Efficacy and Safety of Once-Daily Topical Brimonidine Tartrate Gel 0.5% for the Treatment of Moderate to Severe Facial Erythema of Rosacea: Results of Two Randomized, Double-Blind, Vehicle-Controlled Pivotal Studies

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ABSTRACT

Background: Brimonidine tartrate, a highly selective α_2-adrenergic receptor agonist with potent vasoconstrictive activity, was shown to reduce erythema of rosacea.
Objective: To assess the efficacy and safety of topical brimonidine tartrate gel 0.5% for the treatment of erythema of rosacea.
Methods: Both studies were randomized, double-blind, and vehicle-controlled, with identical design. Subjects with moderate to severe erythema of rosacea were randomized 1:1 to apply topical brimonidine tartrate gel 0.5% or vehicle gel once-daily for 4 weeks, followed by a 4-week follow-up phase. Evaluations included severity of erythema based on Clinician's Erythema Assessment and Patient's Self-Assessment, as well as adverse events.
Results: Topical brimonidine tartrate gel 0.5% was significantly more efficacious than vehicle gel throughout 12 hours on days 1, 15, and 29, with significant difference observed as early as 30 minutes after the first application on day 1 (all $P<.001$). No tachyphylaxis, rebound or aggravation of other disease signs were observed. Slightly higher incidence of adverse events was observed for topical brimonidine tartrate gel 0.5% than for vehicle; however, most of the adverse events were dermatological, mild, and transient in nature.
Limitations: These data generated in controlled trials may be different from those in clinical practice.
Conclusions: Once-daily brimonidine tartrate gel 0.5% has a good safety profile and provides significantly greater efficacy relative to vehicle gel for the treatment of moderate to severe erythema of rosacea, as early as 30 minutes after application.

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INTRODUCTION

Rosacea is a common skin disorder estimated to affect 16 million Americans.[1] Although it is usually observed in patients with light skin phototypes, rosacea has also been diagnosed in patients with darker skin type III – VI.[2-4] The onset of the condition is typically between the ages of 20-50 years, with women being affected more frequently than men.[5] As rosacea is a chronic disease characterized by flushing and persistent erythema in the central facial area,[6] it has considerable psychosocial impact and causes embarrassment, anxiety, and low self-esteem among the patients.[7,8] In addition to flushing and erythema, other cutaneous signs such as telangiectasia, papules, and pustules may also be present.[9,10] Several topical and oral medications are currently approved for the treatment of papules and pustules of rosacea, including metronidazole, azelaic acid, and anti-inflammatory dose doxycycline.[11,12]

Although erythema is the primary feature of rosacea and presents ubiquitously among rosacea patients, there is currently no approved medication for its treatment, making it a key unmet medical need.[5] In the absence of effective treatment, patients are usually advised to identify and avoid environmental and lifestyle triggers that can exacerbate erythema.[11-13] It is hypothesized that facial erythema of rosacea results from dysregulation in the cutaneous vasomotor responses, which leads

to abnormal, involuntary, and persistent dilation of facial blood vessels.[14-16] Therefore, agents with vasoconstrictive activity should be able to reduce erythema effectively.

Recent transcriptomic studies suggest that genes including adrenergic receptor are involved in the neurovascular regulation pathway.[17] Adrenergic receptor agonists with vasoconstrictive activity may therefore be good candidates for the treatment of erythema. Topical and systemic agonists of α- and β-adrenergic receptors, such as oxymetazoline, nadolol, and propranolol, have been used in isolated cases for the treatment of flushing and/or erythema among rosacea patients.[18-20] Brimonidine tartrate (BT) is a highly selective α_2-adrenergic receptor agonist, with potent vasoconstrictive activity.[21] It is currently approved for the treatment of open angle glaucoma, with well-documented efficacy and safety.[22, 23] Topical BT gels of three concentrations (0.07%, 0.18% and 0.5%) were evaluated in the previous Phase IIa study, and a dose-dependent relationship was observed.[24] Three different dose regimens (0.18% once and twice-daily, and 0.5% once-daily) were further selected to be evaluated in the Phase IIb study, and BT gel 0.5% applied once-daily was determined to be the optimal dose regimen for the treatment of erythema of rosacea.[24] In the present two Phase III studies including a 4-week treatment phase and a 4-week follow-up phase, we aimed to assess the efficacy and safety of the once-daily topical BT gel 0.5% in the treatment of moderate to severe erythema of rosacea.

