

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-808

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW**

NDA Number: — /50-808

Submission Date(s): 06/30/05; 08/26/05; 11/16/05; 12/22/05; 02/10/06;
02/15/06

Brand Name: Minocycline Hydrochloride Extended Release
Tablets

Generic Name: SOLODYN

Reviewer: Tapash K. Ghosh, Ph. D.

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OCPB Division: DCP III

OND Division: HFD-540

Sponsor: Medicis, Scottsdale, AZ

Submission Type; Code: 3S

Formulation; Strength(s): 45 mg, 90 mg and 135 mg

Indication: Primary therapy in moderate-to-severe acne
vulgaris

1 Executive Summary

Medicis Pharmaceutical Corp. has developed a new formulation of minocycline as 45 mg, 90 mg and 135 mg tablets as a primary therapy in moderate-to severe acne vulgaris. The new formulation (claimed as modified release) includes the identical active pharmaceutical ingredient to currently marketed minocycline, but it includes additional excipients that are necessary for a modified-release formulation. This new formulation is not bioequivalent to the marketed product. The proposed product was designed as a once-daily dosing regimen for improved compliance. In addition, it is being proposed in new strengths that, according to the sponsor, are dosed proportioned to body weight.

The sponsor conducted twelve biostudies in support of this application. They are three comparative BA/BE studies, one 2-way crossover steady-state pharmacokinetics (PK) study, four pharmacodynamic (PD) studies (drug drug interaction with hormonal contraceptives, antimicrobial effects, effects on spermatogenesis), and three safety and efficacy studies. One safety and efficacy study is still ongoing. Two pivotal BA/BE studies (Food effect and dose proportionality), one steady-state PK study and one drug drug interaction study with oral contraceptives have been reviewed in detail. Two PD studies (antimicrobial effect and spermatogenesis) are also covered in lesser detail.

Medicis tablets have dose-proportional pharmacokinetics and food does not appear to affect either the rate or extent of minocycline absorption from Medicis proposed 135 mg minocycline HCl tablets. The new formulation, however, is absorbed at a relatively slower rate and yields lower dose adjusted systemic exposure than commercially available Minocin Capsules. The sponsor also attempted to evaluate any potential interaction between minocycline from the proposed dosage form with some low dose contraceptives. However, due to the design of this drug drug interaction study, the results could not be interpreted properly. Therefore, it is suggested that the proposed labeling language should be changed.

In terms of antimicrobial effect, the results of the *P. acnes* cultures/counts were inconsistent and did not correlate with clinical improvement. Therefore, no conclusion could be drawn. Also, based on the review of an outside panel of male reproductive specialists, the data from the spermatogenesis study are inconclusive because of methodology and study design issues. Therefore, evidence of minocycline having any effect on spermatogenesis remains unclear at this time.

According to the sponsor, the results of their clinical (efficacy) studies showed that Solodyn significantly reduced the number of inflammatory lesions after 12 weeks, and significantly improved the patient's overall appearance of acne as evaluated by a dichotomized Global Severity Assessment.

Recommendation

Based on the data submitted in NDA ~~50-808~~, the application is acceptable from a clinical pharmacology and biopharmaceutics perspective provided the following comments are adequately addressed.

Comments to be conveyed to the Sponsor:

- Given the pharmacokinetic profile of the proposed product, the term "Extended Release" will provide a better description of the product as opposed to "Modified Release".
- Until a properly designed drug-drug interaction study with oral contraceptives is conducted, the suggested labeling language should be replaced with the following: "In a multi-center study to evaluate the effect of Solodyn on low dose oral contraceptives, hormone levels over one menstrual cycle with and without Solodyn 1 mg/kg once-daily were measured. Based on the results, minocycline-related changes in estradiol, progestinic hormone, FSH, and L, plasma levels can not be ruled out. To avoid contraceptive failure, females are advised to use a second form of contraceptive during treatment with minocycline".

- The sponsor is requested to adopt the following dissolution specification for all strengths (45 mg, 90 mg and 135 mg) of Solodyn tablets in 900 mL of 0.01 N HCl solution using USP Apparatus 1 (basket) at a speed of 100 rpm at $37 \pm 0.5^\circ\text{C}$

1 hour: NLT		and NMT	
2 hours: NLT		and NMT	
4 hours: NLT			

Comments to the Medical Officer:

- BA requirements for the NDA of an extended-release product are listed in § 320.25(f). One of the purposes of an *in vivo* BA study for which an extended release claim is made is to determine that the drug product's steady-state performance is comparable to a currently marketed immediate release or extended release drug product that contains the same active drug ingredient or therapeutic moiety. However, the steady state performance (exposure) of the proposed 135 mg qd Solodyn product is not comparable to that of currently approved bid 100 mg Minocin capsules at the dose adjusted level. Therefore, recommendation in terms of switchability between 135 mg proposed Solodyn *qd* and 100 mg Minocin capsules *bid* has to be based on clinical efficacy and safety data.
- Literature reports that the minimum inhibitory concentration (MIC) for MINOCYCLINE is less than 4 mcg/mL. Intermediate sensitivity is defined as an MIC of 4 to 16 mcg/mL (agar dilution or broth dilution) and 4 to 12.5 mcg/mL (tube dilution). For intermediate sensitivity, organisms should be susceptible if high doses are used or if the infection resides in tissues and fluids in which high antibiotic levels are attained. The organism is considered resistant to MINOCYCLINE if the MIC is greater than 16 mcg/mL (agar dilution or broth dilution) or greater than 12.5 mcg/mL (tube dilution). The elimination phase (last 12 hours of the 24-hr cycle) of minocycline from the proposed formulation is not same compared to that of two Minocin tablets taken at a 12 hour interval (Figure 2). Although the effect of minocycline against *P.acnes* in patients with acne vulgaris is not known, the clinical relevance of this difference in terms of potential for developing resistant organisms should be evaluated.

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3 Summary of CPB Findings

The following is a brief overview of the clinical pharmacology and biopharmaceutics results.

Pharmacokinetics

Solodyn tablets are not bioequivalent to non-extended release minocycline products. Based on pharmacokinetic studies in healthy adults Solodyn tablets produce a delayed T_{max} at 3.5 – 4.0 hours as compared to an immediate-release reference product (T_{max} at 2.25 - 3 hours). At steady state (Day 6), the mean AUC₍₀₋₂₄₎ and C_{max} were 33.32 µg×hr/mL and 2.63 µg/ml for Solodyn tablets and 46.35 µg×hr/mL and 2.92 µg/ml for Minocin capsules at dose-adjusted to 135 mg per day for both products.

A single-dose, four-way crossover study demonstrated that all strengths of Solodyn tablets (45mg, 90mg, 135 mg) exhibited dose-proportional pharmacokinetics.

Extrinsic factors

Food Effect: When Solodyn tablets were administered concomitantly with the FDA recommended high-fat meal that included dairy products, the rate, extent and timing of absorption of minocycline did not differ from that of administration under fasting conditions. No dosing recommendation is needed in terms of food.

Drug-Drug Interactions: Study design was not adequate to support sponsor's proposed labeling language in terms of drug drug interaction with oral contraceptives.

Overview of Biopharmaceutics

Dissolution: The sponsor is requested to adopt the following dissolution specification for all strengths (45 mg, 90 mg and 135 mg) of Solodyn tablets in 900 mL of 0.01 N HCl solution using USP Apparatus 1 (basket) at a speed of 100 rpm at $37 \pm 0.5^{\circ}\text{C}$

1 hour: NLT	and NMT
2 hours: NLT	and NMT
4 hours: NLT	

Overview of Clinical Studies (as excerpted from Sponsor's version):

The safety and efficacy of Solodyn was assessed in three 12-week prospective, multi-center, randomized, double-blind, placebo-controlled studies.

Overview of Efficacy: In two identical Phase III trials, a total of 924 subjects with moderate to severe acne received 1 mg/kg of Solodyn or placebo for a total of 12 weeks. Inflammatory lesion counts were analyzed as a primary efficacy endpoint in both the Phase 2 study and the Phase 3 studies. In the Phase 2 study, the primary efficacy endpoint was the change from Baseline in the number of inflammatory lesions at Day 84 in the ITT population analyzed as absolute lesion counts and as percent change from Baseline. In the Phase 3 studies, one of the 2 primary efficacy endpoints was the percent change from Baseline in the inflammatory lesion count at Day 84 in the ITT population. In both studies, the change from Baseline in noninflammatory lesion counts was analyzed at Day 84 as a secondary efficacy endpoint. The change from Baseline in total lesion count (the sum of inflammatory plus noninflammatory lesion counts) was also analyzed as a secondary efficacy endpoint (Phase 2 study) or as an additional endpoint (Phase 3 studies). Statistics for inflammatory lesion counts at Baseline, the change from Baseline at Day 84, and the percent change from Baseline at Day 84 from the Phase 2 study, the two Phase 3 studies, and all 3 studies pooled are presented in the following Table.

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Summary of Inflammatory Lesion Counts: Phase 2 and Phase 3 Studies, ITT Populations

	MP-0104-01		MP-0104-04		MP-0104-05		Pooled	
	Minocycline* N = 59	Placebo N = 55	Minocycline N = 300	Placebo N = 151	Minocycline N = 315	Placebo N = 158	Minocycline N = 674	Placebo N = 364
Baseline								
Mean ± SD	38.8 ± 2.02	40.3 ± 2.39	39.1 ± 13.3	38.7 ± 13.0	38.9 ± 11.66	38.4 ± 11.82	38.9 ± 12.73	38.8 ± 13.33
Median	34	35	35	35	36	34	35	35
Range	20 - 92	20 - 99	24 - 81	23 - 87	20 - 82	25 - 82	20 - 92	20 - 94
P value†	0.697		0.789		0.847		0.698	
Change from Baseline to Day 84								
Mean ± SD	21.8 ± 2.2	17.2 ± 2.9	16.5 ± 15.1	12.3 ± 15.8	17.2 ± 13.7	11.3 ± 18.1	17.3 ± 14.7	12.6 ± 17.8
Median	18	16	18	14	19	12.5	18	14
Range	-70 - 27	-85 - 50	-64 - 66	-59 - 67	-26 - 65	-93 - 77	-64 - 70	-93 - 83
P value‡	0.213		N/A		N/A		N/A	
Percent change from Baseline to Day 84								
Mean ± SD	56.8 ± 4.2	39.4 ± 5.7	43.1 ± 36.7	31.7 ± 40.3	45.8 ± 34.8	30.8 ± 47.0	45.5 ± 35.6	32.4 ± 43.6
Median	61.0	47.0	48.6	36.1	50.0	33.7	50.0	36.2
Range	-100.0 - 61.0	-95.0 - 135.0	-213.3 - 100.0	-159.5 - 100.0	-81.3 - 100.0	-310.0 - 100.0	-213 - 100	-310 - 100
P value‡	0.015		0.001		<0.001		<0.001	

ITT= intent-to-treat, SD = standard deviation, N/A = not available

*Includes only those subjects randomized to minocycline 1 mg/kg.

