

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**201922Orig1s000**

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

## Clinical Pharmacology Review Addendum

---

NDA #: 201922  
Submission Date(s): February 04, 2011  
Brand Name: Ximino  
Generic Name: Minocycline hydrochloride extended release capsules  
Dosage Form: Extended release capsules  
Dosage Strength: 45 mg, 67.5 mg, 90 mg, 112.5 mg and 135 mg  
Reviewer: Chinmay Shukla, Ph.D.  
Team Leader: Doanh Tran, Ph.D.  
OCP Division: DCP-3  
OND Division: Division of Dermatology and Dental Products  
Sponsor: Ranbaxy Laboratories Limited  
Relevant IND(s): 107,472  
Submission Type: New Drug Application Amendment  
Indication: Treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older

---

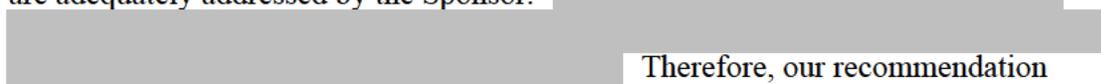
### Background:

(b) (4), (b) (5)



### Recommendation:

The original Clinical Pharmacology review of this NDA (DARRTS dated October 04, 2011) recommended that “the application is acceptable provided the labeling comments are adequately addressed by the Sponsor.” (b) (4), (b) (5)



Therefore, our recommendation remains the same.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

CHINMAY SHUKLA  
06/19/2012

DOANH C TRAN  
06/19/2012

## Clinical Pharmacology Review

---

NDA #: 201922  
Submission Date(s): March 22, 2012  
Brand Name: Ximino  
Generic Name: Minocycline hydrochloride extended release capsules  
Dosage Form: Extended release capsules  
Dosage Strength: 45 mg, 67.5 mg, 90 mg, 112.5 mg and 135 mg  
Reviewer: Chinmay Shukla, Ph.D.  
Team Leader: Doanh Tran, Ph.D.  
OCP Division: DCP-3  
OND Division: Division of Dermatology and Dental Products  
Sponsor: Ranbaxy Laboratories Limited  
Relevant IND(s): 107,472  
Submission Type: New Drug Application Amendment  
Indication: Treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older

---

**Background:** The Division of Dermatology and Dental Products (DDDP) sent an information request (IR) to Ranbaxy on December 14, 2011, asking the applicant to clarify the extent of involvement of the firm's Paonta Sahib and Dewas, India, facilities for NDA 201922 submission (see communication in DARRTS dated 12/14/2011).

(b) (4), (b) (5)

The Sponsor responded to the IR letter on December 27, 2011 and the information provided has been reviewed previously (see reviews in DARRTS by Dr. Yichun Sun dated 01/20/2012 and Dr. Chinmay Shukla dated 01/23/2012).

(b) (4), (b) (5)

(b) (4), (b) (5)

3 Pages Have Been Withheld In Full As b4 and b5 Immediately Following This Page

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

CHINMAY SHUKLA  
06/11/2012

DOANH C TRAN  
06/11/2012

## Clinical Pharmacology Review Addendum

---

NDA #:	201922
Submission Date(s):	February 04, 2011; December 27, 2011
Brand Name:	Ximino
Generic Name:	Minocycline hydrochloride extended release capsules
Dosage Form:	Extended release capsules
Dosage Strength:	45 mg, 67.5 mg, 90 mg, 112.5 mg and 135 mg
Reviewer:	Chinmay Shukla, Ph.D.
Team Leader:	Doanh Tran, Ph.D.
OCP Division:	DCP-3
OND Division:	Division of Dermatology and Dental Products
Sponsor:	Ranbaxy Laboratories Limited
Relevant IND(s):	107,472
Submission Type:	New Drug Application Amendment
Indication:	Treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older

---

**Background:** Concerns of potential invocation of Application Integrity Policy (AIP) on NDA 201922 were raised because 2 of the applicant's facilities (Dewas and Paonta Sahib located in India) are on the AIP list. As a result an IR letter was sent on December 14, 2011 asking the applicant to clarify the extent of involvement of the AIP sites for NDA 201922 submission (see communication in DARRTS dated 12/14/2011).

The Sponsor responded to the IR letter on December 27, 2011 and the information provided has been reviewed and findings are summarized below.

**Review Findings:**

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[Redacted] (b) (4)

[Redacted]

**Conclusion:** [Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted], from a Clinical Pharmacology perspective the Application Integrity Policy would not apply to NDA 201922.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

CHINMAY SHUKLA  
01/23/2012

DOANH C TRAN  
01/23/2012

## Clinical Pharmacology Review

---

NDA #:	201922
Submission Date:	February 04, 2011
Brand Name:	Pending
Generic Name:	Minocycline hydrochloride extended release capsules
Dosage Form:	Extended release capsules
Dosage Strength:	45 mg, 67.5 mg, 90 mg, 112.5 mg and 135 mg
Reviewer:	Chinmay Shukla, Ph.D.
Team Leader:	Doanh Tran, Ph.D.
OCP Division:	DCP-3
OND Division:	Division of Dermatology and Dental Products
Sponsor:	Ranbaxy Laboratories Limited
Relevant IND(s):	107,472
Submission Type:	New-submission
Indication:	Treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older

---

### Table of Contents

1. Executive Summary	*	*	*	*	*	*	*	*	1
1.1 Recommendation	*	*	*	*	*	*	*	*	2
1.2 Post-Marketing Requirements/Commitments				*	*	*	*	*	2
1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings*									2
2. Question Based Review	*	*	*	*	*	*	*	*	5
2.1 General Attributes of the Drug		*	*	*	*	*	*	*	5
2.2 General Clinical Pharmacology	*	*	*	*	*	*	*	*	10
2.3 Intrinsic Factors	*	*	*	*	*	*	*	*	19
2.4 Extrinsic Factors	*	*	*	*	*	*	*	*	21
2.5 General Biopharmaceutics		*	*	*	*	*	*	*	21
2.6 Analytical Section	*	*	*	*	*	*	*	*	22
3. Detailed Labeling Recommendations				*	*	*	*	*	25
4. Individual Study Review	*	*	*	*	*	*	*	*	26
5. Appendix	*	*	*	*	*	*	*	*	34
5.1 Sponsor submitted package insert*				*	*	*	*	*	34
5.2 Effect of gender on minocycline HCl bioavailability (Study 3739)							*	*	35

### 1. Executive Summary

This is a new submission. The original NDA was submitted on May 10, 2010 and a refuse to file (RTF) decision was taken by the agency on July 16, 2010.

For this submission, the Sponsor has chosen a 505(b)(2) regulatory path and has submitted results of 2 pivotal Bioavailability (BA)/ Bioequivalence (BE) trials comparing the plasma concentrations obtained following minocycline HCl, 135 mg ER capsules with those obtained following administration of the listed drug, Solodyn® (minocycline

HCl, 135 mg ER tablets) under fasted (Trial# 3739) and fed (Trial# 3740) conditions in healthy adult subjects. These studies were conducted in a population representative of the United States population and included both male and female subjects. For the lower strengths (45, 67.5, 90, 112.5 mg) the Sponsor submitted a biowaiver request based on dissolution profile comparisons with the highest strength (135 mg).

In addition to the above, the Sponsor has also assessed the effect of food on the 135 mg dose of their minocycline HCl ER capsule (Trial# 3740) and evaluated dose proportionality between 45 mg and 135 mg dose of their ER capsule (Trial# 3739).

The results indicate that minocycline HCl, 135 mg ER capsules are bioequivalent to Solodyn<sup>®</sup> 135 mg ER tablets under fasted and fed conditions. The results of the biowaiver request for lower strengths (45, 67.5, 90, 112.5 mg) based on dissolution profile comparisons with the highest strength (135 mg) were reviewed by Dr. John Z. Duan (Biopharmaceutics reviewer). Dr. Duan concluded that the biowaiver request was acceptable and recommended approval of lower strengths provided the BE trials with the highest dose (135 mg) were deemed acceptable.

### **1.1 Recommendation**

From a Clinical Pharmacology Standpoint, the Sponsor has met the requirements under 21 CFR 320 and the application is acceptable provided the labeling comments are adequately addressed by the Sponsor.

### **1.2 Post-Marketing Requirements/ Commitments**

None.

### **1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings**

To support this NDA the Sponsor has completed 2 BA/BE trials only with their highest proposed strength (135 mg) and submitted a biowaiver request for lower strengths (45, 67.5, 90 and 112.5 mg) based on dissolution profile comparisons with the highest strength (135 mg).

#### **The 2 BA/BE trials were:**

- Trial# 3739 - Conducted under fasted conditions
- Trial# 3740 - Conducted under fed conditions

The results indicated that minocycline HCl 135 mg ER capsules were bioequivalent to Solodyn<sup>®</sup> 135 mg ER tablets under fasted and fed conditions as shown in Table 1 and Table 2, respectively.

**Table 1: Relative bioavailability analysis for minocycline under fasted conditions of Test: 1 minocycline HCl 135 mg ER capsule versus Reference: 1 Solodyn® 135 mg ER tablet**

Parameter	Geometric Mean (% CV)		90% C.I.	Ratio of Means
	Minocycline 135 mg ER Capsule	Solodyn 135 mg ER Tablet		
AUC <sub>0-t</sub> (ng*hr/mL)	13663.60 (30.27)	13681.66 (31.80)	92.94 % to 108.30%	100.32%
AUC <sub>0-inf</sub> (ng*hr/mL)	13873.69 (30.05)	13861.77 (31.51)	93.32% to 108.30%	100.53%
C <sub>max</sub> (ng/mL)	749.54 (37.11)	780.10 (38.85)	88.84% to 105.32%	96.73%

**Table 2: Relative bioavailability analysis for minocycline under fed conditions of Test: 1 minocycline HCl 135 mg ER capsule versus Reference: 1 Solodyn® 135 mg ER tablet**

Parameter	Geometric Mean (% CV)		90% C.I.	Ratio of Means
	Minocycline 135 mg ER Capsule	Solodyn 135 mg ER Tablet		
AUC <sub>0-t</sub> (ng*hr/mL)	13546.24 (21.91)	13229.22 (23.49)	93.89 % to 108.89%	101.11%
AUC <sub>0-inf</sub> (ng*hr/mL)	13850.54 (21.91)	13513.70 (23.40)	93.93% to 108.92%	101.15%
C <sub>max</sub> (ng/mL)	824.57 (24.12)	770.97 (25.75)	98.05% to 114.28%	105.85%

**Biowaiver of lower strengths:**

The Sponsor submitted a biowaiver request for lower strengths (45, 67.5, 90 and 112.5 mg) based on dissolution profile comparisons with the highest strength (135 mg). This was reviewed by Dr. John Z. Duan (Biopharmaceutics reviewer). Dr. Duan concluded that the biowaiver request was acceptable and recommended approval of lower strengths provided the BE trials with the highest dose (135 mg) are deemed acceptable (see review by Dr. John Z. Duan in DARRTS dated 08/31/2011).

**Additional studies:**

**Dose-proportionality (Part of trial # 3739):** Dose-proportionality of the 45 mg and 135 mg ER capsules was evaluated as part of BE trial 3739. The results of dose proportionality evaluation indicated that AUC and C<sub>max</sub> of minocycline increased in a dose proportional manner following oral administration of 45 mg and 135 mg ER capsules. The ratio of dose normalized (per mg) geometric mean AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub>, are shown in Table 3 below.

**Table 3: Results of dose proportionality between 45 mg and 135 mg dose of minocycline HCl ER capsules**

Dose normalized PK parameter (per mg)	45 mg dose (A)	135 mg dose (B)	Ratio (A/B)
AUC <sub>0-t</sub> (hr*ng/mL)	101.56	101.21	1.00
AUC <sub>0-inf</sub> (hr*ng/mL)	105.10	102.68	1.02
C <sub>max</sub> (ng/mL)	6.19	5.55	1.12

**Effects of food (Part of trial # 3740):** The effect of food on minocycline HCl 135 mg ER capsule was evaluated as part of trial# 3740. The results indicated that comparing minocycline HCl 135 mg ER capsule under fed versus fasted conditions showed that the 90% confidence interval (CI) of the ratio of geometric means of AUC<sub>0-t</sub> and AUC<sub>0-∞</sub> were between 80 - 125 %. However, the 90% CI of the ratio of the geometric mean of C<sub>max</sub> was 118.22 -137.61 % which was outside the no effect range of 80 -125% (Table 4).

**Table 4: Relative bioavailability analysis for minocycline administered as minocycline HCl 135 mg ER capsule under fed conditions versus fasting conditions**

Parameter	Minocycline 135 mg ER Capsule Geometric Mean (% CV)		90% C.I.	Ratio of Means
	Fasting	Fed		
AUC <sub>0-t</sub> (ng*hr/mL)	11942.26 (31.72)	13546.24 (21.91)	104.58 % to 121.15%	112.56%
AUC <sub>0-inf</sub> (ng*hr/mL)	12196.75 (31.38)	13850.54 (21.91)	104.72% to 121.28%	112.70%
C <sub>max</sub> (ng/mL)	640.28 (36.64)	824.57 (24.12)	118.22% to 137.61%	127.55%

This increase in C<sub>max</sub> with food is unlikely to result in any safety issues because based on the original approval of Solodyn<sup>®</sup> with only 3 strengths, the actual dose with the approved Solodyn<sup>®</sup> ranged from 1.48 to 0.76 mg/kg while the proposed dose for minocycline ER capsule (5 different strengths) will range from 1.21 to 0.82 mg/kg. The 28% increase in C<sub>max</sub> due to food would still be within the range determined to be safe and effective in the original Solodyn<sup>®</sup> approval. Hence, no dose adjustment with food will be required.

**In-vitro alcohol dose dumping:** This was reviewed by Dr. John Z. Duan (Biopharmaceutics reviewer) and he concluded that minocycline HCl ER capsules did not show dose dumping potential due to alcohol in-vitro (see review by Dr. John Z. Duan in DARRTS dated 08/31/2011).

**DSI Inspection:** DSI inspection was conducted for Trials # 3739 and # 3740 and the clinical and analytical data generated were found to be acceptable for review for both the trials (See review in DARRTS dated 09/02/2011 by Dr. Charles Bonapace).

***Clinical Pharmacology Briefing:*** An Optional Intra-Division Level Clinical Pharmacology briefing was held on September 20, 2011 with the following in attendance: Chinmay Shukla, Doanh Tran, Hae-Young Ahn and E. Dennis Bashaw.

## **2. Question Based Review**

### **2.1 General Attributes of the Drug**

#### ***2.1.1 Regulatory history***

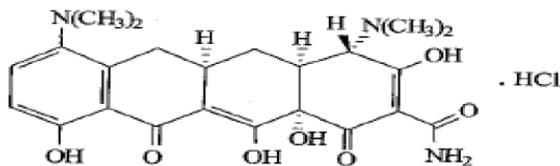
This is a new submission. The original NDA was submitted on May 10, 2010 and a refuse to file (RTF) decision was taken by the agency on July 16, 2010 because the application was deemed incomplete due to the fact that the Sponsor had conducted the pivotal BA/BE trials (Trial# 1974/09 and # 1975/09) in a population of South Asians and not in the population representative of the United States population. Furthermore, these BE studies were conducted only in male subjects when the Sponsor was seeking indication that affects both male and female patients. In addition, minocycline dose is 1 mg/kg. The original submission provided information to support only 135 mg dose and this would not provide for an appropriate dose for patients weighing less than 200 pounds (91 kg) (see communication in DARRTS).

With the original NDA, the Sponsor was seeking approval for minocycline HCl, 135 mg extended release (ER) capsules for the same indication that is approved for Solodyn<sup>®</sup> (minocycline HCl, 135 mg ER tablets) (Medics, the Dermatology Company) (NDA 050808) on the basis of demonstration similar systemic BA. Solodyn<sup>®</sup> 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.

With this new submission the Sponsor has proposed to include additional strengths of minocycline HCl ER capsules. Particularly in addition to the originally proposed 135 mg strength, the other strengths proposed to be included are 45 mg, 67.5 mg, 90 mg and 112.5 mg.

#### ***2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation?***

**Drug substance and Formulation:** The chemical name of minocycline hydrochloride is 4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamide monohydrochloride and its molecular weight is 493.95. It is represented by C<sub>23</sub>H<sub>27</sub>N<sub>3</sub>O<sub>7</sub>·HCl, and has the following chemical structure as shown in Figure 1.



**Figure 1: Structure of Minocycline Hydrochloride**

Each minocycline HCl ER capsule consists of minitabs of different weight and quantity per capsule as shown below.

**Composition of Minocycline Extended Release Capsules 45 mg**

<b>Ingredients</b>	<b>Quantity /Capsule</b>
Minocycline Hydrochloride Extended Release Minitablets, 45 mg	1
EG (Size 0) capsule shell* - Opaque bluish green cap and opaque yellow body hard gelatin capsule (size 0) with 'RI18' imprinted on both cap and body in black ink.	1 No.

**Composition of Minocycline Extended Release Capsules 67.5 mg**

<b>Ingredients</b>	<b>Quantity /Capsule</b>
Minocycline Hydrochloride Extended Release Minitablets, 67.5 mg	1
EG (Size 0) capsule shell - Opaque bluish green cap and white body hard gelatin capsule (size 0) imprinted with 'RI92' on both cap and body in black ink	1 No.

**Composition of Minocycline Extended Release Capsules 90 mg**

<b>Ingredients</b>	<b>Quantity /Capsule</b>
Minocycline Hydrochloride Extended Release Minitablets, 45 mg	2
EG (Size 0) capsule shell* - Opaque light blue cap and body hard gelatin capsule (size 0) with 'RI19' imprinted on both cap and body in black ink.	1 No.

**Composition of Minocycline Extended Release Capsules 112.5 mg**

<b>Ingredients</b>	<b>Quantity /Capsule</b>
Minocycline Hydrochloride Extended Release Minitablets, 56.25 mg	2
EG (Size 0) capsule shell - Opaque light blue cap and white body hard gelatin capsule (size 0) imprinted with 'RI93' on both cap and body in black ink.	1 No.

**Composition of Minocycline Extended Release Capsules 135 mg**

<b>Ingredients</b>	<b>Quantity /Capsule</b>
Minocycline Hydrochloride Extended Release Minitablets, 45mg	3
EG (Size 0) capsule shell* - Opaque bluish green cap and opaque light blue body hard gelatin capsules (size 0) with 'RI20' imprinted on both cap and body in black ink	1 No.

\* The exhibit batches were manufactured using different color of capsule shells:

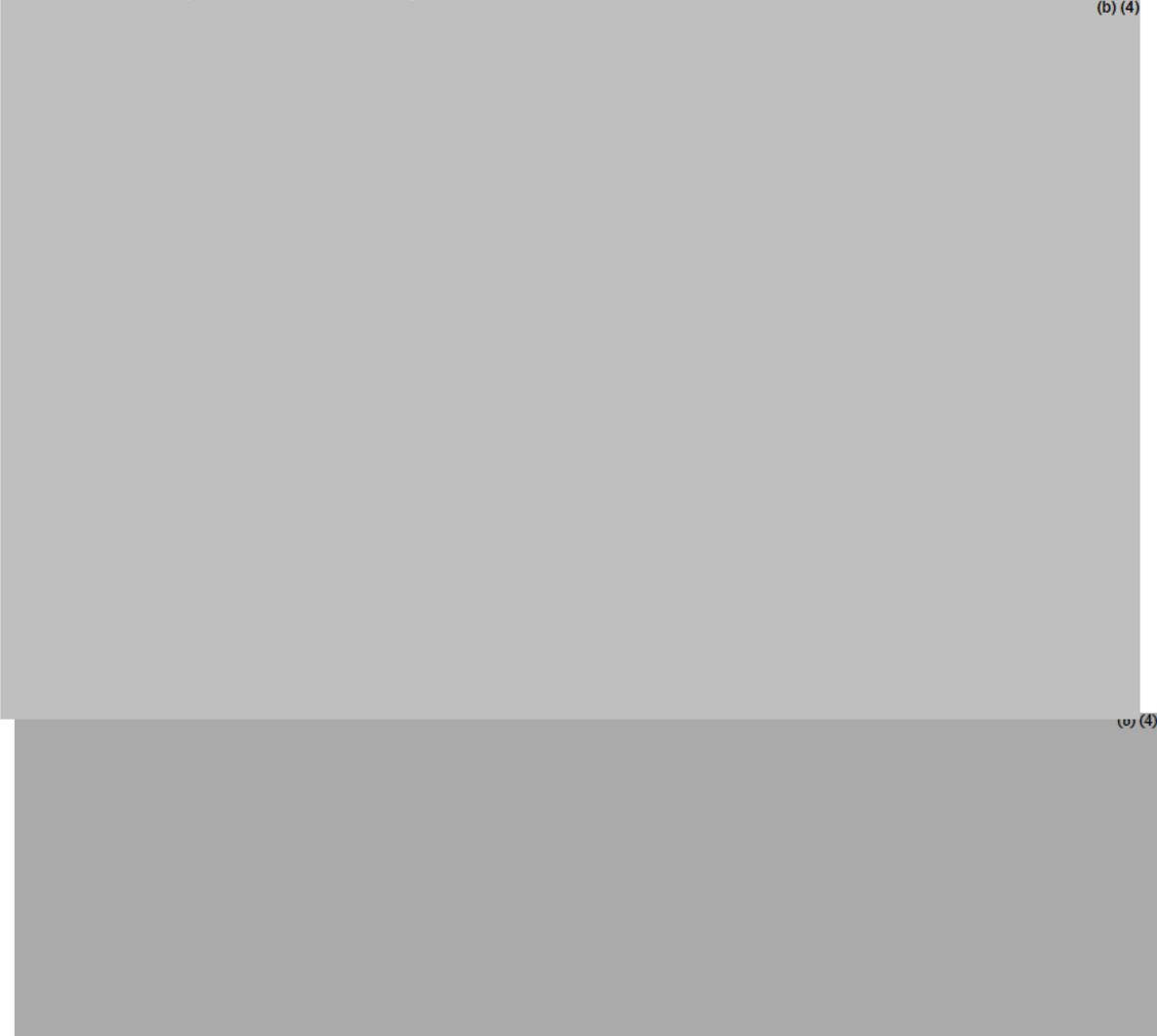
45 mg: *Opaque dark green cap and opaque yellow body*

90 mg: *Opaque light green cap and body.*

135 mg: *Opaque dark green cap and opaque light green body.*

The composition of minocycline ER minitabs is shown in Table 5 while the compendium and function of each ingredient is shown in Table 6. Table 7 shows the composition of minocycline ER capsules.

