Efficacy and Safety of Ivermectin 1% Cream in Treatment of Papulopustular Rosacea: Results of Two Randomized, Double-Blind, Vehicle-Controlled Pivotal Studies

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ABSTRACT

Background: Treatments for papulopustular rosacea (PPR) are limited.
Objective: To demonstrate the efficacy and safety of once-daily ivermectin 1% cream in subjects with moderate to severe PPR.
Methods: Two identically designed, randomized, double-blind, controlled studies of ivermectin 1% cream (IVM 1%) or vehicle once daily for 12 weeks were conducted in subjects with moderate to severe PPR. Efficacy assessments were Investigator's Global Assessment (IGA) of disease severity and inflammatory lesion counts. Safety assessments included incidence of adverse events (AEs) and local tolerance parameters. Subjects evaluated their rosacea and completed satisfaction and quality of life (QoL) questionnaires.
Results: In both studies, a greater proportion of subjects in the IVM 1% group achieved treatment success (IGA "clear" or "almost clear"): 38.4% and 40.1% vs 11.6% and 18.8% for vehicle (both $P<.001$), respectively. Ivermectin was superior to vehicle in terms of reduction from baseline in inflammatory lesion counts (76.0% and 75.0% vs 50.0% for both vehicle groups, respectively). For all endpoints, starting at week 4 and continuing through week 12, IVM 1% was statistically significantly superior ($P<.001$). Fewer subjects treated by IVM 1% reported dermatologic AEs, and a higher proportion of subjects were observed to have no skin dryness or itching compared to vehicle. Significantly more subjects receiving IVM 1% reported having an "excellent" or "good" improvement, along with an improved QoL.
Conclusion: Ivermectin 1% cream was effective and safe in treating inflammatory lesions of papulopustular rosacea.

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INTRODUCTION

Papulopustular rosacea (PPR) is a chronic inflammatory disorder characterized by facial papules, pustules, and persistent erythema.[1] It is highly prevalent and associated with adverse impact on quality of life and depression.[2] The etiology of rosacea is multifactorial. In addition to neurovascular dysregulation, the facial skin of patients with rosacea is affected by augmented proinflammatory immune responses.[3] The principal active cathelicidin peptide (LL-37) is highly concentrated in skin affected by rosacea and can contribute to acute inflammation.[4] Moreover, PPR is characterized by the presence of inflammatory infiltrates that accompany flares, along with a heightened immune response involving neutrophilic infiltration and increased gene expression of IL-8.[5] In addition to exogenous factors (including UV light, heat, and alcohol), it may be triggered by *Demodex folliculorum* mites.[3] Some studies of PPR observed higher mite densities compared to controls.[6-7] Therefore, a multitude of factors can activate neurovascular and/or immune responses, and consequential inflammation leading to flares of rosacea.[3]

Only a few therapeutic alternatives currently exist in the treatment of PPR. In the United States, only three FDA-approved

treatments are indicated for the reduction of inflammatory lesions of rosacea, including two topical treatments. A recent Cochrane review noted some evidence supporting the effectiveness of topical metronidazole and azelaic acid in the treatment of moderate to severe rosacea,[8] yet it is clear that not all patients respond to these medications. In a national survey of current rosacea medication users, 46% of patients had previously changed medications, usually due to a lack of improvement.[9] These factors underscore the need for new effective PPR treatments.

Ivermectin is a member of the avermectin class, which has been shown in immunopharmacological studies to exert anti-inflammatory effects by inhibiting lipopolysaccharide-induced production of inflammatory cytokines, such as tumor necrosis factor alpha and interleukin (IL)-1b, while upregulating the anti-inflammatory cytokine IL-10.[10] Since ivermectin is a macrocyclic lactone derivative, its therapeutic effect is thought to be prominently due to its anti-inflammatory properties, similar to that of other macrolides.[11-12] In addition to its anti-inflammatory mode of action, it possesses antiparasitic properties. Its predecessor, avermectin, is an antiparasitic agent of agricultural importance first isolated in 1974.[13] Ivermectin is 22-23 dihydro-avermectin B1, modified from its parent compound avermectin, and judged to be superior to naturally occurring avermectins B_1 and B_2. Since then, several studies support ivermectin's role in the effective oral treatment of cutaneous demodicidosis (in combination with topical permethrin cream) and scabies, as well as topical treatment of head lice.[14-16]

The objective of the studies described herein was to evaluate the efficacy and safety of once-daily ivermectin 1% cream in subjects with moderate to severe PPR after 12 weeks of treatment.

