

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**021951Orig1s000**

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

<b>BIOPHARMACEUTICS REVIEW - ADDENDUM</b> <b>Office of New Drug Quality Assessment</b>			
<b>Application No.:</b>	NDA 21-951 Resubmission	<b>Reviewer:</b> Minerva Hughes, Ph.D.	
<b>Submission Date:</b>	29 Nov 2011		
<b>Division:</b>	Division of Dermatology and Dental Products	<b>Team Lead/Supervisor:</b> Angelica Dorantes, Ph.D.	
<b>Sponsor:</b>	Cipher	<b>Secondary Reviewer:</b> same as above	
<b>Trade Name:</b>	(b) (4)	<b>Date Assigned:</b>	23 Nov 2012
		<b>GRMP Date:</b>	20 April 2012
		<b>PDUFA Date:</b>	29 May 2012
<b>Generic Name:</b>	isotretinoin capsules	<b>Date of Review:</b>	7 May 2012
<b>Indication:</b>	Severe recalcitrant nodular acne	<b>Type of Submission:</b> NDA Resubmission-Class 2	
<b>Formulation/strengths:</b>	Hard gelatin capsules/ 10, 20, 30, and 40 mg	<b>Type of Review:</b> Addendum to the Original Review: Biopharmaceutics Post Marketing Commitment	

#### **BACKGROUND**

Original NDA 21-951 was submitted on 27 June 2005 in accordance with Section 505(b)2 of the FDC Act for the use of a new formulation of isotretinoin for the treatment of severe recalcitrant nodular acne. Reference is made to the Biopharmaceutics review of 16 April 2012 by this reviewer for the complete review addressing the acceptability of the biopharmaceutics information in NDA 21-951 (i.e., dissolution method and (b) (4)). At the time of the 16 April 2012 review completion, Post Marketing Commitment (PMC) negotiations regarding the dissolution method and finalized acceptance criteria were ongoing with the Applicant. NDA 21-951 was amended on 4 May 2012 with the finalized PMC and associated timelines, as agreed to with the Applicant.

This addendum to the original review includes the finalized Biopharmaceutics PMC for NDA 21-951 and recommended language for the NDA action letter.

#### **REVISED POST MARKETING COMMITMENT**

The following dissolution method and acceptance criteria are acceptable on an interim basis for release and stability, with a post marketing commitment.



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**PMC – 1: Dissolution method development study**

Conduct an in vitro dissolution method development study to define final test method parameters for quality control. Evaluate the utility of a two-tiered dissolution method (e.g., USP dissolution test 1 for isotretinoin capsules), identify different parameters that allow for enzyme use in accordance with USP guidelines, and identify a suitable surfactant that can be used at lower concentrations, ideally <2%. Other test method parameters may be evaluated, as desired, to assure the development of a robust dissolution test in line with the principles of USP <711> and <1092>. The optimal dissolution test method for your isotretinoin capsules should allow for reproducible product profiles (RSDs <10%).

FDA will make a decision on the final dissolution method for your isotretinoin capsules after reviewing your dissolution method report. Once an agreement is reached on the final test method, use the final test method to propose final dissolution acceptance criteria for your isotretinoin capsules. Your proposal should be supported by dissolution data from at least the first three (3) validation-lots of each capsule strength, and two (2) additional commercial batches of each strength. If the dissolution report provides for a new faster-release dissolution method (i.e., complete release/dissolution for all the strengths in < 90 minutes) and the provided data support the approval of this method, you may propose the implementation of a single-point dissolution criterion. Otherwise, implement at least a two-point criteria, with the first time point being a range of appropriate variability (ideally +/- 10%).

**PMC Schedule Milestones**

Final Protocol Submission Date: July 2012

Study Completion Date: 11/29/2012

Final Report Submission Date: 11/29/2012

It is recommended that the above interim dissolution method/acceptance criteria and the Post Marketing Commitment be included in the NDA's action letter.

From the perspective of Biopharmaceutics, the Resubmission of NDA 21-951 for isotretinoin capsules is recommended for approval with a Post Marketing Commitment.

**Attachments**

PMC Development Template

***SIGNATURES*** – see attached electronic signature page

Minerva Hughes, Ph.D.

Biopharmaceutics Reviewer

Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.

Biopharmaceutics Supervisor (Acting)

Office of New Drug Quality Assessment

**PMC DEVELOPMENT TEMPLATE**

## PMR/PMC Development Template: Product Quality

TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review scientist (ONDQA) or (OBP) and included for ***each*** type of PMR/PMC in the Action Package. See #4 for a list of applicable PMR/PMC types.

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NDA #/Product Name: NDA 21-951/ isotretinoin capsules

PMC #1 Description: Dissolution method development study

Conduct an *in vitro* dissolution method development study to define final test method parameters for quality control. Evaluate the utility of a two-tiered dissolution method (e.g., USP dissolution test 1 for isotretinoin capsules), identify different parameters that allow for enzyme use in accordance with USP guidelines, and identify a suitable surfactant that can be used at lower concentrations, ideally <2%. Other test method parameters may be evaluated, as desired, to assure the development of a robust dissolution test in line with the principles of USP <711> and <1092>. The optimal dissolution test method for your isotretinoin capsules should allow for reproducible product profiles (RSDs <10%).

FDA will make a decision on the final dissolution method for your isotretinoin capsules after reviewing your dissolution method report. Once an agreement is reached on the final test method, we request that you use the final test method to propose final dissolution acceptance criteria for your isotretinoin capsules. Your proposal should be supported by dissolution data from at least the first three (3) validation-lots of each capsule strength, and two (2) additional commercial batches of each strength. If the dissolution report provides for a new faster-release dissolution method (i.e., complete release/dissolution for all the strengths in < 90 minutes) and the provided data support the approval of this method, you may propose the implementation of a single-point dissolution criterion. Otherwise, FDA requests the implementation of at least a two-point criteria, with the first time point being a range of appropriate variability (ideally +/- 10%).

In an email dated 11 April 2012 and NDA amendment of 18 April 2012, the Applicant agreed to complete the aforementioned dissolution study and provide a final report within 6 months of the action letter date.

PMC Schedule Milestones:	Final Protocol Submission Date:	<u>July 2012</u>
	Study Completion Date:	<u>11/29/2012</u>
	Final Report Submission Date:	<u>11/29/2012</u>
	Other:	<u>Not applicable</u>

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct postapproval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Dissolution profiles generated using the proposed dissolution method are highly variable and provide for complete drug release over an extended time frame (b) (4) for a drug product designated as immediate release. The test method also does not comply with USP recommendations for enzyme concentrations and utilizes high amounts of surfactant. These issues present a regulatory challenge for actions on post approval CMC changes affecting product performance, where a robust dissolution test method is critical. A suboptimal dissolution test method also introduces an undesired risk for variability in batch-to-batch product performance.

2. Describe the particular review issue and the goal of the study.

The goal of the study is to optimize the current dissolution test method and acceptance criteria for improved quality assurance of batch to batch consistency.

3. [OMIT — for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay Sterility Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The study will evaluate the utility of a two-tiered dissolution method to address capsule rupture efficiency issues, identify different method parameters that allow for enzyme use in accordance with USP guidelines, and identify a more suitable surfactant that can be used at a lower concentration, ideally <2%. At the end of the study, the Applicant will make a proposal to FDA for a final dissolution test method for quality control. Once an agreement is reached between FDA and the Applicant on a final dissolution test method, the final accepted test method will be used to define acceptance criteria in accordance with FDA Guidelines for IR products (i.e., *one or two-point specification, as appropriate*) to improve product quality assurance for this important drug.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs? *yes*
- Are the objectives clear from the description of the PMC? *yes*
- Has the applicant adequately justified the choice of schedule milestone dates? *yes*
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process? *yes*

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MINERVA HUGHES  
05/07/2012

ANGELICA DORANTES  
05/07/2012

<b>BIOPHARMACEUTICS REVIEW</b> <b>Office of New Drug Quality Assessment</b>			
<b>Application No.:</b>	NDA 21-951	<b>Reviewer:</b> Minerva Hughes, Ph.D.	
<b>Submission Date:</b>	29 Nov 2011		
<b>Division:</b>	Division of Dermatology and Dental Products	<b>Team Lead/Supervisor:</b> Angelica Dorantes, Ph.D.	
<b>Sponsor:</b>	Cipher	<b>Secondary Reviewer:</b> same as above	
<b>Trade Name:</b>	(b) (4)	<b>Date Assigned:</b>	23 Nov 2012
		<b>GRMP Date:</b>	20 April 2012
		<b>PDUFA Date:</b>	29 May 2012
<b>Generic Name:</b>	isotretinoin capsules	<b>Date of Review:</b>	16 April 2012
<b>Indication:</b>	severe recalcitrant nodular acne	<b>Type of Submission:</b> NDA Resubmission – Class 2	
<b>Formulation/strengths</b>	hard gelatin capsules/ 10, 20, 30, and 40 mg	-Dissolution Method & Acceptance Criterion	
<b>Route of Administration</b>	Oral	-Drug Product Classification (b) (4)	
<p><b>SUBMISSION:</b> Original NDA 21-951 was submitted on 27 June 2005 in accordance with Section 505(b)2 of the FDC Act for the use of a new formulation of isotretinoin for the treatment of severe recalcitrant nodular acne. The drug product is a hard gelatin capsule containing a (b) (4) isotretinoin and the excipients (b) (4), soybean oil, sorbitan monooleate and propyl gallate. An Approvable letter was issued on 25 April 2007 requiring a clinical study and dissolution method changes as a condition of approval.</p> <p>This resubmission to the NDA provides for the Applicant's complete response to the deficiencies identified in the 25 April 2007 Approvable letter.</p> <p><b>BIOPHARMACEUTIC REVIEW:</b> ONDQA-Biopharmaceutics was assigned to review the acceptability of the proposed dissolution method and acceptance criterion for quality control, and to provide a recommendation on the most appropriate classification for the proposed drug product (i.e., immediate-release (b) (4)).</p> <p><b>RECOMMENDATION:</b> ONDQA-Biopharmaceutics has evaluated the provided information and has the following comments:</p> <ul style="list-style-type: none"> <li> <p><b>Drug product dosage form classification</b></p> <p>The physico-chemical and pharmacokinetic information provided does not meet current regulatory requirements and guidelines for (b) (4) classification. Therefore, the Applicant's proposed designation (b) (4) is not acceptable, and an immediate-release (IR) classification is recommended for isotretinoin capsules.</p> <p>During an industry teleconference held on 29 March 2012, FDA communicated to the Applicant its recommendation of classifying isotretinoin capsules as an IR dosage form. The</p> </li> </ul>			

Applicant agreed with FDA and accepted the IR designation for their drug product

No further action is indicated from Biopharmaceutics on this review issue. The revision of labeling and other applicable submission documents is not further handled by this review discipline.

- ***Dissolution Acceptance Criteria***

The following dissolution method and acceptance criteria are acceptable on an interim basis for release and stability.



On 11 April 2012, the Applicant agreed to the following Post Marketing Commitment:

1. Dissolution Method Development

- To complete the additional dissolution method optimization studies to, **(1)** evaluate the utility of a two-tiered dissolution method (similar to USP dissolution test 1) to address capsule rupture independently of dissolution, **(2)** identify different method parameters that allow for enzyme use in accordance with USP guidelines, and **(3)** identify a more suitable surfactant that can be used at lower concentrations, ideally <2%. The optimal dissolution test method for your isotretinoin capsules should allow for reproducible product profiles (RSDs <10%).
- To provide a dissolution method development report within 6 months of the date of the action letter under an amendment to the IND. A request for review of the dissolution report will be included in the cover page of their submission.

2. Dissolution Acceptance Limits (Final Criteria)

- To provide a proposal for the final acceptance criteria based on the dissolution profile data from at least the first three (3) validation-lots of each capsule strength, and two (2) additional commercial batches of each strength using the final dissolution method

accepted by FDA. The acceptance criteria should be at least a two-point specification, with the first time point being a range of appropriate variability (ideally +/- 10%). The proposal for the final acceptance criteria will be submitted under a prior approval supplement (PAS) to the NDA within 14 months of the date of the action letter and include the final dissolution method development report and all supportive data to support the proposed final dissolution specification.

It is recommended that the above interim dissolution method/acceptance criteria and the Post Marketing Commitment be included in the NDA's action Letter.

From the perspective of Biopharmaceutics, the Resubmission of NDA 21-951 for isotretinoin capsules is recommended for approval with a Post Marketing Commitment.

Minerva Hughes, Ph.D.  
Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.  
Biopharmaceutics Supervisor (Acting)  
Office of New Drug Quality Assessment

cc: see DARRTS

## ONDQA-BIOPHARMACEUTICS REVIEW NOTES

### 1.0 GENERAL INFORMATION

#### 1.1 RELEVANT REGULATORY HISTORY

NDA 21-951 was submitted on 27 June 2005 in accordance with Section 505(b)2 of the FDC Act for the use of a new formulation of isotretinoin for the treatment of severe recalcitrant nodular acne. An Approvable letter was issued on 1 May 2006 and on 25 April 2007 requiring a clinical trial as a condition of approval. FDA expressed safety concerns due to differences in drug exposure using the new formulation compared with the referenced product, Accutane (NDA 18-662, approved 1982).

In addition to the need for a clinical study, the 25 April 2007 Approvable letter included the following CMC approvable issue (CMC Reviewer, Dr. Tarun Mehta):

- *The proposed dosage form is considered to be an (b) (4) capsule. Therefore, the dissolution test should be established with multiple time points (30, 60, 120, and 240 minutes), with respective acceptance criteria.*

A clinical study, entitled A Double-Blind, Randomized, Phase III, Parallel Group Study Evaluating the Efficacy and Safety of CIP-ISOTRETINOIN in Patients with Severe Recalcitrant Nodular Acne, trial number ISOCT.08.01, was initiated in September 2009 to address FDA's clinical concerns.

This submission, dated 28 November 2011, provides for the Applicant's complete response to FDA's Approvable letter of 25 April 2007.

#### 1.2 BIOPHARMACEUTICS REVIEW FOCUS

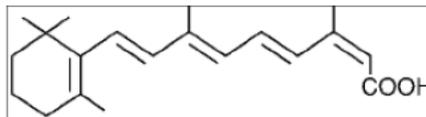
ONDQA-Biopharmaceutics was not involved in the initial review cycles for this NDA. However, the following comment was noted in the Office of Clinical Pharmacology and Biopharmaceutics review of April 2006 (Reviewer: Dr. E. Dennis Bashaw).

*"As has been noted earlier the sponsor is proposing a rather unusual dissolution media (b) (4). In the NDA the sponsor did not submit what would be considered an adequate dissolution section, i.e. lack of comparative media, lack of profiles with early time points. These issues have been summarized by the reviewing chemist in their review for communication to the sponsor. Without this type of data we cannot properly evaluate the proposed method and specification at this time."*

An ONDQA-Biopharmaceutics reviewer was assigned to this Complete Response submission to evaluate the information on product dissolution (test method and acceptance criterion) and on the product classification (b) (4)

### 1.3 DRUG SUBSTANCE OVERVIEW

The drug substance isotretinoin is the retinoid 13-cis-retinoic acid, which inhibits sebaceous gland function and keratinization at certain doses. The substance is chemically related to both retinoic acid and retinol (Vitamin A), as illustrated below.



Structure of isotretinoin

Reference was made to (b) (4) for drug substance chemistry, manufacturing, and controls. The quality control of the drug substance includes tests for appearance, assay, solubility, identification (IR and UV), loss on drying, residue on ignition, heavy metals, impurities, particle size distribution, and residual solvents. (b) (4) tests the drug substance according to the USP monograph requirements. The drug product manufacturer includes the additional tests (e.g., particle size) as part of their incoming specification.

**Reviewer's Comments:** *There were no approvable issues in the 25 April 2007 specific to the drug substance; however, a new drug substance manufacturing facility was added in this complete response. The chemical and physical characteristics of the drug substance appeared comparable between sites. In addition, the Applicant stated no differences in particle size characteristics, which is the most likely quality attribute to impact drug product performance. The manufacturer of Accutane (Roche) attempted to develop an isotretinoin formulation with a reduced food effect as well (Accutane NF, NDA 21-177). Accutane NF used a micronized grade of isotretinoin in the formulation, keeping all other excipients the same as Accutane. This change in drug substance particle size led to notable changes in drug absorption. Reference is made to Dr. Tarun Mehta's Quality Review for additional details on particle size controls.*

### 1.4 DRUG PRODUCT OVERVIEW

The drug product is formulated as a hard gelatin capsule containing isotretinoin and the excipients (b) (4) soybean oil, sorbitan monooleate and propyl gallate. (b) (4). The capsules are packaged into 10-capsule blister packs.

The quantitative composition was summarized as follows.

**Isotretinoin Capsules Composition**

Ingredient and Test Standard	Amount per capsule (mg) Strength 10 mg	Amount per capsule (mg) Strength 20 mg	Amount per capsule (mg) Strength 30 mg	Amount per capsule (mg) Strength 40 mg	Function
Isotretinoin, USP	10	20	30	40	Active
Stearoyl Macroglycerides (b) (4)	(b) (4)				
Soybean Oil, USP					
Sorbitan Monooleate, NF (SPAN 80)					
Propyl Gallate, NF					

(b) (4)

(b) (4)

The drug product manufacturing process consists of (b) (4)  
 (b) (4)

(b) (4). A single formulation blend is used to  
 manufacture the different strengths, (b) (4).

The 40 mg capsule was added in this complete response submission. All other strengths were reviewed in previous review cycles.

**Reviewer's Comments:** The approvable letter referenced issues with control of product dissolution, which is addressed in Section 2.0. In this submission, the Applicant changed (b) (4) from what was reviewed in previous review cycles. An information request was submitted on 12 Jan 2012 for comparative dissolution profile data to support the change. (b) (4)

## 2.0 BIOPHARMACEUTICS REVIEW TOPICS

### 2.1 DRUG PRODUCT CLASSIFICATION (b) (4)

In response to FDA's Chemistry comment in the 25 April 2007 Approvable letter, the Applicant stated that the dosage form is (b) (4) an immediate-release (b) (4), citing the following points.

- (1) The appropriateness of an (b) (4) designation was evaluated and discussed with USP and other industry experts. In consultation with USP, the conclusion was that the proposed formulation differed from other marketed products with respect to a food-effect. (b) (4)

- (2) The drug release pattern (b) (4)  
The Applicant stated that none of the formulation components are (b) (4). Additionally, in vivo bioequivalence comparisons show the same release pattern as the immediate release referenced listed drug Accutane, despite differences in absorption.

- (3) (b) (4)  
The Applicant asserted that there are no FDA guidances or USP stimuli suggesting that *in vitro* dissolution acceptance criterion must be within a specific time range, or that a specific *in vitro* time is used to establish nomenclature. A report entitled Report for CIP-ISOTRETINOIN Dissolution Profile Comparison, dated August 26, 2011, was submitted as justification for the selected dissolution method and acceptance criterion.

#### **Report for Cip-isotretinoin Dissolution Profile Comparison Information Summary**

Dissolution profiles were generated using the proposed dissolution test method with sampling times (b) (4) for each lot. At least 6 samples were used for each tested variable, with 12 samples in some instances. (b) (4)



The Applicant also evaluated the dissolution performance of marketed isotretinoin capsules Claravis and Amnestein using the Applicant's dissolution method to demonstrate the method's discriminating ability. The mean dissolution profiles of the marketed products were illustrated as follows.

***Reviewer's Comments: The report alone was not sufficient to permit an evaluation of the proposed dissolution test method and acceptance criterion.***

*The Applicant correctly noted that in vitro dissolution performance is not a sufficient basis for an (b) (4) designation. However, the submitted in vitro dissolution data do suggest that the drug release profile is atypical (b) (4)*

*As per FDA Guidance for Industry - Dissolution Testing of Immediate Release Solid Oral Dosage Forms, a two-point criterion is recommended for the quality control of (b) (4) drugs such as the isotretinoin capsules. (b) (4)*

*Of note, the Applicant already notes differences in absorption with respect to the immediate release referenced listed drug.*

*Clinical PK studies estimated an MRT(po) (b) (4), suggesting prolonged absorption, which may be partially attributed to the complex dissolution and solubilization properties of lipid-based dosage forms (Chen, *Advanced Drug Delivery Reviews* (2008) 60:768; Pouton, *E. Journal of Pharmaceutical Sciences* (2006) 29:278).*



*ed differences in strength performance, and the role of excipients in the formulation, the Applicant was requested to provide additional information on the following:*

- *Drug solubility*
- *Dissolution method discriminating ability per USP; comparisons with other formulations from a different manufacturer is not appropriate*
- *Role of the (b) (4) excipient in the formulation*
- *The applicability of existing USP dissolution test methods for isotretinoin capsules to the proposed formulation. Current USP dissolution methods do not provide for (b) (4) sampling time. USP dissolution method sampling times range between 60 – 90 minutes depending on the test.*

*See Section 2.2 for an evaluation of the responses, method, and acceptance limits.*

### **In vivo Drug Release Comparison Summary Information**

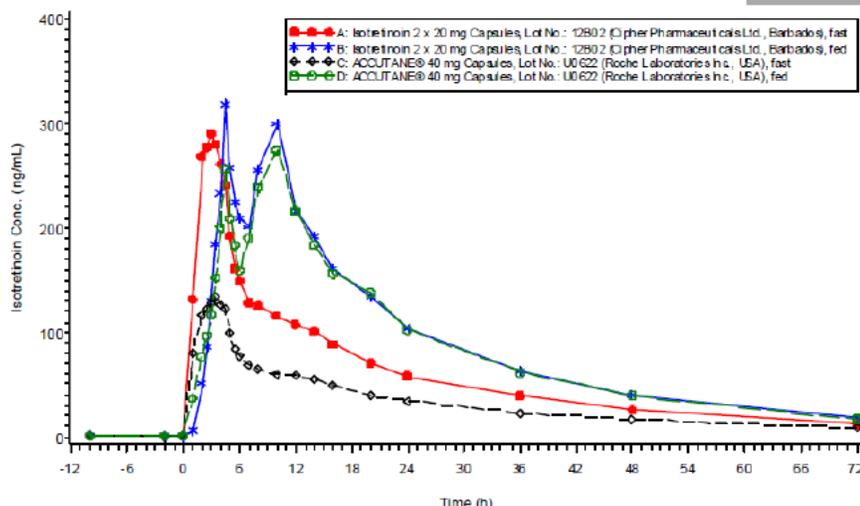
A total of 13 bioavailability and bioequivalence studies, using all four capsule strengths, were conducted. All in vivo bioequivalence and bioavailability information is reviewed by the Office of Clinical Pharmacology. Information relevant to the dosage form designation was evaluated in consultation with the Clinical Pharmacology Reviewer – Dr. Chinmay Shukla to determine if a (b) (4) designation (b) (4) was justified.

With regards to bioequivalence, the FDA concluded in the previous NDA review cycle that the cip-isotretinoin capsules were not bioequivalent to the referenced listed drug in the fasted state, but bioequivalent under fed conditions. The drug exposure response was found to be dose proportional up to 30 mg and less than proportional to 40 mg (see Dr. Shukla's review).

A representative plasma concentration time curve is illustrated below for both fasting and fed conditions.

STUDY No.: 2003-627  
 MEAN MEASURED PLASMA ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES  
 N=57

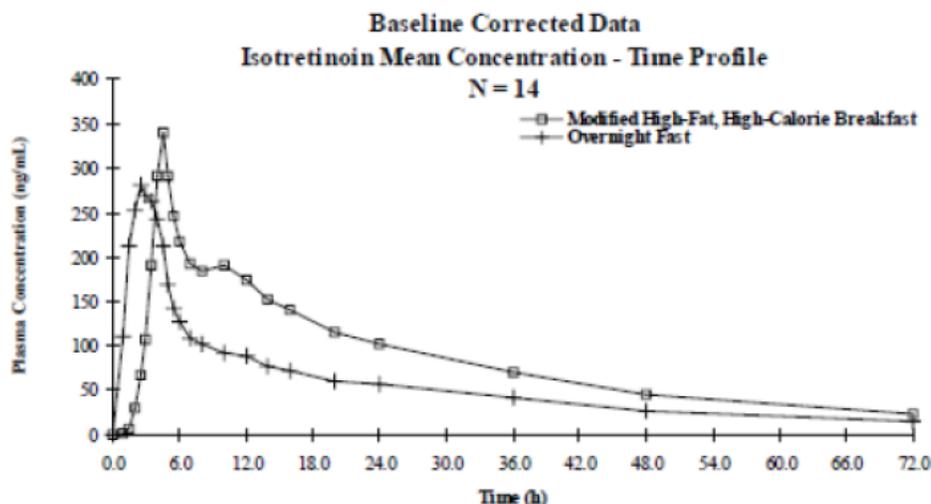
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As submitted in NDA, Figure 15, Section 2.7.1 Summary.

The plasma concentration profiles for each product followed a similar pattern under the same testing conditions. However, the extent and peak exposures differed in the absence of food or how the drug was administered (i.e., 2 x 20 mg vs. 1 x 40 mg). Under fasting conditions, plasma drug levels were generally 60% less than the fed conditions for the listed drug Accutane; whereas, the difference was around 30% for the cip-isotretinoin formulation. Additionally, the time to peak drug concentrations was prolonged under fed conditions with a mean Tmax of about 7 hours. This NDA requests approval for drug administration without regard to food, while the referenced listed drug is labeled to be taken with food. There are no proposed changes to the approved dosing regimen of twice daily, however.

The shift in absorption under fed conditions is illustrated in the plasma time concentration curve below.



As submitted in NDA, Figure 12, Section 2.7.1 Summary.

**Reviewer's Comments:**

(b) (4)

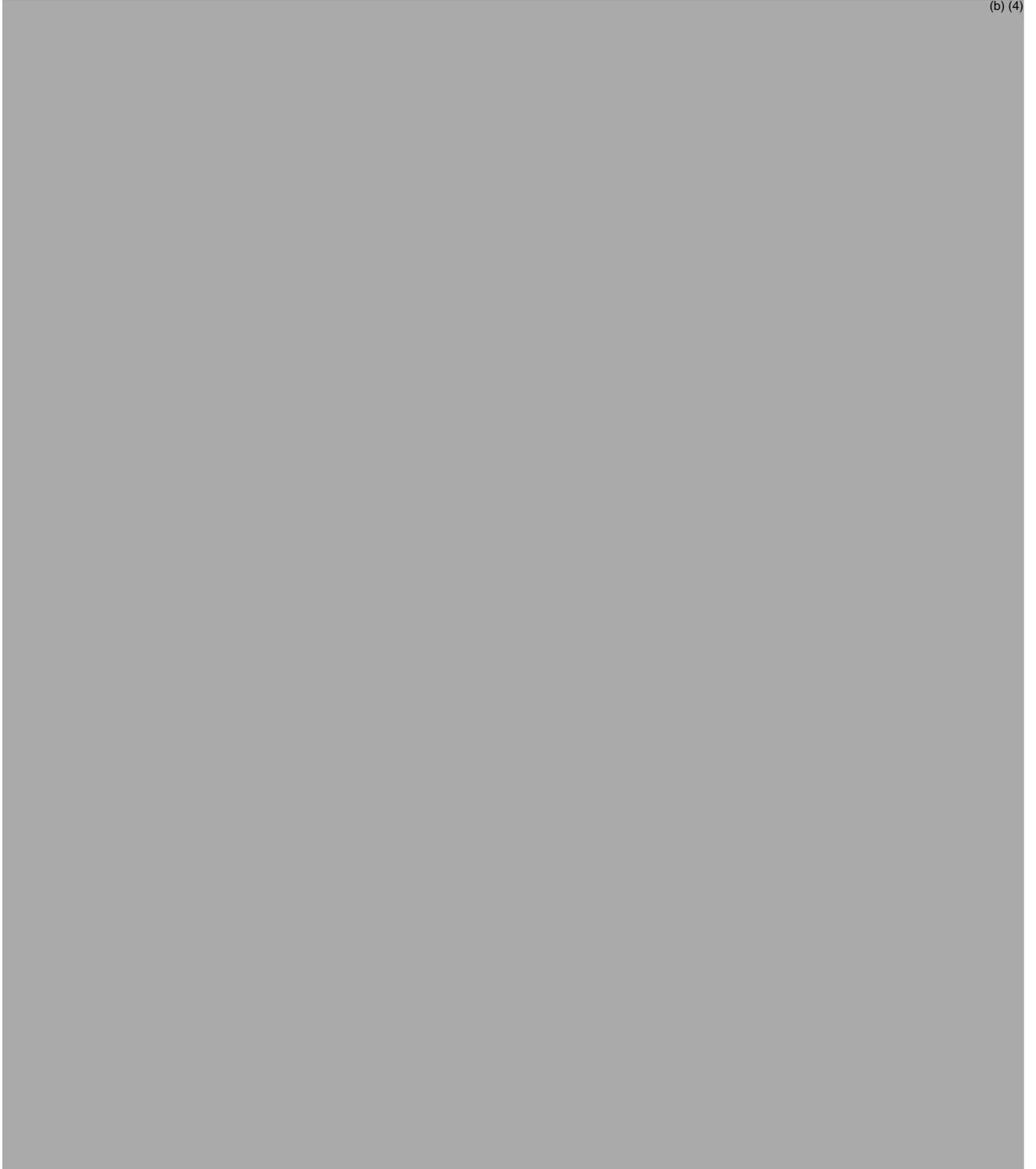
(b) (4)

(b) (4) *the Agency considers the physical appearance of the drug product, physical form of the drug product prior to dispensing to the patient, the way the product is administered, frequency of dosing, and in vivo pharmacokinetics affecting how pharmacists and other health professionals might use the product.*

(b) (4)

## 2.2 DISSOLUTION TEST METHOD

The dissolution method development information described in the subsequent sections was submitted in NDA amendment of 23 Feb 2012, in response to the information request of 12 January 2012.



(b) (4)

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Immediately Following this Page



**Overall Reviewer's Conclusion:** *It is important to establish a robust and useful dissolution method for product quality control.* (b) (4)

(b) (4)

(b) (4) Possible updates could include the following.

- *Studies evaluating different surfactants (types and concentrations), with the objective of identifying the optimal type of surfactant and its concentration (preferably <2%).*
- *Use of a two-tiered dissolution method (similar to USP test method 1) to address capsule rupture independently of dissolution and distinguish between enzyme*

*needed for the gelatin capsule artifacts or lipolysis to release drug from the matrix.*

- *Use of another USP apparatus*

### **2.2.3 USP Dissolution Method Evaluation**

The suitability of existing isotretinoin USP dissolution test methods for evaluating the proposed isotretinoin formulation was evaluated.

(b) (4)



**Reviewer's Comments: Satisfactory.** *The additional dissolution information was requested to better understand the lack of dissolution observed for marketed formulations using the Applicant's proposed method,*

(b) (4)

(b) (4)



(b) (4)



## **2.3 DISSOLUTION ACCEPTANCE LIMITS**

### **2.3.1 Dissolution Acceptance Criterion**

The initially proposed dissolution acceptance criterion was a single-point criterion of:

1.  (b) (4)

Following a meeting on 29 March 2012 between FDA and the Applicant, the Applicant proposed the following criteria for quality control with a commitment to re-evaluate after the manufacture of 20 commercial lots.

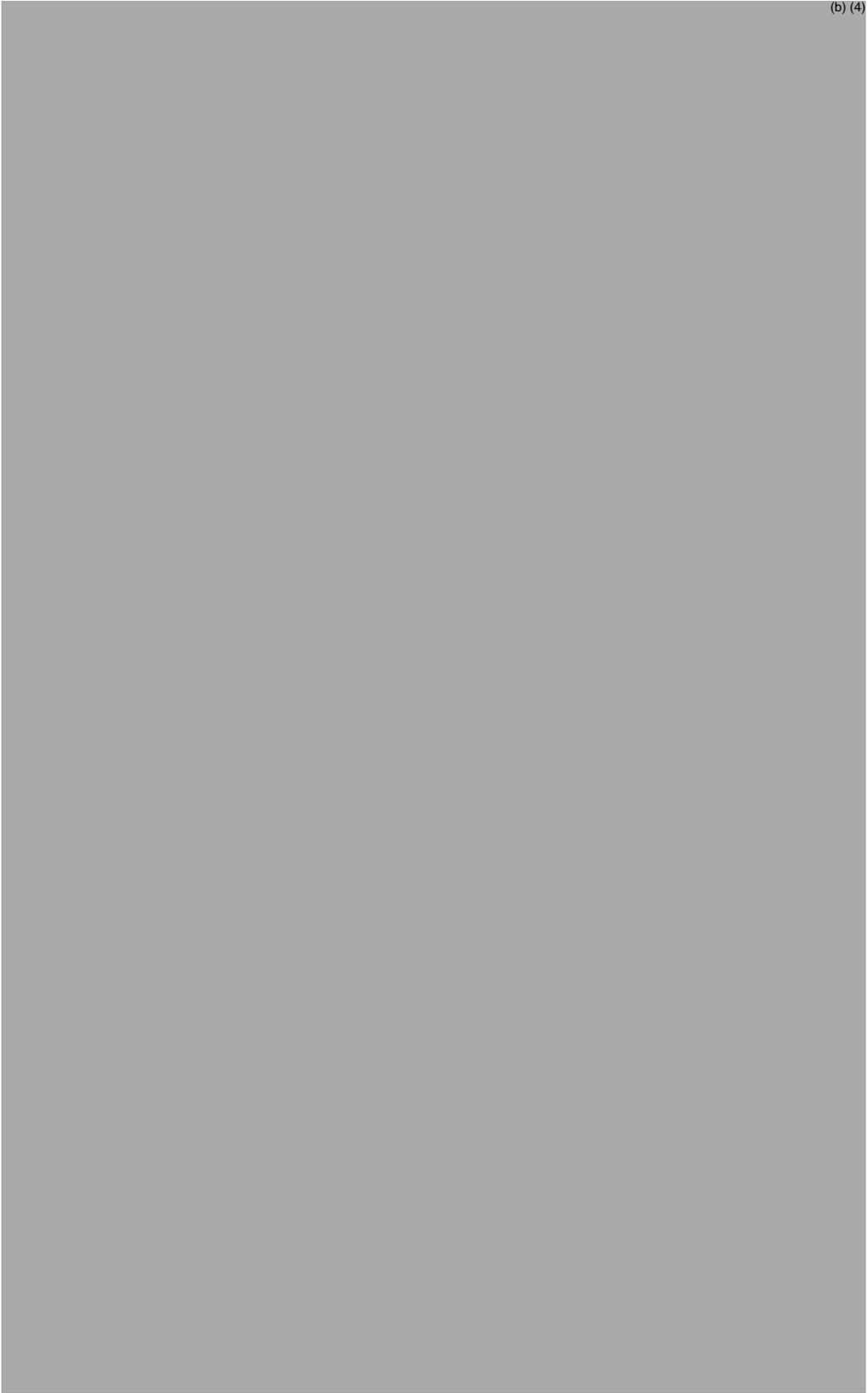


The Applicant's rationale for each approach is evaluated in the following sections.

### **2.3.2 Acceptance Criterion Justification** (b) (4)



(b) (4)



(b) (4)

**Reviewer's Comments:**

(b) (4)

*The acceptance limits should be based on the performance baseline established during clinical studies. In addition, only one lot of 40 mg capsules was available and statistical analysis on only one lot of data is inappropriate. The 40 mg capsule lot also failed to demonstrate bioequivalence in the bioequivalence study (40 mg x two 20 mg) and was not used in the pivotal clinical study.*

*The raw dissolution data were not available for all units to permit a reanalysis by this reviewer; however, on the basis of the dissolution profile data provided in the August report on dissolution, this reviewer evaluated the individual and mean dissolution data for relevant lots and provided the following recommendation to the Applicant.*

(b) (4)

*It should be noted that the biopharmaceutics recommendation was not accepted by the Applicant during the 29 March 2012 teleconference, on the basis that the capsules are an immediate release product. This argument is not valid because multi-point acceptance limits are within the provisions of FDA guidelines on dissolution testing for immediate release solid oral dosage forms and the proposed dissolution method provides for (b) (4). The Applicant needs to develop a new dissolution method if the objective is to have a single-point dissolution acceptance criterion.*

**2.3.3 Revised Acceptance Criterion Justification**

(b) (4)

In response to FDA's comments provided during the 29 March 2012 teleconference, the Applicant provided on 4 April 2012 (by email) the following proposal for revised dissolution acceptance limits.

(b) (4)

In their response, the Applicant acknowledged FDA’s recommendation for acceptance limits based on the data, which show different profiles for the different capsule sizes, but reaffirmed their position that multi-point acceptance criteria are not justified. Additionally, the revised acceptance limits provided for a <sup>(b) (4)</sup> Q value than previously proposed for the 40 mg and 10 mg capsules. The following key points were cited as justification for a single-point acceptance criterion.

- FDA’s recommended acceptance criteria would result in high lot failures.
- The Applicant’s formulation is an immediate-release dosage form.
- There are no intrinsic safety issues related to full or total release, since maximal absorption is under fed conditions and there is no difference in PK between the proposed product and approved isotretinoin products under fed conditions.
- Controlling in vitro release will have no impact on assuring product safety.
- There are no CMC attributes that early time points will assure for product quality.

An analysis of the lot failure rate using FDA’s recommended criteria was summarized as follows.

**Lot Failure Rate Analysis using FDA’s Recommended Acceptance criteria**

Strength [mg]	Lot No.	Passes level			PERCENT of lots being tested at interval			
		L1	L2	L3	L1	L2	L3	FAILURES
10	17F03	N	N	N	100%	100%	50%	50%
	16F032	N	Y	--				
	15D04	N	Y	--				
	15I08	N	N	N				
20	3I02	N	N	N	100%	100%	60%	60%
	4I02	N	N	N				
	5I02	N	N	N				
	16I08	N	Y	--				
	16I082	N	Y	--				
30	8C02	Y	--	--	100%	50%	0%	0%
	29G04	N	Y	--				
40	18E104	N	Y	--	100%	50%	100%	0%

The Applicant requested FDA consideration to the fact that the proposed acceptance limits are based on limited data and seeks agreement to reevaluate the suitability of tighter limits after the manufacture of 20 lots of product.

**Reviewer’s Comments:** *The Applicant’s argument that multipoint criteria are not appropriate simply because FDA has assigned an immediate release designation is not valid. The dissolution acceptance limits should be based on product performance considerations using the proposed method and an understanding of critical quality attributes impacting dissolution.* <sup>(b) (4)</sup>

(b) (4)



*Therefore, the following criteria are recommended for tentative approval with a commitment to improve the method and tighten the limits in the future.*

(b) (4)



*This reviewer has revised the dissolution acceptance criteria recommendation accordingly to provide tentative limits that better reflect the method's variability, while maintaining controls*

*to detect for the dissolution rate changes of greatest concern for product quality* (b) (4)

(b) (4)

A teleconference was held with the Applicant on 12 April 2012 to clarify FDA's recommendation and to reach an agreement on interim acceptance limits for quality control. The meeting summary and final review recommendations are discussed in Section 3.0 and 4.0 of this review.

**2.4** (b) (4) **SUPPLEMENTAL INFORMATION ON EXCIPIENT CHARACTERISTICS**

(b) (4)

Copies of all articles were included in the submission for review along with a copy of the manufacturer's technical information sheet.

**Reviewer's Comment:** *The additional information is acknowledged. Consistent with this reviewer's previous findings, (b) (4) are multi-functional excipients (b) (4). The specific (b) (4) used by this Applicant, however, appears to provide (b) (4). The complexity of drug release from the lipid-matrix, however, is atypical of most immediate release dosage forms and can not be ignored with respect to developing appropriate dissolution acceptance criteria for quality control.*

## 2.5 PRODUCT STABILITY

A shelf-life (b) (4) is requested for the cip-isotretinoin capsules. The Applicant noted that in an amendment dated October 26, 2006, Appendix 7 to stability report ST-014, "Dissolution Data Details 2 hours and 4 hours Results", a 2 hour time point on 10 lots was provided for reference only, as this was done for research and development purposes. These stability data were not re-submitted in eCTD format.

**Reviewer's Comments:** *No dissolution profile data were provided for stability studies for review, as requested. Additionally, the (b) (4) test data were reviewed under previous NDA review cycles. Stability data submitted in the complete response submission were only for protocols ST-046 and ST041. These data included up to 12 months long-term storage for the 40 mg capsules and 3 months long-term storage for all other strengths. Therefore, there is no information for biopharmaceutics to review. Reference is made to the Quality review by Dr. Tarun Mehta for a recommendation on product shelf-life.*

*It is noted in the Applicant's email of 12 April 2012 that defining dissolution acceptance limits based on product performance at release presents a challenge for the product's shelf life. This statement suggests that the Applicant is aware of dissolution rate changes during product storage. Fluctuations in dissolution rates are either related to the dissolution method or product quality, which highlights the importance of additional method improvements and dissolution profile performance (i.e., multi-points) for assuring batch-to-batch consistency.*

## 3.0 INTERACTIVE REVIEW INFORMATION REQUESTS

A list of ONDQA-Biopharmaceutics information requests conveyed during the review process is outlined below.

Biopharmaceutics Information Request of 12 January 2012.

Responses were received on 23 Feb 2012 and incorporated in the review above.

- (1) The solubility and stability profile of the drug substance over the pH range of 1 – 8.0. Please note that that solution pH should be evaluated before and after the test.

- (2) A complete dissolution method development report containing details on the testing performed to select the optimal parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, sinkers, etc.). The type and amount of any additives (enzymes, surfactants, etc.) should be justified with data. We recommend the use of at least twelve samples per testing variable, and include the complete dissolution data (individual, mean, SD, profiles) for your product in the report.
- (3) Please note that comparing the dissolution profiles for your product with another marketed product using the proposed dissolution method is not sufficient to demonstrate the discriminating capabilities of your method as per USP <1092>. Provide a summary of the testing completed to establish that your proposed dissolution method can detect changes in composition or manufacturing process outside the operational ranges that might be expected to affect clinical performance. Your drug product formulation includes the multifunctional excipient (b) (4). Therefore, we recommend that your evaluation of the method's discriminating capabilities include information on the method's ability to detect and reject product manufactured with abnormal levels of drug, (b) (4) and soybean oil, and non validated mixing times and process temperatures. Provide the complete dissolution data (individual, mean, SD, profiles) for all variables tested.
- (4) To better understand the mechanistic basis for the observed differences in dissolution profile characteristics between your proposed product and approved isotretinoin drug products, please provide comparative dissolution profile data for at least one of listed products referenced in your application using the USP monograph dissolution method for that product. Refer to the approved product's labeling for information on which USP test the product complies with.
- (5) As noted in a previous comment, the FDA considers the excipient (b) (4) when formulated with lipophilic drug substances such as isotretinoin based on the available scientific literature. Please provide your scientific rationale as to why it is not appropriate to view the excipient (b) (4) in your formulation. We recommend that you provide copies of any scientific literature used to support your position.
- (6) To support your proposed acceptance criteria time and limit, please provide all available dissolution profile data (i.e., multi-point sampling) for the clinical and registration lots at release and on stability. This information will also be used to support setting an expiration dating period for your product.
- (7) Provide comparative in vitro dissolution data to support the change in capsule shell color for the 20 mg, 30 mg, and 40 mg strengths. Complete dissolution data (individual, mean, RSD, and profiles), with adequate sampling (i.e., 15, 30, 45, 60, 120 minutes etc) until either (b) (4) of the drug is released or an asymptote is reached, using at least 12 samples for the changed and unchanged product is requested. For Similarity f2 testing, the reference product should be the unchanged product.

Biopharmaceutics topics discussed during the 29 March 2012 teleconference.

Additional information received on 3 April 2012 and incorporated in the review above.

- (8) Additional clarification/justification is needed to support the following dissolution method parameters:
- Selection of surfactant concentration
  - Use of enzyme concentrations in excess of USP guidelines
  - Apparatus paddle speed (b) (4)
  - Sources of high data variability at certain time points
- (9) Multi-point criteria are recommended for quality control, as per FDA Guidance - Dissolution Testing of Immediate Release Solid Oral Dosage Forms. Recommended acceptance criteria are as follows:

(b) (4)

Biopharmaceutics Information Request of 4 April 2012.

Responses were received on 5 April 2012 and incorporated in the review above.

- (10) In your response to FDA's recommended dissolution acceptance criteria, you stated that the proposed multi-point acceptance limits would result in failures for clinical lots. Please specify the lot numbers and provide the associated dissolution profile data (mean, individuals, and RSDs) for review. Please note that a dissolution failure means that the lot would fail at stage 3 testing as per USP.
- (11) During the 29 March 2012, FDA believed that we reached an agreement with Cipher that a single acceptance limit was not appropriate for all capsule strengths given the differences in drug release profiles for each strength, the lack of bioequivalence to the listed drug under fasting conditions, and the lack of dose proportionality across all strengths. Your proposed dissolution acceptance limits are unclear in the 3 April 2012 information amendment. Please provide your proposed dissolution acceptance limits for each capsule strength. The dissolution acceptance criteria should be based on the available dissolution data, in accordance with FDA guidelines.

After reviewing the Applicant's proposed (b) (4) dissolution acceptance criteria in the 5 April 2012 email response, Biopharmaceutics recommended a two-point acceptance criteria approach to better control for "slower" dissolution rates. The following information request was issued on 9 April 2012.

- (12) We acknowledge your request to implement a tentative dissolution specification, with a commitment to define a final specification after the manufacture of 20 lots. Your proposed tentative specification is not accepted. We recommend the following tentative specification for product quality control.



The available data showed that differences in the in vitro dissolution rate, in particular the 40 mg capsules compared with the lower strengths, were correlated to absorption differences in vivo. Additionally, the proposed dissolution method provides for

Consequently, FDA is recommending at least a two-point specification approach for quality control. A lower limit, as recommended, should be implemented on an interim basis, with the following commitment.

- Additional Method Development  
Complete additional method optimization studies to (1) evaluate the utility of a two-tiered dissolution method (similar to USP dissolution test 1) to address capsule rupture independently of dissolution, (2) identify different method parameters that allow for enzyme use in accordance with USP guidelines, and (3) identify a more suitable surfactant that can be used at lower concentrations, ideally <2%. The optimal dissolution test method for your isotretinoin capsules should allow for reproducible product profiles (RSDs <10%). Additionally, an improved dissolution method that complies with the isotretinoin USP capsules test method sampling times may justify a single-point specification for your isotretinoin capsules. A report is requested within 1 year of the date of the action letter.
- Specification Refinement  
The revised specification should be at least a two-point specification, with the first time point being a range of appropriate variability (ideally +/- 10%). The final specification should be based on dissolution profile data from at least the first 5 lots of each capsule strength.

The Applicant's responses received by email on 11 April 2012, indicated a clear misunderstanding of FDA's recommendation. A teleconference was held between FDA and the Applicant on 12 April 2012 to clarify FDA's recommendation and to reaffirm the

Agency's request for compliance with the FDA Guidance for Industry on immediate release solid oral dosage forms.

The 12 April 2012 teleconference summary is as follows:

- FDA clarified that the proposed two point dissolution acceptance criteria are based on applying USP L1/L2/L3 testing criteria for multiple time points and do not result in the rejection of clinical batches as purported by the Applicant.
- FDA clarified that for a poor soluble, slow dissolving product such as the cip-isotretinoin capsules, a two-point specification is appropriate and in line with FDA guidelines for immediate release products.
- The Applicant committed to revising the dissolution acceptance limits to include a two point specification for quality control that is in-line with FDA's recommendation.

The revised dissolution acceptance criteria proposed by the Applicant in the email of 13 April 2012 are as follows.



The Applicant also committed to improving the method and finalizing the dissolution acceptance criteria after additional manufacturing experience. The revised dissolution acceptance criteria were based on a re-evaluation of the available dissolution data by the Applicant. The Applicant noted that FDA's proposed limits were based on a limited number of lots, and asserts that this approach increases the likelihood of commercial batches going to L3 and/or batch failure.

***Reviewer's Comments: Tentative limits are accepted.***

- *The key differences between the FDA's criteria and the Applicant's 13 April 2012 proposal are (b) (4) sampling time for the 10 mg and 30 mg capsules and (b) (4) the lower limit criteria for the 20 mg and 40 mg capsules. The Applicant's rationale for this proposal is that there is not enough batch history to understand the variability in commercial batches. This argument is flawed because the available clinical batches should provide the baseline performance for which commercial batches should not exceed. It is not appropriate to implement (b) (4) (b) (4) to account for unknown shifts and avoid lot failures. Nevertheless, it is acknowledged that the proposed method is not optimal and it is reasonable to conclude that (b) (4) changes in dissolution values are indicative of method issues and may not necessarily be a sign of significant product quality changes. Thus, the Applicant's proposal is accepted on an interim basis given the Applicant's commitment to improve*

*the method and revise the specification accordingly to comply with FDA guidelines on dissolution testing for immediate release products.*

#### 4.0 CONCLUSIONS AND RECOMMENDATIONS

From the perspective of Biopharmaceutics, the application is recommended for Approval with a PMC.

The following dissolution acceptance criteria are recommended for approval on an interim basis.



The Applicant's post marketing commitment is to improve the dissolution method to reduce variability associated with inefficiencies in capsule disruption, the amount of surfactant and the amount of enzyme used. The goal of an optimal quality control dissolution method is to achieve reproducible product profiles and not simply performance at a single time point. This is especially important when evaluating post-approval changes whereby the dissolution profile is a measure of product sameness pre and post change.