MATERIALS AND METHODS

These two Phase III pivotal trials with identical design were multicenter, randomized, double-blind, parallel-group, and vehicle-controlled comparison studies carried out in the United States and Canada. The duration of the studies was 8 weeks, including a 4-week treatment phase, and a 4-week follow-up phase. Both studies were conducted in accordance with the ethical principles originating from 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.

Subjects, Treatments, and Assessments

Eligible subjects were men and women, 18 years or older, with a clinical diagnosis of rosacea, less than 3 facial inflammatory lesions, and moderate to severe erythema according to both Clinician's Erythema Assessment (CEA) and Patient's Self-Assessment (PSA)[24] at both the screening visit and the baseline visit. A wash-out period was mandatory for subjects receiving prescription medications for inflammatory conditions, rosacea, or acne. Subjects were randomized in a 1:1 ratio to the groups of BT gel 0.5% and vehicle gel. During the first 4 weeks (treatment phase), subjects were instructed to apply once daily a thin film of gel on the entire face. No medication was applied during the 4-week follow-up phase.

Randomization lists were generated prior to study initiation by an independent statistician using SAS Proc Plan procedure. The randomization lists were then sent to the clinical supply group, and only the personnel directly involved with labeling and packaging had access. The integrity of the blinding was ensured by packaging the topical gels in identical tubes and requiring a third party (designated study personnel) other than the investigator/evaluator to dispense the medication. The labels of the study products identified only the randomization number. Treatment kit was assigned in ascending order to each subject intended to be treated, and no number was to be omitted or skipped.

There were 6 visits in each study: screening visit, days 1, 15, and 29 during the treatment phase, and Weeks 6 and 8 during the follow-up phase. On days 1, 15, and 29, subjects remained at the clinic in standard room temperature conditions for 12 hours, and erythema (CEA and PSA) was assessed prior to study drug application, and at 30 minutes, 3, 6, 9, and 12 hours after application; Telangiectasia [using a 5-point scale ranging from 0 (clear) to 4 (severe)], Investigator's Global Assessment (IGA) of the lesion severity [using a 5-point scale ranging from 0 (clear) to 4 (severe)], and inflammatory lesion counts were also assessed on day 1 prior to study drug application and at Hour 12 on day 29. During the follow-up visits, CEA, PSA, telangiectasia, IGA, and inflammatory lesion counts were assessed at each visit. Safety was evaluated by physical exams and monitoring of adverse events (AEs) and vital signs throughout the study.

Statistical Analysis

All efficacy variables were analyzed based on the intent-to-treat (ITT) population, which is defined as all subjects who were randomized and to whom study drug was administered. Primary analyses were also performed on the Per Protocol (PP) population, which is defined as the ITT subjects who had no major protocol deviations. All safety variables were analyzed based on the safety population, defined as all subjects who had applied the study drug at least once.

Primary efficacy endpoint was the profile of success (defined as 2-grade improvement on both CEA and PSA) on days 1, 15, and 29, using the evaluations at Hours 3, 6, 9, and 12 as representative time points for each day. The primary analyses were to test treatment differences on success between the active and the vehicle groups using the Generalized Estimating Equation methodology in the ITT population. Multiple Imputation procedure was to be used to handle missing data at any time point. The 1-grade improvement on both CEA and PSA was analyzed using the same methodology. Secondary efficacy endpoint was the 30-minute effect, defined as 1-grade improvement from baseline on both CEA and PSA at 30 minutes on day 1. This variable was analyzed by Cochran-Mantel-Haenszel test stratified by analysis center, using general association statistics. The 1-grade and 2-grade improvements on CEA were also analyzed

similarly. Demographic and baseline disease characteristics, as well as adverse events, were descriptively summarized.

The sample size was calculated as the following: based on the results from the Phase IIb study,[24] the treatment difference between the once-daily treatment of BT gel 0.5% and vehicle gel in the average success rate across all time points was 19.9%, 17.6%, and 22.9% for days 1, 15, and 29, respectively. Considering the variability and vehicle effect may be higher in the present Phase III studies, it was assumed that the treatment difference in success rate between the active and controlled groups was 15%, the correlation between repeated measurements was 0.7, and the dropout rate was 10%. A sample size of 260 with 130 subjects per arm was hereinafter estimated to be sufficient to detect the specified treatment difference of 15% in success rate with a statistical power of 90% when conducted as a two-sided test at the 5% significance level.

RESULTS

The two studies were carried out from May, 2011 to Sept, 2011, and from May 2011 to Nov, 2011, respectively. The periods of recruitment were May, 2011 to July, 2011 and May 2011 to Sept, 2011.

Disposition, Demography, and Baseline Characteristics

The two studies were very similar in terms of study disposition, demography, and baseline characteristics.