***Table 5: Composition of minocycline ER minitabs***



(b) (4)

(c) (4)

***Table 6: Compendium and function of each ingredient of minocycline ER minitabs***

(b) (4)



**Table 7: Composition of minocycline ER capsules**

**Composition of Minocycline Extended Release Capsules**

Ingredients	Quantity mg/ Capsule									
	45 mg	% w/w	67.5 mg	% w/w	90 mg	% w/w	112.5 mg	% w/w	135 mg	% w/w
(b) (4)										
Minocycline Hydrochloride USP equivalent to Minocycline <sup>1</sup>	(b) (4)									
(b) (4)										
(b) (4)										
Hypromellose (b) (4)										
(b) (4)										
Lactose Monohydrate <sup>2</sup>										
(b) (4)										
(b) (4)										
Magnesium Stearate										
Colloidal Silicon Dioxide										
<b>Total (Core Tablet)</b>										
<b>Film Coating</b>										
Opadr (b) (4) (Clear) <sup>(b)</sup>										
(b) (4)										
<b>Total (Coated Tablet)</b>	153.000	(b) (4)	229.500	(b) (4)	306.000		382.500	(b) (4)	459.000	(b) (4)
Empty Gelatin Capsule Shell	1	-	1	-	1	-	1	-	1	-



**2.1.3 What are the proposed mechanism of action and the therapeutic indications?**

**Mechanism of action:** Minocycline is a second-generation semi-synthetic derivative of tetracycline with a wide spectrum of antibacterial activity against gram-positive and gram-negative organisms. It exerts its action against susceptible organisms 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, however, the clinical significance of this activity against *P. acnes* in patients with acne vulgaris is not known.

Therapeutic indication: With this application, the Sponsor is seeking identical therapeutic indication as the listed drug Solodyn<sup>®</sup> (minocycline HCl ER tablets) (NDA 50808). Solodyn<sup>®</sup> 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.

#### ***2.1.4 What is the proposed route of administration and dosage?***

Proposed route of administration: Oral.

Proposed dosage: The recommended dosage is 1 mg/kg once daily for 12 weeks for the treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older. Table 8 below shows capsule strength and body weight to achieve approximately 1 mg/kg.

***Table 8: Dosing table for minocycline HCl ER capsules***

<b>Patient's Weight (lbs.)</b>	<b>Patient's Weight (kg)</b>	<b>Capsule Strength (mg)</b>	<b>Actual mg/kg Dose</b>
99 to 122	45 to 55	45	1 to 0.82
123 to 164	56 to 74	67.5	1.21 to 0.91
165 to 212	75 to 96	90	1.20 to 0.94
213 to 276	97 to 125	112.5	1.16 to 0.90
277 to 300	126 to 136	135	1.07 to 0.99

## **2.2 General Clinical Pharmacology**

### ***2.2.1 What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?***

To support this NDA (new submission), the Sponsor has completed 2 pivotal BA/BE trials with their highest proposed strength (135 mg) under fasting and fed conditions. No other clinical studies were conducted.

- Trial# 3739 - Conducted under fasted conditions
- Trial# 3740 - Conducted under fed conditions.

The original submission also contained 2 BA/BE trials:

- Trial# 1974/09 - Conducted under fasted conditions
- Trial# 1975/09 - Conducted under fed conditions

These studies were not considered adequate and a refuse to file decision was taken (see communication in DARRTS dated 07/16/2010). Hence these studies were not reviewed in this review cycle with the new submission.

For the lower strengths (45, 67.5, 90 and 112.5 mg), the Sponsor submitted a biowaiver request based on dissolution profile comparisons with the highest strength (135 mg). This was reviewed by Dr. John Z. Duan (Biopharmaceutics reviewer). Dr. Duan concluded

that the biowaiver request was acceptable and recommended approval of lower strengths provided the BE trials with the highest dose (135 mg) are deemed acceptable. These results will not be discussed further in this review. For additional information, see review by Dr. John Z. Duan dated 08/31/2011 in DARRTS.

In addition to the above, the Sponsor also evaluated dose-proportionality of their 45 mg dose to 135 mg ER capsules in Trial# 3739 and the effect of food on minocycline HCl 135 mg ER capsules in Trial# 3740.

**Trial# 3739** - This was a 3-treatment, 3-period, 3-sequence crossover randomized, open-label, single-dose fasting study in adult male and female subjects comparing:

- Bio-equivalence of minocycline HCl 135 mg ER capsules with Solodyn<sup>®</sup> 135 mg ER tablets under fasting conditions.
- Dose-proportionality of minocycline HCl 45 mg ER capsules and minocycline HCl 135 mg ER capsules both from Ranbaxy Laboratories.

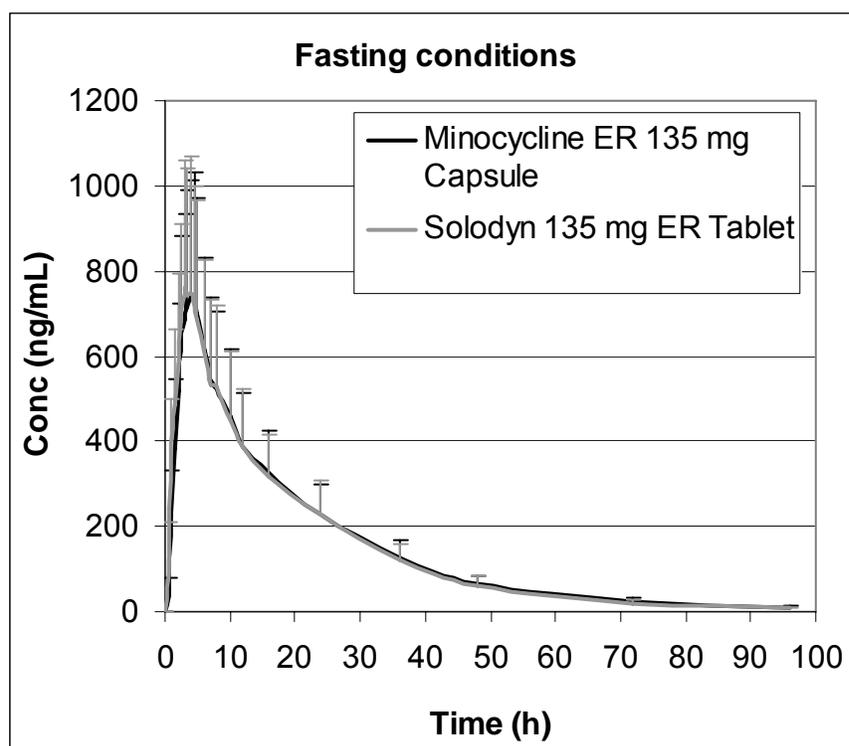
Number of subjects for the BE assessment: 42 subjects were enrolled but only 39 subjects (22 males and 17 females) with a mean age of 43.573 years (range 22 to 62 years) were included in the BE assessment. The subjects included in these analyses consisted of 18 Caucasians, 6 Asians/Orientals, 6 Blacks and 9 Hispanics.

Number of subjects for the dose proportionality assessment: 42 subjects were enrolled but only 37 subjects (21 males and 16 females) with a mean age of 43.5 years (range 22 to 62 years) completed the study and were included in the dose-proportionality assessment. The completing subjects consisted of 18 Caucasians, 5 Asians/Orientals, 6 Blacks, and 8 Hispanics.

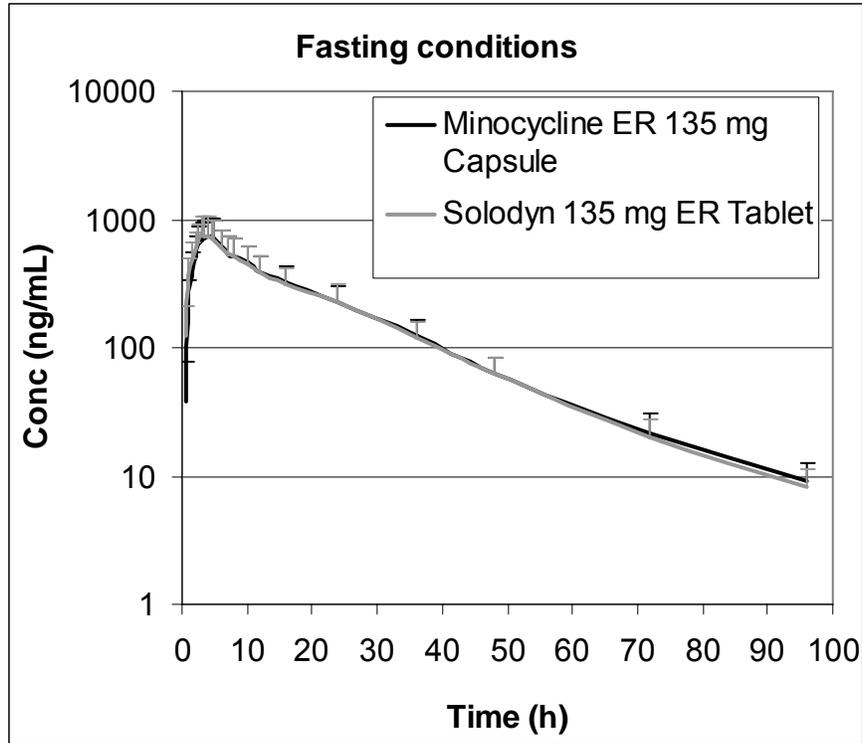
Dose administration: Doses were administered following an overnight fast for at least 10 hours. Subjects received 1 Minocycline HCl 45 mg ER Capsule, or 1 Minocycline HCl 135 mg ER Capsule, or 1 Solodyn<sup>®</sup> 135 mg ER Tablet on Day 1 of each study period. No food was allowed for at least 4 hours post-dose.

Results: The results indicated that the 90% CI of the ratio of the geometric mean of  $AUC_{0-t}$ ,  $AUC_{0-inf}$  and  $C_{max}$  of minocycline HCl 135 mg ER capsule versus Solodyn<sup>®</sup> 135 mg ER tablet were within the no effect range of 80 – 125 % under fasted conditions as shown in the table below. The PK profiles are shown in Figure 2, 3 and 4 below. This indicates that minocycline HCl 135 mg ER capsules were BE to Solodyn<sup>®</sup> 135 mg ER tablets under fasted conditions.

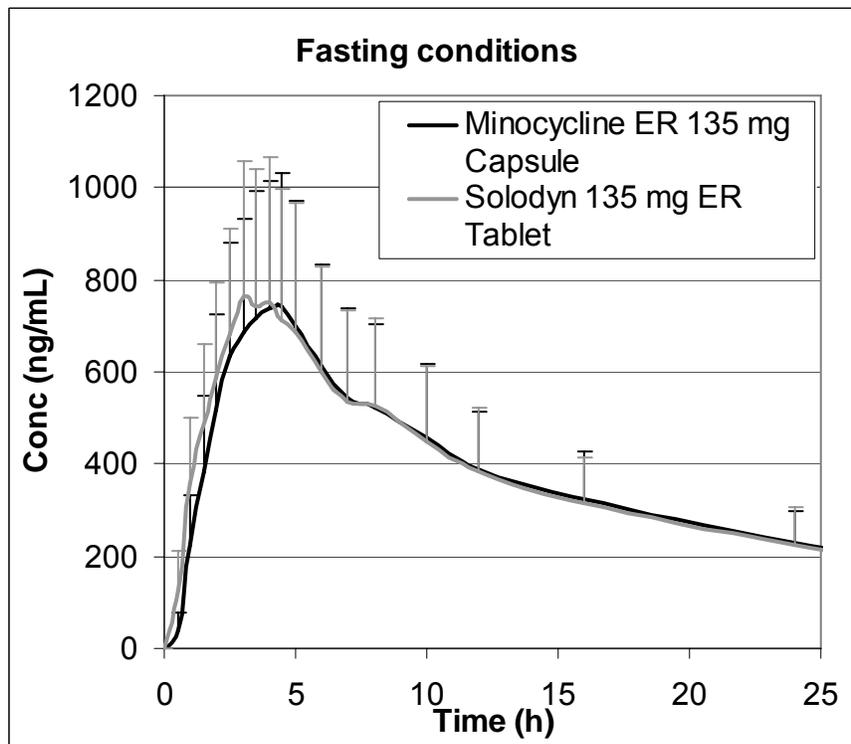
Parameter	Geometric Mean (% CV)		90% C.I.	Ratio of Means
	Minocycline 135 mg ER Capsule	Solodyn 135 mg ER Tablet		
AUC <sub>0-t</sub> (ng*hr/mL)	13663.60 (30.27)	13681.66 (31.80)	92.94 % to 108.30%	100.32%
AUC <sub>0-inf</sub> (ng*hr/mL)	13873.69 (30.05)	13861.77 (31.51)	93.32% to 108.30%	100.53%
C <sub>max</sub> (ng/mL)	749.54 (37.11)	780.10 (38.85)	88.84% to 105.32%	96.73%



**Figure 2: Plasma minocycline concentration (Mean  $\pm$  SD) versus time on linear scale under fasting conditions**



*Figure 3: Plasma minocycline concentration (Mean  $\pm$  SD) versus time on semi-log scale under fasting conditions*



*Figure 4: Plasma minocycline concentration (Mean  $\pm$  SD) versus time up to 25 hours*

The results of dose proportionality indicated that PK of minocycline increased in a dose proportional manner following oral administration of ER capsules between 45 mg and 135 mg dose. Since the 135 mg capsules contains 3 <sup>(b) (4)</sup> 45 mg “minitab” contained in the 45 mg capsules, this data indicate that minocycline exhibit linear PK within the dose range of 45 mg – 135 mg. The ratio of dose normalized (per mg) geometric mean values of AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub>, are shown in the table below.

Dose normalized PK parameter (per mg)	45 mg dose (A)	135 mg dose (B)	Ratio (A/B)
AUC <sub>0-t</sub> (hr*ng/mL)	101.56	101.21	1.00
AUC <sub>0-inf</sub> (hr*ng/mL)	105.10	102.68	1.02
C <sub>max</sub> (ng/mL)	6.19	5.55	1.12

**Trial# 3740** - This was a randomized, open-label, 3-treatment, 3-period, 3-sequence crossover, single-dose study in adult healthy male and female subjects comparing:

- Bio-equivalence of minocycline HCl 135 mg ER capsules with Solodyn<sup>®</sup> 135 mg ER tablets under fed conditions.
- The effect of food on minocycline HCl 135 mg ER capsules.

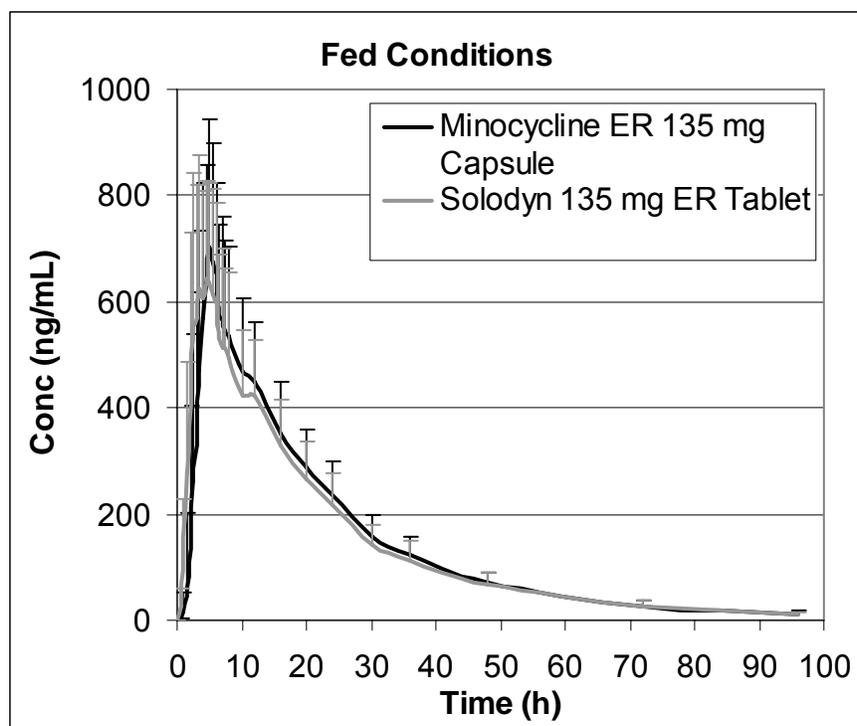
**Number of subjects:** Of the 42 subjects who were dosed in the study, 37 subjects (29 males and 8 females) with a mean age of 42.2 years (range = 20 to 63 years) were included in the pharmacokinetic and statistical analyses. The subjects included in this analysis consisted of 18 Caucasians, 7 Hispanics, 6 Asians/Orientals, 5 Blacks, and 1 mixed race.

**Dose administration:** All subjects in the 3 cohorts fasted overnight for at least 10 hours before drug administration. Subjects in one of these cohorts were administered minocycline HCl 135 mg ER capsule administered under fasting conditions in order to evaluate the effect of food. No food was allowed for at least 4 hours post-dose.

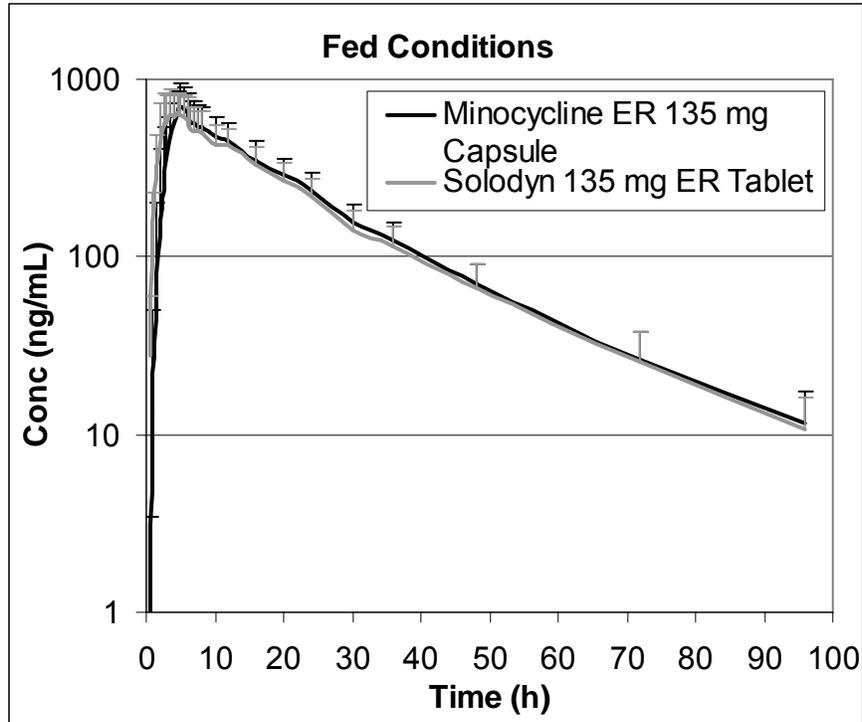
Subjects in other 2 cohorts were administered either minocycline HCl 135 mg ER capsule or Solodyn<sup>®</sup> 135 mg ER tablet following a high fat meal 30 minutes prior to the drug administration. The meal administered was FDA standard high-fat content breakfast and consisted of the following: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes and 8 fluid ounces (≈ 240 mL) of whole milk. No food was allowed for at least 4 hours post-dose.

**Results:** The results indicated that the 90% CI of the ratio of the geometric mean of AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub> of minocycline HCl 135 mg ER capsule versus Solodyn<sup>®</sup> 135 mg ER tablet were within the range of 80 - 125 % under fed conditions as shown in the table below. The PK profile is shown in Figures 5, 6 and 7. This indicates that minocycline HCl 135 mg ER capsules were BE to Solodyn<sup>®</sup> 135 mg ER tablets under fed conditions.