Post Marketing Commitments:

1. Dissolution Method Development

- Complete additional method optimization studies to (1) evaluate the utility of a two-tiered dissolution method (similar to USP dissolution test 1) to address capsule rupture independently of dissolution, (2) identify different method parameters that allow for enzyme use in accordance with USP guidelines, and (3) identify a more suitable surfactant that can be used at lower concentrations, ideally <2%. The optimal dissolution test method for your isotretinoin capsules should allow for reproducible product profiles (RSDs <10%). A report is requested within 6 months of the date of the action letter.

2. Dissolution Acceptance Limits (Final Criteria)

- Define the final acceptance criteria based on dissolution profile data from at least the first three (3) validation-lots of each capsule strength, and two (2) additional commercial batches of each strength using the final dissolution method accepted by FDA. The acceptance criteria should be at least a two-point specification, with the first time point being a range of appropriate variability (ideally +/- 10%).

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/s/  
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MINERVA HUGHES  
04/16/2012

ANGELICA DORANTES  
04/16/2012

## Clinical Pharmacology Review

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NDA #:	021951
Submission Date:	November 29, 2011
Brand Name:	To Be Determined
Generic Name:	Isotretinoin
Dosage Form:	Capsules
Dosage Strength:	10, 20, 30 and 40 mg
Reviewer:	Chinmay Shukla, Ph.D.
Team Leader:	Doanh Tran, Ph.D.
Pharmacometrics Reviewer:	Dhananjay Marathe, Ph.D.
Pharmacometrics Team Leader:	Yaning Wang, Ph.D.
OCP Division:	DCP-3
OND Division:	Division of Dermatology and Dental Products
Sponsor:	Cipher Pharmaceuticals, Inc.
Relevant IND(s):	064,927
Submission Type:	(Resubmission) complete response to approvable letter
Indication:	Treatment of severe recalcitrant nodular acne in patients 12 years of age and older

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### 1. Executive Summary

**Regulatory history:** The original NDA was submitted on July 1, 2005 and the Sponsor had chosen a 505(b)(2) regulatory pathway and had identified Accutane® as a listed drug. This submission received an approvable letter on May 1, 2006 and a number of elements were noted as being inadequate, including demonstration of dose proportionality, chemistry release specifications, appropriate risk management program, etc. The Agency also recommended that the Sponsor conduct a clinical safety and efficacy trial in which

the Sponsor's product is compared with Accutane<sup>®</sup> since the Sponsor failed to demonstrate the lack of clinical relevance due to the observed differences in the pharmacokinetic (PK) profile of their product and Accutane<sup>®</sup> (see communication in DARRTS).

The Sponsor responded with a complete response (CR) on October 26, 2006. This amended application also received an approvable letter on April 25, 2007; again a number of deficiencies were identified and one of them was lack of demonstration of bioequivalence (BE) of their product with listed drug Accutane<sup>®</sup> under fasted conditions (see communication in DARRTS). The Agency expressed concerns that although Accutane<sup>®</sup> is approved to be taken with food, the Sponsor's product showed higher exposure compared to Accutane<sup>®</sup> under fasting conditions and this was considered to be an issue because the potential real world use of Accutane<sup>®</sup> is likely without regards to food [Accutane<sup>®</sup> was originally approved to be administered without regards to meals (Date of approval 05/07/1982). The results of food effect and the recommendation to be administered with a meal were added to the label on 12/31/2001].

This submission is a complete response to the Agency communication dated April 25, 2007 and the Sponsor has submitted results of a Phase 3 trial. The Sponsor also submitted results of 3 new Clinical Pharmacology trials in support of their additional 40 mg strength (original application was for 10, 20 and 30 mg strength).

### **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**

***Findings from the previous submissions:*** This application follows a 505(b)(2) regulatory pathway and the Sponsor plans to rely in part on prior safety and efficacy data obtained with the listed drug, Accutane<sup>®</sup>. With the original application, the Sponsor conducted relative bioavailability (BA) studies with their product and Accutane<sup>®</sup> under fasting and fed conditions, a food effect study, studies to demonstrate proportionality between different strengths under fasting and fed conditions to support interchangeability among different strengths, and single and multiple dose PK estimations obtained by serial blood sampling. These studies were reviewed by Dr. Dennis Bashaw (see review in DARRTS dated 04/21/2006 and 04/09/2007 for further details).

The results of relative BA studies showed that under fed conditions Cipher's isotretinoin formulations (hereafter referred to as CIP-Isotretinoin) was BE with Accutane<sup>®</sup>, but they

were not BE under fasting conditions. Specifically, the exposure of CIP-Isotretinoin was approximately 2 fold higher than Accutane<sup>®</sup> when both the formulations were administered under fasting conditions. It should be noted that the relative BA study was conducted using only the 20 mg strength of CIP-Isotretinoin, but results of proportionality studies support application of these findings to other strengths.

The results of proportionality studies indicated that the BA of CIP-Isotretinoin increased in a proportional manner between 10 mg and 30 mg strength under both fasting and fed conditions. This indicated that these strengths could be used interchangeability to achieve target dosing of 0.5 mg/kg/day to 1 mg/kg/day in 2 divided doses.

The results of the food effect study conducted using 30 mg strength indicated that the effect of food was substantially larger on the Accutane<sup>®</sup> formulation compared to the CIP-Isotretinoin formulation; however, there was still a significant food effect on the CIP-Isotretinoin. In the presence of food, the systemic exposure (AUC) increased on average 1.5 times for CIP-Isotretinoin formulation and approximately 2.5 times for the Accutane<sup>®</sup> formulation, while the peak exposure ( $C_{max}$ ) to isotretinoin increased under fed conditions and was approximately 1.6 times and 2.7 times for CIP-Isotretinoin and Accutane<sup>®</sup> formulations, respectively, compared to fasting conditions.

**Addition of a new strength:** With the original submission, the Sponsor was seeking approval of 3 strengths of the CIP-Isotretinoin capsules, 10 mg, 20 mg and 30 mg. With this resubmission the Sponsor has requested an additional strength of 40 mg along with the previous strengths of 10, 20 and 30 mg.

**New trials:** With the addition of the 40 mg strength, the Sponsor conducted 3 new Clinical Pharmacology trials and one Phase 3 trial as shown below.

- ISOPK.08.02 – Effect of food on the 40 mg strength
- ISOPK.09.01 – Relative BA study of 2 x 20 mg CIP-Isotretinoin vs. 1 x 40 mg CIP-Isotretinoin under **Fed** conditions
- ISOPK.09.02 – Relative BA study of 2 x 20 mg CIP-Isotretinoin vs. 1 x 40 mg CIP-Isotretinoin under **Fasting** conditions
- ISOCT.08.01 – Double blind, randomized, parallel group study evaluating the efficacy and safety of CIP-Isotretinoin and marketed isotretinoin in patients with severe recalcitrant nodular acne (Phase 3 trial was conducted using only the 10 and 20 mg strength. 30 and 40 mg strengths were not used in the dosing).

The results of the effect of food trial (ISOPK.08.02) showed that the exposure of isotretinoin following administration of 40 mg strength was significantly increased when administered with a modified high-fat, high calorie breakfast compared to fasting conditions. Specifically the AUC and  $C_{max}$  under fed conditions were approximately 1.5 and 1.3 fold respectively, higher with food compared to fasting. The effect of food on PK of the new 40 mg strength appears to be similar with that observed with previously evaluated 30 mg strength.

The results of the relative BA trial under Fed conditions (ISOPK.09.01) showed that exposure of 2 x 20 mg and 1 x 40 mg were BE with the 90% confidence interval (CI) of the ratio of the geometric mean of AUC and C<sub>max</sub> within the no effect boundary of 80% to 125 %. This indicates that the PK of isotretinoin increased in a proportional manner between 20 mg to 40 mg strengths under Fed conditions [proportionality between 10 mg to 30 mg strength under both fasting and fed conditions was shown earlier (see review by Dr. Bashaw dated 04/09/2007)]. Isotretinoin dosing is based on body weight and this requires several permutation and combination of different strengths to achieve an ultimate dosing in the range of 0.5 mg/kg/day to 1 mg/kg/day in 2 divided doses. In conclusion, these results would imply that under fed conditions the 4 strengths (10 mg, 20 mg, 30 mg and 40 mg) could be used interchangeably to achieve the target daily dosing between 0.5 mg/kg to 1 mg/kg in 2 divided doses.

The results of the relative BA trial under Fasting conditions (ISOPK.09.02) showed that the exposure of 1 x 40 mg strength was slightly lower than 2 x 20 mg strength indicating that the PK of 40 mg strength capsule increased in a slightly less than dose proportional manner under fasting conditions. Specifically the AUC and C<sub>max</sub> with 1 x 40 mg strength were approximately 15% and 20%, respectively, lower than those following administration of 2 x 20 mg strength. The results are shown in Table 1 below.

**Table 1: Results of relative BA of 1 x 40 mg strength versus 2 x 20 mg strength of CIP-Isotretinoin presented as 90% CI (Baseline Corrected Data)**

	AUC <sub>0-t</sub>	AUC <sub>0-inf</sub>	C <sub>max</sub>
Ratio of geometric mean	0.84	0.85	0.80
90% CI	0.78 – 0.90	0.79 – 0.91	0.74 – 0.87

*Test: CIP-Isotretinoin 1 x 40 mg strength*

*Reference: CIP-Isotretinoin 2 x 20 mg strength*

As noted above, since CIP-Isotretinoin is dosed base on body weigh, the switch-ability between different strengths to permit administration of different combinations to achieve the ultimate dosing is critical. The slightly less than proportional increase in exposure with the 40 mg strength under fasting conditions is not expected to have an effect on efficacy because of the smaller magnitude of the food effect observed with CIP-Isotretinoin compared with Accutane<sup>®</sup> formulations (explained in the following paragraph) and the fact that Accutane<sup>®</sup> was originally approved to be administered without regards to meals (Date of approval 05/07/1982). The results of food effect and associated recommendation to be administered with a meal were added to the label later on 12/31/2001. This would imply that there was 19 years (between 05/08/1982 to 12/31/2001) of clinical experience where Accutane<sup>®</sup> was administered without regards to meals.

The CIP-Isotretinoin systemic exposure under fasting conditions lie in between Accutane<sup>®</sup> fasting and CIP-Isotretinoin and Accutane<sup>®</sup> fed. Specifically, the CIP-Isotretinoin exposure under fasting conditions were approximately 2 fold higher than Accutane<sup>®</sup> fasting (under fed conditions, CIP-Isotretinoin and Accutane<sup>®</sup> were BE).

Hence, this slightly less than proportional increase in exposure with the 40 mg strength of CIP-Isotretinoin under fasting conditions is expected to have minimal effect on drug efficacy based on the observed magnitude of food effect between CIP-Isotretinoin and Accutane<sup>®</sup>. With the aforementioned background in mind, the fact that the Phase 3 trial did not evaluate the 30 and 40 mg strength, and also the Phase 3 trial did not explore the efficacy of CIP-Isotretinoin under fasting conditions should not affect approval.

In conclusion, the CIP-Isotretinoin formulation could be administered without regards to meals.

***Clinical Pharmacology Briefing:*** A Required Inter-Division Level Clinical Pharmacology Briefing was held on March 28, 2012 with the following in attendance: Shiew Mei Huang, E. Dennis Bashaw, John Lazor, Darrell Abernethy, Minerva Hughes, Denise Cook, Gordana Diglisic, Arun Agrawal, Michael Bewernitz, Jianmeng Chen, Jie Wang, Xinning Yang, Dongyang Liu, Xu Yun, Abimbola Adebowale, Doanh Tran and Chinmay Shukla.

## **2. Question Based Review**

### **2.1 Regulatory History**

The original NDA was submitted on July 1, 2005 and the Sponsor had chosen a 505(b)(2) regulatory pathway and had identified Accutane<sup>®</sup> as a listed drug. This submission received an approvable letter on May 1, 2006 and a number of elements were noted as being inadequate, including demonstration of dose proportionality, chemistry release specifications, appropriate risk management program, etc. (see communication in DARRTS).

The Sponsor responded with a complete response (CR) on October 26, 2006. This amended application also received an approvable letter on April 25, 2007; again a number of deficiencies were identified and one of them was lack of demonstration of BE of their product with listed drug Accutane<sup>®</sup> under fasted conditions (see communication in DARRTS). The Agency expressed concerns that although Accutane<sup>®</sup> is approved to be taken with food, the Sponsor's product showed higher exposure compared to Accutane<sup>®</sup> under fasting conditions and this was considered to be an issue because the potential real world use of Accutane<sup>®</sup> is likely without regards to food [Accutane<sup>®</sup> was originally approved to be administered without regards to meals (Date of approval 05/07/1982). The results of food effect and the recommendation to be administered with a meal were added to the label on 12/31/2001].

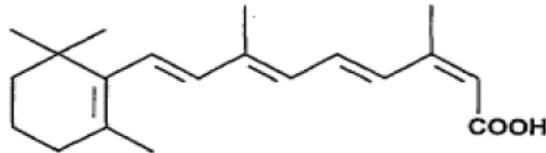
This submission is a complete response to the Agency communication dated April 25, 2007 and the Sponsor has submitted results of a Phase 3 trial. The Sponsor also submitted results of 3 new Clinical Pharmacology trials in support of their additional 40 mg strength (original application was for 10, 20 and 30 mg strength).

## 2.2 General Attributes of the Drug

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

**Drug substance:** The drug substance is isotretinoin; CIP was added in front of isotretinoin (CIP-isotretinoin) only to identify it as a product from Cipher. Chemically, isotretinoin is a retinoid drug and its molecular weight is 300.44 g/mole. The chemical structure of isotretinoin is shown in Figure 1.

**Figure 1: Structure of isotretinoin**



**Formulation:** Isotretinoin is a very poorly water-soluble compound and absorption following oral administration is significantly reduced when taken without food. The Sponsor's purpose of developing this new drug product was to improve drug bioavailability so that it can be administered without regards to meals.

(b) (4)

**Table 2: Composition of CIP-Isotretinoin capsules**

Ingredient and Test Standard	Amount per capsule (mg) Strength 10 mg	Amount per capsule (mg) Strength 20 mg	Amount per capsule (mg) Strength 30 mg	Amount per capsule (mg) Strength 40 mg	Function
Isotretinoin, USP	10	20	30	40	Active
Stearoyl Macrogolglycerides (b) (4)	(b) (4)				
Soybean Oil, USP					
Sorbitan Monooleate, NF (SPAN 80)					
Propyl Gallate, NF					
(b) (4)					

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

**Mechanism of action:** Isotretinoin is a synthetic analog of vitamin A and inhibits sebaceous gland function and keratinization. The exact mechanism in the treatment of severe recalcitrant nodular acne is unknown.

**Therapeutic indication:** Treatment of severe recalcitrant nodular acne vulgaris in patients 12 years of age and older. This indication is identical to that of the innovator (Accutane®) and its generics.

**2.2.3 What is the proposed route of administration and dosage?**

**Proposed route of administration:** Oral

**Proposed dosage:** The recommended dose range for CIP-Isotretinoin is 0.5 to 1 mg/kg/day given in two divided doses with or without food for 15 to 20 weeks.

From the Accutane® package insert, studies comparing 0.1, 0.5, and 1.0 mg/kg/day found that all dosages provided initial clearing of disease, but there was a greater need for re-treatment with the lower dosages.

During treatment, the dose may be adjusted according to response of the disease and/or the appearance of clinical side effects. Adult patients whose disease is very severe with

scarring or is primarily manifested on the trunk may require dose adjustments up to 2.0 mg/kg/day, as tolerated.

If the total nodule count has been reduced by more than 70% prior to completing 15 to 20 weeks of treatment, the drug may be discontinued. After a period of 2 months or more off therapy and if warranted by persistent or recurring severe nodular acne, a second course of therapy may be initiated. The optimal interval before retreatment has not been defined for patients who have not completed skeletal growth. Long-term use of isotretinoin, even in low doses, has not been studied, and is not recommended. It is important that CIP-Isotretinoin be given at the recommended doses for no longer than the recommended duration.

The safety of once daily dosing with CIP-Isotretinoin has not been established and once daily dosing is not recommended. Table 3 provides dosing guidelines based on body weight as per proposed labeling (identical dosing schedule appears in the last approved labeling of Accutane<sup>®</sup> with the only difference being Accutane<sup>®</sup> was recommended to be administered with a meal).

**Table 3: CIP-Isotretinoin dosing by body weight (based on administration with or without food)**

Body Weight		Total mg/day		
Kilograms	pounds	0.5 mg/kg	1 mg/kg	2 mg/kg
40	88	20	40	80
50	110	25	50	100
60	132	30	60	120
70	154	35	70	140
80	176	40	80	160
90	198	45	90	180
100	220	50	100	200

***Reviewer comments: CIP-Isotretinoin is proposed in 4 strengths, 10, 20, 30 and 40 mg oral capsule to be taken without regards to meals in two divided doses in order to achieve dosing of 0.5 to 1 mg/kg/day.***

***Based on the dosing table, with the available strengths it will not be possible to dose patients who weigh 50, 70 and 90 kg if the divided doses are required to be equal in amount (e.g. in order to obtain a 0.5 mg/kg dose in a subject weighing 50 kg, the total recommended daily dose is 25 mg/day. This daily dose will not be possible to be administered with the available strengths in the form of 2 divided doses).***

***In order to address this ambiguity, this reviewer obtained dosing information from the Phase 3 clinical trial ISOCT.08.01. Table 4 below provides information on the body weight based dosing strategy that was used by the Sponsor.***

**Table 4: Dosing used in Phase 3 clinical trial (ISOCT.08.01)**

**Weight based dosing ranges**

Weight Range (kg)	0.5 mg/kg titration dose (Week 1 to Week 4)			1 mg/kg (Week 5 to Week 20)		
	Total Daily Dose (mg)	Individual BID Dose (mg)		Total Daily Dose (mg)	Individual BID Dose (mg)	
		Morning	Evening		Morning	Evening
40.0 – 49.9	20	10	10	40	20	20
50.0 – 59.9	25	10	20	50	20	20 + 10
60.0 – 69.9	30	10	20	60	20 + 10	20 + 10
70.0 – 79.9	35	20	20	70	20 + 10	20 + 20
80.0 – 89.9	40	20	20	80	20 + 20	20 + 20
90.0 – 99.9	45	20	20+10	90	20 + 20	20 + 20 + 10
100.0 – 110.0	50	20	20+10	100	20 + 20 + 10	20 + 20 + 10

*From the above table, it is evident that the recommended daily dosing was not exactly divided into half and unequal amounts were administered (higher fraction was usually administered in the evening). Furthermore, dosing was targeted in such-a-way so as to achieve ultimate dosing between 0.5 mg/kg and 1 mg/kg.*

**2.3 General Clinical Pharmacology**

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

**New Clinical Pharmacology trials:** With the addition of the 40 mg strength, the Sponsor conducted 3 new Clinical Pharmacology trials (Table 5) to satisfy the information need as to the effect of food and proportionality of the exposure the new strength under fasting and fed conditions.

**Table 5: List of new Clinical Pharmacology trials conducted with this submission**

Study No.	Study Objective	Treatment	Subjects
ISOPK.08.02 (82234)	To compare the BA of CIP-Isotretinoin capsules (40 mg) following a single dose under fasting and fed conditions	A: CIP-Isotretinoin Capsules (40 mg) – FED  B: CIP-Isotretinoin Capsules (40 mg) – FASTING	14 Healthy Male Mean Age: 37 years Age Range: (21-52)
ISOPK.09.01 (100005)	To evaluate the comparative BA between CIP-Isotretinoin capsules 2 x 20 mg and 1 x 40 mg after a single dose under FED conditions	A: CIP-Isotretinoin Capsules (2 x 20 mg)  B: CIP-Isotretinoin Capsules (1 x 40 mg)	49 Healthy Male Mean Age: 38 years Age Range: (20-55)
ISOPK.09.02 (100004)	To evaluate the comparative BA between CIP-Isotretinoin capsules 2 x 20 mg and 1 x 40 mg after a single dose under FASTING conditions	A: CIP-Isotretinoin Capsules (2 x 20 mg)  B: CIP-Isotretinoin Capsules (1 x 40 mg)	50 Healthy Male Mean Age: 38 years Age Range: (22-52)

Since isotretinoin dose is based on body weight, patients will be administered the available strengths in permutation and combinations in order to achieve target daily dose between 0.5 mg/kg to 1 mg/kg administered using 2 divided doses. Hence, it is important to demonstrate that the new 40 mg strength has proportional PK under fasting and fed conditions and has a similar magnitude of food effect as observed earlier with the 30 mg strength. Satisfying this informational need will allow interchangeability between different strengths in order to achieve target dosing (see Sections 2.3.2, 2.3.3 and 2.6.3 for further details).

***Phase 3 clinical trial:*** The Phase 3 trial (ISOCT.08.01) was a double blind, randomized, parallel group study evaluating the efficacy and safety of CIP-Isotretinoin and marketed isotretinoin in patients with severe recalcitrant nodular acne. This study administered 10 and 20 mg strengths of CIP-Isotretinoin or marketed isotretinoin to achieve an initial titration dose of 0.5 mg/kg/day via 2 divided doses for the first 4 weeks followed by approximately 1 mg/kg/day via 2 divided doses for 16 weeks. All drugs were administered with meals.

The results as described by the Sponsor showed that the two co-primary efficacy outcomes, which included change from baseline to Week 20 in the total nodular lesion count and the proportion of patients with at least 90% reduction from baseline in the total number of nodular lesions, demonstrated non-inferiority of CIP-Isotretinoin compared to the reference product. Furthermore, the Sponsor also states that the safety profile of CIP-Isotretinoin was comparable to that of the reference product (see Clinical and Biostatistics review for further details).

***2.3.2 What is the effect of food on the 40 mg strength and how do the results compare to previously evaluated effect of food?***

The results of the effect of food trial (ISOPK.08.02) showed that the exposure of isotretinoin following administration of 40 mg strength was significantly increased when administered with a modified high-fat, high calorie breakfast compared to fasting conditions. Specifically the AUC and  $C_{max}$  under fed conditions were approximately 1.5 and 1.3 fold respectively, higher with food compared to fasting. The effect of food on PK with the new 40 mg strength appears to be similar with that observed with previously evaluated 30 mg strength (Table 6) (see review dated 04/21/2006 in DARRTS by Dr. Dennis Bashaw for further details about the effect of food on the 30 mg strength). Further details about the effect of food can be found in Section 2.6.3.

***Table 6: Effect of food on 40 mg and 30 mg strength***

<i>Dose</i>	<i>AUC<sub>0-t</sub> (Fed/Fasting)</i>	<i>AUC<sub>0-inf</sub> (Fed/Fasting)</i>	<i>C<sub>max</sub> (Fed/Fasting)</i>
40 mg	1.5	1.5	1.3
30 mg	1.5	1.4	1.6

***2.3.3 Is 2 x 20 mg strength interchangeable with 1 x 40 mg strength?***

Isotretinoin dosing is based on body weight, and this requires several permutation and combination of different strengths to achieve an ultimate dosing in the range of 0.5 mg/kg/day to 1 mg/kg/day in 2 divided doses. To address the issue interchangeability with the new 40 mg strength, the Sponsor conducted 2 trials:

- ISOPK.09.01 – Relative BA study of 2 x 20 mg CIP-Isotretinoin vs. 1 x 40 mg CIP-Isotretinoin under **Fed** conditions
- ISOPK.09.02 – Relative BA study of 2 x 20 mg CIP-Isotretinoin vs. 1 x 40 mg CIP-Isotretinoin under **Fasting** conditions

The results of the relative BA trial under **fed** conditions (ISOPK.09.01) showed that exposure of 2 x 20 mg and 1 x 40 mg were BE with the 90% confidence interval (CI) of the ratio of the geometric mean of AUC and C<sub>max</sub> within the no effect boundary of 80% to 125 % (Table 7). This indicates that the PK of isotretinoin increased in a proportional manner between 20 mg to 40 mg strengths under fed conditions. Furthermore, the Sponsor has previously demonstrated dosage form proportionality between 3 x 10 mg strength versus 1 x 30 mg strength under both **fasting and fed** conditions indicating that the drug exposure increased proportionally between 10 mg to 30 mg strength (Please note: under fasting conditions, the CI of the ratio of geometric mean of AUC was borderline on the 80% to 125% no effect boundary. Specifically, the PK of 1 x 30 mg strength increased in very slightly less than proportional manner compared to 3 x 10 mg strength. This was considered acceptable by the previous reviewer) (see review by Dr. Bashaw dated 04/09/2007). Combining the results from these studies would indicate that under fed conditions all the strengths (10 mg to 40 mg) could be used interchangeability in combinations to achieve the target dosing between 0.5 mg/kg/day to 1 mg/kg/day in 2 divided doses.

**Table 7: Results of relative BA analysis between 1 x 40 mg versus 2 x 20 mg strength of CIP-Isotretinoin under fed conditions (Trial ISOPK.09.01)**

	AUC <sub>0-t</sub>	AUC <sub>0-inf</sub> <sup>*</sup>	C <sub>max</sub>
Ratio <sup>1</sup>	106.04%	106.08%	106.94%
90 % Geometric C.I. <sup>2</sup>	103.15 % to 109.01 %	103.16 % to 109.09 %	97.35 % to 117.47 %
Intra-Subject CV	7.81 %	7.80 %	26.97 %

<sup>1</sup> Calculated using least-squares means according to the formula:  $e^{(A-B)} \times 100$ .

<sup>2</sup> 90% Geometric Confidence Interval using ln-transformed data.

\* For this parameter, N=44.

*Test: CIP-Isotretinoin 1 x 40 mg strength*

*Reference: CIP-Isotretinoin 2 x 20 mg strength*

The results of the relative BA trial under **fasting** conditions (ISOPK.09.02) showed that the exposure of 1 x 40 mg strength was slightly lower than 2 x 20 mg strength indicating that the PK of 40 mg strength capsule increased in a slightly less than proportional manner. Specifically the AUC and C<sub>max</sub> with 1 x 40 mg strength were approximately 15% and 20% respectively, lower than those following administration of 2 x 20 mg strength. The results are shown in Table 8 below.

**Table 8: Results of relative BA of 1 x 40 mg strength versus 2 x 20 mg strength of CIP-Isotretinoin under fasting conditions (Trial ISOPK.09.02)**

	AUC <sub>0-t</sub>	AUC <sub>0-inf</sub>	C <sub>max</sub>
Ratio of geometric mean	0.84	0.85	0.80
90% CI	0.78 – 0.90	0.79 – 0.91	0.74 – 0.87

*Test: CIP-Isotretinoin 1 x 40 mg strength*

*Reference: CIP-Isotretinoin 2 x 20 mg strength*

The body weight based dosing of isotretinoin has already been introduced and the switch-ability between different strengths to permit administration of different combinations to achieve the ultimate dosing becomes critical. The slight less than proportional increase in exposure with the 40 mg strength under fasting conditions is not expected to have an effect on efficacy because of the smaller magnitude of the food effect observed with CIP-Isotretinoin compared with Accutane<sup>®</sup> formulations (explained in the following paragraph) and the fact that Accutane<sup>®</sup> was originally approved to be administered without regards to meals (Date of approval 05/07/1982). The results of food effect and associated recommendation to be administered with a meal were added to the label later on 12/31/2001. This would imply that there was 19 years (between 05/08/1982 to 12/31/2001) of clinical experience where Accutane<sup>®</sup> was administered without regards to meals.

The CIP-Isotretinoin systemic exposure under fasting conditions lie in between Accutane<sup>®</sup> fasting and CIP-Isotretinoin and Accutane<sup>®</sup> fed. Specifically, the CIP-Isotretinoin exposure under fasting conditions were approximately 2 fold higher than Accutane<sup>®</sup> fasting and under fed conditions, CIP-Isotretinoin and Accutane<sup>®</sup> were BE.

Hence, this slightly less than proportional increase in exposure with the 40 mg strength of CIP-Isotretinoin under fasting conditions is expected to have minimal effect on drug efficacy based on the observed magnitude of food effect between CIP-Isotretinoin and Accutane<sup>®</sup>.

With the aforementioned background in mind, the fact that the Phase 3 trial did not evaluate the 30 and 40 mg strength and did not explore the efficacy of CIP-Isotretinoin under fasting conditions should not affect approval.

Hence, this slightly less than dose proportional increase in exposure with the 40 mg strength of CIP-Isotretinoin under fasting conditions is expected to have minimal effect on drug efficacy based on the observed magnitude of food effect between CIP-Isotretinoin and Accutane<sup>®</sup> and ultimately will have minimal effect on interchangeability between strengths under fasting conditions to achieve dosing between 0.5 mg/kg/day to 1 mg/kg/day in 2 divided doses.

From the information provided in Section 2.3.2 and Section 2.3.3, it was concluded that CIP-Isotretinoin formulation could be administered without regards to meals and the 4 available strengths (10 mg, 20 mg, 30 mg and 40 mg) could be used interchangeability to achieve daily dosing between 0.5 mg/kg to 1 mg/kg in 2 divided doses (refer to Section

2.6.3 and Section 4 of this review for further details on trials ISOPK.08.02, ISOPK.09.01 and ISOPK.09.02)

***Reviewer Comments: Isotretinoin is present endogenously. Baseline corrected data were used for estimation of the PK parameters and relative BA estimation. The baseline sampling schedule used in the 3 new Clinical Pharmacology trials was identical with that used earlier during development (see Clinical Pharmacology reviews by Dr. Dennis Bashaw in DARRTS dated 04/21/2006 and 04/09/2007). Baseline uncorrected data were provided by the Sponsor only as additional support and are included in this review under Section 4.***

## **2.4 Intrinsic Factors**

***2.4.1 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?***

The influence of intrinsic factors on drug exposure was reviewed by Dr. Dennis Bashaw with the earlier submission. With this submission, the Sponsor has not provided any additional information in this area. Provided below is a summary of results from Dr. Bashaw's review findings. For additional information, refer to Clinical Pharmacology review by Dr. Bashaw dated 04/21/2006 in DARRTS.

***2.4.1.1 Effect of gender:*** Preliminary analysis indicated that using gender as a covariate did not reveal a significant difference in drug exposure. Furthermore, the results of the gender analysis indicated that dose adjustment and individualization is needed with this drug, no matter which formulation is used (Accutane<sup>®</sup> vs. CIP-Isotretinoin).

***2.4.1.2 Effect of race:*** The influence of race on the PK of CIP-Isotretinoin has not been evaluated.

***2.4.1.3 Pediatric patients:*** As the appearance of acne occurs after puberty, use by pediatrics below the age of 12 is expected to be limited. Pediatric subjects (aged 12 years and older) were included in the Phase 3 trial ISOCT.08.01 and population PK parameters were evaluated by the Pharmacometrics reviewer Dr. Dhananjay Marathe (See attached Pharmacometrics review in the Appendix). According to Dr. Marathe, the mean isotretinoin exposure in pediatrics (age range 12 – 17 years) was slightly lower than adults (the exposures in pediatric patients were 9.3% and 6.0% lesser than adults for the reference product and CIP-Isotretinoin respectively). This finding is not expected to translate into anything of clinical relevance.

Request for waiver of pediatric studies for aged 0 to 11 years has not been submitted with this application because this submission does not trigger PREA (Pediatric Research Equity Act).

**2.4.1.4 Elderly patients:** Acne is not a condition that occurs in elderly subjects, as such isotretinoin is rarely used in subjects over the age of 50. The proposed package insert for CIP-Isotretinoin contains language identical to Accutane<sup>®</sup> label under “Geriatric Use” sub-section under warnings. Dr. Bashaw recommended in his review dated 04/21/2006 that if this application is approved, similar wording should be incorporated into the package insert.

**2.4.1.5 Renal impairment:** There is no renal impairment data in the Accutane<sup>®</sup> label and studies have not been conducted to date in this population.

**2.4.1.6 Hepatic impairment:** There is no hepatic impairment data in the Accutane<sup>®</sup> label and studies have not been conducted to date in this population.

***Reviewer comments: This application is following a 505(b)(2) regulatory pathway and has identified Accutane<sup>®</sup> as a listed drug. There is no data in the Accutane<sup>®</sup> label regarding PK in renal and hepatic impaired patients. Even though additional data in these patients population may be helpful, the fact that CIP-Isotretinoin was BE with Accutane<sup>®</sup> under fed conditions (Trial ISOPK.03.04) (conditions of highest exposure) does not justify requiring studies in renal and hepatic impaired population for this 505(b)(2) application.***

**2.4.1.7 What pregnancy and lactation use information is there in the application?** Isotretinoin is a potent teratogen (it is a CATEGORY X drug) and is the subject of a stringent pregnancy prevention program called iPLEDGE. The proposed package insert contains a black box for pregnancy and if approved either participation in the iPLEDGE or an equally restrictive program should be mandatory.

## **2.5 Extrinsic Factors**

**2.5.1 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?**

The influence of extrinsic factors on dose-exposure and/or response was not explored.

**2.5.2 Drug-drug interactions:** The Sponsor has not conducted any drug-drug interaction trials and the labeling language under the “Drug Interactions” section (Section 7) in the proposed label is identical to Accutane<sup>®</sup> approved labeling. Specifically, following information appears in the proposed label:



**2.6 General Biopharmaceutics**

**2.6.1 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

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

To-be-marketed formulation was used in the PK trials ISOPK.08.02, ISOPK.09.01 and ISOPK09.02 and the Phase 3 clinical trials ISOCT.08.01.

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

The Sponsor chose a 505(b)(2) regulatory pathway and would like to rely in part on prior safety and efficacy data for the listed drug Accutane<sup>®</sup>. In order to achieve this, the Sponsor conducted a relative BA trial comparing the exposure of 2 x 20 mg strength of CIP-Isotretinoin versus 1 x 40 mg strength of Accutane<sup>®</sup> under both fasting and fed conditions (Trial ISOPK.03.04). This study was reviewed by Dr. Dennis Bashaw; please refer to his review in DARRTS dated 04/21/2006 for further details. Provided here is a summary of results.

The results indicated that under fed conditions the 2 x 20 mg strength of CIP-Isotretinoin were BE with 1 x 40 mg strength of Accutane<sup>®</sup>. However, under fasting conditions, the exposure of 2 x 20 mg CIP-Isotretinoin was about 2 fold higher than 1 x 40 mg Accutane<sup>®</sup>. BE of CIP-Isotretinoin with Accutane<sup>®</sup> using other strengths was not evaluated.

The Phase 3 trial (ISOCT.08.01) was conducted using only the 10 and 20 mg strength under fed conditions. This study neither evaluated fasting conditions nor the 30 mg and 40 mg strengths. This will not be an approvability issue because the new 40 mg strength of CIP-Isotretinoin is BE with the 2 x 20 mg strength of CIP-Isotretinoin under fed conditions (conditions of highest exposure). Furthermore, the proportionality of drug exposure under fasting and fed conditions and the smaller magnitude of food effect on CIP-Isotretinoin compared with Accutane<sup>®</sup> provide the necessary supporting rationale for such decision (see Sections 2.3.2 and 2.3.3 for further details).

Furthermore, a waiver of BE data is not necessary as the proposed-to-be-marketed formulation was used in the Phase 3 trial ISOCT.08.01 and the PK trials ISOPK.08.02, ISOPK.09.01 and ISOPK09.02.

**2.6.3 Effect of food**

**2.6.3.1 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?**

The Sponsor conducted a new food effect study with the 40 mg strength (Trial ISOPK.08.02) in 16 healthy adult male subjects (14 subjects completed this trial). A modified high-fat, high-calorie breakfast was used to simulate fed conditions. Specifically the contents of the breakfast made up for 849 calories (123.2 calories from protein, 265.6 calories from carbohydrates, and 468 calories from fat) with reduced vitamin A content (refer to Section 4 for further details on the contents of the meal that was administered).

The results showed that the exposure of isotretinoin following administration of 40 mg strength is significantly increased when administered with a modified high-fat, high calorie breakfast compared to fasting conditions. Also the  $T_{max}$  was delayed by approximately 3.5 hours under fed conditions. Specifically the AUC and  $C_{max}$  with the 40 mg strength was approximately 1.5 and 1.3 fold higher, respectively, with food compared to fasting. These results obtained with the 40 mg strength were similar to the results reported earlier using the 30 mg strength (Trial ISOPK.02.04) (see review by Dr. Bashaw in DARRTS dated 04/21/2006). The PK parameters calculated from this trial are shown in Table 9 and calculation of relative BA and 90% CI between fasting and fed conditions is summarized in Table 10. The PK profiles under fasted and fed conditions are shown in Figure 2. Table 11 shows the magnitude of food effect for the 40 mg and the 30 mg strengths.

**Table 9: Summary of PK parameters for the baseline corrected data of isotretinoin for each treatment arm (N = 14)**

Parameters	Isotretinoin Administered With a Modified High-Fat, High-Calorie Breakfast (A)			Isotretinoin Administered Under an Overnight Fast of at Least 10 Hours (B)		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC <sub>0-t</sub> (ng·h/mL)	6095.16	1571.91	25.79	4054.76	820.64	20.24
AUC <sub>0-inf</sub> (ng·h/mL)	6889.31	2046.77	29.71	4626.92	1225.31	26.48
AUC <sub>t/inf</sub> (%)	89.45	5.58	6.24	88.67	6.30	7.10
$C_{max}$ (ng/mL)	394.62	152.65	38.68	313.51	81.98	26.15
$T_{max}$ (h)	6.40	3.02	47.19	2.89	0.98	33.99
$T_{max}^*$ (h)	4.50	3.50	-	2.51	1.00	-
$K_{el}$ (h <sup>-1</sup> )	0.0341	0.0094	27.47	0.0307	0.0082	26.77
$T_{1/2\text{el}}$ (h)	21.67	5.45	25.13	24.19	6.80	28.11

\* Medians and interquartile ranges are presented.

**Table 10: Relative BA analysis and calculation of 90% CI**

	AUC <sub>0-t</sub>	AUC <sub>0-inf</sub>	$C_{max}$
Ratio <sup>1</sup>	150.17%	148.93%	121.23%
90 % Geometric C.I. <sup>2</sup>	134.52 % to 167.64 %	134.24 % to 165.23 %	98.94 % to 148.54 %
Intra-Subject CV	16.27 %	15.35 %	30.53 %

<sup>1</sup> Calculated using least-squares means according to the formula:  $e^{(A-B)} \times 100$ .

<sup>2</sup> 90% Geometric Confidence Interval using ln-transformed data.

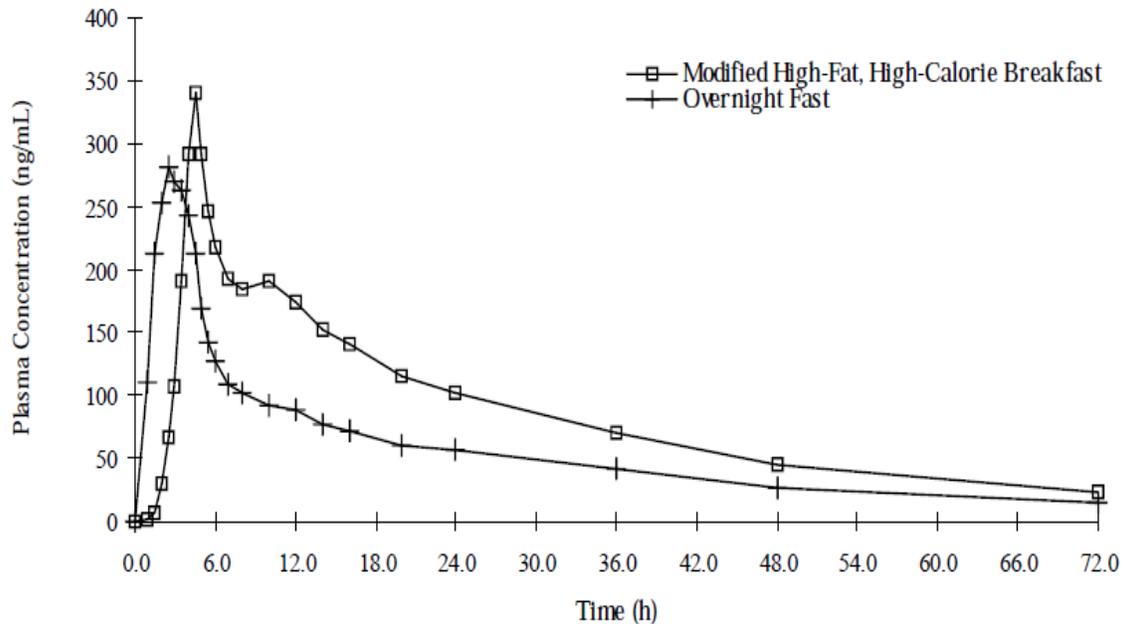
**Table 11: Effect of food on 40 mg and 30 mg strength**

Dose	AUC <sub>0-t</sub> (Fed/Fasting)	AUC <sub>0-inf</sub> (Fed/Fasting)	C <sub>max</sub> (Fed/Fasting)
40 mg	1.5	1.5	1.3
30 mg	1.5	1.4	1.6

**Reviewer Comments:** *The effect of food with 30 mg strength was reviewed earlier by Dr. Dennis Bashaw (see review in DARRTS dated 04/21/2006 and appendix).*

*According to Dr. Bashaw, the Sponsor had used a non-standard FDA high-fat meal; however, it did approximate the FDA standard high fat meal in terms of both total calories and composition.*

**Figure 2: Mean baseline corrected concentration versus time profile of isotretinoin following administration of 40 mg strength under fed and fasting conditions**



**2.6.3.2 What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?**

The Sponsor is proposing to label this formulation to be administered without regards to meals. This is a 505(b)(2) application and the Sponsor has identified Accutane<sup>®</sup> as a listed drug. Accutane<sup>®</sup> is currently labeled to be administered with a meal.

The Sponsor conducted a relative BA study with Accutane<sup>®</sup> under fasting and fed conditions (ISOPK.03.04). This study was reviewed by Dr. Bashaw (see review in DARRTS dated 04/21/2006) and readers are referred to this Clinical Pharmacology review for further details. Provided below is a brief summary of results.

The purpose of this trial (ISOPK.03.04) was to evaluate the relative BA between CIP-Isotretinoin capsules 2 x 20 mg and Accutane capsules 1 x 40 mg following a single dose in healthy volunteers under fasting and fed conditions.

The results indicated that the effect of food was larger on the Accutane<sup>®</sup> formulation compared to the CIP-Isotretinoin formulation; however, there was still a significant food effect with the CIP-Isotretinoin. In the presence of food, the systemic exposure increased on average 1.5 times for CIP-Isotretinoin formulation and approximately 2.5 times for the Accutane<sup>®</sup> formulation. The peak exposure to isotretinoin increased under fed conditions 1.3 times and 2.7 times for CIP-Isotretinoin and Accutane<sup>®</sup> formulations respectively.

PK profile is shown in Figure 3 and a schematic representation of effect of food is shown in Figure 4. PK results and statistical analysis is shown in Table 12.

**Figure 3: Mean concentration versus time profile of CIP-Isotretinoin and Accutane<sup>®</sup> administered using fasted or fed conditions (N = 57)**

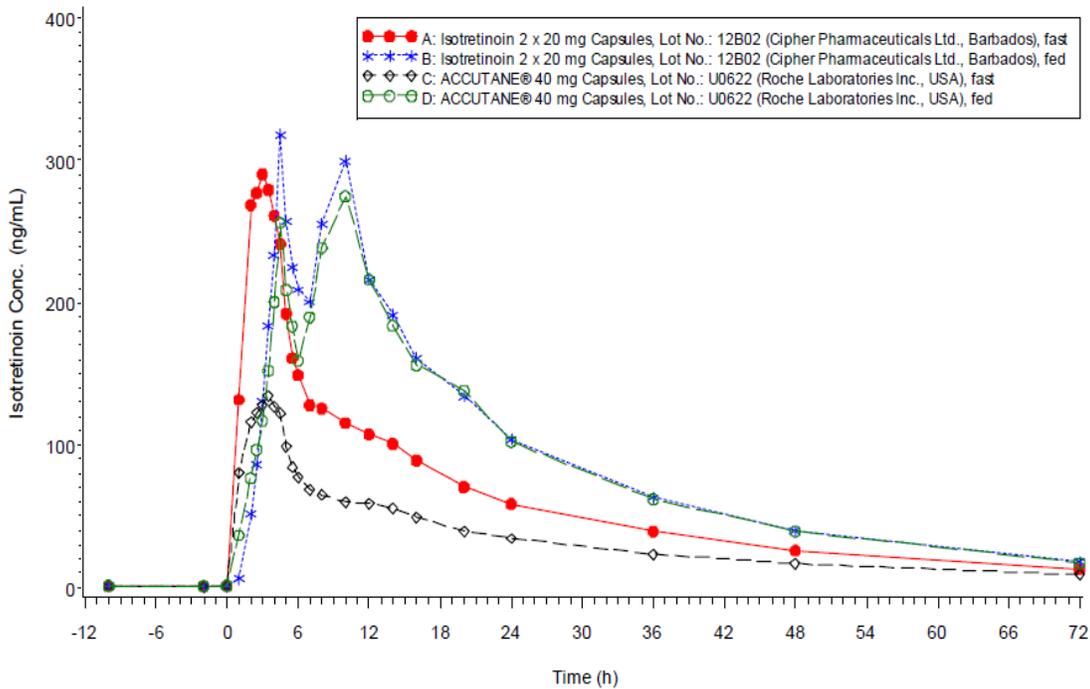


Figure 4: Schematic representation of the effect of food following administration of CIP-Isotretinoin and Accutane®

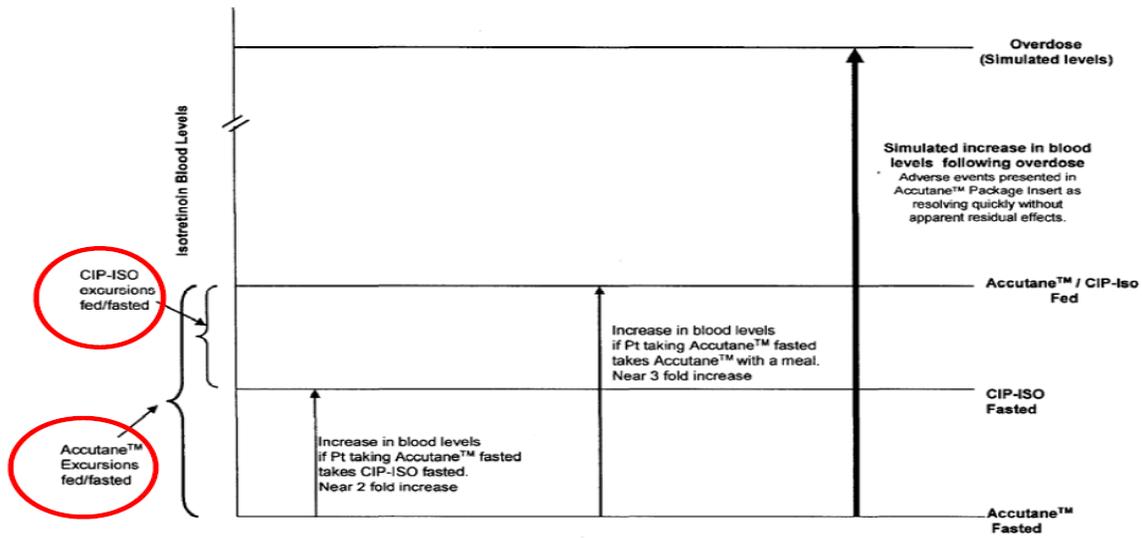


Table 12: PK parameters and statistical analysis of trial ISOPK.03.04 (N=57)

Parameter	Treatment		Means		Type	Code	Contrast Ratio (%)	90% CI (%)	CV%
	Type	Trt	Arithmetic (CV%)	Geometric					
AUC <sub>t</sub> (ng·h/mL)	T - Fast	A	4307.77 (29)	4110.64	T: Food Effect	B vs. A	152.07	142.49 – 162.29	21
	T - Fed	B	6400.04 (20)	6251.05	R: Food Effect	D vs. C	263.46	246.86 – 281.17	
	R - Fast	C	2349.24 (29)	2245.49	T/R - Fast	A vs. C	183.06	171.53 – 195.37	
	R - Fed	D	6145.81 (26)	5915.87	T/R - Fed	B vs. D	105.67	99.01 – 112.77	
AUC <sub>i</sub> (ng·h/mL)	T - Fast	A	4676.08 (28)	4470.45	T: Food Effect	B vs. A	149.78	140.52 – 159.66	21
	T - Fed	B	6858.70 (21)	6695.87	R: Food Effect	D vs. C	252.60	236.98 – 269.26	
	R - Fast	C	2619.26 (30)	2500.01	T/R - Fast	A vs. C	178.82	167.76 – 190.60	
	R - Fed	D	6561.62 (26)	6315.15	T/R - Fed	B vs. D	106.03	99.47 – 113.02	
C <sub>max</sub> (ng/mL)	T - Fast	A	347.00 (35)	323.18	T: Food Effect	B vs. A	134.39	122.60 – 147.32	30
	T - Fed	B	466.43 (38)	434.33	R: Food Effect	D vs. C	267.53	244.05 – 293.28	
	R - Fast	C	169.66 (29)	161.43	T/R - Fast	A vs. C	200.20	182.63 – 219.46	
	R - Fed	D	471.32 (41)	431.88	T/R - Fed	B vs. D	100.57	91.74 – 110.24	
T <sub>max</sub> (h)	T - Fast	A	3.40 (51)	-	T: Food Effect	B vs. A	201.19	-	-
	T - Fed	B	6.85 (41)	-	R: Food Effect	D vs. C	228.40	-	
	R - Fast	C	2.94 (58)	-	T/R - Fast	A vs. C	115.06	-	
	R - Fed	D	6.75 (55)	-	T/R - Fed	B vs. D	101.35	-	
K <sub>el</sub> (1/h)	T - Fast	A	0.0358 (22)	-	T: Food Effect	B vs. A	114.45	-	-
	T - Fed	B	0.0409 (18)	-	R: Food Effect	D vs. C	126.68	-	
	R - Fast	C	0.0327 (22)	-	T/R - Fast	A vs. C	109.33	-	
	R - Fed	D	0.0414 (17)	-	T/R - Fed	B vs. D	98.78	-	
T <sub>half</sub> (h)	T - Fast	A	20.28 (22)	-	T: Food Effect	B vs. A	86.69	-	-
	T - Fed	B	17.56 (21)	-	R: Food Effect	D vs. C	77.55	-	
	R - Fast	C	22.20 (21)	-	T/R - Fast	A vs. C	91.43	-	
	R - Fed	D	17.18 (16)	-	T/R - Fed	B vs. D	102.21	-	
MRT <sub>po</sub> (h)	T - Fast	A	26.06 (23)	-	T: Food Effect	B vs. A	101.95	-	-
	T - Fed	B	26.59 (18)	-	R: Food Effect	D vs. C	89.60	-	
	R - Fast	C	29.42 (22)	-	T/R - Fast	A vs. C	88.62	-	
	R - Fed	D	26.36 (19)	-	T/R - Fed	B vs. D	100.83	-	

T = Test  
R = Reference

Treatments: A = Isotretinoin 2 x 20 mg fasting  
B = Isotretinoin 2 x 20 mg fed  
C = Accutane 1 x 40 mg fasting  
D = Accutane 1 x 40 mg fed

The observed magnitude of the effect of food on CIP-Isotretinoin drug exposure is not expected to have an effect on efficacy because Accutane<sup>®</sup> was originally approved to be administered without regards to meals (Date of approval 05/07/1982). The results of food effect and associated recommendation to be administered with a meal were added to the label later on 12/31/2001. This would imply that there was 19 years (between 05/08/1982 to 12/31/2001) of clinical experience where Accutane<sup>®</sup> was administered without regards to meals. Furthermore, from the Figures 3 and 4 above, CIP-Isotretinoin blood levels under fasting conditions lie in between Accutane<sup>®</sup> fasting and CIP-Isotretinoin and Accutane<sup>®</sup> fed. Specifically, the CIP-Isotretinoin blood levels under fasting conditions were about 2 fold higher than Accutane<sup>®</sup> fasting.

