baseline to week 12 (intent-to-treat/last observation carried forward population). Ivermectin 1% cream (IVM) and placebo (PBO) (n = 138); IVM and doxycycline 40-mg modified-release capsules (DMR) (n = 135). * $P = .007$; † $P < .012$; ‡ $P = .032$.

Post hoc analyses assessed the following: between-treatment differences in the proportion of subjects with IGA and CEA scores of 0 at week 12; the difference from baseline to week 12 in the proportion of subjects with stinging and burning, flushing, and ocular signs and symptoms; and the difference from baseline to last visit in the total mean DLQI score.

Adverse events (AEs) were recorded at each visit.

Statistical methods

Sample size was calculated on the basis of historical data from studies conducted with IVM and DMR as monotherapies.¹³⁻¹⁵ Considering a 15% rate of subjects excluded from the analysis at week 12, 135 subjects per group were to be enrolled to demonstrate at least a 15% difference at week 12 with 90% power.

All variables were analyzed in the intent-to-treat (ITT) population, except for safety variables that were analyzed in all subjects treated. Last observation carried forward was the primary method for imputation of missing data. The primary efficacy end point was analyzed by using the Cochran-Mantel-Haenszel method (the FREQ procedure from SAS software), stratified by center (or analysis center) after rdit transformation with row mean difference statistics, testing the hypothesis of equality on the ITT/last observation carried forward population. The same method was used for secondary end points, patient-reported outcomes, and post hoc analyses.

RESULTS

Subjects

A total of 273 subjects were enrolled and randomized in the study, of whom 251 (91.9%) completed

the study (Fig 1 [first subject screened on July 5, 2017; last subject completed the study on February 8, 2018]). At baseline, the groups were similar. All subjects had severe rosacea (IGA score, 4) and suffered from erythema classified as severe (CEA score, 4) in 60.4% of subjects and moderate in 30.0% of subjects. In addition, more than 85% of subjects reported skin stinging and burning, and more than 40% had ocular signs and symptoms. On average, subjects experienced approximately 5 episodes of flushing per week. Despite having severe rosacea, 56% of all subjects had not received any therapy for it in the past 6 months. Common previous therapies included metronidazole (26.3%), tetracyclines (10.3%), and ivermectin (6.2%). Among the subjects who received prior therapies, 64.8% had used only topical treatments, 25.3% had used both oral and topical treatments, and 9.9% had taken only oral treatments.

Efficacy

Both treatments resulted in a reduction of inflammatory lesions from baseline. This reduction was significantly greater in subjects receiving combination therapy than in those receiving monotherapy starting from week 4 ($P = .007$) across subsequent time points (Fig 2), suggesting a potentially faster onset of efficacy with the combination therapy over monotherapy. The mean percentage reduction in inflammatory lesions at week 12 was -80.3 ± 21.7 versus -73.6 ± 30.5 ($P = .032$) (Fig 2), with median values of -85.9 and -84.2 for combination therapy and monotherapy, respectively. Combination therapy also led to a higher proportion of subjects achieving 100% lesion clearance at week 12 (17.8% vs 7.2% for monotherapy [$P = .006$]). In addition,

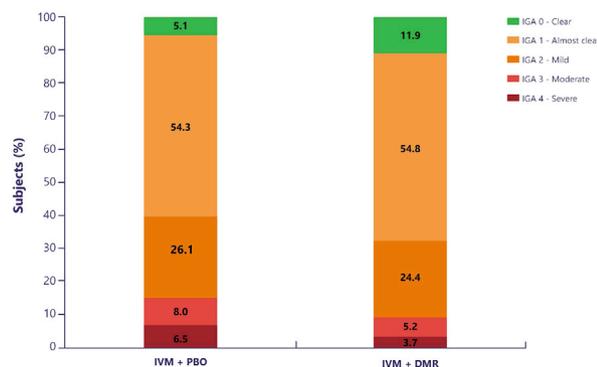


Fig 3. Rosacea. Investigator's Global Assessment (IGA) score assessed at week 12 (intent-to-treat/last observation carried forward population). Ivermectin 1% cream (IVM) and placebo (PBO) (n = 138); IVM and doxycycline 40-mg modified-release capsules (DMR) (n = 135).

combination therapy resulted in a greater improvement in IGA scores at all time points ($P < .05$), including at week 12 ($P = .032$), with a higher proportion of subjects with an IGA score of 0 (clear) at week 12 than in the group treated with monotherapy (11.9% vs 5.1% [$P = .43$] [post hoc analysis]) (Fig 3).

