Brimonidine gel 0.33% rapidly improves patient-reported outcomes by controlling facial erythema of rosacea: a randomized, double-blind, vehicle-controlled study

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Abstract

Background  Facial redness contributes to impaired psychosocial functioning in rosacea patients and the only approved treatment for erythema is topical brimonidine gel 0.33%.

Objectives  To evaluate patient-reported outcomes, as well as efficacy and safety, in subjects with self-perceived severe erythema treated with brimonidine gel 0.33% compared to vehicle.

Methods  An 8-day multicenter, randomized study comparing once-daily brimonidine gel 0.33% with vehicle gel using a facial redness questionnaire, subject satisfaction questionnaire and a patient diary of facial redness control to assess patient-reported outcomes.

Results  Of the 92 included subjects with self-perceived severe erythema, very few were satisfied with their appearance at baseline (4.2% brimonidine group, 0 vehicle group). On Day 8, significantly more brimonidine group subjects were satisfied with their facial appearance compared to vehicle group (36.9% vs. 21.5%; P < 0.05), with the overall treatment effect (69.6% vs. 40.4%; P < 0.01), and with the improvement in their facial redness (67.4% vs. 33.3%; P < 0.001). More brimonidine group subjects were able to control their facial redness daily (e.g. 83.0% vs. 38.9% on Day 1). On Day 8, significantly more brimonidine group subjects than vehicle group had at least a one-grade improvement from baseline in the Clinician Erythema Assessment score (71.7% vs. 35.7%; P = 0.0011) and Patient Self-Assessment score (76.1% vs. 47.6%; P = 0.004). More subjects in the brimonidine group (29.2%) reported treatment-related adverse events than in the vehicle group (15.9%) but most were mild and transient.

Conclusions  Once-daily brimonidine gel 0.33% allowed patients to rapidly control their facial redness and significantly improved patient-reported outcomes in the treatment of persistent facial erythema of rosacea.

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Conflicts of interest

All clinical trial investigators or their institutes received payment for conducting the studies. AML, BH, MS and DBS have served as consultants to Galderma. BH, APB, PL and MS have served as members on the Rosacea advisory board of Galderma, and MAH and MS have received honoraria as speakers for Galderma. NK and YMM are employees of Galderma R & D.

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Introduction
Rosacea is a common chronic inflammatory skin disease estimated to affect approximately 10% of the population in Europe. Although generally reported to be more common in adults of Northern European heritage with fair skin, it widely affects males and females of all ethnicities and skin types. Rosacea has a variety of potential clinical manifestations that vary in presentation and magnitude among different patients but the central diagnostic feature is diffuse central-facial erythema, which persists to varying degrees and increases in intensity during a flare. Other cutaneous signs such as telangectasia, papules and pustules may also be present.

As dermatological conditions are visible, their psychological impact can be debilitating. Rosacea has considerable psychosocial impact and causes embarrassment, anxiety and low self-esteem. The facial redness is one of the main factors contributing to impaired quality of life (QoL) in rosacea patients. Consequentially, adequate treatment for the persistent redness of erythema can improve QoL.

Erythema of rosacea is an extremely complex condition involving both vascular and inflammatory events. Several treatments exist to treat the inflammatory component of rosacea but there are few effective treatments directly targeting the erythema. The only approved topical treatment for facial erythema of rosacea is brimonidine gel 0.33% (Mirvaso; Galderma SA, Lausane, Switzerland) (1 g of gel contains 3.3 mg of brimonidine, equivalent to 5 mg of brimonidine tartrate), which received FDA approval in August 2013 and centralized EMA approval in December 2013.

Brimonidine is a highly selective α2-adrenergic receptor agonist with potent vasoconstrictive activity and this specific formulation of brimonidine gel 0.33% has been demonstrated to have better efficacy than other adrenergic agonists. Well-documented efficacy and safety has been demonstrated in previous Phase II, Phase III pivotal and long-term safety studies conducted in the United States and Canada. These previous studies demonstrated that brimonidine gel 0.33% improves moderate to severe erythema after the first application with a rapid onset of action within around 30 min and a reduction in erythema for up to 12 h.

