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Once-daily topical brimonidine tartrate gel 0.5% is a novel treatment for moderate to severe facial erythema of rosacea: results of two multicentre, randomized and vehicle-controlled studies

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Summary

Background—Erythema of rosacea is thought to result from abnormal cutaneous vasomotor activity. Brimonidine tartrate (BT) is a highly selective α_2 -adrenergic receptor agonist with vasoconstrictive activity.

Objective—To determine the optimal concentration and dose regimen of topical BT gel for the treatment of erythema of rosacea and to evaluate its efficacy and safety.

Methods—In study A, 122 subjects were randomized to receive a single application of BT 0.07%, 0.18%, 0.5% or vehicle. In study B (4-week treatment and 4-week follow-up), 269 subjects were randomized to receive BT 0.5% once daily, BT 0.18% once daily, vehicle once daily, BT 0.18% twice daily or vehicle twice daily. Evaluations included Clinician's Erythema Assessment (CEA), Patient's Self-Assessment (PSA), Chroma Meter measurements and adverse events.

Results—In study A, a single application of topical BT gel reduced facial erythema in a dose-dependent fashion. A significant difference between BT 0.5% and vehicle in Chroma Meter redness value was observed from 30 min to 12 h after application. In study B, BT 0.5% once daily had a statistically superior success profile (defined as a two-grade improvement on both CEA and PSA over 12 h) compared with vehicle once daily on days 1, 15 and 29 (all $P < 0.001$). No tachyphylaxis, rebound of erythema or aggravation of other disease signs (telangiectasia, inflammatory lesions) was observed. All regimens were safe and well tolerated with similarly low incidence of adverse events.

Conclusions—Once-daily BT gel 0.5% is well tolerated and provides significantly greater efficacy than vehicle gel for the treatment of moderate to severe erythema of rosacea.

Rosacea is a common and chronic disorder, characterized by flushing and persistent erythema in the central facial area.^{1,2} The disease onset is typically between the ages of 20 and 50 years, and women are more often affected than men.^{3,4} Rosacea has considerable psychosocial impact and causes embarrassment, anxiety and low self-esteem.^{5,6} Erythema is the primary feature of rosacea and presents ubiquitously among patients. Other cutaneous signs such as telangiectasia, papules, pustules and oedema may also present.^{7,8}

Although several medications are approved for the treatment of inflammatory lesions of rosacea, there is currently no approved medication directly targeting erythema of rosacea, making it a key unmet medical need.⁴ In the absence of effective treatment, patients are usually advised to avoid environmental and lifestyle triggers that can exacerbate erythema.^{9–11} While the exact cause of erythema of rosacea is not known, it is hypothesized that erythema results from dysregulation in the cutaneous vasomotor responses, which leads to abnormal dilation of facial blood vessels upon various stimuli.^{12–14} Therefore, agents with vasoconstrictive activity may have a symptomatic effect on erythema.

Transcriptomic studies suggest the involvement of adrenergic receptors in the neurovascular regulation pathway.¹⁵ Brimonidine tartrate (BT) is a highly selective α_2 -adrenergic receptor agonist, with potent vasoconstrictive activity.¹⁶ It is currently approved for the treatment of open-angle glaucoma, with well-documented efficacy and safety.^{17,18} BT applied topically to the face is hypothesized to reduce erythema of rosacea. In the present two Phase II studies, we aimed to determine the optimal dose regimen of BT in the treatment of moderate to severe erythema of rosacea, and to evaluate the efficacy and safety of the treatment using two specifically developed novel scales for erythema.

Materials and methods

These two studies were conducted in accordance with the Declaration of Helsinki, Good Clinical Practices and 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.

In both studies, randomization lists were generated prior to study initiation by an independent statistician using SAS Proc Plan procedure (SAS Institute, Cary, NC, U.S.A.). The randomization lists were then sent to the clinical supply group, and only the personnel directly involved with labelling and packaging had access. The integrity of the blinding was ensured by packaging the topical gels in identical tubes and requiring a third party other than the investigator/evaluator to dispense the medication. The intent-to-treat (ITT) population included all subjects who were randomized into the studies. The safety population included all subjects who were enrolled into the studies and received the study medication.