†P value for treatment differences was obtained using the 2-way ANOVA.

‡P values for treatment differences were obtained using the 2-way ANOVA in MP-0104-01 and an ANOVA model on the ranks in MP-0104-04 and MP-0104-05.

The results of these studies showed that SOLODYN significantly reduced the number of inflammatory lesions after 12 weeks, and significantly improved the patient's overall appearance of acne as evaluated by a dichotomized Global Severity Assessment.

Overview of Safety: Minocycline was well tolerated in the subject populations studied. This conclusion is based on an overall incidence AEs, including the incidence of vestibular events, which was similar to that of placebo, and based on the lack of evidence of clinically significant changes in the results of laboratory tests.

4 Review

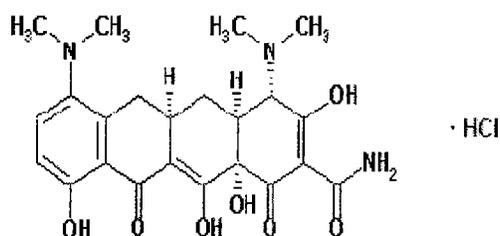
4.1 General Attributes

What are the highlights of the chemistry and physical-chemical properties of the drug substances, and formulation of the drug product?

A. Highlights of the chemistry and physical-chemical properties of the drug substance in Solodyn tablets is as follows:

Minocycline was patented (US) in 1965 and the hydrochloride salt (CAS No. 13614-98-7) is chemically defined as [4S-(4 α , 4a α , 5a α , 12a α)]-4, 7-bis (dimethyl- amino)-1, 4, 4a,

5, 5a, 6, 11, 12a-octahydro-3, 10, 12, 12a-tetra hydro-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride (Figure below). Minocycline has a chemical formula of $C_{23}H_{27}N_3O_7$ and a molecular weight of 457.48 [— for the monohydrochloride, CAS No. 13614-98-7]. Minocycline has a high lipid solubility with an octanol/water partition coefficient (K_{ow}) = 1.1 compared to tetracycline (K_{ow} = 0.036) or doxycycline (K_{ow} = 0.60).



Batch Formula: The drug product is a film-coated caplet containing minocycline hydrochloride, equivalent to minocycline as an active drug substance, and is available in 3 strengths: 45 mg, 90 mg and 135 mg. The unit formula composition for the registration batches of 45 mg, 90 mg, and 135 mg Minocycline HCl Tablets is provided in the following Table.

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Component	Reference to Quality Standard	Amount (g) per Batch			Explanatory Notes
		45 mg	90 mg	135 mg	
Minocycline Hydrochloride ⁵	USP				
Lactose Monohydrate	NF				
Lactose Monohydrate	NF				
Hypromellose, Type 2910	USP				
Colloidal Silicon Dioxide	NF				
Magnesium Stearate	NF				
Total Amount					
Dispensing Formula – Coating					
Opadry II ⁶	n/a				The film coating suspension for the 45 mg, 90 mg, and 135 mg caplet is gray, yellow, and orange-brown (pink), respectively.
	USP				
Carnauba Wax	NF				

What is the proposed dosage and route of administration?

The adult oral proposed dose is 1 mg/kg/day (0.76 – 1.50 mg/kg/day, depending on the weight of the patient, or 29 – 57 mg/m²/day).

What is the proposed mechanism of drug action and, therapeutic indications?

A. Proposed mechanism of drug action(s):

Minocycline (CAS No. 10118-90-8) is a second generation semi-synthetic derivative of tetracycline with comparable antibacterial activity against a number of Gram-negative and Gram-positive organisms, including tetracycline-resistance organisms. Although the exact mechanism of action in acne is unknown, minocycline may act through the suppression of the number of P acnes, suppression of free fatty acid production in the

skin, and reduction of inflammation. Minocycline has been shown to have a high lipid solubility that permits partitioning of the drug to the skin and sebum.

B. Therapeutic Indications:

The proposed formulation of minocycline in 45 mg, 90 mg and 135 mg tablets is designed as a primary therapy in moderate-to severe acne vulgaris.

4.2 General Clinical Pharmacology

Were the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, minocycline was appropriately identified and measured.

What are the pharmacokinetic parameters of minocycline in the proposed formulation?

Pharmacokinetic parameters across the 4 pharmacokinetics studies are presented in the following Table. At all doses, the new formulations yielded lower maximum and minimum mean plasma concentrations than the current marketed formulations, Minocin[®] (innovator) and Dynacin[®] (AB rated generic). Within each study, the mean C_{max} for the new minocycline formulations was lower than that for either marketed formulation, (Dynacin[®] or Minocin[®].) Also, the AUC₍₀₋₂₄₎ was lower in the new formulation. The same trends are observed whether the subjects were fed or fasted and whether they received single or multiple doses of drug. The data suggest that the pharmacokinetic properties of the new formulation of minocycline differ from those of the currently marketed products.

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Study No.	Formulation	Dose Adjusted Least Squares Mean Parameters					
		N	C _{max} (µg/mL)	T _{max} (hr)	AUC* (µg/mL×hr)	C _{min} (µg/mL)	T _{1/2} (hr)
AAI-US-110	Prototype 1 150 mg tablet - fasted	12	1.52	3.58	27.00	NA	13.5
	2 × 75 mg Dynacin* capsules- fasted	12	2.09	2.25	34.30	NA	13.5
	Prototype 2 150 mg tablet - fasted	12	1.40	3.58	26.98	NA	14.3
	2 × 75 mg Dynacin* capsules - fasted	12	2.17	2.25	37.13	NA	14.2
AAI-US-190	1 × 135 mg minocycline caplets -fasted	24	1.84	3.69	39.09	NA	16.3
	1 × 135 mg minocycline caplets -fed	24	1.85	3.52	38.39	NA	16.6
AAI-US-233†	1 × 45 mg minocycline caplets	24	1.33	3.96	28.77	NA	16.9
	1 × 90 mg minocycline caplets	24	1.30	3.90	28.57	NA	17.1
	1 × 135 mg minocycline caplets	24	1.36	3.85	28.75	NA	16.7
	1 × 100 mg Minocin® capsule	24	1.66	2.92	33.60	NA	16.5
MP-0104-15‡	135 mg minocycline caplets	27	2.63	3.34	33.32	0.63	NA
	100 mg Minocin* capsule	27	2.92	3.00	46.35	1.23	NA

*AUC for single-dose studies is to time of last measurable concentration; for the multiple-dose study, the AUC presented is for the 24-hour dosing interval on Day 6.

† All PK parameters for AAI-US-233 are dose-adjusted to 100 mg.

‡All PK parameters for MP-0104-15 are from Day 6 of dosing. PK parameters are dose-adjusted to 135 mg per day.

NA = Not available

4.3 General Biopharmaceutics

What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Food does not appear to affect either the rate or extent of minocycline absorption from Medicis Pharmaceutical Corporation's 135 mg minocycline HCl tablets as appeared from the following table. Therefore, no dosing adjustment is necessary in regards to food.

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Summary of Food Effect on Minocycline Pharmacokinetic Parameters

Parameter	Least-Squares Means ¹		Ratio ²	CV% ³	90% Confidence Interval ⁴	
	Fed	Fasted			Lower	Upper
AUC 0-t (ng-hr/ml)	38392	39085	0.982	-	0.895	1.070
AUCinf (ng-hr/ml)	40800	41331	0.987	-	0.900	1.074
Cmax (ng/ml)	1853	1836	1.010	-	0.893	1.126
Tmax (hour)	3.52	3.69	0.955	-	-	-
Ke (1/hour)	0.0428	0.0437	0.980	-	-	-
T½ (hour)	16.6	16.3	1.021	-	-	-
Ln-Transformed:						
AUC 0-t (ng-hr/ml)	36686	37781	0.971	25.2	0.858	1.098
AUCinf (ng-hr/ml)	38938	39905	0.976	24.5	0.866	1.100
Cmax (ng/ml)	1775	1758	1.010	28.1	0.881	1.158

4.4 Analytical

How were the active moieties identified and measured in plasma in the clinical pharmacology and biopharmaceutics studies?

Sample analysis for AAI-US-110, AAI-US-190, and AAI-US-233 was performed by AAI Deutschland GmbH, Neu-Ulm, Germany, using the same validated methodology for all 3 studies.

Calibration standards and controls were prepared by spiking human interference-free plasma with the minocycline reference material. Calibration standards were prepared to contain concentrations of _____ . Quality control samples were prepared to contain concentrations of _____ .

The assay method involved liquid-liquid extraction of minocycline and the internal standard, demeclocycline, with perchloric acid, followed by chromatographic separation. Detection and peak quantification were based on UV absorbance at _____ nm. The assay was linear over the concentration range 25 ng/mL to 5000 ng/mL.

Sample analysis for MP-0104-15 was performed by _____. The assay method used automated liquid-liquid phase extraction followed by HPLC. Detection and quantitation was performed using tandem mass spectrometry, with demeclocycline as the internal standard. The assay was linear over the range 20 ng/mL to 5000 ng/mL, and the lower limit of quantification was 20 ng/mL.

