CONCURRENT ADMINISTRATION OF IVERMECTIN 1% CREAM WITH BRIMONIDINE 0.33% GEL IMPROVES EFFICACY AND TOLERABILITY IN THE TREATMENT OF MODERATE TO SEVERE ROSACEA

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INTRODUCTION

- Rosacea is often characterized by persistent centrofacial erythema and recurrent inflammatory lesions.
- Individually, ivermectin 1% (IVM) cream and brimonidine 0.33% (BR) gel have been shown to be effective against papules/pustules and persistent facial erythema, respectively, in multiple studies.[1,2]
- The maximal effect of BR on erythema is observable around 3 hours after application.
- The objective was to evaluate the efficacy, safety, and patient satisfaction of IVM in combination with BR (IVM+BR) versus their respective vehicles in subjects with moderate to severe rosacea.

METHODS

Study Design

- This multicenter, randomized, double-blind, vehicle-controlled, and parallel group comparison study included subjects with moderate to severe rosacea (Investigator Global Assessment [IGA] ≥3, scale 0-4), characterized by persistent diffuse moderate to severe erythema (Clinician Erythema Assessment [CEA] ≥3, scale 0-4) and inflammatory lesions (15-70 papules/pustules).

Treatments

- Subjects were randomized 1:1:2 into 2 active and 1 double-blind vehicle group.
- IVM + BR active treatment groups:
  - Once-daily IVM and once-daily BR for 12 weeks (IVM+BR/12W subgroup; n=49)
  - Once-daily IVM for 12 weeks and once-daily BR vehicle for 4 weeks followed by once-daily BR for the remaining 8 weeks (IVM+BR/8W subgroup; n=46)
- Vehicle group:
  - Once-daily IVM vehicle and once-daily BR vehicle for 12 weeks (vehicle group, n=95).
- A daily skin care regimen of gentle cleanser, moisturizing lotion, and facial moisturizer with SPF 15 sunscreen was recommended and provided according to established guidelines.[3,4]

Efficacy and Safety Endpoints

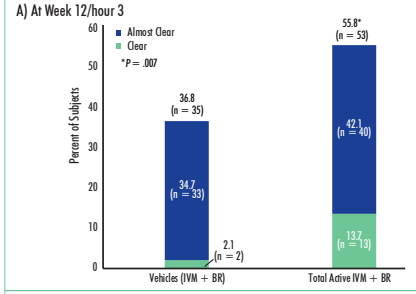
- Primary endpoint of IGA success (0/1, clear/almost clear) on a 5-point scale at week 12, 3 hours after BR application.
- Secondary efficacy endpoints included IGA at each visit, CEA, 100% reduction in inflammatory lesion count, and subject global improvement of rosacea.
- AEs were monitored throughout the study.
- There was no adjustment of the Type I error.

Table 1. Subject Disposition

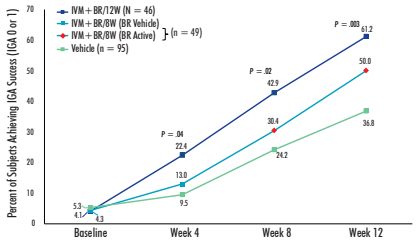
	Active Group		Vehicle Group
	IVM+BR/8W	IVM+BR/12W	
Subjects, n (%)	46 (100)	49 (100)	95 (100)
Completed, n (%)	41 (89.1)	44 (89.8)	86 (90.5)
Discontinued, n (%)	5 (10.9)	5 (10.2)	9 (9.5)
Adverse event, possibly related	1 (2.2)	0	1 (1.1)
Subject's request	4 (8.7)	1 (2.0)	3 (3.2)
Lost to follow-up	0	3 (6.1)	3 (3.2)
Other	0	1 (2.0)	2 (2.1)

Figure 1. Investigator Global Assessment Success (ITT-LOCF)

A) At Week 12/hour 3



B) Percent of Subjects Achieving Success with IVM+BR/12W, IVM+BR/8W, or Vehicle



C) At Week 12/hour 0 Versus Week 12/hour 3 (before versus after application of BR)