Due to the rapid onset and consistent efficacy over time of once-daily brimonidine gel 0.33%, relevant disease-specific patient-reported outcome (PRO) measures can be used to demonstrate the effect of treatment on PRO over a short study duration. This was one of the primary objectives of this Phase IIIb study, as well as evaluating efficacy and safety of brimonidine gel 0.33% compared to the vehicle gel alone.

Methods
This was an 8-day multicenter, randomized, double-blind, vehicle-controlled and parallel-group study at 14 centers in Germany, the United Kingdom and Sweden. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization-Good Clinical Practice principles and in compliance with local regulatory requirements. The study was reviewed and approved by the appropriate Independent Ethics Committees and written informed consent was obtained from all subjects prior to study initiation.

This study was exploratory in nature and therefore involved no statistical rationale for sample size calculation. Subjects were randomized 1:1 to receive either once-daily brimonidine gel 0.33% or vehicle gel for 8 days. A randomization list was generated prior to study initiation using the Ranuni routine of the Statistical Analysis System and the kit number was transmitted to the assigned clinical packaging organization for labelling. The double-blind design was achieved by using indistinguishable primary packaging (tubes) and secondary packaging for brimonidine gel 0.33% and its vehicle, and they were dispensed by a third party so the evaluators (Investigator or designee) did not come into contact with the study medication.

The Intent-to-Treat (ITT) population consisted of the entire population enrolled and randomized and the safety population consisted of all subjects who received the study medication.

Eligible male or female subjects were aged 18 years or older, with severe erythema of rosacea based on a Patient Self-Assessment (PSA) score of 4 (severe) and a Clinician Erythema Assessment (CEA) score of 3 (moderate) or 4 (severe) (described in Fowler et al). Exclusion criteria included more than five facial inflammatory lesions (papules or pustules) of rosacea, particular forms of rosacea (rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin), concomitant facial dermatoses (e.g. perioral dermatitis), demodecticosis, facial keratosis pilaris, seborrhoeic dermatitis, acute lupus erythematosus or actinic telangiectasia. Prior treatment with brimonidine gel 0.33%, any other treatment for erythema of rosacea within 4 weeks prior to inclusion, or any current treatment of a formulation containing brimonidine tartrate were not authorized. Concomitant treatment for inflammatory lesions of rosacea was allowed provided the subject had received a stable dose for at least 3 months.

Subjects were instructed to apply approximately 1 g of gel evenly over the entire face (even if not all facial areas presented erythema) while taking care to avoid application to eyes, eyelids, scalp, neck, ears, mouth, lips or any membrane of the inner nose.

The main study objective was to evaluate PROs measuring psychosocial functioning using a disease-specific facial redness questionnaire (FRQ) on Day 1 (baseline) and 2–4 h after application on Day 2 and Day 8, a subject satisfaction questionnaire (SSQ) on Day 8, and a patient daily diary recording control of facial redness. Efficacy was evaluated on Day 1 (baseline, Hour 3), Day 2 and Day 8 by blinded investigator (CEA) and subject (PSA) assessments, and photographs were taken at baseline and Hour 3 on Day 1 using the equipment of the investigational
sites. Adverse events (AEs) were recorded at each visit and monitored throughout the study.

Baseline demographic and disease characteristics, as well as all AEs, were descriptively summarized. All PROs and efficacy variables were analyzed in the ITT population at each evaluation time point, using the Cochran–Mantel–Haenszel test, stratified by center after riddit transformation with the row mean difference statistics, testing the hypothesis of equality; each test was two-sided at the 0.050 significance level.

**Results**

Between July 2013 and November 2013, 92 subjects were included (48 brimonidine group, 44 vehicle group) and 88 (95.7%) subjects completed the study. Two subjects in each group prematurely discontinued the study due to patient request (1 subject in each group), adverse event (1 brimonidine group subject) and protocol violation (1 vehicle group subject).

