CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	209269
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Submission Type	Original NDA
Applicant	Dr. Reddy's Laboratories Limited
Submission Date	07/08/2016 and 02/16/2017
PDUFA Goal Date	5/8/2017
Brand Name	MINOLIRA®
Generic Name	Minocycline HCl Extended Release Tablets
Dosage Form and Strength	Extended release tablets with a single score line on each tablet, 105 mg and 135 mg
Route of Administration	Oral
Proposed Indication	Treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older
Proposed Dosage Regimen	Once daily at 1 mg/kg/day for 12 weeks
Related IND	120026
Primary reviewer	Yanhui Lu, PhD
Secondary reviewer	Chinmay Shukla, PhD
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Dermatology and Dental Products/ODE3

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1 Executive Summary

The Applicant submitted the current NDA seeking for approval for MINOLIRA, minocycline hydrochloride (HCl) extended release (ER) tablets, 105 mg and 135 mg, for the treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older. Each tablet has a single score line that facilitates splitting of the tablet into two equal halves. Each half of the 105 mg and 135 mg tablets represents a dose of 52.5 mg and 67.5 mg, respectively.

The Applicant is following a 505(b)(2) regulatory path and identified SOLODYN (minocycline HCl) ER tablets (NDA 050808 approved on 05/08/2006) as a listed drug. The Applicant plans to rely on the Agency's findings of safety and efficacy from the listed drug via establishing a clinical bridge. To support this NDA, the applicant submitted results of 2 pivotal relative bioavailability (BA)/bioequivalence (BE) trials, one conducted under fasting conditions (Trial DFD-10-CD-007) and the other conducted under fed conditions (Trial DFD-10-CD-008). Both the pivotal trials used the highest strength of MINOLIRA (135 mg). The studies compared systemic exposure (C_{max} and AUC) of minocycline following a single dose of MINOLIRA 135 mg ER tablets to that following a single dose of SOLODYN (minocycline HCl) 135 mg ER tablets (administered as a combination of SOLODYN ER tablets, 80 mg and 55 mg). The results indicated that MINOLIRA 135 mg ER tablets were bioequivalent to SOLODYN 135 mg ER tablets (80 mg and 55 mg co-administered) under fasting and fed conditions. No other clinical studies were conducted with MINOLIRA.

The Applicant submitted a waiver request of in vivo BA testing for the lower strengths of 52.5 mg (a half of the 105 mg tablet), 67.5 mg (a half of the 135 mg tablet), and 105 mg. This will be reviewed by the Biopharmaceutics reviewer Dr. Hansong Chen. Communication with Dr. Chen suggested that the biowaiver request was acceptable to support approval of lower strengths.

1.1 Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 3 finds NDA 209269 acceptable provided labeling comments are adequately addressed by the Applicant.

1.2 Post-Marketing Commitments/Requirements

None.

1.3 Summary of Clinical Pharmacology Findings

1.3.1 Pharmacokinetics

To support this NDA, the Applicant has completed 2 pivotal relative BA/BE trials for the highest proposed strength, 135 mg, and submitted a biowaiver request for lower strengths.

The 2 pivotal relative BA/BE trials were:

- Trial DFD-10-CD-007 conducted under fasting conditions
- Trial DFD-10-CD-008 conducted under fed conditions

The results of the 2 pivotal trials showed that that the 90% confidence interval (CI) of the geometric mean ratios of C_{max}, AUC_{0-t}, and AUC_{0-inf} were within the no effect boundary of 80% to 125% under both fasting and fed conditions. Summary of the results are shown in Table 1.

Table 1. Summary of relative BA results under fasting and fed conditions for the test (MINOLIRA tablets 135 mg) and reference (SOLODYN tablets 135 mg administered as a combination of SOLODYN ER tablets, 80 mg and 55 mg).

	Fasting Conditions (Trial DFD-10-CD-007) (N=77)		Fed Conditions (Trial DFD-10-CD-008) (N=36)	
Parameters	**Test/Reference Ratio**	**90% CI**	**Test/Reference Ratio**	**90% CI**
C_{max} (ng/mL)	105.92	99.67 - 112.56	94.68	89.62 - 100.03
AUC_{0-t} (ng*h/mL)	97.76	92.32 - 103.52	92.84	89.97 - 95.80
AUC_{0-inf} (ng*h/mL)	97.76	92.45 - 103.38	92.69	89.71 - 95.78

It is noted that under fed conditions, the upper limit of 90% CI for AUC_{0-t} and AUC_{0-inf} were less than 100% (95.80% and 95.78%, respectively). This suggests that the exposure of minocycline following administration of MINOLIRA 135 mg ER tablet was slightly less than that of the approved SOLODYN 135 mg tablets (1 × 80 mg tablet and 1 × 55 mg tablet co-administered). Although this small magnitude of difference in drug exposure would be unlikely to result in lack of efficacy, the use of MINOLIRA as a listed drug for future 505(b)(2) NDA applications should be carefully considered due to the risk of bio-creep.

1.3.2 Biopharmaceutical inspections

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommended accepting data without an on-site inspection for the analytical and clinical sites for the two pivotal trials (See memorandum in DARRTS dated 10/05/2016 by Dr. Shila S. Nkah).

1.4 Clinical Pharmacology Briefing

An optional intra-division level Clinical Pharmacology briefing was held on March 7th, 2017 with the following in attendance: Chinmay Shukla, Hae-Young Ahn, E. Dennis Bashaw, and Yanhui Lu.

2 Question-Based Review

2.1 General Attributes

This NDA is for MINOLIRA (minocycline HCl) ER tablets, 105 mg and 135 mg. Each tablet has a single score line on both upper and lower surfaces. The score line facilitates splitting of the scored tablets into two equal halves. Each half of the 105 mg and 135 mg tablets represents a dose of 52.5 mg and 67.5 mg, respectively. The 105 mg tablet has an "M1" debossed on one surface with "M" and "1" being on either side of the score line; and the 135 mg tablet has an "M3" debossed on one surface with "M" and "3" being on either side of the score line.

The MINOLIRA ER tablets are white to off white rectangular tablets with beads embedded in matrix. Each tablet contains 25% minocycline immediate release (IR) beads and 75% minocycline ER beads.

This NDA application followed a 505(b)(2) regulatory pathway. The lower strengths of 52.5 mg and 67.5 mg, a half of the 105 mg and 135 mg tablets, respectively, are different from approved strengths of the listed drug SOLODYN.

The recommended doses of both MINOLIRA and SOLODYN are approximately 1 mg/kg. With the proposed strengths, MINOLIRA will have a dose range of 0.76-1.17 mg/kg (See Section 2.1.3) while currently approved SOLODYN has a dose range of 0.92-1.11 mg/kg. The difference in body-normalized dose range is not expected to result in an impact on the efficacy and/or safety of MINOLIRA because SOLODYN was originally approved in 3 strengths (45 mg, 90 mg, and 135 mg) with a dose range of 0.76-1.48 mg/kg. Therefore, the proposed dose range of MINOLIRA is within the approved dose range of SOLODYN.

2.1.1 What is the to-be-marketed formulation/product of MINOLIRA?

The formulation composition of MINOLIRA is presented in Table 2.1.1.