Study A

The pharmacodynamics and safety of three concentrations of topical BT gels were evaluated in this randomized, double-blind, parallel-group and vehicle-controlled study carried out at five centres in the U.S.A. Eligible subjects were aged ≥ 18 years, with moderate to severe erythema according to both Clinician's Erythema Assessment (CEA) and Patient's Self-Assessment (PSA) (Table 1). Subjects with three or more facial inflammatory lesions of rosacea were excluded. Subjects were randomized in a 1 : 1 : 1 : 1 ratio to receive a single application of gel containing BT 0.5%, BT 0.18%, BT 0.07% or vehicle to the entire face.

Efficacy was assessed at baseline, 30 min, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 h after application of the study medication. At each time point, erythema was assessed by the blinded investigator (CEA) and by the blinded subjects (PSA). The Chroma Meter (Konica Minolta CR-400; Konic Minolta Sensing Americas, Inc., Ramsey, NJ, U.S.A.) a* parameter (red–green scale) was measured by the blinded study site personnel as an objective evaluation of erythema.¹⁹ Inflammatory lesion counts and severity of telangiectasia [on a five-point scale from 0 (clear) to 4 (severe)] were also assessed. Safety was evaluated by monitoring adverse events (AEs), vital signs and intraocular pressure (IOP) throughout the study.

The cumulative responder rate at each time point for one- or two-grade improvement was summarized based on the Kaplan–Meier survival curve and analysed using the log-rank test, with significance declared at the 0.05 level. Chroma Meter a* data and changes in telangiectasia and inflammatory lesion counts were analysed using the ANCOVA covariance model stratified by analysis centre and treatments, and using the corresponding baseline value as the covariate.

Study B

Efficacy and safety of four topical BT gel dose regimens were evaluated in this randomized, double-blind, parallel-group and vehicle-controlled study carried out at 17 centres in the U.S.A. The study duration was 8 weeks, including a 4-week treatment phase and a 4-week follow-up phase. Eligible subjects were aged ≥ 18 years, with a clinical diagnosis of rosacea, fewer than three facial inflammatory lesions, and moderate or severe erythema according to both CEA and PSA.

Subjects were randomized in a 1 : 1 : 1 : 1 : 1 ratio to the groups of BT 0.5% once daily, BT 0.18% once daily, vehicle once daily, BT 0.18% twice daily and vehicle twice daily. During the first 4 weeks, subjects applied gel once daily in the morning. Subjects in the twice-daily groups performed the second application 6 h after the first application. No medication application was performed during follow-up.

On days 1, 15 and 29 (treatment phase), CEA, PSA and telangiectasia were assessed at 0, 3, 6, 9 and 12 h; inflammatory lesion counts and Investigator's Global Assessment (IGA) of the lesions [scale ranging from 0 (clear) to 4 (severe)] were evaluated at baseline (0 h on day 1) and at 12 h on day 29. On day 30, and at weeks 5, 6 and 8 (follow-up phase), CEA, PSA, telangiectasia, inflammatory lesion counts and IGA were evaluated. Safety was evaluated by monitoring AEs, vital signs and IOP throughout the study.

Assuming that 5% of subjects in the vehicle group had a two-grade improvement on both CEA and PSA, and the minimum difference between the active and vehicle groups was 20%, a sample size of 260 (52 subjects per group) was required with an 80% power when conducted as a two-sided test at the significance level of 2.5%, adjusting for a 10% dropout rate. The primary efficacy endpoint was the profile of success (two-grade improvement on both CEA and PSA over 12 h) on days 29, 15 and 1, using 3, 6, 9 and 12 h as representative time points for each day. The primary analyses tested differences on the profile of success between each active treatment and its corresponding vehicle, using the generalized estimating equation methodology in the ITT population. When data were missing at all four time points, the last-observation-carried-forward method was applied. The rate of one-grade improvement on both CEA and PSA was analysed similarly. No adjustment was made in analysing the variables.

Results

Study A

All of the randomized 122 subjects (28 with BT 0.07%, 31 with BT 0.18%, 31 with BT 0.5% and 32 with vehicle) completed the study. The four groups were comparable in terms of demographic characteristics and baseline erythema severity, except that more subjects in the BT 0.07% group had severe erythema based on PSA (Table 2). The majority of subjects had moderate erythema based on either CEA (76%) or PSA (72%).