In conclusion, the CIP-Isotretinoin could be administered without regards to meals.

## **2.7 Analytical Section**

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

Liquid chromatography with tandem mass spectrometric detection was used to quantify isotretinoin . The term “*Unstripped*” refers to regular human EDTA K2 plasma and “*Stripped*” refers to human EDTA K2 plasma treated with activated charcoal to remove endogenous levels of isotretinoin prior to use.

Validation parameters were evaluated with the quality control (QC) prepared in unstripped matrix. In order to verify that a standard curve made in stripped matrix would result in accurate measurement of isotretinoin in unstripped samples, the concentration of endogenous levels in unstripped plasma was determined using 10 unstripped samples. This measured concentration was added to the spiked amounts to obtain the final nominal concentrations of (lower limit of quantitation) LLOQ, QC1, QC2 and QC3 prepared in unstripped matrix.

The bioanalytical methods used in trial ISOPK.08.02 differed slightly from the method used in trial ISOPK.09.01 and ISOPK09.02 (the bioanalytical method used in trial ISOPK.09.01 and ISOPK09.02 is the same). The basic difference was in the internal standard used. Acitretin was used as an internal standard during analysis of PK samples for trial ISOPK.08.02 while isotretinoin <sup>13</sup>C<sub>3</sub> was used as an internal standard during the analysis of PK samples for trial ISOPK.09.01 and ISPOPK.09.02.

### ***2.7.2 Which metabolites have been selected for analysis and why?***

This application is following a 505(b)(2) regulatory pathway with Accutane<sup>®</sup> as a listed drug. Studies conducted previously assessed systemic levels of isotretinoin and its metabolites: 4-oxo-isotretinoin, retinoic acid and 4-oxo-retinoic acid. In this submission the Sponsor has assessed only the levels of the parent compound.

Since this study focuses on formulation effects, measuring parent compound alone is adequate.

**2.7.3 For all moieties measured, is free, bound, or total measured?**

Total plasma concentrations (unbound and bound) of isotretinoin were measured.

**2.7.4 What is the range of the standard curve?**

<i>Trial</i>	<i>Analyte</i>	<i>Range (ng/mL)</i>
ISOPK.08.02	Isotretinoin	1.01 to 608.16
ISOPK.09.01 and ISOPK.09.02	Isotretinoin	0.5 to 599.52

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

<i>Trial</i>	<i>LLOQ (ng/mL)</i>	<i>% Accuracy</i>		<i>% Precision</i>	
		<i>Intraday</i>	<i>Interday</i>	<i>Intraday</i>	<i>Interday</i>
ISOPK.08.02	1.01	5.85	11.62	5.72	3.88
ISOPK.09.01 and ISOPK.09.02	0.5	2.32	4.76	5.25	9.35

Note: The values reported in the table above are using stripped matrix since calibration curves were prepared using stripped matrix.

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

Long term stability of analyte in solution at - 80°C	389 days
Long term stability of analyte in matrix (charcoal stripped) at - 80°C	386 days
Long term stability of analyte in matrix (unstripped) at - 80°C	98 days
Freeze and thaw stability	4 cycles at - 80°C
Short term stability at 4°C (charcoal stripped)	25 hours
Short term stability at 4°C (unstripped)	25 hours
Long term stability of internal standard (acitretin) at - 80°C	389 days
Long term stability of internal standard (isotretinoin <sup>13</sup> C <sub>3</sub> ) at - 80°C	304 days
Room temperature stability (charcoal stripped)	136 hours
Room temperature stability (unstripped)	137 hours

***Trial ISOPK.08.02: First date of sample collection – Date of last sample analysis:***

January 09, 2009 – April 08, 2009 = 89 days

***Trial ISOPK.09.01: First date of sample collection – Date of last sample analysis:*** April 23, 2010 – July 29, 2010 = 97 days

***Trial ISOPK.09.02: First date of sample collection – Date of last sample analysis:*** April 14, 2010 – July 20, 2010 = 97 days

**2.7.7 Were any of the trials conducted by Cetero Research in Houston, Texas?**

In response to Agency information request dated September 15, 2011, the Sponsor responded on October 13, 2011 and confirmed that there were no studies conducted by Cetero Research in Houston, Texas during the period of concern (April 1, 2005 to June 15, 2010) submitted to NDA 021951.

Analysis of samples from trials ISOPK.08.02, ISOPK.09.01 and ISOPK.09.02 was performed by (b) (4)

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

After submitting their NDA, the Sponsor made several revisions to their label. The following changes are recommended in the Sponsor's proposed labeling version dated 03/16/2012. The **bold and underlined** text indicates insertion recommended by the reviewer and the ~~strikethrough~~ text indicates recommended deletion.



11 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) Immediately Following this Page.

## 4. Detailed Biopharmaceutics Findings

### **Study No: ISOPK.08.02**

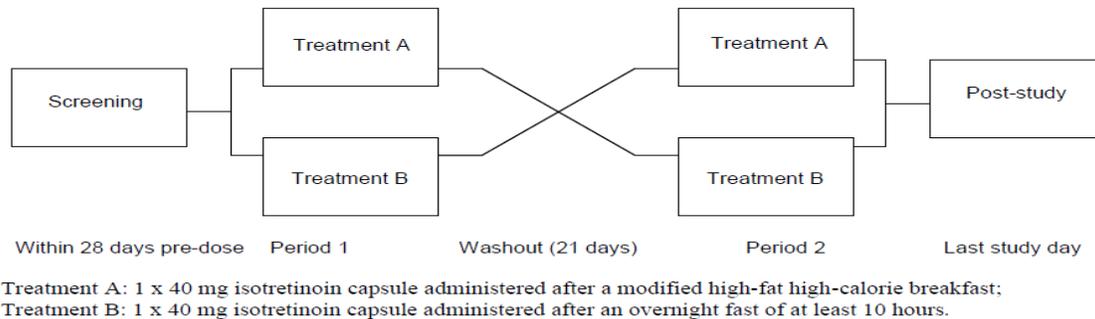
**Title:** An open-label, single-dose, randomized, two-way, food effect study of CIP-Isotretinoin capsules 40 mg, in healthy subjects

**Study objective:** The objective of this study was to evaluate the effect of food on CIP-Isotretinoin 40 mg capsules following a single-dose in healthy subjects.

**Study plan:** This was a single centre, randomized, single-dose, open-label, 2-way crossover, food-effect study to evaluate the effect of food on CIP-Isotretinoin 40 mg capsules after a single dose in healthy subjects.

Subjects were randomized to receive a single-dose of CIP-Isotretinoin 40 mg capsule administered after a modified high-fat, high-calorie breakfast or after an overnight fast of at least 10 hours. For each period, subjects were confined to the clinical research facility from at least 12 hours prior to drug administration and were discharged from the clinic after the 24 hour post-dose blood draw. The treatment phases were separated by a washout period of 21 days. A schematic representation of the study design is shown in Figure 5.

**Figure 5: Schematic study design**



Primary PK analyses were performed with isotretinoin plasma concentrations. Evaluation of safety and tolerability included adverse events, as well as vital signs and clinical laboratory variables.

**Number of subjects:** 16 adult healthy male subjects were enrolled and dosed in the study and 14 of these enrolled subjects completed the study.

### **Treatments Administered:**

**Fed conditions:** A single oral dose of CIP-Isotretinoin as a 1 x 40 mg capsule was administered with 240 mL of water after an overnight fast of at least 10 hours and 30 minutes following a modified high-fat high-calorie breakfast (Treatment A). No other food was allowed for at least 4 hours  $\pm$  15 minutes following drug administration.

**Fasting conditions:** A single oral dose of CIP-Isotretinoin as a 1 x 40 mg capsule was administered with 240 mL of water after an overnight fast of at least 10 hours (Treatment B). The subjects fasted for at least 4 hours ± 15 minutes following drug administration.

**Modified high-fat, high-calorie breakfast:** It consisted of 849 calories (123.2 calories from protein, 265.6 calories from carbohydrates, and 468 calories from fat) with reduced vitamin A content. Details about food administered are shown in the Table 13 below.

**Table 13: Contents of the modified high fat, high calorie breakfast**

Food	Energy (Cal)	Protein (g)	Carbohydrates (g)	Lipids (g)
2 Large eggs + 1 butter	184	12.4	1.2	14
2 Toast (2 x 32g, Durivage Italian style <sup>1</sup> ) + 2 butters	220	5.1	29	10
2 Slice of American style bacon (2 x 8g, Lafleur <sup>1</sup> )	83	4.3	0.6	7.3
2 Hash brown potatoes (2 x 64g, Cavendish <sup>1</sup> )	236	2.2	26	13.8
200 mL of whole milk (3,25 %)	126	6.8	9.6	6.9
Total:	<b>849</b>	<b>30.8</b>	<b>66.4</b>	<b>52</b>
	Energy (Cal):	<b>123.2</b>	<b>265.6</b>	<b>468</b>
	% of Energy <sup>2</sup> :	<b>14.5</b>	<b>31.3</b>	<b>55.1</b>

**Reviewer comments:** According to Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies, the recommended test meal should be approximately 800 – 1000 calories with fat being approximately 50% of the total caloric content. Furthermore, the test meal should derive approximately 150, 250 and 500-600 calories from protein, carbohydrate, and fat respectively. If the test meal is significantly different from the above, the Sponsor should provide a scientific rationale.

The caloric content of the test meal used by this Sponsor does contain approximately 50% of the total caloric content from fat ( $468/849 \times 100 = 55\%$ ), however individual recommended calories from proteins and fat is slightly lower than the recommended (i.e. 123.2 vs. 150 calories for proteins and 468 vs. 500-600 calories from fat). This modified meal according to this reviewer is slightly different from the recommended one and appears to be reasonable.

All subjects were served a controlled meal 4 hours (± 15 minutes) post-dose and standard meals at appropriate times thereafter, during the confinement. These meals were consistent with standard diet; however, restricted compounds were excluded. The post-dose menu was identical in both periods. With the exception of the volume administered at the time of dosing and with the pre-dose breakfast (Treatment A only), fluids were not permitted from 1 hour before dosing to 1 hour after dosing, but water was permitted as required at all other times.

The identity of the investigational product used in this trial is shown in Table 14 below.

**Table 14: Investigational product description**

Parameter	Study Drug
Product	CIP-isotretinoin
Strength	40 mg
Dosage form	capsule
Dose administered	40 mg
Route of administration	oral (administered as a single oral dose of isotretinoin after a modified high-fat high-calorie breakfast for Treatment A or after an overnight fast of at least 10 hours for Treatment B)
Inactive ingredients	(b) (4)
Manufacturer	Galephar Pharmaceutical Research, Inc., Puerto Rico for CIPHER Pharmaceuticals Inc., Canada
Lot no.	IJ08
Manufacture date	Sep 19, 2008
Expiration date	N/AV

**Restrictions:** Subjects were instructed to comply with the following restrictions prior to initiation of the study. Following items were restricted for the 14 days preceding drug administration until completion of the entire study:

- Use of soft or hard drugs, or tobacco products during the study.
- All medications (prescription or over-the-counter). [Non-systemic, topically applied products (prescription or otherwise) or occasional use of common analgesics were allowed].
- Herbal/natural products.
- Nutritional supplements - Subjects with a known daily intake of > 1000 µg for the 30 days prior to study start were excluded from the study.
- No consumption of grapefruit-, alcohol-, caffeine- and/or xanthine-containing products for 48 hours prior to each study period and until after the last sample from each period was collected.
- Limit the amount of foods and nutritional supplements with a high content of vitamin A as per the table shown below for 72 hours prior to each study period until after the last sample from each period was collected. Subjects with a known daily intake of > 75,000 IU within 72 hours of study start were to be excluded from the study.

**Vitamin A content for 100 g of food (International Units IU)**

Animal Source	IU	Plant Source	IU
Butter	3300	Apricots	2790
Cheese	1020	Carrots	12000
Cod Liver oil	85000	Corn, fresh	0
Eel, fresh	2000	Melon	3420
Eggs, uncooked	1140	Orange	190
Liver, calf	22500	Parsley	8320
Liver, beef	20000	Peach	880
Liver, sheep	50500	Potatoes	20
Milk (cow's)	140	Spinach	9420
Sardines	710	Sprouts, corn	650
		Sweet potatoes	7700

At check-in of each study period, adherence to these restrictions were confirmed and recorded for each subject. Subjects who did not comply with these restrictions were to be assessed by the investigator regarding continued participation in the study.

A urine drug screen, an alcohol breath test, and a urine cotinine test were performed for all subjects upon admission to the clinical unit for each period.

**Blinding:** This was an open-label trial; since the study drug administration to subjects was performed using different conditions of administration (i.e. after a modified high-fat high-calorie breakfast or after an overnight fast of at least 10 hours). However, the randomization scheme was not made available to the Bioanalytical Division of [redacted] (b) (4) [Contract Research Organization (CRO)] until the clinical and analytical phases had been completed.

**PK blood sampling:** In each period, blood samples were collected at -10 , -2 and 0 hours pre-dose and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14, 16, 20, 24, 36, 48, and 72 hours post-dose.

**PK parameter estimation:** The Sponsor planned to calculate the following PK parameters:

AUC<sub>(t)</sub>: Area under the plasma concentration-time curve form time 0 to the last time point measurable with analyte

AUC<sub>(inf)</sub>: Area under the plasma concentration-time curve from time 0 to infinity

C<sub>max</sub>: The maximum measured plasma concentration

T<sub>max</sub>: Time of the maximum measured plasma concentration

K<sub>el</sub>: Elimination rate constant

T<sub>1/2el</sub>: The apparent terminal elimination half-life

**Disposition of subjects:** Shown in Table 15 below.

**Table 15: Disposition of subjects for trial ISOPK.08.02**

Screened:	N=55	
Screening failures:	N=21	
Not enrolled*:	N=18	
Enrolled:	N=16	
Randomised:	N=16	
	<b>Treatment A</b>	<b>Treatment B</b>
Dosed in Period 1:	N=8 (50.0%)	N=8 (50.0%)
Dosed in Period 2:	N=6 (37.5%)	N=8 (50.0%)
Withdrawals:	N=1	N=0
Drop-outs:	N=1	N=0
Completed:	N=14 (87.5%)	N=16 (100%)
Completed both periods:	N=14 (87.5%)	

Treatment A: 1 x 40 mg isotretinoin capsule administered after a modified high-fat high-calorie breakfast;

Treatment B: 1 x 40 mg isotretinoin capsule administered after an overnight fast of at least 10 hours.

\* Includes subjects who were judged eligible but decided not to participate on study or who were not selected to participate in the study since there was already a sufficient number of subjects.

**Subject discontinuation:** 2 subjects discontinued. Subject No. 09 was discontinued due to adverse event (increase in blood pressure) and Subject No. 13 withdrew consent. Subject No. 05 and 10 were discontinued pre-dose and were replaced. Details are shown in Table 16 below.

**Table 16: Information on subjects that discontinued in trial ISOPK.08.02**

Subject Number	Treatment	Study Period	Discontinuation Time/Date	Primary Reason for Discontinuation
05 (became Stand-by AA, replaced by Stand-by A)	Not applicable	Pre-dose	2009-01-10 07:29	Adverse event
10 (became Stand-by BB, replaced by Stand-by B)	Not applicable	Pre-dose	2009-01-10 07:29	Adverse event
09	B	1	2009-01-31 07:52	Adverse event
13	B	1	2009-01-30 14:47	Withdrew consent

Treatment A: 1 x 40 mg isotretinoin capsule administered after a modified high-fat high-calorie breakfast;

Treatment B: 1 x 40 mg isotretinoin capsule administered after an overnight fast of at least 10 hours.

*Demographic information and baseline characteristics:* Shown in Table 17 below.

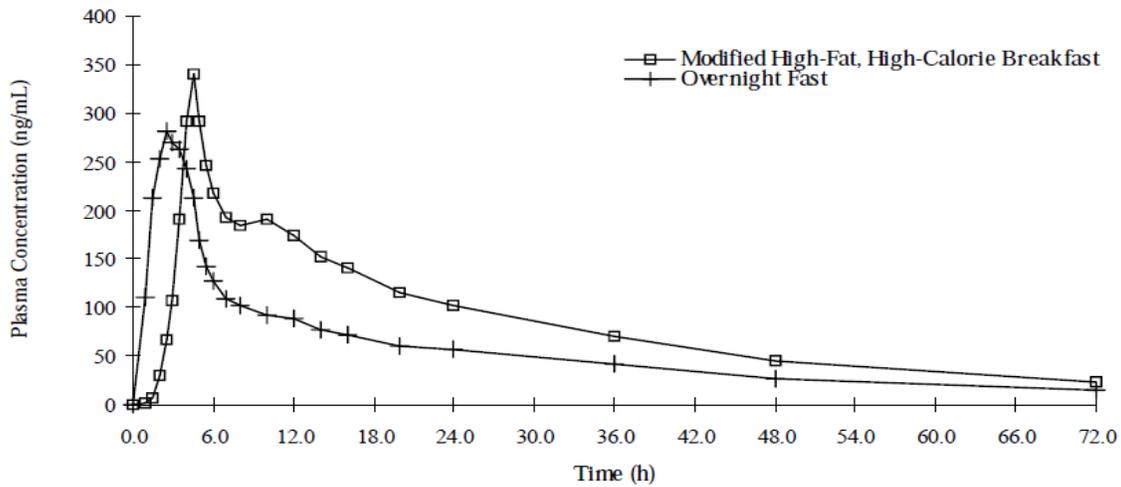
**Table 17: Demographic information for trial ISOPK.08.02**

Category		Treatment	
		Test (A)	Reference (B)
Age (years)	Mean ± SD	37 ± 10	37 ± 10
	Range	21 - 52	21 - 52
	Median	35	35
	N	14	14
Age Groups	<18	0	0
	18-40	10 (71.4 %)	10 (71.4 %)
	41-64	4 (28.6 %)	4 (28.6 %)
	65-75	0	0
	>75	0	0
Gender	Female	0	0
	Male	14 (100.0 %)	14 (100.0 %)
Race	Asian	0	0
	Black	0	0
	White	12 (85.7 %)	12 (85.7 %)
	Other	2 (14.3 %)	2 (14.3 %)
Ethnicity	Not Hispanic	11 (78.6 %)	11 (78.6 %)
	Hispanic	3 (21.4 %)	3 (21.4 %)
Height (cm)	Mean ± SD	175.2 ± 7.7	175.2 ± 7.7
	Range	159.0 - 183.5	159.0 - 183.5
	Median	175.8	175.8
	N	14	14
Weight (kg)	Mean ± SD	77.6 ± 6.7	77.6 ± 6.7
	Range	64.0 - 86.4	64.0 - 86.4
	Median	79.1	79.1
	N	14	14
BMI (kg/m <sup>2</sup> )	Mean ± SD	25.3 ± 3.0	25.3 ± 3.0
	Range	21.1 - 31.3	21.1 - 31.3
	Median	24.3	24.3
	N	14	14

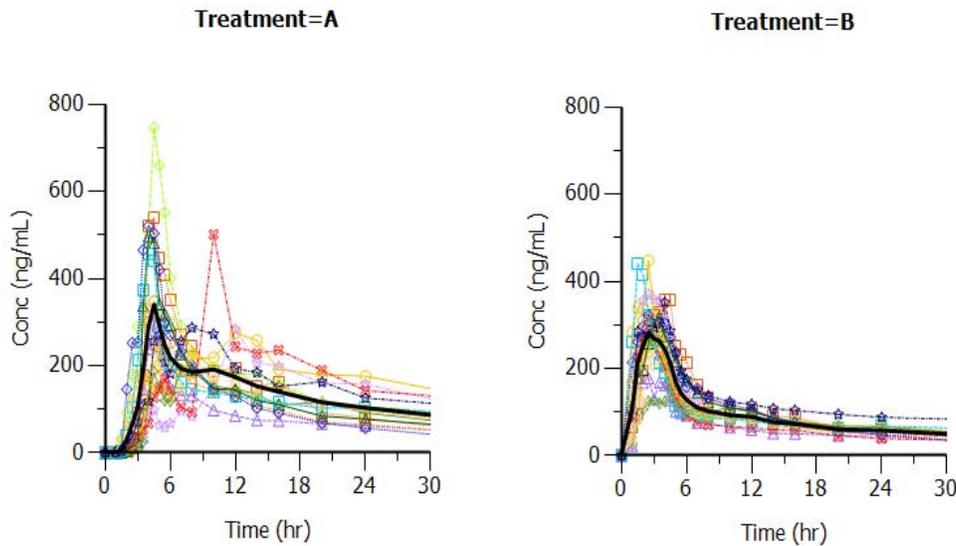
Treatment A: 1 x 40 mg isotretinoin capsule administered after a modified high-fat high-calorie breakfast;  
 Treatment B: 1 x 40 mg isotretinoin capsule administered after an overnight fast of at least 10 hours.

**PK results:** Mean baseline corrected concentration-time profile for isotretinoin (N = 14) is shown in Figure 6 while summary of PK parameters and relative BA analysis are shown in Table 18 and 19 respectively. Individual subject plots (up to 30 hours) are shown in Figure 7 (Mean concentration profile is shown with a dark black line).

**Figure 6: Mean baseline corrected concentration versus time profile of isotretinoin following administration of 40 mg strength under fed and fasting conditions**



**Figure 7: Individual subject baseline corrected concentration versus time (up to 30 h) profile of isotretinoin following administration of 40 mg strength under fed (Treatment A) and fasting (Treatment B) conditions (Mean concentration profile is shown with a dark black line)**



**Table 18: Summary of PK parameters for the baseline corrected data of isotretinoin for each treatment arm (N = 14)**

Parameters	Isotretinoin Administered With a Modified High-Fat, High-Calorie Breakfast (A)			Isotretinoin Administered Under an Overnight Fast of at Least 10 Hours (B)		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC <sub>0-t</sub> (ng·h/mL)	6095.16	1571.91	25.79	4054.76	820.64	20.24
AUC <sub>0-inf</sub> (ng·h/mL)	6889.31	2046.77	29.71	4626.92	1225.31	26.48
AUC <sub>t/inf</sub> (%)	89.45	5.58	6.24	88.67	6.30	7.10
C <sub>max</sub> (ng/mL)	394.62	152.65	38.68	313.51	81.98	26.15
T <sub>max</sub> (h)	6.40	3.02	47.19	2.89	0.98	33.99
T <sub>max</sub> * (h)	4.50	3.50	-	2.51	1.00	-
K <sub>el</sub> (h <sup>-1</sup> )	0.0341	0.0094	27.47	0.0307	0.0082	26.77
T <sub>½ el</sub> (h)	21.67	5.45	25.13	24.19	6.80	28.11

\* Medians and interquartile ranges are presented.

**Table 19: Relative BA analysis and calculation of 90% CI**

	AUC <sub>0-t</sub>	AUC <sub>0-inf</sub>	C <sub>max</sub>
Ratio <sup>1</sup>	150.17%	148.93%	121.23%
90 % Geometric C.I. <sup>2</sup>	134.52 % to 167.64 %	134.24 % to 165.23 %	98.94 % to 148.54 %
Intra-Subject CV	16.27 %	15.35 %	30.53 %

<sup>1</sup> Calculated using least-squares means according to the formula:  $e^{(A-B)} \times 100$ .

<sup>2</sup> 90% Geometric Confidence Interval using ln-transformed data.

The AUC and C<sub>max</sub> under fed conditions was approximately 1.5 and 1.3 fold higher respectively, with modified high-fat, high-calorie breakfast compared to fasting conditions. Moreover, the drug absorption was delayed by approximately 3.5 hours under fed conditions. Specifically the contents of the breakfast made up for 849 calories (123.2 calories from protein, 265.6 calories from carbohydrates, and 468 calories from fat) with reduced vitamin A content.

This increase in exposure of isotretinoin with a modified high-fat, high calorie breakfast observed following administration of 40 mg strength appears to be similar with that observed with previously evaluated 30 mg strength (ISOPK.02.04) as shown in Table 20 below.

**Table 20: Effect of food on 40 mg and 30 mg strength**

Dose	AUC <sub>0-t</sub> (Fed/Fasting)	AUC <sub>0-inf</sub> (Fed/Fasting)	C <sub>max</sub> (Fed/Fasting)
40 mg	1.5	1.5	1.3
30 mg	1.5	1.4	1.6

**Reviewer Comments:** The effect of food with 30 mg strength was reviewed earlier by Dr. Dennis Bashaw (see review in DARTS dated 04/21/2006 and appendix).

***According to Dr. Bashaw, the Sponsor had used a non-standard FDA high-fat meal; however, it did approximate the FDA standard high-fat meal in terms of both total calories and composition.***

***Summary of adverse events:*** According to the Sponsor, a total of 16 treatment-emergent adverse events (TESEs) were reported by 9 of the 16 subjects (safety population) who received at least one dose of the study medication.

The breakdown by treatment group is as follows:

- 6 TEAEs reported by 28.6 % (n= 4) of the 14 subjects who received the study medication under fed conditions (Treatment A)
- 10 TEAEs reported by 37.5 % (n=6) of the 16 subjects who received the study medication under fasting conditions (Treatment B).

No safety issues were observed with respect to clinical laboratory results, physical examinations, and vital signs results. Two TEAEs were reported for abnormal vital signs measurements: one subject experienced Heart rate decreased (fed conditions) and one subject experienced Blood pressure increased (fasting conditions). The latter of these events was considered to be significant since the subject was withdrawn from the study (Subject No. 09). Only two minor physical examination abnormalities were recorded at the time of post-study procedures. No deaths or serious adverse events were reported during this study.

***Reviewer Comments: The safety results reported here are those that were reported by the Sponsor and were not reviewed by this reviewer. For additional information, please refer to Clinical review.***

***Study No: ISOPK.09.01***

***Title:*** An open-label, single-dose, randomized, two-way, comparative BA study of CIP-Isotretinoin capsules 2 x 20 mg vs. 1 x 40 mg, in healthy subjects dosed under fed conditions.

***Objective:*** The objective of this study was to evaluate the comparative BA of CIP-Isotretinoin capsules 2 x 20 mg versus 1 x 40 mg after a single dose in healthy subjects dosed under fed conditions.

***Study design:*** This was a single centre, randomized, single-dose, open-label, 2-way crossover comparative BA study to compare the BA of CIP-Isotretinoin capsules 2 x 20 mg versus CIP-Isotretinoin capsule 1 x 40 mg, under fed conditions. A total of 49 healthy, male non-smokers were randomized in this study. Subjects were confined to the clinical facility from at least 12 hours prior to drug administration until after the 24 hour post-dose blood draw, in each period. Subjects were asked to come back to the clinical facility for return visits. The treatment phases were separated by a washout period of 21 days.

In each period, according to the randomization scheme, subjects were administered a single oral dose of either the 2 x 20 mg capsules versus 1 x 40 mg capsule for a total dose of 40 mg of isotretinoin.

**PK sampling time points:** Blood samples were collected at -10, -2, 0 (within 5 minutes prior dosing), 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 11, 12, 14, 16, 20, 24, 36, 48, and 72 hours post-dose in each period.

**PK parameter estimation:** The Sponsor planned to calculate the following PK parameters:

AUC<sub>(0)</sub>: Area under the plasma concentration-time curve from time 0 to the last time point measurable with analyte

AUC<sub>(inf)</sub>: Area under the plasma concentration-time curve from time 0 to infinity

C<sub>max</sub>: The maximum measured plasma concentration

T<sub>max</sub>: Time of the maximum measured plasma concentration

K<sub>el</sub>: Elimination rate constant

T<sub>1/2el</sub>: The apparent terminal elimination half-life

**Drug Administration:** After a supervised overnight fast of at least 10 hours, subjects were served a modified (reduced vitamin A content) high-fat, high-caloric breakfast 30 minutes before drug administration. Subjects were administered one of two treatments as a single oral dose of CIP-Isotretinoin capsules 2 x 20 mg or CIP-Isotretinoin capsule 1 x 40 mg (total dose of 40 mg), with 240 mL of water. Subjects were instructed not to chew or to break the study medication. Subjects were dosed as specified in the protocol, and subsequently fasted for a period of at least 4 hours.

The identity of the investigational product used in this trial is shown in Table 21 below.

**Table 21: Investigational product description**

Product	Test-1	Test-2
Treatment Identification	A	B
Product Name	CIP-ISOTRETINOIN 20 mg Capsule	CIP-ISOTRETINOIN 40 mg Capsules
Company Responsible For Manufacturing	Cipher Pharmaceuticals Inc., Canada	Cipher Pharmaceuticals Inc., Canada
Lot Number	5D102	5D103
Manufacturing Date	Mar 26, 2010	Mar 28, 2010
Expiration Date	Sept, 2010	Sept, 2010
Strength	20 mg	40 mg
Dosage Form	hard gelatin capsule	hard gelatin capsule
Content Uniformity		(b) (4)
Dose Administered	2 x 20 mg	1 x 40 mg
Route of Administration	oral	oral

**Food and Fluid Intake:** Subjects were served a modified (reduced vitamin A content) high-fat, high caloric breakfast prior to drug administration. After a supervised overnight fast of at least 10 hours, and 30 minutes before drug administration, subjects were served a modified high-fat, high-caloric breakfast of between 800 to 1000 calories (approximately 123 calories from protein, 265 calories from carbohydrates, and 468 calories from fat). The breakfast consisted of two eggs fried in butter, 2 slices of toast with butter, 2 strips of bacon, approximately 64 g of hash brown potatoes, and 200 mL of whole milk. Subjects were required to completely consume this breakfast prior to drug administration.

Subjects were served a controlled meal 4 hours ( $\pm$  15 minutes) post-dose, and at appropriate times thereafter, in each period. Subjects were served post-dose meals similar in composition in each period. With the exception of the volume administered at the time of dosing and with the pre-dose breakfast, fluids were not permitted from 1 hour before dosing to 1 hour after dosing, but water was permitted as required at all other times.

**Restrictions:** Subjects were instructed to comply with the following restrictions prior to initiation of the study. Following items were restricted for the 7 days preceding drug administration until last sample collection of each period:

- All medications (prescription or over-the-counter). [Non-systemic, topically applied products (prescription or otherwise) or occasional use of common analgesics were allowed].
- Herbal/natural products.
- Nutritional supplements - Subjects with a known daily intake of  $> 1000 \mu\text{g}$  for the 30 days prior to study start were excluded from the study.
- No consumption of grapefruit-, alcohol-, caffeine- and/or xanthine-containing products for 48 hours prior to each study period and until after the last sample from each period was collected.
- Limit the amount of foods and nutritional supplements with a high content of vitamin A as per table below for 72 hours prior to each study period until after the last sample from each period was collected. Subjects with a known daily intake of  $> 75,000 \text{ IU}$  within 72 hours of study start were to be excluded from the study.

**Vitamin A content for 100 g of food (International Units IU)**

Animal Source	IU	Plant Source	IU
Butter	3300	Apricots	2790
Cheese	1020	Carrots	12000
Cod Liver oil	85000	Corn, fresh	0
Eel, fresh	2000	Melon	3420
Eggs, uncooked	1140	Orange	190
Liver, calf	22500	Parsley	8320
Liver, beef	20000	Peach	880
Liver, sheep	50500	Potatoes	20
Milk (cow's)	140	Spinach	9420
Sardines	710	Sprouts, corn	650
		Sweet potatoes	7700

At check-in of each study period, adherence to these restrictions were confirmed and recorded for each subject. Subjects who did not comply with these restrictions were to be assessed by the investigator regarding continued participation in the study.

A urine drug screen, an alcohol breath test, and a urine cotinine test were performed for all subjects upon admission to the clinical unit for each period.

**Blinding:** The study was open-label, however, the randomization scheme was not available to the Bioanalytical Division of (b) (4) until the clinical and analytical phases had been completed.

**Disposition of Subjects:** 49 subjects were randomized and dosed in this study; of these 45 subjects completed the study. In accordance with the study protocol, data from all subjects who completed the study and for whom the pharmacokinetic profile was adequately characterized were used for pharmacokinetic and statistical analysis (n=45).

**Subject discontinuation:** A summary of subjects that were withdrawn or withdrew consent from the study is shown in Table 22.

**Table 22: Summary of subjects that were discontinued from trial ISOPK.09.01**

Prior to the first drug administration				
Subject Number	Reason for withdrawal (Date and time of withdrawal/treatment/reason)	Period	Replaced?	Replaced with
36 (became Stand-by AA)	2010-04-24 Not recorded / Not applicable / Subject was withdrawn due to adverse events (Vomiting, Headache, Diarrhea, Abdominal pain, and Nausea).	Not applicable	No	Stand-by A
After receiving at least one dose of the study medication (safety population)				
Subject Number	Reason for withdrawal (Date and time of withdrawal/treatment/reason)	Period	Replaced?	Replaced with
12	2010-04-27 07:25 / Treatment A / Subject was withdrawn due to significant adverse events (Itchiness and Redness on parts of the body).	1	No	Not applicable
18	2010-05-14 22:19 / Treatment B / Subject elected to withdraw; he did not show up for Period 2 confinement.	1	No	Not applicable
24	2010-05-14 21:28 / Treatment B / Subject was withdrawn since an ICF from another CRO was found during baggage check of Period 2 and the subject refused consent for the verification with the other CRO.	1	No	Not applicable
39	2010-05-14 16:41 / Treatment A / Subject was withdrawn since he did not respect study restriction; he participate in another study at the same time.	1	No	Not applicable

Note: A subject was considered as a:

Drop-out: when the subject elected to withdraw after receiving at least one dose of the study medication.

Withdrawal: when the subject was withdrawn by the Sponsor, Investigator, Medical Sub-Investigator, or a delegate after receiving at least one dose of the study medication.

**Demographics:** Shown in Table 23.

**Table 23: Demographic information for trial ISOPK.09.01**

		Subjects who completed the study and were included in the PK population	
Category		Treatment	
		Treatment (A)	Treatment (B)
Age (years)	Mean ± SD	38 ± 9	38 ± 9
	Range	20 - 55	20 - 55
	Median	38	38
	n	45	45
Age Groups	<18	0	0
	18-40	29 (64.4%)	29 (64.4%)
	41-64	16 (35.6%)	16 (35.6%)
	65-75	0	0
	>75	0	0
Gender	Female	0	0
	Male	45 (100%)	45 (100%)
Race	Asian	1 (2.7%)	1 (2.7%)
	Black	6 (16.2%)	6 (16.2%)
	White	30 (81.1%)	30 (81.1%)
	Other	0	0
Ethnicity	Not Hispanic	29 (64.4%)	29 (64.4%)
	Hispanic	16 (35.6%)	16 (35.6%)
Height (cm)	Mean ± SD	175.5 ± 6.3	175.5 ± 6.3
	Range	162.5 - 191.0	162.5 - 191.0
	Median	176.0	176.0
	n	45	45
Weight (kg)	Mean ± SD	78.8 ± 7.2	78.8 ± 7.2
	Range	66.9 - 93.6	66.9 - 93.6
	Median	78.4	78.4
	n	45	45
BMI (kg/m <sup>2</sup> )	Mean ± SD	25.6 ± 2.3	25.6 ± 2.3
	Range	21.4 - 29.7	21.4 - 29.7
	Median	25.5	25.5
	n	45	45

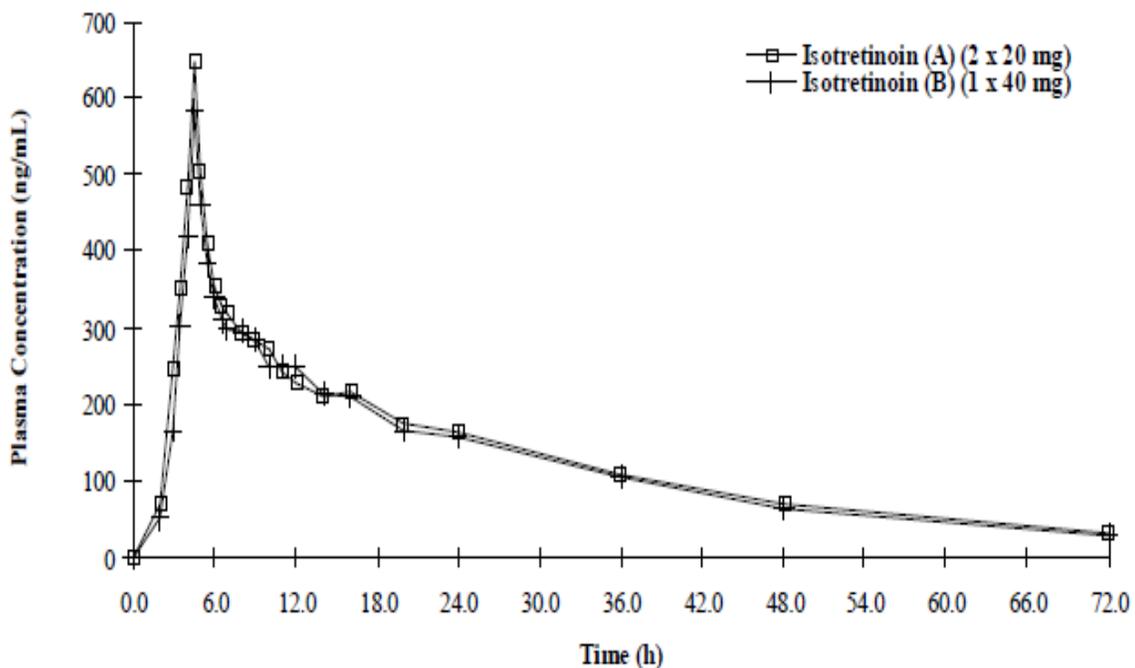
A = CIP-Isotretinoin 2 x 20 mg capsules

B = CIP-Isotretinoin 1 x 40 mg capsule

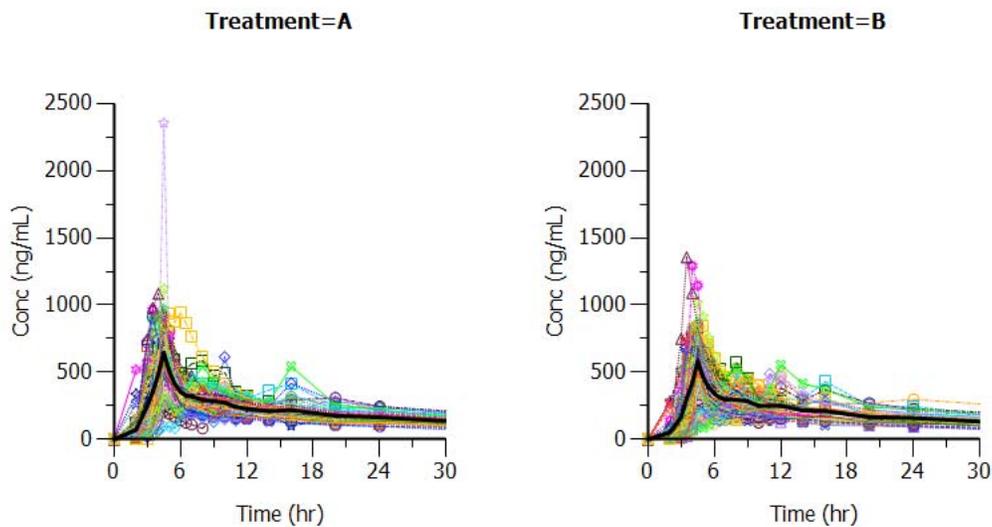
**PK results:**

Baseline corrected data: Mean concentration versus time profile for baseline corrected isotretinoin for each treatment (N = 45) is shown in Figure 8 while summary of PK parameters and relative BA analysis are shown in Table 24 and 25 respectively. Individual subject plots are shown in Figure 9 (mean concentration profile is shown by dark black line).

**Figure 8: Mean baseline corrected concentration versus time profile of isotretinoin following administration of CIP-Isotretinoin as 2 x 20 mg (Treatment A) and 1 x 40 mg (Treatment B) under fed conditions**



**Figure 9: Mean baseline corrected individual subject concentration versus time (up to 30 h) profile of isotretinoin following administration of CIP-Isotretinoin as 2 x 20 mg (Treatment A) and 1 x 40 mg (Treatment B) under fed conditions (mean concentration profile is shown by a dark black line)**



**Table 24: Summary of PK parameters for baseline corrected isotretinoin for each treatment (N = 45)**

Parameters	Isotretinoin (A) (2 x 20 mg)			Isotretinoin (B) (1 x 40 mg)		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC <sub>0-t</sub> (ng·h/mL)	9492.94	1614.12	17.00	8936.04	1471.98	16.47
AUC <sub>0-inf</sub> * (ng·h/mL)	10520.71	1939.54	18.44	9904.44	1745.21	17.62
AUC <sub>t/inf</sub> * (%)	90.75	4.47	4.92	90.77	5.42	5.97
C <sub>max</sub> (ng/mL)	725.96	326.14	44.93	659.10	217.01	32.93
T <sub>max</sub> (h)	5.74	3.76	65.59	5.70	2.72	47.67
T <sub>max</sub> ** (h)	4.50	0.50	-	4.50	0.52	-
K <sub>el</sub> * (h <sup>-1</sup> )	0.0359	0.0077	21.38	0.0370	0.0077	20.74
T <sub>½el</sub> * (h)	20.13	4.01	19.92	19.50	3.95	20.26

<sup>1</sup> For these parameters, N=44.

\*\* Medians and interquartile ranges are presented.

**Table 25: Relative BA analysis and calculation of 90% CI**

	AUC <sub>0-t</sub>	AUC <sub>0-inf</sub> *	C <sub>max</sub>
Ratio <sup>1</sup>	106.04%	106.08%	106.94%
90 % Geometric C.I. <sup>2</sup>	103.15 % to 109.01 %	103.16 % to 109.09 %	97.35 % to 117.47 %
Intra-Subject CV	7.81 %	7.80 %	26.97 %

<sup>1</sup> Calculated using least-squares means according to the formula:  $e^{(A-B)} \times 100$ .

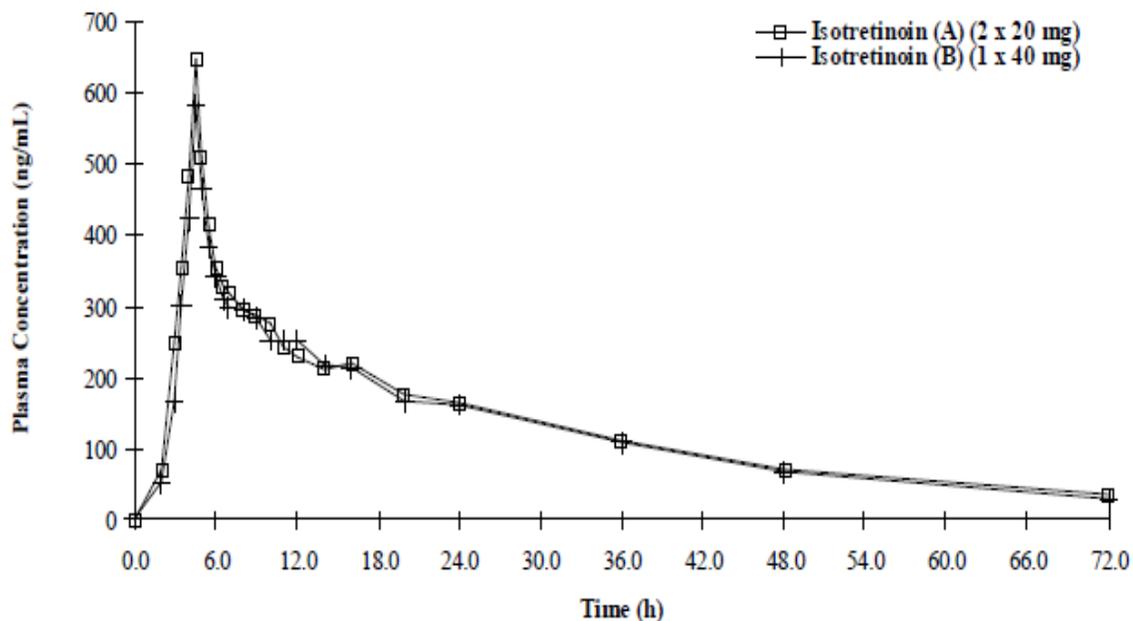
<sup>2</sup> 90% Geometric Confidence Interval using ln-transformed data.

\* For this parameter, N=44.

The PK results show that 1 x 40 mg strength of CIP-Isotretinoin capsules were BE to 2 x 20 mg strength of CIP-Isotretinoin capsules under fed conditions indicating that the PK of the drug increases in a dose proportional manner between 10 mg and 40 mg strength. [Dose proportionality between 10 mg to 30 mg strength has been demonstrated previously under fasting (ISOPK.06.01) and fed conditions (ISOPK.06.02) and the results were reviewed by Dr. Dennis Bashaw (Please Note: under fasting conditions, the CI of the ratio of geometric mean of AUC was borderline on the 80% to 125% no effect boundary. Specifically, the PK of 1 x 30 mg strength increased in very slightly less than proportional manner compared to 3 x 10 mg strength. This was considered acceptable by the previous reviewer) (see review in DARRTS dated 04/09/2007 for more information)].

Baseline uncorrected data: The baseline uncorrected data was provided only as supportive and were not used to infer any conclusions. Mean concentration versus time profile for baseline uncorrected isotretinoin for each treatment (N = 45) is shown in Figure 10 while summary of PK parameters and relative BA analysis are shown in Table 26 and 27 respectively

**Figure 10: Mean baseline uncorrected concentration versus time profile of isotretinoin following administration of CIP-Isotretinoin as 2 x 20 mg (Treatment A) and 1 x 40 mg (Treatment B) under fed conditions**



**Table 26: Summary of PK parameters for baseline uncorrected isotretinoin for each treatment (N = 45)**

Parameters	Isotretinoin (A) (2 x 20 mg)			Isotretinoin (B) (1 x 40 mg)		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC <sub>0-t</sub> (ng h/mL)	9596.85	1621.12	16.89	9044.30	1477.78	16.34
AUC <sub>0-inf</sub> * (ng h/mL)	10688.01	1951.46	18.26	10077.71	1751.48	17.38
AUC <sub>t/inf</sub> * (%)	90.29	4.46	4.94	90.27	5.40	5.98
C <sub>max</sub> (ng/mL)	727.41	326.20	44.84	660.64	217.12	32.86
T <sub>max</sub> (h)	5.74	3.76	65.59	5.70	2.72	47.67
T <sub>max</sub> ** (h)	4.50	0.50	-	4.50	0.52	-
K <sub>el</sub> * (h <sup>-1</sup> )	0.0349	0.0070	20.21	0.0359	0.0071	19.90
T <sub>1/2 el</sub> * (h)	20.62	3.95	19.14	20.04	3.90	19.46

\* For these parameters, N=44.

\*\* Medians and interquartile ranges are presented.