2.1.2 What are the therapeutic indications and proposed mechanism of action?

Therapeutic indication: The Applicant is seeking identical therapeutic indication as the listed drug SOLODYN (minocycline HCl) ER tablets (NDA 50808). SOLODYN is approved for the treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.

Mechanism of action: The mechanism of action of minocycline for the treatment of acne is unknown. Minocycline is a semi-synthetic derivative of tetracycline with a wide spectrum of antibacterial activity by inhibiting protein synthesis. Minocycline is lipid soluble and distributes into the skin and sebum. It has been shown to have in vitro activity against *Propionibacterium acnes*, an organism associated with acne vulgaris. The clinical significance of the activity against *P. acnes* in patients with acne vulgaris is unknown.

2.1.3 What is the route of administration and proposed dosing regimen for MINOLIRA?

Proposed route of administration: Oral.

Proposed dosage: The recommended dosage of MINOLIRA is approximately 1 mg/kg once daily for 12 weeks. The tablets may be split on the score line for dosing of patient weight ranges of 45-59 kg and 60-89 kg, respectively. Table 2.1.3 shows tablet strength and body weight to achieve approximately 1 mg/kg.

Table 2.1.1. The formulation composition of MINOLIRA (minocycline HCl) ER tablets, 105 mg and 135 mg.

Components	Function	Quality standar	% w/w	Amount per unit (mg)	
				105 mg	135 mg
Minocycline hydrochloride $^{\$,*}$	Drug Substance	USP	12.67	113.369	145.760
Microcrystalline cellulose (b) (4)					(b) (4)
Opadry clear (b) (4)					
Polyethylene glycol 400 (b) (4)					
Ethyl cellulose (b) (4)					
Hypromellose (b) (4) (b) (4)					
Triethyl citrate					
Silicified microcrystalline cellulose					
Microcrystalline cellulose (b) (4)					
Sodium stearyl fumarate					
Talc					
Isopropyl alcohol^{+}					
Purified water^{+}					
Total					

Abbreviations: USP=United States Pharmacopeia; NF=National Formulary; q.s.=quantity sufficient , IH=In-house.

*Adjust the quantity of minocycline hydrochloride USP (if calculated assay value on anhydrous basis is less than 100% basis potency calculation).

$^{\$}$113.369 mg of minocycline hydrochloride is equivalent to minocycline 105 mg.

$^{\$}$145.760 mg of minocycline hydrochloride is equivalent to minocycline 135 mg.

$^{+}$Does not appear in the final product except in traces.

Table 2.1.3. Dosing table for MINOLIRA.

Patient's Weight	Recommended Daily Dose	Tablet Strength and Size to Administer	Approximate Actual Dose Range (mg/kg)
45 – 59 kg	52.5 mg	Half of the 105 mg tablet	1.16 –0.88
60 – 89 kg	67.5 mg	Half of the 135 mg tablet	1.13 – 0.76
90 – 125 kg	105 mg	One 105 mg tablet	1.17 – 0.84
126 – 136 kg	135 mg	One 135 mg tablet	1.07 – 0.99

2.2 General Clinical Pharmacology

2.2.1 What are the features of study design of the clinical pharmacology and clinical trials used to support MINOLIRA?

The NDA is based on demonstration of relative BA/BE (similar C_{max} and AUC) of MINOLIRA at the highest proposed strength (135 mg) to the listed drug SOLODYN ER tablets 135 mg under fasting and fed conditions and a bio-waiver request for lower strengths (i.e. 52.5 mg, 67.5 mg, and 105 mg). No clinical safety and efficacy trials were conducted with MINOLIRA.

The Applicant conducted 8 relative BA/BE trials. Five pilot relative BA trials were conducted using prototype formulations; and 3 trials were conducted using final to-be-marketed formulation. The 3 trials using the to-be-marketed formulation include a pilot trial and two pivotal trials. All 3 trials had a crossover study design with single dose administration in each study period and a washout period of at least 7 days between dose administrations.

The pilot trial (DFD-10-CD-006) evaluated the relative BA/BE of MINOLIRA ER tablets 135 mg versus the listed drug under fasting conditions and comparative BA of MINOLIRA ER tablets 135 mg administered with and without applesauce in healthy adult male subjects.

The two pivotal trials, DFD-10-CD-007 and DFD-10-CD-008, evaluated the relative BA/BE of MINOLIRA ER tablets 135 mg versus the listed drug under fasting and fed conditions, respectively, in healthy adult male and female subjects. In trial DFD-10-CD-007 conducted under fasting conditions, subjects fasted overnight for at least 10 hours prior to each study drug administration and continued the fast for at least 4 hours post-dose. In trial DFD-10-CD-008 conducted under fed conditions, the study drugs were administered after an overnight fast of 10 hours and at 30 minutes after start of a standard high-fat and high-calorie breakfast as recommended in the FDA's guidance for industry. No food was allowed for at least 4 hours post the fed dose. The breakfast included 2 slices of buttered toast, 2 fried eggs in butter, 2 strips of bacon, 4 ounces of hash brown potatoes, and 240 mL of whole milk. The food served contained 848 Kcal, consisting of 145, 250, and 453 Kcal from protein, carbohydrates, and fat, respectively.

Reviewer's comments: *In the pilot study (DFD-10-CD-006), the test drug (MINOLIRA ER tablets 135 mg) had approximately 33% higher C_{max} and 16% higher AUC of minocycline compared to the reference drug (SOLODYN ER tablets 135 mg). Apple sauce did not have effects on the BA of MINOLIRA ER tablets 135 mg. The pilot study was conducted in India and in male subjects only. The effect of race and sex on the exposure of minocycline is not known and these factors might impact the results. Due to this, the pilot study would have limited regulatory impact and will not be described in detail within this review.*

2.2.2 What is the relative bioavailability of MINOLIRA ER tablets 135 mg compared to the listed drug SOLODYN ER tablets 135 mg? Does it meet the standard BE criteria for C_{max} and AUC?

The relative bioavailability of MINOLIRA ER tablets 135 mg compared to the listed drug SOLODYN ER tablets at the dose of 135 mg was evaluated in 2 cross-over pivotal trials, DFD-10-CD-007 and DFD-10-CD-008, in healthy adults under fasting and fed conditions, respectively. The dose of SOLODYN 135 mg was administered as 1 × 80 mg tablet and 1 × 55 mg tablet because the SOLODYN ER tablets 135 mg have been discontinued. The relative

BA results from fasting and fed trials are shown in Table 2.2.2.1 and Table 2.2.2.2, respectively. Under fasting conditions, the point estimates (90% CI) of test to reference geometric mean ratios for C_{max} and AUC_{0-t} were 105.92% (99.67-112.56%) and 97.76% (92.32-103.52%), respectively. Under fed conditions, the point estimates (90% CI) of test to reference geometric mean ratios for C_{max} and AUC_{0-t} were 94.68% (89.62-100.03%) and 92.84% (89.97-95.80%), respectively. These relative BA results showed that, under both fasting and fed conditions, the 90% CI of test/reference ratios for C_{max} and AUC were within the no effect boundary of 80-125%.