MATERIALS & METHODS

Two phase 3 multicenter, randomized, double-blinded, parallel-group, vehicle-controlled trials of identical design (hereafter designated Study 1 and Study 2) were conducted in the United States and Canada from December 2011 to July and August, 2013, respectively. The studies had a duration of 12 weeks, and were the first part of a three-part study, the second being active-controlled vs azelaic acid 15% gel over 40 weeks, and the third part lasting 4 weeks as a safety follow-up phase (without treatment). Both studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practices, and in compliance with local regulatory requirements. The studies were reviewed and approved by institutional review boards. All subjects provided their written informed consent prior to entering the studies. Study visits were as follows: screening visits, baseline, and weeks 2, 4, 8, and 12.

Subjects, Treatments, and Assessments

Eligible subjects were 18 years or older, with moderate or severe papulopustular rosacea based on Investigator Global Assessment (IGA; Table 1) and with 15-70 facial inflammatory lesions (papules and pustules). Eligible subjects were randomized by an Interactive Web Registration System (IWRS) in a 2:1 ratio to receive either ivermectin 1% cream (once daily every day at bedtime) or vehicle cream (once daily every day at bedtime) on the entire face for 12 weeks, and were instructed to apply a thin film of cream on the entire face (right and left cheeks, forehead, chin and nose), avoiding the upper and lower eyelids, lips, eyes and mouth. Cleansers and moisturizers were not provided. Subjects were also instructed to avoid rosacea triggers, such as sudden exposure to heat, certain foods, and excessive sun exposure.

TABLE 1.

Investigator's Global Assessment of Rosacea Severity		
Grade	**Score**	**Clinical Description**
Clear	0	No inflammatory lesions present, no erythema
Almost Clear	1	Very few small papules/pustules, very mild erythema present
Mild	2	Few small papules/pustules, mild erythema
Moderate	3	Several small or large papules/pustules, moderate erythema
Severe	4	Numerous small and/or large papules/pustules, severe erythema

Randomization lists were generated prior to study initiation by a statistician, and were then sent to the clinical supply group, and only the personnel directly involved with labeling and packaging (not site personnel) had access. The integrity of the blinding was ensured by packaging the topical creams in identical tubes with no visible difference between the creams, and requiring a third party other than the investigator to dispense the medication.

Efficacy assessments at each visit were the Investigator's Global Assessment (IGA) of disease severity, and inflammatory lesion counts (papules and pustules) on each of the five facial regions (forehead, chin, nose, right cheek, left cheek). Safety assessments included adverse events (AEs) throughout the study, local tolerance parameters (stinging/burning, dryness, itching) at each study visit evaluated on a 4-point scale [from 0 (none) to 3 (severe)], and laboratory parameters (hematology and biochemistry) measured before and after treatment. Other assessments included the subject's evaluation of their rosacea improvement at the end of the study (week 12) compared to their condition at baseline, and two quality of life (QoL) questionnaires [a dermatology-specific instrument, the Dermatology Life Quality Index (DLQI)],[17] and a rosacea-specific instrument, the RosaQoL™ [18] completed at baseline and week 12.

Statistical Analysis

Primary analyses were performed on data for the intent-to-treat (ITT) population, defined as all subjects who were randomized and to whom the study drug was administered. These analyses were repeated in the Per Protocol (PP) population to confirm the results, defined as ITT subjects who had no major protocol deviations.