In both studies, the vast majority of subjects reported normal study completion, with similarly low number of subject discontinuations in the two groups. A total of 260 subjects were enrolled into study A and 254 (97.7%) completed it normally (Figure 1). Among the 293 subjects enrolled into study B, 283 (96.6%) reported normal study completion.

The groups of BT gel 0.5% and vehicle gel were comparable in terms of demographic characteristics in both studies (Table 1.). The majority of subjects were female (79.2% and 72.7% in studies A and B, respectively) and Caucasian/White (98.5% and 98.6%, respectively). Most subjects had a Fitzpatrick skin phototype of II (53.5% and 58.7%, respectively), and the mean age was 48.8 year in study A and 47.5 year in study B. At baseline, the groups of BT gel 0.5% and vehicle gel also had similar severity of erythema in both studies, with the majority of subjects having moderate erythema based on either CEA or PSA.

Efficacy

The results of efficacy analyses were similar between the two studies, with significantly greater efficacy demonstrated for BT gel 0.5% compared with vehicle gel on all efficacy variables in each study.

The primary endpoint of both studies was the profile of success, defined as 2-grade improvement on both CEA and PSA over 12 hours. Significantly greater success was achieved with BT gel 0.5%

FIGURE 1. Erythema of rosacea. Subject disposition (study A).

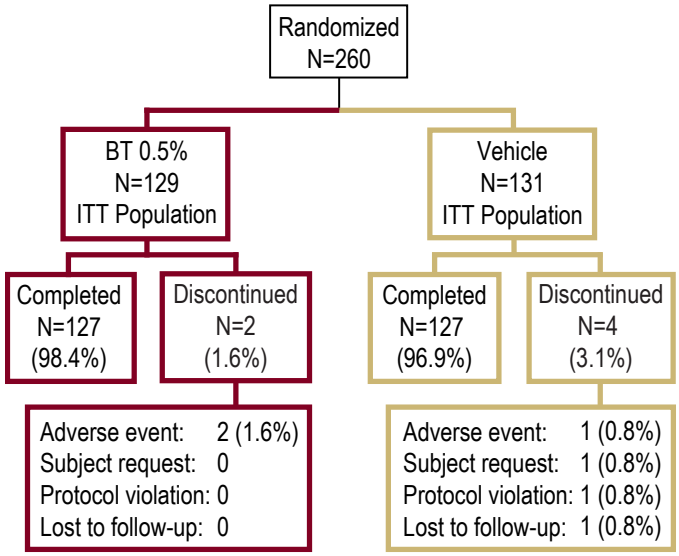


TABLE 1.

Demographic and Baseline Clinical Characteristics (ITT Population)

	Study A		Study B	
	BT 0.5% (N=129)	Vehicle (N=131)	BT 0.5% (N=148)	Vehicle (N=145)
Gender, n (%)				
Male	25 (19.4)	29 (22.1)	43 (29.1)	37 (25.5)
Female	104 (80.6)	102 (77.9)	105 (70.9)	108 (74.5)
Age, year				
Mean ± SD	49.5 ± 11.8	48.1 ± 12.8	48.5 ± 11.9	46.5 ± 12.1
Min, max	20, 76	18, 87	22, 77	19, 78
Phototype, n (%)				
I	19 (14.7)	8 (6.1)	12 (8.1)	13 (9.0)
II	65 (50.4)	74 (56.5)	88 (59.5)	84 (57.9)
III	38 (29.5)	37 (28.2)	36 (24.3)	38 (26.2)
IV	6 (4.7)	11 (8.4)	11 (7.4)	9 (6.2)
V	1 (0.8)	1 (0.8)	1 (0.7)	1 (0.7)
CEA, n (%)				
3=Moderate	111 (86.0)	113 (86.3)	108 (73.0)	115 (79.3)
4=Severe	18 (14.0)	18 (13.7)	40 (27.0)	30 (20.7)
PSA, n (%)				
1=Mild	0	1 (0.8)	0	2 (6.3)
3=Moderate	107 (82.9)	114 (87.0)	129 (87.2)	122 (84.1)
4=Severe	22 (17.1)	16 (12.2)	19 (12.8)	23 (15.9)

FIGURE 2. Erythema of rosacea. Success rate (2-grade of improvement on both CEA and PSA) on day 29 (ITT population; study A) .