It is noted that under fed conditions, the upper limit of 90% CI for AUC_{0-t} and AUC_{0-inf} were less than 100% (95.80% and 95.78%, respectively), suggesting that the exposure of minocycline following administration of MINOLIRA ER tablet 135 mg was slightly less than that of the approved SOLODYN 135 mg (co-administered as 1 × 55 mg tablet and 1 × 80 mg tablet). Although this small magnitude of difference in drug exposure would be unlikely to result in lack of efficacy, the use of MINOLIRA as a listed drug for future 505(b)(2) NDA applications should be carefully considered due to the risk of bio-creep.

Table 2.2.2.1. Statistical comparisons of plasma minocycline PK parameters under fasting conditions (Trial DFD-10-CD-007, N=77): MINOLIRA 135 mg versus SOLODYN 135 mg (80 mg + 55 mg co-administered) *(Source of data: Table 11-2, Clinical Study Report)*

	Geometric Least Square Means				
Parameters	**Test (MINOLIRA 135 mg)**	**Reference [SOLODYN (55+80 mg)]**	**Test/Reference Ratio (%)**	**90% CI**	**Intra-subject CV%**
C_{max} (ng/mL)	668.5	631.1	105.92	99.67 - 112.56	22.81
AUC_{0-t} (ng*h/mL)	10595	10838	97.76	92.32 - 103.52	21.44
AUC_{0-inf} (ng*h/mL)	11158	11413	97.76	92.45 - 103.38	20.91

Table 2.2.2.2. Statistical comparisons of plasma minocycline PK parameters under fed conditions (Trial DFD-10-CD-008, N=36): MINOLIRA 135 mg versus SOLODYN 135 mg (80 mg + 55 mg co-administered) *(Source of data: Table 11-2, Clinical Study Report)*

	Geometric Least Square Means				
Parameters	**Test (MINOLIRA 135 mg)**	**Reference [SOLODYN (55+80 mg)]**	**Test/Reference Ratio (%)**	**90% CI**	**Intra-subject CV%**
C_{max} (ng/mL)	706.6	746.3	94.68	89.62 - 100.03	13.80
AUC_{0-t} (ng*h/mL)	12250	13196	92.84	89.97 - 95.80	7.87
AUC_{0-inf} (ng*h/mL)	13048	14076	92.69	89.71 - 95.78	8.19

2.3 Intrinsic Factors

2.3.1 Pediatric patients

The Applicant is following a 505(b)(2) regulatory pathway using SOLODYN (NDA 050808) as the listed drug. The Applicant is seeking approval for MINOLIRA by demonstrating relative BA with the listed drug under fasting and fed conditions. The age range of the target population for this NDA is 12 years and older which is identical to the approved age range for the listed drug.

An initial pediatric study plan (iPSP) was submitted to the IND 120026, SN0005 on March 22, 2016. The Agency determined that the NDA for MINOLIRA would not trigger Pediatric Research Equity Act (PREA) and an iPSP would not be needed (see communication dated 05/05/2016 in DARRTS under IND 120026).

Reviewer comments: *The influence of intrinsic factors on dose-exposure and/or response was not explored in this submission and is not needed for this 505(b)(2) application.*

2.4 Extrinsic Factors

2.4.1 How does alcohol use influence dose-exposure and/or response?

An in vitro alcohol dose-dumping study was conducted to test the release of MINOLIRA in presence of different concentrations of alcohol. The results were reviewed by Biopharmaceutics team and according to them, no dose-dumping was found in the presence of alcohol.

Reviewer's comments: *The influence of other extrinsic factors on dose-exposure and/or response was not explored in this submission.*

2.4.2 Drug-drug interactions

Drug-drug interactions were not evaluated for MINOLIRA ER tablets because this NDA is a 505(b)(2) application. This Applicant is relying on labeling information for Section 7 "Drug Interactions" from the approved labelling of the listed drug SOLODYN.

2.5 General Biopharmaceutics

2.5.1 Was to-be-marketed formulation used the pivotal clinical trial(s)?

Yes, the to-be-marketed formulation was used in the pivotal relative BA/BE trials (Trials DFD-10-CD-007 and DFD-10-CD-008).

2.5.2 What data were submitted to support a waiver of in vivo BE data?

For lower strengths (52.5 mg, 67.5 mg, and 105 mg), the Applicant submitted a biowaiver request based on dissolution profile comparisons with the highest strength (135 mg). This will be reviewed by the Biopharmaceutics reviewer Dr. Hansong Chen. Communication with Dr. Chen suggested that the biowaiver request was acceptable to support approval of lower strengths.

2.6 Bioanalytical Methods

2.6.1 What bioanalytical assays were used for measurement of the active moieties in the clinical studies?

The active moiety (minocycline) in plasma was measured and quantitated using a high performance liquid chromatography and tandem mass spectrometry (LC-MS/MS) method.

2.6.2 For all moieties measured, is free, bound, or total measured?

The LC-MS/MS assay detected total minocycline concentrations in plasma which was used to calculate PK parameters of minocycline.

2.6.3 Was the bioanalytical method validated?

Yes, the LC-MS/MS assay has been validated to measure minocycline concentrations in the two pivotal relative BA/BE trials. The assay validation results are summarized in Table 2.6.3. The maximum number of days from first sample collection to analysis completion date was 38 days in both Studies DFD-10-CD-007 and DFD-10-CD-008. The stability of these samples was supported by the long term storage stability of 42 days established during assay validation.

Table 2.6.3. The assay validation results of the LC-MS/MS bioanalytical method used for measuring plasma minocycline concentrations in clinical trials DFD-10-CD-007 and DFD-10-CD-008.

Parameters	Assay Validation Results
Matrix	K_2EDTA plasma
Standard curve assay range	9.904 to 3438.750 ng/mL
Intra-run precision	0.7% to 6.1%
Intra-run accuracy	-5.1% to 4.7%
Inter-run precision	1.6% to 2.7%
Inter-run accuracy	-3.3% to 1.9%
Freeze/thaw matrix stability	4 cycles at -80°C
Room temperature stability	6 hours
Auto-sampler stability	76 hours at 4°C
Long term stability	42 Days at -80°C

***Reviewer's comments**: The intra- and inter-run accuracy and precision results met the criteria recommended by draft guidance for industry: Bioanalytical Method Validation (September 2013) (i.e. the values should be within ±15% except at the lower limit of quantitation (LLOQ) where the values should be within ±20%).*

In Study DFD-10-CD-007, 234 study samples (8% of the total samples, 1 or 2 samples from each of the two treatment periods per subject) were selected for incurred sample reanalysis (ISR). The results showed that 94% samples met the criteria of reproducibility (i.e., difference within ± 20% of average of original and repeat value).

In Study DFD-10-CD-008, 144 study samples (10% of the total samples, 2 samples from each of the two treatment periods per subject) were selected for ISR. The results showed that 98% samples met the criteria of reproducibility (i.e., difference within ± 20% of average of original and repeat value).

Reviewer's comments: *The long term storage stability was adequate to support the storage stability of PK samples and the ISR results met the criteria recommended by draft guidance for industry: Bioanalytical Method Validation (September 2013).*

3 Detailed Labeling Recommendations

The following changes are recommendations for sections 12 of the label for MINOLIRA at the time of completion of this review. Deletions are noted as ~~strikethrough~~ and additions are noted as double underlines.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of MINOLIRA for the treatment of acne is unknown.