The two groups were comparable for demographic characteristics. The median age was 54.5 years (range 19–79), most subjects were white women (60.9%), and the majority had a skin phototype (Fitzpatrick) of II or III (90.2%) (Table 1). The rosacea duration was comparable between the two groups and the majority of subjects (59.3%) had had rosacea for more than 5 years (66.7% in the brimonidine group and 51.2% in the vehicle group). At baseline, all subjects subjectively graded their erythema as severe based on the PSA and all had moderate (48.9%) or severe (51.1%) erythema based on the CEA with slightly more CEA severe subjects in the brimonidine 0.33% group than in the vehicle group (58.3% vs. 43.2%) (Table 1). The majority of subjects had no inflammatory lesions.

According to the FRQ at baseline, very few subjects were satisfied with their appearance in both treatment groups with only 4.2% subjects in the brimonidine 0.33% group and none in the vehicle group. However, after 8 days treatment, subjects in the brimonidine 0.33% group were significantly more satisfied with their facial appearance compared to the vehicle group (36.9% satisfied or very satisfied vs. 21.5%; *P* = 0.008) (Fig. 1a). At baseline, the percentages of subjects in each embarrassment category were relatively similar in both treatment groups with only 22.9% subjects in the brimonidine 0.33% group and 15.9% subjects in the vehicle group slightly or not at all embarrassed by their facial redness. At Day 8, this percentage was significantly higher in the brimonidine 0.33% group than in the vehicle group (45.7% vs. 19.0%; *P* = 0.008) (Fig. 1b).

According to SSQ results after 8 days of treatment, significantly more subjects in the brimonidine 0.33% group responded that they thought their facial appearance had become better since starting the treatment (63.0% brimonidine group vs. 26.8% vehicle group; *P* = 0.022). Similarly, after 8 days of treatment, more subjects in the brimonidine 0.33% group than the vehicle group were satisfied with the overall treatment effect (69.6% vs. 40.4%; *P* = 0.007), the improvement of their facial redness (67.4% vs. 33.3%; *P* = 0.0009) and the time it took for

| Table 1 Baseline demographic and clinical characteristics (intent-to-treat) |
|---------------------------------------------------------------|
| Brimonidine 0.33% (N = 48) | Vehicle (N = 44) | Total (N = 92) |
|-----------------------------|-----------------|---------------|
| **Gender, n (%)**          |                 |               |
| Female                      | 30 (62.5)       | 26 (59.1)     | 56 (60.9) |
| Male                        | 18 (37.5)       | 18 (40.9)     | 36 (39.1) |
| **Age, years**              |                 |               |
| Median (Min, Max)           | 54.5 (25, 74)   | 54.5 (19, 79) | 54.5 (19, 79) |
| **Race, n (%)**             |                 |               |
| White                       | 48 (100.0)      | 44 (100.0)    | 92 (100.0) |
| **Phototype, n (%)**        |                 |               |
| I                           | 3 (6.3)         | 6 (13.6)      | 9 (9.8)   |
| II                          | 34 (70.8)       | 27 (61.4)     | 61 (66.3) |
| III                         | 11 (22.9)       | 11 (25.0)     | 22 (23.9) |
| **Rosacea duration**        |                 |               |
| <1 year                     | 4 (8.3%)        | 2 (4.7%)      | 6 (6.6%)  |
| 1 to 5 years                | 12 (25.0%)      | 19 (44.2%)    | 31 (34.1%)|
| >5 years                    | 32 (66.7%)      | 22 (51.2%)    | 54 (59.3%)|
| **Missing data**            | –               | 1             | 1         |
| **PSA, n (%)**              |                 |               |
| 4 – Severe                  | 48 (100.0)      | 44 (100.0)    | 92 (100.0) |
| **CEA, n (%)**              |                 |               |
| 3 – Moderate                | 20 (41.7)       | 25 (56.8)     | 45 (48.9) |
| 4 – Severe                  | 28 (58.3)       | 19 (43.2)     | 47 (51.1) |
| **Median (Min, Max)**       | 4 (3–4)         | 3 (3–4)       | 4 (3–4)   |
| **Inflammatory lesion count, Mean ± SD** | 0.9 ± 1.7 | 0.8 ± 1.3 | 0.8 ± 1.5 |

Figure 1 Facial Redness questionnaire (FRQ) responses to the questions (a) ‘How satisfied are you with the appearance of your facial skin right now?’ and (b) ‘How embarrassed are you about your facial redness right now?’ (all *P* = <0.05).

