Comparative Bioavailability of DFD-29 (minocycline hydrochloride modified release capsules, 40 mg) vs Minocycline Hydrochloride Extended Release, 105 mg Tablets, After a Single Oral Dose: A Randomized, 3-Way Crossover Study

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Srinivas Sidgiddi, MD[1]; Aniruddh Gautam, MPharm[2]
[1]Journey Medical Corporation, Scottsdale, AZ; [2]Dr. Reddy's Laboratories Ltd., Hyderabad, India.

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INTRODUCTION AND SYNOPSIS

- Rosacea is a chronic, inflammatory facial skin disease that affects 5% to more than 10% of the population and can adversely affect quality of life[1,2]
- Papulopustular rosacea is the second most common subtype
- A low-dose formulation of minocycline hydrochloride (HCl), DFD-29, has shown significant therapeutic benefit versus placebo and doxycycline in treating papulopustular rosacea[3]

OBJECTIVES

- To assess the comparative bioavailability of DFD-29 (minocycline HCl modified-release capsules, 40 mg) versus Solodyn® (minocycline HCL, extended-release [ER] tablets, 105 mg)*
- To evaluate the impact of food on DFD-29 bioavailability
- To evaluate the safety and tolerability profile of DFD-29

METHODS

- This single-center, randomized, open-label, laboratory-blinded, 3-way, 6-sequence crossover study compared the pharmacokinetics of a single dose of:
  - **DFD-29 fasting:** DFD-29 40 mg after an overnight fast of ≥10.5 hours
  - **DFD-29 fed:** DFD-29 40 mg after an overnight fast of ≥10.5 hours and 30 minutes after the start of a high-fat, high-calorie breakfast
  - **Minocycline ER :** Minocycline HCL ER 105 mg after an overnight fast of ≥10.5 hours
- Blood samples were collected for PK assessments prior to and up to 72 hours after each drug dose, with a washout period of 7 calendar days between doses
- Safety was evaluated by monitoring adverse events (AEs), vital signs, and laboratory tests

Table 1. Study sequences

Group	Period 1	Period 2	Period 3
Group 1 (n = 4)	DFD-29 fasting	DFD-29 fed	Minocycline ER
Group 2 (n = 4)	DFD-29 fed	Minocycline ER	DFD-29 fasting
Group 3 (n = 4)	Minocycline ER	DFD-29 fasting	DFD-29 fed
Group 4 (n = 4)	DFD-29 fasting	Minocycline ER	DFD-29 fed
Group 5 (n = 4)	DFD-29 fed	DFD-29 fasting	Minocycline ER
Group 6 (n = 4)	Minocycline ER	DFD-29 fed	DFD-29 fasting

*Valeant Pharmaceuticals North America, LLC (Bridgewater, NJ, USA).

RESULTS

- A total of 24 subjects were randomized and 23 subjects completed the study
- One subject in Group 5 prematurely discontinued due to COVID-19 per the physician's discretion
- Mean age of the subjects was 42.4 years (15.5 SD). Most subjects were male (20, 87.0%), white (18, 78.3%), and not Hispanic or Latino (18, 78.3%). Mean BMI was 25.0 kg/m^2 (2.6 SD)

Table 2. Summary of plasma minocycline pharmacokinetic parameters

Parameter	DFD-29 Fasting		DFD-29 Fed		Minocycline ER	
	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)
C_{max} (ng/mL)	244	37.3	225	16.7	497.3	28.5
T_{max} (hours)[a]	1.50	1.0-4.2	4.5	3.0-8.0	4.0	1.5-8.0
T_{lag} (hours)[a]	0.0	0.0-5.0	1.0	0.5-2.0	0	0-0
AUC_{0-T} (ng•h/mL)	3580	32.3	4053	22.0	9624	26.5
$AUC_{0-\infty}$ (ng•h/mL)	3934	31.2	4404	21.0	10103	26.1
$AUC_{\%extrap}$ (%)	9.35	26.6	8.11	23.4	4.8	46.9
T_{half} (hours)	14.7	26.7	14.9	21.5	15.6	15.5

[a]Median and range are presented.

Table 3. Comparative bioavailability of DFD-29 fasting vs minocycline HCL ER

Parameter	Intrasubject CV (%)	Geometric LS means		Ratio, % (90% CI limits)
		DFD-29 Fasting	Minocycline ER	
C_{max} (ng/mL)	20.7	229	477	47.97 (43.25, 53.19)
AUC_{0-T} (ng•h/mL)	19.2	3406	9319	36.55 (33.20, 40.23)
$AUC_{0-\infty}$ (ng•h/mL)	18.4	3759	9800	38.35 (34.98, 42.05)

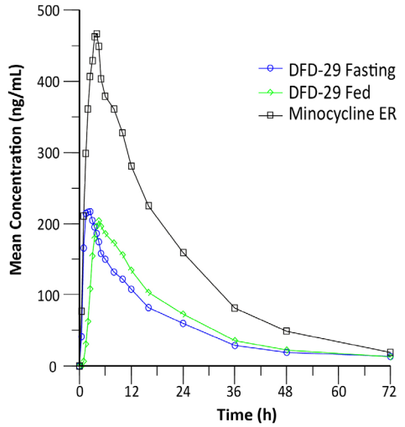
Table 4. Impact of food on DFD-29 bioavailability

Parameter	Intrasubject CV (%)	Geometric LS means		Ratio, % (90% CI limits)
		DFD-29 Fed	DFD-29 Fasting	
C_{max} (ng/mL)	20.7	223	229	97.48 (88.03, 107.94)
AUC_{0-T} (ng•h/mL)	19.2	3979	3406	116.84 (106.29, 128.45)
$AUC_{0-\infty}$ (ng•h/mL)	18.4	4332	3759	115.26 (105.27, 126.20)

Table 5. Overview of TEAEs

Group	DFD-29 Fasting (n = 23)	DFD-29 Fed (n = 23)	Minocycline ER (n = 23)	Overall (n = 24)
TEAEs reported, n	4	12	6	22
Subjects with at least 1 TEAE, n (%)	4 (17.4)	3 (13.0)	5 (21.7)	8 (33.3)
Subjects with at least 1 drug-related TEAE, n (%)	2 (8.7)	2 (8.7)	2 (8.7)	5 (20.8)

Figure 1. Mean minocycline concentration-time profiles after a single dose (n = 23)



- No SAEs were reported
- The most commonly reported TEAE was headache, reported by 3 subjects after administration of DFD-29 fasting, 1 subject after administration of DFD-29 fed, and 1 subject after administration of minocycline ER
- Most TEAEs were mild in severity (21/22; 95.5%)

CONCLUSIONS

- **Bioavailability was significantly lower after a single dose of DFD-29 40 mg under fasting and fed conditions vs minocycline HCl ER 105 mg following a single dose under fasting conditions.**
- **Food intake had no impact on DFD-29 C_{max} but may delay absorption and may slightly increase exposure.**
- **Overall, a single oral dose of DFD-29 40 mg and minocycline HCl ER 105 mg was generally safe and well tolerated.**

ABBREVIATIONS: AEs, adverse events; CI, confidence interval; CV, coefficient of variation; ER, extended release; HCl, hydrochloride; SAE, severe adverse event; LS, least-square; SD, standard deviation; TEAEs, treatment-emergent adverse events.

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