BT gel was effective in a dose-dependent fashion in reducing erythema for 12 h after a single application (Fig. 1). In terms of a one-grade improvement on both CEA and PSA, the responder rate was significantly higher for all three BT gel groups than for the vehicle gel group (84%, 81%, 75% vs. 28%, all $P < 0.001$). The largest effect was observed in the BT 0.5% group, followed by 0.18% and 0.07%. In terms of a two-grade improvement on both CEA and PSA, BT 0.5% also had a significantly higher responder rate than vehicle (55% vs. 12%, $P < 0.001$).

The effect of BT gel on facial erythema was also assessed based on the Chroma Meter a^* parameter, an objective evaluation of redness (Fig. 2). All three BT groups were effective in reducing facial redness compared with vehicle. During the entire study, a^* values with BT 0.5% were significantly lower than those with vehicle (all $P < 0.001$). The onset of effect was rapid, with significantly lower a^* value in the BT 0.5% group vs. the vehicle group as early as the first time point ($P < 0.001$ at 30 min after application). The maximal effect had a duration of 4–6 h, observed between 2 and 8 h after application. Afterwards, the facial redness started to reappear, but never went back to the baseline level.

Figure 3 shows representative photographs of a subject with moderate facial erythema before and after a single application of BT gel 0.5%. No aggravations in the severity of telangiectasia or inflammatory lesion counts were observed during the study.

All three concentrations of BT gel were safe and well tolerated. The numbers of subjects who had AEs during the study were similar among the four groups (six, four, five and six subjects in the BT 0.5%, 0.18%, 0.07% and vehicle groups, respectively). No severe AEs, serious AEs or AEs leading to study discontinuation were reported. Subjects receiving a higher concentration of BT gel did not report more AEs related to the study medication, and the incidence ranged from 6% (BT 0.5%, two subjects) to 14% (BT 0.07%, four subjects). The majority of related AEs were transient, dermatological in nature (skin irritation, erythema, skin burning sensation, dry skin and pruritus) and mild in intensity. Two cases of mild, transient and reversible decreases in IOP were observed (one subject each in the BT 0.5% and 0.18% groups), most probably caused by inadvertent eye contact with the study medication.

Study B

A total of 269 subjects were enrolled and 260 (96.7%) reported normal study completion (Fig. 4). Subjects were randomized to one of the five groups for 4 weeks, and remained untreated for 4 weeks. The groups were comparable in terms of demographic characteristics and baseline erythema severity (Table 3), with a majority of subjects having moderate erythema based on either CEA (84%) or PSA (84%).

The primary endpoint of the study was the profile of success, defined as a two-grade improvement on both CEA and PSA over 12 h. At the end of the treatment phase (day 29), significantly greater success was achieved with BT 0.5% once daily vs. vehicle once daily ($P < 0.001$; Fig. 5). At 3, 6, 9 and 12 h on day 29, the success rate with BT 0.5% once daily

was 30%, 28%, 32% and 19%, respectively (vs. 4%, 7%, 4% and 4% for vehicle once daily). Similarly, BT 0.5% once daily led to a significantly greater success than vehicle once daily on days 1 (Fig. 6) and 15 (data not shown). The profile of success of BT 0.5% once daily was similar to that shown in study A: rapid onset and long duration of effect were observed, with a success rate at 12 h on days 1, 15 and 29 always greater than that with vehicle.

A dose-dependent relationship in the once-daily groups was also observed in this study (Fig. 5). On day 29, the greatest effect in the primary endpoint was observed in the BT 0.5% once-daily group, followed by BT 0.18% once daily, which were both significantly more efficacious than vehicle once daily ($P < 0.001$ and $P < 0.05$, respectively) over 12 h.

Efficacy was also evaluated based on a one-grade improvement on both CEA and PSA. On day 29, the responder rate of BT 0.5% once daily was significantly greater than that of vehicle once daily ($P < 0.001$; 60–76% with BT 0.5% once daily vs. 31–42% with vehicle once daily; Fig. 7). The superiority of BT 0.5% once daily vs. vehicle once daily was also observed on days 1 and 15 (data not shown).

No tachyphylaxis was observed in the study. Statistically significant differences were observed between BT 0.5% once daily and vehicle once daily from the first treatment to the end of the treatment phase (Fig. 6). Efficacy profiles for all active treatments on day 29 were the same or better compared with profiles on day 1.