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the treatment to work (69.5% vs. 33.3%; \(P = 0.0006\)) (Fig. 2). Also, when asked whether they would consider using this treatment again, significantly more subjects in the brimonidine 0.33% group responded yes than in the vehicle group (78.3% vs. 46.3%; \(P = 0.0012\)).

From Day 1 and throughout the study period, more subjects in the brimonidine 0.33% group (around 80% daily) compared to the vehicle group (around 40% daily) were able to control their facial redness, as shown by the patient diary results (Fig. 3).

At all evaluation time points, significantly more brimonidine 0.33% group subjects than vehicle group subjects had at least a 1-grade improvement from baseline on CEA, e.g. on Day 8 (71.7% vs. 35.7%, respectively; \(P = 0.0011\)) (Fig. 4a). Similarly, significantly more brimonidine group subjects than vehicle group subjects had at least a 1-grade improvement from baseline on PSA at all evaluation time points, e.g. on Day 8 (76.1% vs. 47.6%, respectively; \(P = 0.004\)) (Fig. 4b).

Representative photographs of a subject with a 2-grade PSA improvement (severe to mild) and 1-grade CEA improvement (moderate to mild) from baseline to 3 h after study treatment application on Day 1, and a subject with a 2-grade PSA improvement (severe to mild) and 3-grade CEA improvement (severe to almost clear) are shown in Fig. 5.
During the study period, the inflammatory lesion count remained stable with 76.1% and 78.6% of subjects from the brimonidine 0.33% group and vehicle group, respectively, reporting no change in inflammatory lesion counts.

Overall, 21 (22.8%) subjects reported 39 AEs related to study treatments, 38 of which were dermatological in nature. A higher percentage of subjects in the brimonidine 0.33% group reported treatment-related AEs [14 subjects (29.2%) reported 26 AEs] than the vehicle group [7 subjects (15.9%) reported 13 AEs], but the majority were transient, mild in intensity and resolved without additional treatment.

Overall, four subjects (4.3%) experienced a total of six moderate related AEs, including three subjects (6.3%) in the brimonidine 0.33% group (headache, worsened rosacea, swelling face) and one subject (2.3%) in the vehicle group (headache, skin tightness, worsened erythema).

One subject in the brimonidine 0.33% group (2.1%) experienced two related AEs (moderate swelling face and severe worsened erythema) that led to treatment discontinuation; a negative re-challenge result was subsequently reported. There were no other severe related AEs or SAEs in this study.

Discussion
In this study to evaluate PROs following the treatment of erythema of rosacea with brimonidine gel 0.33% compared to vehicle gel, all patients had self-perceived severe erythema (PSA grade 4). However, when assessed by clinicians, around half (51.1%) had severe erythema (CEA grade 4) and around half (48.9%) had moderate erythema (CEA grade 3). The difference in the proportion of subjects with a PSA score of 4 compared to a CEA score of 4 indicates that the subjects in this study over-estimated the severity of their erythema. Disease perception may be affected by depression and healthcare-seeking behaviour is associated with higher subjective disease perception.16,17

Not surprisingly, almost all subjects in this study population were dissatisfied with their appearance at baseline. However, after 8 days of treatment, 36.9% of subjects in the brimonidine 0.33% group were satisfied or very satisfied with their facial appearance, and 28.3% were not at all embarrassed or self-conscious about their facial redness.

The emotional impact of rosacea has been shown to have an important role in patient’s quality of life.7 The subject satisfaction questionnaire showed that significantly more subjects in the brimonidine 0.33% group than in the vehicle group were satisfied with the overall treatment, the improvement in their facial redness, and the time to treatment effect (at least P < 0.05).

