

# Efficacy of a Novel Rosacea Treatment System: An Investigator-Blind, Randomized, Parallel-Group Study

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## ABSTRACT

**Introduction:** A rosacea treatment system (cleanser, metronidazole 0.75% gel, hydrating complexion corrector, and sunscreen SPF30) has been developed to treat rosacea.

**Methods:** Thirty women with mild or moderate erythema of rosacea on their facial cheeks were randomly assigned to use one of the following for 28 days: the rosacea treatment system (RTS); RTS minus metronidazole (RTS-M); or metronidazole 0.75% gel plus standard skin care (standard cleanser and standard moisturizer/sunscreen) (M+SSC).

**Results:** At day 28, global improvement was evident in 90 percent of patients using RTS, 60 percent using RTS-M, and 67 percent using M+SSC. Erythema was significantly lower with RTS from day 14 onward, and unchanged with M+SSC. The proportion of patients reporting their skin was easily irritated at least sometimes was 40 percent with RTS, 70 percent with RTS-M, and 89 percent with M+SSC.

**Conclusion:** The rosacea treatment system may offer superior efficacy and tolerability to metronidazole plus the standard skin care used in this study.

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## INTRODUCTION

Rosacea is a common chronic inflammatory disorder of the facial skin that can result in erythema, flushing, stinging, telangiectasia, and papules and pustules. It can be controlled through a combination of trigger avoidance, appropriate skin care including photoprotection, and medication such as topical metronidazole, sodium sulfacetamide, azelaic acid, or antibiotics. Ideally, the skin care component of this should contain a gentle cleanser, a moisturizer to help maintain the integrity of the skin barrier, and a full spectrum UVA/UVB sunscreen with a sun protection factor (SPF) of at least 15.<sup>1</sup> However, in practice, it can be a challenge to coordinate using all these other products together with topical medication.

A rosacea treatment system providing a more convenient and coordinated approach to managing the different components of treatment has been developed. The system is composed of four products—gentle cleanser, metronidazole 0.75% topical gel, hydrating complexion corrector, and sunscreen. The cleanser contains aloe barbadensis leaf juice to cleanse the skin gently and the hydrating complexion corrector contains anti-inflammatory ingredients (licorice, aloe, and sea whip) to help

calm the skin. The hydrating complexion corrector and the sunscreen also contain light reflectors to camouflage redness and reduce blotchiness—both products contain mica and iron oxides, and the hydrating complexion corrector contains titanium dioxide. Together, the four components of the system help to: cleanse the skin while maintaining the integrity of the skin barrier; reduce inflammation; camouflage erythema; and protect the skin from both UVA and UVB radiation.

Previous reports indicate that treatment systems such as this are popular with dermatology patients, and that many patients prefer the convenience of an all-in-one coordinated approach to treatment over the complexity of a more piecemeal approach.<sup>2</sup> Furthermore, treatment systems may improve patient compliance<sup>2</sup> and therefore, in addition to being more convenient, they may also have the potential to enhance efficacy and patient satisfaction.

In order to evaluate the clinical benefits of this rosacea treatment system, the system as a whole has been compared with the system minus the metronidazole component and also with metronidazole

0.75% topical gel in conjunction with a standard skin care regimen (a standard cleanser and standard moisturizer/sunscreen).

## METHODS

### *Patients*

Adult females (at least 18 years of age) with mild or moderate erythema of rosacea on the malar area of their face were eligible to enroll in this investigator-blind, randomized, parallel-group study (see Table 1 for definitions of mild and moderate erythema).

Participants were required to be willing to refrain from using any non-study products on their face including medications, moisturizers, sunscreens, fragrances, and medicated make-up. However, they were allowed to use oil-free non-comedogenic make-up, mascara, eye liner, eye shadow, and lipstick as long as no new facial make-up products were introduced during the study. Participants were also required to avoid having facial procedures during the study—including facials, chemical peels, microdermabrasion, laser resurfacing, botulinum toxin type A injections, dermal filler injections, hair removal other than eyebrow plucking with tweezers, and non-ablative laser, light, or radiofrequency treatment. In addition, they were required to avoid tanning booth treatments and excessive sun exposure. They were instructed to apply the provided sunscreen daily and to wear protective clothing when exposed to the sun.