The first co-primary efficacy endpoint was the success rate based on IGA score [percent of subjects who achieved "clear" or "almost clear" ratings on the IGA scale at week 12 (ITT-LOCF)], analyzed by the Cochran-Mantel-Haenszel (CMH) test stratified by analysis site, using the general association statistic. The second co-primary efficacy endpoint was the absolute change in inflammatory lesion counts from baseline to week 12 (ITT-LOCF), analyzed by analysis of covariance (ANCOVA). Missing data at week 12 in the ITT population were imputed by the Last Observation Carried Forward (LOCF) approach. Also, sensitivity analyses were conducted to impute missing data in order to assess the robustness of the primary efficacy results.

The secondary efficacy endpoint was percent change in inflammatory lesion counts from baseline at week 12 (ITT-LOCF), analyzed by the Mann-Whitney test using the Cochran-Mantel-Haenszel (CMH) procedure stratified by analysis center, with row mean score difference statistic using ridit score transformation. The endpoint of the subject's assessment of rosacea improvement was analyzed using the CMH test stratified by analysis center, with row mean score difference statistic using ridit score transformation. The QoL questionnaires were analyzed using the Wilcoxon rank sum test, and other variables were descriptively analyzed. High mean scores from the QoL questionnaires indicated a low quality of life.

RESULTS

Subject Disposition and Baseline Characteristics

A total of 683 subjects with moderate to severe PPR were randomized in Study 1 (IVM 1%: 451, vehicle: 232), and 688 subjects in Study 2 (IVM 1%: 459, vehicle: 229) (Figure 1). In Studies 1 and 2, the vast majority of subjects completed the study (91.4% and 92.6%, respectively). The treatment groups were similar at baseline in terms of demographics and baseline disease characteristics, with about 31-33 inflammatory lesions on average and the majority having moderate rosacea (Table 2). Most subjects were female (68.2% and 66.7% in Studies 1 and 2, respectively) and Caucasian/white (96.2% and 95.3%), with a mean age of 50.4 and 50.2 years, respectively. Additionally, treatment groups were comparable regarding rates/reasons for early study discontinuation (Figure 1).

Efficacy

The proportion of subjects achieving IGA success ("clear" or "almost clear") at week 12 for Studies 1 and 2 were 38.4% and 40.1% for IVM 1% compared to 11.6% and 18.8% for vehicle (both $P<.001$; Figure 2). A significant difference between treatment arms in both studies was observed by week 4 (10.9% and 11.8% vs 5.6% and 5.7%, respectively; both $P<.05$).

TABLE 2.

Demographic and Baseline Clinical Characteristics (ITT population)

		Study 1	Study 2
		Total (n=683)	Total (n=688)
Age, years	Mean ± SD Min, Max	50.4 ± 12.09 19,88	50.2 ± 12.29 18, 89
Gender, n (%)	Female Male	466 (68.2%) 217 (31.8%)	459 (66.7%) 229 (33.3%)
Race	White Black or African American Asian Other	657 (96.2%) 9 (1.3%) 6 (0.9%) 11 (1.6%)	656 (95.3%) 10 (1.5%) 15 (2.2%) 7 (1.0%)
Inflammatory lesion counts	Mean ± SD	30.9 ± 14.33	32.9 ± 13.70
IGA	3 = Moderate 4 = Severe	560 (82.0%) 123 (18.0%)	522 (75.9%) 166 (24.1%)