**Table 27: Relative BA analysis and calculation of 90% CI (using baseline uncorrected data)**

	AUC <sub>0-t</sub>	AUC <sub>0-inf</sub> *	C <sub>max</sub>
Ratio <sup>1</sup>	105.92%	105.91%	106.92%
90 % Geometric C.I. <sup>2</sup>	103.05 % to 108.86 %	103.04 % to 108.85 %	97.35 % to 117.43 %
Intra-Subject CV	7.75 %	7.66 %	26.92 %

<sup>1</sup> Calculated using least-squares means according to the formula:  $e^{(A-B)} \times 100$ .

<sup>2</sup> 90% Geometric Confidence Interval using ln-transformed data.

\* For this parameter, N=44.

**Overall conclusion:** In conclusion, the results of this study show that CIP-Isotretinoin 20 mg strength capsules administered as a 40 mg dose is BE in terms of rate and extent of absorption ( $C_{max}$  and AUC) to the to the 40 mg strength capsules under fed conditions. Furthermore, the results from this study would support that PK of 40 mg strength increased in a dose proportional manner under **fed** conditions.

**Summary of Adverse Events:** According to the Sponsor, a total of 21 TEAEs were reported by 12 of the 49 subjects who received at least one dose of the study medication (safety population). The breakdown by treatment group is as follows:

- 11 TEAEs reported by 14.9% (n=7) of the 47 subjects who received Treatment A
- 10 TEAEs reported by 17.0% (n=8) of the 47 subjects who received Treatment B

The most commonly reported TEAEs were “Pruritus” and “Scratch” both reported by 4.1% (n=2) of subjects who constituted the safety population (n=49). All other TEAEs were only reported by one subject.

No deaths or serious adverse events (AEs) were reported during this study. Subject No. 12 experienced the significant AEs “Pruritus” and “Erythema”. The health of this subject was not at risk during the study. Upon conclusion of the clinical portion of the study, the results from the subjects who completed post study procedures, including laboratory tests, physical examinations, and vital signs measurements, confirmed the absence of significant changes in the subjects’ state of health.

***Reviewer Comments:*** *The safety results reported here are those that were reported by the Sponsor and were not reviewed by this reviewer. For additional information, please refer to Clinical review.*

**Study No: ISOPK.09.02**

**Title:** An open-label, single-dose, randomized, two-way, comparative BA study of CIP-Isotretinoin capsules 2 x 20 mg vs. 1 x 40 mg, in healthy subjects dosed under fasting conditions.

**Study Objective:** The objective of this study was to evaluate the comparative BA of Isotretinoin capsules 2 x 20 mg versus 1 x 40 mg after a single-dose in healthy subjects dosed under fasting conditions.

**Study Design:** This was a single centre, randomized, single-dose, open-label, 2-way crossover comparative BA study to compare the BA of CIP-Isotretinoin capsules 2 x 20 mg versus CIP-Isotretinoin capsule 1 x 40 mg, under fasting conditions. A total of 50 healthy, male non-smokers were randomized in this study. Subjects were confined to the clinical facility from at least 12 hours prior to drug administration until after the 24 hour post-dose blood draw, in each period. Subjects were asked to come back to the clinical facility for return visits. The treatment phases were separated by a washout period of 21 days.

In each period, according to the randomization scheme, subjects were administered a single oral dose of either the 2 x 20 mg capsules versus 1 x 40 mg capsule for a total dose of 40 mg of isotretinoin.

**PK sampling time points:** Blood samples were obtained at -10, -2, 0 (within 5 minutes before drug administration), 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14, 16, 20, 24, 36, 48, 72 and 96-hour post dose in each period.

**PK parameter estimation:** The Sponsor planned to calculate the following PK parameters:

AUC<sub>(t)</sub>: Area under the plasma concentration-time curve from time 0 to the last time point measurable with analyte

AUC<sub>(inf)</sub>: Area under the plasma concentration-time curve from time 0 to infinity

C<sub>max</sub>: The maximum measured plasma concentration

T<sub>max</sub>: Time of the maximum measured plasma concentration

K<sub>el</sub>: Elimination rate constant

T<sub>1/2el</sub>: The apparent terminal elimination half-life

**Drug administration:** In each period, according to the randomization scheme, subjects were administered a single oral dose of CIP-Isotretinoin as 2 x 20 mg capsules or 1 x 40 mg capsule under fasting conditions. Subjects were administered the test product as a single oral dose of 2 x 20 mg capsules or 1 x 40 mg capsule with 240 mL of room temperature water following a supervised overnight fast of at least 10 hours. Subjects remained under fasting conditions for at least 4 hours (± 15 minutes) post dose.

The identity of the investigational product used in this trial is shown in Table 28 below.

**Table 28: Investigational product description**

Product	Test	
Treatment Identification	A	B
Product Name	CIP-ISOTRETINOIN 20 mg Capsules	CIP-ISOTRETINOIN 40 mg Capsules
Company Responsible For Manufacturing	Cipher Pharmaceuticals Inc., Canada	Cipher Pharmaceuticals Inc., Canada
Batch/Lot Number	5D102	5D103
Manufacturing Date	Mar 26, 2010	Mar 28, 2010
Expiration Date	Sept, 2010	Sept, 2010
Strength	20 mg	40 mg
Dosage Form	hard gelatine capsule	hard gelatin capsule
Content Uniformity	(b) (4)	
Dose Administered	2 x 20 mg	1 x 40 mg
Route of Administration	oral	oral

**Food and Fluid Intake:** Subjects were served a controlled meal 4 hours ( $\pm$  15 minutes) post-dose, and at appropriate times thereafter, in each period. Post-dose meals were similar in composition in each period. With the exception of the fluid volume administered at the time of dosing, fluids were not permitted from 1 hour before dosing to 1 hour after dosing, but water was permitted as required at all other times.

**Restrictions:** Subjects were instructed to comply with the following restrictions prior to initiation of the study. Following items were restricted for the 7 days preceding drug administration until last sample collection of each period:

- All medications (prescription or over-the-counter). [Non-systemic, topically applied products (prescription or otherwise) or occasional use of common analgesics were allowed].
- Herbal/natural products.
- Nutritional supplements - Subjects with a known daily intake of  $>$  1000  $\mu$ g for the 30 days prior to study start were excluded from the study.
- No consumption of grapefruit-, alcohol-, caffeine- and/or xanthine-containing products for 48 hours prior to each study period and until after the last sample from each period was collected.
- Limit the amount of foods and nutritional supplements with a high content of vitamin A as per table below for 72 hours prior to each study period until after the last sample from each period was collected. Subjects with a known daily intake of  $>$  75,000 IU within 72 hours of study start were to be excluded from the study.

**Vitamin A content for 100 g of food (International Units IU)**

Animal Source	IU	Plant Source	IU
Butter	3300	Apricots	2790
Cheese	1020	Carrots	12000
Cod Liver oil	85000	Corn, fresh	0
Eel, fresh	2000	Melon	3420
Eggs, uncooked	1140	Orange	190
Liver, calf	22500	Parsley	8320
Liver, beef	20000	Peach	880
Liver, sheep	50500	Potatoes	20
Milk (cow's)	140	Spinach	9420
Sardines	710	Sprouts, corn	650
		Sweet potatoes	7700

At check-in of each study period, adherence to these restrictions were confirmed and recorded for each subject. Subjects who did not comply with these restrictions were to be assessed by the investigator regarding continued participation in the study.

A urine drug screen, an alcohol breath test, and a urine cotinine test were performed for all subjects upon admission to the clinical unit for each period.

**Blinding:** This study was open-label But the Bioanalytical Division of (b) (4) was blinded from the treatment sequence throughout the analytical process.

**Disposition of Subjects:** In this study 50 subjects who were dosed of which 41 were included in the PK population. Subject Nos. 04 and 46 missed the last four time points (36, 48, 72, and 96-hour post-dose) in period 2 which could result in an underestimation of the AUC greater than 30%. Therefore, these subjects were excluded from the PK population prior the PK and statistical analyses.

**Subject discontinuation:** A summary of subjects that were withdrawn or withdrew consent from the study is shown in Table 29.

**Table 29: Summary of subjects that were discontinued from trial ISOPK.09.02**

Prior to the first drug administration				
Subject Number	Reason for withdrawal (Date and time of withdrawal/treatment/reason)	Period	Replaced?	Replaced with
04 (became Stand-by AA)	2010-04-14 19:36 / Not applicable / Subject was withdrawn due to a positive result for urine cotinine test	Not applicable	Yes	Stand-by A
09 (became Stand-by CC)	2010-04-15 07:53 / Not applicable / Subject was withdrawn due to increased blood pressure	Not applicable	Yes	Stand-by C
37 (became Stand-by BB)	2010-04-14 19:39 / Not applicable / Subject was withdrawn due to a positive result for urine cotinine test	Not applicable	Yes	Stand-by B
After receiving at least one dose of the study medication (safety population)				
Subject Number	Reason for withdrawal (Date and time of withdrawal/treatment/reason)	Period	Replaced?	Replaced with
14 <sup>†</sup>	2010-05-09 09:19 / Treatment B / Subject elected to withdraw due to personal reason	2	No	Not applicable
15	2010-05-04 10:25 / Treatment B / Subject elected to withdraw due to personal reason	1	No	Not applicable
20	2010-05-06 16:48 / Treatment A / Subject elected to withdraw prior the end of confinement of Period 2 due to personal reason	2	No	Not applicable
26	2010-04-21 09:36 / Treatment A / Subject elected to withdraw due to adverse events "abdominal pain" and "diarrhoea"	1	No	Not applicable
33	2010-05-05 20:22 / Treatment A / Subject elected to withdraw (did not show up for confinement of Period 2)	1	No	Not applicable
36	2010-05-05 13:00 / Treatment A / Subject elected to withdraw due to personal reason	1	No	Not applicable
40	201-05-05 23:15 / Treatment A / Subject was withdrawn due to adverse events "oedema peripheral", "joints stiffness", and "arthralgia"	1	No	Not applicable
46 <sup>‡</sup>	2010-05-07 18:06 / Treatment A / Subject elected to withdraw due to personal reason	2	No	Not applicable
49	2010-05-05 23:22 / Treatment A / Subject was withdrawn due to adverse events "joint dislocation", "pain in extremity", and "oedema peripheral"	1	No	Not applicable

Note: A subject was considered as a:

**Drop-out:** when the subject elected to withdraw after receiving at least one dose of the study medication.

**Withdrawal:** when the subject was withdrawn by the Sponsor, Investigator, Medical Sub-Investigator, or a delegate after receiving at least one dose of the study medication.

<sup>†</sup> This subject missed only the last 2 timepoints in Period 2. However, he was included in the PK population.

*Demographics:* Shown in Table 30.

**Table 30: Demographic information for trial ISOPK.09.02**

		Subjects who completed the study and were included in the PK population	
Category		Treatment	
		Test (A)	Reference (B)
Age (years)	Mean ± SD	38 ± 9	38 ± 9
	Range	22 - 52	22 - 52
	Median	40	40
	n	41	41
Age Groups	<18	0	0
	18-40	22 (53.7%)	22 (53.7%)
	41-64	19 (46.3%)	19 (46.3%)
	65-75	0	0
	>75	0	0
Gender	Female	0	0
	Male	41 (100%)	41 (100%)
Race	Asian	4 (9.8%)	4 (9.8%)
	Black	6 (14.6%)	6 (14.6%)
	White	30 (73.2%)	30 (73.2%)
	Other	1 (2.4%)	1 (2.4%)
Ethnicity	Not Hispanic	24 (58.5%)	24 (58.5%)
	Hispanic	17 (41.5%)	17 (41.5%)
Height (cm)	Mean ± SD	174.0 ± 6.8	174.0 ± 6.8
	Range	159.5 - 185.0	159.5 - 185.0
	Median	174.5	174.5
	n	41	41
Weight (kg)	Mean ± SD	78.6 ± 8.3	78.6 ± 8.3
	Range	63.2 - 93.9	63.2 - 93.9
	Median	78.6	78.6
	n	41	41
BMI (kg/m <sup>2</sup> )	Mean ± SD	25.9 ± 2.0	25.9 ± 2.0
	Range	19.6 - 30.1	19.6 - 30.1
	Median	26.0	26.0
	n	41	41

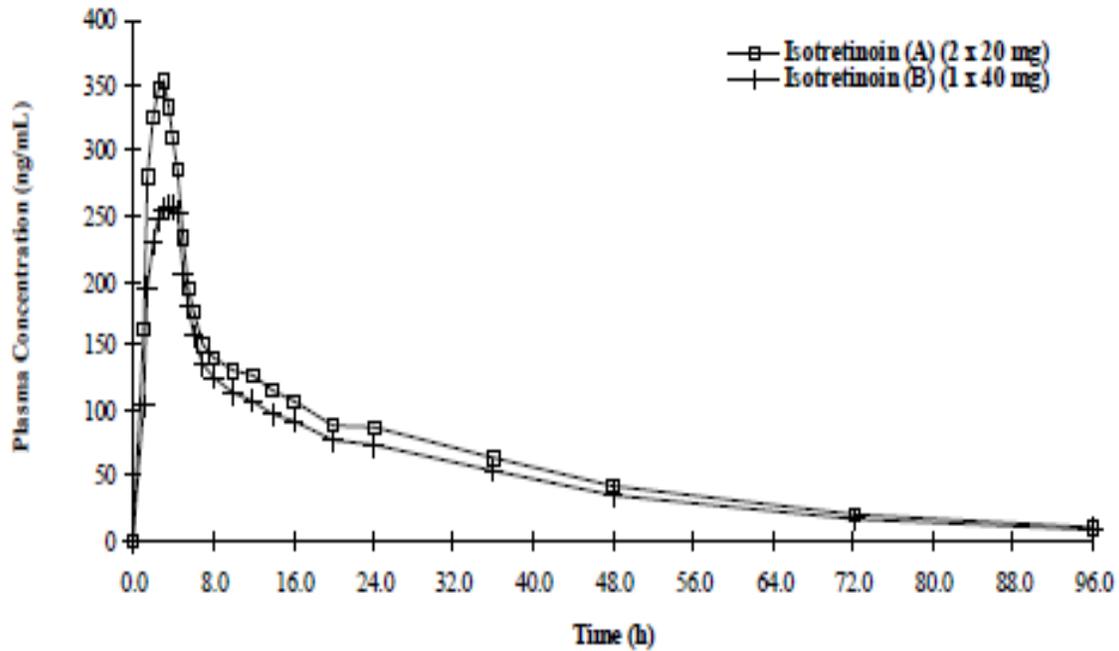
A = CIP-Isotretinoin 2 x 20 mg capsules

B = CIP-Isotretinoin 1 x 40 mg capsule

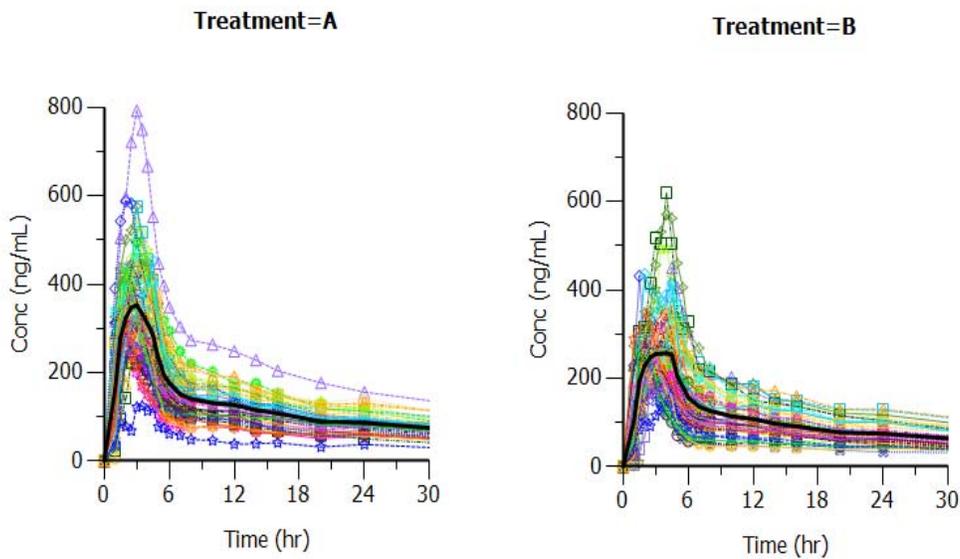
**PK results:**

Baseline corrected data: Mean concentration versus time profile for baseline corrected isotretinoin for each treatment (N = 41) is shown in Figure 11 while summary of PK parameters and relative BA analysis are shown in Table 31 and 32 respectively. Individual subject plots are shown in Figure 12 (mean concentration profile is shown by dark black line).

**Figure 11: Mean baseline corrected concentration versus time profile of isotretinoin following administration of CIP-Isotretinoin as 2 x 20 mg (Treatment A) and 1 x 40 mg (Treatment B) under fasting conditions**



**Figure 12: Mean baseline corrected individual subject concentration versus time (up to 30 h) profile of isotretinoin following administration of CIP-Isotretinoin as 2 x 20 mg (Treatment A) and 1 x 40 mg (Treatment B) under fasting conditions (mean concentration profile is shown by the dark black line)**



**Table 31: Summary of PK parameters for baseline corrected isotretinoin for each treatment (N = 41)**

Parameters	Isotretinoin (A) (2 x 20 mg)			Isotretinoin (B) (1 x 40 mg)		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC <sub>0-t</sub> (ng·h/mL)	6093.02	1891.47	31.04	5111.33	1637.12	32.03
AUC <sub>0-inf</sub> (ng·h/mL)	6443.75	1976.17	30.67	5447.53	1707.72	31.35
AUC <sub>v/inf</sub> (%)	94.54	4.36	4.61	93.63	5.26	5.62
C <sub>max</sub> (ng/mL)	389.49	122.17	31.37	312.63	103.09	32.98
T <sub>max</sub> (h)	2.93	0.88	29.95	3.24	1.07	32.91
T <sub>max</sub> * (h)	3.00	1.00	-	3.50	2.02	-
K <sub>el</sub> (h <sup>-1</sup> )	0.0334	0.0063	18.83	0.0320	0.0075	23.52
T <sub>½ el</sub> (h)	21.46	3.79	17.64	22.78	5.31	23.29

\* Medians and interquartile ranges are presented.

**Table 32: Relative BA analysis and calculation of 90% CI**

	AUC <sub>0-t</sub>	AUC <sub>0-inf</sub>	C <sub>max</sub>
Ratio of geometric mean	0.84	0.85	0.80
90% CI	77.57% – 89.67%	78.50% – 90.88%	73.58% – 86.99%

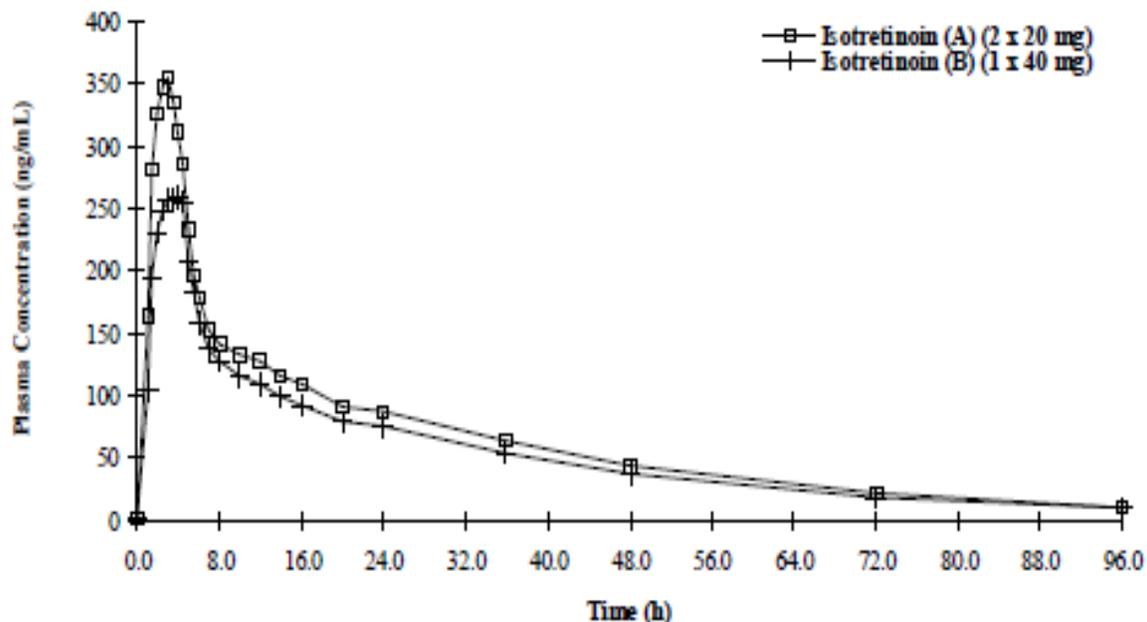
Test: CIP-Isotretinoin 1 x 40 mg strength

Reference: CIP-Isotretinoin 2 x 20 mg strength

The exposure of 1 x 40 mg strength was slightly lower than 2 x 20 mg strength when administered under fasting conditions indicating that the PK of 40 mg strength capsule increased in a less than dose proportional manner under fasting conditions. Specifically the AUC and C<sub>max</sub> with 1 x 40 mg strength were approximately 15% and 20% less respectively, than those following administration of 2 x 20 mg strength. [Dose proportionality between 10 mg and 30 mg strength has been demonstrated previously under fasting (ISOPK.06.01) and fed conditions (ISOPK.06.02) and the results were reviewed by Dr. Dennis Bashaw (Please Note: under fasting conditions, the CI of the ratio of geometric mean of AUC was borderline on the 80% to 125% no effect boundary. Specifically, the PK of 1 x 30 mg strength increased in very slightly less than proportional manner compared to 3 x 10 mg strength. This was considered acceptable by the previous reviewer) (see review in DARRTS dated 04/09/2007 for more information)].

Baseline uncorrected data: The baseline uncorrected data was provided only as supportive and were not used to infer any conclusions. Mean concentration versus time profile for baseline corrected isotretinoin for each treatment (N = 41) is shown in Figure 13 while summary of PK parameters and relative BA analysis are shown in Table 33 and 34 respectively.

**Figure 13: Mean baseline uncorrected concentration versus time profile of isotretinoin following administration of CIP-Isotretinoin as 2 x 20 mg (Treatment A) and 1 x 40 mg (Treatment B) under fasting conditions**



**Table 33: Summary of PK parameters for baseline uncorrected isotretinoin for each treatment (N = 41)**

Parameters	Isotretinoin (A) (2 x 20 mg)			Isotretinoin (B) (1 x 40 mg)		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC <sub>0-t</sub> (ng·h/mL)	6235.39	1899.85	30.47	5261.38	1643.82	31.24
AUC <sub>0-inf</sub> (ng·h/mL)	6658.03	1985.67	29.82	5679.77	1713.87	30.18
AUC <sub>t/inf</sub> (%)	93.53	4.41	4.72	92.34	5.43	5.88
C <sub>max</sub> (ng/mL)	391.02	122.22	31.26	314.24	103.17	32.83
T <sub>max</sub> (h)	2.93	0.88	29.95	3.24	1.07	32.91
T <sub>max</sub> * (h)	3.00	1.00	-	3.50	2.02	-
K <sub>el</sub> (h <sup>-1</sup> )	0.0307	0.0048	15.79	0.0290	0.0058	20.10
T <sub>1/2 el</sub> (h)	23.19	3.76	16.21	24.89	5.29	21.25

\* Medians and interquartile ranges are presented.

**Table 34: Relative BA analysis and calculation of 90% CI (using baseline uncorrected data)**

	AUC <sub>0-t</sub>	AUC <sub>0-inf</sub>	C <sub>max</sub>
Ratio <sup>1</sup>	119.21%	117.33%	124.85%
90 % Geometric C.I. <sup>2</sup>	111.20 % to 127.78 %	109.57 % to 125.64 %	114.88 % to 135.68 %
Intra-Subject CV	18.78 %	18.49 %	22.58 %

<sup>1</sup> Calculated using least-squares means according to the formula:  $e^{(A-B)} \times 100$ .

<sup>2</sup> 90% Geometric Confidence Interval using ln-transformed data.

Reference: CIP-Isotretinoin 1 x 40 mg strength

Test: CIP-Isotretinoin 2 x 20 mg strength

***Reviewer Comments:*** *The relative BA analysis and the calculation of 90% CI using baseline uncorrected should ideally be done using CIP-Isotretinoin 1 x 40 mg strength as Test and CIP-Isotretinoin 2 x 20 mg strength and not the other way around as reported by the Sponsor (shown in Table 47). This analysis was not repeated using the aforementioned conditions because this data is not going to be used to derive any scientific conclusions.*

***Overall conclusions:*** The results of this trial show that the rate and extent of exposure ( $C_{max}$  and AUC) of CIP-Isotretinoin following administration of a 20 mg strength capsules administered as a 40 mg dose was slightly higher compared to the 40 mg strength capsules under fasting conditions.

***Summary of Adverse Events:*** According to the Sponsor, a total of 27 TEAEs were reported by 13 of the 50 subjects who received at least one dose of the study medication (safety population). The breakdown by treatment group is as follows:

- 15 TEAEs reported by 16.3% (n=8) of the 49 subjects who received treatment A
- 11 TEAEs reported by 11.1% (n=5) of the 45 subjects who received treatment B

The most commonly reported TEAEs were abdominal pain, Diarrhea, Oedema peripheral, and Somnolence, each reported by 4.0% (n=2) of subjects who constituted the safety population (n=50). All other TEAEs were only reported by one subject.

No serious AEs were reported during this study. The AEs reported were, tooth infection in Subject No. 23, haemoptysis and cough in Subject No. 27, oedema peripheral, arthralgia and joint stiffness in Subject No. 40, and joint dislocation in Subject No. 49.

***Reviewer Comments:*** *The safety results reported here are those that were reported by the Sponsor and were not reviewed by this reviewer. For additional information, please refer to Clinical review.*

**5. Appendix – Pharmacometrics review**

APPEARS THIS WAY ON ORIGINAL

**OFFICE OF CLINICAL PHARMACOLOGY:  
PHARMACOMETRIC REVIEW**

<b>Application Number</b>	NDA 21951
<b>Compound</b>	CIP-Isotretinoin Capsules 10 mg, 20 mg, 30 mg and 40 mg
<b>Indication</b>	Treatment of severe recalcitrant nodular acne vulgaris in patients 12 years of age and older
<b>Submission Date</b>	11/29/2011
<b>Sponsor</b>	Cipher Pharmaceuticals, INC
<b>PM Reviewer</b>	Dhananjay D. Marathe, PhD
<b>PM Team Leader</b>	Yaning Wang, PhD
<b>Related IND</b>	064927

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## 1 SUMMARY OF FINDINGS

### 1.1 Key Review Questions

The purpose of this review is to address the following key questions:

#### 1.1.1 Is there a difference in steady-state exposure between the cip-isotretinoin formulation and a reference comparator formulation under study usage (where most doses were taken with the food but some taken after fasting)?

The sponsor's population PK model was inadequate in characterizing the PK of isotretinoin (**Figure 1**). Since the model did not capture the observed data reasonably well, average of observed concentrations was used as the metrics for evaluating the difference in exposure between two formulations (reference product and cip-isotretinoin). The exposures are similar for the two formulations at post-titration steady state (**Figure 2**).

#### 1.1.2 Is there a difference in exposures between pediatric (adolescent) and adult patients for the two formulations?

Using the observed concentration data as the metrics, the exposures in pediatric patients (12 to ≤ 17 yrs) were 9.3% and 6.0% lesser than adults for the reference product and cip-isotretinoin respectively. With the combined data across the two formulations, the overall exposures in pediatric patients were less by 7.5% as compared to adults (**Figure 3**). The percentage of patients with 90% reduction in nodule lesion counts (primary efficacy endpoint) was 74.7% in pediatric patients and 77.3% in adult patients in the combined data for two formulations (**Table 3**). Thus the comparable efficacy results between pediatrics and adults are consistent with comparable isotretinoin exposures.

### 1.2 Recommendations

Division of Pharmacometrics has the following recommendations:

- There was no difference in exposures between the two formulations under study usage where most doses were taken with the food but some taken after fasting.
- The efficacies were comparable and consistent with comparable isotretinoin exposures between pediatric and adult patients. Thus, no dose adjustment is recommended for pediatric patients.

## 2 PERTINENT REGULATORY BACKGROUND

Isotretinoin is indicated for the treatment of severe nodular and/or inflammatory acne, acne conglobata, and recalcitrant acne. Oral absorption of marketed isotretinoin formulations is optimal when taken with food or milk. Under fasted conditions, the relative bioavailability of the marketed formulation is ~30% as compared to fed conditions. The current submission is for Cipher Pharmaceuticals's new formulation of isotretinoin (CIP-ISOTRETINOIN), which is bioequivalent to reference marketed product under high-fat conditions, while under fasted

conditions, the relative bioavailability of isotretinoin is ~70% compared to fed conditions (results from Phase 1 study). The phase 3 study was done to address the question of whether there would be differences in cip-isotretinoin exposures (vis-à-vis a currently marketed reference product) due to the differential food effect (as observed in phase 1 single dose study) with real world use and whether it would have any safety issues. The sponsor was strongly encouraged to incorporate into the trial the pharmacokinetic sampling along the lines of either of the following two options:

1. A population pharmacokinetic sampling scheme where a limited number of samples will be collected over the entire study interval in all subjects.
2. A classical geometric pharmacokinetic sampling program in a limited number of individuals in all treatment arms. The sampling profile should include day one, mid-point, and final dose pk profile sampling along with trough samples at selected timepoints during treatment at study visits.

The sponsor implemented the first of the above options in the trial and provided a pharmacometric report which included the population PK model.

### **3 RESULTS OF SPONSOR'S ANALYSIS**

#### **3.1.1 Population Pharmacokinetic Analysis**

The sponsor performed population pharmacokinetic (PPK) analyses in patients to:

1. Describe the disposition of isotretinoin following administration of cip-isotretinoin and reference marketed formulation under real world scenario (no additional special instructions regarding the drug consumption in fed/fasted state)
2. Understand the impact of covariates on the PK and
3. Compare the impact of study administration including possible intake of the drug under fasting conditions on steady-state levels of isotretinoin following the administration of each formulation.

#### **3.1.2 Study Design**

The study was a double-blind, active control, parallel group, multi-center study, consisting of a 20-week treatment phase and a 4-week follow-up phase. The study was designed to compare the efficacy and safety of cip-isotretinoin and a marketed reference comparator formulation of isotretinoin when both were administered twice daily. Eligible patients included healthy males and non-pregnant, nonnursing females with severe recalcitrant nodular acne. The study population included adolescents (12 to 17 years of age) as well as adults.

Study participants received one of two isotretinoin formulations at a dose of approximately 0.5 mg/kg/day for the first 4 weeks and approximately 1 mg/kg/day for Weeks 5 through 20. The total daily dose was to be divided in two and taken with meals, at breakfast and dinner. In addition, patients were instructed to take their last dose prior to Visits 4, 6 and 7 with a meal; however, their last dose prior to Visits 3, 5 and 8 was to be taken under fasting conditions. Blood samples were drawn from selected patients for pharmacokinetic evaluation. Samples were drawn at Screening (Visit 1), Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 8), Visit 6 (Week 12), Visit 7 (Week 16) and Visit 8 (Week 20). In addition, blood samples may also have

been collected at Visit 9 (Week 24). Whenever possible, study visit times were scheduled to provide samples at different post-dose time windows.

### 3.1.3 Methods

All patients with at least 1 detectable post-dose concentration in the phase 3 study were included in the Pop-PK analysis. A total of 3132 concentration observations above the limit of quantitation were available from 522 patients (259 received cip-isotretinoin and 263 received the reference comparator).

Based on the demographics and dosing summary, the two treatment groups were similar to each other in terms of the amount of data available and there did not appear to be any discernable differences in the administered doses which could affect the PK analysis.

### 3.1.4 Results

The final model was a one-compartment model with first-order absorption and first-order elimination. The two formulations were modeled simultaneously. The same population parameters for clearance (CL/F) and volume of distribution (V/F) were used, along with the same inter-subject variability for these parameters. The absorption rate constant (Ka) was assumed to be different between the formulations. A relative bioavailability (Frel) parameter was used to distinguish the expected bioavailability between the two formulations.

The covariates that were tested for inclusion in the model were the concomitant intake of food, weight, age, sex and age group (adolescents versus adults). In order to determine the impact of food on the bioavailability, patients were instructed to take their last dose before specific visits under fed or fasting conditions. All other doses were to be taken with a meal. The condition under which the dose was taken was used as a covariate to determine if there was a significant impact on the bioavailability of the drug and if this change in bioavailability was reflected in the concentrations. The only significant covariates included in the final model were weight and age on CL/F. The residual variability associated with the final model was 40.7%. Food covariate did not significantly improve the fit of the data. Therefore, this covariate was not maintained in the model. There were only approximately 3% of the measured concentrations that were collected after a dose that was reportedly taken under fasting conditions. Thus it is likely that the impact of the last dose at steady-state that was taken under fasting conditions was diluted by the other doses which were taken with food.

A summary of the parameter estimates of the final model is provided in **Table 1**. The goodness of fit (Observed vs individual predicted concentrations) plot is provided in **Figure 1**.

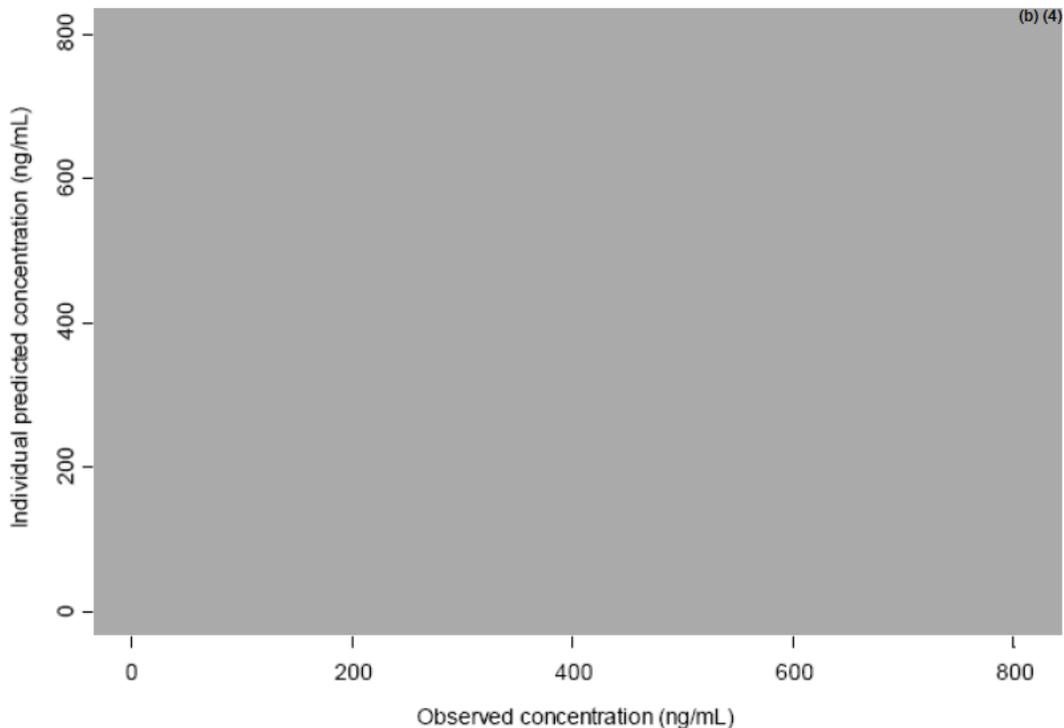
**Table 1: Pharmacokinetic and covariate parameter estimates of the final model**

Population PK Parameter	Typical Value	RSE% <sup>a</sup>
<b>Population Mean</b>		
Ka for CIP-ISOTRETINOIN (1/h)	0.226	25.7
Ka for reference (1/h)	0.171	14.0
CL/F (L/h)	17.6	2.1
V/F (L)	856	20.0
Baseline isotretinoin level (ng/mL)	1.06	1.9
Relative bioavailability for CIP-ISOTRETINOIN	1.0	2.5
Relative bioavailability for doses administered after the titration period	0.698	1.5
<b>Covariate model</b>		
Exponent for weight on CL/F	1.11	4.9
Exponent for age on CL/F	-0.19	20.8
<b>Inter-patient variability (%)</b>		
CL/F (L/h)	0.0378 (19.6%)	11.3
V/F (L)	0.801 (111%)	25.1
Baseline isotretinoin level (ng/mL)	0.0813 (29.1%)	28.2
<b>Error model</b>		
Proportional error (%)	16.6	5.0

<sup>a</sup>RSE% is the relative standard error calculated with respect to the mean parameter value

Source: Sponsor's Pop PK Study Report, Table 6, Page 23

**Figure 1: Goodness of fit (observed vs individual predicted isotretinoin concentrations) plot of the final pharmacokinetic model for phase 3 data** Source: Sponsor's Pop PK Study Report, Figure 7, Page 20



*Reviewer's comments:*

- *Based on the sponsor's goodness of fit plot, it does not appear that the model characterizes the PK of isotretinoin well. The data is widely under-predicted in the observed vs. individual predicted plot for concentrations above 200 and over-predicted for concentrations below 200. Since the model does not capture the observed data reasonably well, any conclusion from the sponsor's population PK analysis needs to be interpreted cautiously including any conclusions about the covariate effects. For a drug with accumulation ratios considerably larger than one, the change in steady state exposures and average concentrations due to food effect would be marginal at best when only one dose in the dosing regimen is taken in fasted state. Thus, the current phase 3 study was not well-suited/designed to glean out the food effect, even though food effect was dominantly seen in the dedicated phase 1 single dose study.*

## **4 RESULTS OF REVIEWER'S ANALYSIS**

### **4.1 Objectives**

Analysis objectives are to:

1. Evaluate whether there is difference in steady-state exposure between the cip-isotretinoin formulation and a reference comparator formulation under study usage
2. Evaluate whether there is a difference in exposures between pediatric (adolescent) and adult patients for the two formulations

### **4.2 Methods**

#### **4.2.1 Data Sets**

Datasets used for the analysis and the link to EDR is provided in Table 2 below.

**Table 2: Analysis Data Sets.**

<b>Study Number</b>	<b>Name</b>	<b>Link to EDR</b>
ISOCT.08.01	c10-2306-pk-data-export.xpt adeff1.xpt	<a href="\\cdsesub1\EVSPROD\NDA021951\0000\m5\datasets\isocf0801-popn-pk\listings\c10-2306-pk-data-export.xpt">\\cdsesub1\EVSPROD\NDA021951\0000\m5\datasets\isocf0801-popn-pk\listings\c10-2306-pk-data-export.xpt</a> <a href="\\cdsesub1\EVSPROD\NDA021951\0000\m5\datasets\isocf0801\analysis\adeff1.xpt">\\cdsesub1\EVSPROD\NDA021951\0000\m5\datasets\isocf0801\analysis\adeff1.xpt</a>

#### **4.2.2 Software**

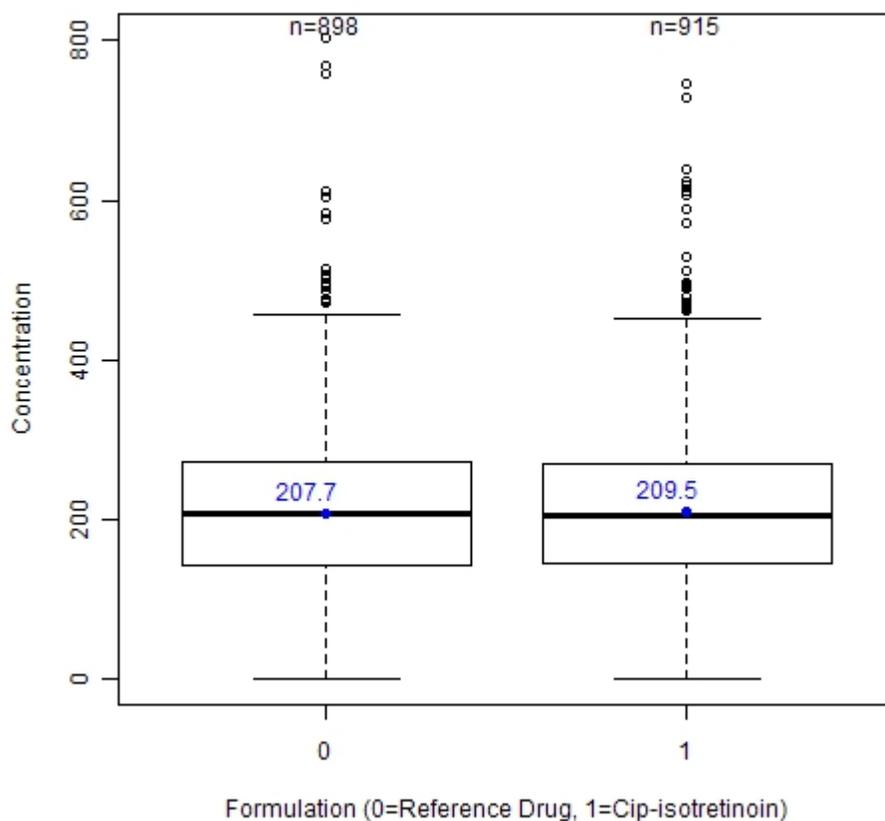
The R software was used for data manipulation along with the Means, Anova and Freq procedures in SAS software.

### 4.3 Results

#### 4.3.1 Differences in exposures between the two formulations (cip-isotretinoin and reference comparator product)

Since the sponsor's population PK model was inadequate in describing the observed concentrations data reasonably well, average of observed concentrations was used as the metrics for evaluating the difference in exposure between two formulations (reference product and cip-isotretinoin). The exposures are similar for the two formulations at post-titration steady state (**Figure 2**).

**Figure 2: Boxplot summary of observed isotretinoin concentrations for different formulations (0= Reference comparator product, 1= Cip-isotretinoin)**



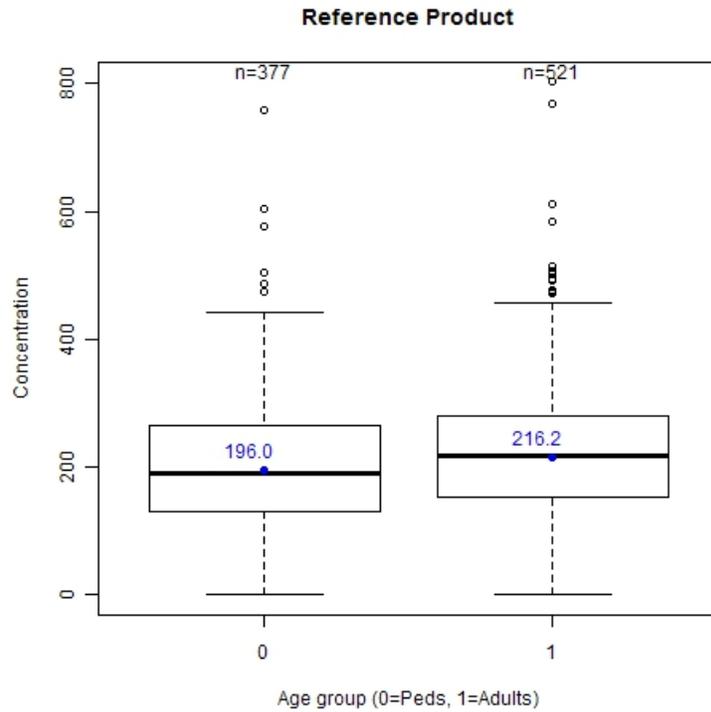
#### 4.3.2 Difference in exposures between pediatric (adolescent) and adult patients

Using the observed concentration data as the metrics, the exposures in pediatric patients (12 to  $\leq 17$  yrs) were 9.3% and 6.0% lesser than adults for the reference product and cip-isotretinoin respectively. With the combined data across the two formulations, the overall exposures in pediatric patients were less by 7.5% as compared to adults (**Figure 3**). The percentage of patients with 90% reduction in nodule lesion counts (primary efficacy endpoint) was 74.7% in pediatric patients and 77.3% in adult patients in the combined data for two formulations (

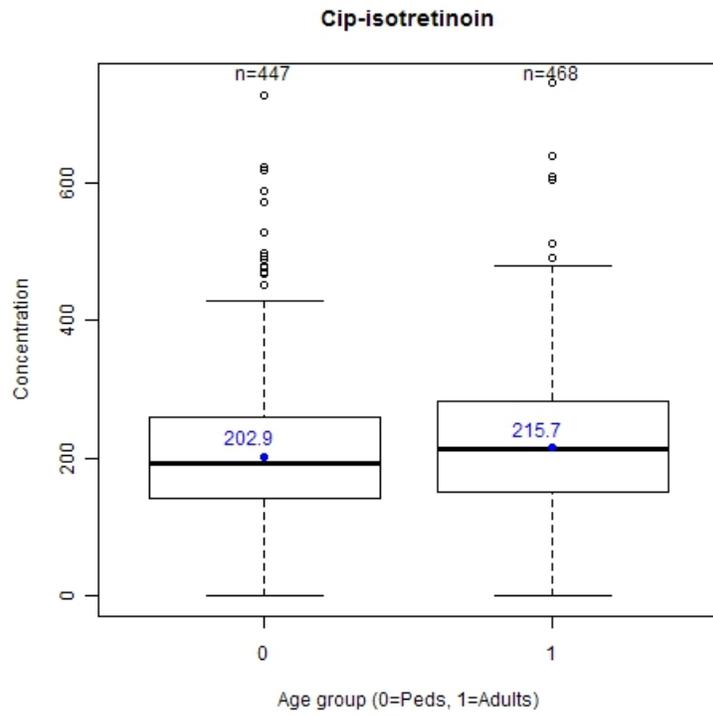
**Table 3).** Thus the comparable efficacy results between pediatrics and adults are consistent with comparable isotretinoin exposures.

**Figure 3: Boxplot summary of observed isotretinoin concentrations (DV) in different age groups (0= Pediatric (12 to ≤17 yrs), 1= Adult patients) for A) Reference product alone, B) Cip-isotretinoin alone, and C) Both products pooled together.**

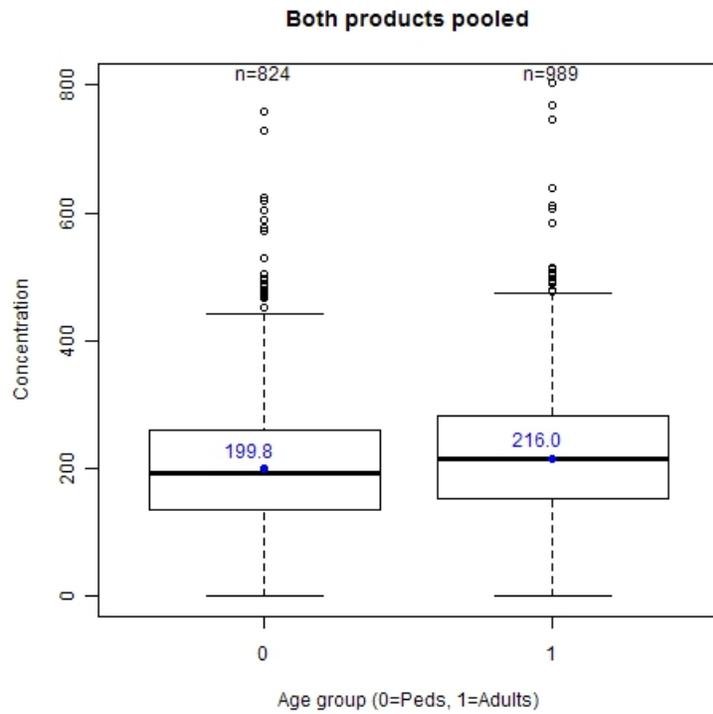
**A.**



**B.**



**C.**



**Table 3: Percentage of patients with 90% reduction in nodule lesion counts (primary efficacy endpoint) in different age groups**

	<b>Pediatrics (12 to ≤17 yrs)</b>	<b>Adults</b>
<b>Reference product alone</b>	76.5 %	79.9 %
<b>Cip-isotretinoin alone</b>	73.1 %	74.4 %
<b>Combined data for both products pooled together</b>	74.7 %	77.3 %

## 5 LISTING OF ANALYSES CODES AND OUTPUT FILES

<b>File Name</b>	<b>Description</b>	<b>Location in \\cdsnas\pharmacometrics\</b>
isotretinoin_analysis_form_age_r	R code to perform data manipulation and box-plotting observed concentration data	<a href="#">\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\CIP-Isotretinoin_NDA21951_DDM\PPK Analyses\codes\isotretinoin_analysis_form_age_r</a>
pk2.txt pk2ref.txt pk2trt.txt demo.txt	Intermediate R code output files to be used as input for sas code below	<a href="#">\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\CIP-Isotretinoin_NDA21951_DDM\PPK Analyses\codes\intermed_files</a>
anova_isotretinoin.sas	Freq, Anova and Means procedures to summarize the observed concentrations across formulations and age groups	<a href="#">\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\CIP-Isotretinoin_NDA21951_DDM\PPK Analyses\codes\anova_isotretinoin.sas</a>

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/s/  
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CHINMAY SHUKLA  
04/12/2012

DHANANJAY D MARATHE  
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YANING WANG  
04/12/2012

DOANH C TRAN  
04/12/2012

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

**NDA:** 21-951

**GENERIC NAME:** Isotretinoin

**TRADE NAME:** UNKNOWN (currently  
CIP-ISOTRETINOIN)

**FORMULATIONS:** 10, 20, 30mg capsules

**APPLICANT:** Cipher Laboratories

**SUBMISSION DATES:** Oct. 26<sup>th</sup>, 2006/ Mar. 9<sup>th</sup> and 15<sup>th</sup>, 2007

**DRAFT REVIEW:** Feb. 23<sup>rd</sup>, 2007

**REVISED REVIEW:** April 6, 2007

**REVIEWER:** E. Dennis Bashaw, Pharm.D.

**OCPB DIVISION:** DCP-3

**CLINICAL DIVISION:** Division of  
Dermatologic and Dental Drug Products

## Review of an NDA Re-Submission

### 1 Executive Summary

Cipher Pharmaceuticals received an “Approvable Letter” on May 1<sup>st</sup>, 2006 for their 505(b)(2) application for isotretinoin. In the letter a number of elements were noted as being inadequate including a safety determination, demonstration of dose proportionality, chemistry release specifications, and an appropriate risk management program (see Appendix, section-1 for a copy of the approvable letter).