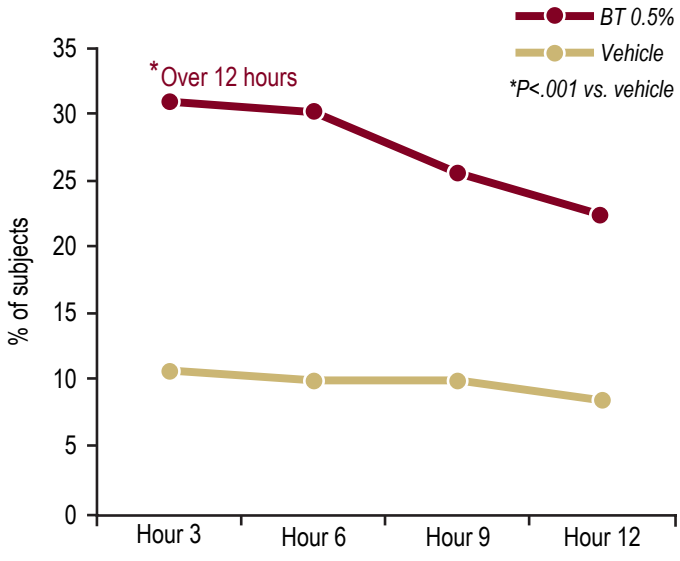
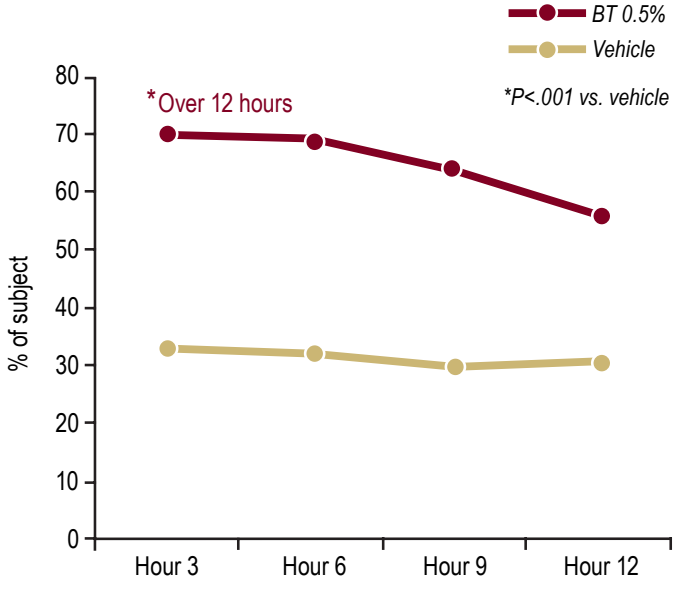
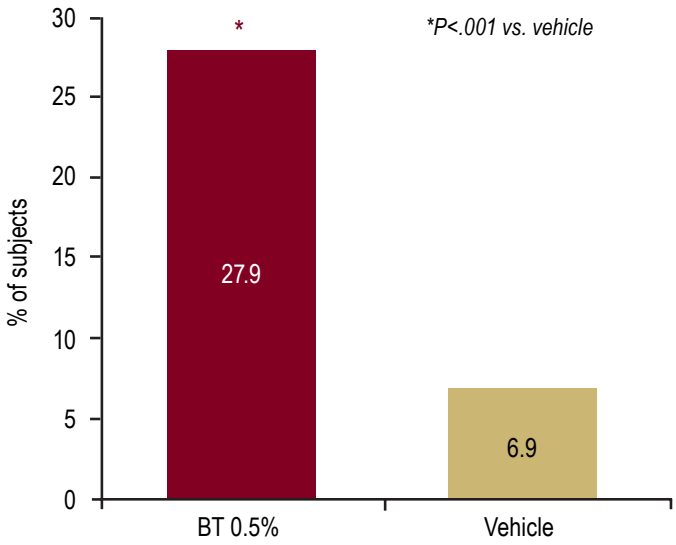


FIGURE 3. Erythema of rosacea. Percentage of subjects having 1-grade of improvement on both CEA and PSA on day 29 (ITT population; study A).



versus vehicle gel in both studies on day 29 (both *P*<.001; ITT analyses). The success rate with BT gel 0.5% at Hours 3, 6, 9, and 12 was 31.5%, 30.7%, 26.0%, and 22.8% in study A, and 25.4%, 25.4%, 17.6%, and 21.1% in study B (vs 10.9%, 9.4%, 10.2%, and 8.6% in study A and 9.2%, 9.2%, 10.6%, and 9.9% in study B for the vehicle gel; Figure 2). Significant difference between BT gel 0.5% and vehicle gel on the profile of success was also confirmed by PP analyses and three different sensitivity analyses in both studies (all *P*<.05).

FIGURE 4. Erythema of rosacea. 30 minutes effect (1-grade improvement on CEA and PSA) 30 minutes after the first application on day 1 (ITT population; study A).