According to the patient daily diary data, subjects saw an almost immediate improvement with 83% of subjects in the brimonidine 0.33% group able to control their redness compared to 39% in the vehicle group from Day 1. The pivotal Phase III studies demonstrated a statistically and clinically significant improvement in erythema from 30 min after application of brimonidine gel 0.33%.14 This fast onset of action explains why an improvement in facial redness, and subsequent decrease in embarrassment due to facial redness, was observed so quickly after the start of the study using this once-daily regimen. The decrease from baseline to Day 8 of the percentage of subjects who were somewhat, moderately or extremely embarrassed about their facial redness was significantly greater in the brimonidine 0.33% group (77.1–54.3%) than in the vehicle group (84.1–81.0%).

The significant decrease in embarrassment and greater improvement in satisfaction with appearance in the brimonidine 0.33% group reflects the good efficacy of brimonidine gel 0.33% in treating facial erythema of rosacea. After 8 days of treatment, significantly more subjects in the brimonidine 0.33% group than in the vehicle group had at least a one-grade improvement in their erythema, as measured by either CEA (71.7% vs. 35.7%; P < 0.005) or PSA (76.1% vs. 47.6%; P < 0.005). Patient satisfaction with the overall appearance of their skin has been shown to be highly correlated with a reduction in their facial erythema.18 Of the subjects who did not have at least a one-grade improvement on both PSA and CEA, very few (10%) were satisfied with their appearance.18

The results confirm the good tolerability of brimonidine gel 0.33%, as observed in the previous long-term safety study.15 Patients with severe rosacea often have sensitive and intolerant skin; nevertheless, most treatment-related AEs were dermatological in nature, mild, transient and resolved spontaneously. There was one recorded case of a patient in the brimonidine 0.33% group with treatment-related AEs of severe erythema and moderate swelling during the treatment period that led to treatment discontinuation; a subsequent re-challenge with brimonidine gel 0.33% gave no symptoms. Treatment-related erythematous events have been reported in brimonidine Phase III clinical trials in 3.6% of brimonidine subjects (n = 277) and all were mild or moderate and led to discontinuation in only one subject (0.4%).19 In a recent publication, the term ‘paradoxical erythema’ was proposed for this early onset reaction (with or without additional symptoms such as burning) and the authors suggested that it can be minimized by preparing the barrier of the skin, using a mild moisturizer for rosacea-prone skin, before starting therapy. Also, they highlighted the need to educate patients to avoid exposure to triggers during treatment and to teach them how to optimize treatment application.19

A possible limitation of this study is the short study duration but previous safety studies and pharmacovigilance data have shown that most adverse events occur within the first 2 weeks of starting treatment.15,19 It is noteworthy that the results may have been influenced by any intra- and inter-day fluctuations in the intensity of erythema in the absence of treatment and/or exposure to environmental and lifestyle triggers. Any perceived worsening erythema after treatment may in fact have been related to normal variation in the presentation of the disease and/or expo-
sure to triggers, which may have had an impact on the PRO for certain subjects. Furthermore, it could be expected that patients who have suffered from erythema for a long time (almost two-thirds of subjects had suffered from rosacea for over 5 years) may need some time to adapt to being able to control their redness, as well as to learn how to apply the medication in a very thin uniform layer. Nevertheless, a significant proportion of subjects in the brimonidine 0.33% group were able to control their facial redness from Day 1, and they became more satisfied with their appearance and less embarrassed by their facial redness within 8 days. In the Phase III long-term safety study, brimonidine gel 0.33% treatment was shown to have a positive impact on social life from the first evaluation at Month 3 and this was maintained during the full 12-month study period. It thus seems reasonable to expect that the improvement reported here could be similarly long-lasting.

In conclusion, once-daily application of brimonidine gel 0.33% in the treatment of persistent facial erythema of rosacea seems reasonable to expect that the improvement reported here

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