In the Oct. 2006 resubmission the sponsor has addressed the issue of dose proportionality across the individual dosage strengths of their own product through two head to head studies (1 fasted and 1 fed) and two biopharmaceutic expert reports written (b) (4). This information, in conjunction with the other dosing information present in the original NDA submission adequately addresses item 3 of the May 1<sup>st</sup> “approvable” letter. The March 2007 amendments address specific data requests made during the review of the resubmission dealing with individual case report forms (March 9<sup>th</sup>) and fractional absorption (March 15<sup>th</sup>)

As to the primary issue, the need to conduct either a clinical study with safety endpoints or to conduct a population pk study (item 1 of the letter), the sponsor has not conducted either study and is instead relying on the fact that their product falls between the extremes of Accutane’s bioavailability under fed and fasted conditions as being sufficient for approval, a position that was rejected by the Agency following the original application submission.

### 1.1 Recommendation

From a pharmacokinetic standpoint, the sponsor has adequately addressed the issue of dose proportionality outlined in item 3 of the May 1<sup>st</sup>, 2006 “approvable” letter. The sponsor has not conducted either the requested clinical study with safety endpoints nor the alternative population pk study. To accept the conclusion reached by the sponsor that fed bioequivalence coupled with levels above those of Accutane under fasted conditions as being sufficient for establishing a link to the Accutane safety and efficacy database would establish a precedent for a very low approval standard for 505(b)(2) applications.

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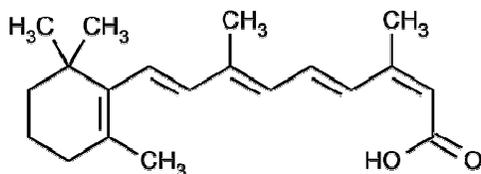
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### 2.1 General Attributes of the Drug

#### 2.1.1 What are the highlights of the chemistry and physico-chemical properties of isotretinoin drug substance and the Cipher Isotretinoin (CIP-ISOTRETINOIN) drug products?

Chemically, isotretinoin or 13-*cis*-retinoic acid, is 13-*cis*-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-*cis*-4-*trans*-6-*trans*-8-*trans*-nonatetraenoic acid.



It is a yellow to reddish-orange crystalline powder and has a molecular weight of 300.44. It is very poorly soluble in aqueous media with a partition coefficient (log P) of 6.6 indicating that it is highly lipophilic. The melting point is 174-175°C, and the maximum UV absorbance is at about 355 nm.

As noted in the previous review the Cipher product is formulated as hard gelatin capsules containing isotretinoin in solution/dispersion, in a semi solid blend (paste). The

present formulation consists of a solution/suspension of isotretinoin in a mixture of oils, fatty acid derivatives and non-ionic surfactant excipients with an antioxidant. Based on analysis of six batches, approximately (b) (4) of the isotretinoin dose is dissolved in the capsule.

**To Be Marketed Formulation**

Ingredient and Test Standard	Amount per Batch of (b) (4)	Amount per Batch of (b) (4)	Amount per Batch of (b) (4)
	Strength: 10 mg	Strength: 20 mg	Strength: 30 mg (b) (4)
Isotretinoin USP	(b) (4)		
Stearoyl Macroglycerides (b) (4)			
Soybean Oil, USP			
Sorbitan Monooleate, NF (SPAN 80)			
Propyl Gallate, NF			

\*\*\*Note in this table the 30mg capsule data is for (b) (4) capsules, thus the amounts are (b) (4) of what would be present in an individual unit.

**2.1.2 What is the proposed mechanism of action of isotretinoin**

Isotretinoin is a synthetic vitamin A analog marketed by Roche Pharmaceuticals under the brand name Accutane™. As such it shares with vitamin A much of the latter's activity regarding cellular regulation and secretory regulation. In vivo, isotretinoin has been shown to decrease the production of sebum via a reduction in sebaceous gland size and cellular differentiation. Although the drug substance is synthetic, isotretinoin itself is present in humans at low levels as a metabolite of tretinoin.

Therapeutically, isotretinoin is highly effective in the treatment of nodular cystic acne, a severe disfiguring form of the common acne vulgaris. Experience with the current marketed forms of isotretinoin (Accutane™ and generics) has demonstrated that only one or two courses of therapy of up to 1mg/kg per day for 20 weeks can result in lasting clearing of the skin. As a vitamin A analog Accutane™ is also a very potent teratogen

and carries a black box warning requiring patient counseling, dual contraceptive methods, and monitoring of pregnancy status prior to and during drug use. Because of its known teratogenic effects isotretinoin is required to have a pregnancy prevention program in place. The current program, re-designed as of 3/1/06, is entitled iPLEDGE (<http://www.ipledgeprogram.com>).

### 3 Approvable Letter Issues

#### 3.1 Dose Proportionality (letter issue #3)

*The NDA does not have an adequate demonstration of proportionality across the proposed dosage strengths. As isotretinoin is dosed on a mg/kg basis and as it is expected that multiple dosage units will be used to obtain doses in the 0.5-1mg/kg range, then the relationship between the different strength capsules will need to be determined for CIP-Isotretinoin*

As noted in the comment provided in the original review the original NDA submission lacked a head-to-head comparison of different strength products to establish dose proportionality. [Instead the NDA consisted of studies of Ciphers product vs. Accutane accompanied by a cross-study comparison of the different strengths of their proposed product as an assessment of proportionality-an approach even their own consultant considered “unusual”.] This issue was felt to be critical for isotretinoin as it is dosed on a mg/kg basis and multiple strengths would be expected to be needed make a dose for a patient. In this NDA the sponsor has submitted the results to two in vivo biopharmaceutic trials:

Study ISOPK.06.01 (2006-1232)- A single dose, comparative bioavailability study of two strengths of Cipher Isotretinoin Capsules under fasting Conditions [3x10mg capsule vs. 1x30mg capsule]

Study ISO PK.06.02 (2006-1233)- A single dose, comparative bioavailability study of two strengths of Cipher Isotretinoin Capsules under fed Conditions [3x10mg capsule vs. 1x30mg capsule]

These studies are noteworthy for two elements, 1.) unlike the previous NDA studies the sponsor did not include an Accutane comparator arm and 2.) the conduct of separate fed/fasted evaluations using their own “peculiar” diet rather than the FDA recommended high fat diet.

As these trials are basically the same trial design (save for the use of a high fat diet) a short overview of any unique elements will be presented followed by a summary of the results from both trials presented together. In order to put this information in the context of the work from the original submission, section 2 of the Appendix has in it that portion of the original Clinical Pharmacology review that provided an overview of the dose proportionality data. The supporting data summaries from the trials in this submission are attached as section 3 (PK.06.01) and section 4 (PK.06.02) in the Appendix.

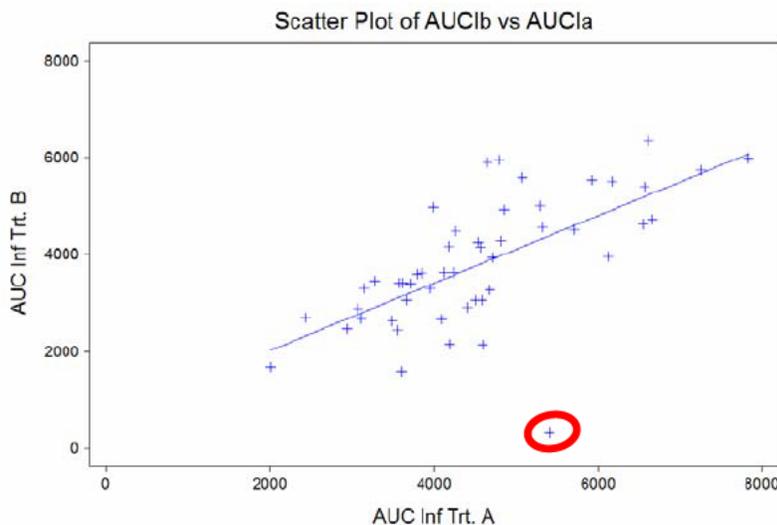
### 3.1.1 Study ISO PK.06.01-1232

This study was a single dose pk study comparing 3x10mg CIPHER isotretinoin capsules to 1x30mg CIPHER isotretinoin capsule in the fasted state. As noted above a summary of the study with supporting tables can be found in section 3 of the Appendix. In general this was a standard pk study in 50 subjects (54 enrolled). Dropouts in the study were for the following reasons: (2) personal reasons, (1) abdominal pain, (1) dismissed for a positive cotinine level in the urine. The trial was a randomized single dose trial with a three week washout period between the treatment legs.

Initial analysis of the data suggests that the two treatments are not equivalent, however, upon examination of the individual data the sponsor came to the conclusion that one subject was driving this finding. Subject 17 had a very different pharmacokinetic profile during treatment B (1x30mg capsule) compared to the rest of the subjects in the trial as summarized in the table below:

	AUC <sub>t</sub> (ng*hr/ml)	AUC <sub>inf</sub> (ng*hr/ml)	C <sub>max</sub> (ng/ml)
TRT B sub. 17	286.39	303.61	29.61
TRT B Study Mean (%CV)	3368 (34%)	3812 (34%)	215 (34%)

A graphical representation of the AUC<sub>inf</sub> data for both treatments shows, as one would expect a general correlation between the two treatment legs. The one outlier pairing, indicated by the circle below is from subject 17.



It is unclear as to what this subject represents, as if there was confusion in the study packaging such that they subject got a single 10mg capsule instead of the 30mg capsule, then the levels would have been approximately 1/3rd of the treatment A values. Instead of being 1/12<sup>th</sup> of the value for AUC. Based on our examination of this subjects individual data, the exclusion of this subject from the dataset is justified and the dataset with this subjects data removed will be the analysis that this study relies upon. Both statistical reports and a plot of the individual subject 17 data is attached in the Appendix in section 3.

### 3.1.2 Study ISO PK.06.02-1233

This study was a single dose pk study comparing 3x10mg Cipher isotretinoin capsules to 1x30mg Cipher isotretinoin capsule in the fed state. Except for this fact it was identical in design as PK.06.01. As noted above a summary of the study with supporting tables can be found in section 4 of the Appendix. In general this was a standard pk study in 52 subjects (54 enrolled). Dropouts in the study were for the following reasons: (1) non-compliance in returning for blood draw, (1) personal reasons. The trial was a randomized single dose trial with a three week washout period between the treatment legs. Examination of the individual study data did not reveal any subjects that could be considered outliers and the primary analysis conducted by the sponsor was found to be acceptable.

### 3.1.3 Dose Proportionality Discussion

Summarized below are the excerpted data tables from studies PK.06.01 and 02. In them it is clear that the sponsor has demonstrated acceptable dose proportionality both between the two treatments (A-3x10mg, B-1x30mg) and between both fed and fasted conditions. While the 90% confidence intervals do not pass for AUC in study PK.06.01, they are just outside of the acceptance interval and for dose-proportionality; the need for strict bioequivalence has never been a requirement.

Summary of Results for Plasma Isotretinoin  
(N = 49, Subject 17, Excluded)

Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra- Subject (CV%)
	Treatment A	Treatment B			
AUCt (ng*h/mL)	3886.15 4026.17 (27)	3270.05 3431.71 (31)	118.84	112.62 - 125.41	16
AUCinf (ng*h/mL)	4385.28 4547.86 (28)	3698.63 3883.99 (31)	118.57	112.35 - 125.13	16
Cmax (ng/mL)	245.03 254.65 (28)	210.10 219.40 (31)	116.63	109.01 - 124.77	20

While the 90% confidence intervals do not pass for AUC in study PK.06.01, they are just outside of the acceptance interval and for dose-proportionality; the need for strict bioequivalence has never been a requirement.

As for trial PK.06.02, all of the 90% confidence intervals do pass for AUC (tau and inf) and Cmax. As one would expect in the presence of food, even though Cipher

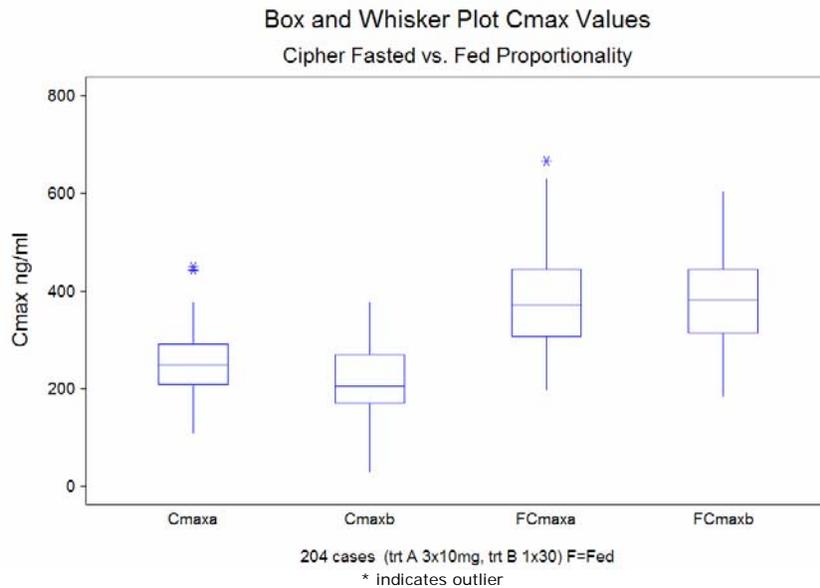
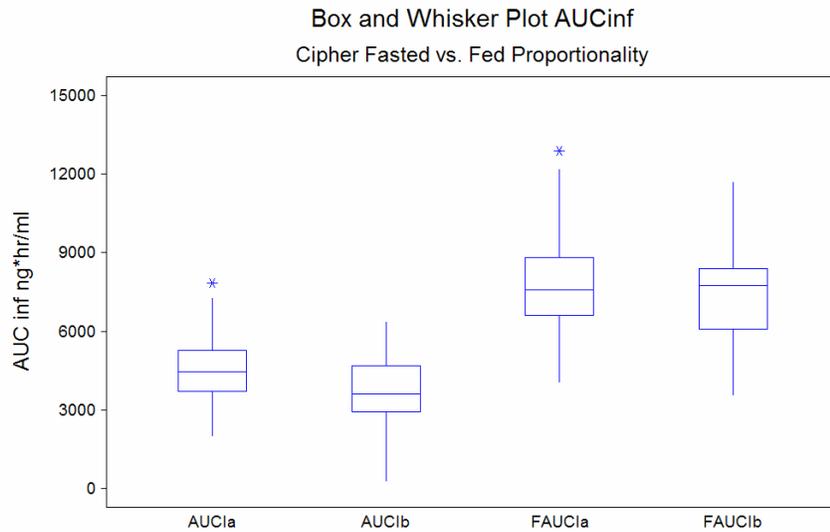
Summary of Results for Plasma Isotretinoin  
(N = 52)

Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra- Subject (CV%)
	Treatment A	Treatment B			
AUCt (ng*h/mL)	6842.88 7008.88 (22)	6641.02 6796.77 (21)	103.04	99.69 - 106.51	10
AUCinf (ng*h/mL)	7580.91 7791.98 (23)	7314.19 7519.89 (23)	103.65	100.22 - 107.19	10
Cmax (ng/mL)	365.76 382.60 (30)	367.99 383.01 (28)	99.39	93.91 - 105.19	17

claims a reduced food effect for their product, it is clear from across the two studies that there is a significant food effect with AUCinf increased by roughly 1.7x and Cmax by 1.5x.

This is more clearly seen in the following set of box-whisker plots which demonstrate the cross study variability in AUCinf, and Cmax from these two studies. The data for AUCtau and Tmax are attached in section 4 of the Appendix. Given that this dataset comprises 204 observations (50 and 52 subjects in two two-way crossover trials) we can have a high degree of confidence in these estimates.

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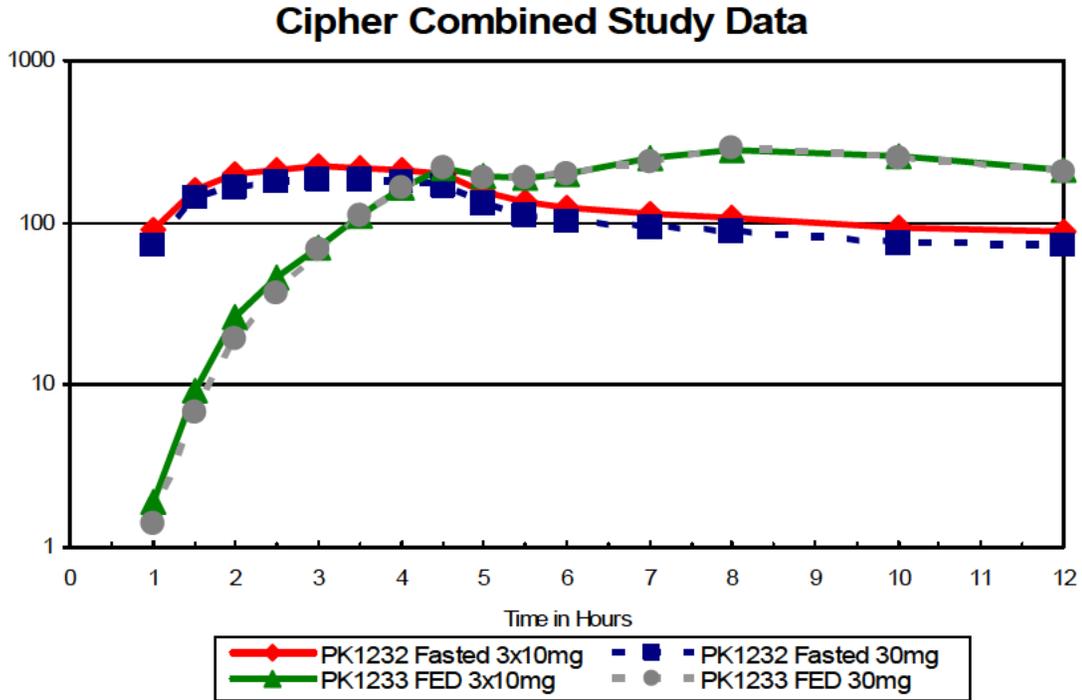


In response to a question from the reviewing chemist regarding the time for absorption to be completed (for the purposes of setting dissolution specifications), a similar analysis was performed on the mean residence time (MRT<sub>po</sub>) for this formulation. The results of this analysis confirm that isotretinoin in this formulation is very poorly soluble with a MRT approximating 30hrs for all treatments

	PK.06.01 (Fasted)		PK.06.02 (Fed)	
Treatments	3x10mg	1x30mg	3x10mg	1x30mg
Mean MRT(%CV)	31.6(27.5%)	31.9(22.7%)	31.8(22%)	31(22%)

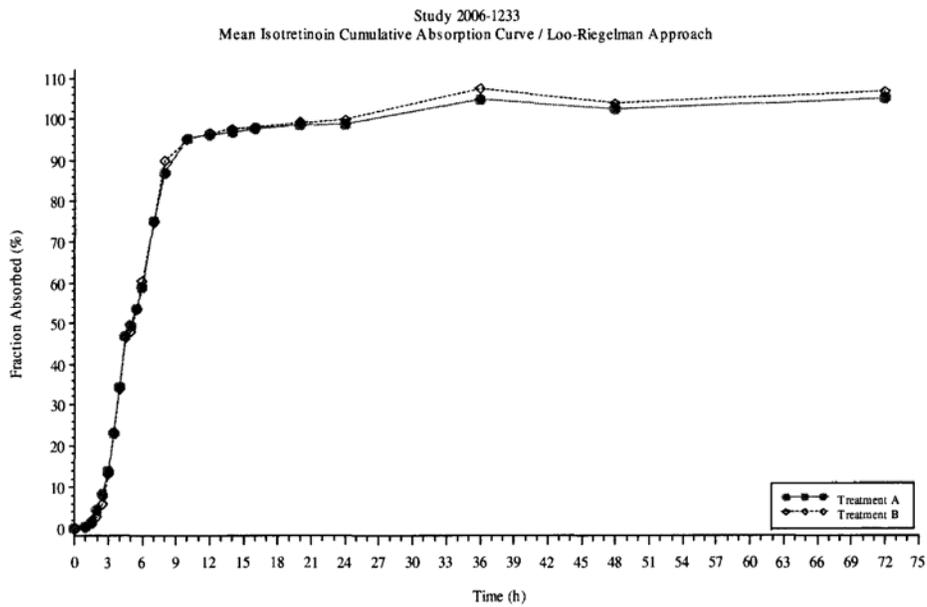
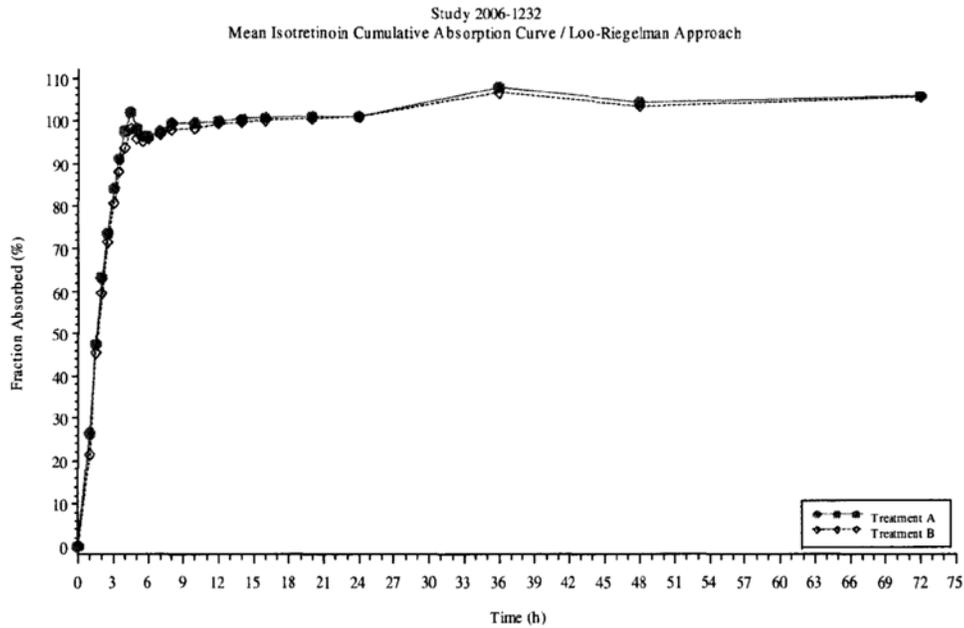
It also demonstrates that the food effect is a rather peculiar one. While the mean data tables above demonstrate an increase in the overall absorption, it does so in such a

manner to suggest that it does not result in a rapid increase in concentration. Reproduced below are the mean plots for the two studies where Treatment A represents 3x10mg caps and Treatment B represents 1x30mg cap.



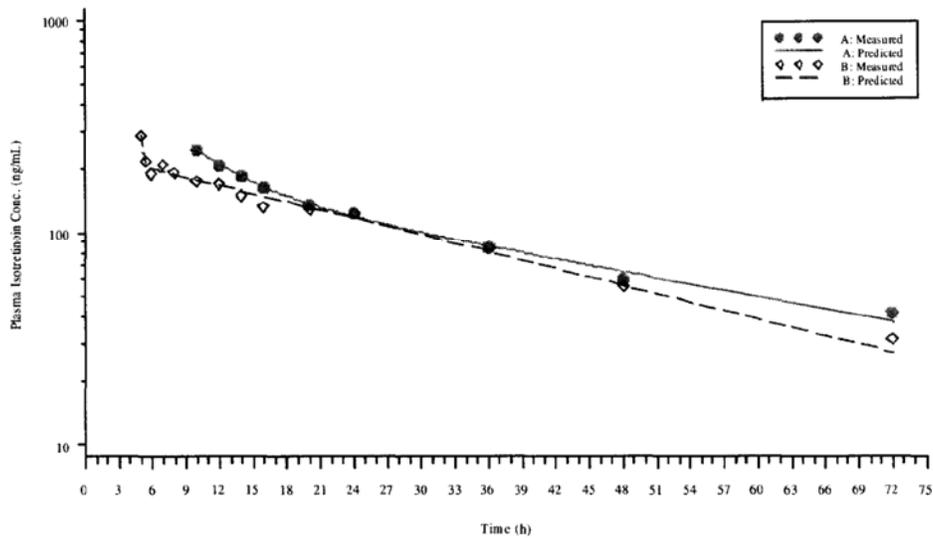
The fact that the MRT(po) is in the range of 30hrs. indicates that the absorption of isotretinoin is prolonged and that absorption must occur throughout the entire GI tract. In this case it would appear that a profile, rather than a single point specification would be more useful, but in any event, dissolution is probably not the rate limiting step vis a vis absorption.

At the request of this reviewer the sponsor undertook an analysis of the fractional absorption of isotretinoin from the data in both of these studies to better determine the effect of food on the overall extent of absorption. Using a modified deconvolution technique that is described in section 5 of the appendix. Reproduced below are the mean plots for the two studies where Treatment A represents 3x10mg caps and Treatment B represents 1x30mg cap. In addition to the mean profiles below, a summary of the individual study analysis along with a single summary plot of the individual subject data is also attached in section 5 of the Appendix.



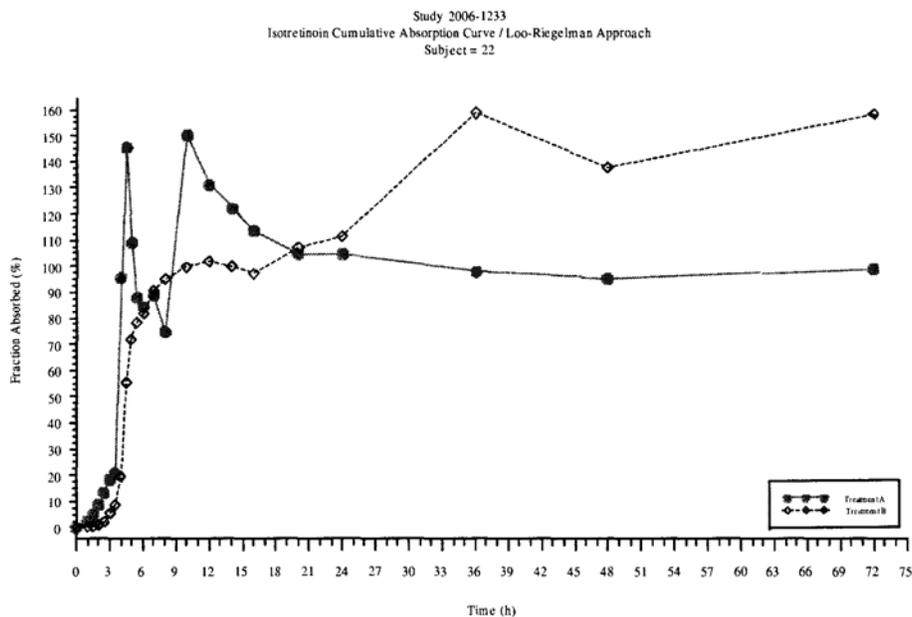
One of the limitations imposed on this analysis is the lack of relevant IV data to allow for a proper deconvolution of the absorption process. The sponsor used the approximation of using the concentration-time values post  $T_{max}$  as a pseudo-IV bolus to allow for estimation of the distribution function. While a generally acceptable approach for most products, this approach is not ideal in this situation as isotretinoin has a prolonged absorption profile (as evidenced by the sponsors analysis) with absorption continuing out for, in most cases, out beyond  $T_{max}$ . For a true IV bolus the contamination of estimation of the disposition function due to continued absorption is minimal, unlike this situation as shown in the data from subject 22 from study 1233.

Study 2006-1233  
 Nonlinear Fitting of the post-absorption phase / 2-Compartment Model / iv-bolus  
 Subject = 22



For this subject the sponsor used the data for the 10mg capsule starting at hr. 9 while for the 30mg capsule post-absorption data at 4.5hrs post dose. In addition to the difference in sampling times used, the two profiles show very different patterns of compartmentalization.

The net result of this is that the overall estimation of fractional absorption for these subjects was poor:



The results of this analysis show that, in general, the fractional absorption of isotretinoin is essentially the same from either 1x30mg or 3x10mg caps. Cross study it is apparent that the absorption of isotretinoin is delayed by food with 90% absorption not occurring until approximately 9hrs post dosing vs. approximately 4hrs in the fasted state.

One should keep in mind though that this is not a finding of equivalency it is fractional absorption, thus these data are not measures of bioavailability per se as it is a measure of the rate of the fractional absorption. That is while study 1232 reaches 100% (and actually exceeds 100% [an artifact of the data analysis employed]) this represents not 100% bioavailability but the time for 100% of what was absorbed to be absorbed for that dosing condition.

### 3.1.3.2 Expert Reports

As part of their response to the dose proportionality issue Cipher retained the services of two experts in the field of biopharmaceutics to review their data and to comment on its appropriateness. These experts are:



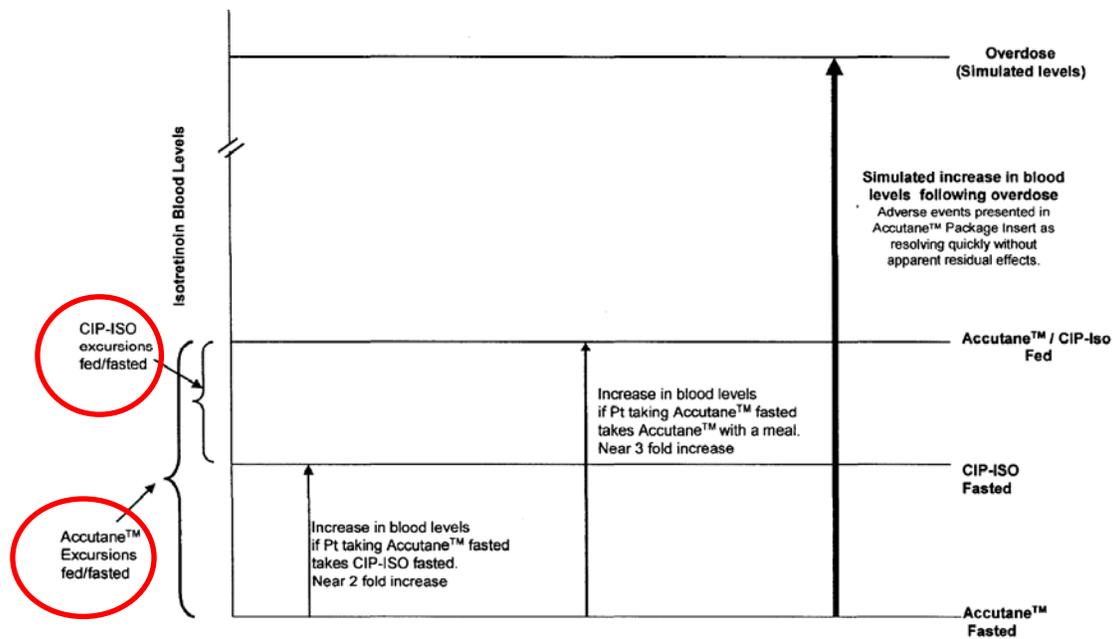
The main thesis of both reports is that Cipher demonstrates adequate dose proportionality through a combination of both the current two studies (PK.06.01 and 02) and the work in the previous NDA submission. What the sponsor and their consultants did not appreciate was that the primary problem with their original data was that their studies were designed not to demonstrate dose proportionality across their strengths but to provide primary comparisons to Accutane. To quote the sponsor in this package:

*“The rationale for this approach was that in the context of a 505(b)(2), it was likely more important to demonstrate that CIPISOTRETINOIN behaved similarly to the RLD across the dosage strengths in order to be able to rely on findings of safety and effectiveness for the RLD.”*

What is disturbing about this approach is that this sponsor was told multiple times during the development cycle that they would need to provide dose proportionality data. Thus, instead of focusing on demonstrating the performance of their product vis a vis the different dosing strengths they focused on trying to make a bio-bridge to Accutane for safety and efficacy purposes. It is this lack of focus on dose proportionality across their own products that resulted in the inconsistent results noted in the previous review (see Section 2 of the Appendix).

In a sense the reports (b) (4) are in fact rendered moot by the conduct of the two biostudies in this supplement. These two studies have demonstrated that, at least for the 10 and 30mg dosage forms that there is dose proportionality. As for linking the product to Accutane via “parallelism” in regards to declining bioavailability with increasing dose, as this is not a “generic” (in the 505 (j) sense) and will not receive an “AB” rating, thus the implied issue of substitution is not relevant.

Before leaving these reports one must comment on the repeated statements in both these reports and the body of the re-submitted April 18<sup>th</sup>, 2006 submission<sup>1</sup> that the Cipher product should be approved as it is bioequivalent to Accutane. This conclusion is based upon the fed treatment arms from the original NDA submission. At that time the Agency concluded that the products under fed conditions were generally equivalent. Under fasted conditions they are not equivalent. The sponsor and their consultants are taking the position that as Accutane was approved with both fed and fasted data, that then so long as they fall within these broad limits, then their product should be allowed to use the finding of safety and efficacy for their 505(b)(2) approval. The sponsor's arguments are summed up in the following figure that accompanies this submission:



While conceding that this product does fall within these very wide parameters, what is lost in this argument is the recognition that in vivo food studies are done to stress the dosage for to assess dose-dumping, not to assess improvements in bioavailability nor to mimic the day-to-day effect of meals on the dosage form. At the present time there are 3 approved AB rated generic products: Claravis-Barr, Amnesteem-Genpharm, and Sotret-Ranbaxy. All of which have been able to demonstrate equivalence at both the fasted and fed levels.

While conceding that this is not a generic drug, the sponsor does have an obligation under a 505(b)(2) approach to provide the information necessary to allow for the FDA to make a determination of safety and efficacy. This information can be either an appropriately designed bio-bridge or through clinical studies. One of the problems with the sponsors conclusion is that it ignores the fact that Accutane was approved in 1982, and the FDA high fat diet did not come into general use until the late 80s, a time

<sup>1</sup> This submission was not reviewed as part of the original NDA review as it was submitted at the very end of the review cycle and in fact contained no new data, beyond a re-statement by the sponsor as to the bioequivalent nature of this product. The material is included in its entirety as part of this re-submission by the sponsor.

long after the Accutane studies were done. If it was to come in today, de novo, it is unclear if the same package of clinical studies would be acceptable without additional delineation of the food effect in the target population.

It should also be pointed out that the overall safety of Accutane itself is subject to strong debate, especially with recent (last 5yrs) recognition of the psychiatric effects of isotretinoin. It is unknown if a product that resided in the higher portion of the overall Accutane levels in the figure above would or would not present a different safety profile with regards to these admittedly rare but severe events.

Finally, Roche, the Accutane NDA holder themselves tried to develop a formulation like Cipher's in NDA 21-177. This application was discussed at a open public advisory committee meeting, whose transcripts are posted on the FDA website (<http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3639b1.htm>). Many of these same issues were discussed at this meeting and the approach of falling between the extreme ranges consistent with Accutane was not considered a valid approach to determining the safety of a more consistently available form of isotretinoin under a 505(b)(2) metric.

## **APPENDIX**

<b>1.) Approvable Letter Dated 5/1/06</b>	<b>pg 15</b>
<b>2.) Dose Proportionality Section of original Review of NDA 21-951</b>	<b>pg 19</b>
<b>3.) Study ISO PK.06.01 (2006-1232)</b>	<b>pg 21</b>
<b>4.) Study ISO PK.06.02 (2006-1233)</b>	<b>pg 30</b>
<b>5.) Fractional Absorption of Isotretinoin over Time</b>	<b>pg 39</b>

## 1-Approvable Letter Dated 5/1/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-951

Galephar P.R., Inc. for Cipher Pharmaceuticals, Ltd.  
Attention: Arthur Deboeck, Vice President and General Manager  
Road 198 km 14.7 #100  
Juncos Industrial Park  
Juncos 00777-3873, Puerto Rico

Dear Mr. Deboeck:

Please refer to your new drug application (NDA) dated June 27, 2005, received July 1, 2005, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for CIP-Isotretinoin Capsules 10, 20, and 30 mg.

We acknowledge receipt of your submissions dated November 2, 3, and 17, and December 23, 2005 (2), and February 1 and 9, 2006. We also acknowledge receipt of your submission dated April 18, 2006. This submission was not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

This new drug application proposes the use of CIP-Isotretinoin 10, 20, and 30 mg Capsules for the treatment of severe recalcitrant nodular acne.

We have completed our review of this application, as amended, and it is approvable once the deficiencies outlined below are resolved.

### Clinical

1. The application did not establish, by way of bioavailability data comparing CIP-Isotretinoin to Accutane®, an adequate basis for the Agency to rely on the previous finding of safety and effectiveness for the referenced listed drug, Accutane, to approve CIP-Isotretinoin. In addition, you have not demonstrated that the difference in the pharmacokinetic profile of CIP-Isotretinoin as compared to Accutane is not clinically meaningful with regard to the safety profile and efficacy of CIP-Isotretinoin. Your claim of no difference in terms of safety and effectiveness between CIP-Isotretinoin and the listed drug cannot be supported without clinical trial data.

To address this deficiency, we recommend that you conduct a clinical safety and efficacy trial in patients with severe, recalcitrant nodular acne in which CIP-Isotretinoin is compared to Accutane at a dose of 1.0 mg/kg/day. This trial should have a sufficient number of patients to

detect adverse events which occur at an incidence of 1% of the population for safety. The following additional items are important for adequate labeling and should be addressed in the same study:

- Prospective assessment for psychiatric and CNS events by specialists and appropriate instruments, with attention to risk factors and response to intervention
- Adequate monitoring for bone mineral density changes and premature closure of the epiphyses
- Adequate testing for hearing and vision impairment with sufficient follow-up to inform labeling regarding reversibility
- Thorough follow-up of all patients with abnormal laboratory tests to inform labeling regarding reversibility

As an alternative to the clinical trial described above, you could conduct a comparative population pk study in a suitably large number of subjects (>200 per arm) with severe recalcitrant nodular acne. The study would use pre-defined measures of comparability to demonstrate that the plasma levels for the test and reference product are similar under real world conditions for a suitable duration (dosed for a clinical course of 20 weeks). The actual design elements would have to be agreed upon with the Agency and the Pharmacometrics group within the Office of Clinical Pharmacology prior to initiation. Depending on the results of this trial, a second trial with clinical safety and efficacy endpoints maybe necessary if the variability seen in the data is deemed sufficient to raise concern.

2. We acknowledge your commitment to inclusion in a risk management program, such as iPLEDGE, for prevention of fetal exposure to isotretinoin.
3. The NDA does not have an adequate demonstration of proportionality across the proposed dosage strengths. As isotretinoin is dosed on a mg/kg basis and as it is expected that multiple dosage units will be used to obtain doses in the 0.5-1mg/kg range, then the relationship between the different strength capsules will need to be determined for CIP-Isotretinoin.

#### Chemistry, Manufacturing and Controls

4. Refer to ND A section 3.2.P.3.1 titled "Manufacture": List the testing facilities that will perform quality control test on bulk drug substance, components, intermediates, container/closure system and stability samples of finished drug product.
5. Refer to ND A section 3.2.P.3.4 titled "Control of Critical Steps and Parameters": Justify the in-process controls for the proposed commercial scale batches as the process parameters used in the manufacture of clinical batches differ from the proposed commercial scale process parameters. See the comparison table below.



(b) (4)

6. Refer to NDA section 3.2.P.5.1 titled "Specification": Establish multiple time points (30, 60, 120, and 240 minutes) based on typical dissolution profiles for the final (b) (4) dissolution test and for setting the acceptance criterion for each time point.
7. Refer to NDA section 3.2.P.5.3 titled "Validation of Analytical Procedure": The analytical method for the dissolution test is not the same as what had been used for the assay determination. If it is to be different, establish the LOQ, LOD for this specific method. In addition, establish the stability (shelf life) of the dissolution samples at room temperature stored in the HPLC vials.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Dermatology and Dental Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Melinda Harris-Bauerlien, M.S., Regulatory Project Manager, at (301) 796-2110.

Sincerely,

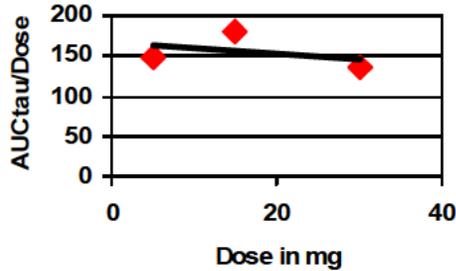
*{See appended electronic signature page}*

Stanka Kukich, M.D.  
Acting Director  
Division of Dermatology & Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

## 2-Dose Proportionality Excerpt from Original Clin Pharm Review

### 2.2.5.8 Based on pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the isotretinoin dose-concentration relationship?

The sponsor has not conducted a dose-proportionality study with their current formulation. An earlier dose proportionality study (study 443), done when the sponsor was still pursuing a (b) (4), dosage form used a 5, 15, and 30mg capsules. Of these the 5 and 15mg capsules were replaced with a 10 and 20mg capsule in the study program, once the proposed (b) (4) program was abandoned. The results of this study, while not strictly related to this application demonstrated a lack of dose proportionality between the strengths.



This is especially disturbing as the formulation uses varying amounts of the same (b) (4) for each strength, thus the capsules would be expected to be dose proportional. The lack of dose proportionality is a problem as it indicates that interchange between dosage units is not possible as there would be a difference in exposure related to how it is dosed (i.e. 2x10mg vs. 1x20mg). To demonstrate the degree of “confusion” in the data the sponsor presented the following table in their report where A=5mg, B=15mg, and C=30mg (“=” represents bioequivalent):

Isotretinoin  
AUCi C < B B > A C = A  
Cmax C < B B > A C > A

4-oxo-isotretinoin  
AUCi C < B B > A C > A  
Cmax C < B B > A C > A

Tretinoin  
AUCi C < B B < A C < A  
Cmax C < B B > A C = A

The sponsor’s conclusion from this trial is ...”that the results are contradictory and no clear trend can be defined”, for a drug product that is dose on a mg per kg body weight basis, dose proportionality would be crucial to the understanding of dosing, especially in the absence of in vivo clinical data of the products safety and efficacy. There is no head to head comparison across all three dosage strengths in the current NDA.

The sponsor has attempted to deal with this lack of information by conducting a series of single dose in vivo bioavailability studies of each of their strengths to the corresponding Accutane™ capsule, except for their 30mg capsule which is compared in a dose normalized fashion to the 40mg Accutane™ formulations. All of these trials demonstrated that under FED conditions the products produced a similar exposure to that

of Accutane™, but peak level for the 20 and 30mg capsules were not equivalent to their Accutane™ comparators under fed conditions.

Cross-Study Summary of Dose Proportionality Data  
Geometric Means-FED Data ONLY

	Cipher	Accutane™	90% CI
Study 734 (10mg)			
AUCt	1981.2	1990.8	92.8-106.7
C <sub>MAX</sub>	125.6	124.3	90.2-113
T <sub>max</sub>	6.83	7.31	
Study 727 (20mg)			
AUCt	3554	3904	87.4-94.8
C <sub>MAX</sub>	215	270.3	73.5-86
T <sub>max</sub>	6.84	6.9	
Study 627 (40mg)*			
AUCt	6251	5915	99-112.7
C <sub>MAX</sub>	434	431	91.7-110
T <sub>max</sub>	6.85	6.75	
Study 441(40mg normalized)**			
AUCt	6770	6781	90.9-109.6
C <sub>MAX</sub>	512	624	71.9-93.6
T <sub>max</sub>	5.9	6.2	

\*Cipher product administered as 2x20mg as a single dose

\*\*Cipher product administered as 1x30mg, Accutane™ administered as 1x40mg

While true dose proportionality is not common, usually a lack of dose proportionality is consistent in that both AUC and C<sub>max</sub> track each other. As noted above the lack of comparability across parameters and strengths is again disturbing and suggests again that the fasted comparison of the Cipher product to the reference Accutane™ is a necessary component to understand the dosing of this formulation. The most likely cause of this “apparent” lack of dose proportionality is the poor solubility of isotretinoin in aqueous media. A similar lack of dose proportionality is seen across these studies for Accutane™, and the nature of a cross study comparison such as this does have limitations. In any event, demonstration of dose proportionality would be a component of an NDA with a range of doses. The lack of such a determination here, coupled with the in vivo trial using slightly lower doses, represents an informational gap in this application.

-END OF EXCERPT-

### 3- Study ISO PK.06.01 (2006-1232)

#### 4.0 Synopsis

<b>Title:</b>	A Single-Dose, Comparative Bioavailability Study of Two Strengths of CIPHER Isotretinoin Capsules Under Fasting Conditions
<b>Sponsor:</b>	Cipher Pharmaceuticals Ltd. 409 Matheson Blvd. E. Mississauga, Ontario, Canada L4Z 2H2
<b>Protocol Number:</b>	ISOPK.06.01 PMRI Study No: 2006-1232 Version: 1
<b>Objectives:</b>	The objective of this study is to evaluate the comparative bioavailability between Isotretinoin 3 x 10 mg Capsules (Cipher Pharmaceuticals Ltd., Canada) and Isotretinoin 30 mg Capsules (Cipher Pharmaceuticals Ltd., Canada), after a single-dose of 30 mg in healthy subjects under fasting conditions.
<b>Treatment A: (Test)</b>	Isotretinoin 10 mg Capsules; Lot No.: 5D04 (Cipher Pharmaceuticals Ltd., Canada) [3 x 10 mg capsules administered after an overnight fast of at least 10 hours]
<b>Treatment B: (Reference)</b>	Isotretinoin 30 mg Capsules; Lot No.: 29G04 (Cipher Pharmaceuticals Ltd., Canada) [1 x 30 mg capsule administered after an overnight fast of at least 10 hours]
<b>Number of Subjects:</b>	Fifty-four (54) [33 male and 21 female] subjects were dosed in Period 1, and 50 subjects completed the entire study.
<b>Study Dosing Dates:</b>	Period 1: June 16, 2006 Period 2: July 07, 2006
<b>Sampling Schedule:</b>	Blood samples were obtained at 10 and 2 hours pre-dose, immediately prior to dosing, and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14, 16, 20, 24, 36, 48 and 72 hours following drug administration.
<b>Adverse Events:</b>	There were 63 adverse events (AEs) involving 31 subjects in the study. There were 30 adverse events associated with Treatment A. There were 33 adverse events associated with Treatment B. No serious adverse events were reported during the study.
<b>Analytical Specifications:</b>	Analyte: Isotretinoin Assay: LC-MS/MS Calibration Range: 1.00 - 750 ng/mL Analyte: 4-oxo-isotretinoin Assay: LC-MS/MS Calibration Range: 1.00 - 750 ng/mL

### **Demographics-Subject Disposition**

Fifty-four (54) healthy, non-smoking [33 male and 21 female] subjects were dosed in Period I on June 16, 2006. After completing Period I and prior to dosing in Period 2, Subjects 28 and 38 voluntarily withdrew for personal reasons, Subject 29 withdrew due to an adverse event (abdominal pain) and Subject 42 was dismissed after testing positive for cotinine. The remaining 50 subjects were dosed in Period 2 on July 07, 2006 and all 50 [29 male and 21 female] subjects completed the study.

The mean, standard deviation and range of the demographic data for the 50 subjects who were included in the data set, were as follows, mean  $\pm$  SD (range):

- Age:  $37 \pm 9$  yrs (21 — 54 yrs)
- Height:  $170.3 \pm 7.8$  cm (155.5 — 187.0 cm)
- Weight:  $75.2 \pm 9.4$  kg (56.1 — 90.8 kg)
- BMI:  $25.9 \pm 2.3$  (19.7— 29.9)

### **Adverse Events and Health Status Monitoring**

Subjects were questioned regarding their health status throughout the study. There were 63 adverse events (AEs) in this study.

Treatment Group	Severity			Relation to the Drug				Intervention	
	Mild	Mod	Severe	Unrelated	Unlikely	Possible	Probable	Required Drug Therapy	Required Non-Drug Therapy
A	30	0	0	11	0	14	5	0	1
B	33	0	0	12	0	18	3	1	0
<b>Total</b>	<b>63</b>	<b>0</b>	<b>0</b>	<b>23</b>	<b>0</b>	<b>32</b>	<b>8</b>	<b>1</b>	<b>1</b>

#### Treatment A

There were 30 AEs associated with Treatment A, which consisted of:

- HYPERCHOLESTEREMIA (4)
- HEADACHE (3)
- HYPERLIPEMIA (2)
- CREATININE INCREASE (2)
- DIZZINESS (2)
- TACHYCARDIA (2)
- SWEAT (2)
- PALLOR (2)
- DRY MOUTH (2)
- SGOT INCREASE (2)
- THROMBOCYTOPENIA (1)
- BRADYCARDIA (1)
- NAUSEA (1)
- HYPERGLYCEMIA (1)
- VASODILATION (1)

- HYPERTENSION (1)
- HYPOCHOLESTEREMIA (1)

#### Treatment B

There were 33 AEs associated with Treatment B, which consisted of:

- SGPT INCREASE (4)
- TACHYCARDIA (3)
- HYPERCHOLESTEREMIA (3)
- SGOT INCREASE (3)
- HEADACHE (3)
- URINARY ABNORMALITY (3)
- LDH INCREASE (2)
- ECCHYMOSIS (2)
- RASH (1)
- DIZZINESS (1)
- HYPERTENSION (1)
- GGTP INCREASE (1)
- PAIN ABDOMEN (1)
- BUN INCREASE (1)
- CREATININE INCREASE (1)
- NAUSEA (1)
- DIARRHEA (1)
- HYPERLIPEMIA (1)

Subject 29 had abdominal pain and was diagnosed with a parasitic infection during the 21-day washout interval. Subject 29 took 250 mg Apo-Metronidazole for 7 days beginning on June 20, 2006, as prescribed by a physician. Subject 29 withdrew from the study due to the adverse events.