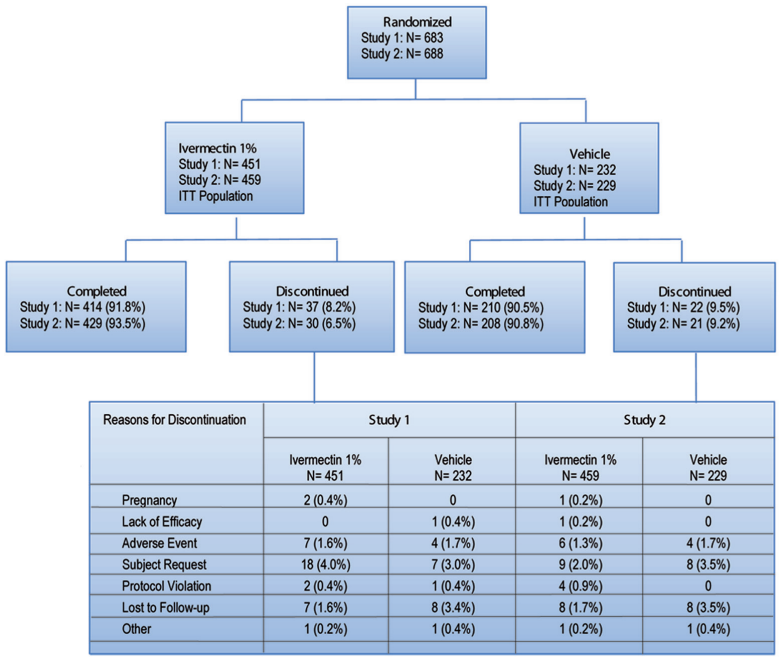
For inflammatory lesion counts, the mean difference between IVM 1% and vehicle from baseline to week 12 was -8.13 lesions for Study 1 and -8.22 for Study 2 (both $P<.001$ vs vehicle), with a 95% CI of [-10.12, -6.13] and [-10.18, -6.25], respectively. Median reduction from baseline in inflammatory lesion counts for both studies was 76.0% and 75.0%, respectively, vs 50.0% for both vehicle groups ($P<.001$), with significant difference observed by week 2 (Figure 3).

Safety

The incidence of AEs was comparable between Studies 1 and 2 (40.5% and 36.5% for IVM 1% vs 39.4% and 36.5% for vehicle, respectively). Fewer subjects in IVM 1% groups tended to report related AEs than in vehicle groups (4.2% and 2.6% vs 7.8% and 6.5%, respectively), as well as for related dermatologic AEs (3.5% and 1.5% vs 6.9% and 5.7%) and related AEs leading to discontinuation (1.3% and 0.2%, vs 1.7% for both vehicle groups). A similarly low proportion of subjects reported serious AEs for IVM 1% and vehicle groups (0.7% and 1.5% vs 0.4% and 1.7%). There were no related serious AEs. The most common related AE in Study 1 was sensation of skin burning: 8 (1.8%) in IVM 1% subjects vs 6 (2.6%) for vehicle. For Study 2, the most common related AEs for IVM 1% were pruritus and dry skin [3 subjects each (0.7%)] compared to 0 and 2 subjects (0.9%) for vehicle, respectively. In addition, laboratory tests did not demonstrate clinically significant abnormalities.

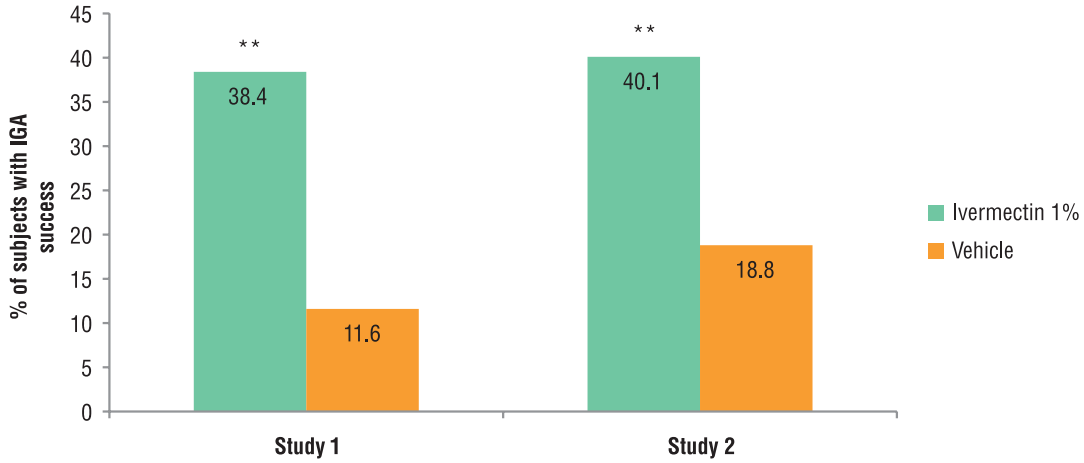
At baseline before treatment application, a large proportion of subjects presented with local cutaneous symptoms consistent

FIGURE 1. Subject disposition.