Efficacy was also evaluated based on the 1-grade improvement on both CEA and PSA, which represents a clinically relevant effect that is noticeable by both clinicians and patients. In study A, the responder rate of BT gel 0.5% was significantly greater than that of vehicle gel (*P*<.001) on day 29, with 70.9%, 69.3%, 63.8%, and 56.7% of subjects in the BT gel 0.5% group having 1-grade improvement on both CEA and PSA at Hours 3, 6, 9, and 12, respectively (vs 32.8%, 32.0%, 29.7%, and 30.5% for vehicle gel; Figure 3). A significant difference between the two groups was also observed on day 29 in study B, with a responder rate of 71.1%, 64.8%, 66.9%, and 53.5% in the BT gel 0.5% group at Hours 3, 6, 9, and 12, respectively (versus 40.1%, 43.0%, 39.4%, and 40.1% for vehicle gel; *P*<.001).

Onset of action of BT gel 0.5% was evaluated based on the 30-minute effect, defined as the 1-grade improvement on CEA, and PSA 30 minutes after the drug application on day 1. In both studies, significantly greater effect was observed with BT gel 0.5% compared with vehicle gel (both *P*<.001). In study A, 27.9% of subjects in the BT gel 0.5% group had 1-grade improvement on CEA and PSA at 30 minutes on day 1, compared with 6.9% in the vehicle gel group (Figure 4). In study B, 28.4% of subjects in the group of BT gel 0.5% and 4.8% of subjects in the group of vehicle gel demonstrated the 30 minutes effect. This significant and more rapid onset of action of BT gel 0.5% versus vehicle gel was also confirmed in PP analyses.

Superiority of BT gel 0.5% over vehicle gel was observed in terms of profile of success throughout both studies, with statistically significant differences observed on days 1 and 15, as well as day 29 (all *P*<.001). Similarly, BT gel 0.5% was also significantly more

FIGURE 5. Erythema of rosacea. Standardized photos of a representative subject before and after an application of topical BT gel 0.5% on day 15 √ 1-grade improvement on both CEA and PSA; √√ 2-grade improvement on both CEA and PSA.

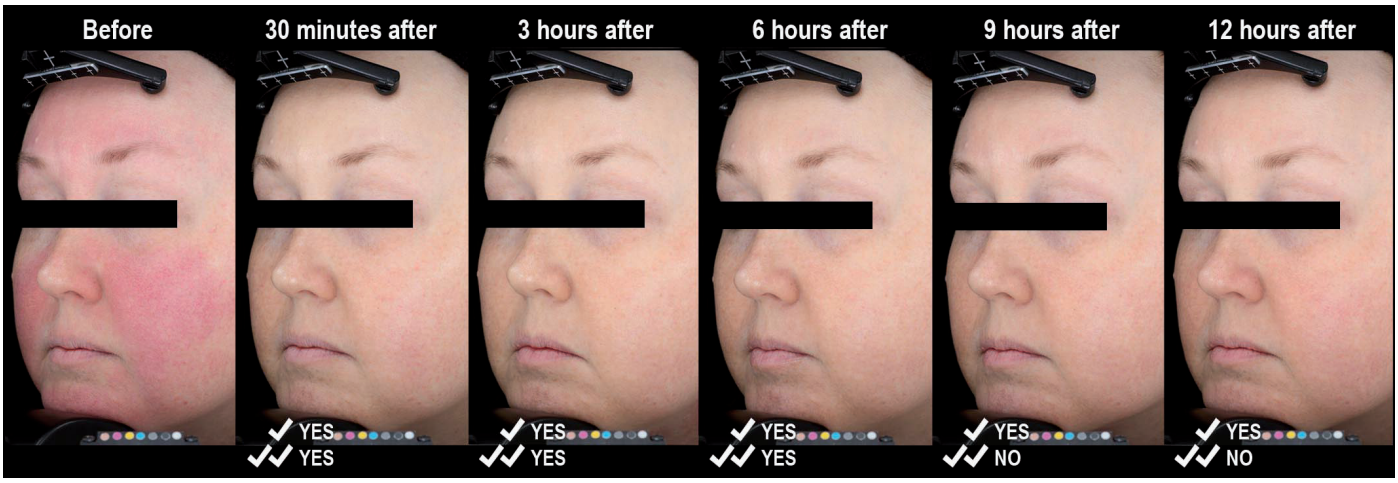
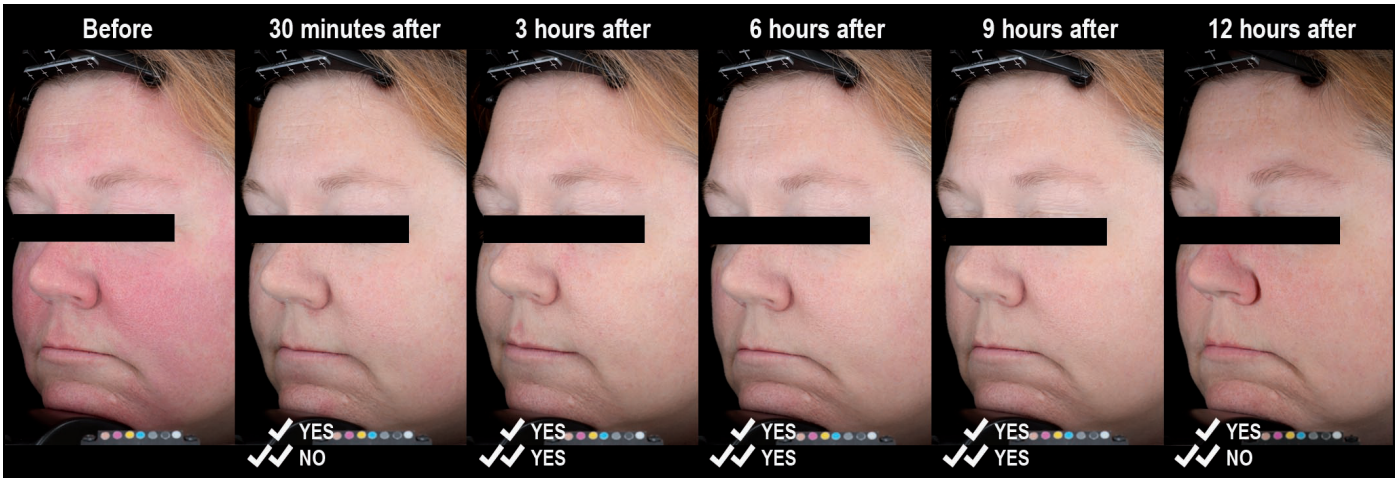