Summary of Results for Plasma Isotretinoin  
(N = 50)

Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra- Subject (CV%)
	Treatment A	Treatment B			
AUC <sub>t</sub> (ng*h/mL)	3908.15 4047.60 (27)	3105.06 3368.81 (34)	125.86	113.16 - 139.99	33
AUC <sub>inf</sub> (ng*h/mL)	4403.53 4565.03 (27)	3507.09 3812.38 (34)	125.56	112.90 - 139.64	32
C <sub>max</sub> (ng/mL)	245.97 255.42 (28)	201.44 215.61 (34)	122.10	110.59 - 134.82	30
T <sub>max</sub> <sup>a</sup> (h)	3.19 (29)	3.21 (31)	-	-	-
K <sub>el</sub> <sup>a</sup> (1/h)	0.0317 (26)	0.0308 (25)	-	-	-
Thal <sup>a</sup> (h)	23.36 (27)	23.72 (23)	-	-	-

<sup>a</sup> Presented as arithmetic mean (CV%) only.

Summary of Results for Plasma Isotretinoin  
(N = 49, Subject 17, Excluded)

Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra- Subject (CV%)
	Treatment A	Treatment B			
AUC <sub>t</sub> (ng*h/mL)	3886.15 4026.17 (27)	3270.05 3431.71 (31)	118.84	112.62 - 125.41	16
AUC <sub>inf</sub> (ng*h/mL)	4385.28 4547.86 (28)	3698.63 3883.99 (31)	118.57	112.35 - 125.13	16
C <sub>max</sub> (ng/mL)	245.03 254.65 (28)	210.10 219.40 (31)	116.63	109.01 - 124.77	20
T <sub>max</sub> <sup>a</sup> (h)	3.20 (29)	3.25 (30)	-	-	-
K <sub>el</sub> <sup>a</sup> (1/h)	0.0315 (26)	0.0306 (25)	-	-	-
Thal <sup>a</sup> (h)	23.48 (27)	23.85 (23)	-	-	-

<sup>a</sup> Presented as arithmetic mean (CV%) only.

Treatment A: Isotretinoin 10 mg Capsules; Lot No.: 5D04 (Cipher Pharmaceuticals Ltd., Canada)  
[3 x 10 mg capsules were administered after an overnight fast of at least 10 hours]

Treatment B: Isotretinoin 30 mg Capsules; Lot No.: 29G04 (Cipher Pharmaceuticals Ltd., Canada)  
[1 x 30 mg capsule was administered after an overnight fast of at least 10 hours]

Summary of Results for Plasma 4-oxo-isotretinoin  
(N = 50)

Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra- Subject (CV%)
	Treatment A	Treatment B			
AUCt (ng*h/mL)	5846.67 6123.12 (31)	4583.80 5059.76 (37)	127.55	112.97 - 144.01	37
AUCinf (ng*h/mL)	9497.74 9821.12 (34)	7744.05 8798.62 (53)	122.65	106.06 - 141.83	44
Cmax (ng/mL)	115.78 122.96 (36)	89.37 98.60 (39)	129.55	114.49 - 146.60	38
Tmax* (h)	19.09 (56)	19.39 (58)	-	-	-
Kel* (1/h)	0.0168 (35)	0.0155 (37)	-	-	-
Thalf* (h)	47.86 (45)	52.88 (53)	-	-	-

\* Presented as arithmetic mean (CV%) only.

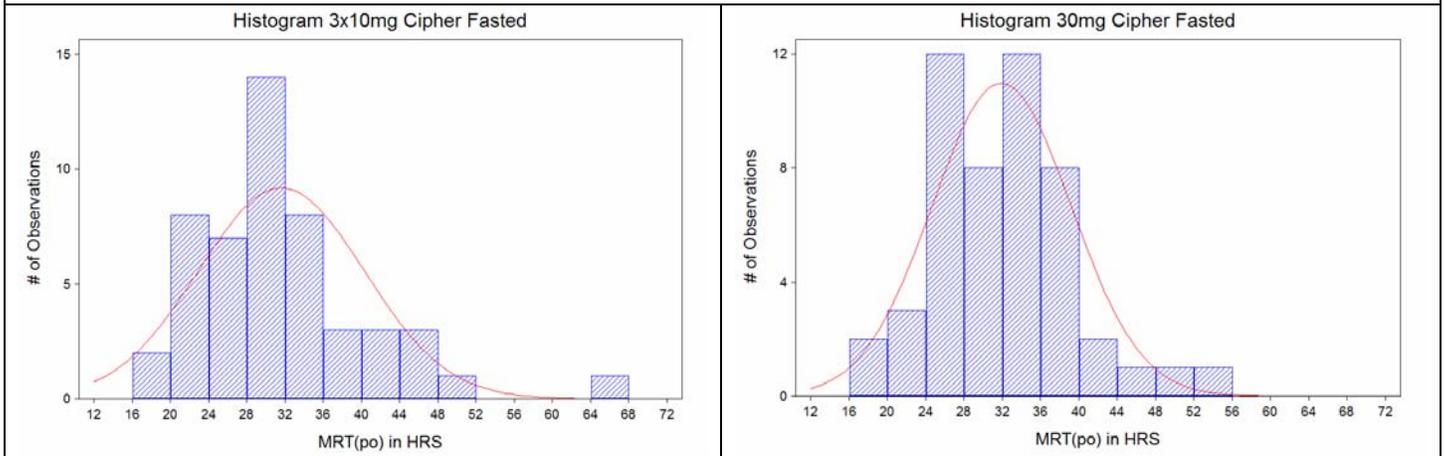
Summary of Results for Plasma 4-oxo-isotretinoin  
(N = 49, Subject 17 Excluded)

Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra- Subject (CV%)
	Treatment A	Treatment B			
AUCt (ng*h/mL)	5813.67 6091.53 (32)	4856.74 5156.59 (34)	119.70	111.96 - 127.98	20
AUCinf (ng*h/mL)	9419.58 9807.03 (34)	8301.08 8974.24 (51)	113.47	103.85 - 124.00	26
Cmax (ng/mL)	114.86 121.94 (36)	94.32 100.46 (36)	121.77	113.02 - 131.20	22
Tmax* (h)	19.07 (56)	19.50 (58)	-	-	-
Kel* (1/h)	0.0167 (35)	0.0152 (36)	-	-	-
Thalf* (h)	48.17 (45)	53.49 (52)	-	-	-

\* Presented as arithmetic mean (CV%) only.

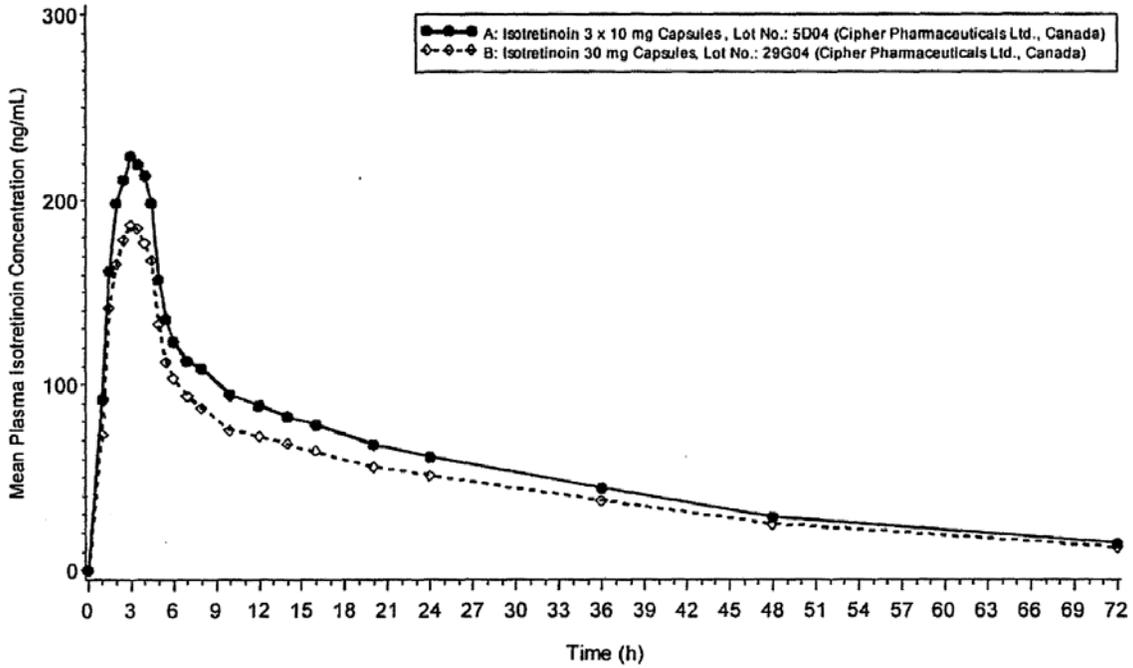
Treatment A: Isotretinoin 10 mg Capsules; Lot No.: 5D04 (Cipher Pharmaceuticals Ltd., Canada)  
[3 x 10 mg capsules were administered after an overnight fast of at least 10 hours]  
Treatment B: Isotretinoin 30 mg Capsules; Lot No.: 29G04 (Cipher Pharmaceuticals Ltd., Canada)  
[1 x 30 mg capsule was administered after an overnight fast of at least 10 hours]

## Mean Residence Time in Hours

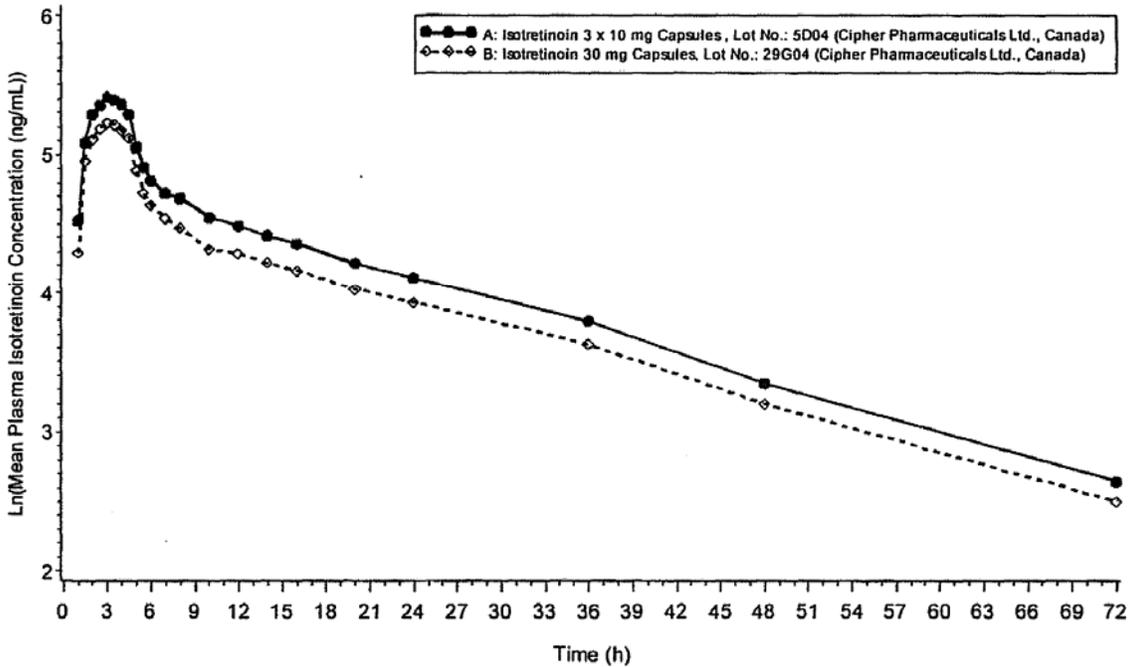


	3x10mg	1x30mg
N	50	50
Lo 95% CI	29.138	29.865
Mean	31.609	31.931
Up 95% CI	34.080	33.997
SD	8.6946	7.2696
Variance	75.597	52.847
SE Mean	1.2296	1.0281
C.V.	27.507	22.767
Minimum	17.200	16.480
1st Quart.	25.297	25.910
Median	30.680	31.865
3rd Quart.	34.118	36.343
Maximum	66.160	53.700

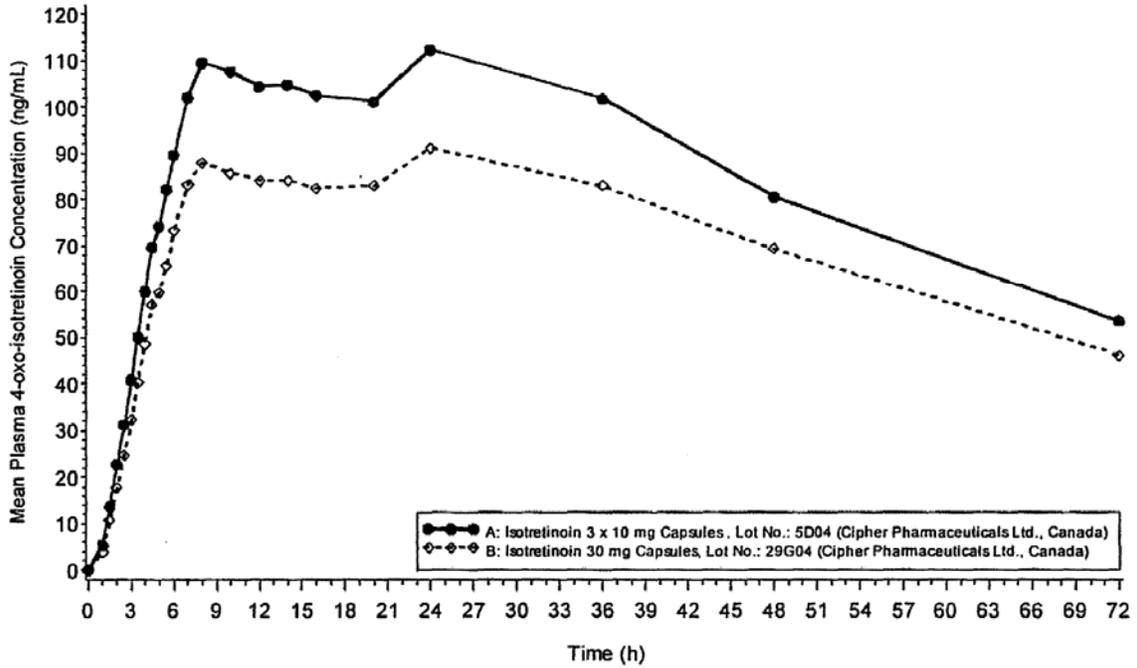
STUDY No.: 2006-1232 / ISOPK.06.01  
MEAN PLASMA ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES  
N=50



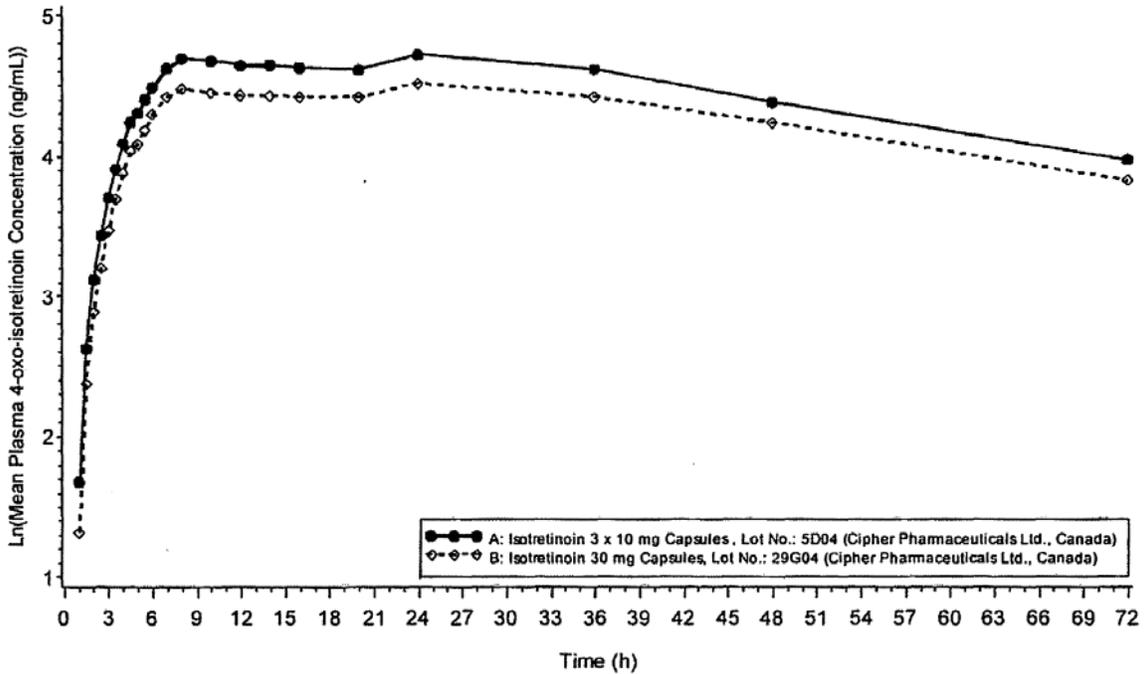
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LOG MEAN PLASMA ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES  
N=50



STUDY No.: 2006-1232 / ISOPK.06.01  
MEAN PLASMA 4-OXO-ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES  
N=50

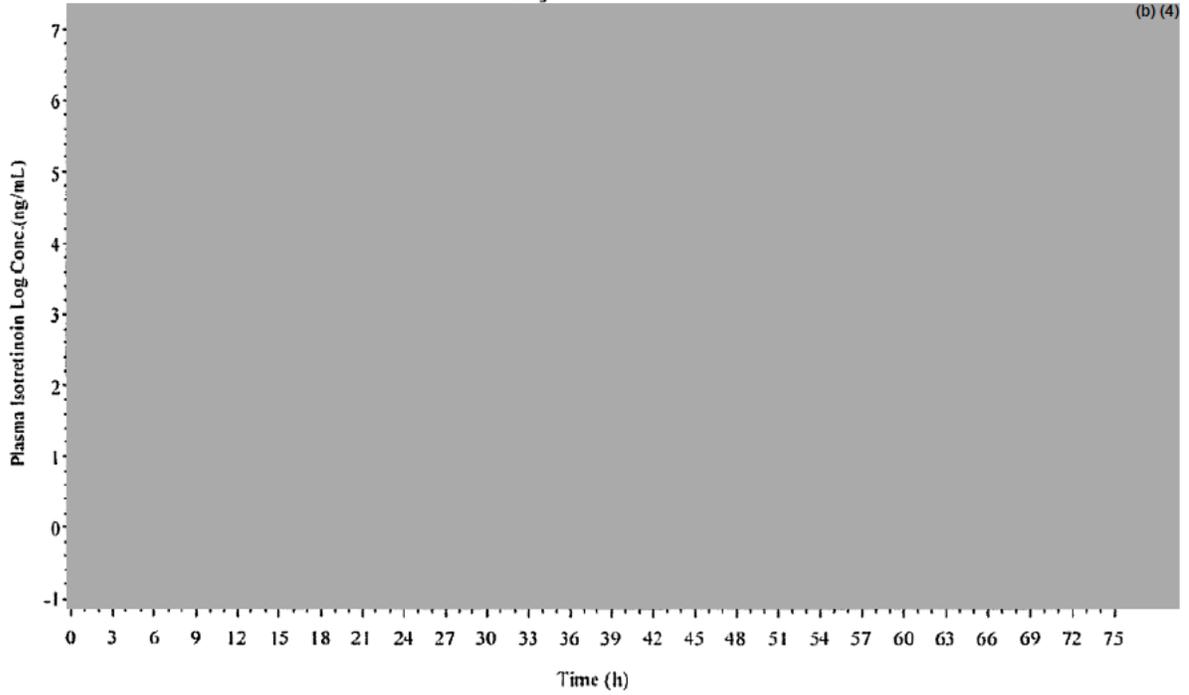


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LOG MEAN PLASMA 4-OXO-ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES  
N=50

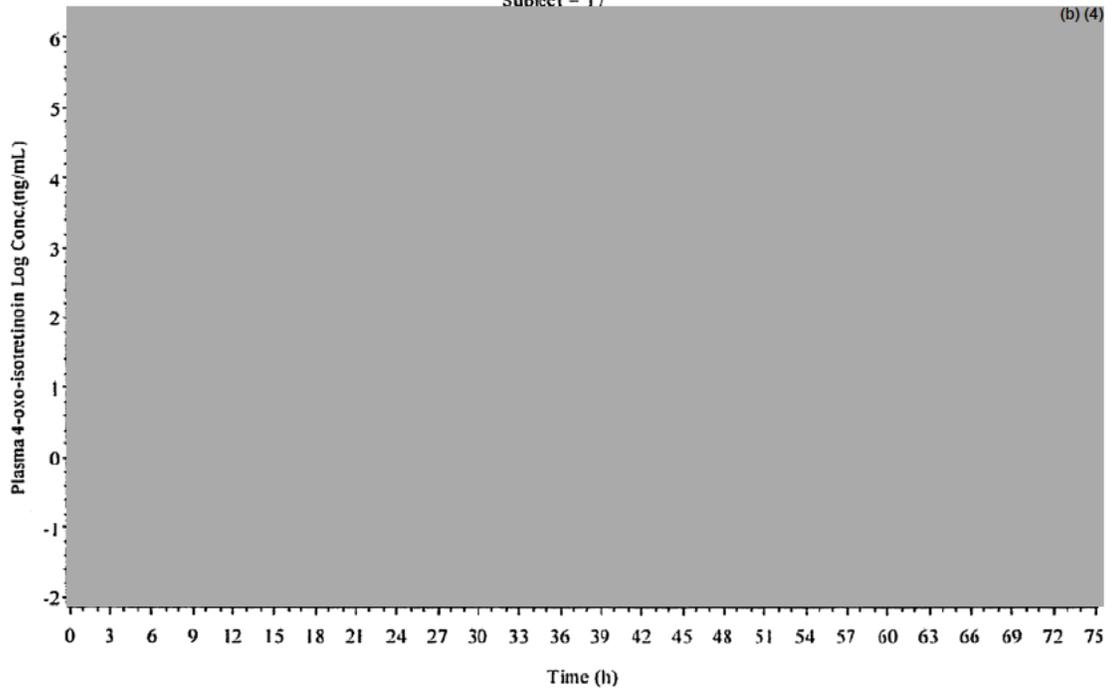


SUBJECT #17

STUDY No.: 2006-1232  
PLASMA ISOTRETINOIN LOG CONCENTRATION VERSUS TIME CURVES  
Subject = 17



STUDY No.: 2006-1232  
PLASMA 4-OXO-ISOTRETINOIN LOG CONCENTRATION VERSUS TIME CURVES  
Subject = 17



#### 4-Study ISO PK.06.02 (2006-1233)

**Title:** A Single-Dose, Comparative Bioavailability Study of Two Strengths of Cipher Isotretinoin Capsules Under Fed Conditions

**Sponsor:** Cipher Pharmaceuticals Ltd.  
409 Matheson Blvd. E.  
Mississauga, Ontario, Canada  
L4Z 2H2

**Protocol Number:** ISOPK.06.02  
PMRI Study No: 2006-1233 Version: 1

**Objectives:** The objective of this study is to evaluate the comparative bioavailability between Isotretinoin 3 x 10 mg Capsules (Cipher Pharmaceuticals Ltd., Canada) and Isotretinoin 30 mg Capsules (Cipher Pharmaceuticals Ltd., Canada), after a single-dose of 30 mg in healthy subjects under fed conditions.

**Treatment A:  
(Test)** Isotretinoin 10 mg Capsules  
Lot No.: 5D04 (Cipher Pharmaceuticals Ltd., Canada)  
[3 x 10 mg capsules administered after a modified high fat, high calorie breakfast]

**Treatment B:  
(Reference)** Isotretinoin 30 mg Capsules  
Lot No.: 29G04 (Cipher Pharmaceuticals Ltd., Canada)  
[1 x 30 mg capsule administered after a modified high fat, high calorie breakfast]

**Number of Subjects:** Fifty-four (54) [30 male and 24 female] subjects were dosed in Period 1, and 52 subjects completed the entire study.

**Study Dosing Dates:** Period 1: June 20, 2006  
Period 2: July 11, 2006

**Sampling Schedule:** Blood samples were obtained at 10 hours and 2 hours pre-dose, immediately prior to dosing and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14, 16, 20, 24, 36, 48 and 72 hours following drug administration.

**Adverse Events:** There were 48 adverse events (AEs) involving 20 subjects in the study. There were 22 adverse events associated with Treatment A. There were 26 adverse events associated with Treatment B.  
No serious adverse events were reported during the study.

**Analytical  
Specifications:** Analyte: Isotretinoin  
Assay: LC-MS/MS  
Calibration Range: 1.00 - 750 ng/mL  
Analyte: 4-oxo-isotretinoin  
Assay: LC-MS/MS  
Calibration Range: 1.00 - 750 ng/mL

### Demographics

The mean, standard deviation and range of the demographic data for the 52 subjects who were included in the data set, were as follows, mean  $\pm$  SD (range):

- Age: 35 $\pm$ 9yrs (21-55yrs)
- Height: 169.8  $\pm$  8.9 cm (152.0-189.0 cm)
- Weight: 71.8  $\pm$  10.6 kg (49.2-93.6 kg)
- BMI: 24.8  $\pm$  2.5 (20.4-29.1)

### Dietary

For some unknown reason Cipher does not follow the recommended FDA high fat diet, but again chooses to use what can only be described as an “unusual” diet. The menu and nutritional breakdown for their modified high-fat, high- calorie breakfast was as follows:

<b>Food</b>	<b>Calories</b>	<b>Carb</b>	<b>Protein</b>	<b>Fat</b>
1 Regular Bagel	300	67 g	12 g	3 g
3 Tablespoons Peanut Butter	250	9 g	12 g	22 g
5 Slices of Bacon	125	0.2 g	10 g	10 g
8oz Apple Juice	110	28 g	0.1 g	0.1 g
1 Dutchie Donut	250	33 g	3 g	15 g
<b>Total</b>	<b>1035</b>	<b>137.2 g</b>	<b>37.1 g</b>	<b>50.1 g</b>
<b># Calories</b>		<b>548.8</b>	<b>148.4</b>	<b>450.9</b>
<b>% of Total Calories</b>		<b>48</b>	<b>13</b>	<b>39</b>

### Adverse Events and Health Status Monitoring

Subjects were questioned regarding their health status throughout the study. There were 48 adverse events (AEs) in this study.

<b>Treatment Group</b>	<b>Severity</b>			<b>Relation to the Drug</b>				<b>Intervention</b>	
	<b>Mild</b>	<b>Mod</b>	<b>Severe</b>	<b>Unrelated</b>	<b>Unlikely</b>	<b>Possible</b>	<b>Probable</b>	<b>Required Drug Therapy</b>	<b>Required Non-Drug Therapy</b>
<b>A</b>	22	0	0	7	0	5	10	1	0
<b>B</b>	26	0	0	18	2	4	2	0	0
<b>Total</b>	<b>48</b>	<b>0</b>	<b>0</b>	<b>25</b>	<b>2</b>	<b>9</b>	<b>12</b>	<b>1</b>	<b>0</b>

### Treatment A

There were 22 AEs associated with Treatment A (3x10mg capsules), which consisted of:

- PRURITUS (6)
- HEADACHE (2)
- HYPERTENSION (2)
- HYPERGLYCEM (2)
- DIZZINESS (1)
- HYPOTENS (1)
- DRY MOUTH (1)
- RHINITIS (1)

- ECCHYMOSIS (1)
- STOMATITIS (1)
- ACNE (1)
- THIRST (1)
- HYPERCHOLESTEREM (1)
- HYPERLIPEMIA (1)

#### Treatment B

There were 26 AEs associated with Treatment B (1x30mg), which consisted of:

- HYPERTENSION (5)
- LEUKOCYTOSIS (3)
- THROMBOCYTOPENIA (2)
- HEADACHE (2)
- URINARY ABNORMALITY (2)
- RHINITIS (2)
- SOMNOLENCE (2)
- PAIN ABDOMEN (1)
- RASH (1)
- CREATININE INCREASE (1)
- NAUSEA (1)
- EDEMA FACE (1)
- DIARRHEA (1)
- PRURITUS (1)
- CONFUSION(1)

At the present time no CRFs have been submitted as there were no discontinuations for AEs, however, the appearance of a report of confusion on treatment B has triggered a request that the subjects be identified and the reports submitted. It should be noted that as these are single dose studies the ability of these studies to demonstrate significant adverse events is very low.

**Summary of Results for Plasma Isotretinoin  
(N = 52)**

Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra- Subject (CV%)
	Treatment A	Treatment B			
AUC <sub>t</sub> (ng*h/mL)	6842.88 7008.88 (22)	6641.02 6796.77 (21)	103.04	99.69 - 106.51	10
AUC <sub>inf</sub> (ng*h/mL)	7580.91 7791.98 (23)	7314.19 7519.89 (23)	103.65	100.22 - 107.19	10
C <sub>max</sub> (ng/mL)	365.76 382.60 (30)	367.99 383.01 (28)	99.39	93.91 - 105.19	17
T <sub>max</sub> <sup>a</sup> (h)	7.21 (30)	7.15 (31)	-	-	-
K <sub>el</sub> <sup>a</sup> (1/h)	0.0366 (27)	0.0371 (25)	-	-	-
Thal <sup>a</sup> (h)	20.14 (24)	19.68 (22)	-	-	-

<sup>a</sup> Presented as arithmetic mean (CV%) only.

**Summary of Results for Plasma 4-oxo-isotretinoin  
(N = 52)**

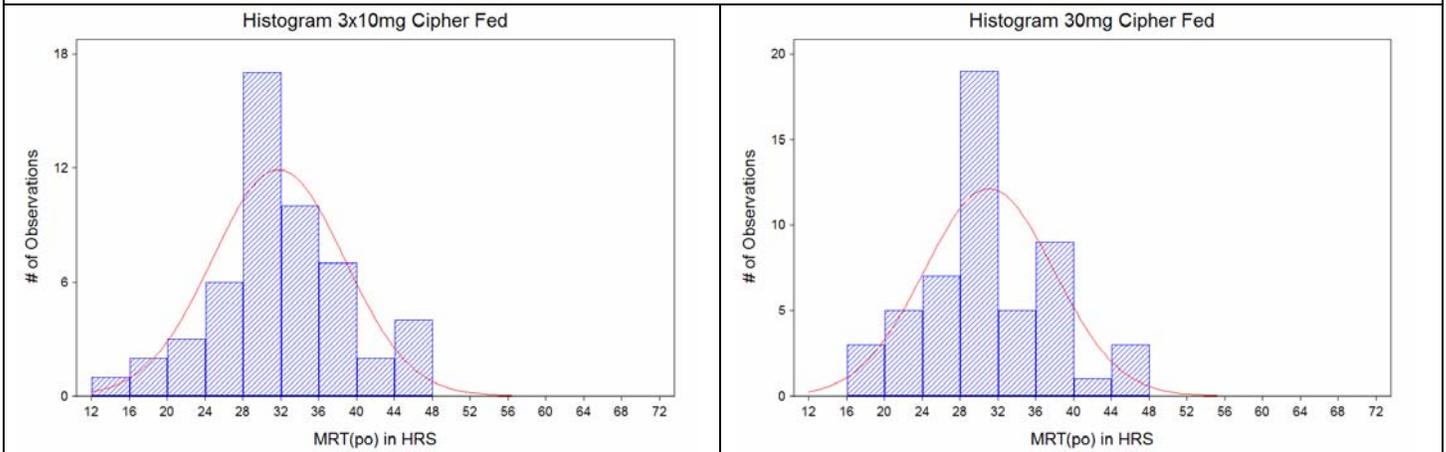
Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra- Subject (CV%)
	Treatment A	Treatment B			
AUC <sub>t</sub> (ng*h/mL)	11868.8 12159.2 (22)	11376.3 11663.1 (22)	104.33	100.25 - 108.58	12
AUC <sub>inf</sub> (ng*h/mL)	19424.4 19741.3 (26)	18569.6 19753.9 (43)	104.60	98.26 - 111.36	18
C <sub>max</sub> (ng/mL)	243.91 251.68 (26)	231.59 238.48 (24)	105.32	100.64 - 110.22	14
T <sub>max</sub> <sup>a</sup> (h)	24.32 (40)	22.32 (45)	-	-	-
K <sub>el</sub> <sup>a</sup> (1/h)	0.0167 (35)	0.0169 (34)	-	-	-
Thal <sup>a</sup> (h)	46.59 (34)	47.00 (44)	-	-	-

<sup>a</sup> Presented as arithmetic mean (CV%) only.

Treatment A: Isotretinoin 10 mg Capsules; Lot No.: 5D04, (Cipher Pharmaceuticals Ltd., Canada)  
[3 x 10 mg capsules were administered after a modified high fat, high calorie breakfast]

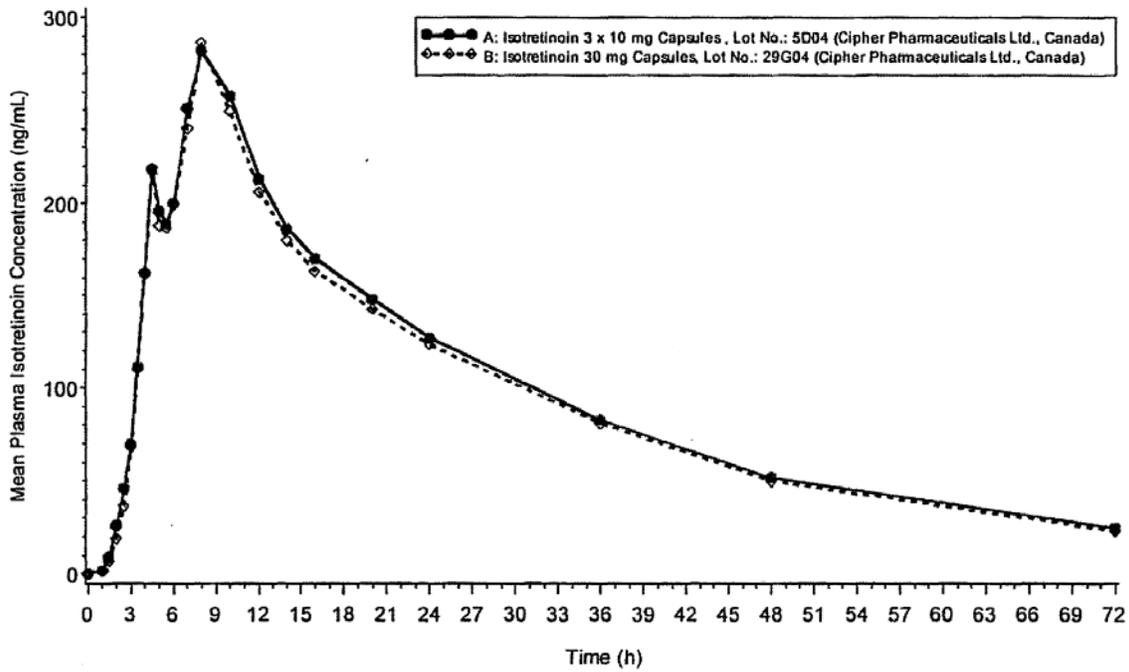
Treatment B: Isotretinoin 30 mg Capsules; Lot No.: 29G04, (Cipher Pharmaceuticals Ltd., Canada)  
[1 x 30 mg capsule was administered after a modified high fat, high calorie breakfast]

## Mean Residence Time in Hours

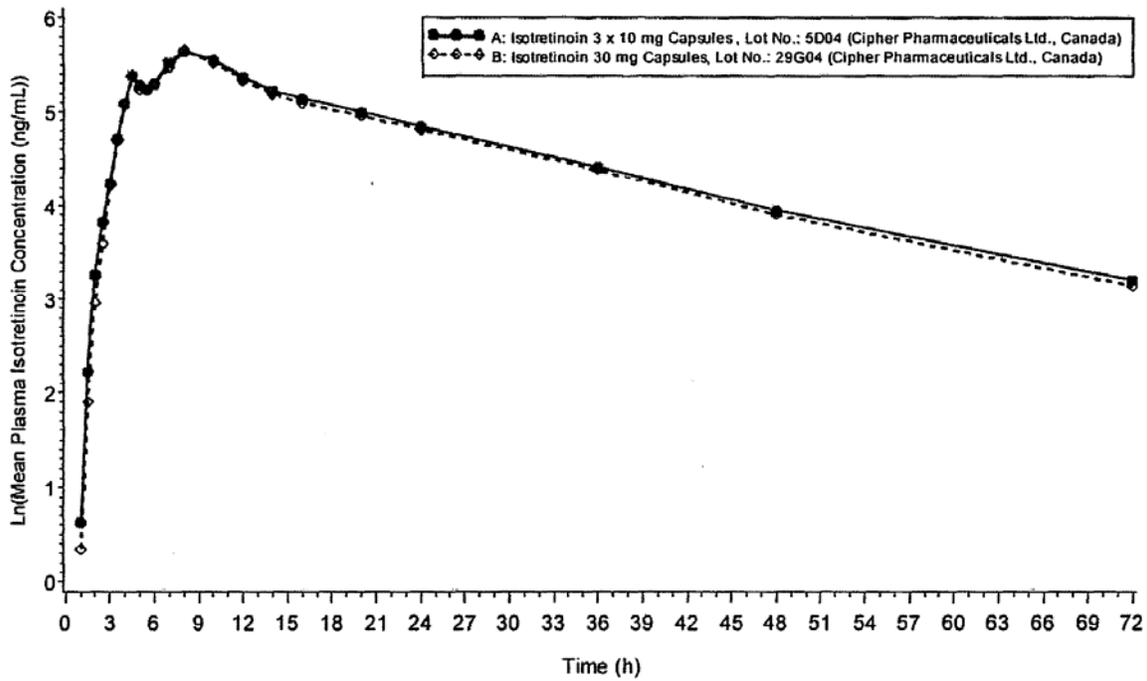


	3x10mg Fed	30mg Fed
N	52	52
Lo 95% CI	29.822	29.177
Mean	31.760	31.082
Up 95% CI	33.697	32.988
SD	6.9596	6.8433
Variance	48.437	46.831
SE Mean	0.9651	0.9490
C.V.	21.913	22.017
Minimum	14.370	16.540
1st Quart.	28.433	27.265
Median	31.270	30.760
3rd Quart.	36.110	35.663
Maximum	46.030	47.740

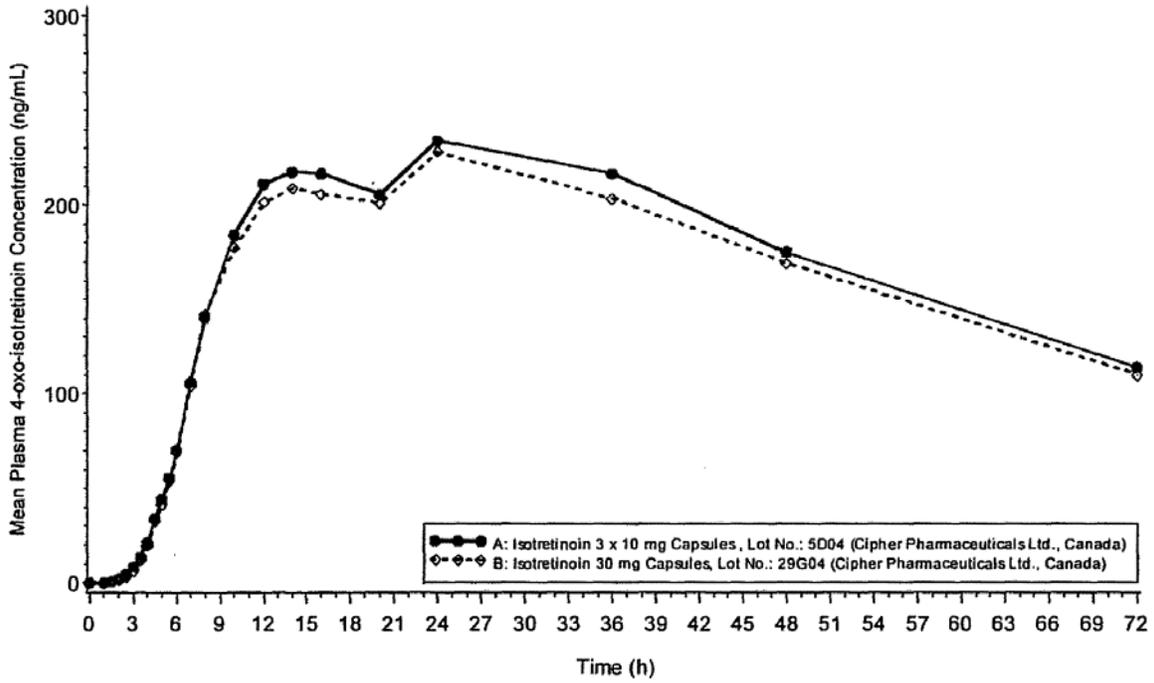
STUDY No.: 2006-1233 / ISOPK.06.02  
MEAN PLASMA ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES  
N=52



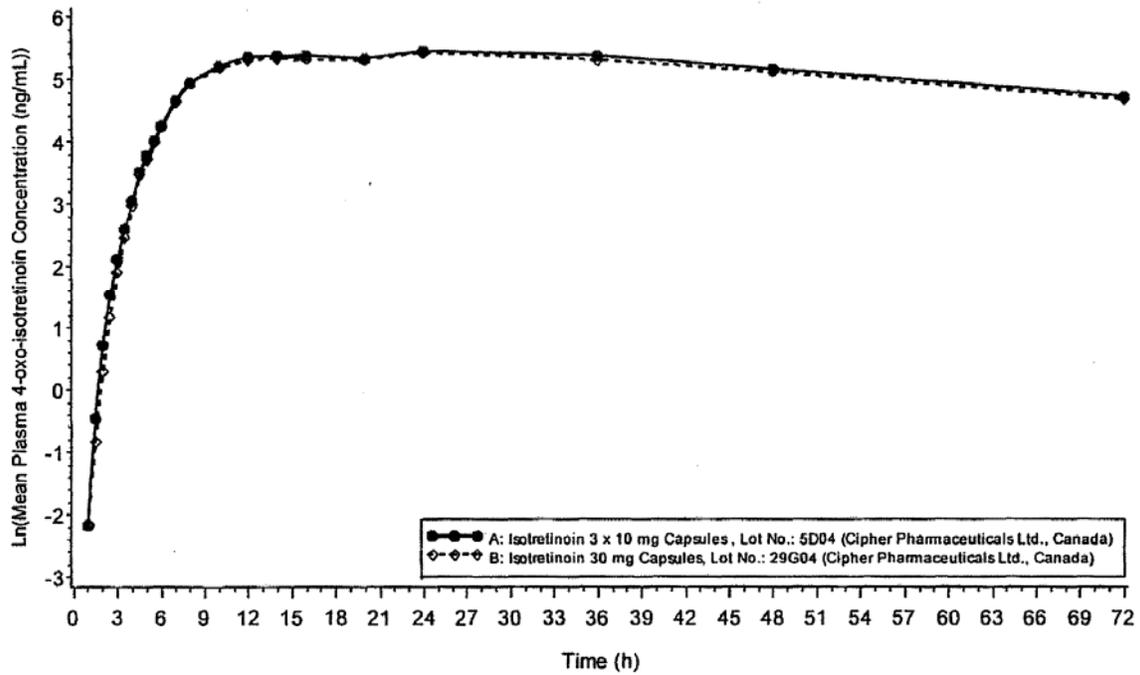
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LOG MEAN PLASMA ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES  
N=52



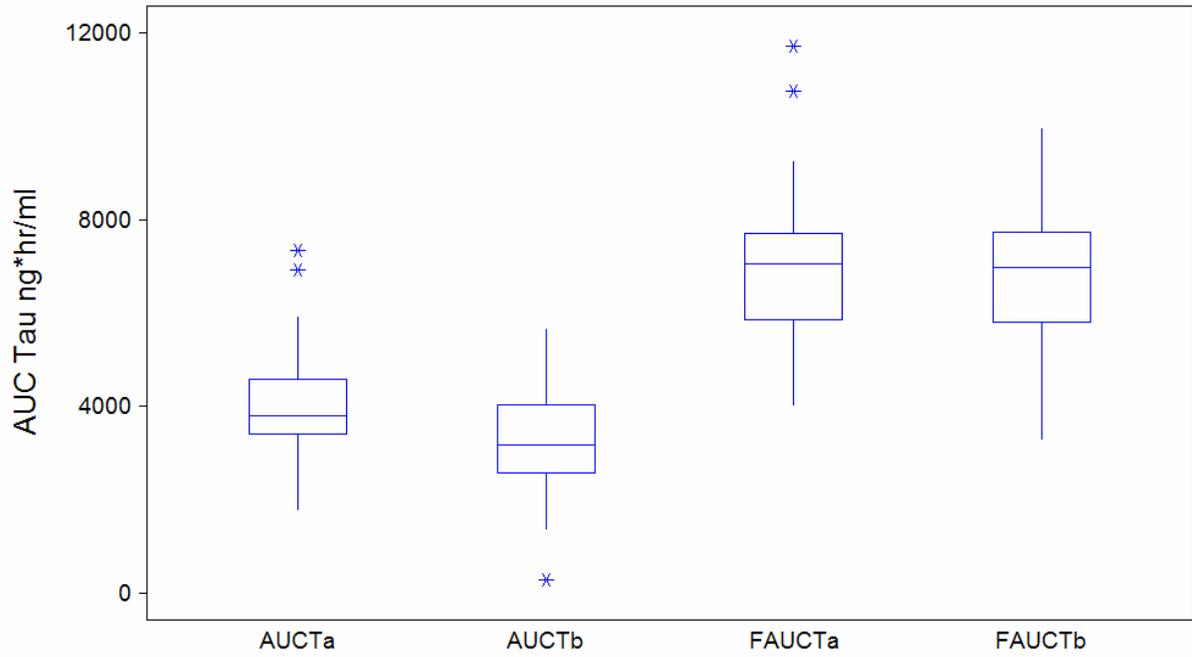
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 MEAN PLASMA 4-OXO-ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES  
 N=52



STUDY No.: 2006-1233 / ISOPK.06.02  
 LOG MEAN PLASMA 4-OXO-ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES  
 N=52

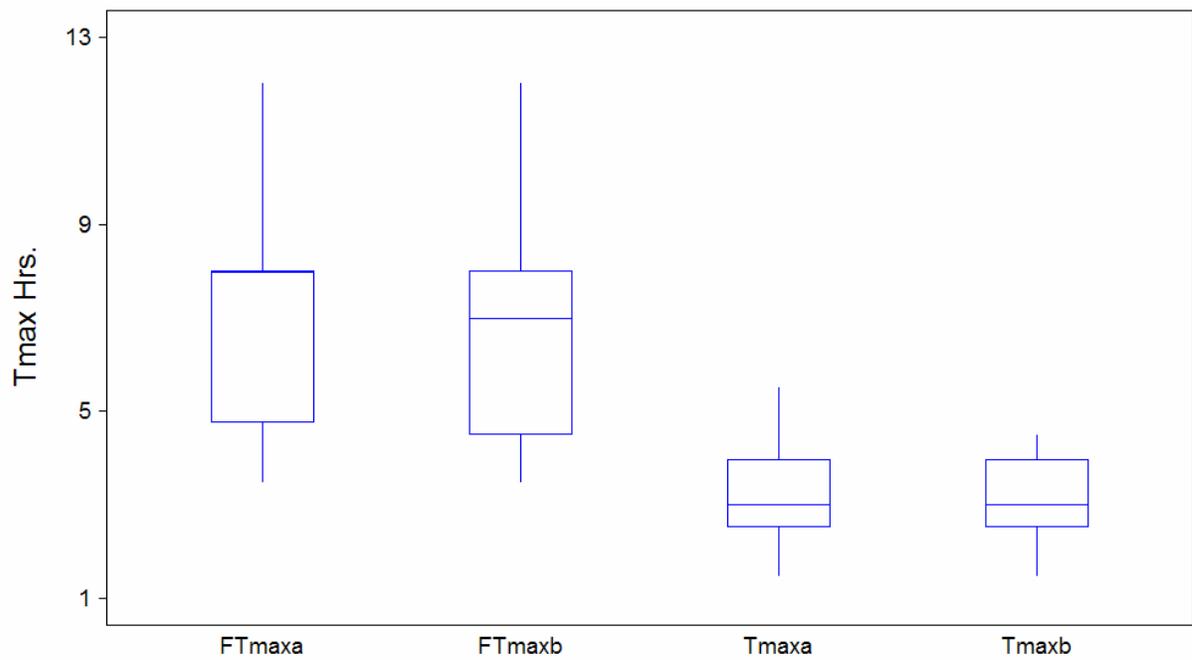


**Box and Whisker Plot AUCTau**  
Ciper Fasted vs. Fed Proportionality



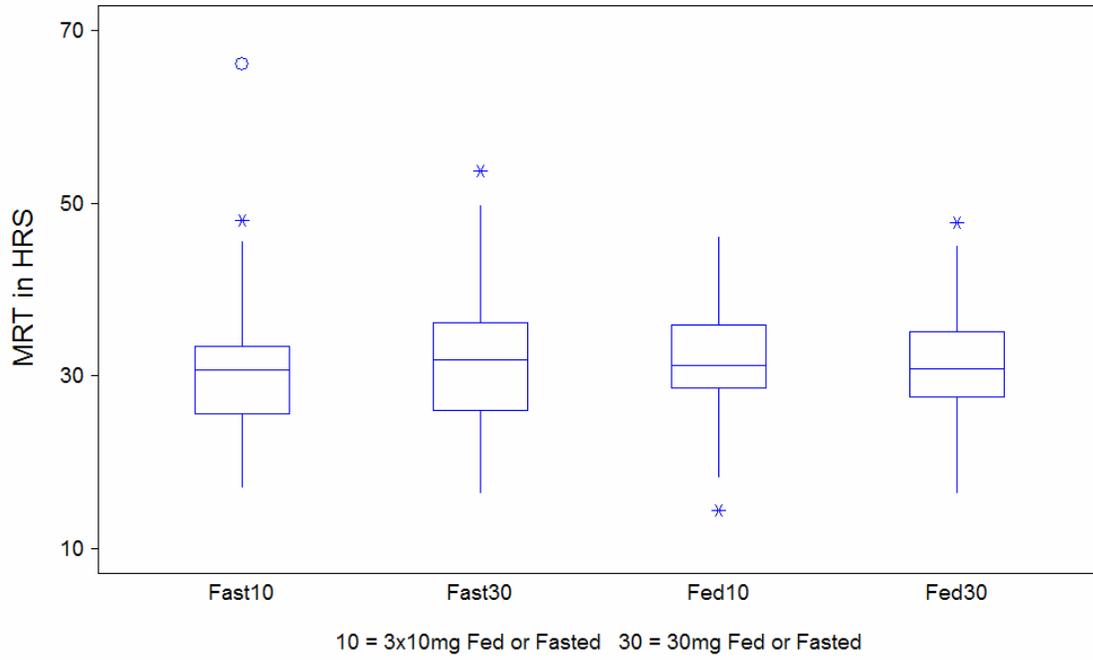
204 cases (trt A 3x10mg, trt B 1x30) F=Fed

**Box and Whisker Plot Tmax Values**  
Ciper Fasted vs. Fed Proportionality



204 cases (trt A 3x10mg, trt B 1x30) F=Fed

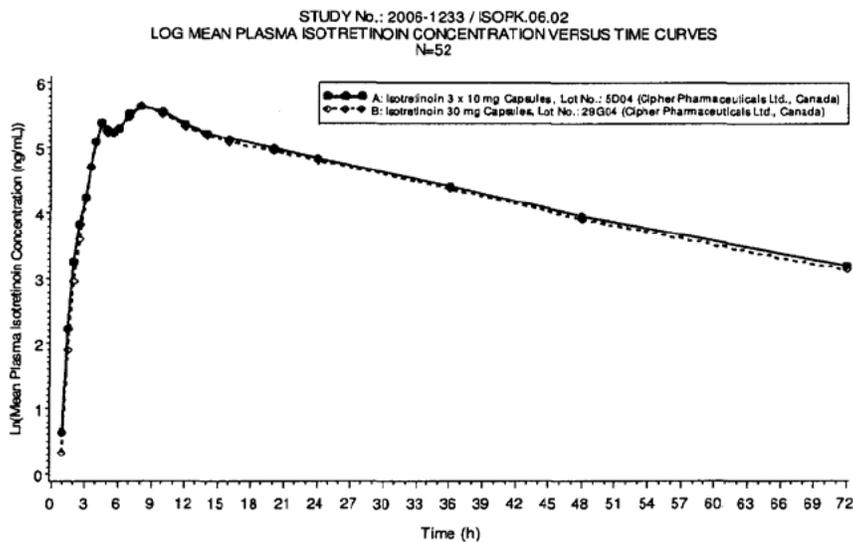
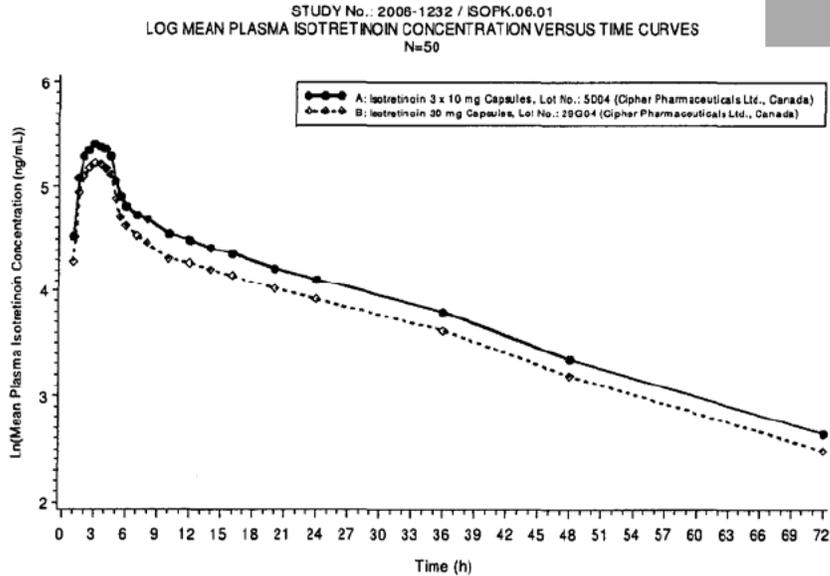
Box and Whisker Plot-Combined MRT(po)  
Fed and Fasted Data



## 5-Fractional Absorption of Isotretinoin Over Time

The examination of the plasma isotretinoin concentration-time profiles generated in the two studies revealed a multi-compartment disposition.