12.2 Pharmacodynamics

The pharmacodynamics of MINOLIRA for the treatment of acne are unknown.

12.3 Pharmacokinetics

(b) (4)

The pharmacokinetics of minocycline following oral administration of a single dose of MINOLIRA (135 mg) was investigated in (b) (4) 77 healthy male and female adult subjects under fasting conditions. The pharmacokinetic parameters of minocycline under fasting conditions are presented in Table 3.

Table 3 : Pharmacokinetic Parameters [redacted] of Minocycline Following Administration of a Single Dose of MINOLIRA (135 mg) under Fasting Conditions (N = 77)				
	C_{max} (ng/mL) [redacted]	**T_{max} (hr)*** [redacted]	**$AUC_{0-\infty t}$ (ng.hr/mL)** [redacted]	**$T_{1/2}$ (hr)** [redacted]
[redacted] Mean ± SD	700 ± 261	2.0 [redacted] (1.0 [redacted] – 4.5 [redacted])	[redacted] 10874 ± [redacted] 3717	15.6 ± 2.46

*Median (Min-Max)

In a separate trial, a single dose of MINOLIRA (135 mg) was administered orally with a high-fat, high-calorie meal that included dairy products to 36 healthy male and female adult subjects. The estimated calorie content of the meal was 848 Kcal, consisting of 145 Kcal from protein, 250 Kcal from carbohydrates, and 453 Kcal from fat. The pharmacokinetic parameters of minocycline under fed conditions are presented in Table 4.

Table 4 : Pharmacokinetic Parameters [redacted] of Minocycline Following Administration of a Single Dose of MINOLIRA (135 mg) under Fed Conditions (N = 36)				
	C_{max} (ng/mL) [redacted]	**T_{max} (hr)*** [redacted]	**$AUC_{0-\infty t}$ (ng.hr/mL)** [redacted]	**$T_{1/2}$ (hr)** [redacted]
[redacted] Mean ± SD	707 ± 190	3.5 (-1.5 [redacted] – 6.0 [redacted])	[redacted] 12000 ± [redacted] 2967	17.1 ± 3.03

*Median (Min-Max)

Minocycline is lipid soluble and distributes into the skin and sebum.

4 Appendix: Individual Study Summary

Reviewer's note: *MINOLIRA had a company code, DFD-10, during development. Therefore, MINOLIRA 135 mg ER tablets are referred to as DFD-10 (minocycline HCl) Extended Release Tablets 135 mg in the studies described below.*

4.1 Study DFD-10-CD-007

Title: A Randomized, Single-Dose, Two-Way Crossover Comparative Bioavailability Study of DFD-10 (minocycline HCl) Extended Release Tablets 135 mg of Dr. Reddy's Laboratories Limited, India Versus SOLODYN® (minocycline HCl) Extended Release Tablets 80 mg + 55 mg (co administered) of Medicis, The Dermatology Company, USA, in Healthy Adult Human Subjects Under Fasting Conditions

Studied period:

Study Initiation Date (first subject enrolled): 20 December 2015

Study Completion Date (last subject completed): 08 February 2016

Bioanalysis Completion Date: 27 January 2016

Objectives:

The primary objective was to assess the comparative bioavailability of the test formulation, DFD-10 (minocycline HCl) Extended Release Tablets 135 mg (Dr. Reddy's Laboratories Limited, India) versus SOLODYN® (minocycline HCl) Extended Release Tablets 80 mg + 55 mg (co-administered) (Medicis, The Dermatology Company, USA), following a single oral dose of 135 mg under fasting conditions in healthy human subjects.

The secondary objective was to evaluate and compare the safety and tolerability profiles of each investigational product.

Study design:

This was an open-label, randomized, 2-period, 2-sequence, 2-treatment, crossover study under fasting conditions. Healthy male or female adults (18-55 years of age, inclusive) who were continuous non-smokers and had body mass index (BMI) ≥ 18.5 and ≤ 30.0 kg/m^2 and weight > 50 kg were enrolled.

Subjects were randomized to receive either DFD-10 (Treatment A: Test) or SOLODYN (Treatment B: Reference) under fasting conditions in 2 study periods in the following sequences: AB or BA. There was a washout period of 7 days between the two study periods. Subjects received a single 135 mg oral dose of minocycline HCl Extended Release Tablets (either DFD-10 (minocycline HCl) Extended Release Tablets 135 mg or co-administration of SOLODYN® 80 mg and SOLODYN® 55 mg Extended Release Tablets).

Subjects fasted overnight for at least 10 hours prior to each study drug administration and continued the fast for at least 4 hours post-dose. The washout period was 7 days between the doses of minocycline HCl. In each period, subjects were housed from the day prior to dosing (at least 10 hours prior to the scheduled start time of dosing) until after the 48-hour blood draw. The clinic contacted all subjects (including subjects who terminated the study early) approximately 14 (± 1) days after the last dose to determine if any adverse events had occurred since the last dose of study drug.

PK samplings and analysis:

During each period, blood samples were collected into tubes containing K_2EDTA at pre-dose, and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours post minocycline HCl dose. Plasma samples were prepared and stored at -80°C or below until analyzed.

The PK parameters were calculated through non-compartmental approach from the plasma minocycline concentration-time data using Phoenix® WinNonlin® Version 6.3. The primary endpoints were the 90% CIs of the ratios of least-squares means derived from the analyses of the log transformed PK parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} of the Test (Treatment A, DFD-10 [minocycline HCl]) to Reference (Treatment B, SOLODYN® [minocycline HCl]) formulation of minocycline HCl.

Number of subjects (planned and analyzed):

Eighty-four healthy, adult, non-tobacco using, male and female subjects were planned to be enrolled. A total of 79 subjects were randomized to study treatment. A summary of subject disposition is summarized in Table 4.1.1.

Table 4.1.1. Disposition summary of study DFD-10-CD-007. (*Source of data: Table 10-1, Clinical Study Report*)

	Treatment Sequence		
Category	**AB**	**BA**	**Overall**
Dosed	39(100%)	40(100%)	79(100%)
Completed Study	37(95%)	39(98%)	76(96%)
Dropped From Study	2(5%)	1(3%)	3(4%)
Lost To Follow-Up	1(3%)	1(3%)	2(3%)
Personal Reason	1(3%)	0(0%)	1(1%)

Dosed = any subject who received at least one dose of any study drug

Treatment A: A single oral dose of 135 mg DFD-10 (minocycline HCl) (1 × 135 mg Extended Release Tablet) on Day 1 following an overnight fast

Treatment B: A single oral dose of 135 mg SOLODYN® (1 × 80 mg Extended Release Tablet + 1 × 55 mg Extended Release Tablet [co-administered]) on Day 1 following an overnight fast

A total of 76 subjects completed the study according to protocol. There were 3 subjects who did not complete the study according to protocol:

- Subject (b) (6) (Sequence BA, 46-year-old white male of Hispanic ethnicity): This subject successfully completed Period 1 of the study but did not return to the clinic for Period 2.
- Subject (b) (6) (Sequence AB, 42-year-old white female of Hispanic ethnicity): This subject completed Periods 1 and 2 dosing per protocol but failed to complete the end-of-study phone call after all PK blood samples were collected. This subject's data were included in the relative BA/BE assessment and summary statistics of PK parameters.
- Subject (b) (6) (Sequence AB, 53-year-old American Indian or Alaska Native female): This subject completed dosing in Period 1 according to protocol but decided to withdraw from the study (after dosing) after completing the 2.5 hour post-dose blood draw on Day 1 of Period 1 due to personal reasons.