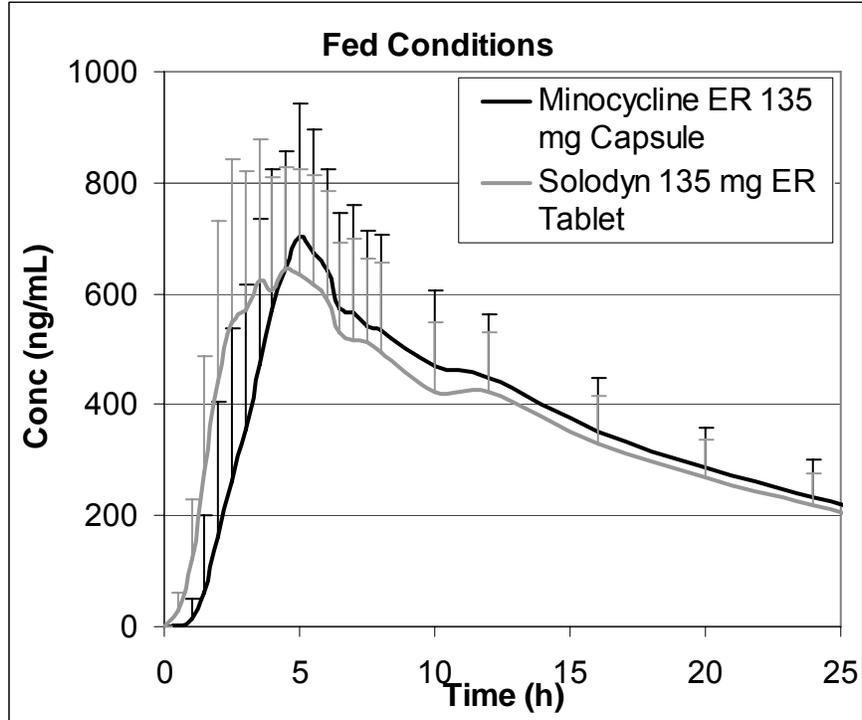
Parameter	Geometric Mean (% CV)		90% C.I.	Ratio of Means
	Minocycline 135 mg ER Capsule	Solodyn 135 mg ER Tablet		
AUC <sub>0-t</sub> (ng*hr/mL)	13546.24 (21.91)	13229.22 (23.49)	93.89 % to 108.89%	101.11%
AUC <sub>0-inf</sub> (ng*hr/mL)	13850.54 (21.91)	13513.70 (23.40)	93.93% to 108.92%	101.15%
C <sub>max</sub> (ng/mL)	824.57 (24.12)	770.97 (25.75)	98.05% to 114.28%	105.85%



*Figure 5: Plasma minocycline concentration (Mean  $\pm$  SD) versus time on linear scale under fed conditions*



**Figure 6:** Plasma minocycline concentration (Mean  $\pm$  SD) versus time on semi-log scale under fed conditions



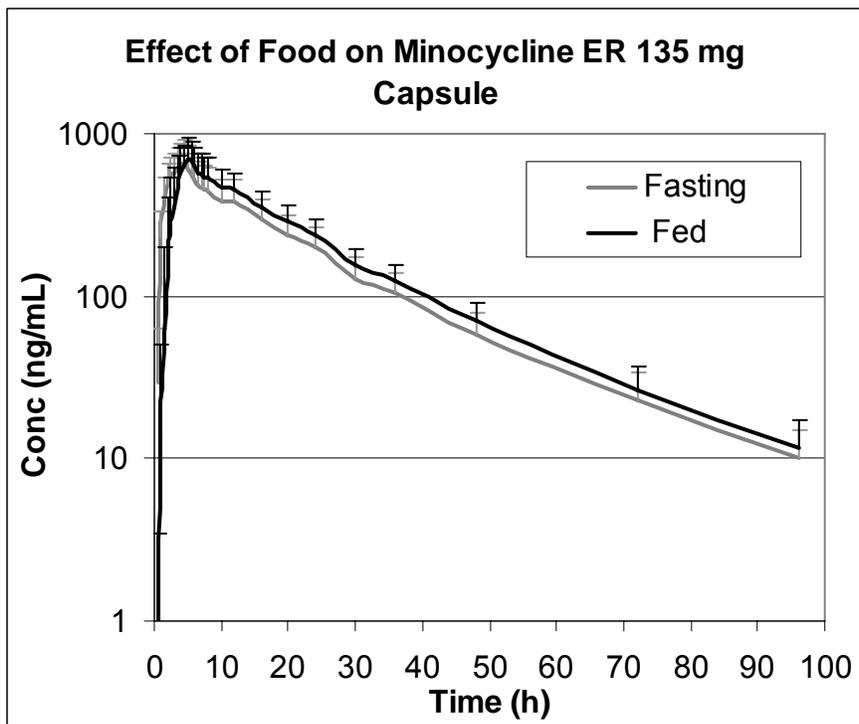
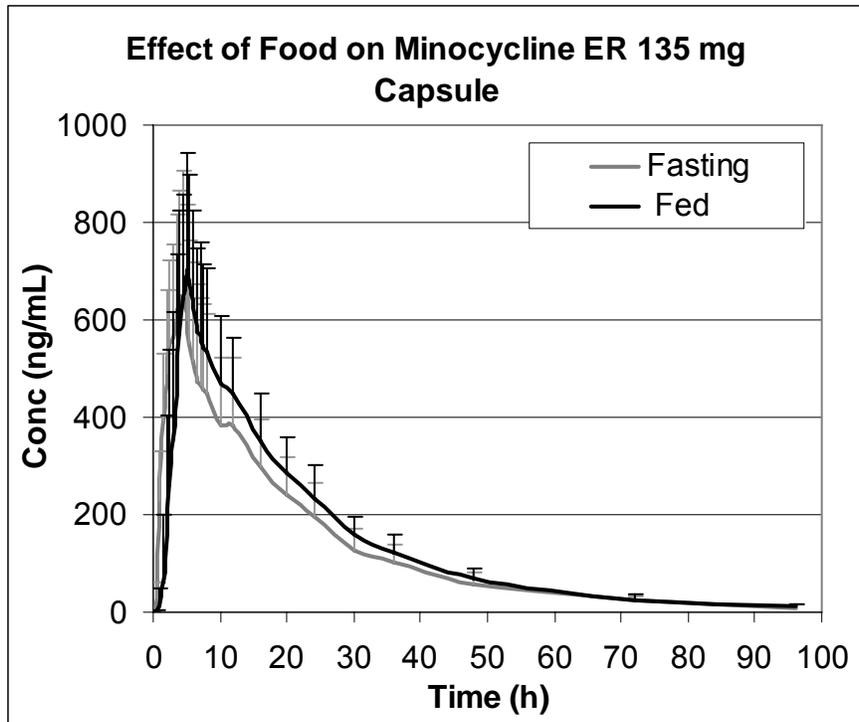
**Figure 7:** Plasma minocycline concentration (Mean  $\pm$  SD) versus time up to 25 hours

***Reviewer comments: From Figure 5 above, there appears to be a delay (~ 1 hour) in the drug absorption with minocycline HCl 135 mg ER capsules compared to Solodyn<sup>®</sup> 135 mg ER tablets [median T<sub>max</sub> (range) was 4.5 hr (2.0 hr -7.0 hr) and 3.5 hr (1.5 hr - 6.5 hr) with minocycline HCl 135 mg ER capsules and Solodyn<sup>®</sup> respectively] under fed conditions, although BE criteria were met. This is unlikely to have any effect on drug efficacy because the proposed treatment regimen is a chronic regimen to treat moderate to severe acne vulgaris. Such a delay in drug absorption might be more relevant in case of time sensitive therapy, e.g. treatment of acute pain.***

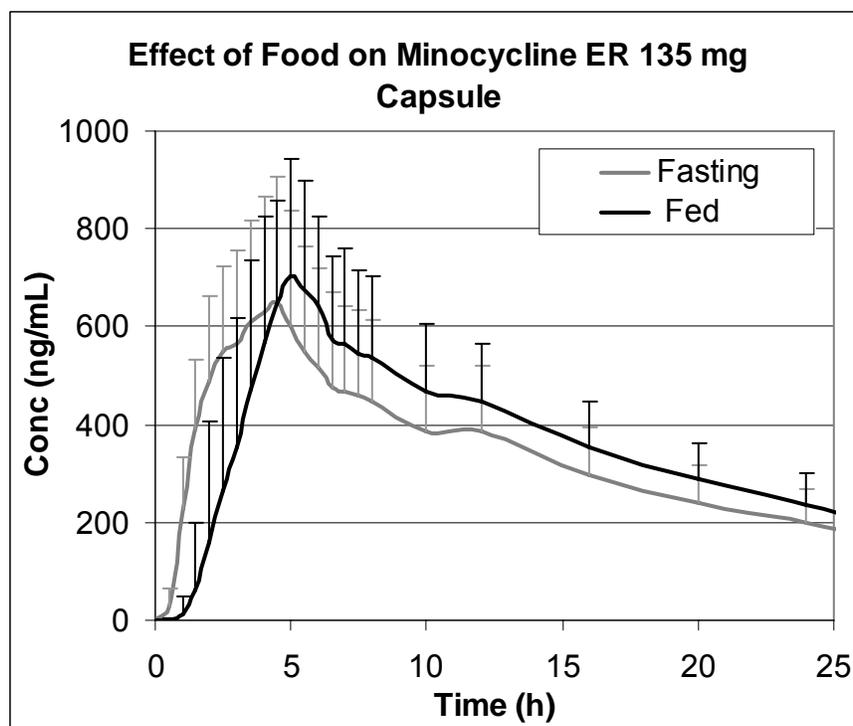
The results of the effect of food study indicated that comparing minocycline HCl 135 mg ER capsule under fed versus fasted conditions showed that the 90% CI of the ratio of geometric means of AUC<sub>0-t</sub> and AUC<sub>0-∞</sub> were between 80 - 125 %. However, the 90% CI of the ratio of the geometric mean of C<sub>max</sub> was 118.22 -137.61 % which was outside the no effect range of 80 -125% as shown in the table below. The PK profiles are shown in Figure 8 and 9.

Parameter	Minocycline 135 mg ER Capsule Geometric Mean (% CV)		90% C.I.	Ratio of Means
	Fasting	Fed		
AUC <sub>0-t</sub> (ng*hr/mL)	11942.26 (31.72)	13546.24 (21.91)	104.58 % to 121.15%	112.56%
AUC <sub>0-inf</sub> (ng*hr/mL)	12196.75 (31.38)	13850.54 (21.91)	104.72% to 121.28%	112.70%
C <sub>max</sub> (ng/mL)	640.28 (36.64)	824.57 (24.12)	118.22% to 137.61%	127.55%

This increase in C<sub>max</sub> with food is unlikely to result in any safety issues because based on the original approval of Solodyn<sup>®</sup> with only 3 strengths, the actual dose with the approved Solodyn<sup>®</sup> ranged from 1.48 to 0.76 mg/kg while the proposed dose for minocycline ER capsule (5 different strengths) will range from 1.21 to 0.82 mg/kg. The 28% increase in C<sub>max</sub> due to food would still be within the range determined to be safe and effective in the original Solodyn<sup>®</sup> approval. Hence, no dose adjustment with food will be required.



**Figure 8: Plasma minocycline concentration (Mean  $\pm$  SD) versus time on linear scale (upper panel) and semi-log scale (lower panel) under fed conditions**



**Figure 9: Plasma minocycline concentration (Mean ± SD) versus time up to 25 hours**

**Reviewer comments:** From Figure 7 above, there appears to be a delay (~ 1 hour) in the drug absorption with minocycline HCl 135 mg ER capsules under fed conditions compared to fasted conditions [median  $T_{max}$  (range) was 4.5 hr (2.0 hr -7.0 hr) and 3.5 hr (1.5 hr - 5.0 hr) under fed and fasting conditions respectively]. This delay in drug absorption with food is unlikely to have any effect on drug efficacy because the proposed treatment regimen is a chronic regimen to treat moderate to severe acne vulgaris. Such a delay in drug absorption might be more relevant in case of time sensitive therapy, e.g. treatment of acute pain.

## 2.3 Intrinsic Factors

**2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?**

### 2.3.1.2 Effect of Gender

The effect of gender on the PK parameters was not determined by the Sponsor in this submission. However data for Study 3739 were explored further to evaluate the effect of gender on BA. Data for Study 3740 were not explored further due to uneven gender based distribution compared to Study 3739 (There were 22 males and 17 females in Study 3739 versus 29 males and 8 females in Study 3740).

The results showed that BA in females was higher compared to males. Particularly, the  $C_{\max}$  was higher by approximately 60% and AUC was higher by approximately 40% in both minocycline HCl ER capsules and Solodyn<sup>®</sup> arms (See Appendix 5.2 for further details). When  $C_{\max}$  and AUC values were normalized by total body weight, this apparent difference in drug exposure between males and females appears to diminish. This was evident by the decrease in the  $R^2$  values when the body weight normalized  $C_{\max}$  and AUC were plotted against body weight compared to the  $R^2$  values obtained when  $C_{\max}$  and AUC values were plotted against body weight (See Appendix 5.2 for further details). Since minocycline HCl ER capsules is dosed based on body weight, no gender based adjustment of dose is recommended.

When additional posthoc BE analysis was conducted separated by gender, the results showed that minocycline HCl ER capsules were BE with Solodyn<sup>®</sup> in both males and females with the 90% CI of the ratio of the geometric mean of  $C_{\max}$  and AUC between the no effect boundary of 80% - 125% (See Appendix 5.2 for further details).

### ***2.3.2.1 Pediatric patients***

For this application, the Sponsor is using a 505(b)(2) regulatory pathway and refers to the clinical studies performed by the listed drug, Solodyn<sup>®</sup> (NDA 050808) and is seeking approval for their minocycline HCl ER capsules by demonstrating BE with the listed drug under fasted and fed conditions.

The Sponsor is seeking approval in patients 12 years of age and older, which is identical to the approved age range for the listed drug. As per listed drug (Solodyn<sup>®</sup>) labeling, the safety and effectiveness in pediatric patients below the age of 12 has not been established. Therefore, the Sponsor requested a waiver for the age group of 0-12 years.

Furthermore, the applicant holder of NDA 050808 (Solodyn<sup>®</sup>) has established the safety and effectiveness in pediatric patients of 12-16 years of age. According to Guidance for Industry “Bioavailability and Bioequivalence Studies for Orally Administered Drug Products (March 2003)” and “E11 Clinical investigation of medicinal products in the pediatric population (December 2000)”, BE studies for 505(b)(2) applications typically need not enroll pediatric patients and are usually conducted in healthy adult subjects. Therefore, the Sponsor has also requested a waiver for conducting pediatric studies in the age group of 12-16 years.

***Reviewer comments: The Sponsor’s waiver requests were approved by the PeRC PREA Subcommittee at a meeting held on September 07, 2011.***

### ***2.3.2.2 Renal impairment***

No clinical studies have been conducted to evaluate the effect of renal impairment on the PK of minocycline ER capsules.

### ***2.3.2.3 Hepatic impairment***

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the PK of minocycline ER capsules.

#### ***2.3.2.4 What pregnancy and lactation use information is there in the application?***

This is a 505(b)(2) application and the two BA/BE trials conducted under fasting and fed conditions excluded pregnant and lactating females. The Sponsor is relying on labeling information for Section 8.1 “Pregnancy” from the listed drug Solodyn<sup>®</sup> approved label.

### **2.4 Extrinsic Factors**

#### ***2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure or response?***

*Alcohol use:* The results of in-vitro study to assess the potential for alcohol to cause dose dumping were reviewed by Dr. John Z. Duan (Biopharmaceutics reviewer) and he concluded that the study did not show a dose dumping potential (see review by Dr. John Z. Duan in DARRTS dated 08/31/2011).

***Reviewer 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***

Since this is a 505(b)(2) application, drug-drug interactions were not evaluated for minocycline HCl ER capsules. This Sponsor is relying on labeling information for Section 7 “Drug Interactions” from the listed drug Solodyn<sup>®</sup> approved label.

### **2.5 General Biopharmaceutics**

#### ***2.5.1 Based on biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?***

Not Applicable

#### ***2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?***

The proposed-to-be-marketed formulation is the same as the formulation used in the pivotal BA/BE trials (Trial# 3739 and # 3740).

##### ***2.5.2.1 What data support or do not support a waiver of in vivo BE data?***

For lower strengths (45, 67.5, 90 and 112.5 mg), the Sponsor submitted a biowaiver request based on dissolution profile comparisons with the highest strength (135 mg). This was reviewed by Dr. John Z. Duan (Biopharmaceutics reviewer) and he concluded that the biowaiver request was acceptable and recommended approval of lower strengths provided the BE trials with the highest dose (135 mg) are deemed acceptable.

**2.5.3 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?**

In trial no. 3740, the Sponsor evaluated the effect of food on minocycline HCL ER capsule by using FDA standard high-fat content breakfast.

The results as shown in the table below indicated that comparing minocycline HCl 135 mg ER capsule under fed versus fasting conditions showed that the 90% CI of the ratio of geometric means of AUC<sub>0-t</sub> and AUC<sub>0-∞</sub> were between 80 - 125 %. However, the 90% CI of the ratio of the geometric mean of C<sub>max</sub> was 118.22 -137.61 % which was outside the no effect range of 80 -125%.

Parameter	Minocycline 135 mg ER Capsule Geometric Mean (% CV)		90% C.I.	Ratio of Means
	Fasting	Fed		
AUC <sub>0-t</sub> (ng*hr/mL)	11942.26 (31.72)	13546.24 (21.91)	104.58 % to 121.15%	112.56%
AUC <sub>0-inf</sub> (ng*hr/mL)	12196.75 (31.38)	13850.54 (21.91)	104.72% to 121.28%	112.70%
C <sub>max</sub> (ng/mL)	640.28 (36.64)	824.57 (24.12)	118.22% to 137.61%	127.55%

This increase in C<sub>max</sub> with food is unlikely to result in any safety issues because based on the original approval of Solodyn<sup>®</sup> with only 3 strengths, the actual dose with the approved Solodyn<sup>®</sup> ranged from 1.48 to 0.76 mg/kg while the proposed dose for minocycline ER capsule (5 different strengths) will range from 1.21 to 0.82 mg/kg. The 28% increase in C<sub>max</sub> due to food would still be within the range determined to be safe and effective in the original Solodyn<sup>®</sup> approval. Hence, no dose adjustment with food will be required.

**2.6 Analytical Section**

**2.6.1 How are the active moieties identified, and measured in the plasma and urine in the clinical pharmacology and biopharmaceutics studies?**

The active moiety (minocycline) was identified using high performance liquid chromatography and tandem mass spectrometry.

**2.6.2 Which metabolites have been selected for analysis and why?**

This is a 505(b)(2) application and metabolites levels were not evaluated in this application.

**2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?**

Total concentration of minocycline, the parent compound, was measured. This is a 505(b)(2) application and the relative BA/BE should be evaluated using the parent compound.

**2.6.4 What is the range of the standard curve? How does it relate to the requirements for clinical studies?**

Range: 4.114 to 3510.500 ng/mL. Drug concentrations obtained in the BA/BE studies were below 1100 ng/mL. Hence the range of standard curve is adequate.

**2.6.5 What are the accuracy, precision, and selectivity at LLOQ?**

- LLOQ = 4.114 ng/mL

Values*	Accuracy (Reported as % RE)	Precision (Reported as % CV)
<i>Intra-assay (n=6)</i>	2.4	2.5
<i>Inter-assay (n=24)</i>	-2.0	6.1

\* Limits: %RE and % CV must be within  $\pm 20.0\%$  for LLOQ and  $\pm 15.0\%$  for all other QC levels)

**2.6.6 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?**

The results shown below are adequate to support stability of minocycline samples.

<b>Analyte name</b>	Minocycline
<b>Freeze-thaw Stability (cycles)</b>	4 cycles at $-70^{\circ}\text{C} \pm 10^{\circ}\text{C}$
<b>In Process Stability (hrs)</b>	24 hours at $4^{\circ}\text{C} \pm 4^{\circ}\text{C}$
<b>Autosampler Stability (hrs)</b>	69 hours at $7^{\circ}\text{C} \pm 4^{\circ}\text{C}$
<b>Whole Blood Stability (hrs)</b>	2 hours at room temperature 2.5 hours at $4^{\circ}\text{C} \pm 4^{\circ}\text{C}$
<b>Analyte Stock Solution Stability</b>	35 days at $-25^{\circ}\text{C} \pm 10^{\circ}\text{C}$ 19 hours at room temperature
<b>Internal Standard Stock Solution Stability</b>	35 days at $-25^{\circ}\text{C} \pm 10^{\circ}\text{C}$ 19 hours at room temperature
<b>Internal Standard Working Solution Stability</b>	35 days at $-25^{\circ}\text{C} \pm 10^{\circ}\text{C}$ 19 hours at room temperature
<b>Long-term Stability in Matrix (days)</b>	114 days at $-70^{\circ}\text{C} \pm 10^{\circ}\text{C}$

Trial 3739:

- **Long term stability:** Date of first sample collection is October 12, 2010 and date of last sample analysis is November 25, 2010. Therefore, time between sample collection and analysis is ~ 44 days. The long term stability of 114 days is adequate to support the stability of the stored PK samples.
- **Incurred sample analysis:** Total of 2435 samples was collected from 37 subjects. Incurred sample analysis performed on 192 samples (approximately 7.8% samples were reanalyzed). Incurred sample repeats were performed on November 20, 23 and 24, 2010. The results indicate that approximately 96% of the samples had the % difference between the original concentration and repeat concentration within  $\pm$  20%.

Trial 3740:

- **Long term stability:** Date of first sample collection is October 14, 2010 and date of last sample analysis is December 2, 2010. Therefore, time between sample collection and analysis is ~ 49 days. The long term stability of 114 days is adequate to support the stability of the stored PK samples.
- **Incurred sample analysis:** Total of 2907 samples collected from 36 subjects. Incurred sample analysis performed on 200 samples (approximately 6.9% samples were reanalyzed). Incurred sample repeats were performed on November 28, December 01 and 02, 2010. The results indicate that for all the samples the % difference between the original concentration and repeat concentration was within  $\pm$  20%.

### **3. Detailed Labeling Recommendations**

The following changes are recommended in section 12.3 Pharmacokinetics of the Sponsor's proposed labeling (Appendix shows the Clinical Pharmacology section of Sponsor submitted package insert). The **bold and underlined** text indicates insertion recommended by the reviewer and the ~~strike through~~ text indicates recommended deletion.

#### **7.5 Low Dose Oral Contraceptives**

In a multi-center study to evaluate the effect of minocycline hydrochloride **(administered as another extended release formulation which is bioequivalent to TRADE NAME)** on low dose oral contraceptives, hormone levels over one menstrual cycle with and without minocycline hydrochloride 1 mg/kg once-daily were measured. Based on the results of this trial, minocycline-related changes in estradiol, progestinic hormone, FSH and LH plasma levels, of breakthrough bleeding, or of contraceptive failure, can not be ruled out. To avoid contraceptive failure, female patients are advised to use a second form of contraceptive during treatment with minocycline.