FIGURE 6. Erythema of rosacea. Standardized photos of a representative subject before and after an application of topical BT gel 0.5% on day 29 √ 1-grade improvement on both CEA and PSA; √√ 2-grade improvement on both CEA and PSA.



efficacious than vehicle gel based on the 1-grade improvement on CEA and PSA on days 1 and 15, in addition to day 29 (all $P<.001$). Therefore, no tachyphylaxis or loss of efficacy was observed during the 4-week treatment period of either study.

Photos of two representative subjects prior to application of BT gel 0.5%, and at various time points after the application are illustrated in Figures 5 and 6. A 2-grade improvement on both CEA and PSA was achieved at 30 minutes, 3 hours, and 6 hours after drug application in one subject (Figure 5), and at 3 hours, 6 hours, and 9 hours after drug application in the other subject (Figure 6). Marked and clinically meaningful improvement (eg 1-grade improvement on both CEA and PSA) compared to baseline was observed at the 9 hour and 12 hour time points in Figure 5 and at the 30 minute and 12 hour time points in Figure 6.

Rebound was defined as worsening of erythema compared to baseline after treatment cessation. There was no clinically meaningful aggravation of facial erythema observed during the follow-up phase, in comparison to the baseline assessments. In both studies, the mean scores of CEA and PSA during the visits of follow-up phase were similar to or lower than the mean scores of CEA and PSA during the visits of treatment phase prior to drug application. Few subjects in the group of BT 0.5% showed worsening in scores in the follow-up phase relative to baseline: In study A, 4.0% for CEA and 2.4% for PSA at week 6, and 4.7% for CEA and 1.6% for PSA at week 8; In study B, 3.6% for CEA and 4.3% for PSA at week 6, and 2.1% each for CEA and PSA at week 8. Furthermore, similar incidence of worsening was observed in the vehicle group in both studies.

No aggravations in the severity of telangiectasia, IGA or inflammatory lesion counts were observed during either the treatment or follow-up phase of either study.

Safety

The once-daily BT gel 0.5% was safe and well tolerated during 4 weeks of continuous application as demonstrated in both studies. The incidence of AEs in the active treatment and vehicle groups was 29.5% vs 25.2% in study A, and 33.8% vs 24.1% in study B. In study A, the incidence of related AE was 11.6% for the group of BT gel 0.5% and 5.3% for the group of vehicle gel; while in study B, the incidence was similarly low for both groups (9.5% and 9.7%). In both studies, the majority of related AEs were cutaneous in nature, transient in duration, and mild in intensity. The most frequent related AEs included worsening of erythema and/or flushing (7 subjects in each study), pruritus (4 and 1 subject in studies A and B, respectively), skin irritation (3 subjects in study A), and worsening of rosacea (1 and 2 subjects, respectively). No serious related AEs occurred in any study subjects. During the two studies, no abnormal changes in blood pressure or heart rate were observed.