Other rosacea symptoms similarly improved with either treatment. Both treatments reduced CEA scores from baseline to week 12. The proportion of subjects with a CEA score of 0 (clear) increased more rapidly with combination therapy, and at week 12 the proportion was 14.1% versus 7.2% with monotherapy ($P = .087$ [post hoc analysis]). Most subjects experienced a reduction in skin stinging and burning from baseline, with approximately 74% of subjects in both groups being symptom-free at week 12 ($P < .001$ for both treatments [post hoc analysis]).

On average, the number of flushing episodes per week decreased from baseline to week 12 (by $-55.7 \pm 96.4\%$ and $-62.6 \pm 61.0\%$ with combination therapy and monotherapy, respectively). In addition, the proportion of subjects without flushing (no episodes) increased from baseline to week 12 by 47.2% with combination therapy and by 41.9% with monotherapy ($P < .001$ for both treatments; post hoc analysis).

Both treatments also reduced the proportion of subjects with ocular signs and symptoms from baseline to week 12: -60.0% with combination therapy and -60.7% with monotherapy ($P < .001$ for both treatments [post hoc analysis]).

Overall, for both treatments, approximately 95% of subjects evaluated their rosacea as improved in comparison with their condition before the study. Photographs of subjects at baseline and week 12 are presented in Figs 4 and 5.

Patient-reported outcomes

The DLQI score was substantially improved from baseline, with the percentage of subjects experiencing no effect on their quality of life ranging from less than 20% at baseline to higher than 65% at last visit (in both treatment arms). Mean changes in DLQI score improved by last visit and reached the minimal clinically important difference (mean change, -4.4 ± 5.1 with combination therapy and -4.3 ± 5.8 with monotherapy [$P < .001$ for both treatments, post hoc analysis]).¹⁶ In particular, the proportion of subjects without itchiness, soreness, painfulness, or stinging increased from baseline to last visit: from 23.7% and 21.7% to 72.8% and 63.6% with combination therapy and monotherapy, respectively. Similarly, the proportion of subjects who did not experience embarrassment and self-consciousness increased from baseline to last visit: from 20.0% and 15.9% to 72.0% and 66.7% with combination therapy and monotherapy, respectively. Although more subjects were satisfied overall or very satisfied with combination therapy than with monotherapy (93.6% vs 79.8%), the difference was not significant.

Safety

The safety population comprised all 273 subjects in the ITT population. The incidence of treatment-related AEs was generally low, although slightly lower in subjects receiving combination therapy (4.4% vs 7.2% for monotherapy). Most treatment-related AEs were dermatologic and reported with similar frequency in subjects receiving combination therapy or monotherapy (2.2% vs 2.8%, respectively). Gastrointestinal treatment-related AEs were reported in a small proportion of subjects: in 1.5% versus 2.9% for combination therapy and monotherapy, respectively. Treatment-related AEs leading to discontinuation were reported only in subjects receiving monotherapy (2.2%).

DISCUSSION

This study demonstrated that the combination of IVM and DMR was significantly superior to IVM and PBO (monotherapy) in terms of percentage reduction in inflammatory lesions from baseline and the proportion of subjects achieving 100% lesion clearance at week 12. The significantly greater proportion of clear subjects (IGA score, 0 [ie, with no inflammatory lesions or erythema]) at the end of the study was more than 2-fold higher with combination therapy than with monotherapy. This is an important finding in light of a recent pooled analysis demonstrating that patients who had an IGA score of 0 (clear) exhibited a better quality of life and longer time to

