DFD-03 (0.1% tazarotene), twice-daily, short-contact lotion formulation, showed similar pharmacokinetic exposure (AUC_{0-24}) to the marketed cream product Tazorac® (tazarotene) with once daily overnight application

Srinivas Sidgiddi, MD[1]; Usha Ranganathan, MD[1]; Anirudh Gautam, MPharm[2]
[1]Promius Pharma, a subsidiary of Dr. Reddy's Laboratories, Princeton, NJ, USA [2]Dr. Reddy's Laboratories SA., Basel, Switzerland

Introduction

- The American Academy of Dermatology states that retinoids are the core of topical therapy for acne.
- Common side effects include erythema, peeling, and dryness.
- Results of a phase 1 bioavailability study comparing DFD-03 (tazarotene 0.1%) lotion twice daily (1-minute application), DFD-03 lotion once daily (1-minute application), and Tazorac cream once daily (overnight application), are presented here.

Methods

- This was a single center, randomized, multiple dose, laboratory-blinded, open-label, 3-arm, parallel design study with 16 healthy subjects in each arm.
- In each treatment group, approximately 5 g of test product was applied to the face, neck, shoulders, upper chest and upper back (approximately 15% body surface area) on days 1 through 14.
- In treatment group 1, DFD-03 lotion was applied twice daily, 12 hours apart, and rinsed off after 1-minute contact.
- In treatment group 2, DFD-03 lotion was applied once daily and rinsed off after 1-minute contact.
- In treatment group 3, Tazorac cream was applied once daily and rinsed off after 12-hours contact.
- Blood samples were collected on days 1, 7 and 14, prior to product application and for up to 24 hours after product application.

Results

- Tazarotenic acid plasma concentrations were more than two times higher after twice daily 1-minute contact than after once daily 1-minute contact (Table 1).
- Tazarotenic acid exposure (AUC_{0-24}) after multiple twice daily, 1-minute applications of DFD-03, was 83.21% of exposure following multiple once daily, 12-hour applications of Tazorac cream (Table 1).
- The C_{max} after multiple twice daily applications of DFD-03 was 62.99% of the C_{max} of multiple once daily applications of Tazorac cream (Table 1).
- Erythema was the most common AE in this study, reported by nine subjects (64%) following twice daily 1-minute application of DFD-03, five subjects (33%) following once daily, 12-hour application of Tazorac cream, and no subjects following once daily 1-minute application of DFD-03 (Table 2).

Table 1. Summary of the Statistical Analysis of Tazarotenic Acid – Day 14

Parameter	CV (%)	Geometric LS Means			Comparison	Ratio (%)	90% Confidence Limits (%)	
		Treatment Group 1	Treatment Group 2	Treatment Group 3			Lower	Upper
C_{max}	54.7	164.20	77.72	260.66	1 vs 2	211.26	151.58	294.45
	54.7	164.20	77.72	260.66	1 vs 3	62.99	45.48	87.26
	54.7	164.20	77.72	260.66	2 vs 3	29.82	21.39	41.56
AUC_{0-24}	53.6	3797.48	1492.58	4563.57	1 vs 2	254.42	199.60	324.31
	18.9	3797.48	1492.58	4563.57	1 vs 3	83.21	57.63	120.15
	71.4	3797.48	1492.58	4563.57	2 vs 3	32.71	24.18	44.24

Table 2. Summary of Adverse Events by System Organ Class

System Organ Class MedDRA Preferred Term	Treatment Group 1 (N=14); n (%)	Treatment Group 2 (N=14); n (%)	Treatment Group 3 (N=14); n (%)
Subjects with at least 1 AE	10 (71)	4 (29)	6 (40)
Skin And Subcutaneous Tissue Disorders	10 (71)	3 (21)	5 (33)
Erythema	9 (64)	0	5 (33)
Dry Skin	0	3 (21)	0
Skin Burning Sensation	2 (14)	1 (7)	0
Pruritus	1 (7)	1 (7)	0
Rash	1 (7)	0	0
Skin Discomfort	1 (7)	0	0
Skin Irritation	0	0	1 (7)
Nervous System Disorders	2 (14)	1 (7)	2 (13)
Burning Sensation	1 (7)	0	1 (7)
Dizziness	1 (7)	1 (7)	0
Hyperaesthesia	1 (7)	0	1 (7)
Musculoskeletal And Connective Tissue Disorders	0	0	1 (7)
Arthralgia	0	0	1 (7)
Respiratory, Thoracic, And Mediastinal Disorders	1 (7)	0	0
Nasal Discomfort	1 (7)	0	0

Conclusions

- The parameters AUC_{0-24} and C_{max} of DFD-03 lotion were significantly impacted by frequency of dosing. Systemic exposure to tazarotenic acid appeared to be dependent on the duration of dosing for all treatments.
- DFD-03, lotion formulation applied twice daily for 1-minute showed similar pharmacokinetic exposure (AUC_{0-24}) to Tazorac cream with once daily overnight application.

Financial Support: This study was funded and sponsored by the Dr. Reddy's Laboratories group of companies
DRL Publication #815