Reasons for Discontinuation	Study 1		Study 2	
	Ivermectin 1% N= 451	Vehicle N= 232	Ivermectin 1% N= 459	Vehicle N= 229
Pregnancy	2 (0.4%)	0	1 (0.2%)	0
Lack of Efficacy	0	1 (0.4%)	1 (0.2%)	0
Adverse Event	7 (1.6%)	4 (1.7%)	6 (1.3%)	4 (1.7%)
Subject Request	18 (4.0%)	7 (3.0%)	9 (2.0%)	8 (3.5%)
Protocol Violation	2 (0.4%)	1 (0.4%)	4 (0.9%)	0
Lost to Follow-up	7 (1.6%)	8 (3.4%)	8 (1.7%)	8 (3.5%)
Other	1 (0.2%)	1 (0.4%)	1 (0.2%)	1 (0.4%)

FIGURE 2. Proportions of subjects achieving IGA success ("clear" or "almost clear") at week 12. ** *P*<.001



with rosacea, especially mild or moderate dry skin (for Studies 1 and 2, 63.0% and 57.0% for IVM 1%, and 59.3% and 60.0% for vehicle, respectively) and mild or moderate itching (57.3% and 49.4% for IVM 1%, and 45.4% and 49.1% for vehicle). At week 12 (last available data observed), the majority of subjects had none of the 3 cutaneous symptoms. A trend was observed in terms of absence of dryness in 83-86% of IVM 1% subjects vs 72-76% for vehicle, as well as for absence of itching in 82-85% for IVM 1% vs 70-78% for vehicle.

Patient-Reported Outcomes

Improvement after treatment was rated by subjects as "excellent" or "good" by 69% and 66.2% for IVM 1% compared to 38.6% and 34.4% for vehicle (*P*<.001), respectively (Figure 4). "Excellent" improvement was reported by 34.3% and 32.0% for IVM 1% vs 9.5% and 7.3% for vehicle.

After 12 weeks of treatment, improved QoL scores were observed for subjects in the IVM 1% compared to vehicle groups. For the DLQI, it is of note that no difference between treatment groups was observed at baseline. At the end of each study, more subjects in the IVM 1% group (about 53%) than vehicle (about 35%) considered that their disease had no effect on their overall QoL (*P*<.001). For RosaQoL™, improvement in QoL from baseline was higher in both studies for IVM 1% (-0.64 ± 0.7 and -0.60 ± 0.6 vs -0.35 ± 0.5 for both vehicle groups (*P*<.001 and *P*=.001 for Studies 1 and 2, respectively).

FIGURE 3. Median percent change from baseline in inflammatory lesion counts (ITT-LOCF) in **a)** Study 1 and **b)** Study 2.* *P*<.01, ** *P*<.001