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The segment of the concentration-time profiles following immediately after the peak, the “distribution phase”, is much more clearly defined in Study 2006-1232 (fasting study) than in Study 2006-1233 (fed study). This behavior is easily observable in the log-linear graphs of the mean concentrations for the two studies.

Due to the multi-compartment pharmacokinetics displayed by isotretinoin, the Wagner-Nelson approach to calculate the fraction of the dose absorbed cannot be applied.

Furthermore, the lack of data following an i.v. administration prohibits the application of either Loo-Riegelman or standard deconvolution methods.

Therefore, Method 3A suggested by Wagner J.G et al<sup>2</sup> was employed in this report. It was assumed that a 2-compartment model will adequately describe the pharmacokinetics of isotretinoin (an assumption that was not borne out by a number of subjects). The following steps describe the process that led to the generation of the absorption curves by the sponsor:

1) The post-absorption phase of each individual concentration-time profiles was fit to a pharmacokinetic model specific to an iv-bolus administration with a 2-compartment model with elimination from the central compartment (Equation from reference 1).

$$C = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t}$$

With few exceptions, all data points following the T<sub>max</sub> were used in the nonlinear fitting. The pharmacokinetic constants  $\alpha$  and  $\beta$  were determined.

2) The values for the AUC<sub>inf</sub> were calculated using the AUC<sub>t</sub>, the predicted last concentration and  $\beta$  (Equation 5 from reference 1).

$$AUC_{inf} = AUC_t + \frac{C_{last}}{\beta}$$

3) Post-absorptive concentration-time data of each individual concentration-time profiles were fitted to Equation 5 from reference 1 to obtain the values for the  $k_{10}$  and  $t_s$  parameters.

$$C = \frac{AUC_{inf}}{\alpha - \beta} \left[ \beta \cdot (\alpha - k_{10}) \cdot e^{-\beta \cdot (t - t_s)} + \alpha \cdot (k_{10} - \beta) \cdot e^{-\alpha \cdot (t - t_s)} \right]$$

4) The values for the  $k_{21}$  and  $k_{12}$  were then calculated using equations 3 and 4 from reference 1.

$$k_{21} = \frac{\alpha \cdot \beta}{k_{10}}$$

$$k_{12} = \alpha + \beta - k_{10} - k_{21}$$

5) The exact Loo-Riegelman equation<sup>3</sup> was used to calculate the amount absorbed per unit volume, At/V.

$$\frac{At}{V} = C_t + k_{el} \cdot \int_0^t C \cdot dt + k_{12} \cdot e^{-k_{21} \cdot t} \cdot \int_0^t C \cdot e^{k_{21} \cdot t} \cdot dt$$

<sup>2</sup> Wagner JO, Ganes DA, Midha KK, Gonzalez-Younes I, Sackellares JC, Olson LD, J Pharmacokinetic Biopharm 1991;19:413-455

<sup>3</sup> Wagner JG, J Pharm Sci 1983;72:838-842

6) The fraction of the dose absorbed was then calculated by dividing the  $A_t/V$  values to the total amount absorbed at time (t) equal to infinity,  $A_{inf}/V$ .

7) The final data for the fraction of dose absorbed were presented in individual graphs by subjects, in mean graphs by treatments and in graphs contained all subject curves for each treatment.

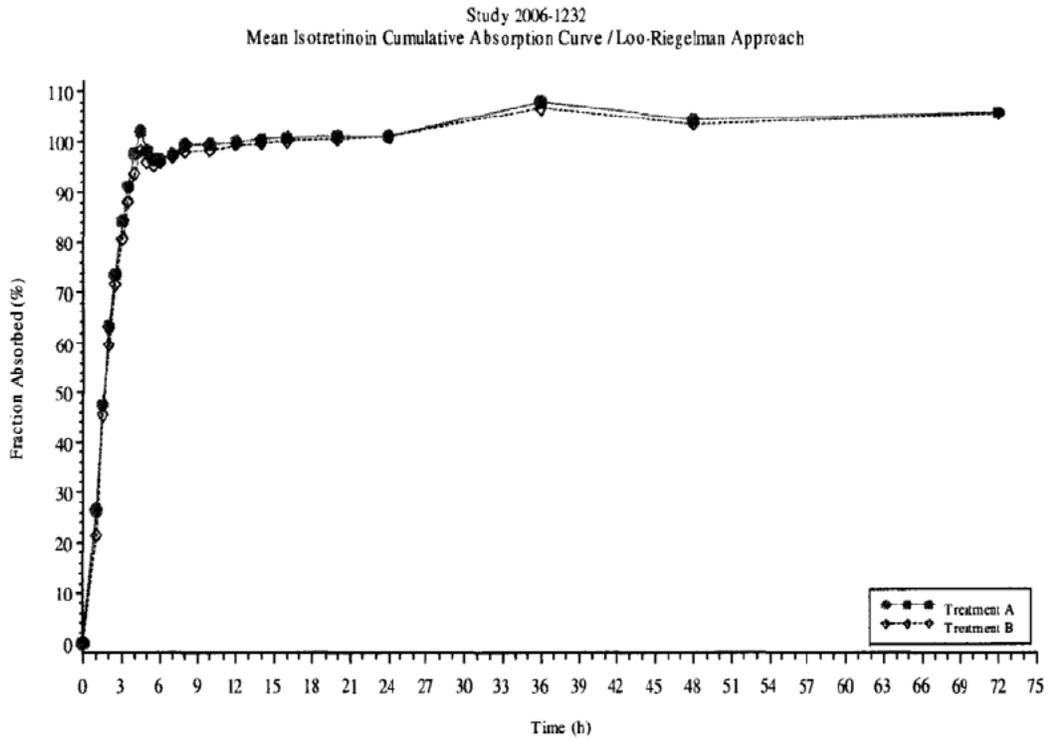
Then nonlinear fitting was performed with the procedure NLIN in SAS® version 9.1.

**Study 2006-1232**

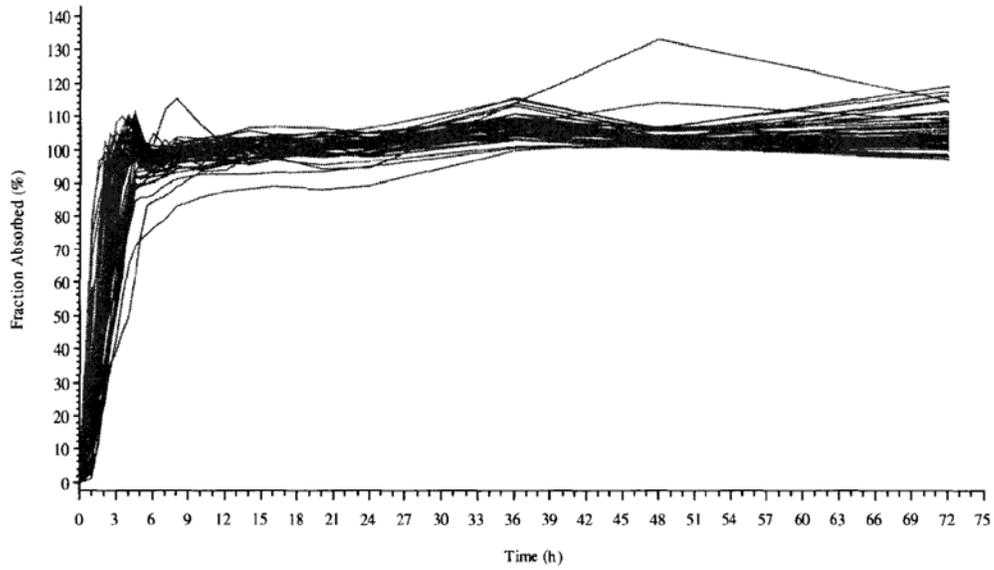
In this study, with the exceptions of Subject 36 for Treatment A, there is a good agreement between the measured and predicted isotretinoin concentrations. However, some of the values for the pre-exponential term A, are quite high. This may be the result of poor definition of the disposition phase in the concentration-time profiles after the Tmax.

The estimation of the fraction absorbed led to acceptable cumulative absorption curves for the majority of subjects. In three instances, the approximation of the absorption was not acceptable and these profiles were excluded from the mean and subjects-by-treatment plots: Subjects 07, 18 and 36 for Treatment A.

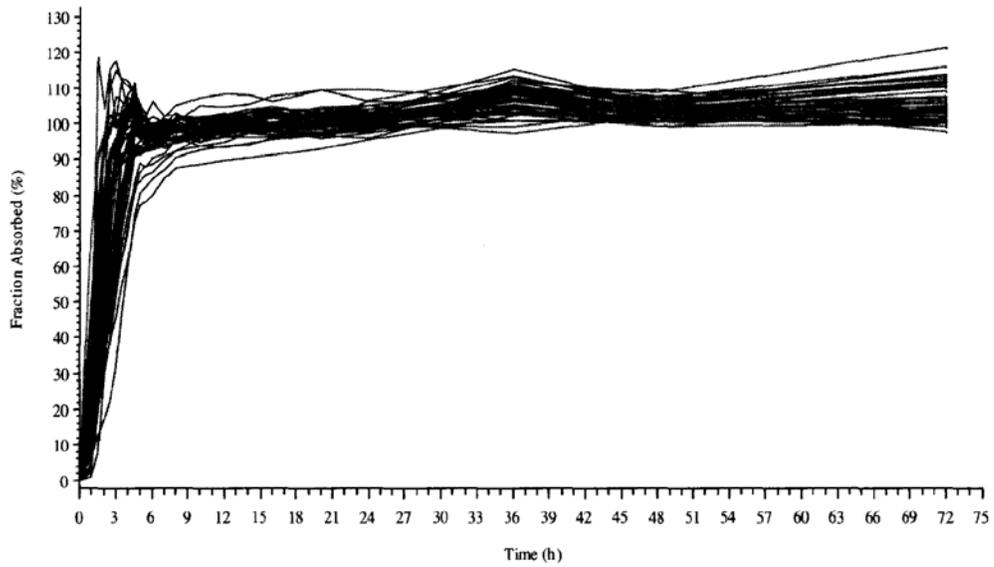
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Study 2006-1232  
Isotretinoin Cumulative Absorption Curves / Loo-Riegelman Approach  
Treatment A



Study 2006-1232  
Isotretinoin Cumulative Absorption Curves / Loo-Riegelman Approach  
Treatment B



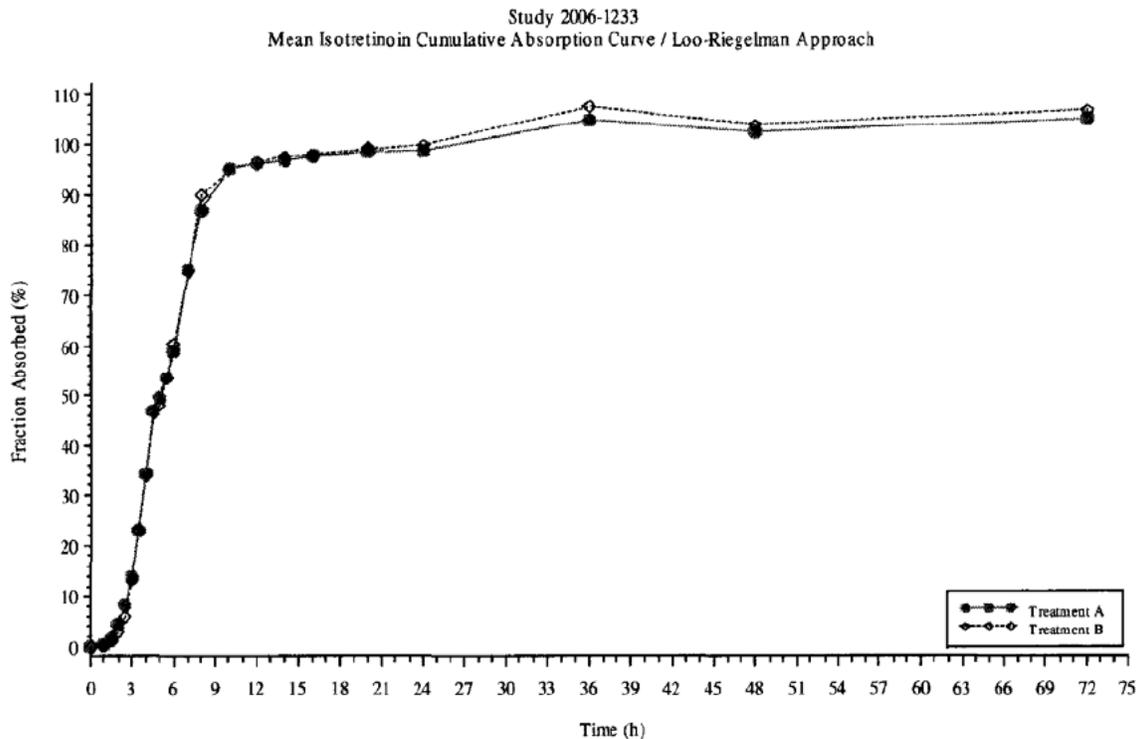
### Study 2006-1233

The poor definition of the disposition phase in the isotretinoin concentration-time profiles measured after the oral administration of the capsules hampered the estimation of the  $\alpha$  and  $\beta$  rate constants. For many subjects the data did not support a 2-compartment model and the post-absorptive profiles were almost linear in the log-linear plots. This is reflected in the poor quality of some of the predicted versus measured profiles in and in some of the values obtained for pharmacokinetic parameters and is likely due to the impact of food and gastric transit time differences on absorption.

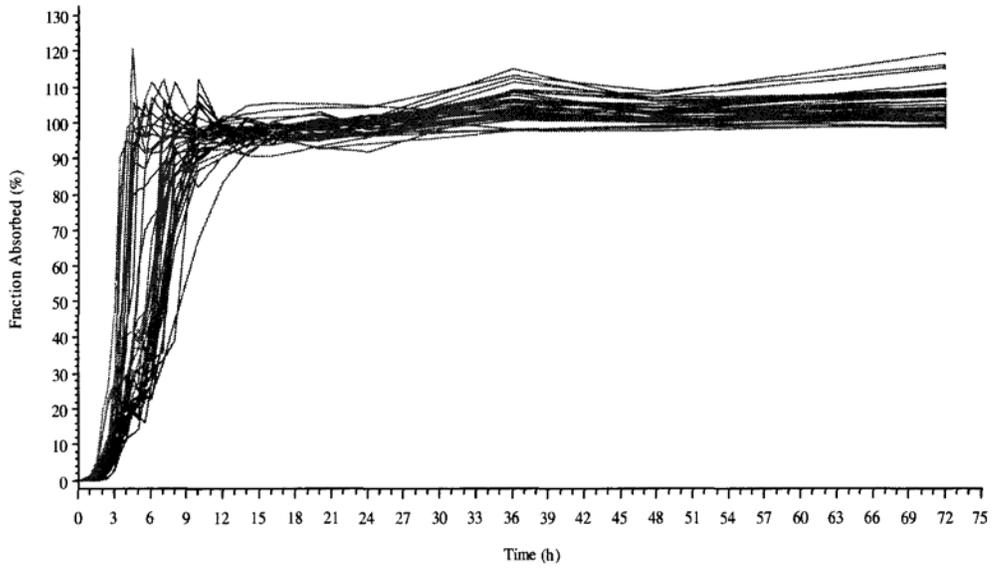
As a result, the cumulative absorption curves were of poor quality in quite a few instances:

- Subjects 05, 14, 19, 32, 39 and 53 for Treatment A
- Subjects 02, 04, 07, 10, 21, 23, 24, 27, 36 and 47 for Treatment B
- Subjects 09, 13, 22, 26, 31, 33, 41 and 52 for both treatments. These profiles were excluded from the estimation of the mean cumulative absorption curves and from the overlaid individual subject curves by treatment.

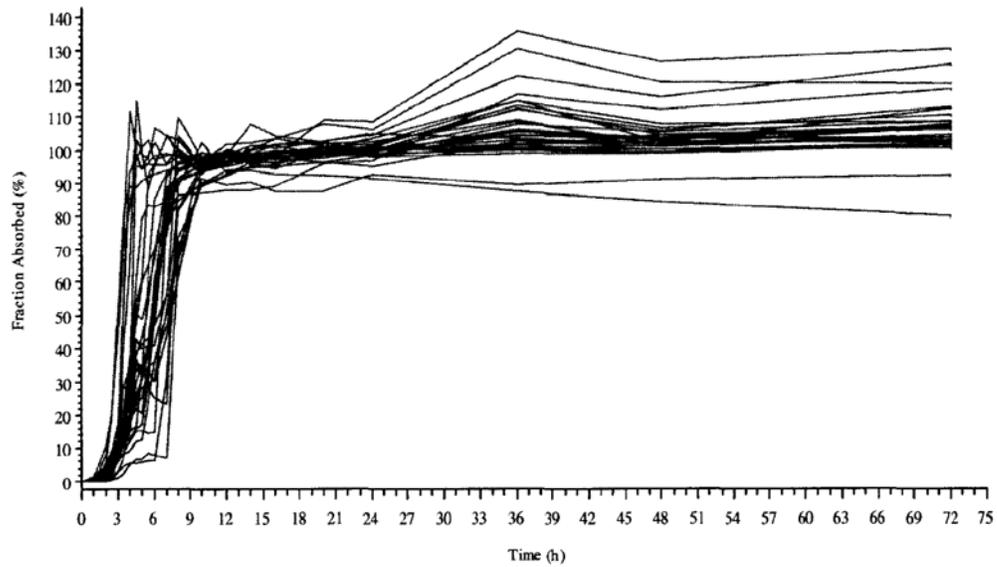
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Study 2006-1233  
Isotretinoin Cumulative Absorption Curves / Loo-Riegelman Approach  
Treatment A



Study 2006-1233  
Isotretinoin Cumulative Absorption Curves / Loo-Riegelman Approach  
Treatment B



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/s/

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Dennis Bashaw  
4/9/2007 11:09:56 AM  
BIOPHARMACEUTICS

Shiew-Mei Huang  
4/9/2007 11:46:01 AM  
BIOPHARMACEUTICS

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

**NDA:** 21-951

**GENERIC NAME:** Isotretinoin

**TRADE NAME:** UNKNOWN (currently  
CIP-ISOTRETINOIN)

**FORMULATIONS:** 10, 20, 30mg capsules

**APPLICANT:** Cipher Laboratories

**SUBMISSION DATES:** 6/27/05, 12/23/05, 2/1/06

**DRAFT REVIEW:** April 14<sup>th</sup>, 2006

**REVIEWER:** E. Dennis Bashaw, Pharm.D.

**OCPB DIVISION:** DCP-3

**CLINICAL DIVISION:** Division of  
Dermatologic and Dental Drug Products

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**1 Executive Summary**

**1.1 Recommendation**

The clinical pharmacology studies submitted in support of this NDA are incomplete as they do not fully establish a bio-bridge from the CIP-Isotretinoin capsule product back to the previous finding of safety and efficacy for the reference listed drug Accutane™ (Roche brand of isotretinoin). The data in this NDA does demonstrate that under fed conditions, the CIP-isotretinoin product has a similar rate and extent of

exposure as that of Accutane™. Under fasted condition, however, the products are markedly different. It is this difference, coupled with the known adverse event profile of isotretinoin that has prompted the Agency to question whether or not under the uncontrolled dietary settings of actual use if the CIP-isotretinoin product would have a different safety and efficacy profile. The clinical pharmacology information contained in this NDA cannot answer this question as the multiple dose studies were done under very controlled conditions related to diet, diet composition and the timing of meals in relation to dosing. All of the available in vivo biopharmaceutic information contained in the NDA suggests that under actual use conditions (where these dietary factors will vary from day to day) that the relatively good bioavailability under fasted conditions for the Cipher product (compared to Accutane™) would result in higher average blood levels over the course of therapy. Such increased levels were seen in one steady-state study (#441) where the C<sub>min</sub> value following once daily dosing was ~22% higher.

Absent any in vivo clinical trials to demonstrate the safety and efficacy of this drug product and without an established exposure-response relationship there appears to be insufficient data present in the application to establish the required bio-bridge to the reference product.

As a path forward, the sponsor could conduct a comparative population pk study in a suitably large number of subjects (>200) with severe recalcitrant nodular acne. The study would use pre-defined measures of comparability to demonstrate that the levels between the test and reference product are similar under real world conditions for a suitable duration. The actual design elements would have to be agreed on with the Agency and the Pharmacometrics group within the Office of Clinical Pharmacology prior to initiation. Depending on the results of this trial, a second trial with clinical safety and efficacy endpoints may be necessary if the variability seen in the data is deemed sufficient in the opinion of the reviewing clinical division to raise concern.

In addition to the suggested population pk trial, the sponsor will also need to address the issue of dosage form proportionality across their dosage strengths. The current NDA submission does not have an adequate determination of proportionality. As isotretinoin is dosed on a mg/kg basis and as it is expected that multiple dosage units will be used to obtain doses in the 0.5-1mg/kg range, then the relationship between the different strength capsules will need to be determined.

### ***1.2 Phase 4 Commitments***

None

### ***1.3 Summary of Clinical Pharmacology and Biopharmaceutic Findings***

The product that is the subject of this NDA is a new hard gelatin capsule formulation of isotretinoin. While it was submitted under the provisions of 505(b)(2), there is some concern that it should have been submitted as a “generic” under 505(j) as there appears to be no advantage to this product over any of the currently marketed forms.

(b) (4)

Current marketed isotretinoin products are poorly bioavailable and subjects are instructed to take the drug with meals. In the presence of a high fat meal, peak isotretinoin levels approach an approximate 3 fold increase. Initial discussions with

this sponsor regarding the product were predicated on a new (b) (4) dosage form that could be given at a lower mg per day dose and without regards to meals. (b) (4)

The present formulation consists of a solution/suspension of isotretinoin in a mixture of oils, fatty acid derivatives and non-ionic surfactant excipients with an antioxidant.

The current development program consisted of eight in vivo bioavailability trials (six single dose trials and two multiple dose trials) of which one single dose and one multiple dose trial are “legacy” trials from the earlier (b) (4) and are not the focus of the review in this package. All of the trials consisted of the Cipher product and direct comparisons to Accutane™ under fed and or fasted conditions and are listed below:

### 1.3.1 Single Dose Bioequivalence

<i>Single Dose Study Listing</i>
Study No. ISOPK.02.04 (02-444): An Open-Label, Single-Dose, Randomized, Two-Way Crossover, Food-Effect Bioavailability Study of Isotretinoin 30 mg Capsules (Cipher) in Healthy Subjects
Study No. ISOPK.02.03 (02-443): An Open-Label, Single-Dose, Randomized, Three-Way Crossover, Dose Proportionality Study of 5, 15 and 30 mg Cipher Isotretinoin Capsules in Healthy Subjects, Under Fed Conditions
Study No. ISOPK.03.04 (2003-627): An Open Label, Single-Dose, Four-Way, Randomized, Crossover Comparative Bioavailability of Two Formulations of Isotretinoin Capsules (Accutane™ vs. Cipher) in Healthy Volunteers Under Fed and Fasting Conditions as 2x20mg capsules.
Study No. ISOPK.04.02 (2004-727): A Single-Dose, Comparative Bioavailability Study of Two Formulations of Isotretinoin Capsules (Accutane™ vs. Cipher) 20 mg, Under Fed Conditions
Study No. ISOPK.04.03 (2004-734): A Single-Dose, Food Effect and Fed Comparative Bioavailability Study of Two Formulations of Isotretinoin Capsules (Accutane™ vs. Cipher) 10 mg in Healthy Volunteers
Study No. ISOPK.02.01 (02-441): An Open-Label, Single-Dose, Randomized, Three-Way Crossover, Relative Bioavailability Study of Cipher Isotretinoin Capsules (30 mg) Versus Accutane™ (40 mg) in Healthy Subjects, Under Fasting and Fed Conditions

As can be seen from the study listing above, the majority of the single dose comparative trials with the exception of study 627 were conducted under fed conditions. It has long been the policy of the Office of Clinical Pharmacology (and its predecessors) that fasted comparisons are the ones used for determination of bioequivalency as the effect of food, much like the use of surfactants in dissolution testing, can have the effect of masking differences. It has recently come to light that for some other drug products where the label does indicate that the reference product should be taken with food, that fed bioequivalence under the 505(b)(2) metric has been used as a route of approval. However, for Cipher, due to the magnitude of the food effect, the impact of it related to the bioavailability of other marketed products (i.e., currently generic forms of Accutane™ are required to demonstrate both fasted and fed equivalency), and the toxicity of isotretinoin, both comparisons (fasted and fed) should be given weight for Cipher’s approval in the absence of clinical safety and efficacy studies.

Although all of these studies contribute to the knowledge base for the proposed product, the only fasted in vivo bioequivalency characterization is contained in study 627 (i.e. it incorporates a fasted head-to-head comparison of the CIP-isotretinoin and

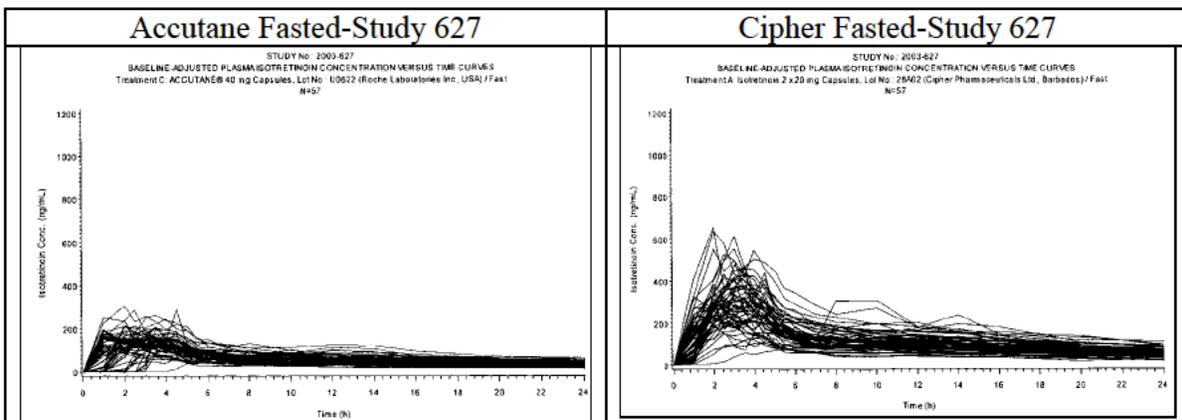
Accuane™ products). As seen below, the products do produce similar levels under fed conditions, but are demonstrably different under fasted conditions (comparison A vs. C):

**Summary Results**  
**Study 627-Pivotal Bioequivalency Study**  
**(baseline adjusted)**

Parameter	Treatment		Means		Type	Code	Ratio (%)	90% CI (%)
	Type	Trt*	Arithmetic (CV%)	Geometric				
AUC <sub>t</sub> (ng·h/mL)	T - Fast	A	4307.77 (29)	4110.64	T: Food Effect	B vs. A	152.07	142.49 – 162.29
	T - Fed	B	6400.04 (20)	6251.05	R: Food Effect	D vs. C	263.46	246.86 – 281.17
	R - Fast	C	2349.24 (29)	2245.49	T/R - Fast	A vs. C	183.06	171.53 – 195.37
	R - Fed	D	6145.81 (26)	5915.87	T/R - Fed	B vs. D	105.67	99.01 – 112.77
AUC <sub>inf</sub> (ng·h/mL)	T - Fast	A	4676.08 (28)	4470.45	T: Food Effect	B vs. A	149.78	140.52 – 159.66
	T - Fed	B	6858.70 (21)	6695.87	R: Food Effect	D vs. C	252.60	236.98 – 269.26
	R - Fast	C	2619.26 (30)	2500.01	T/R - Fast	A vs. C	178.82	167.76 – 190.60
	R - Fed	D	6561.62 (26)	6315.15	T/R - Fed	B vs. D	106.03	99.47 – 113.02
C <sub>max</sub> (ng/mL)	T - Fast	A	347.00 (35)	323.18	T: Food Effect	B vs. A	134.39	122.60 – 147.32
	T - Fed	B	466.43 (38)	434.33	R: Food Effect	D vs. C	267.53	244.05 – 293.28
	R - Fast	C	169.66 (29)	161.43	T/R - Fast	A vs. C	200.20	182.63 – 219.46
	R - Fed	D	471.32 (41)	431.88	T/R - Fed	B vs. D	100.57	91.74 – 110.24

\*A=Cipher Fasted, B=Cipher Fed, C=Accutane™ Fasted, D=Accutane™ Fed

This table shows both the impact that food has on Accutane™ levels (note the >2.5 fold increase of AUC and C<sub>max</sub> for Accutane™ in the presence of food) and the “relatively” reduced food effect (1.3-1.5 fold increase) seen with the Cipher product (although if approved it would still require food guidance in the label). Between the formulations there is a marked difference between the products under fasted conditions. As demonstrated in the following figures, isotretinoin is a highly variable drug, even under the influence of the “favorable” absorption conditions of a high fat meal:

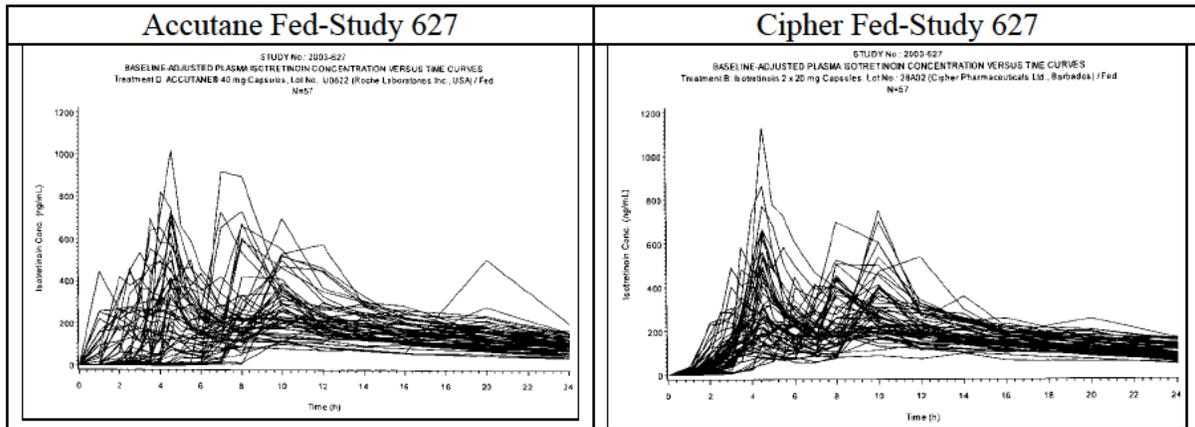


The co-administration of a high fat meal does (as would be expected) “homogenize” the absorption between the two products such that they are “equivalent”

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under these conditions. But if one only looks at the mean data, as presented in the table on the previous page, versus an examination of the actual individual plasma level time curves, the latter reveals a different picture, one showing an extreme degree of variability, even under fed conditions. Under fed conditions the Cipher product produces isotretinoin levels at an earlier time point than Accutane™ does. By 4 hrs all subjects in the Cipher arm had levels above background, while for Accutane™ absorption in some subjects were delayed out to 8 hrs in the presence of a meal.

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As noted earlier, the use of a fed treatment as a determination of bioequivalency is not a generally accepted methodology, although it has been used recently, on a case by case basis. Normally the use of fed treatments for bioequivalency testing is reserved for those drugs where bioavailability is so poor under fasted conditions that meaningful plasma concentration time profiles are not possible (i.e. some griseofulvin products). Clearly, although reduced, Accutane™ under fasted conditions produces meaningful plasma levels.

In addition, as part of their development program the sponsor did head-to-head bioavailability trials against Accutane™ using comparable strengths, under fed conditions. Surprisingly, even under these favorable conditions, the 20mg and 30mg Cipher products were inequivalent to the reference treatment with regards to Cmax. The sponsor in this case indicates that AUC and not Cmax is a determinate of clinical success and discounts the finding of inequivalency for Cmax, but provides no primary clinical data to bolster these assertions.

Study 727 and 441 Geometric Means

	Cipher	Accutane™	90% CI
Study 727 (20mg)			
AUCt	3554	3904	87.4-94.8
C <sub>MAX</sub>	215	270.3	73.5-86
T <sub>max</sub>	6.84	6.9	
Study 441(30mg normalized to 40mg)**			
AUCt	6770	6781	90.9-109.6
C <sub>MAX</sub>	512	624	71.9-93.6
T <sub>max</sub>	5.9	6.2	
**Cipher product administered as 1x30mg, Accutane™ administered as 1x40mg			

This finding of C<sub>max</sub> inequivalence, coupled with that of the lack of a demonstration of fasted bioequivalence, highlights the need of clinical studies to demonstrate the true nature and impact of the observed differences. This is compounded by the fact that isotretinoin, although markedly effective, carries with it significant safety risks that have not been fully understood in regards to onset and magnitude or for at-risk populations as in the case of psychiatric events.

During development, the sponsor was informed of this informational need (fasted bioequivalence and/ or clinical trials) in multiple face-to-face meetings with the Agency. Most notably at a guidance meeting on 4/28/04 (which itself refers to a 5/12/03 meeting, where similar information was conveyed to the sponsor), the relevant portion of the 4/28/04 meeting minutes (excerpted from DFS) are provided below:

**Sponsor's Question 2:**

Assuming that the additional studies are completed as described, and that the results are satisfactory, is the development plan described by Cipher Pharmaceuticals sufficient to support the filing of an NDA for 10, 20, and 30 mg CIP-Isotretinoin.

**Agency's Response:**

Regarding the completeness of the package, this is ultimately a review issue. From a bioequivalence standpoint, the pivotal in vivo bioequivalency trials are considered to be those under fasted conditions. This is done to minimize outside influences on the biopharmaceutics of the dosage form itself. While conceding that the current labeled recommendation is that isotretinoin be taken with food to enhance its bioavailability, the issue of fed vs. fasted bioequivalency testing has been discussed at upper levels of the Office of Clinical Pharmacology and Biopharmaceutics and the application of fasted bioequivalency testing in this situation has been confirmed. Other information as to product performance under other conditions may be taken into consideration by the reviewing Medical Officer in determining the need for additional or supplemental in vivo clinical trials as has previously been mentioned in communication with the Sponsor (minutes of 5/21/03 meeting).

Thus, the sponsor was made well aware of the Agency's concerns during their development program. They contend that their product should not have to demonstrate fasted bioequivalency as it was not developed to do so (and thus would not pass as a 505(j) application). While not claiming such an advantage (which would require in vivo clinical trials under 505(b)(2)), the development of this product has been predicated upon the minimization of the Accutane™ food effect as a *raison d'être*. As Accutane™ is capable of producing acceptable in vivo blood levels under fasted conditions, as this is a published policy of the Office of Clinical Pharmacology that the sponsor was made aware of (multiple times), and as the Office of Generic Drugs has required the approved isotretinoin generics to demonstrated fasted BE to Accutane™, it would appear that there is still an outstanding informational need under a 505(b)(2) rubric for this product in the area of clinical safety as the effect of diet would be expected to have a different impact on isotretinoin levels from CIP-isotretinoin than from Accutane™. It would seemingly be inappropriate to approve this drug, on the current informational database, and yet not approve a generic formulation that failed in the same manner, without some demonstrated

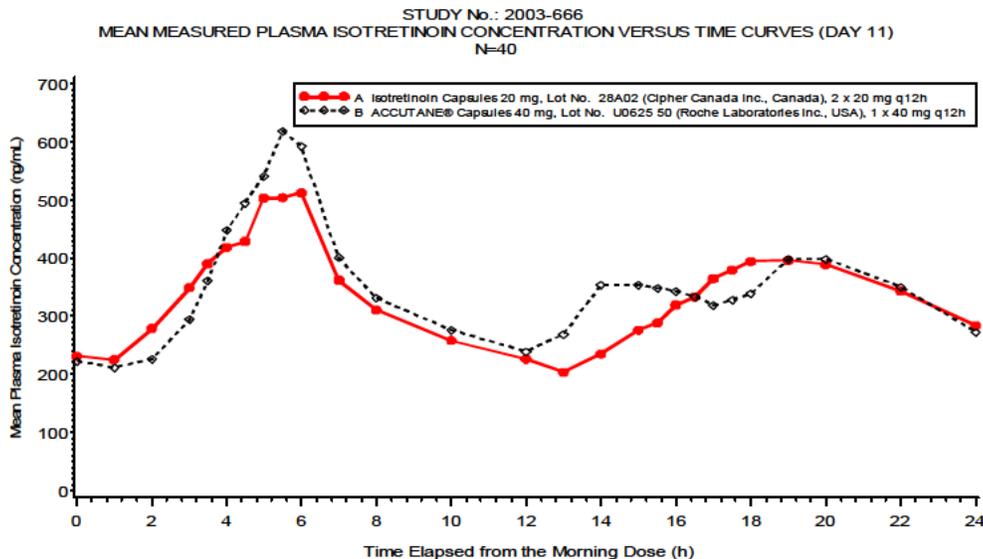
benefit in terms of safety and/or efficacy or a clinical study to delineate these safety concerns in an adequate fashion.

### 1.3.2 Multiple Dose Study Overview

Multiple Dose Study Listing
Study No. ISOPK.03.02 (2003-666): An Open-Label, Multiple-Dose, Randomized, Two-way Crossover, Relative Bioavailability Study of Cipher Isotretinoin Capsules (2 x 20 mg) versus Accutane(tm)® (40 mg) Administered as a 40 mg Dose Twice a Day, in Healthy Subjects, Under Fed Conditions
Study No. ISOPK.02.02 (02-442): An Open-Label, Multiple-Dose, Randomized, Two-Way Crossover, Relative Bioavailability Study of Cipher Isotretinoin Capsules (30 mg) Versus Accutane(tm)® (40 mg) in Healthy Subjects, Under Fed Conditions

The two multiple dose studies contained in this application were conducted to demonstrate the relative peak to peak comparisons of the Cipher product to Accutane™. The two studies differed in that Study 666 used equivalent doses of isotretinoin (40mg) while Study 442 used the highest individual capsule strengths (30mg for Cipher and 40mg for Accutane™). Both of these studies were unique, relative to most multiple dose pk trials, in that the subjects were housed for the entire treatment duration and were given a controlled diet.

Looking at the data from 666, as it requires no dose adjustment, the general pattern of blood levels is somewhat similar; however, the initial dosing interval of 0-12hrs does show a difference in peak blood levels, with the Accutane™ arm producing higher blood levels.



The sponsor has interpreted the results of both studies in a similar fashion, namely that as the peak-to-trough differences are less, this must convey some benefit-even though they cannot quantify what such a benefit would be. As noted with the single dose studies, the lack of supporting clinical data to demonstrate such a “benefit” is not provided.

Parameter	Interval (hours)	Geometric Means		Ratio of Geometric Means (%)	90% Confidence Interval (%)
		Arithmetic Means (CV%)			
		20mg CIPHER	20mg Accutane(tm)		
AUC <sub>tau</sub> (ng*h/mL)	0 – 12	3839.63 3946.30 (24)	3974.46 4120.57 (25)	96.61	92.56 – 100.84
	12 – 24	3755.33 3836.70 (23)	3955.89 4050.92 (21)	94.93	90.72 – 99.34
AUC <sub>24</sub> (ng*h/mL)	0 – 24	7616.47 7782.35 (23)	7958.80 8171.26 (22)	95.70	92.81 – 98.68
C <sub>max</sub> (ng/mL)	0 – 12	639.11 673.10 (30)	768.57 817.09 (34)	83.16	76.38 – 90.53
	12 – 24	518.95 534.22 (27)	582.09 600.71 (24)	89.15	81.71 – 97.28
	0 – 24	675.12 700.87 (26)	801.75 840.24 (30)	84.21	78.36 – 90.48

Ultimately, the steady-state data does not significantly impact the acceptance of this application, as they were done under such controlled conditions (i.e. confinement and fixed meals eaten in fixed relationship to dosing) that they do not properly represent the steady-state performance in clinical use. While it is true that the label does state that, “Accutane should be administered with a meal..” the DOSAGE and ADMINISTRATION section does not define the parameters of such a meal. The diet used in the FDA Food Effect trial is a high fat diet and was never intended to be used as a surrogate for a general dietary evaluation. The FDA high fat meal was designed to look at those extrinsic factors that can affect absorption and to maximize them. What the impact, for example, of a low fat, high carbohydrate, low protein diet or other type of diet is unknown. A concern that was presented to the sponsor again and again at meetings with them is the observation that the likely target audience (teenagers/young adults) often skip meals or eat nutritionally unbalanced meals such that generalizations regarding a so called “population” food effect around the results of the diet used here is impossible. As mentioned previously, the controlled housing and dietary conditions used here would tend to minimize any differences between the two products by controlling the primary variable of absorption, ie. diet. While this is also undeniably true for the Accutane™ treatment arm we do have clinical trials that have delineated the safety and efficacy of the approved product which we do not have for the CIPHER product.

Furthermore, in a previous NDA (NDA 21-177) that was the subject of an open advisory committee meeting for Accutane™ NF, a formulation also designed to minimize the effect of food and for once daily dosing, the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) called for additional clinical trials to assess psychiatric safety, studies that are lacking here.

### 1.3.3 Summary Conclusions

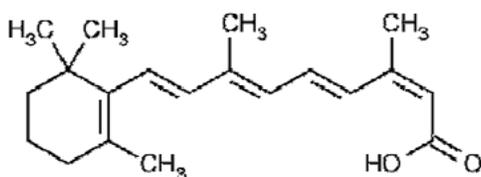
As has been noted previously, the sponsor has described the pharmacokinetics of their formulation isotretinoin under fed conditions. The sponsor has not adequately established a bridge between their product and the reference product Accutane™ under fasted conditions. Nor has the sponsor adequately addressed the issue of dose proportionality within the dosage range. Both of these issues would need to be fully delineated to allow for the proper use and dosing of this agent.

## 2 Question Based Review

### 2.1 General Attributes of the Drug

#### 2.1.1 What are the highlights of the chemistry and physico-chemical properties of isotretinoin drug substance and the Ciper Isotretinoin (CIP-ISOTRETINOIN) drug products?

Chemically, isotretinoin or 13-*cis*-retinoic acid, is 13-*cis*-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-*cis*-4-*trans*-6-*trans*-8-*trans*-nonatetraenoic acid.



It is a yellow to reddish-orange crystalline powder and has a molecular weight of 300.44. It is very poorly solubility (b) (4)

As noted previously the Ciper product is formulated as hard gelatin capsules containing isotretinoin (b) (4)

Based on analysis of six batches, approximately (b) (4) of the isotretinoin dose is dissolved in the capsule.

	Amount per Batch of	Amount per Batch of	Amount per Batch of (b) (4)
<b>Ingredient and Test Standard</b>	<b>Strength:</b>	<b>Strength:</b>	<b>Strength:</b>
Isotretinoin USP	10 mg	20 mg	30 mg
Stearoyl Macroglycerides (b) (4)	(b) (4)		
Soybean Oil, USP	(b) (4)		
Sorbitan Monooleate, NF (SPAN 80)	(b) (4)		
Propyl Gallate, NF (b) (4)	(b) (4)		

\*\*\*Note in this table the 30mg capsule data is for (b) (4) capsules, thus the amounts are (b) (4) of what would be present in an individual unit.

The sponsor has proposed (b) (4)

They are proposing a specification (b) (4) At the time of this review neither this reviewer nor the reviewing chemist supported the adoption of this method. The chemist in their review has highlighted a number of problems with this method, including the lack of supporting data showing the need for the added substances in the media. An acceptable dissolution method remains an outstanding issue.