Exclusion criteria included: a history of any facial skin condition/disease that might interfere with diagnosis or evaluation in the study; a nodular lesion or more than two inflammatory lesions (total of papules and pustules) on the face (because the study was evaluating the erythema of rosacea and inflammatory lesions can intensify erythema); known allergy or hypersensitivity to any ingredients in the study products; history or evidence of blood dyscrasia or Crohn's disease; current use of coumarin or warfarin; anticipated need for concurrent use of other medicated products on the face during the study; facial sunburn at baseline or sunbathing in the preceding two weeks; facial tattoos; and pregnancy, breastfeeding, or planning a pregnancy during the study.

The following washout periods were required: 1 week for medicated facial cleansers and facial hair removal; 2 weeks for topical medications or bleaching products on the face, photosensitizing medication or procedures, and UV light therapy; 3 weeks for topical tretinoin applied to the face; 4 weeks for vasodilators; 30 days for participation in an investigational drug or device study; 8 weeks for facial microdermabrasion; 12 weeks for chronic use of systemic steroids; 3 months for drugs known to be potentially toxic to a major organ; and 6 months for laser resurfacing and the use of acitretin, isotretinoin, methotrexate, and photoallergic, phototoxic, or photosensitizing drugs.

The protocol was approved by the relevant institutional review board and conducted in accordance with the Declaration of Helsinki (2004 version). All patients signed informed consent.

### *Treatment regimen*

Patients were randomly assigned (in a 1:1:1 ratio) to receive one of the treatments detailed in Table 2 for 28 days: (1) the rosacea treatment system,<sup>3</sup> (2) the rosacea treatment system omitting the metronidazole 0.75% topical gel, and (3) metronidazole 0.75% topical gel plus a standard skin care regimen (standard gentle cleanser plus standard moisturizer/sunscreen). The cleanser component of the rosacea treatment system contains aloe barbadensis leaf juice to cleanse the skin gently. The hydrating complexion corrector component of the rosacea treatment system is a moisturizing product containing anti-inflammatory ingredients and, in addition, light reflectors to camouflage redness and help balance the complexion.

Patients were instructed to apply each component of their treatment regimen in the order shown in Table 2. All study products were applied twice daily except the skin balancing sunscreen in the rosacea treatment system, which was applied each morning and as needed.

### *Outcome measures*

The investigator performed a global assessment and assessed the level of erythema present (Table 1). The patients reported: their perception of the severity of their rosacea; the effectiveness of their study treatment in reducing dryness (compared with a baseline photograph); how comfortable their skin felt immediately after applying the study products; how easily their skin became irritated (for example, by products such as cosmetics, aftershaves, and cleansers); and their level of satisfaction with their study treatment (Table 1).

### *Statistical analyses*

A Student's t-test was used to evaluate inter-group differences in erythema scores and rosacea severity scores. A paired t-test was used to evaluate intra-group differences in erythema scores and rosacea severity scores relative to baseline. An  $\alpha$ -level of 0.05 was used to determine statistical significance.

## RESULTS

### *Patients*

Of 30 patients evaluated (10 per group), 29 (97%) completed. One patient (3%) withdrew due to an unwillingness to apply multiple products to the face (metronidazole plus standard skin care group). The patients' mean age was 45 years and all were Caucasian and had a Fitzpatrick skin type of I (30%), II (60%), or III (10%). At baseline, 77 percent considered their skin to be red and 67 percent considered their skin to be sensitive. The average time since the onset of their rosacea was 17 years.