Rebound was defined as worsening of erythema, assessed using CEA and PSA, after treatment cessation compared with baseline. During the 4-week follow-up phase, there was no clinically meaningful aggravation of facial erythema. In some isolated cases, worsening in CEA or PSA was observed. However, the incidence was comparable between the active treatment and the vehicle groups. No aggravations in telangiectasia or inflammatory lesions were observed in any of the five groups during the entire study.

All dose regimens of BT gels were safe and well tolerated during 4 weeks of continuous application. The incidence of AEs was similar among the five groups, ranging from 32% with vehicle twice daily to 46% with BT 0.18% twice daily. There were two serious but nonrelated AEs (one gastric reflux in the BT 0.18% once-daily group, one deep vein thrombosis in the vehicle once-daily group) and one related AE leading to subject-requested discontinuation (mild skin burning, BT 0.18% twice-daily group). The incidence of related AEs was comparable among the groups of BT 0.5% once daily, BT 0.18% once daily, vehicle once daily and BT 0.18% twice daily (11–19%). A lower incidence of related AEs was observed for vehicle twice daily (2%) than for the other groups. The majority of related AEs were dermatological, transient and mild. During the study, there were no clinically meaningful shifts or changes observed in mean IOP, blood pressure or heart rate.

Discussion

Validated scales of erythema severity did not exist previously in the literature. The CEA and PSA scales were specifically developed and statistically validated as tools for evaluation of erythema (publication in preparation). A one-grade improvement on both CEA and PSA represents an effect that is noticeable by both investigators and patients, and is therefore clinically relevant; a two-grade improvement on both CEA and PSA is a stringent criterion for success, and is required for regulatory approval.

The objective of the present two studies was to choose the optimal dose/regimen of topical BT gel in the treatment of moderate to severe facial erythema of rosacea. Dose selection was first based on the magnitude and duration of effect achieved after a single application of BT gels of three various concentrations. The optimal dose of BT gel should be safe and effective

in reducing erythema, leading to a noticeable improvement for as long as possible and a maximal improvement for a sustained period. In study A, a single application of BT gel 0.5% led to a rapid onset of action, 12 h of noticeable effect and 4–6 h of maximal effect. A dose–response relationship was also demonstrated in the study, with the greatest effect observed in the group of BT 0.5%, followed by 0.18% and 0.07%. In study B, BT 0.5% once daily was significantly more efficacious than vehicle once daily throughout the study. At 3 h on day 29, 76% and 30% of subjects in the BT 0.5% once-daily group had one-grade and two-grade improvement on both CEA and PSA, respectively. A once-daily regimen is also more convenient for patients compared with a twice-daily regimen. Therefore, BT 0.5% once daily was the final dose regimen selected for future Phase III studies to confirm the efficacy and safety of the treatment.

Tachyphylaxis (loss of activity) and rebound are two major concerns of treatments with some α -adrenergic receptor agonists when used as nasal sprays.²⁰ It has been reported that long-term use of nasal sprays containing these compounds can lead to rebound mucosal swelling, nasal hyper-reactivity, and histopathological changes to nasal mucosa. The efficacy of nasal sprays containing α -adrenergic receptor agonists has also been documented to decrease after prolonged usage. However, no evidence of tachyphylaxis or rebound was observed during a 1-year study of BT ophthalmic solution used twice daily for the treatment of glaucoma and ocular hypertension.^{21,22} In study B, no tachyphylaxis of topical BT gel was observed in the treatment of erythema, as the efficacy was similarly high at the beginning and the end of the treatment phase. Only a marginal number of subjects from each group reported erythema worse than baseline after cessation of treatment, and there was no difference in the incidence of rebound between the active and vehicle groups. Moreover, no aggravation of other disease signs was observed during the study.

The 4-week continuous treatment with once-daily BT 0.5% gel was well tolerated and safe among patients with moderate to severe erythema of rosacea. Burning and stinging sensations are common secondary features of rosacea, and patients usually have barrier disruption and easily irritated skin.^{23,24} In study B, the incidence of related AEs was similar between the BT 0.5% once-daily and the vehicle once-daily groups, and the majority of related AEs were dermatological, mild in intensity and transient in nature. Only one subject (with BT 0.18% twice daily) experiencing mild burning sensation requested study discontinuation.