5. Detailed Labeling Recommendations:

14 Page(s) Withheld

 Trade Secret / Confidential

 8 Draft Labeling

 Deliberative Process

INDIVIDUAL STUDY REPORTS

NDA: /50-808/Study AAI-US-190

Study Dates: Apr '04 – May '04

A Randomized Single Dose Two-Way Crossover Study of the Effect Of Food On The Pharmacokinetics Of Minocycline Tablets In Healthy Volunteers

Objective: The purpose of this study was to determine the relative bioavailability of minocycline from 135 mg minocycline HCl tablets after administration of single doses to normal healthy subjects under fed and fasted conditions.

Study Design: The study was performed as a single-dose (one 135 mg caplet), two-way crossover study with an adequate washout period (7 days) between the two periods of the study and with an equal number of subjects randomly assigned to receive the study test drug in a fasted state (Treatment A) and after receiving the FDA recommended high-fat Breakfast (Treatment B). A total of 24 non-smoking subjects (12 men and 12 women) were included in this study, of which all 24 finished the study according to the protocol. The mean age was 24.1 years with a range of 20 to 36. Venous blood samples were collected over a 72-hour period of time post drug administration.

Samples were analyzed for the content of minocycline by a validated HPLC/UV assay. Detection and peak quantification were based on UV absorbance at 351 nm. The assays were linear over the concentration range 25.0 ng/ml to 5000 ng/ml.

Results: Table 1 summarizes the results of the fed-to-fasted comparisons for the pharmacokinetic parameters. Comparisons of the minocycline levels at each sampling time are summarized in Table 2 and in the accompanying figures.

Table 1: Summary of Minocycline Pharmacokinetic Parameters

Parameter	Least-Squares Means ¹		Ratio ²	CV% ³	90% Confidence Interval ⁴	
	Fed	Fasted			Lower	Upper
AUC 0-t (ng-hr/ml)	38392	39085	0.982	-	0.895	1.070
AUCinf (ng-hr/ml)	40800	41331	0.987	-	0.900	1.074
Cmax (ng/ml)	1853	1836	1.010	-	0.893	1.126
Tmax (hour)	3.52	3.69	0.955	-	-	-
Ke (1/hour)	0.0428	0.0437	0.980	-	-	-
T½ (hour)	16.6	16.3	1.021	-	-	-
Ln-Transformed:						
AUC 0-t (ng-hr/ml)	36686	37781	0.971	25.2	0.858	1.098
AUCinf (ng-hr/ml)	38938	39905	0.976	24.5	0.866	1.100
Cmax (ng/ml)	1775	1758	1.010	28.1	0.881	1.158

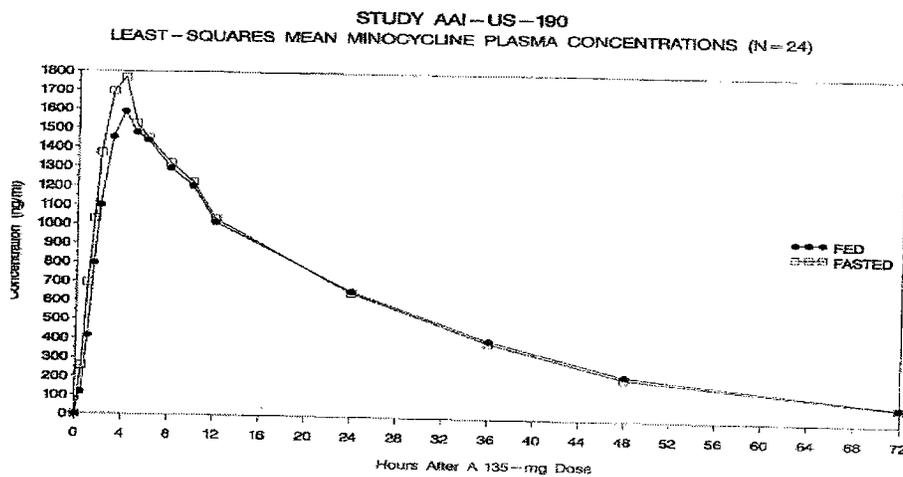
¹ Least-squares geometric means for ln-transformed data.; ² Ratio calculated as the Fed least-squares mean divided by the Fasted least-squares mean. None of the comparisons

was detected as statistically significant by ANOVA ($\alpha=0.05$).³ Estimated intra-subject coefficient of variation, $CV\%=100*\text{SQRT}(e\text{MSE}-1)$, where MSE is the mean square error term from the ANOVA.⁴ Confidence interval on the ratio.

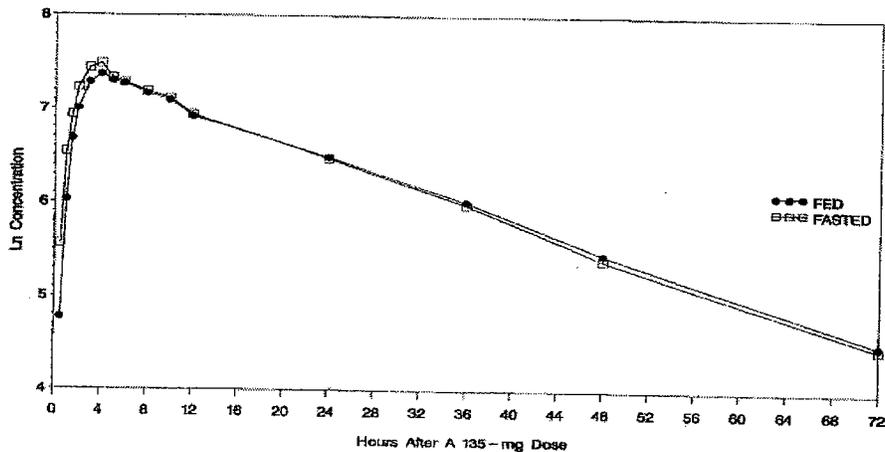
Table 2: Summary of Plasma Minocycline Concentrations at each Sampling Time Point

Collection (Hour)	Least-Squares Means (ng/ml)		Significance * (p<0.05)
	Fed	Fasted	
0.00	0.00	0.00	None
0.50	118	259	0.0055
1.00	415	693	0.0028
1.50	797	1029	None
2.00	1100	1373	None
3.00	1454	1696	None
4.00	1586	1771	None
5.00	1479	1524	None
6.00	1436	1448	None
8.00	1293	1319	None
10.0	1204	1225	None
12.0	1015	1032	None
24.0	659	651	None
36.0	410	398	None
48.0	235	222	None
72.0	91.4	87.8	None

Results of the statistical evaluation by ANOVA ($\alpha=0.05$) for the hypothesis of equal treatment effects. None indicates that no statistically significant difference was detected between treatment means ($p>0.05$) at the sampling time evaluated.



STUDY AAI-US-190
LOG OF LEAST-SQUARES MEAN MINOCYCLINE PLASMA CONCENTRATIONS (N=24)



Conclusions: The 90% confidence intervals for the geometric mean fed-to-fasted area and peak concentration ratios were within the bioequivalence interval 0.80-1.25. Food does not appear to affect either the rate or extent of minocycline absorption from Medicis Pharmaceutical Corporation's 135 mg minocycline HCl tablets. According to the sponsor, the treatments were well tolerated.

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A Single Dose Four-Way Crossover Dose Proportionality Study of Minocycline Tablets in Healthy Volunteers

Objective: The purpose of this single-dose, four-way crossover, dose proportionality study was to determine the pharmacokinetics of minocycline after giving increasing doses to normal healthy subjects under fasted conditions to determine the dose proportionality of the different strengths of the Medicis formulation and to compare the minocycline bioavailability of the Medicis formulation to that of commercially available Minocin[®] capsules.

Overall Study Design: The study was performed as a single-dose four-way crossover, dose proportionality study using increasing doses of minocycline with an adequate washout period (7 days) between subsequent periods of the study. A total of 24 non-smoking subjects (14 men and 10 women) were included in this study, of which 19 finished all four periods of the study according to the protocol. The mean age was 26.1 years with a range of 18 to 48.

An equal number of subjects were randomly assigned to each of four dosing sequences (ABCD, BCDA, CDAB, DABC) to receive the study treatments, 2 X 45 mg tablets(A), 1 X 90 mg caplet(B), 1 X 135 mg caplet(C) and 1 X 100 mg Minocin[®] capsule(D). Blood samples were analyzed for the content of minocycline by a fully-validated HPLC/UV assay with Detection and peak quantification based on UV absorbance at 351 nm.

Statistical analyses were conducted on the pharmacokinetic values derived from the reported minocycline concentrations and also on the values following dose adjustment to a common 100 mg dose. The dose adjustment was accomplished by multiplying the area and C_{max} values for each subject in each period by the ratio 100/Dose, where Dose was that administered in the given period.

Results: Statistical analyses were performed to compare each of the three Medicis tablets to each other and to the Minocin[®] capsule. Tables 1 and 2, which follow, summarize the mean results for the major pharmacokinetic parameters for each of the treatments before and after dose adjustment. Table 3 summarizes the comparisons of the Medicis tablets to the Minocin[®] capsule. Table 4 summarizes the comparisons conducted to evaluate the dose-proportionality of the three Medicis tablets.

Table 1: Summary of least-squares means minocycline results, prior to dose- adjustment.

Parameter	Least-Squares Arithmetic Means			
	45-mg (2 X 45 mg Dose)	90-mg (1 X 90 mg Dose)	135-mg (1 X 135 mg Dose)	Minocin® (1 X 100 mg Dose)
AUC _{0-t} (ng-hr/mL)	25920	25732	38718	33595
AUC _{inf} (ng-hr/mL)	27828	27631	41228	35702
C _{max} (ng/mL)	1193	1171	1829	1661
Parameter	Least-Squares Geometric Means			
	45-mg (2 X 45 mg Dose)	90-mg (1 X 90 mg Dose)	135-mg (1 X 135 mg Dose)	Minocin® (1 X 100 mg Dose)
AUC _{0-t} (ng-hr/mL)	24524	24733	37356	32340
AUC _{inf} (ng-hr/mL)	26329	26470	39715	34335
C _{max} (ng/mL)	1130	1125	1766	1596

Table 2: Summary of least-squares means of dose-adjusted minocycline results.