Identity of investigational products:

The study drugs administered in the study are shown in the Table 4.1.2.

Bioanalytical methods:

Plasma samples were analyzed for minocycline concentration measurement using a validated high performance LC-MS/MS method with an LLOQ of 9.904 ng/mL. See more details in section 2.6.3 of this review.

Table 4.1.2. Identity of the test and reference drugs used in Study DFD-10-CD-007. (*Source of data: section 9.4.2 of Clinical Study Report*)

	Test (Treatment A)	Reference (Treatment B)	
Name	Minocycline HCl Extended Release Tablets 135 mg	Solodyn® (Minocycline HCl, USP) Extended Release Tablets 55 mg	Solodyn® (Minocycline HCl, USP) Extended Release Tablets 80 mg
Manufacture	Dr. Reddy's Laboratories Limited, India	(b) (4)	
Batch No.(test) /Lot No.(reference)	ET15030	5D5253	5B4934
Expiration date	December 2016	April 2018	February 2018

Results

Demographics:

Demographic descriptions of study subjects are summarized in Table 4.1.3. The mean age of the subjects who completed relative BA/BE assessment was 39.2 years (range 19 to 55 years). The mean weight was 76.0 kg (range 58.5 to 106.6 kg). There were more males than females (82% versus 18%).

Minocycline pharmacokinetics:

The plasma concentration-time profiles of minocycline are shown in Figures 4.1.1 (linear scale) and 4.1.2 (semi-log scale). The PK parameters of minocycline from a single dose administration of the test drug, DFD-10 (minocycline HCl) 135 mg, and the reference drug, SOLODYN 135 mg (1 × SOLODYN 80 mg tablet + 1 × SOLODYN 55 mg tablet [co-administered]), are summarized in Table 4.1.4. Statistical comparisons of plasma minocycline PK parameters between the test and reference drugs are presented in Table 2.2.2.1.

The PK results from this study showed the followings:

- Following administration of a single dose DFD-10 (minocycline HCl) 135 mg under fasting conditions, the mean ± SD values of C_{max} and AUC_{0-t} were 700.35 ± 261.25 ng/mL and 10873.5 ± 3717.09 ng*h/mL, respectively.
- Following administration of a single dose SOLODYN 135 mg (1 × SOLODYN 80 mg tablet + 1 × SOLODYN 55 mg tablet [co-administered]) under fasting conditions, the mean ± SD values of C_{max} and AUC_{0-t} were 656.76 ± 229.91 ng/mL and 11013.6 ± 3475.67 ng*h/mL, respectively.
- The point estimates (90% CI) of test to reference geometric mean ratios for C_{max} and AUC_{0-t} were 105.92% (99.67 - 112.56%) and 97.76% (92.32 - 103.52%), respectively.

The relative BA results indicated that under fasting conditions, the 90% CI of test/reference ratios for C_{max} and AUC were within the no effect boundary of 80% to 125%.

Table 4.1.3. Demographics of subjects in Study DFD-10-CD-007.

		All subjects enrolled			Subjects who completed relative BA/BE assessment		
		Sequence AB(N=39)	Sequence BA(N=40)	Overall (N=79)	Sequence AB(N=38)	Sequence BA(N=39)	Overall (N=77)
	*Age (years)	40.5(9.9)	38.5(10.1)	39.5(10.0)	40.2(9.8)	38.3(10.2)	39.2(10.0)
	*Weight (kg)	74.8 (9.9)	76.8(12.0)	75.8(11.0)	75.0(10.0)	77.1(11.9)	76.0 (11.0)
	*BMI (kg/m^2)	26.1(2.2)	26.1(2.6)	26.1(2.4)	26.1(2.2)	26.2(2.6)	26.1(2.4)
Gender	Female	11(28%)	4(10%)	15(19%)	10(26%)	4(10%)	14(18%)
	Male	28(72%)	36(90%)	64(81%)	28(74%)	35(90%)	63(82%)
Race	American Indian/Alaska Native	1(3%)	0(0%)	1(1%)	0	0	0
	Black/African American	4(10%)	4(10%)	8(10%)	4(11%)	4(10%)	8(10%)
	Black or African American, American Indian/Alaska Native (mixed race)	1(3%)	0(0%)	1(1%)	1(2.6%)	0(0%)	1(1.3%)
	White	32(82%)	36(90%)	68(86%)	32(84%)	35(90%)	67(87%)
	White/Black/ African American (mixed race)	1(3%)	0(0%)	1(1%)	1(2.6%)	0(0%)	1(1.3%)
Ethnicity	Hispanic/ Latino	27(69%)	29(73%)	56(71%)	27(71%)	28(72%)	55(71%)
	Not Hispanic/Latino	12(31%)	11(28%)	23(29%)	11(29%)	11(28%)	22(29%)

*Data presented as arithmetic mean (standard deviation).

BA=bioavailability; BE=bioequivalence; BMI=body mass index.

Treatment A = A single oral dose of 135 mg DFD-10 (minocycline HCl) (1 × 135 mg Extended Release Tablet) on Day 1 following an overnight fast

Treatment B = A single oral dose of 135 mg SOLODYN® (1 × 55 mg Extended Release Tablet + 1 × 80 mg Extended Release Tablet [co-administered]) on Day 1 following an overnight fast

