EFFICACY AND SAFETY OF ADAPALENE 0.3% / BENZOYL PEROXIDE 2.5% GEL PLUS DOXYCYCLINE IN SUBJECTS WITH SEVERE INFLAMMATORY ACNE (NON-NODULOCYSTIC) THAT ARE CANDIDATES FOR ORAL ISOTRETINOIN

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INTRODUCTION

- Acne vulgaris (AV) is the 8th most prevalent disease worldwide
  - AV affects an estimated 85% of individuals between 12 and 24 years of age[1,2]
- Prompt and effective treatment is needed to prevent long term consequences, such as scarring
- Oral isotretinoin (OI) is considered an effective treatment for many severe AV patients; however,
  - OI has known and serious side effects
  - Treatment cannot always be initiated immediately
    - Isotretinoin is a potent teratogen, and exposure should be avoided by women who are or may become pregnant
- Current acne treatment guidelines for first-line treatment of severe acne suggest using OI or a topical therapy combined with oral antibiotics[3]
  - Adapalene 0.3%/benzoyl peroxide 2.5% (A/BPO 0.3%/2.5%) gel is approved for the treatment of AV
    - A/BPO 0.3%/2.5% gel attacks 3 of the 4 major pathogenic factors of AV
    - A/BPO 0.3%/2.5% gel has strong clinical efficacy and excellent safety and tolerability in subjects with moderate to severe AV[4]

Figure 1. Investigator Assessed OI Candidacy and IGA by Study Visit (ITT, LOCF, n = 186)

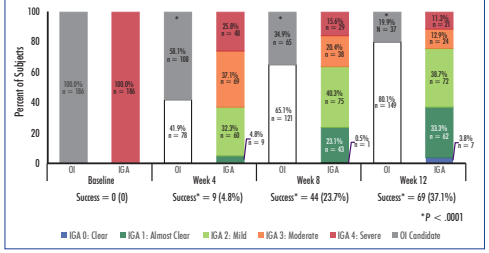
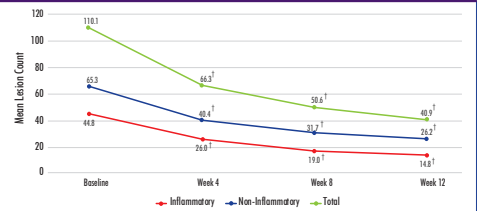


Figure 2. Lesion Counts (ITT, LOCF, n = 185*)



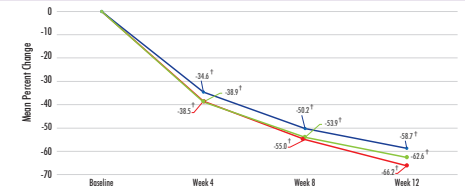
*Baseline lesion counts missing for 1 patient (ITT, n = 186); †P < .0001 vs baseline, at all post-baseline assessments

SUBJECTS and METHODS

- Open label, single arm, 12-week, multicenter study of A/BPO 0.3%/2.5% gel + DOX† 200 mg
- Twenty-three sites enrolled males and females, 12 years of age or older, with a clinical diagnosis of severe inflammatory acne (Investigator's Global Assessment [IGA] score = 4) who had never received OI, and, in the opinion of the investigator, were candidates for OI
  - Subjects had ≤ 4 nodules/cysts > 1 cm in diameter on the face
    - Subjects were excluded if they had nodulocystic or conglobate acne, acne fulminans, or secondary acne (eg, chloracne, drug-induced acne)
- Treatments:
  - Topical A/BPO 0.3%/2.5% gel, once daily for 12 weeks
  - DOX 200 mg (2x 50 mg tablets, Mayne, DORYX), twice daily (morning and evening) for 12 weeks
  - Cetaphil® Gentle Cleanser* (or equivalent), twice daily
  - Cetaphil® Daily Facial Moisturizer SPF 15* (or equivalent), at least once daily and re-apply as needed
- Endpoints and Assessments:
  - Reduction and percent reduction in lesions at Weeks 4, 8, and 12
  - IGA (IGA, 0 – 4 scale): Success (subjects rated IGA 0 or 1) at weeks 0, 4, 8, and 12
  - Number and percent of subjects who, in the opinion of the investigator, are candidates for oral isotretinoin at Weeks 0, 4, 8, and 12
    - Investigator evaluation of each subject's candidacy to OI was performed independently at each visit, without consideration of previous visits
  - Photographs were taken of all subjects enrolled in the study at all study visits
  - Incidence of adverse events (AEs) and local tolerability (0 [none] – 3 [severe] scale)