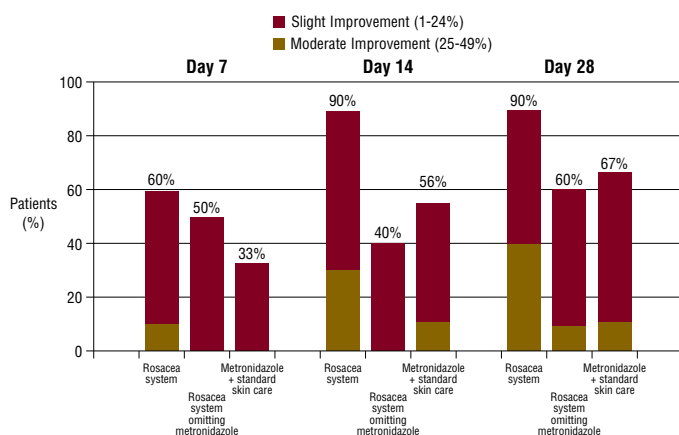
TABLE 1.

Scales Used in Assessments						
Investigator Assessments		Patient Assessments				
Global Assessment	Erythema	Perception of Severity of Rosacea	Effectiveness in Reducing Dryness	Skin Feeling Comfortable	Skin Easily Irritated	Satisfaction With Study Treatment
Clear	0 = None (no redness present)	0 = None	Very effective	Agree completely	Never	Very satisfied
Almost clear (75-99%)	1 = Very mild (slight pinkness)	1 = Trace	Effective	Agree	Rarely	Satisfied
Marked improvement (50-74%)	2 = Mild (pink to light red)	2 = Mild	Somewhat effective	Somewhat agree	Sometimes	Indifferent
Moderate improvement (25-49%)	3 = Moderate (definite redness; easily recognized)	3 = Moderate	Ineffective	Disagree	Often	Dissatisfied
Slight improvement (1-24%)	4 = Severe (marked erythema; fiery red)	4 = Severe	—	—	All the time	Very dissatisfied
No change	—	—	—	—	—	—
Worse	—	—	—	—	—	—

*Investigator evaluations*

At day 28, the proportion of patients with global improvement was 90 percent with the rosacea treatment system, 60 percent with the rosacea treatment system minus the metronidazole, and 67 percent with metronidazole plus standard skin care (Figure 1). At the same timepoint, the proportion of patients with moderate global improvement (i.e., at least 25% global improvement) was 40 percent with the rosacea treatment system, 10 percent with the rosacea treatment system minus the metronidazole, and 11 percent with metronidazole plus standard skin care (Figure 1).

FIGURE 1. Investigator global assessment.



Between baseline and day 28, the mean erythema score declined from 2.8 to 2.4 with the rosacea treatment system and declined from 2.5 to 2.3 with the rosacea treatment system minus the metronidazole—whereas it remained unchanged at 2.3 with metronidazole plus the standard skin care regimen (Figure 2). The reduction in erythema score from baseline in the rosacea treatment system group was statistically significant at days 14 and 28 ( $P \leq 0.05$ ).