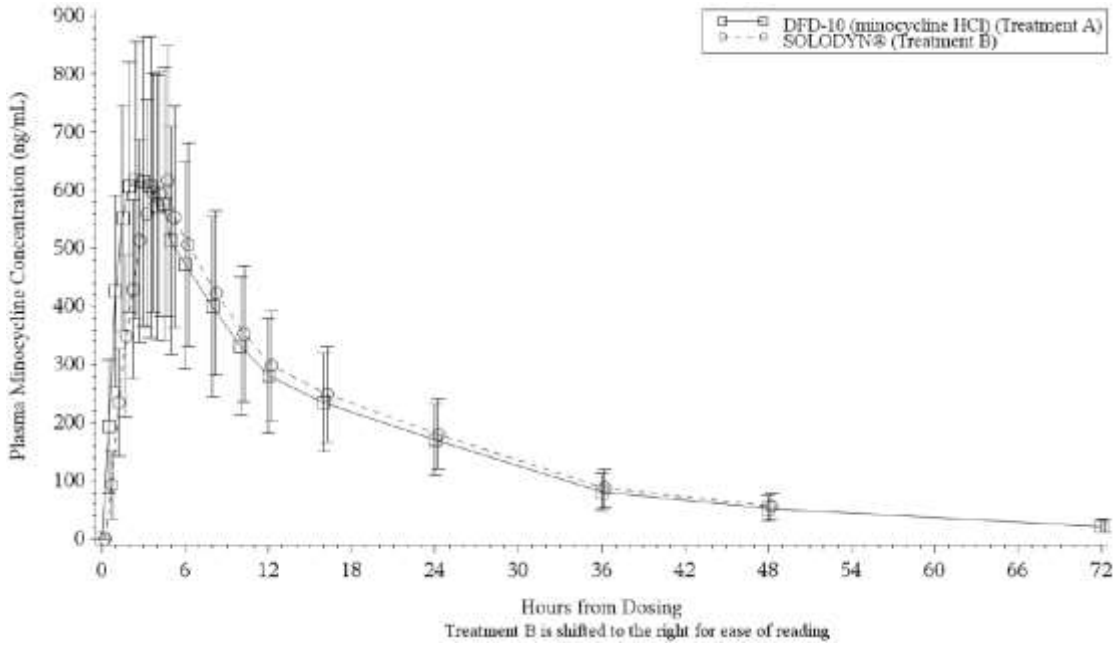

Figure 4.1.1. Mean (±SD) plasma minocycline concentration-time profiles on a linear scale under fasting conditions in Study DFD-10-CD-007. A single dose of DFD-10 (minocycline HCl) 135 mg or SOLODYN 135 mg (1 × SOLODYN 80 mg tablet + 1 × SOLODYN 55 mg tablet [co-administered]) was administered in each of the two study periods with a 7-day washout period between the two doses.

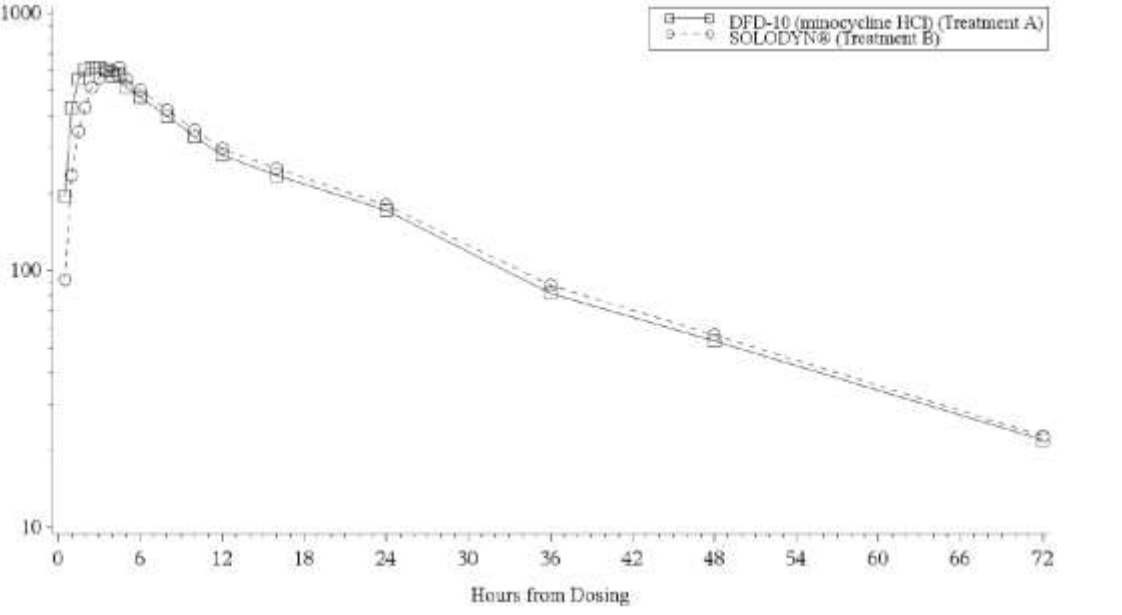

Figure 4.1.2. Mean plasma minocycline concentration-time profiles on a semi-log scale under fasting conditions in Study DFD-10-CD-007. A single dose of DFD-10 (minocycline HCl) 135 mg or SOLODYN 135 mg (1 × SOLODYN 80 mg tablet + 1 × SOLODYN 55 mg tablet [co-administered]) was administered in each of the two study periods with a 7-day washout period between the two doses.

Table 4.1.4. PK parameters (mean ± SD) of minocycline following a single oral dose of DFD-10 (minocycline HCl) 135 mg or SOLODYN 135 mg under fasting conditions in Study DFD-10-CD-007. A single dose of DFD-10 (minocycline HCl) 135 mg or SOLODYN 135 mg (1 × SOLODYN 80 mg tablet + 1 × 55 SOLODYN 55 mg tablet [co-administered]) was administered in each of 2 study periods with a 7-day washout period between the two doses. *T_{max} is presented as median (range). (*Source of data: Table 11-1, Clinical Study Report*)

Parameters	DFD-10 135 mg (N=77)	SOLODYN 135 mg (N=78)
C_{max} (ng/mL)	700.35 ± 261.25	656.76 ± 229.91
AUC_{0-t} (ng*h/mL)	10873.5 ± 3717.09	11013.6 ± 3475.67
AUC_{0-inf} (ng*h/mL)	11410.4 ± 3891.05	11569 ± 3688.53
$T_{1/2}$ (h)	15.6 ± 2.46	15.6 ± 2.62
T_{max} (h)*	2.0 (1.0, 4.5)	4.0 (1.5, 6.0)

4.2 Study DFD-10-CD-008

Title: A Randomized, Single-Dose, Two-Way Crossover Comparative Bioavailability Study of DFD-10 (minocycline HCl) Extended Release Tablets 135 mg of Dr. Reddy's Laboratories Limited, India Versus SOLODYN® (minocycline HCl) Extended Release Tablets 80 mg + 55 mg (co-administered) of Medicis, The Dermatology Company, USA, in Healthy Adult Human Subjects Under Fed Conditions

Studied period:

Study Initiation Date (first subject enrolled): 08 December 2015

Study Completion Date (last subject completed): 11 January 2016

Bioanalysis Completion Date: 15 January 2016

Objectives:

The primary objective was to assess the comparative bioavailability of the test formulation, DFD-10 (minocycline HCl) Extended Release Tablets 135 mg (Dr. Reddy's Laboratories Limited, India) versus SOLODYN® (minocycline HCl) Extended Release Tablets 80 mg + 55 mg (co-administered) (Medicis, The Dermatology Company, USA), following a single oral dose of 135 mg under fed conditions in healthy human subjects.

The secondary objective was to evaluate and compare the safety and tolerability profiles of each investigational product.

Study design:

This was an open-label, randomized, 2-period, 2-sequence, 2-treatment, crossover study under fed conditions. Healthy male or female adults (18-55 years of age, inclusive) who were

continuous non-smokers and had BMI ≥ 18.5 and ≤ 30.0 kg/m^2 and weight > 50 kg were enrolled.

Subjects were randomized to receive either DFD-10 (Treatment A: Test) or SOLODYN (Treatment B: Reference) under fed conditions in 2 study periods in the following sequences: AB or BA. There was a washout period of 7 days between the two study periods. Subjects received a single 135 mg oral dose of minocycline HCl Extended Release Tablets (either DFD-10 (minocycline HCl) Extended Release Tablets 135 mg or co-administration of SOLODYN® 80 mg and SOLODYN® 55 mg Extended Release Tablets).

On Day 1 of each period, subjects were required to fast overnight for at least 10 hours until 30 minutes prior to their scheduled morning dose. Subjects had a standard high-fat and high-calorie (approximately 800-1000 Kcal) breakfast within 30 minutes of serving. Study medications were administered orally with approximately 240 mL of water 30 minutes after the start of breakfast.