#### **12.3 Pharmacokinetics**

~~(b) (4)~~ **TRADE NAME** is not bioequivalent to non-modified release minocycline products ~~(b) (4)~~

**Following administration of a single dose TRADE NAME (135 mg) to healthy male and female adult subjects, the mean (SD)  $AUC_{(0-\infty)}$  and  $C_{max}$  were 12.87 (4.04) mcg x hr/mL and 0.68 (0.25) mcg/mL, respectively, under fasting conditions.**

**When a single dose TRADE NAME (135 mg) was administered with a high fat meal to the same subjects in the same study in a crossover design, the mean (SD)  $AUC_{(0-\infty)}$  and  $C_{max}$  were 14.16 (3.10) mcg x hr/mL and 0.85 (0.20) mcg/mL, respectively.**

A single-dose ~~(b) (4)~~ crossover study demonstrated that **TRADE NAME** ~~(b) (4)~~ (45 mg and 135 mg) exhibited dose-proportional pharmacokinetics.

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

#### **4. INDIVIDUAL STUDY REVIEW**

##### **Trial Number: 3739**

**Title:** A Three-Way Crossover, Open-Label, Balanced, Randomized, Single-Dose, Fasting, BE and Dose Proportionality Study of Minocycline HCl 45 mg ER Capsules, Minocycline HCl 135 mg ER Capsules, and Solodyn<sup>®</sup> 135 mg ER Tablets in Normal, Healthy, Non-Smoking Male and Female Subjects

**Study Center:** Lambda Therapeutic Research Inc., 460 Comstock Road, Toronto, Ontario, Canada M1L 4S4. Tel – (416) 752-3636. Fax – (416) 752-7610.

**Principal Investigator:** Pierre Geoffroy, M.D., C.M., M.Sc., F.C.F.P.

**Analytical work done by:**

(b) (4)

**Study Objectives:** This study was designed to:

1. Demonstrate BE between the following products under fasting conditions:
  - Test (B): Minocycline HCl 135 mg ER Capsules
  - Reference (R): Solodyn<sup>®</sup> 135 mg ER Tablets
2. Assess the dose proportionality of the following products under fasting conditions:
  - Test (A): Minocycline HCl 45 mg ER Capsules
  - Test (B): Minocycline HCl 135 mg ER Capsules

##### **Study Drugs:**

- Test (A): Minocycline HCl 45 mg ER Capsule
  - Manufacturer: Ranbaxy Laboratories Limited, India
  - Lot#: 2060265
- Test (B): Minocycline HCl 135 mg ER Capsule
  - Manufacturer: Ranbaxy Laboratories Limited, India
  - Lot#: 2061751
- Reference (R): Solodyn<sup>®</sup> 135 mg ER Tablet
  - Manufacturer: Well Spring Pharmaceutical Canada Corp., Canada for Medics, The Dermatology Company, U.S.A.
  - Lot# OC7554

**Study Design:** The study followed a randomized, open-label, single-dose, 3-treatment, 3-period, 3-sequence crossover design in 42 normal, healthy, non-smoking male and female subjects under fasting conditions. Subjects were admitted to the clinic the day before dosing, and remained until the 24 hour post-dose blood draw of each period, at which time they were allowed to leave the clinic and after which they were required to return for subsequent blood draws. This was an open-label study; however, the bioanalytical group was blinded to the randomization schemes. These schemes were made available for statistical and reporting purposes only after the completion of the bioanalytical portion of the study.

Following an overnight fast for at least 10 hours, subjects received 1 Minocycline HCl 45 mg ER Capsule, or 1 Minocycline HCl 135 mg ER Capsule, or 1 Solodyn® 135 mg ER Tablet on Day 1 of each study period. No food was allowed for at least 4 hours post-dose.

**Subjects:**

**Bioequivalence assessment:** 42 subjects were enrolled but only 39 subjects (22 males and 17 females) with a mean age of 43.573 years (range 22 to 62 years) were included in the bio-equivalency assessment. The subjects included in these analyses consisted of 18 Caucasians, 6 Asians/Orientals, 6 Blacks and 9 Hispanics.

**Dose proportionality assessment:** 42 subjects were enrolled but only 37 subjects (21 males and 16 females) with a mean age of 43.5 years (range 22 to 62 years) completed the study and were included in the dose-proportionality assessment. The completing subjects consisted of 18 Caucasians, 5 Asians/Orientals, 6 Blacks, and 8 Hispanics.

**Subject Demographics:** Shown in the table below.

Parameter	Variable	Treatment			Completed Subjects (n=37)	Included Subjects in PK Analysis (n=39)	All Subjects (n=42)
		X (n=39)	Y (n=41)	Z (n=38)			
Age (years)	Mean ± SD	43.3 ± 9.7	43.6 ± 9.5	43.5 ± 9.8	43.5 ± 9.9	43.3 ± 9.7	43.5 ± 9.4
	Median	44.0	44.0	43.5	44.0	44.0	44.0
	Min, Max	22, 62	22, 62	22, 62	22, 62	22, 62	22, 62
Height (cm)	Mean ± SD	168.3 ± 11.5	167.8 ± 11.7	168.5 ± 11.5	168.6 ± 11.7	168.3 ± 11.5	167.7 ± 11.6
	Median	168.0	168.0	169.0	170.0	168.0	168.0
	Min, Max	146.0, 192.0	145.4, 192.0	146.0, 192.0	146.0, 192.0	146.0, 192.0	145.4, 192.0
Weight (kg)	Mean ± SD	73.2 ± 12.3	73.0 ± 12.6	73.7 ± 12.1	73.6 ± 12.2	73.2 ± 12.3	73.1 ± 12.5
	Median	73.7	73.7	74.0	73.7	73.7	74.0
	Min, Max	52.6, 100.8	50.8, 100.8	52.6, 100.8	52.6, 100.8	52.6, 100.8	50.8, 100.8
Body Mass Index (kg/m <sup>2</sup> )	Mean ± SD	25.7 ± 2.2	25.8 ± 2.2	25.8 ± 2.1	25.8 ± 2.1	25.7 ± 2.2	25.8 ± 2.2
	Median	25.9	25.9	26.2	25.9	25.9	26.2
	Min, Max	20.6, 29.5	20.6, 29.5	20.6, 29.5	20.6, 29.5	20.6, 29.5	20.6, 29.5
Sex	Male	22 (56.4%)	23 (56.1%)	22 (57.9%)	21 (56.8%)	22 (56.4%)	24 (57.1%)
	Female	17 (43.6%)	18 (43.9%)	16 (42.1%)	16 (43.2%)	17 (43.6%)	18 (42.9%)
Race	Caucasian	18 (46.2%)	19 (46.3%)	18 (47.4%)	18 (48.6%)	18 (46.2%)	19 (45.2%)
	Black	6 (15.4%)	6 (14.6%)	6 (15.8%)	6 (16.2%)	6 (15.4%)	6 (14.3%)
	Hispanic	9 (23.1%)	9 (22.0%)	9 (23.7%)	8 (21.6%)	9 (23.1%)	10 (23.8%)
	Asian/Oriental	6 (15.4%)	7 (17.1%)	5 (13.2%)	5 (13.5%)	6 (15.4%)	7 (16.7%)

Treatment X : Reference (R): 1 Solodyn® 135 mg ER Tablet (Treatment dose = 135 mg)  
 Treatment Y : Test (B): 1 Minocycline HCl 135 mg ER Capsule (Treatment dose = 135 mg)  
 Treatment Z : Test (A): 1 Minocycline HCl 45 mg ER Capsule (Treatment dose = 45 mg)

**Discontinued subjects and the reason for discontinuation:** Shown in table below.

Last Dosing (Period Number)	Subject Number	Dismissed or Withdrew	Timeframe	Reason
II	004	Withdrew	Before Period III dosing	Personal reasons
I	005	Withdrew	During washout	Personal reasons
I	018	Withdrew	During washout	Personal reasons
II	029	Withdrew	During washout	Personal reasons
I	034	Dismissed	During confinement	Emesis within 24 hours of dosing

Subject # 004 and # 029 did not complete the study due to personal reasons but were included in the PK analysis because there were sufficient data points to allow for meaningful analysis. Bioanalytical determination of plasma minocycline data was also conducted on samples from subject #034 who was dismissed from the study because of emesis within 24 hours of dosing. Data from subject # 034 were not included in PK analysis.

**PK Blood Sampling Time:** During each study period, 22 blood samples (4 mL each) were collected from each subject by direct venipuncture. Blood samples were collected at 0.00 (pre-dose), and at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00, 72.00, and 96.00 hours post-dose.

**PK Parameters:** The pharmacokinetic parameters for minocycline derived for all 3 treatments using standard, non-compartmental methods were:

Primary parameters:

- $AUC_{0-t}$  = area under the concentration-time curve from time zero to time of last measurable concentration, calculated using the linear trapezoidal rule
- $AUC_{0-inf}$  = area under the concentration-time curve from time zero to infinity
- $C_{max}$  = maximum plasma concentration after dosing

Secondary parameters:

- $AUC_{Extrap}$  = percentage of extrapolated area under the plasma concentration versus time curve from the last measurable concentration to infinity, calculated as:  

$$[(AUC_{0-inf} - AUC_{0-t}) / AUC_{0-inf}] * 100$$
- $T_{max}$  = time to reach peak plasma concentration
- $\lambda_z$  = first order terminal elimination rate constant
- $t_{1/2}$  = terminal half-life

**Results:**

PK Parameters: Table below shows the PK parameters calculated in Trial 3739.

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean $\pm$ SD		
	Treatment Z: Test (A): 1 Minocycline HCl 45 mg ER Capsule (n=37)	Treatment Y: Test (B): 1 Minocycline HCl 135 mg ER Capsule (n=39)	Treatment X: Reference (R): 1 Solodyn <sup>®</sup> 135 mg ER Tablet (n=39)
<b>Unadjusted</b> AUC <sub>0-t</sub> (ng·hr/mL)	4569.97 (34.01) 4841.02 $\pm$ 1646.50	13663.60 (30.27) 14372.02 $\pm$ 4351.12	13681.66 (31.80) 14380.52 $\pm$ 4572.67
AUC <sub>0-t</sub> <sup>†</sup> (ng·hr/mL)	13709.90 (34.01) 14523.05 $\pm$ 4939.50	N/AP	N/AP
<b>Unadjusted</b> AUC <sub>0-inf</sub> (ng·hr/mL)	4729.48 (32.80) 4986.79 $\pm$ 1635.86	13873.69 (30.05) 14580.98 $\pm$ 4381.20	13861.77 (31.51) 14558.43 $\pm$ 4586.98
AUC <sub>0-inf</sub> <sup>†</sup> (ng·hr/mL)	14188.44 (32.80) 14960.37 $\pm$ 4907.57	N/AP	N/AP
AUC <sub>Extrap</sub> (%)	2.92 (59.26) 3.35 $\pm$ 1.99	1.37 (48.05) 1.51 $\pm$ 0.73	1.19 (42.46) 1.30 $\pm$ 0.55
<b>Unadjusted</b> C <sub>max</sub> (ng/mL)	278.58 (35.72) 297.41 $\pm$ 106.23	749.54 (37.11) 805.16 $\pm$ 298.76	780.10 (38.85) 839.22 $\pm$ 326.03
C <sub>max</sub> <sup>†</sup> (ng/mL)	835.75 (35.72) 892.23 $\pm$ 318.68	N/AP	N/AP
T <sub>max</sub> (hr)*	3.00 (1.00 - 4.53)	3.50 (2.00 - 4.57)	3.50 (2.00 - 5.00)
t <sub>1/2</sub> (hr)	14.02 $\pm$ 2.18	14.68 $\pm$ 2.07	14.56 $\pm$ 1.79
λ <sub>z</sub> (hr <sup>-1</sup> )	5.06E-02 $\pm$ 8.19E-03	4.82E-02 $\pm$ 7.65E-03	4.83E-02 $\pm$ 6.17E-03

<sup>†</sup> AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, and C<sub>max</sub> for Test (A) were dose-normalized by multiplying with a correction factor of 135/45

\* median (min – max)

N/AP – Not Applicable

**BA/BE analysis under fasting conditions:** Discussed under Section 2.2.1

**Dose-proportionality:** Discussed under Section 2.2.1

### Safety:

**Brief Summary of Adverse Events:** According to the Sponsor, 11 subjects experienced a total of 18 adverse events (AEs) during the study. The most frequent AEs are expressed as fractions, relative to the total number of AEs experienced after each treatment. After treatment with Minocycline HCl 45 mg ER Capsules, the most frequent AE was headache (2/4). After treatment with Minocycline HCl 135 mg ER Capsules, the most frequent AE was headache (4/9). No AE was reported more than once after treatment with Solodyn<sup>®</sup> 135 mg ER Tablets (3 AEs reported in total). At the end-of study exam, the most frequent AE was aspartate aminotransferase increased (2/2). (See review by medical officer Dr. Patricia Brown for further details).

### **Trial Number: 3740**

**Title:** A Three-Way Crossover, Open-Label, Balanced, Randomized, Single-Dose, BE and Food-Effect Study of Minocycline HCl 135 mg ER Capsules and Solodyn<sup>®</sup> 135 mg ER Tablets in Normal, Healthy, Non-Smoking Male and Female Subjects

**Study Center:** Lambda Therapeutic Research Inc., 460 Comstock Road, Toronto, Ontario, Canada M1L 4S4. Tel – (416) 752-3636. Fax – (416) 752-7610.

**Principal Investigator:** Pierre Geoffroy, M.D., C.M., M.Sc., F.C.F.P.

**Analytical work done by:** [REDACTED]

(b) (4)

**Study Objectives:** This study was designed to:

1. Demonstrate BE between the following products under fed conditions:
  - Test (A): Minocycline HCl 135 mg ER Capsules
  - Reference (R): Solodyn® 135 mg ER Tablets
2. Assess the effect of food on the following products:
  - Test (A): Minocycline HCl 45 mg ER Capsules administered under fed conditions
  - Test (B): Minocycline HCl 135 mg ER Capsules administered under fasting conditions

**Study Drugs:**

- Test (A) and Test (B): Minocycline HCl 135 mg ER Capsule
  - Manufacturer: Ranbaxy Laboratories Limited, India
  - Lot#: 2061751
- Reference (R): Solodyn® 135 mg ER Tablet
  - Manufacturer: Well Spring Pharmaceutical Canada Corp., Canada for Medics, The Dermatology Company, U.S.A.
  - Lot# OC7554

**Study Design:** The study followed a randomized, open-label, 3-treatment, 3-period, 3-sequence crossover, single-dose, food-effect design in 42 normal, healthy, non-smoking male and female subjects. Subjects were admitted to the clinic the day before dosing, and remained until the 36 hour post-dose blood draw of each period, at which time they were allowed to leave the clinic and after which they were required to return for subsequent blood draws. There was a 14-day washout period between study treatments. This was an open-label study; however, the bioanalytical group was blinded to the randomization schemes. These schemes were made available for statistical and reporting purposes only after the completion of the bioanalytical portion of the study.

On Day 1 of each study period, subjects received one of the following treatments:

- Test (A): 1 Minocycline HCl 135 mg ER Capsule administered under fed conditions
- Test (B): 1 Minocycline HCl 135 mg ER Capsule administered under fasting conditions
- Reference (R): 1 Solodyn® 135 mg ER Tablet administered under fed conditions

Subjects receiving Test (B) fasted overnight for at least 10 hours before drug administration. Following an overnight fast of at least 10 hours, subjects receiving Test (A) and Reference (R) began a high fat meal 30 minutes prior to drug administration. Subjects consumed this meal in 30 minutes or less. The FDA standard high-fat content breakfast consisted of the following: 2 eggs fried in butter, 2 strips of bacon, 2 slices of

toast with butter, 4 ounces of hash brown potatoes and 8 fluid ounces ( $\approx$  240 mL) of whole milk. No food was allowed for at least 4 hours post-dose.

Water was provided *ad libitum* until 1.0 hour pre-dose and after 1.0 hour post-dose. With the exception of the whole milk provided to the subjects receiving Test (A) and Reference (R) during a high fat meal, the only fluid intake allowed during this time was 240 mL of ambient temperature dosing water.

**Type of food:** The FDA standard high-fat content breakfast consisted of the following: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes and 8 fluid ounces ( $\approx$  240 mL) of whole milk.

**Subjects:** Of the 42 subjects who were dosed in the study, 36 subjects (28 males and 8 females) with a mean age of 42.7 years (range = 20 to 63 years) completed the study. The completing subjects consisted of 18 Caucasians, 7 Hispanics, 6 Asians/Orientals, 4 Blacks, and 1 Mixed race.

The pharmacokinetic and statistical analyses were performed on data from 37 evaluable subjects, 36 subjects of whom completed the 3 study periods, and 1 subject (Subject #025) for whom there were sufficient data to allow for a meaningful analysis.

Hence PK analysis had 37 subjects (29 males and 8 females) with a mean age of 42.2 years (range = 20 to 63 years). The subjects included consisted of 18 Caucasians, 7 Hispanics, 6 Asians/Orientals, 5 Blacks, and 1 Mixed race.

Subject Demographics: Shown in the table below.

Parameter	Variable	Treatment			Completed Subjects (n=36)	Included Subjects in PK Analysis (n=37)	All Subjects (n=42)
		X (n=41)	Y (n=37)	Z (n=38)			
Age (years)	Mean $\pm$ SD	42.4 $\pm$ 10.3	42.2 $\pm$ 11.1	42.1 $\pm$ 11.0	42.7 $\pm$ 10.9	42.2 $\pm$ 11.1	42.0 $\pm$ 10.5
	Median	42.0	42.0	42.0	43.5	42.0	42.0
	Min, Max	20, 63	20, 63	20, 63	20, 63	20, 63	20, 63
Height (cm)	Mean $\pm$ SD	171.6 $\pm$ 8.6	171.9 $\pm$ 8.8	171.9 $\pm$ 8.7	171.8 $\pm$ 8.9	171.9 $\pm$ 8.8	171.7 $\pm$ 8.5
	Median	173.6	174.0	173.8	173.8	174.0	173.8
	Min, Max	150.0, 194.0	150.0, 194.0	150.0, 194.0	150.0, 194.0	150.0, 194.0	150.0, 194.0
Weight (kg)	Mean $\pm$ SD	75.8 $\pm$ 12.4	75.7 $\pm$ 12.8	75.4 $\pm$ 12.7	75.6 $\pm$ 12.9	75.7 $\pm$ 12.8	75.9 $\pm$ 12.2
	Median	76.1	76.1	75.8	75.8	76.1	76.8
	Min, Max	49.9, 110.7	49.9, 110.7	49.9, 110.7	49.9, 110.7	49.9, 110.7	49.9, 110.7
Body Mass Index (kg/m <sup>2</sup> )	Mean $\pm$ SD	25.6 $\pm$ 2.5	25.5 $\pm$ 2.5	25.4 $\pm$ 2.5	25.5 $\pm$ 2.6	25.5 $\pm$ 2.5	25.6 $\pm$ 2.5
	Median	26.1	26.0	25.9	26.1	26.0	26.1
	Min, Max	20.5, 29.8	20.5, 29.8	20.5, 29.8	20.5, 29.8	20.5, 29.8	20.5, 29.8
Sex	Male	32 (78.0%)	29 (78.4%)	29 (76.3%)	28 (77.8%)	29 (78.4%)	33 (78.6%)
	Female	9 (22.0%)	8 (21.6%)	9 (23.7%)	8 (22.2%)	8 (21.6%)	9 (21.4%)
Race	Caucasian	19 (46.3%)	18 (48.6%)	19 (50.0%)	18 (50.0%)	18 (48.6%)	19 (45.2%)
	Black	5 (12.2%)	5 (13.5%)	5 (13.2%)	4 (11.1%)	5 (13.5%)	6 (14.3%)
	Hispanic	9 (22.0%)	7 (18.9%)	7 (18.4%)	7 (19.4%)	7 (18.9%)	9 (21.4%)
Race	Asian/Oriental	7 (17.1%)	6 (16.2%)	6 (15.8%)	6 (16.7%)	6 (16.2%)	7 (16.7%)
	Other	1 (2.4%)	1 (2.7%)	1 (2.6%)	1 (2.8%)	1 (2.7%)	1 (2.4%)

Treatment X : Reference (R): 1 Solodyn® 135 mg ER Tablet administered under fed conditions (Treatment dose = 135 mg)  
 Treatment Y : Test (B): 1 Minocycline HCl 135 mg ER Capsule administered under fasting conditions (Treatment dose = 135 mg)  
 Treatment Z : Test (A): 1 Minocycline HCl 135 mg ER Capsule administered under fed conditions (Treatment dose = 135 mg)

Discontinued subjects and the reason for discontinuation: Shown in table below.

Last Dosing (Period Number)	Subject Number	Dismissed or Withdrew	Timeframe	Reason
I	001	Dismissed	Before Period II dosing	Administrative reasons [positive test result for cannabinoids (THC)]
I	005	Dismissed	Before Period II dosing	Administrative reasons (positive test result for cocaine)
II	010	Withdrew	During confinement	Personal reasons
I	019	Withdrew	During washout	Personal reasons
II	025	Withdrew	During washout	Personal reasons
I	033	Withdrew	During washout	Personal reasons

The bioanalytical determination, pharmacokinetic analysis, and statistical analysis of plasma minocycline data were conducted on 37 evaluable subjects, 36 subjects of whom completed the study, and 1 subject (Subject #025) for whom there were sufficient data to allow for a meaningful analysis.

**PK blood sampling time:** During each study period, 27 blood samples (4 mL each) were collected from each subject by direct venipuncture. Blood samples were collected at 0.00 (pre-dose), and at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 10.00, 12.00, 16.00, 20.00, 24.00, 30.00, 36.00, 48.00, 72.00, and 96.00 hours post-dose.