*Patient evaluation of efficacy*

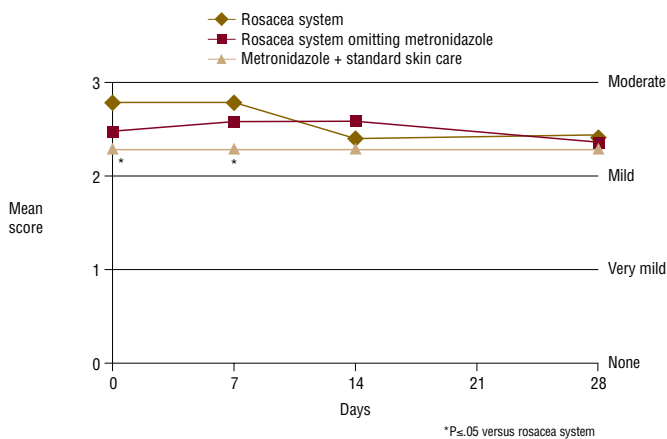
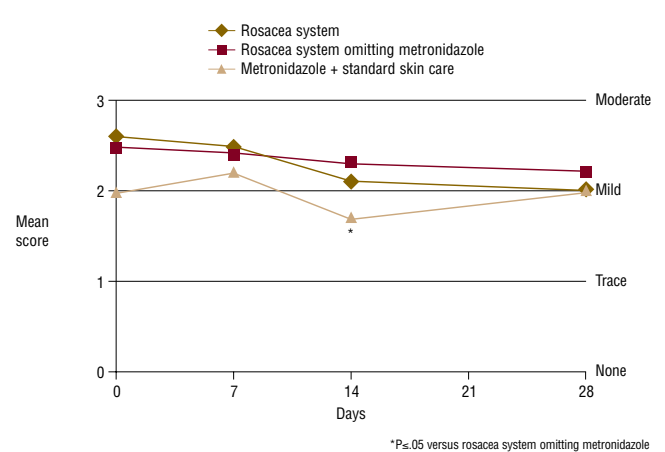
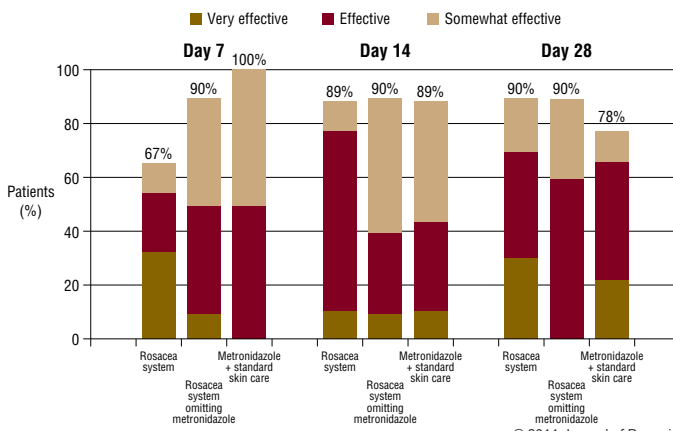
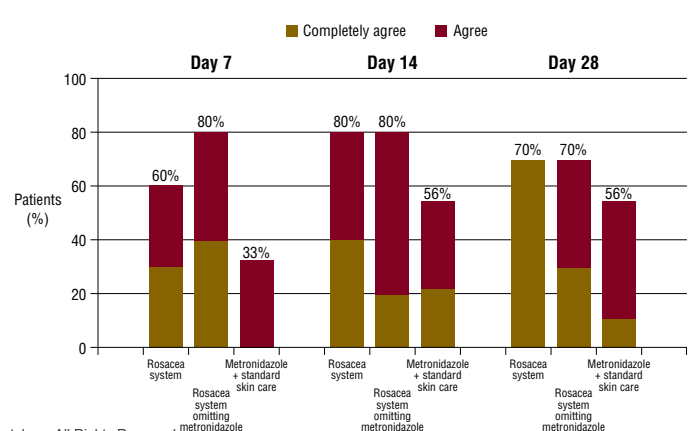
Between baseline and day 28, the patients' mean perception of the severity of their rosacea declined from 2.6 to 2.0 with the rosacea treatment system and declined from 2.5 to 2.2 with the rosacea treatment system minus the metronidazole—whereas it remained unchanged at 2.0 with metronidazole plus standard skin care (Figure 3). The reduction in severity score from baseline in the rosacea treatment group was statistically significant at days 14 and 28 ( $P \leq 0.05$ ).

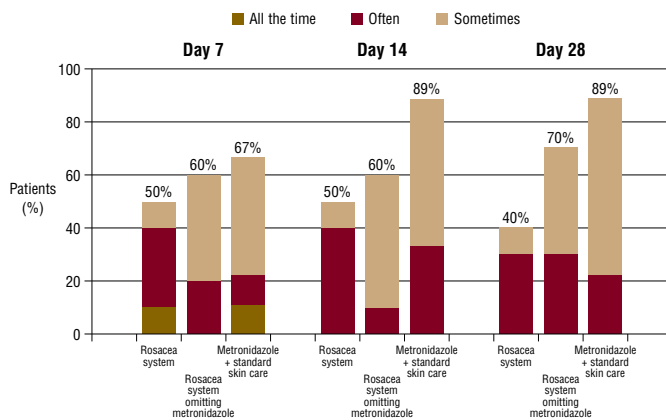
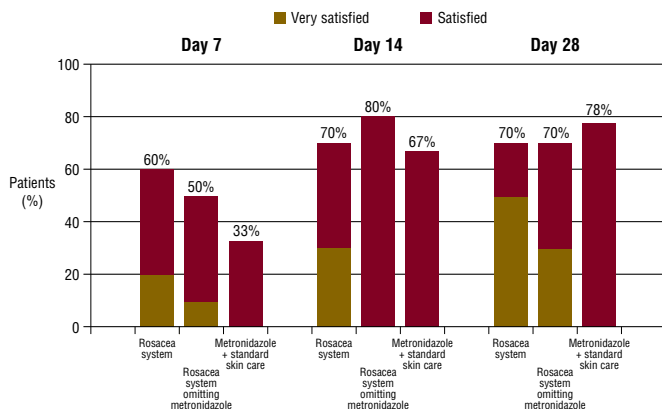
*Patient evaluations of tolerability*