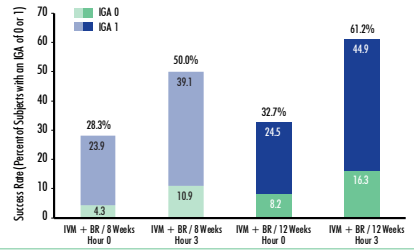


Figure 2. Clinician Erythema Assessment at Week 12/hour 3 (ITT-LOCF)

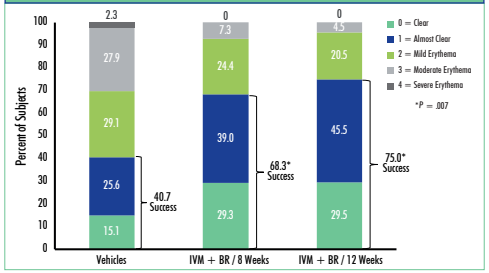
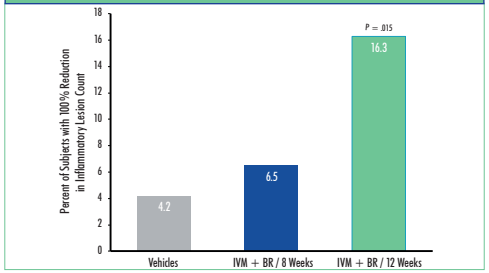


Figure 3. Percentage of Subjects with 100% Reduction in Inflammatory Lesion Count (ILC) at Hour 3 Week 12 (ITT-LOCF)



SUMMARY

- Simultaneous administration of IVM 1% cream with BR 0.33% gel demonstrated superior efficacy compared to their respective vehicles for the treatment of moderate to severe rosacea.
- Early introduction of BR (from day 1), along with a complete daily skin care regimen, may exert additional efficacy benefit and accelerate treatment success without impairing tolerability.
- The IVM + BR association was well tolerated, with less than 5% related AEs.
- This regimen is a promising option for the comprehensive management of this complex disease.

RESULTS

Subject Disposition

- 190 subjects (95 subjects per group) were enrolled at 26 sites in the United States and Canada and 171 (90%) completed the study (Table 1).
- Subjects were predominantly Caucasian (91.1%) and female (72.1%), with a mean age of 49.5 y and a history of chronic rosacea >5 y (70%).

Efficacy

- At week 12 hour 3, the total combined active group receiving the combination of IVM + BR showed superior efficacy (IGA success 0/1) compared to vehicle (55.8% vs. 36.8%, $P = .007$; Figure 1A).
- An advantage for patients receiving BR from day 1 was observed, with the IVM+BR/12W subgroup showing superior efficacy (61.2% vs. 36.8%, $P = .003$) at the end of the study and early onset compared to vehicle (Figure 1B).
- IGA change was statistically significant to vehicle in the IVM+BR/12W group from week 4 onwards (22.4% at week 4; Figure 1B).
- At week 12, comparison of the effect of BR before and 3h after application showed that, in the IVM+BR/12W subgroup, the success rate almost doubled (from 32.7% to 61.2% at hour 0 and hour 3, respectively; Figure 1C).
- Improvements in the IVM+BR/12W and IVM+BR/8W subgroups compared to the vehicle group were also observed for CEA ($P < 0.015$; Figure 2)
- After 12 weeks of treatment, 16.3% of subjects in the IVM+BR/12W group had 100% reduction in inflammatory lesion count ($P = .015$ compared to vehicle; Figure 3).
- A trend towards higher efficacy was observed in the IVM+BR/12W compared to the IVM+BR/8W subgroup for both outcomes, corroborating the additive effect of BR when taken concomitantly with IVM treatment.

Subject Reported Outcomes

- The subject global improvement of rosacea rate of excellent and good improvement was 77.7%, 66.7%, and 55.2% in the IVM+BR/12W, IVM+BR/8W, and vehicle groups, respectively.

Safety

- Only 8 treatment-related AEs in 6 subjects (3.2%) were reported; none were serious or severe.
- One related AE leading to discontinuation (allergic dermatitis on the chest) was reported in the IVM+BR/8W group.
- Related worsening of rosacea was observed in similar frequency with 1 (2.2%) AE in the active IVM+BR/8W group vs. 3 (2.1%) AEs in the vehicle group.

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