**PK Parameters:** The pharmacokinetic parameters for minocycline derived for all 3 treatments using standard, non-compartmental methods were:

Primary parameters:

- $AUC_{0-t}$  = area under the concentration-time curve from time zero to time of last measurable concentration, calculated using the linear trapezoidal rule
- $AUC_{0-inf}$  = area under the concentration-time curve from time zero to infinity
- $C_{max}$  = maximum plasma concentration after dosing

Secondary parameters:

- $AUC_{Extrap}$  = percentage of extrapolated area under the plasma concentration versus time curve from the last measurable concentration to infinity, calculated as:  

$$[(AUC_{0-inf} - AUC_{0-t}) / AUC_{0-inf}] * 100$$
- $T_{max}$  = time to reach peak plasma concentration
- $\lambda_z$  = first order terminal elimination rate constant
- $t_{1/2}$  = terminal half-life

**Results:**

PK Parameters: Table below shows the PK parameters calculated in Trial 3740.

Pharmacokinetic Parameter	Geometric Mean (%CV) Arithmetic Mean ± SD		
	Treatment Z: Test (A): 1 Minocycline HCl 135 mg ER Capsule administered under fed conditions (n=37)	Treatment Y: Test (B): 1 Minocycline HCl 135 mg ER Capsule administered under fasting conditions (n=37)	Treatment X: Reference (R): 1 Solodyn <sup>®</sup> 135 mg ER Tablet administered under fed conditions (n=36)
AUC <sub>0-t</sub> (ng·hr/mL)	13546.24 (21.91) 13844.62 ± 3033.91	11942.26 (31.72) 12608.67 ± 3999.52	13229.22 (23.49) 13636.26 ± 3202.76
AUC <sub>0-inf</sub> (ng·hr/mL)	13850.54 (21.91) 14158.50 ± 3102.80	12196.75 (31.38) 12865.36 ± 4037.27	13513.70 (23.40) 13929.22 ± 3259.86
AUC <sub>Extrap</sub> (%)	1.87 (56.26) 2.19 ± 1.23	1.80 (54.61) 2.08 ± 1.14	1.77 (65.92) 2.10 ± 1.38
C <sub>max</sub> (ng/mL)	824.57 (24.12) 847.24 ± 204.37	640.28 (36.64) 684.14 ± 250.65	770.97 (25.75) 797.00 ± 205.20
T <sub>max</sub> (hr)*	4.50 (2.00 – 7.00)	3.50 (1.50 – 5.00)	3.50 (1.50 – 6.50)
t <sub>1/2</sub> (hr)	16.02 ± 2.56	16.16 ± 2.56	16.77 ± 2.81
λ <sub>z</sub> (hr <sup>-1</sup> )	4.43E-02 ± 6.83E-03	4.39E-02 ± 6.81E-03	4.25E-02 ± 7.46E-03

\* median (min – max)

BA/BE analysis under fed conditions: Discussed under Section 2.2.1

Effect of food: Discussed under Section 2.2.1

### Safety:

Brief Summary of Adverse Events: According to the Sponsor, 9 subjects experienced a total of 14 AEs during the study. The most frequent AEs are expressed as fractions, relative to the total number of AEs experienced after each treatment. No AE was reported more than once after minocycline HCl 135 mg ER capsules were administered under fed conditions [Test (A); 1 AE in total]. No AE was reported more than once after minocycline HCl 135 mg ER capsules were administered under fasting conditions [Test (B); 5 AEs in total]. No AEs were reported after Solodyn<sup>®</sup> 135 mg ER Tablets were administered under fed conditions [Reference (R)]. At the end-of-study exam, the most frequent AEs were the following: alanine aminotransferase increased (3/8) and aspartate aminotransferase increased (2/8). (See review by medical officer Dr. Patricia Brown for further details).

## 5. Appendix

### 5.1 Sponsor Submitted Package Insert – Clinical Pharmacology Section

#### 12 CLINICAL PHARMACOLOGY

##### 12.1 Mechanism of Action

The mechanism of action of minocycline hydrochloride for the treatment of acne is unknown.

##### 12.2 Pharmacodynamics

The pharmacodynamics of minocycline hydrochloride for the treatment of acne are unknown.

##### 12.3 Pharmacokinetics

(b) (4) not bioequivalent to non-modified release minocycline products. (b) (4)

A single-dose (b) (4) crossover study demonstrated that (b) (4) (45 mg and 135 mg) exhibited dose-proportional pharmacokinetics.

(b) (4)

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

## 5.2 Effect of gender on minocycline HCl BA (Study 3739)

An analysis was conducted on the PK data for Study 3739 to evaluate the effect of gender on BA of minocycline HCl. Data for Study 3740 were not explored further due to uneven gender based distribution compared to Study 3739 (There were 22 males and 17 females in Study 3739 versus 29 males and 8 females in Study 3740).

The results showed that AUC and  $C_{max}$  in females were higher by approximately 40% and 60% respectively compared to males for both minocycline extended release capsules (Table 9) and Solodyn<sup>®</sup> (Table 10).

**Table 9: Bioavailability of minocycline HCl 135 mg ER capsule in females versus males**

Parameter	Minocycline 135 mg ER Capsule Geometric Mean (% CV)		90% C.I.	Ratio of Means
	Female (n = 17)	Male (n = 22)		
AUC <sub>0-t</sub> (ng*hr/mL)	16439.66 (23.66)	11817.21 (27.87)	118.43 % to 163.41%	139.12%
AUC <sub>0-inf</sub> (ng*hr/mL)	16629.33 (23.66)	12046.34 (27.75)	117.61% to 162.03%	138.96%
C <sub>max</sub> (ng/mL)	991.45 (25.75)	603.85 (30.27)	138.69 % to 194.38%	164.19%

**Table 10: Bioavailability of Solodyn<sup>®</sup> 135 mg in females versus males**

Parameter	Solodyn <sup>®</sup> 135 mg Geometric Mean (% CV)		90% C.I.	Ratio of Means
	Female (n = 17)	Male (n = 22)		
AUC <sub>0-t</sub> (ng*hr/mL)	16531.24 (28.82)	11816.98 (20.39)	120.13 % to 162.91%	139.89%
AUC <sub>0-inf</sub> (ng*hr/mL)	16689.97 (28.69)	12010.65 (20.46)	119.38% to 161.75%	138.96%
C <sub>max</sub> (ng/mL)	1028.04 (27.96)	630.28 (32.33)	138.03 % to 192.74%	163.11%

Furthermore, the results of t-test also indicated that the differences in AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub> in males and females were statistically significant ( $p < 0.05$ ) for both minocycline HCl ER capsules and Solodyn.

The value of terminal half life ( $t_{1/2}$ ) was also significantly different between males and females ( $p < 0.05$ ) with the ratio of the geometric mean of  $t_{1/2}$  (female/male) was found to be approximately 0.8. This indicates that  $t_{1/2}$  in females was shorter by approximately 20% compared to males.

The values of both apparent clearance (Cl/F, where F is the bioavailability fraction) and apparent volume of distribution (Vd/F) were statistically significant between males and

females ( $p < 0.05$ ) and the ratio of the geometric means were 0.72 and 0.61, respectively. This indicates that Cl/F and Vd/F were lower in females by approximately 30% and 40%, respectively than males.

The geometric mean values of Cl/F, Vd/F,  $t_{1/2}$  and Kel, separated by gender for each treatment arm are shown in Table 11. Further, when the ratio of the geometric means of PK parameters were calculated as female:male, the values obtained were independent of the formulation (i.e., the ratios were similar for both formulations) as shown in the Table 12 below.

**Table 11: Geometric mean values of PK parameters separated by gender for each treatment arm**

Treatment	PK Parameters	Geometric mean (CV) (Female)	Geometric mean (CV) (Male)
Minocycline HCl ER capsules	Cl/F (L/hr)	8.12 (37.07)	11.21 (33.81)
	Vd/F (L)	159.05 (31.67)	259.97 (35.07)
	$t_{1/2}$ (hr)	13.58 (15.65)	16.08 (15.30)
	Kel (1/hr)	0.051 (17.03)	0.043 (15.02)
Solodyn	Cl/F (L/hr)	8.01 (40.07)	11.24 (25.02)
	Vd/F (L)	155.58 (35.10)	255.72 (21.63)
	$t_{1/2}$ (hr)	13.33 (11.78)	15.77 (12.54)
	Kel (1/hr)	0.052 (11.75)	0.044 (12.78)

**Table 12: Ratio of the geometric mean values of PK parameters (Female/Male)**

Treatment	PK Parameters	Ratio of geometric mean (Female/Male)
Minocycline HCl ER capsules	Cl/F	0.72
	Vd/F	0.61
	$t_{1/2}$	0.84
	Kel	1.18
Solodyn	Cl/F	0.72
	Vd/F	0.61
	$t_{1/2}$	0.85
	Kel	1.18

**Exploratory BE analysis separated by gender:** The data were further explored to evaluate the relative BA of the two formulations by gender and the results indicated that the ratio of the geometric mean of AUC and  $C_{max}$  were between 80% - 125% no effect boundary in both females and males respectively. The results are shown in Table 13 and 14 respectively.

**Table 13: Relative Bioavailability of minocycline HCl 135 mg ER capsule versus Solodyn® in females (n = 17)**

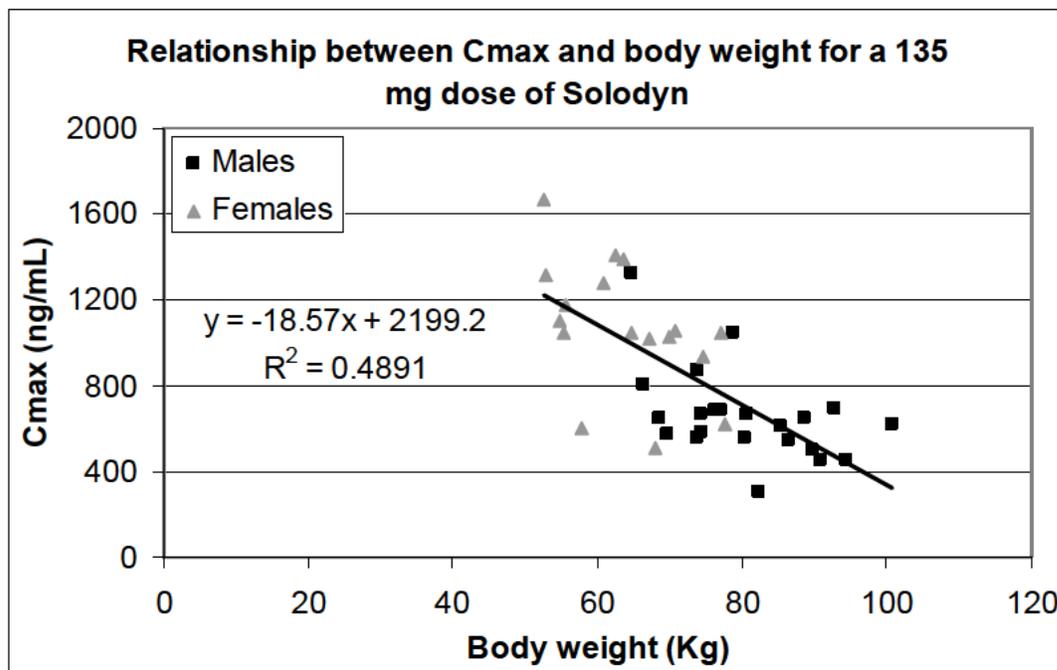
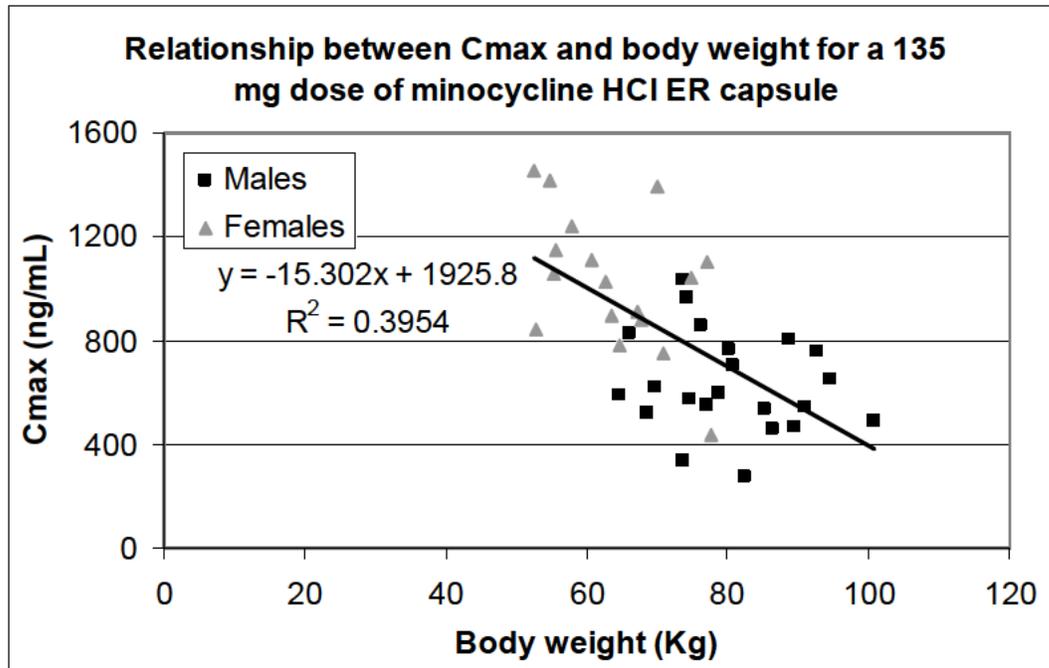
Parameter	Geometric Mean (% CV)		90% C.I.	Ratio of Means
	Minocycline 135 mg ER Capsule	Solodyn® 135 mg ER Tablet		
AUC <sub>0-t</sub> (ng*hr/mL)	16439.66 (23.66)	16531.24 (28.82)	86.99 % to 113.68%	99.45%
AUC <sub>0-inf</sub> (ng*hr/mL)	16629.33 (23.66)	16689.97 (28.69)	87.15% to 113.91%	99.64%
C <sub>max</sub> (ng/mL)	991.45 (25.75)	1028.04 (27.97)	83.49 % to 111.41%	96.44%

**Table 14: Relative Bioavailability of minocycline HCl 135 mg ER capsule versus Solodyn® in males (n = 22)**

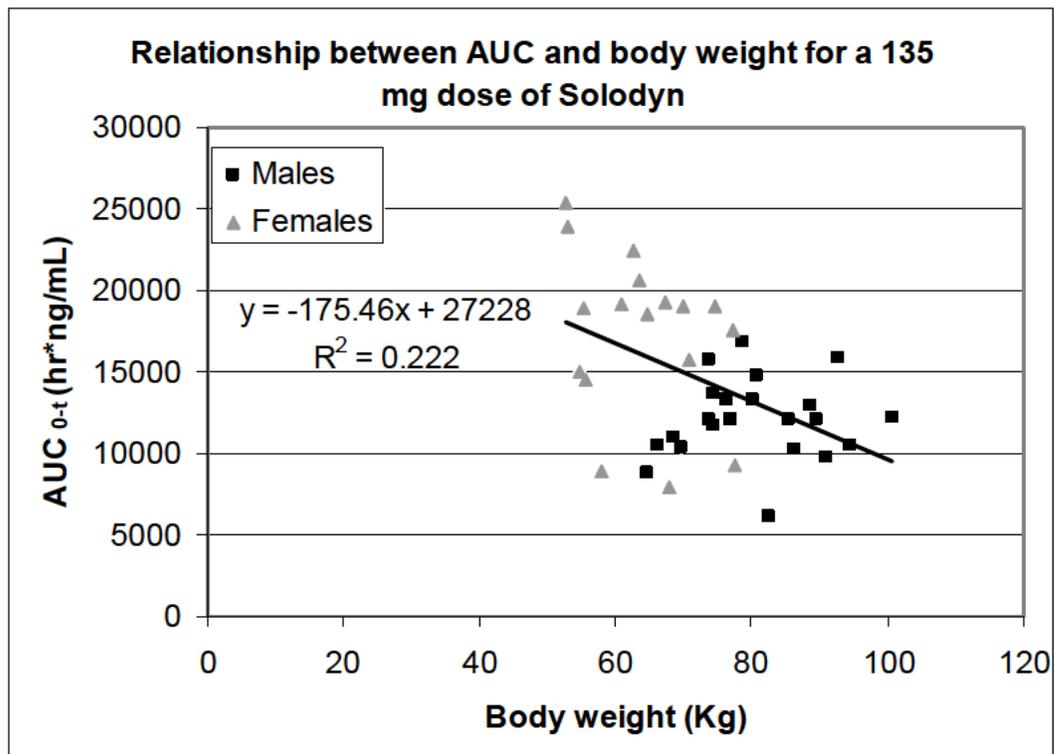
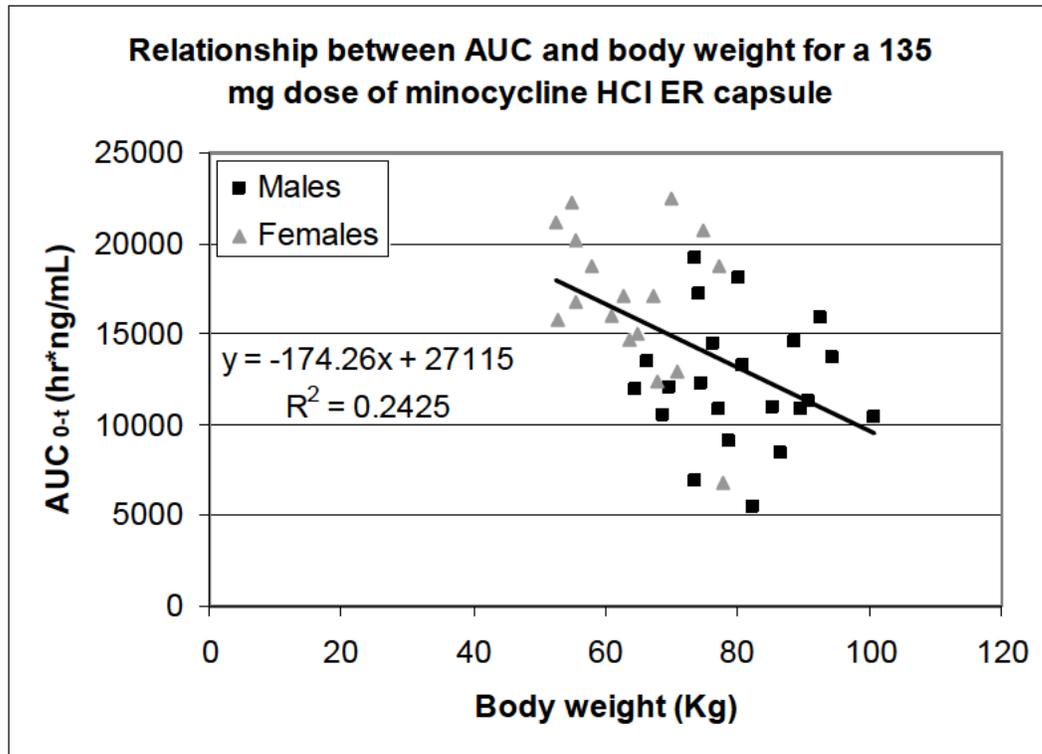
Parameter	Geometric Mean (% CV)		90% C.I.	Ratio of Means
	Minocycline 135 mg ER Capsule	Solodyn® 135 mg ER Tablet		
AUC <sub>0-t</sub> (ng*hr/mL)	11817.21 (27.87)	11816.98 (20.39)	90.96 % to 109.94%	100.00%
AUC <sub>0-inf</sub> (ng*hr/mL)	12046.34 (27.75)	12010.65 (20.46)	91.31% to 110.17%	100.30%
C <sub>max</sub> (ng/mL)	603.85 (30.27)	630.28 (32.33)	85.31 % to 110.17%	95.81%

In conclusion, higher BA of minocycline HCl was observed in females compared to males however, there was no difference in the relative BA of minocycline HCl 135 mg ER capsule versus Solodyn® 135 mg ER tablet within each gender.

**Relationship between minocycline exposure and body weight:** It was noted that while females had higher drug exposure compared to males in study 3739, females also had lower body weight (mean ± SD body weight of 63.9 ± 8.4 kg in females versus 80.4 ± 9.7 kg in males). Therefore, it was further explored if there is a relationship between body weight and drug exposure. The relationship between C<sub>max</sub> and body weight and AUC and body weight for a 135 mg dose of minocycline HCl ER capsules and Solodyn are shown in Figures 10 and 11, respectively.



**Figure 10: Relationship between C<sub>max</sub> and body weight for a 135 mg dose of minocycline HCl ER capsules (upper panel) and 135 mg Solodyn (lower panel)**



**Figure 11: Relationship between AUC and body weight for a 135 mg dose of minocycline HCl ER capsules (upper panel) and 135 mg Solodyn (lower panel)**

Figures 12 and 13 show the relationship between body weight normalized C<sub>max</sub> and AUC, respectively, with body weight for each treatment arm. C<sub>max</sub> and AUC were weight normalized by multiplying the observed C<sub>max</sub> and AUC values by the individual total body weight.