At day 28, the study regimens were considered to be very effective, effective, or somewhat effective in reducing dryness in 90 percent of patients using the rosacea treatment system, 90 percent of patients using the rosacea treatment system minus the metronidazole, and 78 percent of patients using metronidazole plus standard skin care (Figure 4).

**TABLE 2.****Treatment Arms in the Study**

Rosacea Treatment System <sup>3</sup>	Rosacea Treatment System <sup>3</sup> Omitting the Metronidazole	Metronidazole + Standard Skin Care Regimen
Gentle cleanser (proprietary to rosacea treatment system) <sup>a</sup>	Gentle cleanser (proprietary to rosacea treatment system) <sup>a</sup>	Gentle cleanser <sup>b</sup>
Metronidazole 0.75% topical gel <sup>c</sup>	—	Metronidazole 0.75% topical gel <sup>c</sup>
Hydrating complexion corrector <sup>d</sup>	Hydrating complexion corrector <sup>d</sup>	Moisturizer containing sunscreen SPF 30 <sup>e</sup>
Skin balancing sunscreen SPF 30 <sup>f</sup>	Skin balancing sunscreen SPF 30 <sup>f</sup>	—

<sup>a</sup>Rosaclear™ System Gentle Cleanser, OMP, Inc., Long Beach, CA.<sup>b</sup>Cetaphil® Gentle Skin Cleanser, Galderma Laboratories, LP, Fort Worth, TX.<sup>c</sup>Indicated for the treatment of inflammatory papules and pustules of rosacea.<sup>d</sup>Rosaclear™ Hydrating Complexion Corrector, OMP, Inc., Long Beach, CA (a moisturizing product containing anti-inflammatory ingredients and, in addition, light reflectors to camouflage redness and help balance the complexion).<sup>e</sup>Healthy Defense® Daily Moisturizer SPF 30, Neutrogena Corporation, Los Angeles, CA (an untinted UVA/UVB sunscreen containing ensulizole 2.0%, octocrylene 7.5%, and zinc oxide 1.9%).<sup>f</sup>Rosaclear™ System Skin Balancing Sun Protection SPF 30, OMP, Inc., Long Beach, CA (a tinted UVA/UVB sunscreen containing zinc oxide 15.5% and titanium dioxide 2% as sunscreens and light-reflecting ingredients to camouflage redness and help balance the complexion). Sold separately to the other components in the rosacea treatment system.**FIGURE 2.** Investigator evaluation of erythema. Erythema was significantly reduced from baseline only in the rosacea system group at days 14 and 28 ( $P \leq 0.05$ ).**FIGURE 3.** Patient ratings of rosacea severity. Rosacea severity was significantly reduced from baseline only in the rosacea system group at days 14 and 28 ( $P \leq 0.05$ ).**FIGURE 4.** Patient ratings of effectiveness of study regimens in reducing dryness.**FIGURE 5.** Patients agreeing that their skin felt comfortable immediately after applying the study products.

**FIGURE 6.** Patients reporting that their skin was easily irritated.**FIGURE 7.** Patient satisfaction with their rosacea treatment.

At day 28, the proportion of patients agreeing or completely agreeing that their skin felt comfortable immediately after applying the study products was 70 percent with the rosacea treatment system, 70 percent with the rosacea treatment system minus the metronidazole, and 56 percent with metronidazole plus standard skin care (Figure 5).