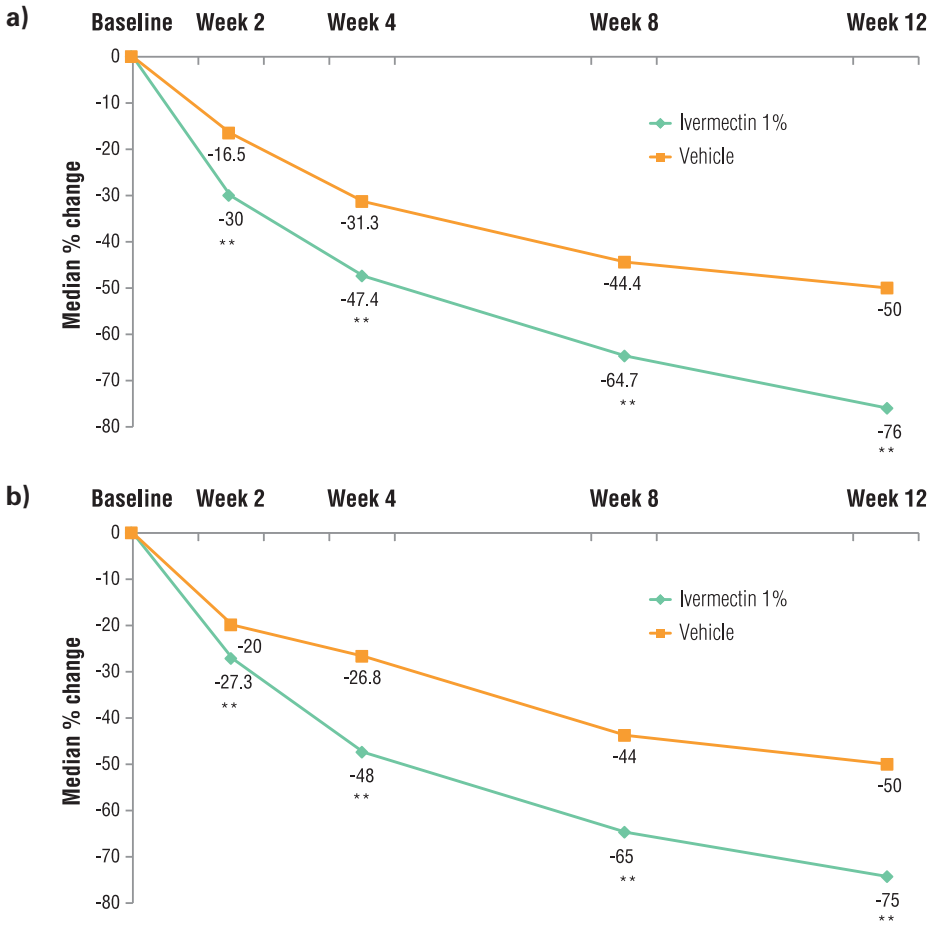
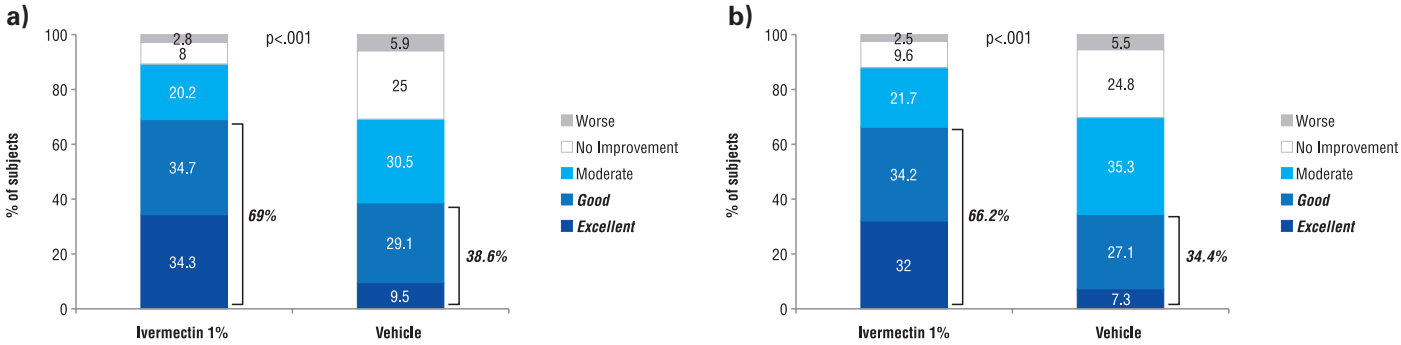


FIGURE 4. Subjects' rating of rosacea improvement in **a)** Study 1 and **b)** Study 2 at week 12.



DISCUSSION

Results of these two pivotal studies demonstrate the efficacy and safety of topical ivermectin 1% cream in the treatment of inflammatory lesions of rosacea, emphasizing the reproducibility of this data. These results are particularly robust when considering the stringent inclusion criteria (including the high number of lesions on average at baseline) and outcome assessments (absence of erythema included in the definition of "clear") used in these studies. At week 12, IVM 1% showed a treatment effect that was highly significant (*P*<.001) in all primary and secondary endpoints, with greater efficacy observed by week 4 in each study. About 40% of patients in the ivermectin group were deemed to be "clear" or "almost clear" in terms of disease severity. In addition, IVM 1% was significantly superior to vehicle as early as week 2 regard-

FIGURE 5. Photographs of female patient at **a)** baseline with IGA= 4 and 63 inflammatory lesions; **b)** at week 12 with IGA= 1 and 2 inflammatory lesions.

