

Dermal and Systemic Pharmacokinetics of Oral DFD-29 (minocycline hydrochloride modified release capsules, 40 mg) vs Oral Doxycycline 40 mg in Healthy Subjects

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SYNOPSIS

- Rosacea is a common, chronic, inflammatory facial skin disease that can significantly impair quality of life^{1,2}
- A modified low-dose formulation of minocycline hydrochloride (HCl), DFD-29, has shown significant therapeutic benefit versus placebo and doxycycline in treating papulopustular rosacea³
- However, the dermal and systemic pharmacokinetics (PK) of DFD-29 in comparison to doxycycline are unknown

OBJECTIVES

- To compare the dermal and systemic PK of DFD-29 40 mg and doxycycline 40 mg in healthy, adult subjects

METHODS

- This randomized, open-label, single-center, parallel-group study evaluated the systemic and dermal PK of once-daily administration of oral DFD-29 40 mg capsules versus oral doxycycline 40 mg for 21 days in healthy adult volunteers
- On Day 1, subjects were randomized to either DFD-29 40 mg or doxycycline 40 mg under fasting conditions
 - Blood was sampled before drug administration, every 30 minutes for 4 hours, hourly for 4 hours, and 12 and 24 hours post dose
 - Dermal interstitial fluid (ISF) was sampled using three open-flow microperfusion probes before dosing, hourly for 8 hours, and at 11-12, 15-16, and 23-24 hours post dose
- After discharge, subjects continued to take assigned study drug once daily through Day 21,
- Safety was evaluated by monitoring adverse events (AEs), vital signs, and laboratory tests

RESULTS

- A total of 24 subjects (12 men; 12 women) were randomized and completed the study
- Mean age of subjects was 24.3 years (SD 3.0) in the DFD-29 group and 27.8 years (SD 5.8) in the doxycycline group

CONCLUSIONS

- With its modified-release formulation, DFD-29 40 mg provides higher dermal concentration than doxycycline from Day 1 onward at a similar dose.
- The higher concentration from Day 1 at the site of action is expected to translate into a clinically meaningful impact in the treatment of patients with rosacea

RESULTS (cont'd)

- On Day 1, mean plasma C_{max} levels with DFD-29 (382.8 ng/mL) and doxycycline (405.9 ng/mL) were comparable (Pr > 0.716). By Day 21, mean plasma C_{max} had nearly doubled with doxycycline but remained constant with DFD-29 (701.9 vs 337.7 ng/mL; Pr > 0.037)
- Mean plasma AUC was also significantly greater with doxycycline than with DFD-29 at Day 21 (Pr > 0.013)

Table 1. Summary of plasma and dermal (ISF) PK parameters after treatment on Day 1 and Day 21

	Day 1 Mean (SD)		Day 21 Mean (SD)	
	DFD-29 40 mg (n = 8)	Doxycycline 40 mg (n = 8)*	DFD-29 40 mg (n = 8)	Doxycycline 40 mg (n = 8)
Plasma				
AUC ₀₋₂₄ (ng/mL x h)	3549.6 (1438.6)	4377.5 (1232.3)	3957.6 (1099.0)	6074.8 (1979.9)
C _{max} (ng/mL)	382.8 (188.7)	405.9 (170.1)	337.7 (95.5)	701.9 (534.2)
T _{max} (h)	1.9 (0.5)	2.5 (2.3)	1.7 (0.8)	1.6 (0.6)
C _{min} (ng/mL)	3.3 (1.9)	5.2 (5.2)	97 (47.9)	186.3 (72.6)
C _{avg} (ng/mL)	187.4 (77.5)	211.0 (75.30)	210 (53.1)	340.4 (151.9)
Dermal				
AUC ₀₋₂₄ (ng/mL x h)	1412.3 (484.8)	1088.6 (261.8)	1604.8 (454.3)	1573.6 (381.0)
C _{max} (ng/mL)	109.7 (32.8)	81.5 (28.0)	125.7 (55.1)	114.7 (37.7)
T _{max} (h)	3.4 (0.7)	4.0 (1.2)	3.1 (1.4)	4.0 (1.5)
C _{min} (ng/mL)	2.8 (1.9)	0.8 (0.9)	39.9 (17.0)	39.0 (13.0)
C _{avg} (ng/mL)	63.6 (20.8)	49.5 (14.7)	76.9 (21.4)	75.8 (20.1)

*n=7 for dermal PK.