Also at day 28, the proportion of patients who reported their skin was easily irritated at least sometimes was 40 percent with the rosacea treatment system, 70 percent with the rosacea treatment system minus the metronidazole, and 89 percent with metronidazole plus the standard skin care regimen (Figure 6).

Two adverse events were reported, both in the metronidazole plus standard skin care group—mild dryness on the chin in one patient and a mild burning sensation in another patient.

#### Patient satisfaction

Patients reported the following levels of satisfaction with their rosacea treatment at day 28: 50 percent of the rosacea treatment group were very satisfied (with 70% being satisfied or very satisfied); 30 percent of the rosacea treatment system mi-

nus metronidazole group were very satisfied (with 70% being satisfied or very satisfied); and 0 percent of the metronidazole plus standard skin care regimen were very satisfied (with 78% being satisfied or very satisfied).

## DISCUSSION

These results suggest that the rosacea treatment system may offer superior efficacy and tolerability, and a greater degree of patient satisfaction, than metronidazole 0.75% plus the standard skin care regimen used in this study. The rosacea treatment system contains several ingredients that were not present in the standard skin care regimen used in this study and which could contribute to this—for example, aloe, licorice, and sea whip (which have been reported to have anti-inflammatory activity),<sup>4-6</sup> lavender (which has been reported to have antibacterial activity),<sup>7</sup> and mica (which is a light-reflecting mineral and is included to help camouflage erythema). Although it is possible that the clinical superiority of the rosacea treatment system could be attributed to some or all of these ingredients, definitive attributions are not possible—because each study regimen contains multiple ingredients, many of which are present in one regimen but not in the other (Tables 3-4). For example, the rosacea treatment system appears to contain more than 50 ingredients that are not present in the standard skin care regimen—15 contributed by the cleanser and 40 contributed by the hydrating complexion corrector or skin balancing sunscreen (Table 3). Another factor confounding any interpretation of the differences among regimens is the concentration of each ingredient and, as this is proprietary information, such data are not available.

Erythema is one of the key manifestations of rosacea and a lessening in erythema can be one of the most visually obvious changes and one of the most welcomed by patients. In this study, mean erythema levels were significantly different between the rosacea treatment system group and the metronidazole plus standard skin care group at baseline. Nevertheless, it is evident that there was no change in mean erythema levels in the metronidazole plus standard skin care group during the study while the rosacea treatment system group showed a significant reduction from day 14 onward. These results suggest that there could be a synergy among metronidazole and the other components of the rosacea treatment system, because erythema was significantly reduced only in the group whose treatment contained both of these and not in the other groups, each of which contained only one of these. Although it would be valuable to confirm these findings in a split-face study, it is possible that the complexity of maintaining different multi-component regimens on each side of the face could impair patient compliance to such an extent as to prevent meaningful analysis.

Perhaps the largest difference among treatment groups was in the proportion of patients reporting that their skin was easily

**TABLE 3.****Ingredients Present in the Rosacea Treatment System but Not in the Standard Skin Care Regimen**

Component of regimen	Ingredient	
Rosacea treatment system cleanser <sup>a</sup>	Sodium lauroyl oat amino acids	
	Cocamidopropyl betaine	
	Sodium laureth sulfate	
	Aloe barbadensis leaf juice	
	Glycereth-7	
	Prunus armeniaca (apricot) kernel oil	
	Panthenol	
	Acrylates/C10-30 alkyl acrylate crosspolymer	
	Oleyl lactate	
	Ethoxydiglycol	
	Salvia officinalis (sage) leaf extract	
	Borago officinalis extract	
	Saponins	
	Fragrance	
	Yellow 5	
Hydrating complexion corrector <sup>b</sup> or skin balancing sunscreen <sup>c</sup>	Titanium dioxide	Pentylene glycol
	Ethylhexyl palmitate	Magnesium aluminum silicate
	Coco-caprylate/caprate	Talc
	PEG-6	Alumina
	Dipropylene glycol	Silica
	Isocetyl behenate	Sodium cocoyl amino acids
	C13-15 alkane	PEG-8
	Allantoin	Sarcosine
	Tocopheryl acetate	Potassium aspartate
	Avena sativa (oat) beta glucan	Magnesium aspartate
	Avena sativa (oat) kernel extract	Hydroxyethyl acrylate/sodium acryloyldimethyl taurate copolymer
	Hydrolyzed oat protein	Polysorbate 60
	Aloe barbadensis leaf juice	Iron oxides
	Lavandula angustifolia (lavender) extract	Mica
	Bacopa monniera extract	C12-15 alkyl benzoate
	Arnica montana flower extract	Coco-glucoside
	Cupressus sempevirens seed extract	Polyhydroxystearic acid
	Polygonatum multiflorum rhizome/root extract	Triethoxycaprylylsilane
	Sea whip extract	Isopropyl titanium triisostearate/triethoxycaprylylsilane crosspolymer
	Glycyrrhiza glabra (licorice) root extract	
	Hydroxyethylcellulose	