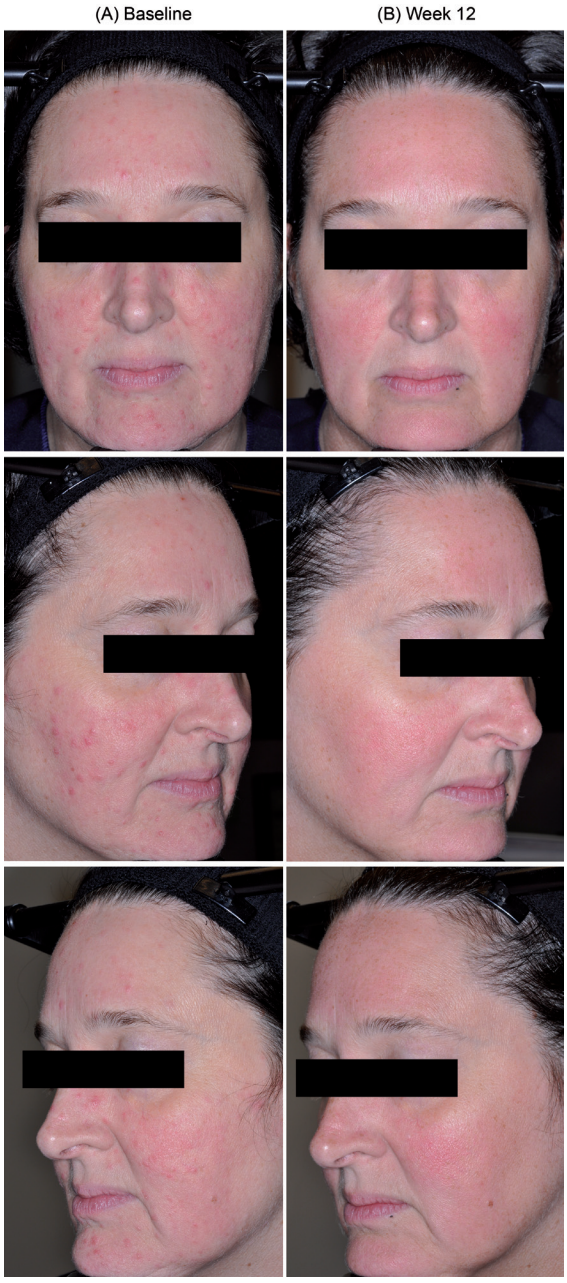
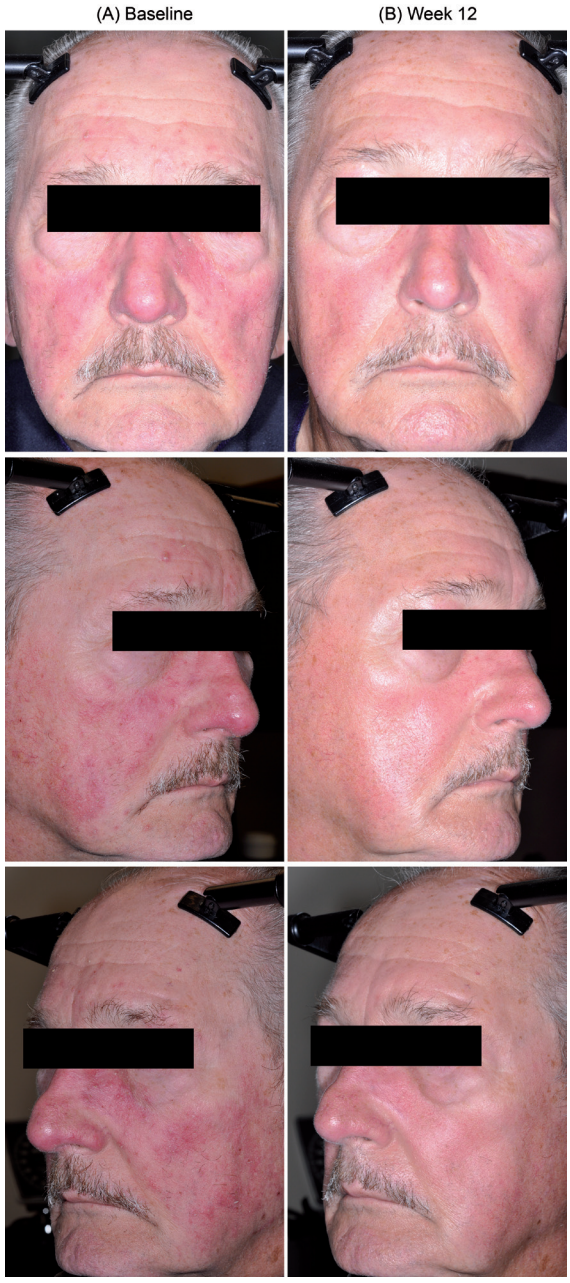