DISCUSSION

The results of these two pivotal studies of identical design confirm the efficacy and safety of once-daily topical BT gel 0.5% for the treatment of erythema of rosacea. The primary endpoint was the 2-grade improvement on both CEA and PSA, which is a very stringent criterion to evaluate the effectiveness of a treatment. Efficacy was also evaluated based on the 1-grade improvement on both CEA and PSA, which represents an effect that is noticeable to both clinicians and patients, and thus clinically relevant. In both studies, BT gel 0.5% provided significantly greater efficacy compared with the vehicle gel in terms of 2-grade and 1-grade improvement on both CEA and PSA, with a good profile of safety and tolerability. Maximal drug effects were typically observed 3 hours after application and continued to about 6 hours after application, when about 70% of subjects had an improvement based on the assessment by the clinicians and the patients themselves.

Fast onset of action of the topical BT gel 0.5% was first observed in the Phase II studies and confirmed in the present two pivotal studies. Thirty minutes after the first application on day 1, significantly greater effect was observed with BT gel 0.5% compared with vehicle gel, with about 28% of subjects having an improvement on both CEA and PSA. A single application of BT gel 0.5% also resulted in a long duration of effect, with more than 50% of subjects reporting 1-grade improvement on both CEA and PSA 12 hours after the application. The fast onset and long duration allow the condition of erythema to be managed with a once-daily regimen, which is considerably more convenient for patients compared to a twice-daily regimen.

Tachyphylaxis (loss of previous noted effect) and rebound (worsening of condition as compared to baseline) were reported to be associated with nasal spray treatments containing some but not all α-adrenergic receptor agonists.[25] During a 1-year study on the treatment of glaucoma and ocular hypertension, twice-daily usage of BT ophthalmic solution did not lead to tachyphylaxis or rebound.[26, 27] In the previous Phase IIb study and the present two pivotal studies, where topical BT gel was used once-daily for 4 weeks, no evidence of tachyphylaxis was observed, as the efficacy remained similarly high at the beginning and the end of the treatment phase in each study.[24] Similarly, during the 4-week follow-up phase in all three studies, no rebound or worsening of erythema was observed. In the Phase IIb study, similarly low incidence of rebound was reported between the active treatment and the vehicle groups; [24] In the present Phase III studies, the mean score of erythema before treatment was same during the follow-up phase and during the treatment phase, with only isolated cases of worsening observed. Moreover, no aggravation of other disease signs or symptoms was observed during any studies. Nevertheless, the safety of topical BT gel 0.5% should be further evaluated in a longer-term study.

> "Although erythema is the primary feature of rosacea and presents ubiquitously among rosacea patients, there is currently no approved medication for its treatment, making it a key unmet medical need."

In summary, there is currently no approved medication for the effective treatment of the facial erythema of rosacea. Results from these two Phase III pivotal studies demonstrate that once-daily BT gel 0.5% provides significantly greater efficacy and a faster onset of action compared to the vehicle gel for the treatment of the facial erythema of rosacea, without evidence of tachyphylaxis, rebound, or aggravation of the other common clinical signs of rosacea.