Parameter	Least-Squares Arithmetic Means			
	45-mg (2 X 45 mg Dose)	90-mg (1 X 90 mg Dose)	135-mg (1 X 135 mg Dose)	Minocin® (1 X 100 mg Dose)
AUC _{0-t} (ng-hr/mL)	28769	28573	28748	33598
AUC _{inf} (ng-hr/mL)	30886	30684	30611	35702
C _{max} (ng/mL)	1326	1300	1358	1661
T _{max} (hour)	3.96	3.90	3.85	2.92
K _e (1/hour)	0.0424	0.0424	0.0425	0.0429
T _½ (hour)	16.9	17.1	16.7	16.5
Parameter	Least-Squares Geometric Means			
	45-mg (2 X 45 mg Dose)	90-mg (1 X 90 mg Dose)	135-mg (1 X 135 mg Dose)	Minocin® (1 X 100 mg Dose)
AUC _{0-t} (ng-hr/mL)	27249	27481	27671	32340
AUC _{inf} (ng-hr/mL)	29254	29411	29418	34335
C _{max} (ng/mL)	1255	1250	1308	1596

Table 3: Summary of statistical comparisons between Medicis tablets and Minocin® capsules (dose-adjusted results).

Medicis Caplet	Least-Squares Medicis- to-Minocin® Ratios*					
	AUC _{0-t} (ng-hr/mL)	AUC _{inf} (ng-hr/mL)	C _{max} (ng/mL)	T _{max} (hour)	K _e (1/hour)	T _½ (hour)
45-mg (2 X 45 mg Dose)	0.843	0.852	0.787	1.355	0.988	1.024
90-mg (1 X 90 mg Dose)	0.850	0.857	0.783	1.336	0.990	1.032
135-mg (1 X 135 mg Dose)	0.856	0.857	0.820	1.317	0.992	1.008

*

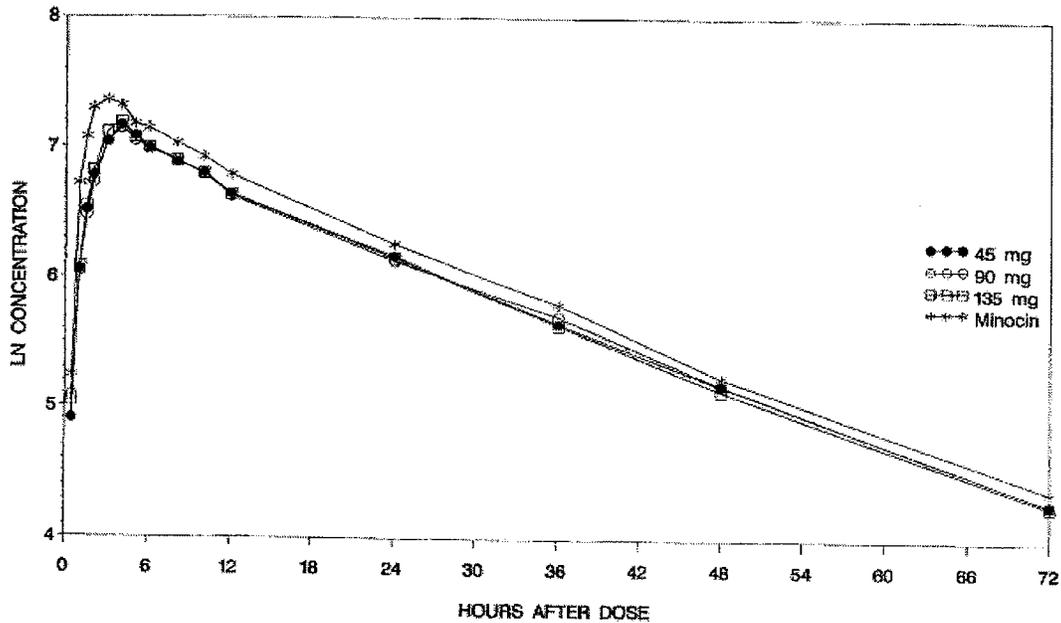
For AUC_{0-t}, AUC_{0-∞} and C_{max} results are geometric mean ratios; for other parameters, results are arithmetic mean ratios. All comparisons were detected as statistically significant by ANOVA ($\alpha=0.05$) except for those involving the elimination parameters K_e and T_½.

Table 4: Summary of statistical comparisons for dose-proportionality of the Medicis tablets (dose-adjusted results).

Medicis Caplet	Least-Squares Geometric Means Ratios*		
	AUC _{0-t} (ng-hr/mL)	AUC _{inf} (ng-hr/mL)	C _{max} (ng/mL)
45-mg vs. 90-mg	0.992	0.995	1.005
45-mg vs. 135-mg	0.985	0.994	0.959
90-mg vs. 135-mg	0.993	1.000	0.955

Each of the three Medicis tablets produced comparable exposure (AUC) but relatively lower rate (C_{max}) than did the Minocin® capsule. The Medicis mean time of peak was approximately 1 hour later than the mean for the Minocin® capsule, a difference which was detected as statistically significant ($p<0.05$). The 90% confidence intervals for the area and C_{max} geometric mean ratios for all possible pair-wise comparisons of the Medicis tablets were within the bioequivalence acceptance region, 0.80 to 1.25. In addition, the mean time peak concentration for each of the three tablets was essentially the same.

LOG OF LEAST-SQUARES MEAN MINOCYCLINE PLASMA CONCENTRATIONS (N=19, Dose Adjusted)



Conclusions: While the Medicis tablets and the Minocin® capsule appear to have comparable extents of minocycline absorption, the rate of absorption from the Medicis tablets, as measured by T_{max} , is slower. All three Medicis tablets are bioequivalent to each other in the dose-adjusted evaluations indicating that the Medicis tablets have dose-proportional pharmacokinetics.

Comments: *In light of the fact that Medicis tablets and the Minocin® capsule appear to have comparable extents of minocycline absorption but the time to maximal concentration from the Medicis tablets is little slower and the Medicis mean time of peak was only about 1 hour later than the mean for the Minocin® capsule, the Medicis tablets may not be designated as modified release tablets. "Extended release" is considered a better description of the product.*

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A Two-Way Crossover Steady-State Study of Minocycline Tablets in Healthy Volunteers

Study Objectives: The purpose of this study was to determine the pharmacokinetics of two minocycline formulations after administration of multiple doses to normal, healthy subjects. These data were evaluated statistically to determine the relative bioavailability at steady state between Modified-Release Minocycline HCl Tablets under review and commercially available Minocin® (minocycline HCl) Capsules (the Orange Book RLD).

Overall Study Design: The study was a randomized 2-way crossover study in 28 healthy males and females (7 men and 21 women, ranging in age from 19 to 50 years old) to evaluate the pharmacokinetics of minocycline during 6 days of once daily treatment with Modified-Release Minocycline HCl Tablets, 135 mg (Test product). The reference product was commercially available Minocin® (minocycline HCl) Capsules, 100 mg (Lederle) administered every 12 hours for 6 days. Each dose was taken at approximately the same time each day with or without food, except for the morning dose on Day 6 of each period which was taken in a fasting state.

Each subject received treatment with either the Test or the Reference products in each of the 2 study periods, in randomized sequence. The first dose of the second period was administered 20 days after the first dose of Period 1. Blood samples for minocycline analysis were drawn pre-dose on Day 1, Day 4, and Day 5 of each period. Sampling on Day 6 was pre-dose and at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0, 12.5, 13.0, 13.5, 14.0, 15.0, 16.0, 17.0, 18.0 and 20.0 hours post-dose. On Day 7, subjects were discharged from the research facility after a 24-hour post-dose sample was obtained. Subjects returned to the clinic each morning on Days 8 and 9 (at 48 and 72 hours postdose, respectively) for additional sampling.

Plasma concentrations were determined by a validated and sensitive bioanalytical method over a Concentration Range of _____ using a High Performance Liquid Chromatographic Method _____ developed and validated at _____. The analytical data were utilized to compare the formulations in regard to plasma concentrations at each collection, C_{max} , T_{max} , and AUC for each dose.

Treatment Assignment: Subjects were assigned upon enrollment to a sequence of treatments according to a predetermined randomization schedule. A subject could either receive once daily Modified-Release Minocycline HCl Tablets, 135 mg, in Period 1 and twice daily Minocin® (minocycline HCl) Capsules, 100 mg, in Period 2 (sequence=QB); or twice daily Minocin® (minocycline HCl) Capsules, 100 mg, in Period 1 and once daily Modified-Release Minocycline HCl Tablets, 135 mg, in Period 2 (sequence=BQ).

Pharmacokinetics Evaluation: The PK parameters (AUC_{0-24} , C_{max} , T_{max} , C_{min} , C_{av} , and PTF i.e., Percent fluctuation from peak to trough at steady state) was analyzed using an analysis of variance model with terms for subject, subject within sequence, period, and treatment. The sequence effect was tested against the variance for subject within sequence; all other effects were tested against the residual variance of the model. Least squares means for each treatment, and the difference between the treatment least squares means were calculated. For $AUC_{(0-24)}$, C_{max} , and C_{min} the parameters were also analyzed after log transformation. Ninety percent 2-sided confidence intervals were constructed on the treatment differences of the untransformed parameters, and on the ratio of geometric means for $AUC_{(0-24)}$, C_{max} , and C_{min} .

The plasma minocycline concentrations were plotted versus sampling point for each individual subject and period as well as for the means by treatment. The achievement of steady state was investigated by performing an analysis of variance with effects of period, day, and period-day interaction for each treatment separately, using only the pre-dose minocycline concentrations on Days 4, 5, 6, and 7.

Dose adjustment was achieved by multiplying all minocycline concentrations from Reference product data by the factor 135/200.

Results: The results of the planned analysis of the steady state PK parameters for this study are presented in Table 1. The analysis of variance revealed a statistically significant effect of sequence which appeared consistently across most of the PK parameters. Further investigation showed that there was a statistically significant difference in the PK parameters between periods within each treatment group. A supplementary analysis of the PK parameters was therefore carried out taking the data from each period separately. The applicable analysis of variance was a 1-way model, with treatment as the only independent term. The following Table 2 shows the results.