<sup>a</sup>Rosaclear™ System Gentle Cleanser, OMP, Inc., Long Beach, CA<sup>b</sup>Rosaclear™ Hydrating Complexion Corrector, OMP, Inc., Long Beach, CA<sup>c</sup>Rosaclear™ System Skin Balancing Sun Protection SPF 30, OMP, Inc., Long Beach, CA

irritated at least sometimes—40 percent with the rosacea treatment system, 70 percent with the rosacea treatment system minus metronidazole, and 89 percent with metronidazole plus standard care at day 28. This suggests that metronidazole plays some role in enhancing tolerability (reducing the proportion of patients with easily irritated skin from 70% to 40%), but that the ingredients in the rosacea treatment system have an even larger effect (reducing the proportion from 89% to 40%).

Other measures of tolerability (specifically, the effectiveness in reducing dryness, and how comfortable the skin felt after applying the study products) also showed the superiority of the rosacea treatment system compared to metronidazole 0.75% plus the standard skin care regimen. This further supports the contention that the presence of at least one ingredient in the

rosacea treatment system enhances tolerability.

As might be expected, the data presented here also suggest that the rosacea treatment system offers superior efficacy and tolerability to the rosacea treatment system minus the metronidazole, suggesting that the metronidazole component plays a role in enhancing both these outcomes. The overall results from this study confirm previous findings that the clinical effects achieved with rosacea treatment are dependent on more than a single medication such as metronidazole, and treatment with such an anti-rosacea medication is improved when used in conjunction with a gentle cleanser, moisturizer, and sunscreen.

While such a multi-pronged approach to treatment brings



**TABLE 4.****Ingredients Present in the Standard Skin Care Regimen but Not in the Rosacea Treatment System**

Component of regimen	Ingredient
Standard cleanser <sup>a</sup>	Sodium lauryl sulfate
Standard moisturizer <sup>b</sup>	Ensulizole Octocrylene Butyloctyl salicylate Cyclopentasiloxane Behenyl alcohol Sodium hyaluronate Codium tomentosum BHT (butylated hydroxytoluene) Tocopherol Calcium pantothenate Dicetyl phosphate Ceteth 10 phosphate Butylene glycol Trimethylolpropane triethylhexanoate Caprylic/capric triglycerides Sodium acrylates copolymer

<sup>a</sup>Cetaphil® Gentle Skin Cleanser, Galderma Laboratories, LP, Fort Worth, TX<sup>b</sup>Healthy Defense® Daily Moisturizer SPF 30, Neutrogena Corporation, Los Angeles, CA

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clinical benefits, it can complicate treatment regimens to the potential detriment of patient compliance. An all-in-one approach to treatment with a structured and defined regimen is helpful in encouraging optimal compliance and, ultimately, optimal efficacy, tolerability, and satisfaction too.

**CONCLUSION**

The rosacea treatment system offers a convenient all-in-one approach to treating rosacea that appears to be more effective and better tolerated than metronidazole 0.75% plus the standard skin care regimen used in this study.

**DISCLOSURES**

This study was funded by OMP, Inc. and Dr. Leyden has been an investigator and consultant for OMP, Inc.

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