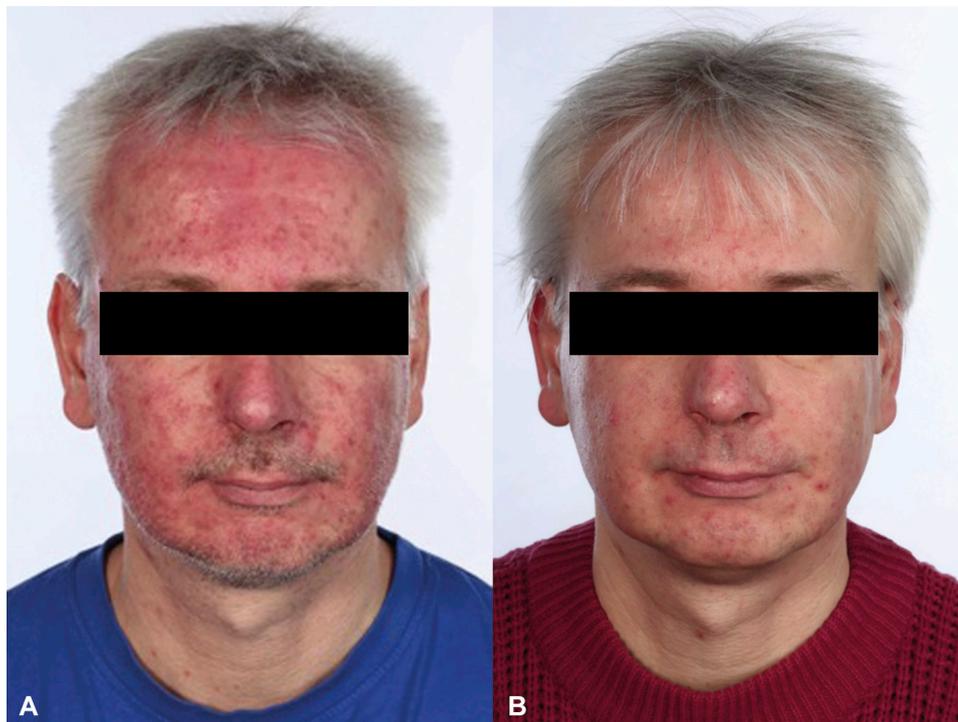


Fig 4. Rosacea. Photographs of a male subject in the ivermectin 1% cream (IVM) and placebo (PBO) treatment arm at baseline with 69 inflammatory lesions, an Investigator's Global Assessment (IGA) score of 4, and a Clinician's Erythema Assessment (CEA) score of 3 (**A**) and at week 12 with 25 inflammatory lesions, an IGA score of 2, and a CEA score of 2 (**B**).

relapse than did patients with an IGA score of 1 (“almost clear”).¹⁷ As the burden of rosacea translates to impaired quality of life, treating until clear represents an optimal approach to relieving the burden of rosacea and is a rational goal to strive for when evaluating rosacea improvement.¹⁸

In terms of erythema, both treatments similarly reduced the CEA score. Although the proportion of subjects with clear skin (CEA score, 0) at week 12 nearly doubled with combination therapy compared with monotherapy, the groups were not significantly different. This observation is not surprising, especially with the high mean number of papulopustular lesions at baseline, as IVM and DMR can both independently reduce inflammatory lesions, which could lead to a concurrent reduction in lesional and perilesional erythema. Furthermore, a meta-analysis in patients with rosacea revealed an increased density of *Demodex* mite infestation not only when papules and pustules were present, but also in association with erythema.¹⁹ As both treatment arms included IVM, it can be speculated that improvement of erythema, especially when associated with papulopustular lesions, may be related to both the anti-inflammatory and acaricidal effects of IVM.²⁰

Importantly, this study also supports the high efficacy of IVM in subjects with severe rosacea and its role in this combination therapy. Observed reductions in erythema, stinging and burning, flushing episodes, and ocular signs and symptoms, and the improvement in quality of life were similar between treatments. Amelioration of the patient's general outlook regarding their physical appearance and improvement in their quality of life may in turn reduce their overall stress level, with increased stress being reported to be a potential inducer of flushing in rosacea.²¹

Although the 2 study treatment regimens exhibited similar efficacy for several of the assessed variables, the beneficial effects in terms of reduction in percentage of inflammatory lesions and increase in proportion of subjects with a CEA score of 0 (clear skin) were noticeable earlier with combination therapy. The quicker onset of these visible effects is likely to result in enhanced patient adherence to treatment and better outcomes.