The difference between treatments was statistically significant for all PK parameters in Period 1, showing the Test product to be less bioavailable and more slowly absorbed than the Reference product. In contrast, the difference between treatments was statistically significant only for C_{max} and PTF in Period 2, with the Reference product showing a higher C_{max} than the Test product. Thus, the Period 2 results are qualitatively different from the Period 1 results in this study.

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Table 1: Summary of Planned Analysis of Steady-State Pharmacokinetics Parameters from All Completed Subject (N=27)

Parameter	Least Squares Means			Ratio of GMs (90% CI)	p values		
	Test	Ref*	Difference (90% CI)		Seq	Period	Treat
C _{max} (µg/mL)	2.63	2.92	-0.28 (-0.52, -0.04)	90% (82%, 99%)	0.002	0.947	0.069
AUC ₍₀₋₂₄₎ (µg×hr/mL)	33.32	46.35	-13.0 (-16.8, -9.2)	72% (65%, 79%)	0.003	0.920	<0.001
T _{max} (hr)	3.34	3.00	0.34 (-0.93, 1.62)	--	0.085	0.315	0.651
C _{min} (µg/mL)	0.63	1.23	-0.60 (-0.72, -0.48)	49% (42%, 58%)	0.015	0.541	<0.001
C _{av} (µg/mL)	1.39	1.93	-0.54 (-0.70, -0.38)	--	0.005	0.220	<0.001
PTF (%)	144.8	88.4	56.4 (48.0, 64.8)	--	0.778	0.614	<0.001

*Note: All Reference product parameters have been dose-adjusted to 135 mg total dose. CI= confidence interval, Seq= Sequence; P values are from analysis of variance with effects of subject, subject within sequence, period, and treatment. For AUC₍₀₋₂₄₎, C_{max}, and C_{min}, the data were log-transformed prior to analysis.

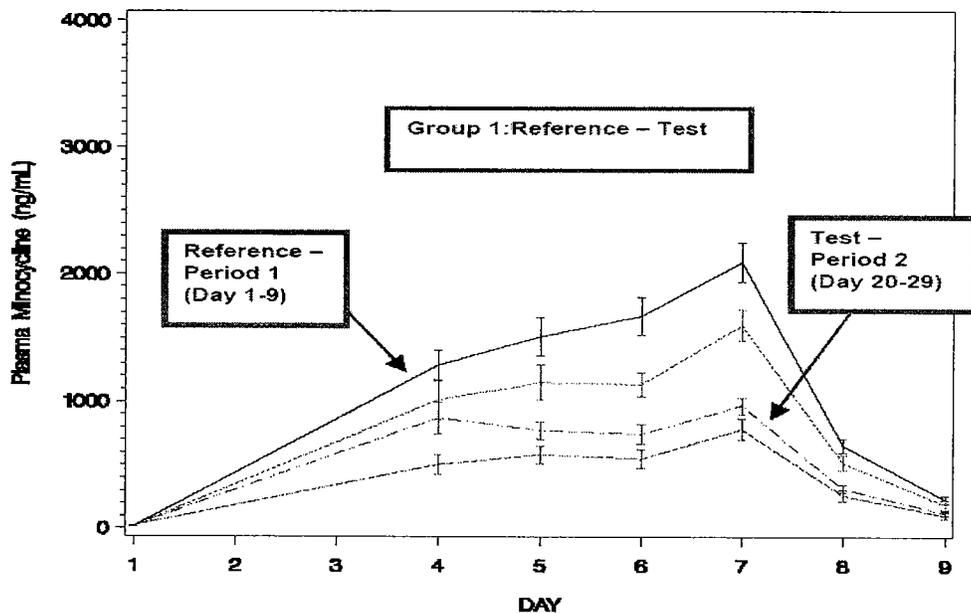
Table 2: Summary of Supplementary Analysis of Steady-State Pharmacokinetics Parameters By Period, By Treatment for All Completed Subjects (N=27)

Parameter	Period	Least Squares Means			Ratio of Geom Means / 90% CI	P Value
		Test	Reference*	Difference / 90% CI		
C _{max} (µg/mL)	1	2.20	2.45	-1.25 (-1.84, -0.67)	43% (31%, 78%)	0.001
	2	3.07	2.38	0.69 (0.19, 1.18)	128% (108%, 153%)	0.021
AUC ₍₀₋₂₄₎ (µg×hr/mL)	1	38.4	54.1	-15.7 (-34.7, -16.7)	52% (43%, 65%)	<0.001
	2	38.2	38.5	-0.4 (-7.1, 6.3)	99% (83%, 117%)	0.901
T _{max} (hr)	1	3.62	1.96	1.65 (1.18, 2.12)	--	<0.001
	2	3.07	4.04	-0.97 (-3.44, 1.51)	--	0.671
C _{min} (µg/mL)	1	0.52	1.49	-0.98 (-1.25, -0.70)	34% (27%, 43%)	<0.001
	2	0.74	0.97	-0.13 (-0.42, -0.04)	70% (51%, 88%)	0.030
C _{av} (µg/mL)	1	1.18	2.25	-1.07 (-1.45, -0.69)	--	<0.001
	2	1.59	1.61	-0.02 (-0.29, 0.25)	--	0.924
PTF (%)	1	142.6	82.1	54.5 (40.8, 68.3)	--	0.001
	2	147.0	88.7	58.2 (44.0, 72.5)	--	0.001

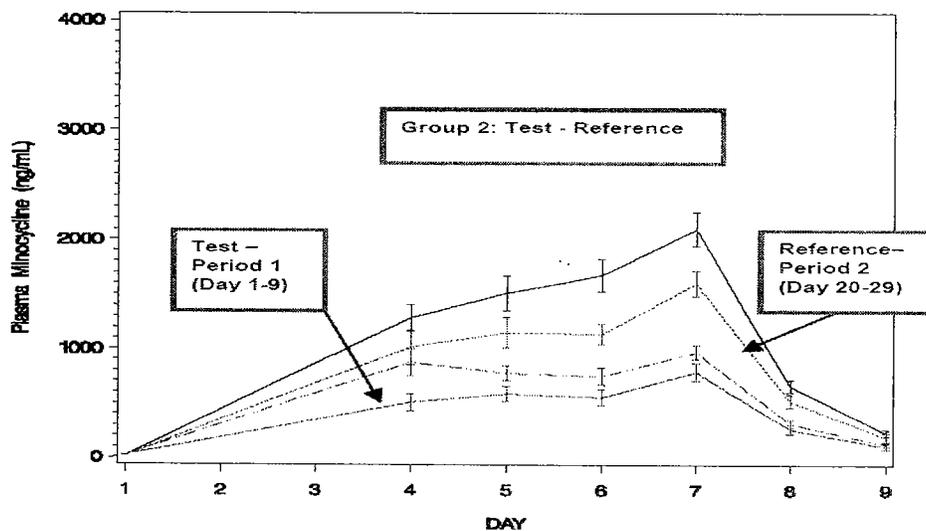
*Note: All Reference product parameters have been dose-adjusted to 135 mg total dose. CI= confidence interval, P values are from analysis of variance with effects of treatment. For AUC₍₀₋₂₄₎, C_{max}, and C_{min}, the data were log-transformed prior to analysis.

The mean dose-adjusted concentration curves are displayed by treatment and period in Figures 1 and 2.

Figure 1: Mean Dose-Adjusted Plasma Minocycline Trough Concentrations By Period, By Treatment for All Completed Subjects (N=27)



GROUP — Reference - Period 1 - - - Reference - Period 2
 - - - Test - Period 1 - - - Test - Period 2



GROUP — Reference - Period 1 - - - Reference - Period 2
 - - - Test - Period 1 - - - Test - Period 2

Figure 2: Mean Dose-Adjusted Day 6 Plasma Minocycline Concentrations By Period, By Treatment for All Completed Subjects (N=27)

