RE-FORMULATING THE OLD TRETINOIN: UNIQUE MICROENCAPSULATED TRETINOIN WITH MICROENCAPSULATED BENZOYL PEROXIDE COMBINATION PRODUCT FOR ACNE VULGARIS

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INTRODUCTION

- Topical tretinoin was approved by the United States Food and Drug Administration (FDA) in 1971 for the treatment of acne
- The American Academy of Dermatology (AAD) and Global Alliance to Improve Outcomes in Acne (Global Alliance) recommend the use of a topical retinoid alone or in combination with benzoyl peroxide (BPO) as first-line treatment of all severities of inflammatory and non-inflammatory acne[1,2]
- Historically, tretinoin use within acne has been limited by poor tolerability and molecular instability[3,4]
- Tretinoin 0.1% has a higher rate of irritant adverse events (AEs) than lower concentrations of tretinoin
- When used concurrently with benzoyl peroxide (BPO), the unencapsulated tretinoin molecule is unstable and is oxidized by the BPO
- New technology may allow tretinoin use in patient populations and clinical situations that were previously not feasible[5]

Tretinoin Use in Clinical Practice

- Acne and acne sequelae
  - Tretinoin is comedolytic and anti-inflammatory[6]
  - Tretinoin has shown significant clinical improvement in inflammatory acne and decreases comedones[7]
- Preadolescent patients
  - Three tretinoin products have FDA approval for preadolescents: tretinoin 0.05% gel (≥10 years of age), tretinoin 0.05% lotion (≥9 years of age), and a combination cream containing silica-microencapsulated 0.1% tretinoin with 3% BPO (≥9 years of age)[8-10]
  - Data from 4 pivotal studies evaluating tretinoin in preadolescent subjects show high efficacy, good tolerability, and no new safety signals[11-13]
  - American Academy of Dermatology and American Academy of Pediatrics evidence-based guidelines note that tretinoin and BPO can be safely used for acne management in preadolescent patients[2,14]
- Patients with skin of color
  - An 8-week study of 27 Black subjects with acne showed a significant decrease in papules, pustules, and hyperpigmentation in 83% of subjects treated with tretinoin 0.025% cream compared with a 13% reduction with vehicle. In this study, skin irritation and inflammation were comparable with active treatment and vehicle[15]
  - A post-hoc analysis of 308 Black, 69 Asian, and 766 Hispanic subjects treated with tretinoin 0.05% lotion found it was effective, safe, and well tolerated for the treatment of acne with a low incidence of reported adverse events[16-18]

Role of Tretinoin in Limiting Antibiotic Use

- If topical or oral antibiotics are necessary to treat acne, the AAD guidelines recommend antibiotic use for a maximum of 3-4 months and a concomitant retinoid[2]
- The AAD recommends a topical retinoid as first-line treatment of acne of all severities and after completion of antibiotic therapy as maintenance therapy[2]
- One study found that monotherapy with a topical retinoid had similar efficacy to a topical retinoid plus oral minocycline, after 12 weeks of maintenance therapy[19]
  - After 24 weeks of treatment, >80% of subjects in each group maintained a ≥50% global improvement in acne from baseline

OBJECTIVE

- Determine if a re-formulated combination of microencapsulated tretinoin 0.1% and microencapsulated BPO 3% (E-BPO/T) provides a stable and well tolerated product

Historical Limitations of Unencapsulated Tretinoin

- Unencapsulated tretinoin use has historically been limited by cutaneous tolerability issues (ie, dryness, peeling, scaling, erythema, pruritis, pain)[2,3]
- Tretinoin can increase sun sensitivity and it is therefore recommended to avoid sun exposure and/or wear sunscreen/sun-protective clothing while using tretinoin[20,21]
- Unencapsulated tretinoin is unstable and rapidly degraded in the presence of light[4]
- Unencapsulated tretinoin is easily oxidized by BPO, reducing effectiveness.[22] This is problematic since a topical retinoid plus BPO is recommended as first-line treatment of inflammatory and noninflammatory acne of all severities[2]
- Historically, concurrent use of tretinoin and BPO has not been possible; the products need to be applied at different times potentially reducing compliance[2,23]

Tretinoin Encapsulation Technology

- The Sol-Gel process allows microencapsulation of active drug molecules within a silica-based shell. This extends drug release time and may reduce skin irritation while enhancing efficacy[13,24] (Figure 1)
- The Sol-Gel process controls the release rate of the active ingredient to the skin
- Encapsulation technology allows, for the first time, a chemically stable fixed-dose combination of tretinoin and BPO for acne treatment