The standard high-fat and high-calorie breakfast served included 2 slices of buttered toast, 2 fried eggs in butter, 2 strips of bacon, 4 ounces of hash brown potatoes, and 240 mL of whole milk, as suggested in the FDA guidance for industry: *Food Effect Bioavailability and Fed Bioequivalence Studies*. The meal served contained 848 Kcal, consisting of 145, 250, and 453 Kcal from protein, carbohydrates, and fat, respectively. Subjects fasted for at least 4 hours following administration of the dose.

In each period, subjects were housed from the day prior to dosing (at least 10 hours prior to the scheduled start time of the standard high-fat and high-calorie breakfast on Day 1) until after the 48-hour blood draw. The clinic contacted all subjects (including subjects who terminated the study early) approximately 14 (± 1) days after the last dose to determine if any adverse events had occurred since the last dose of study drug.

PK samplings and analysis:

During each period, blood samples were collected into tubes containing K_2EDTA at pre-dose, and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours post minocycline HCl dose. Plasma samples were prepared and stored at -80°C or below until analyzed.

The PK parameters were calculated through non-compartmental approach from the plasma minocycline concentration-time data using Phoenix® WinNonlin® Version 6.3. The primary endpoints were the 90% CIs of the ratios of least-squares means derived from the analyses of the log transformed PK parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} of the Test (Treatment A, DFD-10 [minocycline HCl]) to Reference (Treatment B, SOLODYN® [minocycline HCl]) formulation of minocycline HCl.

Number of subjects (planned and analyzed):

Thirty-six healthy, adult, non-tobacco using, male and female subjects were planned to be enrolled. A total of 36 subjects were randomized to study treatment. All subjects completed the study. A summary of subject disposition is summarized in Table 4.2.1.

Table 4.2.1. Disposition summary of Study DFD-10-CD-008. (*Source of data: Table 10-1, Clinical Study Report*)

	Treatment Sequence		
Category	**AB**	**BA**	**Overall**
Dosed	18(100%)	18(100%)	36(100%)
Completed Study	18(100%)	18(100%)	36(100%)
Dropped From Study	0(0%)	0(0%)	0(0%)

Dosed = any subject who received at least one dose of any study drug

Treatment A: A single oral dose of 135 mg DFD-10 (minocycline HCl) (1 × 135 mg Extended Release Tablet) on Day 1 under fed conditions

Treatment B: A single oral dose of 135 mg SOLODYN® (1 × 80 mg Extended Release Tablet + 1 × 55 mg Extended Release Tablet [co-administered]) on Day 1 under fed conditions

Identity of investigational products:

The study drugs administered in the study are shown in Table 4.2.2 below.

Table 4.2.2. Identity of the test and reference drugs used in Study DFD-10-CD-008. (*Source of data: section 9.4.2 of Clinical Study Report*)

	Test (Treatment A)	**Reference (Treatment B)**	
Name	Minocycline HCl Extended Release Tablets 135 mg	Solodyn® (Minocycline HCl, USP) Extended Release Tablets 55 mg	Solodyn® (Minocycline HCl, USP) Extended Release Tablets 80 mg
Manufacture	Dr. Reddy's Laboratories Limited, India	(b) (4)	
Batch No.(test) /Lot No.(reference)	ET15030	5D5253	5B4934
Expiration date	December 2016	April 2018	February 2018

Bioanalytical methods:

Plasma samples were analyzed for minocycline concentration measurement using the same LC-MS/MS method used in Study DFD-10-CD-007 with an LLOQ at 9.904 ng/mL. See more details in section 2.6.3 of this review.

Results:

Demographics

Demographic descriptions of study subjects are summarized in Table 4.2.3. The mean age of the subjects was 38.9 years (range 18 to 54 years). The mean weight was 75.14 kg (range 51.9 to 99.6 kg). There were more males than females (83% versus 17%).

Table 4.2.3. Demographics of subjects in Study DFD-10-CD-008. (*Source of data: Table 14.1.3, Clinical Study Report*)

		Sequence AB(N=18)	Sequence BA(N=18)	Overall (N=36)
	*Age (years)	40.1(10.9)	37.8(11.4)	38.9(11.1)
	*Weight (kg)	75.59(12.76)	74.69(11.49)	75.14(11.97)
	*BMI (kg/m^2)	26.21(2.97)	25.76(3.03)	25.99(2.97)
Gender	Female	2(11%)	4(22%)	6(17%)
	Male	16(89%)	14(78%)	30(83%)
Race	Black or African American	1(6%)	2(11%)	3(8%)
	White	17(94%)	16(89%)	33(92%)
Ethnicity	Hispanic/Latino	15(83%)	13(72%)	28(78%)
	Not Hispanic/Latino	3(17%)	5(28%)	8(22%)

*Data presented as arithmetic mean (standard deviation).

Abbreviations: BMI=body mass index.

Treatment A = A single oral dose of 135 mg DFD-10 (minocycline HCl) (1 × 135 mg Extended Release Tablet) on Day 1 under fed conditions

Treatment B = A single oral dose of 135 mg SOLODYN® (1 × 80 mg Extended Release Tablet + 1 × 55 mg Extended Release Tablet [co-administered]) on Day 1 under fed conditions

Minocycline pharmacokinetics:

The plasma concentration-time profiles of minocycline are shown in Figures 4.2.1 (linear scale) and 4.2.2 (semi-log scale). The PK parameters of minocycline from a single dose administration of the test drug, DFD-10 (minocycline HCl) 135 mg, and the reference drug, SOLODYN 135 mg (1 × SOLODYN 80 mg tablet + 1 × SOLODYN 55 mg tablet [co-administered]), are summarized in Table 4.2.4. Statistical comparisons of plasma minocycline PK parameters between the test and reference drugs are presented in Table 2.2.2.2.

The PK results from this study showed the followings:

- Following administration of a single dose DFD-10 (minocycline HCl) 135 mg under fed conditions, the mean ± SD values of C_{max} and AUC_{0-t} were 707.40 ± 189.82 ng/mL and 11999.6 ± 2966.98 ng*h/mL, respectively.
- Following administration of a single dose SOLODYN 135 mg (1 × SOLODYN 80 mg tablet + 1 × SOLODYN 55 mg tablet) under fed conditions, the mean ± SD values of C_{max} and AUC_{0-t} were 749.60 ± 208.10 ng/mL and 12851.2 ± 2821.86 ng*h/mL, respectively.
- The point estimates (90% CI) of test to reference geometric mean ratios for C_{max} and AUC_{0-t} were 94.68% (89.62 - 100.03%) and 92.84% (89.97 - 95.80%), respectively.

The relative BA results indicated that under fed conditions, the 90% CI of test/reference ratios for C_{max} and AUC were within the no effect boundary of 80% to 125%.