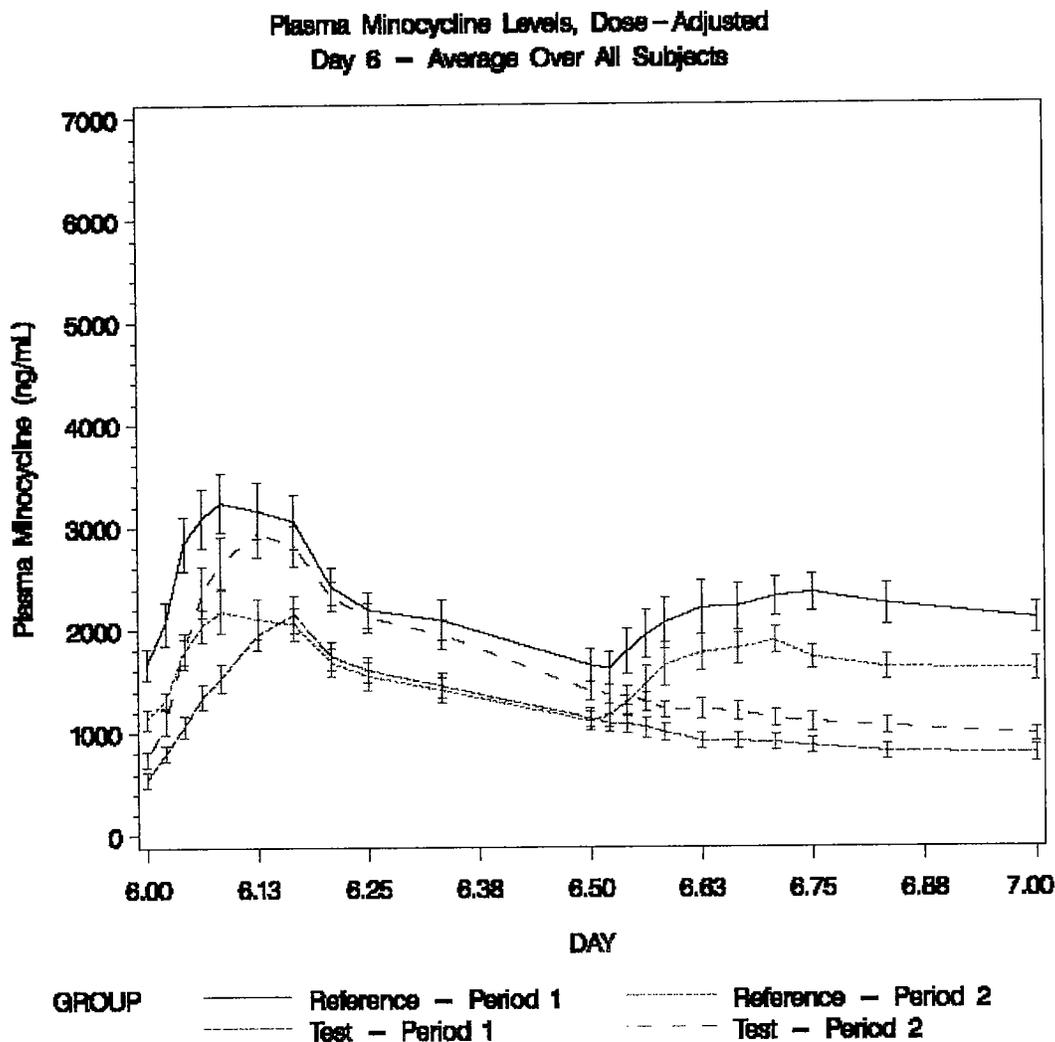


Figure 1 suggests that trough concentrations were still increasing on Day 6. An analysis of variance was performed to test whether steady state had been achieved. The analysis was performed separately for each treatment on the data from combined periods (including effects of period, day, and period-day interaction), and on the data from each treatment and each period separately (including effects of day only). Only the trough concentrations from Day 5, Day 6, and Day 7 were included in the analysis. The results showed a statistically significant effect of day, indicating that the trough plasma concentrations were increasing between Day 5 and Day 7 for both treatments and in both periods.

Discussion: In Period 1, the Test product was found to be less bioavailable and more slowly absorbed than the Reference product. In contrast, in Period 2, the reference product was found to be less bioavailable and more slowly absorbed than the test product. Thus, the Period 2 results are qualitatively different from the Period 1 results in this study. Because of the persistent period/sequence effect on the PK parameters observed in the study, the sponsor was asked to explain the possible reason. Their best possible explanation was that by chance the subjects randomized to sequence group 1 had a greater steady state minocycline levels than the subjects randomized to sequence group 2. It is noteworthy that the ratio of mean AUC (Test/Reference) for sequence group 1 is approximately equal to the ratio of mean AUC (Test/Reference) for sequence group 2 (0.707 and 0.735, respectively). This is consistent with an explanation of the sequence effect based on within subject variability, independent of treatment formulation and confounded by the study design which was outpatient until Day 6 when subjects were confined in the clinic until the morning of Day 7.

These results are consistent with the findings of the single-dose bioavailability study AAI-US-233. In that study, a single dose of Modified-Release Minocycline HCl Tablets, 135 mg, yielded a mean AUC of 41.2 $\mu\text{g}\times\text{hr}/\text{mL}$ and mean C_{max} of 1.83 $\mu\text{g}/\text{mL}$. The dose-adjusted results for Minocin Capsules, 100 mg, in that study were a mean AUC of 48.2 $\mu\text{g}\times\text{hr}/\text{mL}$ and a mean C_{max} of 2.24 $\mu\text{g}/\text{mL}$. The respective mean values of T_{max} after a single dose were 3.85 hours and 2.92 hours. The ratio of geometric means of AUC and C_{max} in the single-dose study were 86% and 82%, respectively. Comparison of the results from the current study with Study AAI-US-233 are summarized below. It appears that the single-dose PK results for these products are consistent with the findings of Period 1 in the present repeat-dose study in showing that the new minocycline formulation is less bioavailable and more slowly absorbed than the marketed product.

Current Study: Period 1		
	Test	Reference
C_{max}	2.20	3.45
AUC_{0-24}	28.40	54.10
T_{max}	3.62	1.96
Current Study: Period 2		
C_{max}	3.07	2.38
AUC_{0-24}	38.30	38.60
T_{max}	3.07	4.04
Study AAI-US-233		
C_{max}	1.83	2.24
AUC_{0-24}	41.2	48.2
T_{max}	3.85	2.92

The sponsor was also asked to explain how the study can be qualified as a steady state study as the data reveals that trough level of minocycline was still increasing following Day 7. According to the sponsor, the study design was an outpatient study until Day 6 when the study medication was administered in a fasting state during inpatient confinement. Twenty-four hours later, Day 7 trough levels were obtained. Therefore, it

would not be unexpected that steady state trough levels obtained on Day 4, 5, and 6 (fed state) might be slightly lower than on Day 7 (fasting conditions) because the AUC under fasting conditions is slightly greater in the fed state.

The lowest exposures which yielded adverse effects in the repeat-dose primate toxicology studies were on the order of 15 µg/mL for 4 weeks and 7 µg/mL for 13 weeks. These exposures are well above the levels observed in this study. The results showed a statistically significant effect indicating that the trough plasma concentrations were increasing between Day 5 and Day 7 for both treatments and in both periods. The most commonly observed adverse events in this study were headache, fatigue, somnolence, dizziness, and nausea. These adverse events were observed at the levels expected for the dose range of minocycline administered in this study (approximately 2 to 3 mg/kg/day), as indicated in current minocycline labeling.

Comments: *While the sponsor's explanation for sequence effect and non-achievement of steady state of trough levels are satisfactory to some extent, it does not satisfy the questions to their entirety. However, given that minocycline is a well known molecule and period 1 data is consistent with single dose data, it is not unreasonable to state that the new formulation is absorbed at a relatively slower rate and yields a lower dose adjusted systemic exposure than commercially available Minocin Capsules.*

One of the purposes of an in vivo BA study for which an extended release claim is made is to determine that the drug product's steady-state performance is comparable to a currently marketed immediate release or extended release drug product that contains the same active drug ingredient or therapeutic moiety. However, the steady state performance (exposure) of the proposed 135 mg qd Solodyn product is not comparable to that of currently approved bid 100 mg Minocin capsules at the dose adjusted level. Therefore, recommendation in terms of switchability between 135 mg proposed Solodyn qd and 100 mg Minocin capsules bid has to be based on clinical efficacy and safety data.

Literature reports that the minimum inhibitory concentration (MIC) for MINOCYCLINE is less than 4 mcg/mL. Intermediate sensitivity is defined as an MIC of 4 to 16 mcg/mL (agar dilution or broth dilution) and 4 to 12.5 mcg/mL (tube dilution). For intermediate sensitivity, organisms should be susceptible if high doses are used or if the infection resides in tissues and fluids in which high antibiotic levels are attained. The organism is considered resistant to MINOCYCLINE if the MIC is greater than 16 mcg/mL (agar dilution or broth dilution) or greater than 12.5 mcg/mL (tube dilution). The elimination phase (last 12 hours of the 24-hr cycle) of minocycline from the proposed formulation is not same compared to two Minocin tablets taken at 12 hours interval (Figure 2). The clinical relevance of this difference in terms of efficacy as well as the potential for developing resistant. Organisms e should be considered by the reviewing microbiologist.

An Open-Label Phase 1 Study to Examine the Effects of Minocycline on Low-Dose Ethinyl Estradiol Contraceptive Therapy

Objective: The primary objective of the study was to determine the effect, if any, that a modified release minocycline has on ethinyl estradiol by evaluating naïve and post minocycline samples from women using low-dose contraceptive therapy containing no more than 20 µg of ethinyl estradiol. The secondary objectives of the study were to study the effects of modified-release minocycline on progestinic steroids and on FSH and LH

Overall Study Design: This was a multicenter, 2-period study of the interaction of a new modified-release minocycline with low-dose contraceptive therapy. The mean age of subjects was 29.0 years, with a range of 16 years to 47 years. Overall, 73.3% of the subjects were White, 13.3% were Black, 10.0% were Asian/Pacific Islander, and 3.3% were Hispanic. Prior to the study all subjects were receiving hormonal contraceptives containing progestogens and estrogens in a fixed combination. The contraceptive formulations used by the subjects in this study were a combination of ethinyl estradiol and one of the following progestogens: etonogestrel (11 subjects), norelgestromin (10 subjects), levonorgestrel (6 subjects), or norethindrone (2 subjects). At screening, subjects were asked to indicate the date of their last menstrual period. Period 1 of the study began on Day 6 (\pm 1 day) of the next monthly cycle following screening, with the sixth day following the start of menstrual flow considered to be Day 1 of Period 1. During Period 1, subjects did not receive minocycline therapy, but continued to take their regular contraceptive therapy. Blood was drawn at 0, 6, and 12 hours of Study Day 1 and then once daily at the same time as the 0 hour blood draw every day up to Study Day 11 in order to establish minocycline-naïve levels of estradiol, progestinic steroids, FSH, and LH during each subject's cycle. Period 2 of the study began approximately 28 days from Day 1 of treatment Period 1. The first day of Period 2 was Day 6 (\pm 1 day) of the subject's next monthly cycle, as defined above. On the first day of Period 2, subjects returned to the clinic to receive their first dose of minocycline to be administered once daily (QD). Subjects continued to take their regular contraceptive therapy and took a daily dose of minocycline 1 mg/kg for 7 days. Subjects were advised not to eat grapefruit or drink grapefruit juice during the minocycline phase of the study. Subjects took the first dose of study drug in the clinic and took the bottle of study drug home when they left the clinic so that they could continue daily dosing. Blood was drawn at 0, 6, and 12 hours of Study Day 1 and then once daily at the same time as the 0-hour blood draw every day up to Study Day 11 to establish estradiol, progestinic steroids, FSH, and LH and minocycline levels.