- Mean dermal C_{max} concentrations were numerically higher with DFD-29 (40 mg) than doxycycline at Day 1 (109.7 vs 81.5 ng/mL; Pr > 0.117) and Day 21 (125.7 vs 114.7 ng/mL; Pr > 0.681)
- Mean dermal AUC at Day 1 was greater with DFD-29 vs. doxycycline (Pr > 0.213), and at Day 21 it was similar in the two groups (Pr > 0.954)
- Both DFD-29 and doxycycline were well tolerated by the healthy volunteers

Figure 1. Plasma C_{max} concentrations of DFD-29 40 mg and doxycycline 40 mg on Day 1 and Day 21

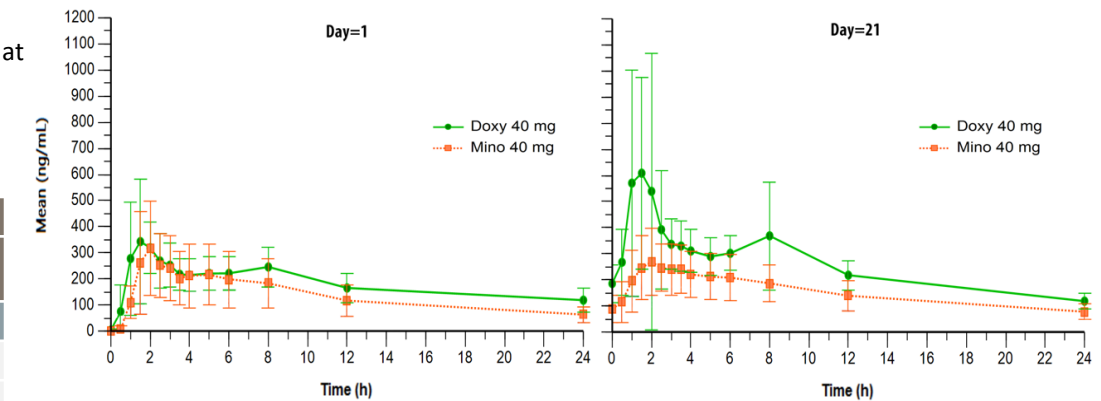
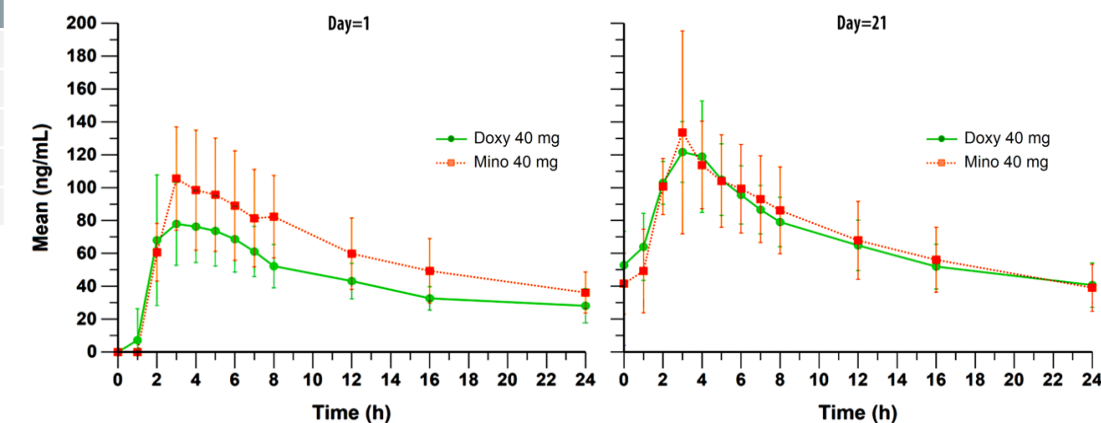


Figure 2. Dermal C_{max} concentrations of DFD-29 40 mg and doxycycline 40 mg on Day 1 and Day 21



- A total of 18 AEs were reported in 9 subjects, including 4 (50%) receiving DFD-29 and 5 (62.5%) receiving doxycycline. Headache was the most commonly reported AE
- All AEs were mild to moderate in severity and the majority (13 of 18 [72%]) were considered unlikely to be related to study drug