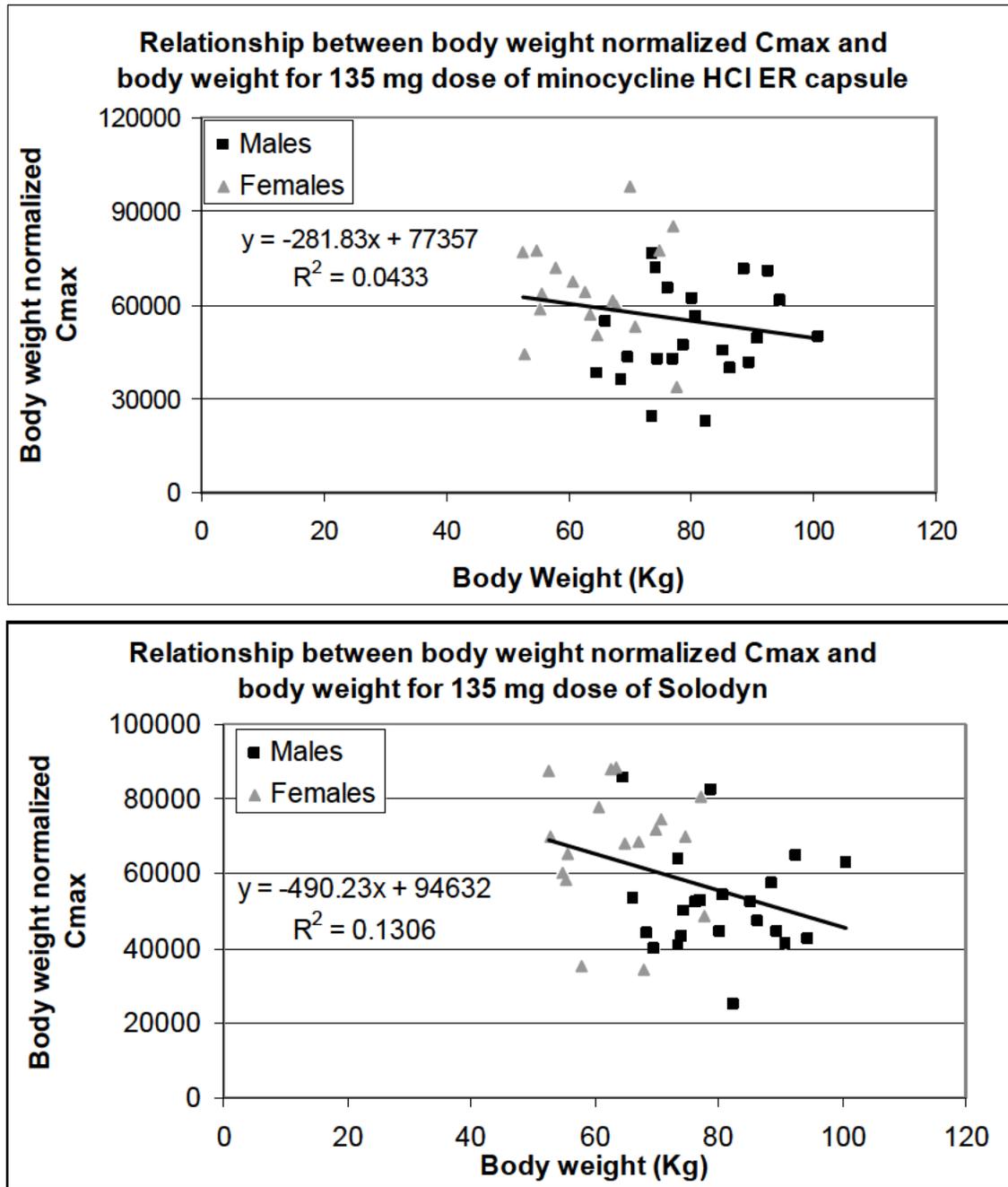
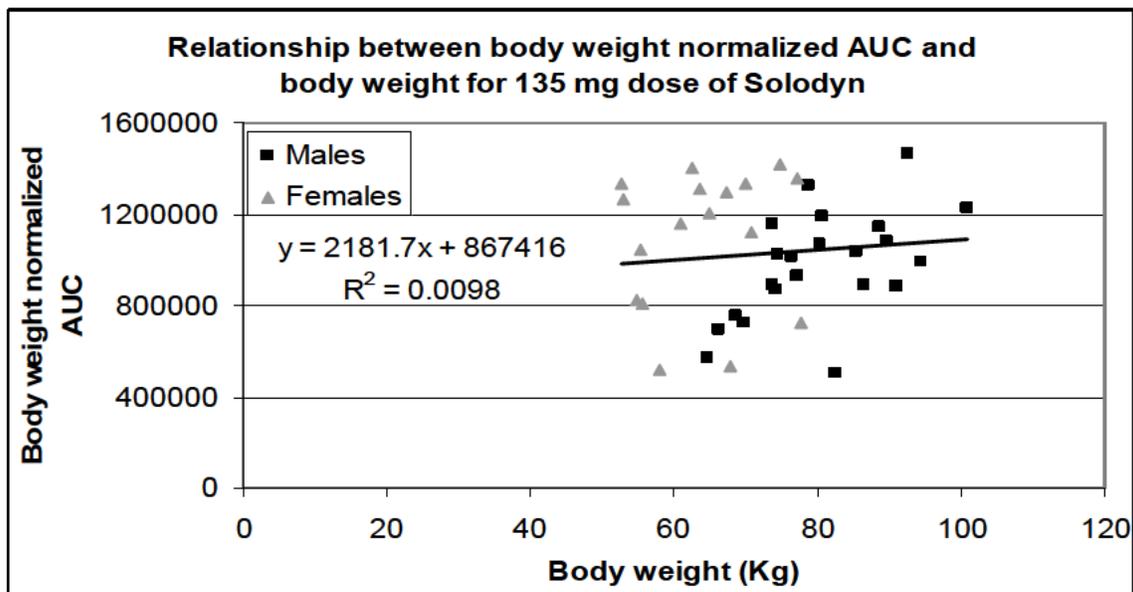
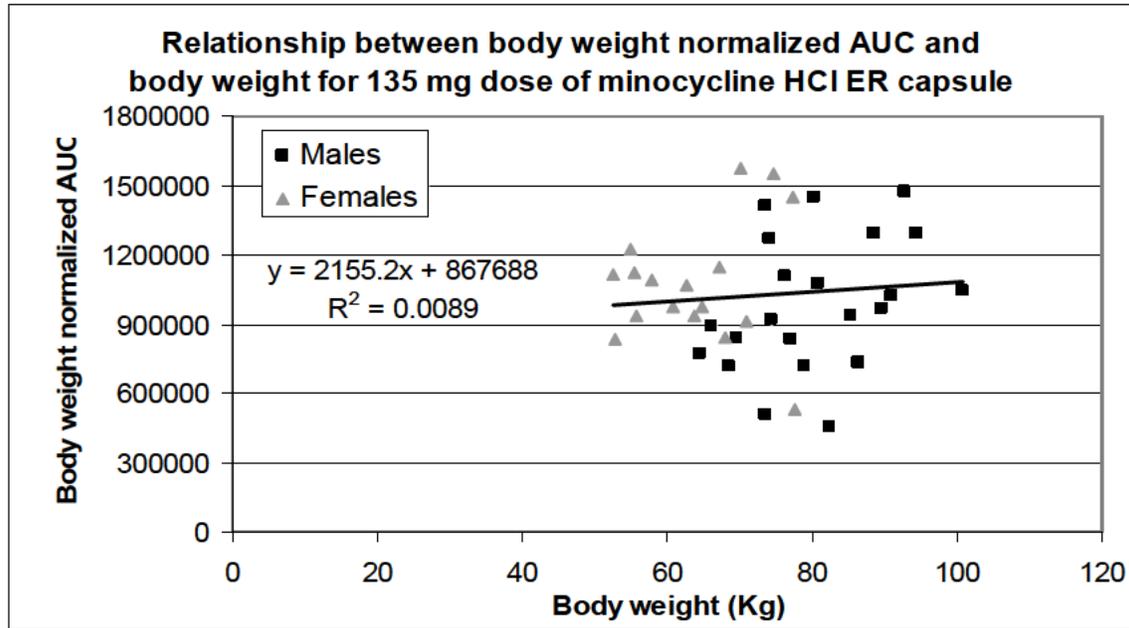


Figure 12: Relationship between body weight normalized C<sub>max</sub> and body weight for a 135 mg dose of minocycline HCl ER capsules (upper panel) and 135 mg Solodyn (lower panel)



**Figure 13: Relationship between body weight normalized AUC and body weight for a 135 mg dose of minocycline HCl ER capsules (upper panel) and 135 mg Solodyn (lower panel)**

From Figures 10, 11, 12 and 13, when  $C_{max}$  and AUC values were normalized by weight, the apparent difference in drug exposure between males and females appears to diminish. This was evident by the decrease in the  $R^2$  values when the body weight normalized  $C_{max}$  and AUC were plotted against body weight compared to the  $R^2$  values obtained when  $C_{max}$  and AUC values were plotted against body weight. Since minocycline HCl ER capsules is dosed based on body weight, no gender based adjustment of dose is recommended.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

CHINMAY SHUKLA  
10/04/2011

DOANH C TRAN  
10/04/2011

## ONDQA BIOPHARMACEUTICS REVIEW

---

<b>NDA#:</b>	<b>201-922</b>
<b>Submission Date:</b>	02/04/2011, 3/28/2011, 6/27/2011, 8/12/2011
<b>Generic Name:</b>	Minocycline HCl USP
<b>Formulation:</b>	Capsules ER
<b>Strength:</b>	45, 67.5, 90, 112.5, 135mg
<b>Applicant:</b>	Ranbaxy Lab
<b>Reviewer:</b>	John Duan, Ph.D.
<b>Submission Type:</b>	Re-Submission

---

Minocycline Hydrochloride Extended Release Capsule is submitted pursuant to 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The RLD product is Solodyn Extended Release Tablets. (NDA 50-808) of Medicis.

### COMMENTS

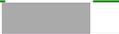
1. The IVIVC study is not acceptable due to the following facts.



2. The biowaiver request for the lower strengths (45, 67.5, 90, 112.5 mg) is acceptable based on the dissolution profile comparisons with the highest strength (135 mg), which is the subject of a bioequivalence study. If the bioequivalence study is deemed acceptable, an approval of the lower strengths is recommended.
3. The in vitro alcohol dose dumping study is acceptable. The study did not show any dose dumping potential.
4. The applicant accepted the following dissolution acceptance criteria with slight modifications for the 1.5 h time point for the different strengths. We consider these modifications acceptable.

0.5 hours:  (b) (4)

1.5 hours: based on the strengths as shown below.

45 mg	67.5 mg	90 mg	112.5 mg	135 mg
 (b) (4)				

3.0 hours: NLT  (b) (4)

Using the following dissolution conditions.

Apparatus: USP 1 (basket); Rotation: 100 rpm; edium: 0.1 N HCl; Volume: 900 mL;  
Temperature: 37 ± 0.5°C

**RECOMMENDATION**

The Applicant accepted the Agency’s recommendation for the dissolution acceptance criteria (with slight modifications) and they updated the relevant sections of the NDA. No further action is necessary at this time.

From the Biopharmaceutics perspective, NDA 201-922 for Minocycline ER Capsules is acceptable.

\_\_\_\_\_  
John Duan, Ph.D.  
Reviewer  
ONDQA Biopharmaceutics

\_\_\_\_\_  
Date

\_\_\_\_\_  
Angelica Dorantes, Ph.D.  
ONDQA Biopharmaceutics Team Leader

\_\_\_\_\_  
Date

cc: NDA 201-922  
Patrick Marroum, John Duan

**APPENDIX. Summary of the information related to Biopharmaceutics**

**1. The composition of the drug products**

The compositions of minocycline extended release minitables in different strengths are shown in the following table.



**Composition of Minocycline Extended Release Capsules**

Ingredients	Quantity mg/ Capsule									
	45 mg	% w/w	67.5 mg	% w/w	90 mg	% w/w	112.5 mg	% w/w	135 mg	% w/w
(b) (4)										
Minocycline Hydrochloride USP equivalent to Minocycline <sup>1</sup>										(b) (4)
(b) (4)										
(b) (4)										
Hypromellose (b) (4)										
Lactose Monohydrate <sup>2</sup>										
(b) (4)										
(b) (4)										
Magnesium Stearate										
Colloidal Silicon Dioxide										
<b>Total (Core Tablet)</b>										
<b>Film Coating</b>										
Opady (b) (4) Clear <sup>(4)</sup>										
(b) (4)										
<b>Total (Coated Tablet)</b>	153,000	(b) (4)	229,500	(b) (4)	306,000		382,500	(b) (4)	459,000	(b) (4)
<b>Empty Gelatin Capsule Shell</b>	1	-	1	-	1	-	1	-	1	-

## 2. The Biowaiver Request

The bioequivalence study comparing the highest strength of the proposed Minocycline Hydrochloride Extended Release Capsules 135 mg and the RLD, Solodyn 135 mg Extended Release Tablets (NDA 050808) of Medicis was submitted. However, the Applicant also intends to market four additional strengths, including 45, 67.5, 90, and 112.5 mg. The submission includes a biowaiver request for these strengths based on the following.

1. The proposed Minocycline Hydrochloride Extended Release Capsules 45 mg, 67.5 mg, 90 mg, 112.5 mg and 135 mg are dose proportionate formulations, as shown in the above tables.
2. The data comparing the dissolution profile of the Minocycline Hydrochloride Extended-Release Capsules, 45 mg, 67.5 mg, 90 mg, 112.5 mg and 135 mg with the corresponding strengths of Solodyn® Tablets, was also provided. Solodyn® Tablets are not available in 67.5 mg and 112.5 mg strengths. Therefore, the Applicant's 67.5 mg and 112.5 mg strengths were compared with the innovator's 135 mg strength. A summary of the in-vitro dissolution studies conducted on the bioequivalence batch is provided in the following table:

**Summary of In-Vitro Dissolution Studies.**

	Ranbaxy's Minocycline Hydrochloride Extended Release Capsules	Solodyn ® (Minocycline Hydrochloride Extended-Release Tablets, 45/90/135 mg ) (Medicis)
Strength	Lot Numbers	Lot Numbers
45 mg	2060265	B080186
	2066625	
	2065675	
67.5mg	2129745	8K5057
	2132008	
	2142165	
90 mg	2061749	8L5389
	2065676	
	2066647	
112.5	2129749	8K5057
	2142166	
	2132003	
135 mg	2061751	8K5057 OC7554 <sup>1</sup>
	2066644	
	2065673	

The batch size for the 45 mg, 90 mg and 135 mg strength is (b) (4) capsules, and (b) (4) capsules for 67.5 mg strength and (b) (4) capsules for 112.5 mg strength.

The dissolution conditions used:

Apparatus: USP, Apparatus I (b) (4) Basket)  
 Speed: 100 rpm  
 Medium: 0.1N Hydrochloric acid  
 Volume: 900 mL  
 Time: 0.5, 1.5, and 4.0 hours  
 Temperature: 37 ± 0.5°C

Dissolution testing of the drug product was also conducted in the following media.

1. Water
2. pH 4.5 Acetate buffer
3. pH 6.8 Phosphate buffer

For the 45 mg, 90 mg, 67.5 mg and 112.5 mg the dissolution testing in the above mentioned media has been done on one batch.

The dissolution profiles comparing the innovator versus the Applicant's product in the above listed multimedia are provided as shown below. It should be noted that the dissolution data comparing the RLD product to the Applicant's product are not needed. Only generic products require these data.

Per request, the Applicant submitted f2 calculations for the profile comparisons between the lower strengths and the highest strength that had the bioequivalence data, and between the corresponding strengths manufactured by the Applicant and the innovator. The reviewer confirmed the calculation as shown in the following table. The last column shows the results of the reviewer's calculations. Values less than 50 are highlighted.

### **Comparisons between lower strengths and the highest strength**

<b>Product Comparison Details</b>	<b>Dissolution Medium</b>	<b>F2</b>	<b>F2 (Reviewer)</b>
Minocycline Hydrochloride Extended Release Capsules, 135 mg B # 2061751 Vs Minocycline Hydrochloride Extended Release Capsules 45 mg B # 2060265	0.1 N HCl	67.92	67.5
	pH 4.5 Acetate buffer	76.35	75.1
	pH 6.8 phosphate buffer	41.21	40.5
	Mili Q water	65.49	64
Minocycline Hydrochloride Extended Release Capsules, 135 mg B # 2061751 Vs Minocycline Hydrochloride Extended Release Capsules 45 mg B # 2066625	0.1 N HCl	58.53	58.3
	0.1 N HCl	59.32	58.4
Minocycline Hydrochloride Extended Release Capsules, 135 mg B # 2061751 Vs Minocycline Hydrochloride Extended Release Capsules 45 mg B # 2065675	0.1 N HCl	90.49	87.8
	pH 4.5 Acetate buffer	65.42	65.8
	pH 6.8 phosphate buffer	66.24	67.8
	Mili Q water	87.48	84.6
Minocycline Hydrochloride Extended Release Capsules, 135 mg B # 2061751 Vs Minocycline Hydrochloride Extended Release Capsules 67.5 mg B # 2129745	0.1 N HCl	64.46	63.9
	0.1 N HCl	64.88	65.2
Minocycline Hydrochloride Extended Release Capsules, 135 mg B # 2061751 Vs Minocycline Hydrochloride Extended Release Capsules 90 mg B # 2061749	0.1 N HCl	62.51	62.6
	pH 4.5 Acetate buffer	84.95	82
	pH 6.8 phosphate buffer	48.67	48.1
	Mili Q water	74.13	74.4
Minocycline Hydrochloride Extended Release Capsules, 135 mg B # 2061751 Vs Minocycline Hydrochloride Extended Release Capsules 90 mg B # 2065676	0.1 N HCl	73.97	73
	0.1 N HCl	61.09	60.6
Minocycline Hydrochloride Extended Release Capsules, 135 mg B # 2061751 Vs Minocycline Hydrochloride Extended Release Capsules 90 mg B # 2066647	0.1 N HCl	84.42	83.6
	pH 4.5 Acetate buffer	76.98	77.1
	pH 6.8 phosphate buffer	61.03	60.7
	Mili Q water	68.22	67.9
Minocycline Hydrochloride Extended Release Capsules, 135 mg B # 2061751 Vs Minocycline Hydrochloride Extended Release Capsules 112.5 mg B # 2129749	0.1 N HCl	59.32	59.8

Capsules 112.5 mg B # 2142166			
Minocycline Hydrochloride Extended Release Capsules, 135 mg	0.1 N HCl	57.61	57.5
B # 2061751 Vs Minocycline Hydrochloride Extended Release			
Capsules 112.5 mg B # 2132003			

The results showed that the lower strengths are similar to the highest strength in most cases.

### 3. Dissolution Method and Acceptance Criteria:

The proposed dissolution condition and acceptance criteria are as follows.

Apparatus: USP 1 (basket)

Rotation: 100 rpm

Medium: 0.1 N HCl

Volume: 900 mL

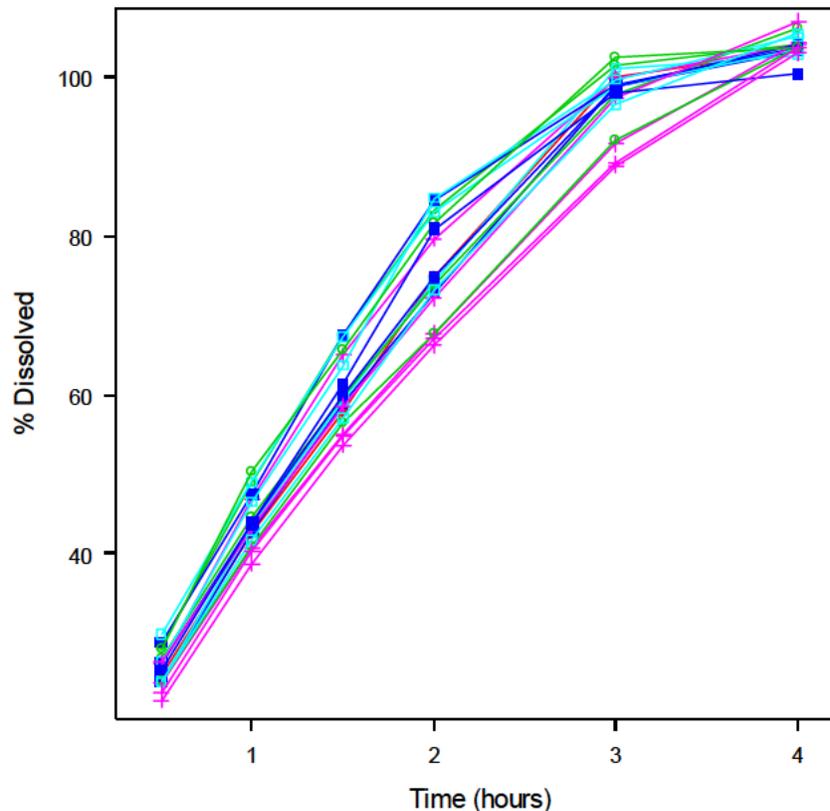
Temperature:  $37 \pm 0.5^\circ\text{C}$

0.5 h: (b) (4)

1.5 h: (b) (4)

4.0 h: NLT (b) (4)

The following figure shows the dissolution profiles for different strengths in the proposed medium of 0.1 N HCl.



Since the proposed IVIVC is not acceptable, there is no basis to widen the dissolution acceptance criteria from the ordinary  $\pm 10\%$  limits. The following will examine whether the data provided

can meet the  $\pm 10\%$  criteria. The following figure shows the individual dissolution data at 0.5 hour. The acceptance criteria can be tightened from (b) (4) to (b) (4).

**Dissolution at 0.5 hour**



Batch No.

Although the 1-hour time point was not proposed as acceptance criteria, it can meet the limits of (b) (4) as shown in the following figure.

**Dissolution at 1 hour**



Batch No.

The following figure shows that the proposed criteria at 1.5 hours can be tightened from (b) (4) to (b) (4)

### Dissolution at 1.5 hour



Batch No.

From the comparison of the following two figures, it seems that a criterion set at (b) (4) at 3 hours is more appropriate than that set (b) (4) at 4 hours.

### Dissolution at 3 hour



Batch No.

Batch No.

Therefore, the recommended acceptance criteria are as follows.

0.5 h: (b) (4)  
1.5 h: (b) (4)  
3.0 h: NLT (b) (4)

The criteria are set using the following conditions.