Agonists of α - and β -adrenergic receptors, such as oxy-metazoline and nadolol, have only been used in isolated cases for the treatment of flushing/erythema among patients with rosacea,^{25–27} while the current studies are the first reported randomized and controlled trials to support the safety and effectiveness of a topical α -agonist in this indication. In subcutaneous tissue, vasoconstriction of the small, distal resistance arteries has been shown to depend mainly on postsynaptic α_2 -adrenergic receptor stimulation of vascular smooth muscle.^{28,29} Therefore, topical application of a highly selective α_2 -adrenergic receptor agonist such as BT should be more efficacious than α_1 - and β -adrenergic agonists, with fewer systemic safety issues.

Rosacea patients with erythema and flushing may also have papules and pustules on the central portion of the face. Several medications including topical metronidazole, azelaic acid and oral antibiotics have been used successfully to reduce inflammatory lesion counts, but their effect on the erythema of rosacea has not been successfully demonstrated. We hypothesize that the combination of topical BT gel with one of the above-mentioned reference therapies would be effective among patients with both disease manifestations.

In summary, facial erythema is perhaps the most common and debilitating aspect of rosacea. It is poorly responsive to available pharmaceutical therapies, and there is currently no approved medication for its effective treatment. Results of the current studies demonstrated that once-daily BT gel 0.5% is a well-tolerated novel treatment for moderate to severe erythema of rosacea, with good clinical safety and significantly greater efficacy compared with vehicle.

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What's already known about this topic?

- There is currently no approved medication for the treatment of erythema of rosacea.
- Compounds with vasoconstrictive action, such as brimonidine tartrate (BT), may provide symptomatic relief of visible erythema.

What does this study add?

- A single application of topical BT gel significantly reduced erythema in a dose-dependent fashion.
- Once-daily BT 0.5% was well tolerated and provided significantly greater efficacy compared with the vehicle gel in the treatment of moderate to severe erythema of rosacea.

Fig 1.

Study A. Percentage of total subjects who had one-grade or two-grade improvement on Clinician's Erythema Assessment (CEA), Patient's Self-Assessment (PSA) and both CEA and PSA for 12 h after a single application. ** $P < 0.001$ vs. vehicle gel; * $P < 0.05$ vs. vehicle. BT, brimonidine tartrate.

Fig 2.

Study A. Median change in Chroma Meter a* (redness) values at each time point after a single application. ** $P < 0.001$ vs. vehicle; * $P < 0.05$ vs. vehicle. BT, brimonidine tartrate.

Fig 3.
Study A. Standardized photographs of a subject with moderate erythema (a) before, and (b) 30 min, (c) 3 h and (d) 10 h after a single application of brimonidine tartrate gel 0.5%.

Fig 4.
Study B. Study flow chart. BT, brimonidine tartrate; QD, once daily; BID, twice daily.

Fig 5. Study B. Success rate (two-grade improvement on both Clinician's Erythema Assessment and Patient's Self-Assessment) on day 29 (intent-to-treat-last-observation-carried-forward). ** $P < 0.001$ vs. vehicle once daily on day 29; * $P < 0.05$ vs. vehicle once daily on day 29. BT, brimonidine tartrate; QD, once daily; BID, twice daily.

Fig 6. Study B. Success rate (two-grade improvement on both Clinician's Erythema Assessment and Patient's Self-Assessment) on days 1 and 29 (intent-to-treat-last-observation-carried-forward). ** $P < 0.001$ vs. vehicle QD. BT, brimonidine tartrate; QD, once daily.

Fig 7. Study B. Percentage of subjects having one- or two-grade improvement on both Clinician's Erythema Assessment (CEA) and Patient's Self-Assessment (PSA) at 3 h on day 29 (intent-to-treat-last-observation-carried-forward). ** $P < 0.001$ vs. vehicle. BT, brimonidine tartrate; QD, once daily.