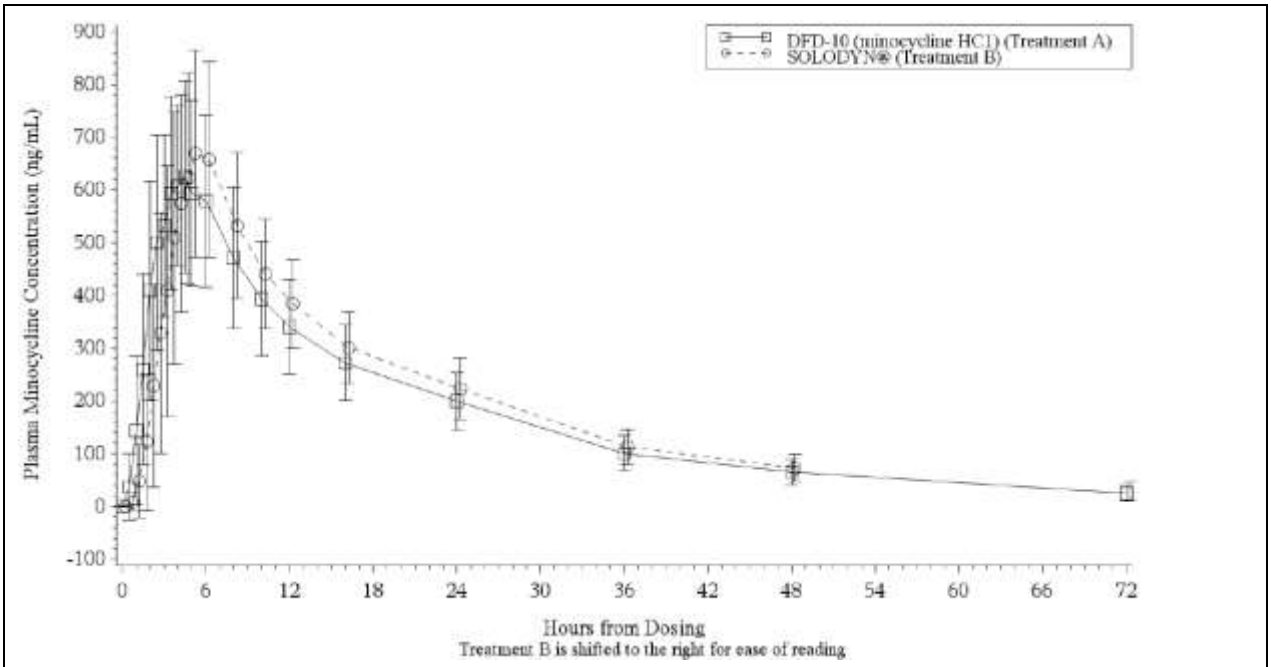

Figure 4.2.1. Mean (±SD) plasma minocycline concentration-time profiles on a linear scale under fed conditions in Study DFD-10-CD-008. A single dose of DFD-10 (minocycline HCl) 135 mg or SOLODYN 135 mg (1 × SOLODYN 80 mg tablet + 1 × SOLODYN 55 mg tablet [co-administered]) was administered in each of the two study periods with a 7-day washout period between the two doses.

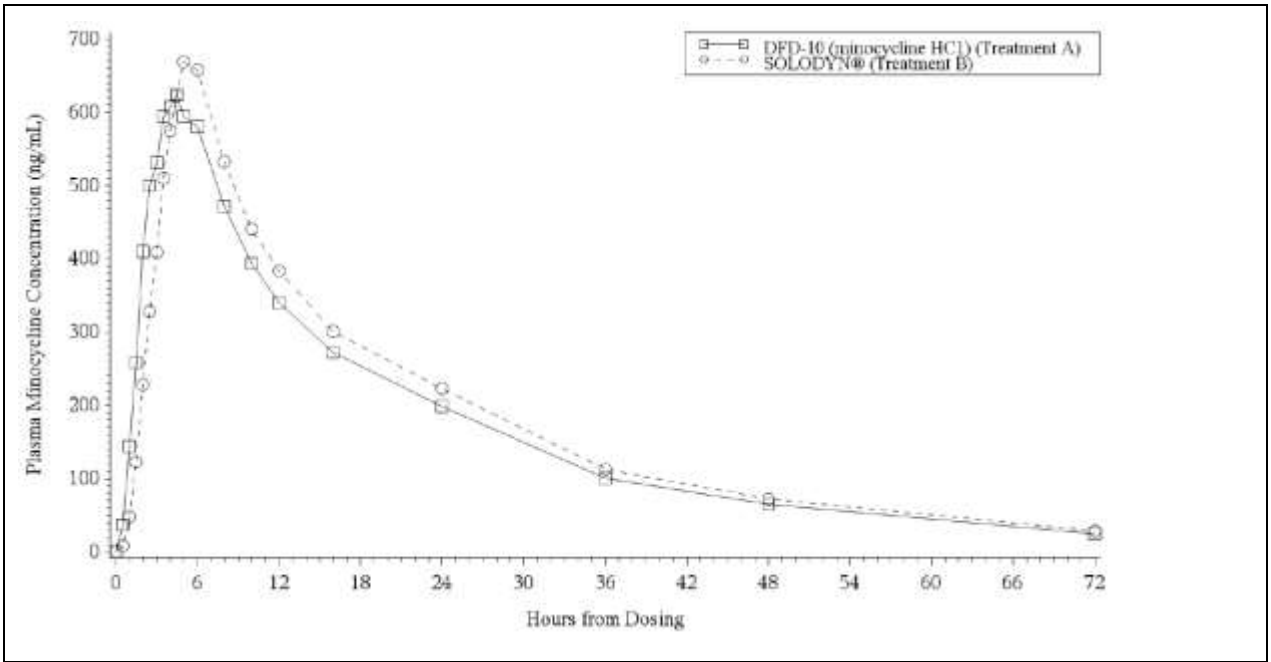

Figure 4.2.2. Mean plasma minocycline concentration-time profiles on a semi-log scale under fed conditions in Study DFD-10-CD-008. A single dose of DFD-10 (minocycline HCl) 135 mg or SOLODYN 135 mg (1 × SOLODYN 80 mg tablet + 1 × SOLODYN 55 mg tablet [co-administered]) was administered in each of the two study periods with a 7-day washout period between the two doses.

Table 4.2.4. PK parameters (mean ± SD) of minocycline following a single oral dose of DFD-10 (minocycline HCl) 135 mg or SOLODYN 135 mg under fed conditions in Study DFD-10-CD-008. A single dose of DFD-10 (minocycline HCl) 135 mg or SOLODYN 135 mg (1 × SOLODYN 80 mg tablet + 1 × SOLODYN 55 mg tablet [co-administered]) was administered in each of 2 study periods with a 7-day washout period between the two doses. *T_{max} is presented as median (range). (*Source of data: Table 11-1, Clinical Study Report*)

Parameters	DFD-10 135 mg (N=36)	SOLODYN 135 mg (N=36)
C_{max} (ng/mL)	707.40 ± 189.82	749.60 ± 208.10
AUC_{0-t} (ng*h/mL)	11999.6 ± 2966.98	12851.2 ± 2821.86
AUC_{0-inf} (ng*h/mL)	12724.4 ± 3341.2	13690.5 ± 3540.3
$T_{1/2}$ (h)	17.1 ± 3.03	17.6 ± 4.42
T_{max} (h)*	3.5 (1.5, 6.0)	5.0 (2.0, 6.0)

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/s/

YANHUI LU
03/09/2017

CHINMAY SHUKLA
03/10/2017