Apparatus: USP 1 (basket)  
Rotation: 100 rpm  
Medium: 0.1 N HCl  
Volume: 900 mL  
Temperature:  $37 \pm 0.5^{\circ}\text{C}$

#### **4. Dose Dumping Studies:**

To rule out the possibility of dose dumping when the drug product is taken with alcohol, additional dissolution testing using the highest concentration of ethanol in the dissolution media was carried out on the development batch manufactured using the finalized formulation and process, using the following conditions:

Apparatus: USP 1 (basket)  
Rotation: 100 rpm  
Medium: 0.1 N HCl  
Volume: 900 mL  
Temperature:  $37 \pm 0.5^{\circ}\text{C}$

with (40% v/v) and without alcohol, and data was collected every 15 minutes for a total of 2 hours.

Based on the results obtained (Table 4.1-Table 4.6 shown below, the test formulation is not dumping the drug in the presence of alcohol. The test formulation is behaving in the same way as the Innovator in the dissolution conditions containing Alcohol USP (40%v/v).

Table 4.1: Dissolution of Innovator and IH formulation-45 mg strength (0.1N HCl without alcohol)

0.1N HCl/900mL/USPI/100rpm		
Time (min)	Solodyn 45mg B070065	AF(4074)038A 45mg
0	0	0
15	16 (15-16)	16 (15-16)
30	26 (25-26)	27 (25-28)
45	35 (34-35)	37 (36-38)
60	43 (42-44)	48 (47-49)
75	49 (49-50)	56 (56-57)
90	56 (55-57)	64 (63-66)
105	64 (62-66)	73 (72-74)
120	70 (68-71)	79 (78-81)
f2	ref	60

Table 4.2: Dissolution of Innovator and IH formulation-45 mg strength (0.1N HCl with 40% alcohol)

0.1N HCl with 40% alcohol/900mL/USPI/100rpm		
Time (min)	Solodyn 45mg B070065	AF(4074)038A 45mg
0	0	0
15	8 (8-8)	8 (7-10)
30	15 (15-15)	16 (15-18)
45	22 (21-23)	23 (22-25)
60	28 (28-29)	30 (24-31)
75	35 (34-36)	37 (36-38)
90	41 (41-41)	44 (42-45)
105	46 (45-47)	50 (47-51)
120	52 (51-53)	56 (54-58)
f2	ref	78

Table 4.3: Dissolution of Innovator and IH formulation-90 mg strength (0.1N HCl without alcohol)

0.1N HCl/900mL/USPI/100rpm		
Time (min)	Solodyn 90mg 8F4410	AF(4074)038B 90mg
0	0	0
15	16 (16-16)	13 (11-16)
30	27 (27-27)	26 (24-28)
45	36 (36-37)	36 (34-38)
60	46 (45-46)	46 (44-48)
75	55 (54-55)	56 (54-57)
90	63 (63-64)	63 (61-65)
105	72 (72-73)	71 (69-73)
120	79 (78-80)	79 (77-80)
f2	ref	90

Table 4.4: Dissolution of Innovator and IH formulation-90 mg strength (0.1N HCl with 40% alcohol)

0.1N HCl with 40% alcohol/900mL/USPI/100rpm		
Time (min)	Solodyn 90mg 8F4410	AF(4074)038B 90mg
0	0	0
15	9 (9-9)	4 (3-6)
30	16 (15-17)	12 (10-15)
45	23 (22-23)	20 (19-22)
60	29 (29-30)	26 (25-28)
75	36 (35-37)	34 (31-36)
90	42 (42-42)	39 (38-42)
105	47 (47-48)	44 (41-47)
120	54 (54-54)	50 (49-53)
f2	ref	72

Table 4.5: Dissolution of Innovator and IH formulation-135 mg strength (0.1N HCl without alcohol)

0.1N HCl/900mL/USPI/100rpm		
Time (min)	Solodyn 135mg 9A5668	AF(4074)038C 135mg
0	0	0
15	14 (14-15)	13 (10-16)
30	26 (25-26)	26 (24-27)
45	35 (35-35)	36 (34-38)
60	44 (44-45)	46 (43-47)
75	53 (52-54)	55 (54-56)
90	61 (60-62)	63 (61-64)
105	69 (68-70)	70 (69-72)
120	76 (75-76)	78 (77-80)
f2	ref	87

Table 4.6: Dissolution of Innovator and IH formulation-135 mg strength (0.1N HCl with 40% alcohol)

0.1N HCl with 40% alcohol/900mL/USPI/100rpm		
Time (min)	Solodyn 135mg 9A5668	AF(4074)038C 135mg
0	0	0
15	8 (8-8)	8 (7-8)
30	15 (15-15)	13 (12-14)
45	22 (22-22)	20 (19-21)
60	29 (29-29)	26 (26-27)
75	38 (37-38)	32 (32-33)
90	44 (44-45)	38 (37-39)
105	51 (50-52)	43 (42-44)
120	59 (58-60)	49 (48-50)
f2	ref	62

5. Effect of (b)(4) on dissolution

(b)(4) of Minocycline HCl blend was done: (b)(4)

Table: Effect of (b) (4) on the dissolution of capsules

--	--

The results show that there is no significant difference in the dissolution profile of capsules filled with (b) (4)

**Table 4.2 Formulations Prepared for Studying Variations in Functional Polymers**

S.N.	Ingredients	(b) (4)				
		A	B	C	D	
1	Minocycline HCl USP	(b) (4)				
2	(b) (4)					
3						
4						
5						
6						
7						
8						
9						
Total weight of tablet (mg)						

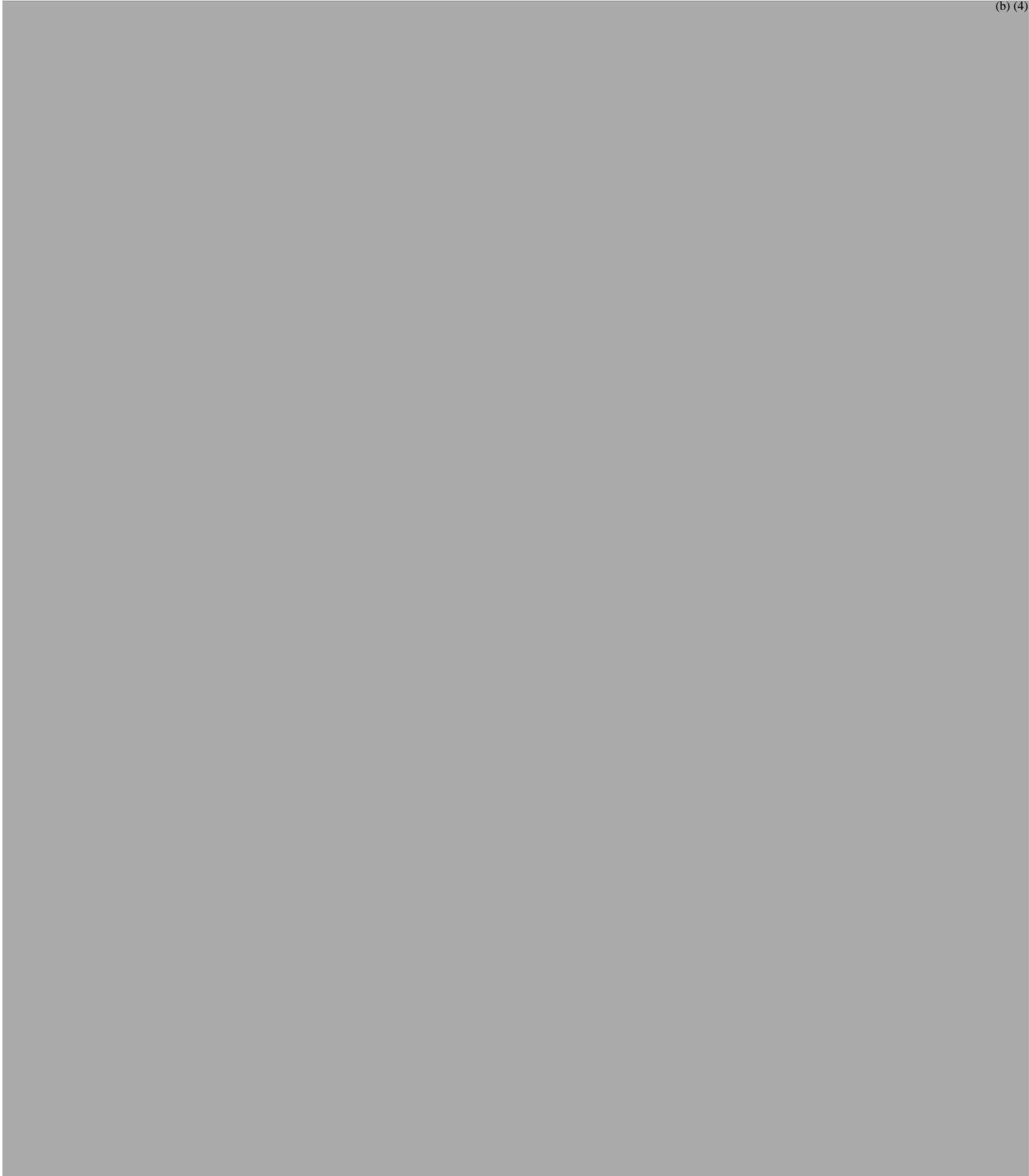
**Table 4.3 DR Profiles Showing Influence of Changes in Functional Polymer Quantities [0.1 N HCl / 900 mL / USP 1 / 100 rpm]**

Time [hr]	(b) (4)
0.5	(b) (4)
1.5	
4	

**6. IVIVC study**

As part of the pilot biostudy, 316\_MJNOC\_08, two preliminary prototypes of Minocycline HCL USP 135mg ER Capsules, Test A (Batch no. KV(3683)43E) and Test B (Batch no, KV(3683)48A), with each product containing 135mg equivalent of minocycline were compared to the innovator lot of Solodyn Tablets, also containing 135 mg of minocycline.

(b) (4)



**Reviewer's comments:**

**1. The IVIVC model is not acceptable.**

(b) (4)

**2. The Applicant accepted the Agency's recommendation for the dissolution acceptance criteria with modifications at 1.5 h for the different strengths, which are acceptable.**

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

JOHN Z DUAN  
08/31/2011

ANGELICA DORANTES  
08/31/2011

## ONDQA BIOPHARMACEUTICS FILING REVIEW

---

<b>NDA#:</b>	<b>201-922</b>
<b>Submission Date:</b>	02/04/2011, 3/28/2011
<b>Generic Name:</b>	Minocycline HCl USP
<b>Formulation:</b>	Capsules ER
<b>Strength:</b>	45, 67.5, 90, 112.5, 135mg
<b>Sponsor:</b>	Ranbaxy Lab
<b>Reviewer:</b>	John Duan, Ph.D.
<b>Submission Type:</b>	Resubmission

---

Minocycline Hydrochloride Extended Release Capsule is submitted pursuant to 505(b)(2) of the Federal Food, Drug, and Cosmetic Act referred to Solodyn Extended Release Tablets.

### COMMENTS

The following information requests were sent to the sponsor on 3/22/2011.

1. Provide all the data for the in-vitro in-vivo correlation (IVIVC) report, including in vivo data for each subject and in vitro data for each unit both for the model building and the validation. The data can be provided in SAS transport file format.
2. It is noted that in the pharmaceutical development report provided in 3.2.P.2, you investigated the effects of different manufacturing process. However, the investigation was focused on (b) (4)

The data can be provided in SAS transport file format.

On 3/28/2011, the applicant submitted the responses to these requests, which will be reviewed to decide whether it is adequate for the proposed acceptance criteria of the dissolution testing and the dissolution profile comparisons. However, these are not filing issues.

### RECOMMENDATION

There are no filing issues from a biopharmaceutics perspective.

---

John Duan, Ph.D.  
Reviewer  
ONDQA Biopharmaceutics

---

Date

---

Patrick Marroum, Ph.D.  
ONDQA Biopharmaceutics

---

Date

cc: NDA 201922  
Angelica Dorantes, Patrick Marroum, John Duan

**APPENDIX.**

**1. The composition of the drug products**

The compositions of minocycline extended release minitables in different strengths are shown in the following table.



(b) (4)

Composition of Minocycline Extended Release Capsules

Ingredients	Quantity mg/ Capsule									
	45 mg	% w/w	67.5 mg	% w/w	90 mg	% w/w	112.5 mg	% w/w	135 mg	% w/w
(b) (4)										
Minocycline Hydrochloride USP equivalent to Minocycline <sup>1</sup>										(b) (4)
(b) (4)										
(b) (4)										
Hypromellose										
(b) (4)										
Lactose Monohydrate <sup>2</sup>										
(b) (4)										
(b) (4)										
Magnesium Stearate										
Colloidal Silicon Dioxide										
<b>Total (Core Tablet)</b>										
<b>Film Coating</b>										
Opady (b) (4) Clear <sup>(4)</sup>										
(b) (4)										
<b>Total (Coated Tablet)</b>	153.000	(b) (4)	229.500	(b) (4)	306.000		382.500	(b) (4)	459.000	(b) (4)
<b>Empty Gelatin Capsule Shell</b>	1	-	1	-	1	-	1	-	1	-

**2. The biowaiver request**

The bioequivalence/food effect and bioequivalence/dose proportionality studies conducted by (b) (4) on Minocycline Hydrochloride Extended Release Capsules 135 mg and 45 mg respectively and Solodyn<sup>o</sup> 135 mg Extended Release Tablets (NDA 050808) of Medicis are submitted.

The in-vitro dissolution profiles for Ranbaxy's Minocycline Hydrochloride Extended Release Capsules 45 mg, 67.5 mg, 90 mg, 112.5 mg and 135 mg are compared to those of the reference listed drug product Solodyn Extended Release Tablets 45 mg, 90 mg and 135 mg of Medicis. In addition, the in-vitro dissolution profile for the proposed 45 mg, 67.5 mg, 90 mg and 112.5 mg strengths are also compared to those of the proposed 135 mg strength. The comparative in-vitro dissolution profiles for Ranbaxy's Minocycline Hydrochloride Extended Release Capsules 45 mg, 67.5 mg, 90 mg, 112.5 mg and 135 mg and the reference listed drug product Solodyn Extended Release Tablets 45 mg, 90 mg and 135 mg of Medicis are presented in the submission.

Ranbaxy's Minocycline Hydrochloride Extended Release Capsules 45 mg, 67.5 mg, 90 mg, 112.5 mg and 135 mg are dose proportionate formulations, as shown in the above table.

Comparative in-vitro dissolution data, comparing the dissolution profile of the following batches of Minocycline Hydrochloride Extended-Release Capsules, 45 mg, 67.5 mg, 90 mg, 112.5 mg and 135 mg with the corresponding strengths of Solodyn<sup>®</sup> Tablets, is provided. Solodyn<sup>®</sup> Tablets are not available in 67.5 mg and 112.5 mg strengths. Therefore, Ranbaxy's 67.5 mg and 112.5 mg strengths have been compared with the innovator's 135 mg strength.

A summary of the in-vitro dissolution studies conducted on the bioequivalence batch is provided in the following table: Summary of In-Vitro Dissolution Studies.

	Ranbaxy's Minocycline Hydrochloride Extended Release Capsules	Solodyn <sup>®</sup> (Minocycline Hydrochloride Extended-Release Tablets, 45/90/135 mg) (Medicis)
Strength	Lot Numbers	Lot Numbers
45 mg	2060265	B080186
	2066625	
	2065675	
67.5mg	2129745	8K5057
	2132008	
	2142165	
90 mg	2061749	8L5389
	2065676	
	2066647	
112.5	2129749	8K5057
	2142166	
	2132003	
135 mg	2061751	8K5057 OC7554 <sup>1</sup>
	2066644	
	2065673	

<sup>1</sup> This lot of the RLD was used during the pivotal bioequivalence studies, Study No. 3739 and 3740. The bioequivalence studies were planned to be conducted at a CRO in (b) (4) but the RLD samples could not be sent to Ranbaxy India for testing due to the unavailability of the required import license. Therefore, this lot of RLD was tested at Ohm Laboratories Inc, 14 Terminal Road, New Brunswick, NJ 08901 prior to the bioequivalence studies. The dissolution results reported in the RLD COA from Ohm has been generated using (b) (4) baskets. However, it is

observed that the dissolution data of this lot (generated using the (b) (4) baskets) is similar to that of the RLD lot 8K5057 (generated using (b) (4)). All future testing shall be performed using (b) (4).

The batch size for the 45 mg, 90 mg and 135 mg strength batches is (b) (4) capsules, for 67.5 mg strength, the batch size is (b) (4) capsules and for 112.5 mg strength, the batch size is (b) (4) capsules.

The Analytical testing data for Minocycline Hydrochloride Extended Release Capsules, 45 mg, 67.5 mg, 90 mg, 112.5 mg and 135 mg and the RLD Solodyn® tablets, 45 mg, 90 mg and 135 mg is provided.

### 3. Dissolution method

The dissolution method used by Ranbaxy is based on the Agency's recommendations for dissolution testing for Minocycline Hydrochloride Extended Release Tablets at the OGD online database "Dissolution Methods for Drug Products".

The dissolution conditions used:

Apparatus: USP, Apparatus I (10 mesh Basket)  
Speed: 100 rpm  
Medium: 0.1N Hydrochloric acid  
Volume: 900 mL  
Time: 0.5 h, 1.5h, 4.0h  
Temperature:  $37 \pm 0.5^{\circ}\text{C}$

Dissolution testing of the drug product was also conducted in the following multimedia using USP apparatus type I (basket) at 100 rpm in 900 mL of the media for both the innovator and the Ranbaxy's 135 mg strength batches:

1. Water
2. pH 4.5 Acetate buffer
3. pH 6.8 Phosphate buffer

For 45 mg, 90 mg, 67.5 mg and 112.5 mg the dissolution testing in the above mentioned media has been done on one batch.

The dissolution profiles comparing the innovator versus the Ranbaxy product in the above listed multimedia and the OGD recommended media are provided as shown below.

#### 4. Dose Dumping Studies

To rule out the possibility of dose dumping when the drug product is taken with alcohol, additional dissolution testing using the highest concentration of ethanol in the dissolution media was carried out on the development batch manufactured using the finalized formulation and process, using the following conditions:

900 mL;

0.1 N HCl;

Apparatus 1 (basket);

100 rpm,

with (40% v/v) and without the alcohol and data was collected every 15 minutes for a total of 2 hours.

Based on the results obtained (Table 4.1, Table 4.2, Table 4.3, Table 4.4, Table 4.5 and Table 4.6 of Addendum 2 to Development Report MCRC /M/F-01-2009 and Table 10 and Table 11 of the Addendum 3 of Development Report DR/MCRCA/B-01-2009. The test formulation is not dumping the drug in the presence of alcohol. The test formulation is behaving in the same way as the Innovator in the dissolution conditions containing Alcohol USP (40%v/v).

Table 4.1: Dissolution of Innovator and IH formulation-45 mg strength (0.1N HCl without alcohol)

0.1N HCl/900mL/USPI/100rpm		
Time (min)	Solodyn 45mg B070065	AF(4074)038A 45mg
0	0	0
15	16 (15-16)	16 (15-16)
30	26 (25-26)	27 (25-28)
45	35 (34-35)	37 (36-38)
60	43 (42-44)	48 (47-49)
75	49 (49-50)	56 (56-57)
90	56 (55-57)	64 (63-66)
105	64 (62-66)	73 (72-74)
120	70 (68-71)	79 (78-81)
f2	ref	60

Table 4.2: Dissolution of Innovator and IH formulation-45 mg strength (0.1N HCl with 40% alcohol)

0.1N HCl with 40% alcohol/900mL/USPI/100rpm		
Time (min)	Solodyn 45mg B070065	AF(4074)038A 45mg
0	0	0
15	8 (8-8)	8 (7-10)
30	15 (15-15)	16 (15-18)
45	22 (21-23)	23 (22-25)
60	28 (28-29)	30 (24-31)
75	35 (34-36)	37 (36-38)
90	41 (41-41)	44 (42-45)
105	46 (45-47)	50 (47-51)
120	52 (51-53)	56 (54-58)
f2	ref	78

Table 4.3: Dissolution of Innovator and IH formulation-90 mg strength (0.1N HCl without alcohol)

0.1N HCl/900mL/USPI/100rpm		
Time (min)	Solodyn 90mg 8F4410	AF(4074)038B 90mg
0	0	0
15	16 (16-16)	13 (11-16)
30	27 (27-27)	26 (24-28)
45	36 (36-37)	36 (34-38)
60	46 (45-46)	46 (44-48)
75	55 (54-55)	56 (54-57)
90	63 (63-64)	63 (61-65)
105	72 (72-73)	71 (69-73)
120	79 (78-80)	79 (77-80)
f2	ref	90

Table 4.4: Dissolution of Innovator and IH formulation-90 mg strength (0.1N HCl with 40% alcohol)

0.1N HCl with 40% alcohol/900mL/USPI/100rpm		
Time (min)	Solodyn 90mg 8F4410	AF(4074)038B 90mg
0	0	0
15	9 (9-9)	4 (3-6)
30	16 (15-17)	12 (10-15)
45	23 (22-23)	20 (19-22)
60	29 (29-30)	26 (25-28)
75	36 (35-37)	34 (31-36)
90	42 (42-42)	39 (38-42)
105	47 (47-48)	44 (41-47)
120	54 (54-54)	50 (49-53)
f2	ref	72

Table 4.5: Dissolution of Innovator and IH formulation-135 mg strength (0.1N HCl without alcohol)

0.1N HCl/900mL/USPI/100rpm		
Time (min)	Solodyn 135mg 9A5668	AF(4074)038C 135mg
0	0	0
15	14 (14-15)	13 (10-16)
30	26 (25-26)	26 (24-27)
45	35 (35-35)	36 (34-38)
60	44 (44-45)	46 (43-47)
75	53 (52-54)	55 (54-56)
90	61 (60-62)	63 (61-64)
105	69 (68-70)	70 (69-72)
120	76 (75-76)	78 (77-80)
f2	ref	87

Table 4.6: Dissolution of Innovator and IH formulation-135 mg strength (0.1N HCl with 40% alcohol)

0.1N HCl with 40% alcohol/900mL/USPI/100rpm		
Time (min)	Solodyn 135mg 9A5668	AF(4074)038C 135mg
0	0	0
15	8 (8-8)	8 (7-8)
30	15 (15-15)	13 (12-14)
45	22 (22-22)	20 (19-21)
60	29 (29-29)	26 (26-27)
75	38 (37-38)	32 (32-33)
90	44 (44-45)	38 (37-39)
105	51 (50-52)	43 (42-44)
120	59 (58-60)	49 (48-50)
f2	ref	62

5. Effect of <sup>(b) (4)</sup> time on dissolution

<sup>(b) (4)</sup> of Minocycline HCl blend was done:

<sup>(b) (4)</sup>

Data is shown in the following table.