A surprising outcome from this study was the improvement in ocular signs and symptoms. Despite instructions to avoid application of IVM to the eyelid area, both treatments resulted in a significant reduction in ocular signs and symptoms. The overall



Fig 5. Rosacea. Photographs of a female subject in the ivermectin 1% cream (IVM) and doxycycline 40-mg modified-release capsules (DMR) treatment arm at baseline with 66 inflammatory lesions, an Investigator's Global Assessment (IGA) score of 4, and a Clinician's Erythema Assessment (CEA) score of 4 (**A**) and at week 12 with 13 inflammatory lesions, an IGA score of 3, and a CEA score of 3 (**B**).

reduction in facial inflammation may have triggered a concurrent reduction in eyelid inflammation as well, thereby reducing ocular signs and symptoms. A particularly notable result is the reduction in stinging and burning shown here and in previous clinical trials,^{9,10,13} as these symptoms can substantially add to patient discomfort whereas their impact is often underestimated by physicians.¹⁸

Limitations to this study include the fact that diagnosis of the severity of ocular rosacea was not undertaken by ophthalmologists and other ocular diagnoses could have confounded these results. Nevertheless, as described in treatment recommendations that involved ophthalmologists, dermatologists are expected to recognize most features of ocular rosacea, but not to manage anything beyond mild cases.³ Moreover, further studies of ocular rosacea are necessary, as highlighted by a recent Cochrane review that identified only 2 studies with usable data yet with a low quality level of evidence.⁵ Other limitations include lack of a control group and the short study duration, which did not allow for evaluation of possible recurrences.

Although both treatments were well tolerated, the incidence of treatment-related AEs was lower with

combination therapy than with monotherapy. In addition, there were no treatment-related AEs leading to discontinuation in subjects taking combination therapy and the presence of DMR did not increase the incidence of gastrointestinal treatment-related AEs. These data show that the better efficacy profile observed with combination therapy is not likely to compromise the safety profile, resulting in a favorable risk-benefit balance. Proper skin care may reduce the incidence of dermatologic AEs, possibly owing to improvements in the skin barrier.⁷ Therefore, the use of rosacea skin care products might have contributed to the overall positive tolerability and safety profile.

In conclusion, these study results suggest that using a combination of IVM and DMR, each once daily, along with a properly selected skin care regimen, can improve treatment results. Faster onset of visible improvement, greater efficacy, a reduction in flushing episodes, and a decrease in facial stinging and burning were all observed, offering the opportunity to reach skin clearance (IGA score, 0) in more patients while not compromising safety. Ultimately, overall patient satisfaction was achieved more frequently in those subjects who utilized the combination therapy.

The authors would like to thank the subjects and investigators participating in this study. They also thank Emma Eden, MSc, Monica Milani, PhD, and Galadriel Bonnel, PhD, who provided writing assistance in the preparation of this article that was funded by Galderma.