METHODS

- E-BPO/T cream combines microencapsulated tretinoin 0.1% and microencapsulated BPO 3%
- Tretinoin crystals and BPO crystals are separately encapsulated in silica core shell structures, enabling inclusion of both actives in one cream[10]
- Silica shells control the rate at which the active ingredients are released, allowing efficacy while helping to reduce AEs and optimizing tolerability[13]

RESULTS

- Two Phase 3, multicenter, double-blind, randomized studies of once daily application of E-BPO/T cream (n=571) or vehicle cream (n=287)
- E-BPO/T was found superior to vehicle on Investigator's Global Assessment (IGA) success rate, absolute mean change in inflammatory lesions (IL), and absolute mean change in non-inflammatory lesions (NIL) from baseline to Week 12 (Table 1)
  - IGA success became significant at Week 8; mean NIL reduction was significant at Week 2 in both studies
- Nearly all AEs were mild or moderate in severity (Table 2)
- Mean tolerability parameters (including erythema, dryness, scaling, pigmentation, itching, burning, and stinging) of both E-BPO/T and vehicle stayed below 1 (scale of 0-3) and were not statistically different. Erythema, scaling, and dryness all peaked below mild at Week 2, and then decreased in severity

Table 2. E-BPO/T Phase 3 Trials[10] Tolerability Assessment Results at Week 12

	Study 1			Study 2		
Percent	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	33.0	6.9	0.2	26.9	8.0	0
Pigmentation	27.3	6.3	0.4	26.5	4.5	0
Dryness	22.3	5.3	0.4	16.7	2.3	0
Scaling	16.4	2.6	0	12.9	0.8	0
Burning	5.9	2.2	0	3.4	0.8	0
Itching	11.1	1.8	0	8.7	2.7	0
Stinging	5.3	0.2	0	1.9	1.1	0

SUMMARY

- E-BPO/T is a combination of microencapsulated tretinoin 0.1% and microencapsulated BPO 3% that is FDA approved for once daily use in patients ≥9 years of age for the treatment of acne
- Unique microencapsulation technology enables combining BPO 3% and tretinoin 0.1% into one cream for concurrent use of both actives for acne treatment with a manageable tolerability profile

Figure 1. Process of Microencapsulation for BPO and Tretinoin[24]

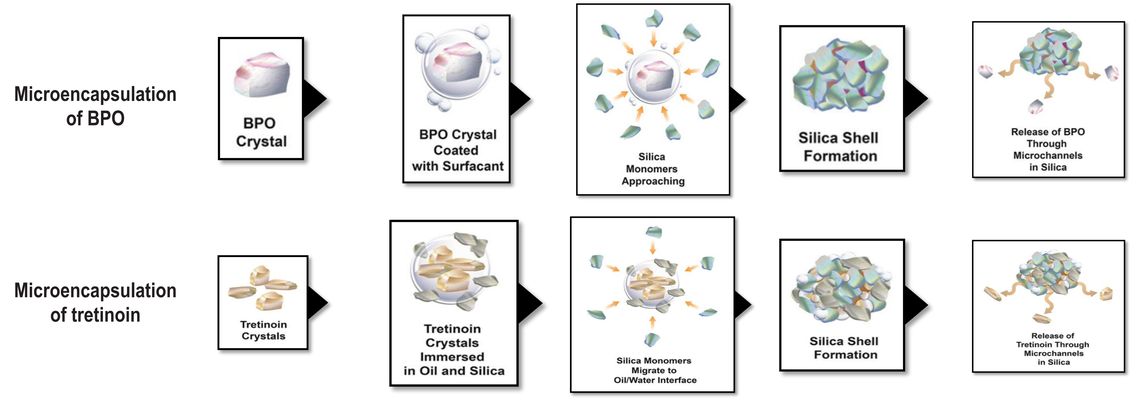

Table 1. Phase 3 Trials Efficacy Results[10]

	Study 1		Study 2	
	E-BPO/T Cream (N=281)	Vehicle (N=143)	E-BPO/T Cream (N=290)	Vehicle cream (N=144)
IGA success*	39.9%	14.3%	26.8%	15.1%
95% CI	17.1%, 34.2%		3.6%, 19.7%	
Mean absolute change in IL from baseline†	-21.6	-14.8	-16.2	-14.1
95% CI	-9.1, -4.6		-3.9, -0.4	
Mean absolute change in NIL from baseline†	-29.7	-19.8	-24.2	-17.4
95% CI	-13.0, -6.8		-9.9, -3.7	

CI = confidence interval; IGA = Investigator's Global Assessment; IL = inflammatory lesion; NIL = noninflammatory lesion. *IGA success was defined as an IGA score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade reduction from baseline. †Means presented are least square means.

Figure 2. Subject Treated with E-BPO/T in Clinical Study

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