Table 1

Clinician's Erythema Assessment (CEA) and Patient's Self-Assessment (PSA)

Scores	CEA	PSA
0, Clear	Clear skin with no signs of erythema	Clear of unwanted redness
1, Almost clear	Almost clear; slight redness	Nearly clear of unwanted redness
2, Mild	Mild erythema; definite redness	Somewhat more redness than I prefer
3, Moderate	Moderate erythema; marked redness	More redness than I prefer
4, Severe	Severe erythema; fiery redness	Completely unacceptable redness

Table 2

Study A: demographic and baseline clinical characteristics (intent-to-treat)

	BT 0-5% (n = 31)	BT 0-18% (n = 31)	BT 0-07% (n = 28)	Vehicle (n = 32)	Total (n = 122)
Sex, n (%)					
Male	6 (19.4)	10 (32.3)	6 (21.4)	8 (25.0)	30 (24.6)
Female	25 (80.6)	21 (67.7)	22 (78.6)	24 (75.0)	92 (75.4)
Age (years)					
Mean $\pm$ SD	45.8 $\pm$ 11.9	46.3 $\pm$ 12.4	43.7 $\pm$ 10.7	46.7 $\pm$ 13.4	45.7 $\pm$ 12.1
Min., max.	18, 63	18, 65	24, 69	20, 74	18, 74
Skin phototype, n (%)					
I	1 (3.2)	2 (6.5)	2 (7.1)	2 (6.3)	7 (5.7)
II	17 (54.8)	14 (45.2)	21 (75.0)	20 (62.5)	72 (59.0)
III	11 (35.5)	14 (45.2)	5 (17.9)	9 (28.1)	39 (32.0)
IV	2 (6.5)	0	0	1 (3.1)	3 (2.5)
V	0	1 (3.2)	0	0	1 (0.8)
CEA, n (%)					
3, Moderate	23 (74.2)	23 (74.2)	22 (78.6)	25 (78.1)	93 (76.2)
4, Severe	8 (25.8)	8 (25.8)	6 (21.4)	7 (21.9)	29 (23.8)
PSA, n (%)					
2, Mild	0	1 (3.2)	1 (3.6)	2 (6.3)	4 (3.3)
3, Moderate	26 (83.9)	24 (77.4)	12 (42.9)	26 (81.3)	88 (72.1)
4, Severe	5 (16.1)	6 (19.4)	15 (53.6)	4 (12.5)	30 (24.6)
Chroma Meter a*, mean $\pm$ SD	19.7 $\pm$ 3.7	19.9 $\pm$ 3.3	20.2 $\pm$ 2.7	20.3 $\pm$ 3.4	20.0 $\pm$ 3.3

BT, brimonidine tartrate; CEA, Clinician's Erythema Assessment; PSA, Patient's Self-Assessment.

Table 3

Study B: demographic and baseline clinical characteristics (intent-to-treat)

	BT 0.5% QD (n = 53)	BT 0.18% QD (n = 54)	Vehicle QD (n = 55)	BT 0.18% BID (n = 54)	Vehicle BID (n = 53)
Sex, n (%)					
Male	11 (20.8)	10 (18.5)	10 (18.2)	12 (22.2)	9 (17.0)
Female	42 (79.2)	44 (81.5)	45 (81.8)	42 (77.8)	44 (83.0)
Age (years)					
Mean $\pm$ SD	44.9 $\pm$ 11.5	46.9 $\pm$ 12.7	43.4 $\pm$ 12.7	43.2 $\pm$ 12.3	43.0 $\pm$ 12.3
Min., max.	21, 67	22, 72	21, 73	19, 69	18, 74
Skin phototype, n (%)					
I	7 (13.2)	8 (14.8)	12 (21.8)	6 (11.1)	8 (15.1)
II	26 (49.1)	28 (51.9)	23 (41.8)	33 (61.1)	28 (52.8)
III	16 (30.2)	14 (25.9)	18 (32.7)	12 (22.2)	12 (22.6)
IV	4 (7.5)	4 (7.4)	2 (3.6)	3 (5.6)	5 (9.4)
CEA, n (%)					
3, Moderate	47 (88.7)	44 (81.5)	48 (87.3)	42 (77.8)	44 (83.0)
4, Severe	6 (11.3)	10 (18.5)	7 (12.7)	12 (22.2)	9 (17.0)
PSA, n (%)					
3, Moderate	44 (83.0)	45 (83.3)	46 (83.6)	45 (83.3)	45 (84.9)
4, Severe	9 (17.0)	9 (16.7)	9 (16.4)	9 (16.7)	8 (15.1)

BT, brimonidine tartrate; QD, once daily; BID, twice daily; CEA, Clinician's Erythema Assessment; PSA, Patient's Self-Assessment.