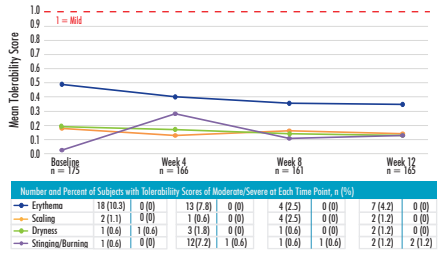
*Cetaphil® Gentle Cleanser and Cetaphil® Daily Facial Moisturizer SPF 15 are manufactured by Galderma Laboratories, L.P.
†DOX = doxycycline 200 mg (2x 50 mg tablets, Mayne, DORYX)

Figure 3. Percent Reduction in Lesion Count (ITT, LOCF, n = 185*)



*Baseline lesion counts missing for 1 patient (ITT, n = 186); †P < .0001 vs baseline, at all post-baseline assessments

Figure 4. Local Tolerability (Safety population)



Number and Percent of Subjects with Tolerability Scores of Moderate/Severe at Each Time Point, n (%)

	Baseline		Week 4		Week 8		Week 12	
Erythema	18 (10.3)	0 (0)	13 (7.8)	0 (0)	4 (2.5)	0 (0)	7 (4.2)	0 (0)
Scaling	2 (1.1)	0 (0)	1 (0.6)	0 (0)	4 (2.5)	0 (0)	2 (1.2)	0 (0)
Dryness	1 (0.6)	1 (0.6)	3 (1.8)	0 (0)	1 (0.6)	0 (0)	2 (1.2)	0 (0)
Stinging/Burning	1 (0.6)	0 (0)	12(7.2)	1 (0.6)	1 (0.6)	1 (0.6)	2 (1.2)	2 (1.2)

NOTE: Tolerability data was only collected at study visits (no tolerability data was collected for weeks 1 through 3).

Figure 5. Representative Subject Photographs

RESULTS

- The study enrolled 186 subjects
  - 175 subjects received at least one dose of the study treatment
  - Male (n = 78) and female (n = 97)
  - Mean age = 19.6 ± 7.3 (56% ≤ 17 years of age)
  - Most subjects were white (79%) and not Hispanic or Latino (81%)
  - Baseline lesion counts; Mean (SD)
    - Inflammatory = 44.8 (21.7); Non-inflammatory = 65.3 (39.4); Total = 110.1 (49.4)
- Subjects who were NOT considered candidates for OI by the investigator (Figure 1)
  - 41.9% after 4 weeks; 65.1% after 8 weeks; 80.1% (149/186) after 12 weeks
- 75.8% of subjects were rated IGA 2 (mild) or better by week 12 (Figure 1)
- IGA success rate (clear and almost clear; Figure 1)
  - 4.8% at week 4; 23.7% at week 8; 37.1% at week 12
- Mean number of lesions: Significantly reduced compared with baseline ($P < .0001$ vs baseline, all study visits; Figure 2)
  - At week 12 the total mean reduction in lesions was -26.2 lesions compared with baseline ($P < .0001$)
- Percent lesion reduction: Significant reduction compared with baseline ($P < .0001$ vs baseline, all study visits; Figure 3)
  - At week 12 the total mean percent reduction in lesions was -62.6% compared with baseline ($P < .0001$)
- Safety
  - A/BPO 0.3% was well tolerated and most AEs were mild (Figure 4)
  - The number of subjects experiencing any treatment emergent AE was 46 (26.3%)
  - The number of subjects with any treatment related AE was 27 (15.4%)
  - The most common treatment related AEs were skin burning sensation (n = 6, [3.4%]) and erythema (n = 5, [2.9%])

SUMMARY

- This study observed that 12 weeks of A/BPO 0.3%/2.5% gel plus DOX 200 mg was an effective, safe, and well tolerated therapy for subjects with severe AV (non-nodulocystic, non-conglobate)
  - Mean lesion count reduction and mean percent reduction in lesions were significant compared with baseline ($P < .0001$ vs baseline, all study visits)
  - 37.1% of subjects received an IGA of clear or almost clear (IGA success) at week 12
  - Most subjects (80.1%) were no longer assessed as candidates for OI by the investigators after 12-weeks of A/BPO 0.3%/2.5% gel plus DOX 200 mg treatment
- Twelve weeks of A/BPO 0.3%/2.5% gel plus DOX 200 mg is an effective and safe regimen
  - For subjects with severe AV (non-nodulocystic, non-conglobate) who are also candidates for OI
  - For subjects who must wait before starting oral isotretinoin
  - As an alternative option for those unwilling to use oral isotretinoin
  - For those unable to use oral isotretinoin due to contraindications

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