FIGURE 6. Photographs of male patient at **a)** baseline with IGA= 4 and 47 inflammatory lesions; **b)** at week 12 with IGA= 1 and 2 inflammatory lesions.



ing reduction of inflammatory lesion counts from baseline (about 75% vs 50% for vehicle in both studies).

Ivermectin was also well-tolerated and safe over the 12 week duration. The most frequent adverse reactions were skin disorders, with a lower incidence for IVM 1% than vehicle. In addition, a higher proportion of patients were observed to have no skin dryness and itching after treatment with IVM 1%, suggesting improvement of rosacea symptoms. This better tolerability profile and implied anti-inflammatory effect is consistent with the known properties of the avermectin class of drugs.[8] Furthermore, patient-reported outcomes were consistent with these efficacy and safety results, with significantly more subjects treated with IVM 1% evaluating their rosacea improvement to be "good" or "excellent." These findings are congruent with a greater proportion of IVM 1% subjects reporting improvement in general cutaneous- and also rosacea-specific quality of life measures.

Ivermectin has 2 mechanisms of action in PPR: anti-inflammatory and anti-parasitic. This agent improved the survival rate of mice challenged with lipopolysaccharide (LPS) and reduced the production of TNF-α and IL-1ß[19] (proinflammatory cytokines that are elevated in rosacea[20]). This effect was hypothesized to be through inhibition of nuclear factor-kB pathway, thereby inhibiting the LPS-induced production of inflammatory cytokines.

The antiparasitic effect of ivermectin is mediated through selective, high affinity, long-term binding to glutamate-gated chloride channels, which occur in invertebrate nerve and muscle cells.[21] Oral ivermectin has also been demonstrated to be an effective anti-parasitic agent in reducing the number of *Demodex* mites in demodicidosis and in blepharitis.[22-23] Although the exact role of *Demodex* in the pathogenesis of rosacea is not completely understood, it is hypothesized that these mites or bacteria associated with them (*Bacillus oleronius*) could trigger the inflammatory or specific immune reactions in rosacea patients.[24-28] Therefore, ivermectin may not only reduce the inflammatory responses like other rosacea medications such as sub-antimicrobial doxycycline, but also affect the upstream trigger of inflammatory responses by directly eliminating mites.

Medications with both anti-inflammatory and anti-parasitic activity have not yet been developed for rosacea treatment. Accordingly, ivermectin 1% cream is an innovative therapy addressing these relevant pathogenic factors in PPR and is a novel option for treatment of this condition. Future research directions are warranted to further investigate the pathogenesis of rosacea, as well as the role of ivermectin in the possible elimination of *Demodex* mites and their possible role as a rosacea trigger.

CONCLUSION

Ivermectin 1% cream was effective and safe in the treatment of papulopustular rosacea, and can be considered to be an innovative, novel addition to the current treatment armamentarium.

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