REFERENCES

1. Steinhoff M, Schmelz M, Schaubert J. Facial erythema of rosacea - aetiology, different pathophysiologies and treatment options. *Acta Derm Venereol*. 2016;96(5):579-586.
2. Holmes AD, Steinhoff M. Integrative concepts of rosacea pathophysiology, clinical presentation and new therapeutics. *Exp Dermatol*. 2017;26(8):659-667.
3. Schaller M, Almeida LM, Bewley A, et al. Rosacea treatment update: recommendations from the global ROSacea COnsensus (ROSCO) panel. *Br J Dermatol*. 2017;176(2):465-471.
4. Korting HC, Schollmann C. Current topical and systemic approaches to treatment of rosacea. *J Eur Acad Dermatol Venereol*. 2009;23(8):876-882.
5. van Zuuren EJ, Fedorowicz Z, Carter B, et al. Interventions for rosacea. *Cochrane Database Syst Rev*. 2015;4:CD003262.
6. Bhatia ND, Del Rosso JQ. Optimal management of papulopustular rosacea: rationale for combination therapy. *J Drugs Dermatol*. 2012;11(7):838-844.
7. Gold LS, Papp K, Lynde C, et al. Treatment of rosacea with concomitant use of topical ivermectin 1% cream and brimonidine 0.33% gel: a randomized, vehicle-controlled study. *J Drugs Dermatol*. 2017;16(9):909-916.
8. Fowler JF Jr. Combined effect of anti-inflammatory dose doxycycline (40-mg doxycycline, USP monohydrate controlled-release capsules) and metronidazole topical gel 1% in the treatment of rosacea. *J Drugs Dermatol*. 2007;6(6):641-645.
9. Taieb A, Ortonne JP, Ruzicka T, et al. Superiority of ivermectin 1% cream over metronidazole 0.75% cream in treating inflammatory lesions of rosacea: a randomized, investigator-blinded trial. *Br J Dermatol*. 2015;172(4):1103-1110.
10. Taieb A, Khemis A, Ruzicka T, et al. Maintenance of remission following successful treatment of papulopustular rosacea with ivermectin 1% cream vs. metronidazole 0.75% cream: 36-week extension of the ATTRACT randomized study. *J Eur Acad Dermatol Venereol*. 2016;30(5):829-836.
11. Schaller M, Dirschka T, Kemeny L, et al. Superior efficacy with ivermectin 1% cream compared to metronidazole 0.75% cream contributes to a better quality of life in patients with severe papulopustular rosacea: a subanalysis of the randomized, investigator-blinded ATTRACT study. *Dermatol Ther (Heidelb)*. 2016;6(3):427-436.
12. Steinhoff M, Vocanson M, Voegel JJ, et al. Topical ivermectin 10 mg/g and oral doxycycline 40 mg modified-release: current evidence on the complementary use of anti-inflammatory rosacea treatments. *Adv Ther*. 2016;33(9):1481-1501.
13. Stein Gold L, Kircik L, Fowler J, et al. Efficacy and safety of ivermectin 1% cream in treatment of papulopustular rosacea: results of two randomized, double-blind, vehicle-controlled pivotal studies. *J Drugs Dermatol*. 2014;13(3):316-323.
14. Del Rosso J, Preston N, Caveney S, Gottschalk R. Effectiveness and safety of modified-release doxycycline capsules once daily for papulopustular rosacea monotherapy results from a large community-based trial in subgroups based on gender. *J Drugs Dermatol*. 2012;11(6):703-707.
15. di Nardo A, Holmes A, Muto Y, et al. Improved clinical outcome and biomarkers in adults with papulopustular rosacea treated with doxycycline modified-release capsules in a randomized trial. *J Am Acad Dermatol*. 2016;74(6):1086-1092.
16. Basra MK, Salek MS, Camilleri L, et al. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. *Dermatology*. 2015;230(1):27-33.
17. Webster G, Schaller M, Tan J, et al. Defining treatment success in rosacea as 'clear' may provide multiple patient benefits: results of a pooled analysis. *J Dermatolog Treat*. 2017;28(5):469-474.
18. The BMJ Hosted Content. Rosacea: beyond the visible. Available at: <https://hosted.bmj.com/rosaceabeyondthevisible>. Accessed February 8, 2019.
19. Chang YS, Huang YC. Role of Demodex mite infestation in rosacea: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2017;77(3):441-447.e6.
20. Schaller M, Gonser L, Belge K, et al. Dual anti-inflammatory and anti-parasitic action of topical ivermectin 1% in papulopustular rosacea. *J Eur Acad Dermatol Venereol*. 2017;31(11):1907-1911.
21. Walsh RK, Endicott AA, Shinkai K. Diagnosis and treatment of rosacea fulminans: a comprehensive review. *Am J Clin Dermatol*. 2018;19(1):79-86.