Table: Effect of (b) (4) time on dissolution of capsules

(b) (4)

The results show that there is no significant difference in the dissolution profile of capsule (b) (4)

**Table 4.2 Formulations Prepared for Studying Variations in Functional Polymers**

S.N.	Ingredients	(b) (4)			
		A	B	C	D
1	Minocycline HCl USP	(b) (4)			
2	(b) (4)	(b) (4)			
3		(b) (4)			
4		(b) (4)			
5		(b) (4)			
6		(b) (4)			
7		(b) (4)			
8		(b) (4)			
9		(b) (4)			
Total weight of tablet (mg)		(b) (4)			

**Table 4.3 DR Profiles Showing Influence of Changes in Functional Polymer Quantities [0.1 N HCl / 900 mL / USP 1 /100 rpm]**

Time [hr]		(b) (4)	(b) (4)
0.5	(b) (4)		(b) (4)
1.5	(b) (4)		(b) (4)
4	(b) (4)		(b) (4)

**6. IVIVC study**

As part of the pilot biostudy, 316\_MJNOC\_08, two preliminary prototypes of Minocycline HCL USP 135mg ER Capsules, Test A (Batch no. KV(3683)43E) and Test B (Batch no, KV(3683)48A) of Ranbaxy Research Laboratories, India, with each product containing 135mg equivalent of minocycline were compared to the innovator lot of Solodyn Tablets (Reference R, Batch No. B070022), also containing 135 mg of minocycline.



3 Pages Have Been Withheld As b4(CCI/TS) Immediately Following This Page

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

JOHN Z DUAN  
04/05/2011

PATRICK J MARROUM  
04/05/2011

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

**Office of Clinical Pharmacology**

*New Drug Application Filing and Review Form*

General Information About the Submission

	Information		Information
NDA/BLA Number	201922	Brand Name	To be determined
OCP Division (I, II, III, IV, V)	III	Generic Name	Minocycline HCl
Medical Division	DDDP	Drug Class	Tetracycline
OCP Reviewer	Chinmay Shukla, Ph.D.	Indication(s)	Treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris
OCP Team Leader	Doanh Tran, Ph.D.	Dosage Form	Extended release capsule, 45 mg, 67.5 mg, 90 mg, 112.5 mg, 135 mg
Pharmacometrics Reviewer	NA	Dosing Regimen	Once daily
Date of Submission	February 04, 2011	Route of Administration	Oral
Estimated Due Date of OCP Review	September 1, 2011	Sponsor	Ranbaxy Laboratories Ltd.
Medical Division Due Date	September 15, 2011	Priority Classification	Standard
PDUFA Due Date	December 04, 2011		

*Clin. Pharm. and Biopharm. Information*

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
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			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

single dose:	<b>X</b>	<b>2</b>		Study No. 3739 (Fasting BE and Dose Proportionality Study) and Study No. 3740 (Fed BE and Effect of Food Study)
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD -</b>				
Phase 2:				
Phase 3:				
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:	<b>X</b>	<b>2</b>		Solodyn® (Minocycline extended release (ER) tablet 135 mg used as a listed drug)
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	<b>X</b>	<b>2</b>		Single dose trial
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>				
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		2		

On **initial** review of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	The pivotal PK studies have been conducted with a formulation that differed only in the color of the capsule shell compared to the “to be marketed” formulation. Other than this, the formulations were the same.
2	Has the applicant provided metabolism and drug-drug interaction information?		X		
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			The rationale for dose selection is the same as that of the currently marketed listed drug Solodyn <sup>®</sup> . Dosing of this new ER capsule dosage form is going to be based on body weight.
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Pediatric subjects were not included in the BE trials
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? \_\_**  
**\_\_Yes\_\_**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

N.A.

Chinmay Shukla, Ph.D.

Reviewing Clinical Pharmacologist

Date

Doanh Tran, Ph.D.

Team Leader

Date

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

## Filing Memo

---

### Clinical Pharmacology Review

**NDA:** 201922  
**Compound:** Minocycline HCl extended release capsule 45 mg, 67.5 mg, 90 mg, 112.5 mg and 135 mg  
**Indication:** Treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris  
**Sponsor:** Ranbaxy Laboratories Ltd.  
**Date of Submission:** 02/04/2011 (Resubmission)  
**Reviewer:** Chinmay Shukla, Ph.D.  
**Team Leader:** Doanh Tran, Ph.D.  
**Related IND:** 107472

**Background:** This is a resubmission. The original NDA was submitted on May 10, 2010 and a Refuse to File (RTF) decision was taken by the agency on July 16, 2010 (see communication in DARRTS).

With the original NDA, the Sponsor was seeking approval for minocycline HCl, 135 mg extended release (ER) capsules for the same indication that is approved for Solodyn<sup>®</sup> (minocycline HCl, 135 mg ER tablets) on the basis of demonstration similar systemic bioavailability. Solodyn<sup>®</sup> 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.

With this resubmission the Sponsor has proposed to include additional strengths of minocycline HCl ER capsules. Particularly in addition to the originally proposed 135 mg strength, the other strengths proposed include 45 mg, 67.5 mg, 90 mg and 112.5 mg.

The Sponsor has chosen a 505(b)(2) regulatory path for this application and submitted results of 2 pivotal bioequivalence studies comparing the blood levels following minocycline HCl, 135 mg ER capsules with the plasma concentrations of the listed drug, Solodyn<sup>®</sup> (minocycline HCl, 135 mg ER tablets) (Medics, the Dermatology Company) under fasted and fed conditions in healthy adult subjects. In addition, the Sponsor has also assessed the effect of food on the 135 mg dose of their minocycline HCl ER capsule and dose proportionality of the 45 mg and 135 mg dose of their ER capsule.

**BA/BE Trials:** Two clinical study reports have been submitted with this application.

**Study No. 3739** - A 3-treatment, 3-period, 3-sequence crossover randomized, open-label, single-dose fasting study in adult male and female subjects comparing:

- Bio-equivalence of minocycline HCl 135 mg ER capsules with Solodyn<sup>®</sup> 135 mg ER tablets under fasting conditions.

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

- Dose-proportionality of minocycline HCl 45 mg ER capsules and minocycline HCl 135 mg ER capsules both from Ranbaxy Laboratories.

According to the Sponsor, the results showed bioequivalence between minocycline HCl 135 mg ER capsules and Solodyn® 135 mg ER tablets under fasting conditions and values of the 90% confidence interval (CI) of the ratio of geometric means of  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ , and  $C_{max}$  were between 80 – 125 %. Further,  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ , and  $C_{max}$  appear to increase in a dose proportional manner when comparing the results between 45 mg and 135 mg ER capsule dose.

**Study No. 3740** - A randomized, open-label, 3-treatment, 3-period, 3-sequence crossover, single-dose study in adult healthy male and female subjects comparing:

- Bio-equivalence of minocycline HCl 135 mg ER capsules with Solodyn® 135 mg ER tablets under fed conditions.
- The effect of food on minocycline HCl 135 mg ER capsules.

According to the Sponsor, the results showed bioequivalence between minocycline HCl 135 mg ER capsules and Solodyn® 135 mg ER tablets under fed conditions and values of the 90% CI of the ratio of geometric means of  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ , and  $C_{max}$  were between 80 – 125 %. The results of the effect of food show that the 90% CI of the ratio of geometric means of  $AUC_{0-t}$  and  $AUC_{0-\infty}$  were between 80 – 125 %. However, the result of the 90% CI of the ratio of the geometric mean of  $C_{max}$  was 118.22 – 137.61 % which was outside the no effect range of 80 – 125%. The implication of this to any safety concerns will be a review issue.

**Distribution, Metabolism and Excretion** - The Sponsor is relying on available information from Solodyn® label and has not conducted any additional studies.

**Pediatric Waiver:** Since the listed drug Solodyn® is not approved for use in patients below 12 years of age, the Sponsor has submitted for a waiver for age group 0 -12 years. Further, the Sponsor has requested a waiver for pediatric assessment for age group 12 -16 years.

**In-Vitro Dissolution Studies:** The Sponsor has also submitted in-vitro dissolution data to show that extended release capsules 45 mg, 67.5 mg, 90 mg, 112.5 mg and 135 mg are comparable to those of the listed drug Solodyn® extended release tablets (Medics, The Dermatology Company) 45 mg, 90 mg and 135 mg.

**Reviewer Comments:** *The Sponsor has submitted a bio-waiver request for 45 mg, 67.5 mg, 90 mg and 112.5 mg based on in-vitro dissolution studies comparing dissolution profiles of their ER capsule with the listed drug Solodyn®. The in-vitro data and bio-waiver request will be reviewed by Office of New Drug Quality Assessment (ONDQA).*

**Labeling Information:** According to the Sponsor, all labeling language except DESCRIPTION and HOW SUPPLIED sections for minocycline HCl ER capsules are the same as those for Solodyn®.

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

***Reviewer Comments:*** *There are also differences in the Sponsor proposed labeling language for minocycline HCl ER capsules when compared to the approved label for Solodyn® in the following sections: Section 2 - Dosage and Administration, Section 3 - Dosage Forms and Strengths, and Section 12.3 – Pharmacokinetics. This will be a review issue.*

**Analytical Method:** The plasma concentrations of minocycline were determined by a validated High Performance liquid Chromatography Tandem Mass Spectrometric (LC-MS/MS) method. The LLOQ is reported to be 4.114 ng/mL and the linearity range is reported to be 4.114 ng/mL to 3510.500 ng/mL. Three QC concentrations were used and they are 12.342, 658.219 and 2808.400 ng/mL. The Sponsor has also determined bench-top stability in human plasma, bench-top stability during extraction, bench-top stability in blood, stock stability of the drug and internal standard, short term stability of the drug and internal standard, In-injector stability, freeze thaw stability, dilution integrity, and long-term stability.

**Recommendation:** The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 210922 is fileable.

**DSI Inspection Request:** Since pivotal bioequivalence Studies 3739 and 3740 provides a primary link between the new minocycline HCl ER capsules and approved minocycline ER tablets (Solodyn®) for safety and efficacy, this reviewer recommends that a Division of Scientific Investigation (DSI) consult be sent for the inspection of clinical study sites and bioanalysis site listed below that were used for these studies.

Site information	Address
<b><i>Clinical Facility</i></b>	<p><b><i>Lambda Therapeutics Research Inc.</i></b> 460 Comstock Road Toronto, Ontario, Canada M1L 4S4 Tel: (416) 752-3636 Fax: (416) 752-7610</p> <p><b><i>Lambda Therapeutics Research Inc.</i></b> 689 Warden Ave. Unit 1 Toronto, Ontario, Canada M1L 4R6 Tel: (416) 686-6334 Fax: (416) 690-1880</p>
<b><i>Bio-analytical Facility, Pharmacokinetic, Statistical and Reports Facility</i></b>	(b) (4)

**Comments to be sent to the Sponsor:** None

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

CHINMAY SHUKLA  
04/04/2011

DOANH C TRAN  
04/04/2011

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

**Office of Clinical Pharmacology**

*New Drug Application Filing and Review Form*

*General Information About the Submission*

	Information		Information
NDA/BLA Number	201922	Brand Name	
OCP Division (I, II, III, IV, V)	III	Generic Name	Minocycline HCl
Medical Division	DDDP	Drug Class	Tetracycline
OCP Reviewer	Chinmay Shukla, Ph.D.	Indication(s)	Treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris
OCP Team Leader	Doanh Tran, Ph.D.	Dosage Form	Extended release capsule, 135 mg
Pharmacometrics Reviewer	NA	Dosing Regimen	Once daily
Date of Submission	May 20, 2010	Route of Administration	Oral
Estimated Due Date of OCP Review		Sponsor	Ranbaxy Laboratories Ltd.
Medical Division Due Date		Priority Classification	Standard
PDUFA Due Date	March 20, 2011		

*Clin. Pharm. and Biopharm. Information*

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
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			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

single dose:	<b>X</b>	<b>2</b>		Study No. 1974/09 (Fasting BE Study) and Study No. 1975/09 (Fed BE Study)
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD -</b>				
Phase 2:				
Phase 3:				
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:	<b>X</b>	<b>2</b>		Solodyn <sup>®</sup> (Minocycline extended release tablet 135 mg used as a listed drug)
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	<b>X</b>	<b>2</b>		Single dose trial
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>				
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

<b>Literature References</b>				
<b>Total Number of Studies</b>		2		

On **initial** review of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			The pivotal PK studies have been conducted with a formulation that differed in the color of the capsule shell compared to the “to be marketed” formulation.
2	Has the applicant provided metabolism and drug-drug interaction information?		X		
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			The proposed dose 135 mg is the same as the highest dose of the currently marketed listed drug Solodyn <sup>®</sup> (Minocycline HCl extended release tablets).
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?		X		See Filing Memorandum for further details.
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal			X	

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

	studies)?				
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Pediatric subjects were not included in the BE trials
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		X		
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?		X		See Filing Memorandum for further details.
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? \_\_**  
**\_\_No\_\_**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please see Recommendation section at the end of filing memorandum.

Chinmay Shukla, Ph.D.

\_\_\_\_\_  
 Reviewing Clinical Pharmacologist

\_\_\_\_\_  
 Date

Doanh Tran, Ph.D.

\_\_\_\_\_  
 Team Leader/Supervisor

\_\_\_\_\_  
 Date

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

## Filing Memorandum

---

### Clinical Pharmacology Review

**NDA:** 201922  
**Compound:** Minocycline HCl extended release capsule, 135 mg  
**Indication:** Treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris  
**Sponsor:** Ranbaxy Laboratories Ltd.  
**Date:** 06/17/2010  
**Reviewer:** Chinmay Shukla  
**Related IND:** 107472

**Background:** With this NDA, the Sponsor is seeking approval for its minocycline HCl extended release capsules for the same indication that is approved for Solodyn<sup>®</sup> (minocycline HCl, 135 mg extended release tablets) on the basis of demonstration similar systemic bioavailability. To support this, the Sponsor has chosen a 505(b)(2) regulatory path and submitted results of pivotal bioequivalence studies under fasted and fed conditions comparing their minocycline HCl, 135 mg extended release capsules with listed drug, Solodyn<sup>®</sup> (minocycline HCl, 135 mg extended release tablets). The rationale for development of minocycline extended release formulation was to lower the dosing frequency and systemic side effects associated with immediate release minocycline formulations.

**BA/BE Trials:** Two BA-BE study reports have been submitted with this application.

- **Study No. 1974/09** – A single dose fasting in-vivo bioequivalency study comparing minocycline HCl 135 mg extended release capsule of Ranbaxy with Solodyn<sup>®</sup> minocycline HCl, 135 mg extended release tablets of Medicis. This trial was an open label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover BE study with a washout period of 12 days between the 2 periods.
- **Study No. 1975/09** - A single dose fed in-vivo bioequivalency study comparing minocycline HCl 135 mg extended release capsule of Ranbaxy with Solodyn<sup>®</sup> minocycline HCl, 135 mg extended release tablets of Medicis. This trial was an open label, balanced, randomized two-treatment, two-period, two-sequence, single-dose, crossover BE study with a washout period of 13 days between the 2 periods.

**Number of subjects:**

- **Study No. 1974/09 (Fasting)** – 30 healthy male subjects – 29 completed (Age 20-39 years)
  - \* Subject 20 – withdrawn from the study due to an adverse event (upper respiratory tract infection)
- **Study No. 1975/09 (Fed)** – 30 healthy male subjects – 27 completed (Age 18-45 years)
  - \* Subject 02 – withdrawn from the study due to an adverse event (fever)
  - \* Subject 29 – withdrawn from the study because the subject failed to consume the 800 Kcal breakfast required by the protocol

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

\* Subject 19 – dropped out from the study in Period II

**Sponsor's Conclusions:** The results indicate that Ranbaxy's minocycline HCl extended release capsule (135 mg) is bioequivalent to the listed drug; Solodyn<sup>®</sup> [minocycline HCl (135 mg) extended release tablets] under fasting and fed conditions. In the fasting study, the drug was administered after a 10 hour over night fast and meals were provided 4 hours post dose. High calorie high fat diet was provided for the fed studies and subjects had to consume 800 Kcal in order to participate in the trial. A summary of the results is shown in the tables below.

**Table – 1: Statistical summary of comparative bioavailability data for fasting BE study**

Minocycline Dose (135 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study (Study No.1974/09)				
Parameter	Test	Reference	Ratio (%)	90% C.I. (%)
AUC <sub>0-t</sub>	14.8876 (µg.h/ml)	16.2207 (µg.h/ml)	91.78	84.86 to 99.27
AUC <sub>0-∞</sub>	15.8005 (µg.h/ml)	17.1888 (µg.h/ml)	91.92	85.68 to 98.62
C <sub>max</sub>	0.6937 (µg/ml)	0.7646 (µg/ml)	90.73	83.43 to 98.68

**Table – 2: Statistical summary of comparative bioavailability data for fed BE study**

Minocycline Dose (135 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study (Study No.1975/09)				
Parameter	Test	Reference	Ratio (%)	90% C.I. (%)
AUC <sub>0-t</sub>	15.5342 (µg.h/ml)	15.3621 (µg.h/ml)	101.12	96.08 to 106.43
AUC <sub>0-∞</sub>	16.5035 (µg.h/ml)	16.3192 (µg.h/ml)	101.13	96.48 to 106.00
C <sub>max</sub>	0.8450 (µg/ml)	0.8093 (µg/ml)	104.42	99.78 to 109.28

**Distribution, Metabolism and Excretion** - The Sponsor is relying on available information from Solodyn<sup>®</sup> label and has not conducted any additional studies.

**Labeling Information:** According to the Sponsor, all labeling language except DESCRIPTION and HOW SUPPLIED sections for minocycline HCL extended release capsules, 135 mg are the same as those for Solodyn<sup>®</sup> minocycline HCl, 135 mg extended release tablets.

**Analytical Method:** The plasma concentrations of minocycline were determined by a validated LC-MS/MS method. (b) (4) was used as an internal standard. The LLOQ is reported to be 0.022 µg/mL and the linearity range is reported to be 0.022 µg/mL to 2.521 µg/mL. Three QC concentrations were used and they are 0.0599, 0.7878 and 1.9696 µg/mL. Method validation and bioanalytical reports for BE studies 1974/09 (fasting) and 1975/09 (fed) are available for review.

**Reviewer Comments:**

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

- *The Sponsor conducted their BE studies 1974/09 and 1975/09 in an ethnically homogenous population of South Asians. This population is not representative of the US. The Agency conveyed their concerns regarding the study population in an Advice/Information Request letter on 1/14/2010 in response to the initial IND filing which included the protocol for study 1974/09 (Fasting study) and 1975/09 (Fed study).*
- *Although the Sponsor is seeking approval for an indication that affects both male and female patients their pivotal BE studies 1974/09 and 1975/09 have incorporated only male subjects.*
- *In the NDA the Sponsor has not directly addressed the issue of ethnic diversity nor have they addressed the issue of gender exclusion in their trials.*

### **Recommendation:**

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 210922 is not fileable based on 21 CFR 314.101(d)(3).

This refuse to file (RTF) recommendation is based on New Drug Evaluation Guidance Document: Refusal To File (July 12, 1993), which clarified that the Agency, under 21 CFR 314.101(d)(3) can exercise its RTF authority for several reason including the following: “Omission of critical data, information or analyses needed to evaluate effectiveness and safety or provide adequate direction for use”. An example cited in the guidance that fit this definition is: “clearly inadequate evaluation for safety and/or effectiveness of the population intended to use the drug, including pertinent subsets, such as gender, age, and racial subsets.” The Sponsor conducted their pivotal bioequivalence studies in South Asian males, which is not representative of the target population in terms of gender and race.

It should be noted that the sponsor, at the time of the submission of the initial IND request had already started one study and was in the process of initiating the second study (one day after IND filing). Thus the studies were completed prior to receiving the FDA’s comments regarding their trial design.

### **Comments for the Sponsor:**

The *Guidance for Industry - Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* recommends that in-vivo bioequivalence (BE) studies be conducted in individuals representative of the general population, taking into account age, gender and race. It further states that if the drug product is intended for use in both genders, the Sponsor should attempt to include similar proportions of males and females in the study.

- The Sponsor conducted their BE studies 1974/09 and 1975/09 in an ethnically homogenous population of South Asians. This population is not representative of the United States population. These concerns regarding the study population were conveyed to the sponsor in an Advice/Information Request letter on 1/14/2010.
- The Sponsor is seeking approval for an indication that affects both male and female patients; however, BE studies 1974/09 and 1975/09 have incorporated only male subjects.

## **CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Action to resolves the above issues:

- The Sponsor should conduct and submit results from a BE study in subjects that are representative of the target population in the United States.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201922	ORIG-1	RANBAXY LABORATORIES LTD	MINOCYCLINE ER CAPSULES 135 mg

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

---

/s/

---

CHINMAY SHUKLA  
07/06/2010

DOANH C TRAN  
07/06/2010

EDWARD D BASHAW  
07/06/2010