CONSISTENT EFFICACY AND SAFETY IN FOUR DOUBLE-BLIND, VEHICLE-CONTROLLED STUDIES OF IVERMECTIN 1% CREAM IN THE TREATMENT OF MODERATE TO SEVERE PAPULOPUSTULAR ROSACEA

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INTRODUCTION

- Rosacea is a chronic inflammatory disease.
- Rosacea has traditionally been classified as erythematotelangiectatic (ETR), papulopustular (PPR), phymatous, or ocular rosacea.
- PPR is characterized by facial papules, pustules, and persistent erythema.
- The pathogenesis of PPR is not yet completely understood; however, current studies indicate that underlying causes may include dysregulation of the innate immune system, overgrowth of commensal skin organisms, aberrant neurovascular signaling, and the production of inflammatory mediators in facial skin.[1]
- Ivermectin 1% cream (IVM) is an effective and safe topical therapy approved to treat the inflammatory lesions of rosacea.[2]
  - During the development of IVM, 2 Phase 2 and 2 Phase 3 vehicle-controlled studies were conducted in more than 1600 subjects.

METHODS

Study Design

- Objectives
  - This analysis reviews the consistency of efficacy and safety results of 4 (two phase 2 and 2 phase 3) 12-week, vehicle-controlled studies (N = 1683) conducted during the development of IVM.
- Methods
  - Phase 2, Study 1
    - 6-arm, 12 week, dose ranging, multicenter, randomized, investigator-blind, vehicle- and active-controlled study
      - Ivermectin 0.1%, QD; Ivermectin 0.3%, QD; Ivermectin 1%, QD; Ivermectin 1%, BID ; Metronidazole 0.75%, BID; and Vehicle, QD
    - Subjects were male or female, ≥ 18 years of age, with PPR (≥ 15 lesions)
    - For the sake of consistency of this analysis, only data from the Ivermectin 1% and the vehicle QD arms are reported here.
  - Phase 2, Study 2
    - 12 week, multicenter, prospective, randomized, double-blind, vehicle-controlled study
      - Ivermectin 1%, QD; Vehicle, QD
    - Subjects were male or female, ≥ 18 years of age, with PPR (≥ 15 lesions)
  - Phase 3, Study 1 and 2
    - Two 12 week, multicenter, randomized, double-blind, parallel-group, vehicle-controlled studies of identical design
      - Ivermectin 1%, QD; Vehicle, QD
    - Subjects were male or female, ≥ 18 years of age, with PPR (≥ 15 lesions)
  - Endpoints
    - IGA success (IGA 0 or 1; IGA scale 0 [Clear] to 4 [Severe])
    - Lesion counts (absolute change and mean percent reduction from baseline)
    - Tolerability
    - Adverse events

REFERENCES

1. Holmes, A. D., Steinhoff, M. (2016). Integrative concepts of rosacea pathophysiology, clinical presentation and new therapeutics. *Exp Dermatol*. doi:10.1111/exd.13143
2. Stein L, Kircik L, Fowler J, et al. Efficacy and safety of ivermectin 1% cream in treatment of papulopustular rosacea: results of two randomized, double-blind, vehicle-controlled pivotal studies. *J Drugs Dermatol*. 2014 Mar;13(3):316-23.

Table 1. Subject Disposition

Reason for Discontinuation, n (%)	Phase 2				Phase 3			
	Study 1 (n = 102)		Study 2 (n = 210)		Study 1 (n = 683)		Study 2 (n = 688)	
	Ivermectin 1% Enrolled, n = 52 Discontinued, n = 3 Discontinued (%), 5.8	Vehicle Enrolled, n = 50 Discontinued, n = 7 Discontinued (%), 14.0	Ivermectin 1% Enrolled, n = 104 Discontinued, n = 5 Discontinued (%), 4.8	Vehicle Enrolled, n = 106 Discontinued, n = 10 Discontinued (%), 9.4	Ivermectin 1% Enrolled, n = 451 Discontinued, n = 37 Discontinued (%), 8.2	Vehicle Enrolled, n = 232 Discontinued, n = 22 Discontinued (%), 9.5	Ivermectin 1% Enrolled, n = 459 Discontinued, n = 30 Discontinued (%), 6.5	Vehicle Enrolled, n = 229 Discontinued, n = 21 Discontinued (%), 9.2
Adverse Event	1 (1.9%)	0	2 (1.9%)	2 (1.9%)	7 (1.6%)	4 (1.7%)	6 (1.3%)	4 (1.7%)
Pregnancy	0	0	0	0	2 (0.4%)	0	1 (0.2%)	0
Lack of Efficacy	1 (1.9%)	1 (2.0%)	0	0	0	1 (0.4%)	1 (0.2%)	0
Withdrawal	1 (1.9%)	5 (10.0%)	1 (1.0%)	5 (4.7%)	18 (4.0%)	7 (3.0%)	9 (2.0%)	8 (3.5%)
Protocol Violation	0	1 (2.0%)	0	1 (0.9%)	2 (0.4%)	1 (0.4%)	4 (0.9%)	0
Lost to Follow-up	0	0	0	1 (0.9%)	7 (1.6%)	8 (3.4%)	8 (1.7%)	8 (3.5%)
Other	0	0	2 (1.9%)	1 (0.9%)	1 (0.2%)	1 (0.4%)	1 (0.2%)	1 (0.4%)