Treatment Assignment: Each subject received a daily dose of 1 mg/kg minocycline administered as a caplet containing 45 mg, 90 mg, or 135 mg minocycline. Caplet strength was selected according to the body weight of the subject as shown below:

Weight (lb)	Weight (kg)	Caplet Combination (mg)	Actual Dose Range (mg/kg)
99 – 131	45.00 – 59.54	45	1.00 – 0.76
132 – 199	60.00 – 90.45	90	1.50 – 1.00
200 – 300	90.91 – 136.36	135	1.48 – 0.99

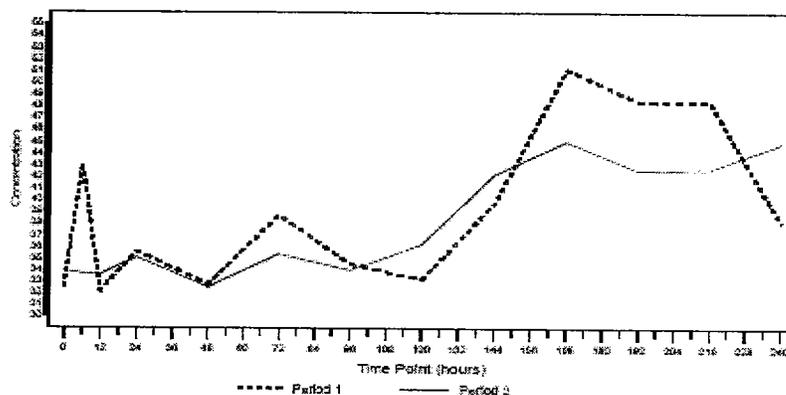
Contraceptive Therapy

Hormonal Contraceptive Therapy: Low-dose oral and patch contraceptives were allowed during the study. Low dose contraceptives are defined as those contraceptives delivering no more than 20 µg ethinyl estradiol (ie, Ortho Evra, Mircette, Alesse, Loestrin Fe 1/20, Levlite). Subjects were asked to take their contraceptive therapy as prescribed by their physician.

Hormonal Assessments

Primary Endpoint – Plasma Concentration of Ethinyl Estradiol: Mean plasma concentrations of ethinyl estradiol over time before treatment with minocycline (Period 1) and in the same subjects during and after 7 days of treatment with minocycline 1 mg/kg (Period 2) are compared in Figure 1. Summary statistics for ethinyl estradiol plasma levels over time during Period 1 and Period 2 are displayed in Table 1.

Figure 1: Time Course of Mean Ethinyl Estradiol Plasma Concentration (pg/mL) During Period 1 (Minocycline Naïve) and Period 2 (Post-Treatment with Minocycline)



In both Period 1 and Period 2, the mean plasma concentration of ethinyl estradiol increased gradually from the start of the contraceptive cycle through 168 hours (Day 7). The maximum mean value of plasma ethinyl estradiol concentration, achieved at Day 7 (Hour 168) for both periods, was 51.1 ± 10.0 pg/mL for Period 1 and 45.0 ± 9.5 pg/mL

for Period 2. Pharmacokinetic parameters for the Day 1 plasma concentration of estradiol during Period 1 and Period 2 are displayed in Table 1.

Table 1: Summary of Ethinyl Estradiol Pharmacokinetics During Period 1 (Minocycline Naive) and Period 2 (Post-treatment with Minocycline)

Pharmacokinetic Parameters	Day 1	
	Period 1 (N = 26; Mean ± SE)	Period 2 (N = 27; Mean ± SE)
AUC ₀₋₂₄ (pg×h/mL)	855 ± 218	746 ± 197
C _{max} (pg/mL)	57.9 ± 14.9	41.7 ± 9.5
	Day 7	
	Period 1 (Mean ± SE)	Period 2 (Mean ± SE)
C _{max} (pg/mL)	51.1 ± 10.0 pg/mL	45.0 ± 9.5

The concentration data and time course plots from individual subjects showed great variability from one subject to another, both with regard to the range of plasma concentrations and the time of highest concentration. Individual C_{max} values during Period 1 ranged from 0 to 333 pg/mL, with a median of 27.4 pg/mL. Individual C_{max} values during Period 2 ranged from 0 to 216 pg/mL with a median of 30.0 pg/mL.

Secondary Endpoints: Plasma Concentrations of Progestinic Steroids, Follicle Stimulating Hormone, and Luteinizing Hormone Progestinic Hormones

Etonogestrel: Etonogestrel concentrations (N = 11) increased gradually over the observation period. During Period 1, mean plasma concentrations increased from 0.47 at Hour 0 to a peak value of 1.99 ng/mL at Hour 192 (Day 8). During Period 2, mean plasma concentrations increased from 1.12 ng/mL at Hour 0 to 2.22 ng/mL at Hour 240 (Day 10). Comparison of the mean levels on each sampling point on both periods demonstrates that etonogestrel concentrations were higher in period 2 compared to period 1.

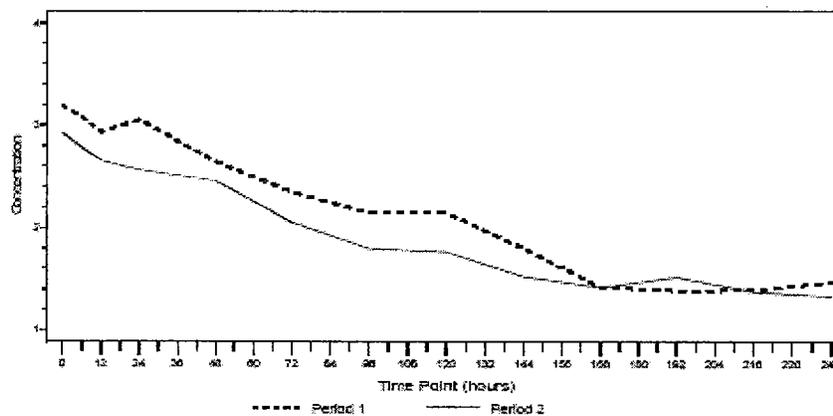
Levonorgestrel: During Period 1, mean levonorgestrel levels (N = 6) peaked to 1150 pg/mL at Hour 6, declined to 729 pg/mL at Hour 24 and then rose again, reaching a second peak of 1500 pg/ml at Hour 240 (Day 10). During Period 2, mean levonorgestrel levels showed a pattern similar to that seen in Period 1 up until Hour 120: hormone concentrations peaked at 960 pg/ml at Hour 6, fell to 681 pg/mL at Hour 24, and then began a slow increase which continued to the end of the observation period.

Norethindrone: Compared to other progestinic hormones, effect of minocycline on norethindrone is highly variable though only 2 subjects received ethinyl estradiol in combination with norethindrone. Comparison of mean norethindrone levels of 2 periods shows both increase and decrease of norethindrone levels at period 2 compared to period 1.

Norelgestromin: During both periods, mean plasma concentrations of norelgestromin (N = 10) increased gradually to maximum mean concentrations of 1.27 ng/mL (Hour 192; Day 8) during Period 1 and 1.18 ng/mL (Hour 144; Day 6) during Period 2. The levels of norelgestromin in two periods remain comparable.

Follicle Stimulating Hormone: Mean plasma concentrations of FSH over time before treatment with minocycline (Period 1) and in the same subjects during and after 7 days of treatment with minocycline 1 mg/kg (Period 2) are compared in Figure 2.

Figure 2: Time Course of FSH Plasma Concentration (mIU/mL) During Period 1 (Minocycline Naïve) and Period 2 (Post-Treatment with Minocycline)

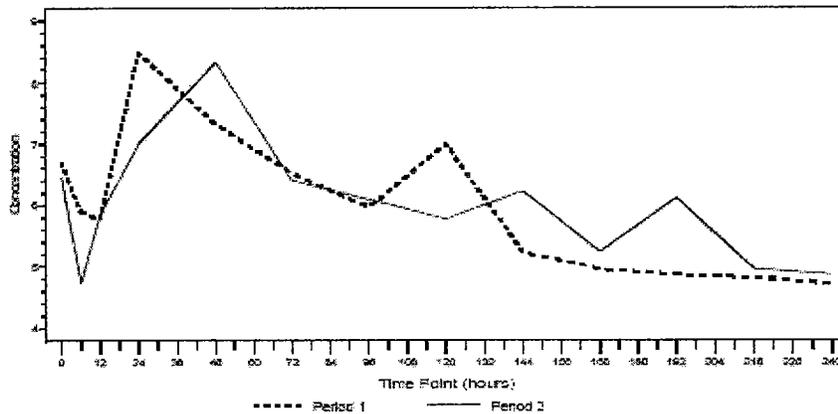


During both periods, the plasma concentrations of FSH decreased over time from Hour 24 to Hour 240. FSH plasma concentrations during Period 2 were statistically significantly less than those during Period 1 ($P = 0.0130$), an effect opposite to that expected if minocycline decreased the estrogen or progestogen plasma concentrations. There was no evidence of an increase in FSH above normal basal levels in any subject in either period. The greatest observed concentration was 7.61 mIU/mL.

Luteinizing Hormone: Mean plasma concentrations of LH over time before treatment with minocycline (Period 1) and in the same subjects during and after 7 days of treatment with minocycline 1 mg/kg (Period 2) are compared in Figure 3. During both periods, the plasma concentrations of LH showed an early peak at the end of Hour 24 (Period 1) or Hour 48 (Period 2) and then decreased.

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Figure 3: Time Course of LH Plasma Concentration (mIU/mL) During Period 1 (Minocycline Naïve) and Period 2 (Post-Treatment with Minocycline)



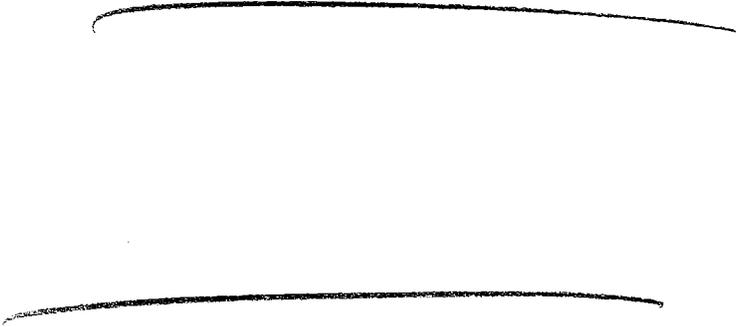
Discussion: Oral contraceptives maintain plasma levels of estrogen and progestinic hormones over the course of the menstrual cycle, thereby suppressing the secretion of FSH and LH and preventing follicular development and ovulation. Inspection of the mean plots of plasma ethinyl estradiol concentrations versus time, together with review of the results of the statistical analysis of the data apparently does not show any evidence of an antagonistic effect of minocycline on blood estradiol levels over the 7-day course of minocycline treatment. However, review of individual subjects data reveals that in at least two subjects (2006 and 4011) estradiol levels were low (during coadministration with minocycline) with corresponding higher levels of FSH following administration of OC with minocycline in period 2 in comparison with period 1 (without minocycline) (see below). The clinical relevance of these lower levels of estradiol associated with higher levels of FSH in terms of contraceptive failure needs to be evaluated .