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DISCLOSURE

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REFERENCES

1. Rosacea riddle now threatens more than 16 million Americans. Available at http://www.rosacea.org/weblog/2010/04/01/rosacea_incidence_on_rise/index.php Accessed April 1, 2010.
2. Conde JF, Yelverton CB, Balkrishnan R, Fleischer AB, Feldman SR. Managing rosacea: A review of the use of Metronidazole alone and in combination with oral antibiotics. *J Drugs Dermatol.* 2007;6:495-8.
3. Wilkin J, Dahl M, Detmar M, Drake L, Liang MH, Odom R et al. Standard classification of rosacea: report of the National Rosacea Society expert committee on the classification and staging of rosacea. *J Am Acad Dermatol.* 2002;46:584-7.
4. Berg M, Liden S. An epidemiological study of rosacea. *Acta Derm Venereol.* 1989;69:419-23.
5. Gupta AK, Chaudhry MM. Rosacea and its management: an overview. *J Eur Acad Dermatol Venerol.* 2005;19:273-85.
6. Crawford GH, Pelle MT, James WD. Rosacea: I. Etiology, pathogenesis, and subtype classification. *J Am Acad Dermatol.* 2004;51:327-41.
7. Wolf JE Jr. Del Rosso JQ. The CLEAR trial: results of a large community-based study of metronidazole gel in rosacea. *Cutis.* 2007;79:73-80.
8. Aksoy B, Altaykan-Hapa A, Egemen D, Karagöz F, Atakan N. The impact of rosacea on quality of life: effects of demographic and clinical characteristics and various treatment modalities. *Br J Dermatol.* 2010;163:719-25.
9. Wilkin J, Dahl M, Detmar M, Drake L, Liang MH, Odom R et al. Standard grading system for rosacea: report of the National Rosacea Society expert committee on the classification and staging of rosacea. *J Am Acad Dermatol.* 2004;50:907-12.
10. Odom R, Dahl M, Dover J, Draelos Z, Drake L, Macsai M et al. Standard management options for rosacea, Part I: overview and broad spectrum of care. *Cutis.* 2009;84:43-7.
11. Odom R, Dahl M, Dover J, Draelos Z, Drake L, Macsai M et al. Standard management options for rosacea, Part II: option according to subtype. *Cutis.* 2009;84:97-104.
12. Singer MI. Drug therapy of rosacea: a problem-directed approach. *J Cutan Med Surg.* 1998; 2 (Suppl. 4):20-3.
13. Powell FC. Rosacea. *N Engl J Med.* 2005;352:793-803.
14. Wilkin JK. Rosacea: pathophysiology and treatment. *Arch Dermatol.* 1994;130:359-62.
15. Del Rosso JQ. Advances in understanding and managing rosacea: part1: connecting the dots between pathophysiological mechanisms and common clinical features of rosacea with emphasis on vascular changes and facial erythema. *J Clin Aesthet Dermatol.* 2012;5:16-25.
16. Steinhoff M, Buddenkotte J, Aubert J, Sulk M, Novak P, Schwab VD et al. Clinical, cellular and molecular aspects in the pathophysiology of Rosacea. *J Invest Dermatol Symp Proc.* 2011;15:2-11.
17. Schwab VD, Sulk M, Seeliger S, Nowak P, Aubert J, Mess C et al. Neurovascular and neuroimmune aspects in the pathophysiology of rosacea. *J Invest Dermatol Symp Proc.* 2011;15:53-62.
18. Shanler SD, Ondo AL. Successful treatment of the erythema and flushing of rosacea using a topically applied selective α_1-adrenergic receptor agonist, Oxymetazoline. *Arch Dermatol.* 2007;143:1369-71.
19. Wilkin JK. Effect of nadolol on flushing reactions in rosacea. *J Am Acad Dermatol.* 1989; 20:202-5.
20. Craige H, Cohen JB. Symptomatic treatment of idiopathic and rosacea-associated cutaneous flushing with propranolol. *J Am Acad Dermatol.* 2005;53:881-4.
21. Rahman MQ, Ramaesh K, Montgomery DNI. Brimonidine for glaucoma. *Expert Opin Drug Saf.* 2010;9:483-91.
22. Katz LJ. Brimonidine tartrate 0.2% twice daily vs timolol 0.5% twice daily: 1-year results in glaucoma patients. Brimonidine study group. *Am J Ophthalmol.* 1999;127:20-6.
23. Serle JB. A comparison of the safety and efficacy of twice daily brimonidine 0.2% versus betaxolol 0.25% in subjects with elevated intraocular pressure. The brimonidine study group III. *Surv Ophthalmol.* 1996; 41 (Suppl 1):S39-47.
24. Fowler J, Jarratt M, Moore A, Meadows K, Pollack A, Steinhoff M et al. Once-daily topical brimonidine tartrate gel 0.5% is a novel treatment for moderate to severe facial erythema of rosacea: results of two multicenter, randomized and vehicle-controlled studies. *Br J Dermatol.* 2012; 166(3): 633-41.
25. Graf P. Long-term use of oxy- and xylometazoline nasal sprays induces rebound swelling, tolerance, and nasal hyperreactivity. Rhiology 1996;34:9-13.
26. Adkins JC, Balfour JA. Brimonidine. A review of its pharmacological properties and clinical potential in the management of open-angle glaucoma and ocular hypertension. *Drugs Aging.* 1998;12:225-41.
27. Schuman JS, Horwitz B, Choplin NT, David R, Albracht D, Chen K. A 1-year study of brimonidine twice daily in glaucoma and ocular hypertension. A controlled, randomized, multicenter clinical trial. *Arch Ophthalmol. 1*997;115:847-52.

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