RESULTS

Efficacy

- 1683 subjects in 4 studies (two phase 2, two phase 3) are included in this analysis
- All 4 studies confirmed the statistical superiority of IVM vs vehicle
  - Success rate (IGA 0 or 1) was statistically superior for IVM vs vehicle in all 4 studies (Figure 1)
    - Phase 2 studies: a statistically superior rate of success was seen, compared to vehicle
      - 65.4%; Week 12, Phase 2, Study 1, n = 102, $P < .05$
      - 55.8%; Week 12, Phase 2, Study 2, n = 210, $P < .01$
    - Phase 3 studies: a statistically superior rate of success was seen, compared to vehicle
      - 38.4%; Week 12, Phase 3, Study 1, n = 683, $P < .001$
      - 40.1%; Week 12, Phase 3, Study 2, n = 688, $P < .001$
  - Lesion reduction was statistically superior for IVM vs vehicle in all 4 studies (Figure 2).

Safety

- The treatment was highly tolerable in all 4 studies, and there were few study discontinuations (Table 1)
  - Discontinuations Due to AEs in the IVM arm
    - Phase 2, Study 1: 1 (1.9%)
    - Phase 2, Study 2: 2 (1.9%)
    - Phase 3, Study 1: 7 (1.6%)
    - Phase 3, Study 2: 6 (1.3%)
- No serious adverse events related to IVM were observed in any of the 4 studies
- The incidences of treatment related AEs were low, and comparable in both treatment groups
  - Related AEs: Phase 2, Study 1; IVM: 6 (5 subjects, 4.8%); Vehicle: 5 (5 subjects, 4.7%)
  - Related AEs: Phase 2, Study 2; IVM: 5 (3 subjects, 5.8%); Vehicle: 6 (5 subjects, 10.0%)
  - Related AEs: Phase 3, Study 1; IVM: 24 (19 subjects, 4.2%); Vehicle: 25 (18 subjects, 7.8%)
  - Related AEs: Phase 3, Study 2; IVM: 17 (12 subjects, 2.6%); Vehicle: 20 (15 subjects 6.5%)

SUMMARY

- In these 4 studies, IVM demonstrated strong efficacy, tolerability, and safety
- The data supporting efficacy, tolerability, and safety was replicated with a high level of consistency
- The low incidence of AEs, good tolerability, and high efficacy make IVM an excellent treatment choice for PPR

Figure 3. Representative Photographs - Subject 18171-8129-008

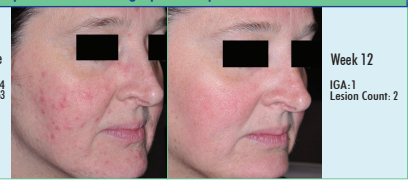


Figure 1. Significant IGA Success

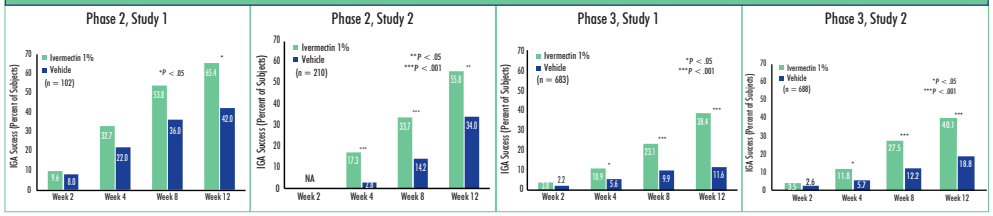
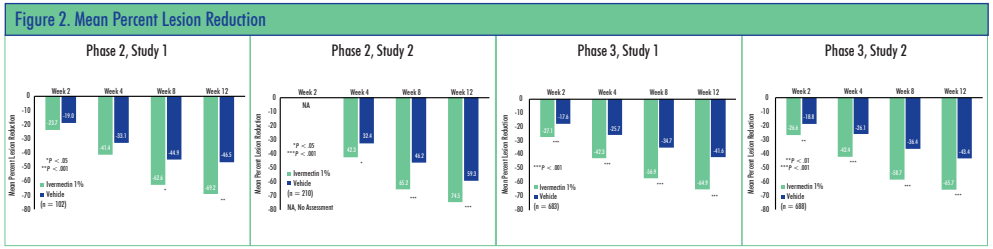


Figure 2. Mean Percent Lesion Reduction



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