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X Trade Secret / Confidential

 Draft Labeling

 Deliberative Process



Overall, in the present study, out of 29 women receiving low-dose contraceptive therapy, two subjects (2/29 ~ 7%) showed evidence that minocycline suppressed estradiol levels through cycle Day 15 during coadministration. While disposition of OC components can be variable among individuals, coadministration of OC with drug like minocycline with proven effect of fetal abnormality should be given special consideration to rule out any chance of OC failure. In terms of progestin components of OC, as different subjects received different forms of progestins, drawing inference on effect of minocycline on general class of progestins is not feasible. Nonetheless, based on results of this study, an interaction between estradiol and minocycline can not be ruled out. Therefore, the sponsor's proposed labeling language "*In a multi-center study to evaluate the effect of SOLODYN on low dose oral contraceptives, hormone levels over one menstrual cycle with and without SOLODYN 1 mg/kg once-daily were measured. The study found no evidence of drug-related effects on plasma concentrations of estradiol, FSH, LH, or progestinic hormones. There were no observations of minocycline-related changes in estradiol plasma concentrations, of breakthrough bleeding, or of contraceptive failure*" can not be supported. Future appropriately designed study can address the specific nature (extent) of interaction so that it can be addressed in the label.

According to the sponsor, there were no instances of breakthrough bleeding or contraceptive failure and minocycline was well tolerated in the subject population studied.

Comments:

- *Study design was not adequate to support any labeling language in terms of blood sampling time. Blood was drawn at 0, 6, 12 and 24 hrs of Study Day 1 (Periods 1 and 2): These sampling times are insufficient to capture the exposure of EE. C_{max} values of EE from the approved combination OCs are usually around 1-2 (mean) with a range of 1-4 hours. In general, AUC₂₄ and AUC_{inf} are usually measured in a single-dose OC study and we generally recommend more frequent sampling (e.g., Loestrin 24: at pre-dose, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 30, 36, 48, and 60 hours post-dose).*
- *AUCs of EE at Day 1 of Period 1 and Period 2 were compared: This design does not address the effect of multiple-dose of minocycline on EE.*
- *C_{max} of EE from Day 1 and Day 7 were compared (see Table 1): As I indicated in the first bullet, the blood sampling times do not adequately capture the C_{max} of EE. Therefore, there is no data to compare C_{max} before and after minocycline treatment. In addition, there were some women who were on Ortho Evra (patch). The C_{max} of EE from Ortho Evra is much lower compared to EE from OCs.*
- *Figure 1 is misleading. Blood samples for EE determination were collected at pre-dose, 6, and 12 hours of Day 1, then once daily at the same time as the 0 hour blood draw every day up to Study Day 11. However, 0 hour blood draw every day up to Day 11 cannot be considered as C_{trough} since it is not known exactly when these women took their daily pills.*
- *Individual data (from 2 patients does not support complete safety)*
- *C_{max} values in Period 1 and 2 on Day 1 for estradiol does not match the description and profiles (Table 1 and Figure 1).*
- *Progesterone levels were not monitored*

Until a properly designed drug drug interaction study with oral contraceptives is undertaken with results that can be interpret, the suggested labeling language is “In a multi-center study to evaluate the effect of SOLODYN on low dose oral contraceptives, hormone levels over one menstrual cycle with and without SOLODYN 1 mg/kg once-daily were measured. Based on the results, minocycline-related changes in estradiol, progestinic hormone, FSH, and L, plasma levels can not be ruled out. To avoid contraceptive failure, females are advised to use a second form of contraceptive during treatment with minocycline”.

An Evaluation of the Anti-Microbial Effects *in vivo* of Minocycline Tablets in Humans

Objectives: The objective of the study was to determine the relative antimicrobial effects of a new modified-release formulation of minocycline by measuring its inhibitory action against *P acne* counts *in vivo*.

Methodology: This was an open label, 16-week, uncontrolled, single-center study of a new modified-release formulation of minocycline administered in a 1 mg/kg daily dosing regimen, in subjects with moderate-to-severe facial acne. The study consisted of a 12-week treatment phase and a 4-week follow-up phase. After Screening and Baseline evaluations, subjects returned to the clinic at Day 28, Day 56, Day 84 (± 2 day margin), and at Day 112 (± 3 day margin). The primary efficacy endpoint was the change from Baseline to Day 84 in log *P acnes* counts. The secondary efficacy endpoints included the change from Baseline to Days 28 and 56 in log *P acnes* counts.

Results: According to the sponsor, the results of the *P acnes* cultures/counts in this study were inconsistent and did not correlate with clinical improvement. The therapeutic outcomes showed no evidence of association with the *P acnes* culture results.

Comments: *In view of the inconsistencies in the results described above, the study was not reviewed in detail.*

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An Open-Label Phase 1 Study to Examine the Effects of Minocycline on Spermatogenesis in Human Males

Objectives: The primary objective of the study was to investigate the effect of minocycline on sperm count, motility and morphology. The secondary objective was to investigate the effect of minocycline on levels of FSH, LH, and testosterone.

Methodology: In this Phase 1, open-label study, normal healthy male volunteers (N=30) with normal Baseline semen analysis as defined by WHO criteria were administered 1 mg/kg of modified-release minocycline once daily for 84 days and were followed for an additional 72 days. Modified-release minocycline is available as 45 mg, 90 mg, and 135 mg tablets. Each subject received 1 caplet per day. The strength of caplet administered to each subject was determined from the subject's weight at Baseline, where the subject received the caplet that provided the closest possible dose to the 1 mg/kg targeted dose. Safety laboratory testing performed at Screening, prior to dosing on Day 1 and repeated on Day 28, and at the post-study follow-up visit on Day 156 included hematology and serum chemistry. A full urinalysis panel was performed at Screening and prior to dosing on Day 1. Endocrinology labs (follicle stimulating hormone [FSH], luteinizing hormone [LH], and total serum testosterone) were performed on Day 1 and were to be repeated on Days 28, 56, and 84, and at the post-study follow-up visit on Day 156. Semen analyses (volume of ejaculation, pH, total sperm count, percent motility, morphology [percent normal], white blood cells [WBC], and red blood cells [RBC]) were performed at Screening (2 screening samples required) and were to be repeated on Day 28 (± 2 days), Day 56 (± 2 days), Day 84 (± 2 days), and Day 156 (± 7 days).

Results: A total of 29 subjects were enrolled in the study. Due to the early termination of the study as a result of Hurricane Katrina, data were not available for 3 of the 29 subjects enrolled in the study. For subjects who completed the Day 84 visit and the Day 156 follow-up visit, the mean values at the time of the Day 156 follow-up visit were sperm count $148.8 \times 10^6/\text{mL}$ (range: 10.8 to 408.0); percent motility 57.2% (range: 37.0% to 64.0%); and percent normal morphology 30.0% (range: 8.0% to 57.0%). The mean change from Baseline in sperm count was $-66.8 \times 10^6/\text{mL}$ (range: -263.2 to 71.7); the mean change in forward motility was -12.0% (range: -43.6% to 4.0%); and the mean change in percent normal morphology was -2.8% (range: -23.0% to 29.0%). The reported mean values were within normal range for sperm count ($\geq 40 \times 10^6/\text{mL}$), percent motility ($\geq 15\%$), percent normal morphology ($\geq 15\%$), as defined by WHO criteria. All parameters of sperm function (count, mobility and morphology) for 11 of 14 (78.6%) subjects who remained in the study through Day 156 were within normal range. *Two subjects showed abnormally low sperm counts of which one also showed low percent motility. A third subject showed low percent normal morphology, but normal count and motility.*

Comments:

According to the sponsor, based on the review of an outside panel of male reproductive specialists, the data for this study are inconclusive because of methodology and study design issues.

Therefore, evidence of minocycline having any effect on spermatogenesis remains unclear until further investigation.

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4.2.1 Office of Clinical Pharmacology and Biopharmaceutics

5 New Drug Application Filing and Review Form

5.1.1.1.1 General Information About the Submission

	Information		Information
NDA Number	150-808	Brand Name	Solodyn
OCPB Division (I, II, III)	III	Generic Name	Minocycline HCl
Medical Division	540	Drug Class	Antibiotic
OCPB Reviewer	Tapash K. Ghosh	Indication(s)	Moderate to severe acne
OCPB Team Leader	Edward D. Bashaw	Dosage Form	Modified Release Tablets, 45 mg, 90 mg, 135 mg
		Dosing Regimen	1 caplet/day
Date of Submission	6/30/05	Route of Administration	Oral
Estimated Due Date of OCPB Review	1/15/06	Sponsor	Medicis
PDUFA Due Date	4/30/06	Priority Classification	3S
	2/15/06		
5.1.1.2	Division Due Date		

5.1.1.2.1.1.1 Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
5.2 Healthy Volunteers-				
single dose:				
multiple dose:	X	1		
5.2.1 Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	X	1		
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:	X			
(IVVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4		
5.2.1.1.1.1				
5.2.1.1.1.2	Filability and QBR comments			
5.2.1.2	"X" if yes	5.2.1.2.1.1.1.1.1 Comments		
5.2.1.3	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
5.2.1.4		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
5.2.1.5				
QBR questions (key issues to be considered)	Can the dosage form be defined as "Modified Release" caplet?			
Other comments or information not included above				
Primary reviewer Signature and Date	Tapash Ghosh			
Secondary reviewer Signature and Date	Dennis Bashaw			

CC: _____, HFD-850 (Electronic Entry or Lee), HFD-540(Curtis), HFD-880(TL, DD, DDD), CDR (B. Murphy)

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