### 2.1.2 What is the proposed mechanism of action of isotretinoin

Isotretinoin is a synthetic vitamin A analog marketed by Roche Pharmaceuticals under the brand name Accutane™. As such it shares with vitamin A much of the latter's activity regarding cellular regulation and secretory regulation. In vivo, isotretinoin has been shown to decrease the production of sebum via a reduction in sebaceous gland size and cellular differentiation. Although the drug substance is synthetic, isotretinoin itself is present in humans at low levels as a metabolite of tretinoin.

Therapeutically, isotretinoin is highly effective in the treatment of nodular cystic acne, a severe disfiguring form of the common acne vulgaris. Experience with the current marketed forms of isotretinoin (Accutane™ and generics) has demonstrated that only one or two courses of therapy of up to 1mg/kg per day for 20 weeks can result in lasting clearing of the skin. As a vitamin A analog Accutane™ is also a very potent teratogen and carries a black box warning requiring patient counseling, dual contraceptive methods, and monitoring of pregnancy status prior to and during drug use. Because of its known teratogenic effects isotretinoin is required to have a pregnancy prevention program in place. The current program, re-designed as of 3/1/06, is entitled iPLEDGE (<http://www.ipledgeprogram.com>).

### **2.1.3 What is the proposed indication?**

The indications for *CIP-ISOTRETINOIN* are identical to that of the innovator (Accutane™) and its generics. It is indicated for the treatment of severe recalcitrant nodular acne. (Nodules are inflammatory lesions with a diameter of 5 mm or greater. The nodules may become supportive or hemorrhagic.) “Severe,” by definition, means “many” as opposed to “few or several” nodules. It is **NOT** indicated and should not be used in the treatment of common acne or *Ance Vulgaris*.

### **2.1.4 What are the proposed dosing regimens for Isotretinoin?**

The recommended dosage range for *CIP-ISOTRETINOIN* is 0.5 to 1.0 mg/kg/day given in two divided doses with food for 15 to 20 weeks. From the Accutane™ package insert, studies comparing 0.1, 0.5, and 1.0 mg/kg/day found that all dosages provided initial clearing of disease, but there was a greater need for re-treatment with the lower dosages. During treatment, the dose may be adjusted according to response of the disease and/or the appearance of clinical side effects - some of which may be dose related. Adult patients whose disease is very severe with scarring or is primarily manifested on the trunk may require dose adjustments up to 2.0 mg/kg/day, as tolerated.

Although commonly used in the community, the safety and efficacy of once daily dosing with *CIP-ISOTRETINOIN* has not been established. Once daily dosing is **not** recommended.

If the total nodule count has been reduced by more than 70% prior to completing 15 to 20 weeks of treatment, the drug may be discontinued. After a period of 2 months or more off therapy, and if warranted by persistent or recurring severe nodular acne, a second course of therapy may be initiated.

The optimal interval before retreatment has not been defined for patients who have not completed skeletal growth. Long-term use of isotretinoin, even in low doses, has not been studied, and is not recommended. It is important that *CIP-ISOTRETINOIN* be given at the recommended doses for no longer than the recommended duration. The effect of long-term use of isotretinoin on bone loss is unknown (all isotretinoin products carry warnings for bone mineral density, hyperostosis, and premature epiphyseal closure).

## **2.2 General Clinical Pharmacology**

### **2.2.1 What are the design features of the pivotal clinical trials?**

There were no in vivo clinical trials conducted in support of this application.

### **2.2.2 What is the basis for selecting the response endpoints?**

The studies conducted were in vivo pk only and no response endpoints were monitored.

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

Yes, in this NDA the sponsor provided in vivo pk data on the parent isotretinoin and its metabolites tretinoin, 4-oxo-isotretinoin, and 4-oxo-tretinoin. Primary

determination of bioequivalency was based upon the parent isotretinoin per the FDA General BA/BE Guidance document. The analytical method used was a liquid chromatographic tandem mass spectrometric method for the determination of Isotretinoin, Tretinoin, 4-Oxo-isotretinoin and 4-Oxo-Tretinoin in human plasma by (b) (4). The method used another retinoid, Acitretin (b) (4), as the internal standard. The procedure has demonstrated the following performance characteristics in their validation study:

Lower limit of Quantitation-all species	1ng/mL
Concentration Range-all species	1-500ng/mL
Correlation Coefficient	≥0.999

Individual assay performance data was submitted for each trial.

#### 2.2.4 Exposure-response

As noted above, the studies in this NDA did not include clinical endpoints of acne lesion counts, or clearing. In the current trials, little useable safety data was generated due to the relatively short duration of most of the trials (i.e. single dose). Of the two multiple dose trials 666 and 442 some safety data was generated in the pattern of adverse events reported.

Specifically, there were 302 adverse events (AEs) in Study 666. Of them the top 10 are listed in the following table by treatment.

Top 10 ADRs(#)-Study 666

Cipher 2x20mg BID		Accutane™ 40mg BID	
dry lips (26)		headache (36)	
headache (25)		dry lips (31)	
dry skin (9)		dry skin (13)	
diarrhea (7)		metallic taste in mouth (6)	
dry skin on face (4)		elevated ALT (6)	
nose bleed (4)		elevated AST (5)	
elevated blood pressure (3)		elevated blood pressure (4)	
sore throat (3)		eye irritation (4)	
dry and cracked lips (2)		elevated gamma GT (3)	
flatulence (2)		diarrhea (3)	
Total:	<b>128</b>	Total:	<b>174</b>

Of these dry lips and headaches represent almost 40% of the total ADRs seen in this study. All of the observed ADRs in this study are consistent with treatment isotretinoin, and are similar to the effects of Hypervitaminosis A. According to the sponsor the elevated AST, ALT and GGT levels returned to normal following discontinuation.

In study 442, where a lower total daily dose of isotretinoin was used, the adverse events were less severe (253)

Cipher 30mg QD		Accutane™ 40mg QD	
headache (11)		headache (10)	
dry skin (10)		pain (8)	
pruritus (9)		dry mouth (8)	
dry mouth (7)		rash (9)	
rash (6)		pruritis (5)	
asthenia (6)		dry skin (4)	
headache intermittent (4)		asthenia (4)	
acne (3)		insomnia(4)	
conjunctivitis (3)		conjunctivitis (4)	
nose bleed (3)		constipation (3)	
Total:	<b>127</b>	Total:	<b>126</b>

While these studies were not designed to collect truly meaningful safety data, due to both their small size and limited duration of dosing, the ADRs do tend to replicate what is seen with Accutane™’s package insert. The difference in the relative ranking of the events and their numbers are likely due to the higher dose used in study 666, as study 442 is a legacy study from the (b) (4) program previously referenced. No particular ADR stood out as being unusual in these two studies.

#### **2.2.4.1 A note on Psychiatric Adverse Events**

As has been noted previously, the bulk of the pharmacokinetic trials in this application were single dose trials. Isotretinoin use has been associated with mood changes and psychiatric disturbances and has been the subject of an open advisory committee meeting and labeling revisions. In looking at the subjects participating in the two multiple dose trials a number of subjects in the CIP-Isotretinoin arm were discontinued for psychiatric reasons including “feelings of rage” and actual physical harm to oneself (i.e. one subject repeated beat the wall with their fists until restrained). Although again recognizing that these trials were not powered sufficiently to establish a reliable estimate of rate of psychiatric events, their mere presence in relatively small trials of limited duration (<2 weeks) require additional consideration. The affected volumes from the pk section of the NDA were delivered to the reviewing medical officer Dr. Denise Cook who will cover these events in her review/summary memo.

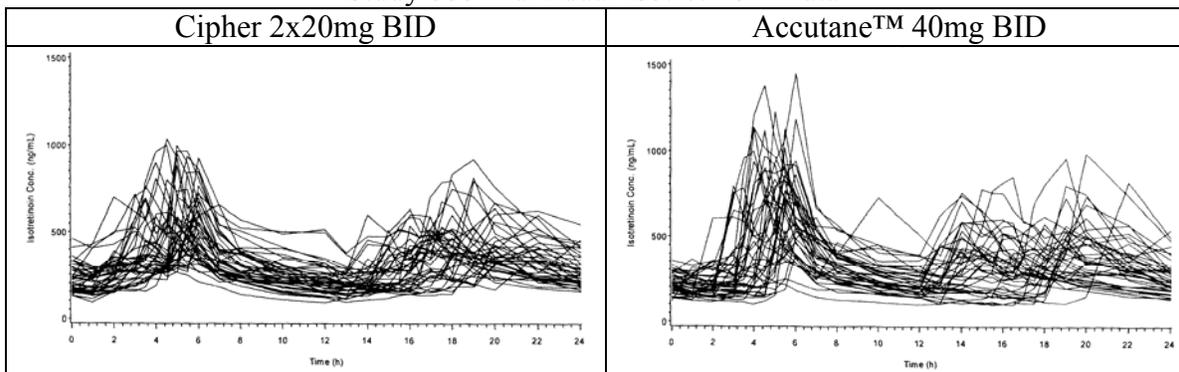
#### **2.2.5 Pharmacokinetic characteristics**

##### **2.2.5.1 What are the single dose and multiple dose PK parameters?**

As noted previously, this NDA contained the results of eight in vivo clinical pharmacology/biopharmaceutic studies (six single dose and two multiple dose). Of these seven studies were reviewed as part of this NDA. All of these studies were primarily designed as fed treatment studies, with only occasional fasted treatments. The pivotal trial in this application is study 627 which compares the Cipher product to Accutane™ under both fed and fasted conditions. As the single and multiple dose data has previously been summarized in sections 1.3.1 and 1.3.2, these results will not be repeated here.

In general the single dose pharmacokinetics of isotretinoin are similar to that of Accutane™ under the influence of a high fat meal. As noted previously, the FDA High Fat meal was intended not as a general test, but as a test that would stress a dosage form. The unanswered question here is, for a drug that has a significant food effect in the presence of high amounts of fat, how this variability plays out in a real world setting, with real diets and timings of meals that change from day to day

Study 666-Individual Isotretinoin Data



Clearly, even in this study where the subjects were given a fixed diet, there is still a significant amount of variability in the dataset. As this data is under fed conditions which tend to homogenize differences in absorption, the effect of a low fat meal or fasted conditions can have a major impact on absorption and thus tolerability. Considering the observed safety data from the previous section under controlled conditions, it is likely that the adverse event profile will be markedly different, due to the designed differences in the CIPHER products drug release. As the sponsor has not been able to demonstrate fasted bioequivalence, it is clear that properly designed and powered clinical trials are needed as having both fasted and fed bioequivalence would give one a higher degree of assurance that the safety data from Accutane™ could be extrapolated to the CIPHER product.

**2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?**

Acne, as an inflammatory skin condition, has not been shown to affect the pharmacokinetics of orally administered isotretinoin. All of the PK studies done in support of this NDA were done in normal volunteers.

**2.2.5.3 What are the characteristics of drug absorption?**

As noted above, the absorption of isotretinoin is highly influenced by the presence of a high fat meal. This is most likely due to its high degree of lipid solubility, however, the effects of other meal compositions on in vivo bioavailability have not been systematically evaluated. In this NDA the sponsor used a rather unusual high fat meal in their studies instead of either of the FDA recommended diets. Specifically they used:

- (1) Regular Bagel with 3 tablespoons of peanut butter
- (5) Slices of Bacon

- (1) Dutchie Donut (~230calories, 6gms fat, 40gms carbohydrate-<http://www.timhortons.com>)  
 (6) Fluid Ounces of Apple Juice

**2.2.2.5.4 What are the characteristics of drug distribution?**

No specific binding studies were done in support of this NDA, however, from the literature, in vitro, isotretinoin is 99.9% bound to plasma proteins, principally albumin, at plasma drug concentrations of 0.08-2.3 mcg/mL. Isotretinoin does not appear to be displaced from binding sites by its metabolites. Given its high degree of lipophilicity, it is likely that isotretinoin is widely distributed throughout the body.

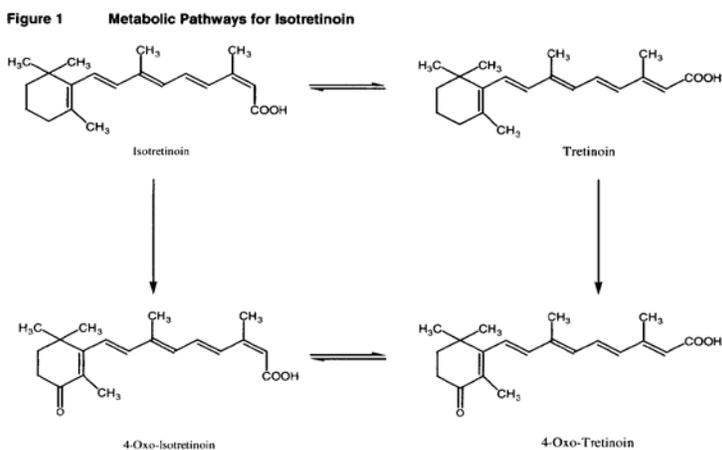
**2.2.2.5.5 Mass Balance Study**

No mass balance study was conducted. The Accutane(tm) package insert indicates that roughly equal amounts of radiolabeled isotretinoin are recovered in the urine and feces.

**2.2.2.5.6 What are the characteristics of isotretinoin metabolism?**

Following oral administration of isotretinoin, at least three metabolites have been identified in human plasma: 4-oxo-isotretinoin, retinoic acid (tretinoin), and 4-oxo-retinoic acid (4-oxo-tretinoin). Retinoic acid and 13-cis-retinoic acid are geometric isomers and show reversible interconversion. Thus, the administration of one isomer will give rise to the other. Isotretinoin is also irreversibly oxidized to 4-oxo-isotretinoin, which forms its geometric isomer 4-oxo-tretinoin.

Throughout this NDA the primary pharmacokinetic focus is upon isotretinoin. While it is true that 4-oxo-isotretinoin is present in the plasma in amounts 2-5 times that of isotretinoin, it only has 10% of the activity of the parent compound in in vitro models. The other two metabolites, present at low levels, are half as active as isotretinoin. The clinical significance of these models is unknown.



While this sponsor has not undertaken any evaluation of metabolic routes, the Accutane(tm) Package Insert contains the following information:

In vitro studies indicate that the primary P450 isoforms involved in isotretinoin metabolism are 2C8, 2C9, 3A4, and

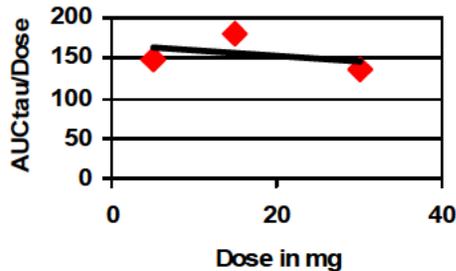
2B6. Isotretinoin and its metabolites are further metabolized into conjugates, which are then excreted in urine and feces.

**2.2.5.7 What are the characteristics of isotretinoin excretion?**

See Mass Balance above.

**2.2.5.8 Based on pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the isotretinoin dose-concentration relationship?**

The sponsor has not conducted a dose-proportionality study with their current formulation. An earlier dose proportionality study (study 443), done when the sponsor was still pursuing a (b) (4) dosage form used a 5, 15, and 30mg capsules. Of these the 5 and 15mg capsules were replaced with a 10 and 20mg capsule in the study program, once the proposed (b) (4) program was abandoned. The results of this study, while not strictly related to this application demonstrated a lack of dose proportionality between the strengths.



This is especially disturbing as the formulation uses varying amounts of the same (b) (4) for each strength, thus the capsules would be expected to be dose proportional. The lack of dose proportionality is a problem as it indicates that interchange between dosage units is not possible as there would be a difference in exposure related to how it is dosed (i.e. 2x10mg vs. 1x20mg). To demonstrate the degree of “confusion” in the data the sponsor presented the following table in their report where A=5mg, B=15mg, and C=30mg (“=” represents bioequivalent):

Isotretinoin  
AUCi C < B B > A C = A  
Cmax C < B B > A C > A

4-oxo-isotretinoin  
AUCi C < B B > A C > A  
Cmax C < B B > A C > A

Tretinoin  
AUCi C < B B < A C < A  
Cmax C < B B > A C = A

The sponsor’s conclusion from this trial is ...”that the results are contradictory and no clear trend can be defined”, for a drug product that is dose on a mg per kg body weight basis, dose proportionality would be crucial to the understanding of dosing, especially in the absence of in vivo clinical data of the products safety and efficacy. There is no head to head comparison across all three dosage strengths in the current NDA.

The sponsor has attempted to deal with this lack of information by conducting a series of single dose in vivo bioavailability studies of each of their strengths to the corresponding Accutane™ capsule, except for their 30mg capsule which is compared in a dose normalized fashion to the 40mg Accutane™ formulations. All of these trials demonstrated that under FED conditions the products produced a similar exposure to that of Accutane™, but peak level for the 20 and 30mg capsules were not equivalent to their Accutane™ comparators under fed conditions.

Cross-Study Summary of Dose Proportionality Data  
Geometric Means-FED Data ONLY

	Cipher	Accutane™	90% CI
Study 734 (10mg)			
AUCt	1981.2	1990.8	92.8-106.7
C <sub>MAX</sub>	125.6	124.3	90.2-113
T <sub>max</sub>	6.83	7.31	
Study 727 (20mg)			
AUCt	3554	3904	87.4-94.8
C <sub>MAX</sub>	215	270.3	73.5-86
T <sub>max</sub>	6.84	6.9	
Study 627 (40mg)*			
AUCt	6251	5915	99-112.7
C <sub>MAX</sub>	434	431	91.7-110
T <sub>max</sub>	6.85	6.75	
Study 441(40mg normalized)**			
AUCt	6770	6781	90.9-109.6
C <sub>MAX</sub>	512	624	71.9-93.6
T <sub>max</sub>	5.9	6.2	

\*Cipher product administered as 2x20mg as a single dose

\*\*Cipher product administered as 1x30mg, Accutane™ administered as 1x40mg

While true dose proportionality is not common, usually a lack of dose proportionality is consistent in that both AUC and C<sub>max</sub> track each other. As noted above the lack of comparability across parameters and strengths is again disturbing and suggests again that the fasted comparison of the Cipher product to the reference Accutane™ is a necessary component to understand the dosing of this formulation. The most likely cause of this “apparent” lack of dose proportionality is the poor solubility of isotretinoin in aqueous media. A similar lack of dose proportionality is seen across these studies for Accutane™, and the nature of a cross study comparison such as this does have limitations. In any event, demonstration of dose proportionality would be a component of an NDA with a range of doses. The lack of such a determination here, coupled with the in vivo trial using slightly lower doses, represents an informational gap in this application.

***2.2.5.9 How do isotretinoin pharmacokinetic parameters change with time following chronic dosing?***

There is not a direct comparison between the single dose and steady-state pharmacokinetics of isotretinoin in this application, nor is there any reference to such data in the Accutane™ package insert. Examination of the data generated in this NDA (using the 20mg data from single dose study 727 and the multi-dose study 666 (2x20mg BID)) shows that there is a less than expected increase in Cmax and AUC. Using the single dose half-life estimate of ~19hrs, it would be expected that with twice daily dosing that drug accumulation or “R” would approximately 2.8. Instead for Cmax the observed increase is only 1.6 and for AUC it is ~0.98. This fall off in accumulation is most likely due to the aforementioned lack of dose proportionality cited in section 2.2.5.8 and is due to the poor solubility of isotretinoin in the GI tract. As noted earlier, this falling off in bioavailability has implications for dosing in that increasing the dose will not result in proportional changes in concentration, re-inforcing the fact that dosing of isotretinoin must be individualized to the patient.

**2.2.5.10 What is the inter- and intra-subject variability of pharmacokinetic parameters in volunteers, and what are the major causes of variability.**

The inter-subject variability in pharmacokinetic parameters with isotretinoin is approximately 30-60% for isotretinoin and its metabolites. Using the fasted data from study 627 (2x20mg Cipher fed vs. Accutane 40mg fed) we have the following estimates of inter subject variability for parent and metabolites for both treatment arms:

Study 627 Variability (N=55)-FASTED DATA ONLY

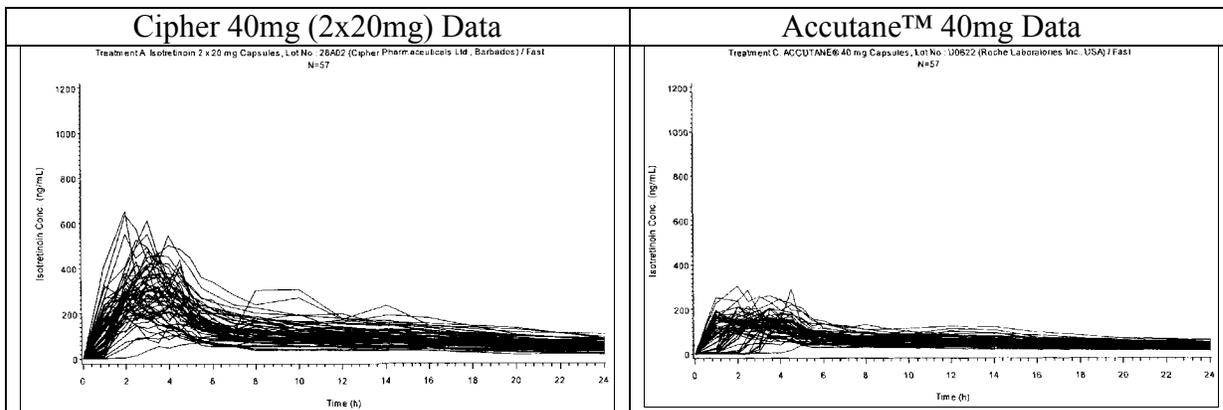
Inter Subject (%CV)	Cipher			Accutane™		
	AUCt	AUCinf	Cmax	AUCinf	AUCt	Cmax
Isotretinoin	29	28	35	29	30	29
4-oxo-isotretinoin	33	43	39	33	46	35
Tretinoin	68	68	69	67	69	60
4-oxo-tretinoin	153	75	109	231	109	150

Between the two formulations the inter subject variability in pk parameters is comparable, with increased variability being seen in the downstream metabolites-as one would expect.

As for intra subject variability, the relatively large number of subjects in this trial (N=55) is reflected in the relatively low intra subject variability. The one exception to this being the 4-oxo-tretinoin value for AUCt. As noted above as the 4-oxo-tretinoin is a tertiary metabolite, it would be expected to have a higher degree of variability in its parameters.

Intra Subject (%CV)	Pooled		
	AUCt	AUCinf	Cmax
Isotretinoin	21	21	30
4-oxo-isotretinoin	28	31	31
Tretinoin	33	34	42
4-oxo-tretinoin	110	42	49

Examination of the raw data from this trial shows that there is quite a degree of variability in Tmax (~50%) for both products. Suggesting again that the relatively poor absorption of isotretinoin is being reflected not only in the AUC and Cmax but in the Tmax values which may play a role in the time course of adverse events.



## 2.3 Intrinsic Factors

### 2.3.1 What intrinsic factors influence exposure or response to isotretinoin? What is the impact of these factors on exposure and response?

The sponsor did not systematically evaluate any intrinsic factors in their NDA. At this reviewer's request, a secondary analysis using gender as a covariate was undertaken by the sponsor. Most of the following information, here for completeness only, has been extracted from the literature or from the Accutane(tm) package insert or both.

### 2.3.2 Based on what is known about exposure-response relationships, what dosage regimen adjustments, if any, are recommended for each subgroup listed below?

#### 2.3.2.1 Elderly

Acne Vulgaris is not a condition that occurs in elderly subjects, as such isotretinoin is rarely used in subjects over the age of 50. The current package insert for Accutane(tm) contains the following general warning in the *Geriatric Use* sub-section of Warnings:

*Clinical studies of isotretinoin did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Although reported clinical experience has not identified differences in responses between elderly and younger patients, effects of aging might be expected to increase some risks associated with isotretinoin therapy*

Should this application ever become approvable, similar wording should be incorporated into the package insert.

### 2.3.2.2 Pediatric Patients

As the appearance of Acne Vulgaris occurs after puberty, there is no expected pediatric use below the age of 12. The Accutane(tm) package insert contains data from a study in pediatric subjects between the ages of 12 and 15. In this study no statistically significant differences were noted between these subjects and adults in the same study.

### 2.3.2.3 Gender

Due to the large number of female subjects enrolled in this NDA the sponsor was asked to undertake a secondary analysis of the data using gender as a covariate. Of the six trials 441, 442, 627, and 734 were found to have a significant gender enrollment. Of these four trials, approximately 36% of the subjects were female (57/165). Study 627 had the largest female enrollment (20) and as it was the study that incorporated the only single dose fasted comparison in the NDA, the data from it was selected by this reviewer for inclusion here (summary tables for the other studies are attached with the respective study reports in the Appendix.)

As noted previously, study 627 was a four-way crossover study comparing 2x20mg of the Cipher product to a single 40mg dose of Accutane™ under both fed and fasted conditions. An analysis of variance was applied to the log-transformed AUCs and Cmax data with GENDER as the single factor.

Study 627-Gender Alone

Treatment	Parameter	Gender	n	Arithmetic		Analysis for Gender	
				Mean	CV%	Geometric Mean	Test for Gender (Prob > F)
A	AUCinf	Female	20	4853.08	27	4690.25	0.41082
		Male	37	4580.40	29	4371.92	
	AUCt	Female	20	4386.05	29	4213.40	0.70232
		Male	37	4265.45	29	4076.07	
	Cmax	Female	20	350.76	39	329.70	0.86188
		Male	37	344.97	34	323.85	
C	AUCinf	Female	20	2669.57	32	2529.01	0.86903
		Male	37	2592.06	28	2493.51	
	AUCt	Female	20	2383.80	33	2255.62	0.98014
		Male	37	2330.56	27	2250.92	
	Cmax	Female	20	173.10	36	162.16	0.92761
		Male	37	167.81	24	163.36	

For each treatment, the number of subjects, the arithmetic means and the inter-subject coefficient of variation (CV%) are presented by gender within each pharmacokinetic parameter. The next two columns present the geometric means and the calculated probability for the significance of gender effect. Preliminary analysis of these results indicate that using GENDER as a covariate does not reveal a significant difference in this dataset. Similar results were obtained for the fed treatment legs in the other studies.

However, due to the intrinsic difference in the weight between males and females combined with the fact that in all these studies the dose was constant across all subjects; a second analysis was performed where WEIGHT was added as a covariate.

### Study 627-Gender and Weight

Treatment	Parameter	Gender	n	Arithmetic		Analysis for Gender and Weight		
				Mean	CV%	Geometric Mean	Test for Gender (Prob > F)	Test for Weight (Prob > F)
A	AUCinf	Female	20	4853.08	27	4382.08	0.73369	0.07119
		Male	37	4580.40	29	4535.52		
	AUCt	Female	20	4386.05	29	3895.70	0.39144	0.03983
		Male	37	4265.45	29	4252.51		
Cmax	Female	20	350.76	39	277.71	0.02646	0.00007	
	Male	37	344.97	34	355.32			
C	AUCinf	Female	20	2669.57	32	2398.64	0.51374	0.16519
		Male	37	2592.06	28	2565.88		
	AUCt	Female	20	2383.80	33	2117.30	0.34102	0.08815
		Male	37	2330.56	27	2329.25		
Cmax	Female	20	173.10	36	138.28	0.00248	0.00000	
	Male	37	167.81	24	178.05			

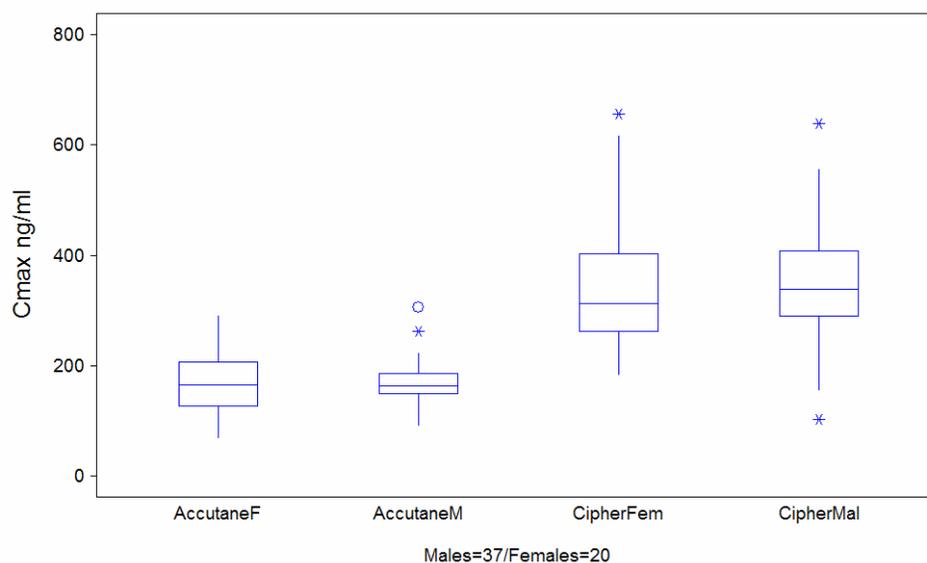
In this analysis a statistical difference was noted in the Cmax values for both fasted treatments in the study. The fact that this finding is not repeated in the fed treatment legs for either this study or the other three studies speaks to the sensitivity of the fasted dataset in uncovering differences in the dataset.

	AccutaneF	AccutaneM	CipherF	CipherM
N	20	37	20	37
Lo 95% CI	143.91	154.16	287.27	305.68
Mean	173.10	167.80	350.76	344.70
Up 95% CI	202.29	181.44	414.25	383.72
SD	62.368	40.914	135.66	117.04
Variance	3889.8	1674.0	18404	13698
SE Mean	13.946	6.7263	30.335	19.241
C.V.	36.031	24.383	38.676	33.954
Minimum	68.740	92.700	183.62	103.00
1st Quartiles	122.50	144.76	258.94	281.53
Median	165.43	162.67	311.93	337.91
3rd Quartiles	211.19	188.49	438.47	415.02
Maximum	290.15	305.92	655.90	638.17

In terms of variability, under fasted conditions, it appears that the Cipher product is more variable, in terms of Cmax, than Accutane is. Suggesting that while the Cipher product may have an “improved” bioavailability profile; it is still subject to significant variability in the fasted state.

### Box and Whisker Plot-Study 627

FASTED DATA ONLY



As to the clinical significance of this finding, as isotretinoin is dosed on a mg/kg basis, unlike the studies here, it is unlikely that these differences would be clinically detectable. Again, the results of the gender analysis clearly indicate that dose adjustment and individualization is needed with this drug, no matter which formulation is used.

#### **2.3.2.4 Race**

No systematic studies of the impact of race on the pharmacokinetics of isotretinoin have been undertaken.

#### **2.3.2.5 Renal impairment**

Currently, there is no renal impairment data in the current Accutane(tm) package insert. No studies have been done to date in this population.

#### **2.3.2.6 Hepatic impairment**

Currently, there is no hepatic impairment data in the current Accutane(tm) package insert. No studies have been done to date in this population.

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

As noted previously, isotretinoin is a potent teratogen (it is a CATEGORY X drug) and is the subject of a stringent pregnancy prevention program called iPLEDGE. The proposed package insert contains a black box for pregnancy and if approved either participation in the iPLEDGE or an equally restrictive program will be mandatory.

### **2.4 Extrinsic Factors**

#### **2.4.1 What are the extrinsic factors that influence exposure or response?**

#### **2.4.2 Drug-drug interactions**

No drug-drug interaction trials were conducted with the proposed dosage form. The Accutane™ package insert contains the following warnings:

- **Vitamin A:** Because of the relationship of Accutane(tm) to vitamin A, patients should be advised against taking vitamin supplements containing vitamin A to avoid additive toxic effects.
- **Tetracyclines:** Concomitant treatment with Accutane(tm) and tetracyclines should be avoided because Accutane(tm) use has been associated with a number of cases of pseudotumor cerebri (benign intracranial hypertension), some of which involved concomitant use of tetracyclines.
- **Micro-dosed Progesterone Preparations:** Micro-dosed progesterone preparations ("minipills" that do not contain an estrogen) may be an inadequate method of contraception during Accutane(tm) therapy. Although other hormonal contraceptives are highly effective, there have been reports of pregnancy from female patients who have used combined oral contraceptives, as well as transdermal patch/injectable/implantable/vaginal ring hormonal birth control products. These reports are more frequent for female patients who use only a single method of contraception. It is not known if hormonal contraceptives differ in their effectiveness when used with Accutane(tm). Therefore, it is critically important for female patients of childbearing potential to select and commit to use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form (see **PRECAUTIONS** ).
- **Norethindrone/ethinyl estradiol:** In a study of 31 premenopausal female patients with severe recalcitrant nodular acne receiving OrthoNovum® 7/7/7 Tablets as an oral contraceptive agent, Accutane(tm) at the recommended dose of 1 mg/kg/day, did not induce clinically relevant changes in the pharmacokinetics of ethinyl estradiol and norethindrone and in the serum levels of progesterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Prescribers are advised to consult the package insert of medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products.
- **St. John's Wort:** **Accutane(tm) use is associated with depression in some patients (see WARNINGS : Psychiatric Disorders and ADVERSE REACTIONS : Psychiatric )**. Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort.
- **Phenytoin:** Accutane(tm) has not been shown to alter the pharmacokinetics of phenytoin in a study in seven healthy volunteers. These results are consistent with the in vitro finding that neither isotretinoin nor its metabolites induce or inhibit the activity of the CYP 2C9 human hepatic P450 enzyme. Phenytoin is known to cause osteomalacia. No formal clinical studies have been conducted to assess if there is an interactive effect on bone loss between phenytoin and Accutane(tm). Therefore, caution should be exercised when using these drugs together.
- **Systemic Corticosteroids:** Systemic corticosteroids are known to cause osteoporosis. No formal clinical studies have been conducted to assess if there is an interactive effect on bone loss between systemic corticosteroids and Accutane(tm). Therefore, caution should be exercised when using these drugs together.

### ***2.4.3 What issues related to dose, dosing regimens, or administrations are unresolved and represent significant omissions?***

As noted previously, the regulatory status of this application as a 505(b)(2) application is still in question, the sponsor is attempting to demonstrate sameness between its product and Accutane™. The key issue that is the subject of debate is whether or not the sponsor should have conducted their key in vivo pk studies under fasted or fed conditions. This issue has been reviewed previously in section ***1.3.1 Single Dose Bioequivalence***

Beyond this issue, and the issue of a lack of clinical trials, the lack of a demonstration of dose proportionality is a problem that normally could be handled through labeling. In this case, as there was an expectation of equivalence, based on the formulation, and given that there is even for Accutane™ a tailing off of bioavailability, the sponsor should be required to demonstrate the degree (or lack of) single dose fasted dose proportionality.

## ***5 General Biopharmaceutics***

### ***2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation?***

While definitive permeability studies have not been conducted, it is clear from the data that isotretinoin has low aqueous solubility.

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

As has been noted before, there is not a clinical safety efficacy component in the current NDA package. Using the Study 627, **fasted** treatment legs, the Ciper capsules are approximately 200% as bioavailable as equivalent doses of Accutane™. It should be noted that this program was originally developed to produce a (b) (4) form of isotretinoin.

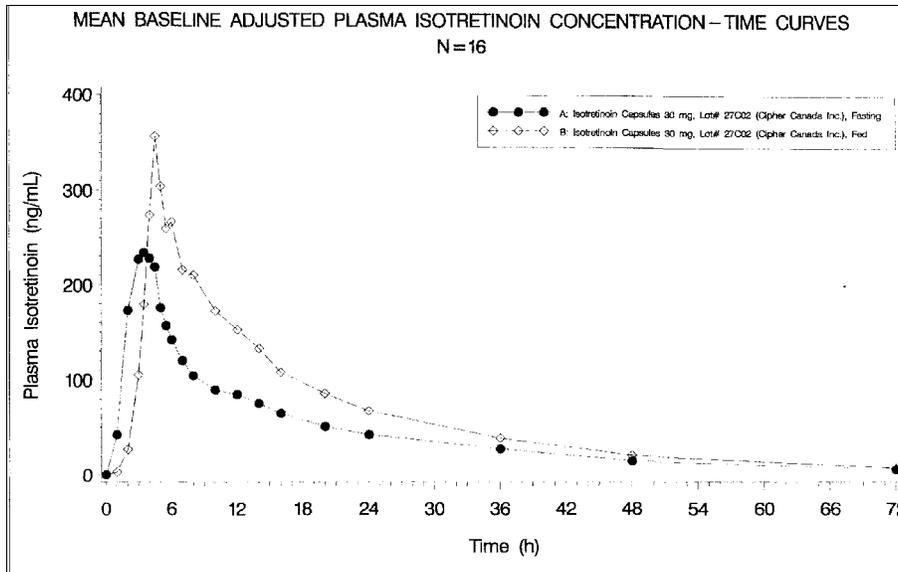
Study 627 Fasted Treatments (n=57) Arithmetic Means			
	Ciper 2x20mg	Accutane(tm) 40mg	T/R*100
AUCt (ng*hr/ml)	4307 (29%)	2349 (29%)	183%
AUCinf (ng*hr/ml)	4676 (28%)	2619 (30%)	179%
Cmax (ng/mL)	347 (35%)	169 (29%)	205%
Study 627 Fed Treatments**			
AUC24 (ng*hr/ml)	6400 (20%)	6145 (26%)	104%
AUCinf (ng*hr/ml)	6858 (21%)	6561 (26%)	104%
Cmax (ng/mL)	466 (38%)	471 (41%)	98.9%

It was the finding that under fed conditions that the product offered no advantage in bioavailability that led to the subsequent dropping of this improvement claim by the sponsor.

**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?**

As this issue of the food effect with isotretinoin has been exhaustively covered elsewhere, it will not be repeated here, beyond stating that within the Ciper product itself, the effect is minimized but still present as is seen in Study 444 with the 30mg capsule, the highest proposed strength.

Study 444 Summary Data 30mg Ciper				
Parameter	Fed	Fasted	Ratio of Geometric Means (%)	90% Confidence Interval (%)
	Geometric Mean Arithmetic Mean CV (%)			
AUCt (ng·h/mL)	4506.68 4576.45 (16)	3083.36 3161.10 (23)	146.16	134.76 – 158.53
AUCi (ng·h/mL)	4704.29 4779.42 (17)	3259.24 3336.29 (23)	144.34	133.41 – 156.16
Cmax (ng/mL)	408.39 437.27 (36)	250.00 257.51 (30)	163.36	134.95 – 197.75



Clearly, even for this formulation, bioavailability is increased by 45% for AUC and by 74% for C<sub>max</sub>. Admittedly a more “modest” increase, relative to Accutane’s™ food effect, but still one requiring labeling. What is unanswered is whether or not there is a clinical implication to this food effect that sets this product apart from Accutane™ in terms of safety or efficacy whereby the accumulated experience with Accutane™ will not be adequate to describe this product appropriately.

#### ***2.5.4 When would a fed BE study be appropriate and was one conducted?***

For this product to be a 505(b)(2) and NOT have supporting clinical data, then the sponsor should be required to demonstrate both fed and fasted bioequivalence as irrespective of the “take with food” direction in the label, it is inappropriate to use the fed study condition in an NDA as a general statement of food effects. As this sponsor is not making any superiority claims, only an decrease in the effect of food with an implied benefit of improved safety and efficacy, in with the absence of any supportive clinical data, such an application should be filed as a 505(j).

#### ***2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?***

As has been noted earlier the sponsor is proposing a rather unusual dissolution media (b) (4). In the NDA the sponsor did not submit what would be considered an adequate dissolution section, i.e. lack of comparative media, lack of profiles with early timepoints. These issues have been summarized by the reviewing chemist in their review for communication to the sponsor. Without this type of data we cannot properly evaluate the proposed method and specification at this time.

## 2.6 Analytical Section

### 2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

As noted earlier, parent and the three primary metabolites were determined in all of the in vivo clinical pharmacology/biopharmaceutic studies. Although this review has focused on the parent drug, the appendices contain supportive tables and figures for the metabolites.

### 2.6.2 For all moieties measured, was free, bound, or total measured? What is the basis for that decision, and is it appropriate?

Historically, all of the work with Accutane™ and its generics have been done using total drug concentrations. Accordingly total concentrations were determined here.

### 2.6.3 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Yes, the method validation report accompanying the NDA describes a liquid chromatographic tandem mass spectrometric analytical method capable of quantifying isotretinoin, tretinoin, 4-oxo-isotretinoin and 4-oxo-tretinoin in human plasma. As there are low endogenous levels of these analytes in human plasma, some of the validation tests were performed in charcoal stripped human plasma.

The following tests were performed in both human plasma and charcoal stripped human plasma: sensitivity (lower limit of quantitation), within and between batch precision and accuracy (accuracy determined for charcoal stripped human plasma only), dilution integrity, bench top stability, short term refrigerated stability, auto sampler stability, freeze-thaw stability, storage stability of extracted/reconstituted samples, and evaporated stability. Matrix effect, selectivity and concomitant medication interference tests were performed only in human plasma. However, due to the presence of endogenous levels of these analytes in human plasma, recovery test was performed in charcoal stripped human plasma. In addition the calibration standards were also prepared in charcoal stripped plasma.

For each of the studies a standard curve was produced for each analyte utilizing a suitable of known concentrations over a range from 1- up to 750ng/mL (depending upon the analyte. Independent quality control samples were routinely run at 3, 100, and 400ng/mL for each analyte throughout the analytical run for QC purposes. As the pivotal trial in this NDA was Study 627, the summary tables for the standard curves from this trial are reproduced below.

	Isotretinoin Study 627-Back Calculated Standard Concentrations-(ng/mL)							
	1	2	6	20	60	175	400	750
Mean	0.99	1.98	6.09	19.70	61.70	175	398	752
SD	0.069	0.073	0.206	0.80	3.00	7.28	14.80	10.30
% CV	7.00	3.70	3.40	4.10	4.90	4.20	3.70	1.40
N	31	27	29	30	30	31	30	31
%Nominal	99.00	99.00	101.50	98.50	102.80	100.00	99.50	100.30

4-oxo-isotretinoin Study 627-Back Calculated Standard Concentrations-(ng/mL)								
	1	2	6	2	60	175	400	750
Mean	1.03	1.99	6.01	19.30	60.70	174	403	748
SD	0.080	0.097	0.247	1.24	3.36	6.97	15.30	9.03
%CV	7.80	4.90	4.10	6.40	5.50	4.00	3.80	1.20
N	31	27	29	30	30	31	30	31
%Nominal	103.00	99.50	100.20	96.50	101.20	99.40	100.80	99.70

Tretinoin Study 627-Back Calculated Standard Concentrations-(ng/mL)								
	1	2	5	15	45	90	175	250
Mean	1.04	1.97	4.99	14.5	44.8	91.9	173	251
SD	0.0508	0.0955	0.193	0.609	2.13	3.35	6.88	4.07
% CV	4.9	4.8	3.9	4.2	4.8	3.6	4	1.6
N	31	30	29	29	30	31	30	31
%Nominal	104	98.5	99.8	96.7	99.6	102.1	98.9	100.4

4-oxo-tretinoin Study 627-Back Calculated Standard Concentrations-(ng/mL)								
	1	2	5	15	45	90	175	250
Mean	1.03	1.99	4.96	14.60	44.60	92.10	173	251
SD	0.058	0.10	0.211	0.774	1.95	3.08	5.55	3.07
% CV	5.60	5.20	4.30	5.30	4.40	3.30	3.20	1.20
N	30	28	28	29	29	30	29	30
%Nominal	103.00	99.50	99.20	97.30	99.10	102.30	98.90	100.40

Examination of these tables shows that the assay had a %CV of less than 8%, and a working range %CV of less than 5% for most concentrations. Overall the analytical development validation report was complete and the day to day functioning of the assay did not reveal any systematic weaknesses.

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

In the absence of clinical trials, it is unlikely that this application will be approved at this time. As such detailed labeling recommendations will not be generated. The proposed label is attached in the appendix for reference.

DUE TO DIFFICULTIES WITH DFS THE ATTACHMENTS ARE CONTAINED IN A SEPARATE DOCUMENT IN DFS-N21951CPAPPENDIX

### ***4 Appendices***

#### ***4.1 Individual Study Review***

#### ***4.2 Proposed Package Insert (Original and Annotated)***

#### ***4.3 Cover Sheet and OCPB Filing/Review Form***

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

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Dennis Bashaw  
4/19/2006 01:29:20 PM  
BIOPHARMACEUTICS

John P. Hunt  
4/21/2006 12:15:37 PM  
BIOPHARMACEUTICS

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Study PK.02.04(2002-444)

**Sponsor:** Cipher Canada Inc.  
6560 Kennedy Road  
Mississauga, Ontario  
Canada L5T 2X4

**Treatment A:** Isotretinoin 30 mg Capsules (Cipher Canada Inc.); Manufacturer: GALEPHAR P.R. Inc.; Lot # 27C02; Exp. Date: N/A administered following an overnight fast of at least 10 hours.

**Treatment B:** Isotretinoin 30 mg Capsules (Cipher Canada Inc.); Manufacturer: GALEPHAR P.R. Inc.; Lot # 27C02; Exp. Date: N/A taken within 5 minutes after a **high fat, high calorie breakfast**, which was consumed within 25 minutes and served 30 minutes prior to drug administration.

**Number of Subjects:** Eighteen (18) male subjects were dosed in the first period, and 16 subjects completed the study.

**Study (Dosing) Dates:** Period I: June 17, 2002  
Period II: July 08, 2002

**Blood Sampling Times:** Blood samples were collected at -10 (2 x 7 mL), -2 and 0 hours pre-dose and 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14, 16, 20, 24, 36, 48, and 72 hours post-dose (1 x 7 mL) (23 time points).

This study was a single dose fed/fasted study to quantify the effect of food on the 30mg Cipher isotretinoin drug product. It was part of the original drug development program for a (b) (4) and was used as a “proof-of-concept” study for the program.

All subjects who were selected for the study met the inclusion and exclusion criteria described in the study protocol, and were judged by an Investigator to be medically healthy based on medical history, physical examination, vital sign measurements, 12-lead ECG, and clinical laboratory tests.

As noted above, eighteen (18) healthy, non-smoking, male subjects were dosed in Period I. Subject #07 was disqualified prior to Period I drug administration, due to elevated blood pressure. A standby subject was used to replace Subject #07. This standby was labeled Subject #19. Subject #09 did not return for Period II for personal reasons. Subject #17 was dismissed during Period II check-in, due to a positive urine drug test (methadone). Therefore, 16 subjects were dosed in Period II, and 16 subjects completed the study.

Demographic information for the 16 subjects who completed the study is as follows,:

mean  $\pm$  SD (range):

Age	28 $\pm$ 7 yrs (18 – 45 yrs)
Height	176.5 $\pm$ 7.3 cm (166.5 – 192.5 cm)
Weight	73.0 $\pm$ 8.2 kg (59.7 – 91.4 kg)

### **Study Procedures**

A single dose (1 x 30 mg) of the drug product was administered according to the Dosage Regimen for Period I and Period II, respectively, beginning at 07:01 hours. Subjects were dosed at approximately one-minute intervals and remained seated or in a semi-reclined position for 4 hours following drug administration, unless required to ambulate for study specific procedures, and resumed normal activity thereafter.

As noted above, subject #19 received Subject #07's drug treatment, because Subject #07 was disqualified prior to drug administration in Period I due to elevated blood pressure.

Subjects on Treatment A, received the study drug with 240 mL of water after a 10-hour overnight fast. Subjects on Treatment B, were served a modified high fat, high calorie breakfast 30 minutes prior to drug administration. All subjects completed the meal within 25 minutes of being served. The study drug was subsequently ingested with 240 mL of water 5 minutes after completion of the high fat, high calorie breakfast. Water was restricted from 1 hour pre-dose until 1 hour post-dose, with exception of water ingested with each dose. All subjects fasted for 4 hours following drug administration. There was a 21 day washout period between the treatments.

### **Adverse Events**

Throughout the study adverse events were monitored and recorded. A total of five (5) adverse events occurred in 5 different subjects. Interestingly, all AEs occurred with the fasted treatment (Treatment A). Four (4) AEs were rated mild and 1 was rated moderate. AEs consisted of skin rash (2), abdomen pain (1), headache (1), and elevated blood pressure (1). The adverse events associated with Treatment A were judged possibly (4) and unrelated (1) to the study drugs by the Principal Investigator. All reported adverse events resolved without medication and are summarized in the following table

<b>Subject No.</b>	<b>Period/Regimen</b>	<b>Adverse Event (COSTART)</b>	<b>Duration (hrs.)</b>	<b>Severity</b>	<b>Action Taken</b>	<b>Relationship to the Study Drug</b>	<b>Outcome</b>
01	II/A	Elevated blood pressure	0.5	Mild	None	Unrelated	Resolved
04	II/A	Red spot (arm & body) (Rash)	42	Mild	None	Possible	Resolved
11	II/A	Burning sensation in stomach (Pain Abdo)	0.5	Mild	None	Possible	Resolved

14	I/A	Skin rash (Rash)	23.67	Mild	None	Possible	Resolved
18	II/A	Headache (Headache)	12	Moderate	None	Possible	Resolved

There were no adverse events associated with Treatment B.

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## Results

Tables of the individual pharmacokinetic profiles, mean plasma level time profiles, box whisker plots, and associated statistical tables are attached.

Summary of Individual Isotretinoin Pharmacokinetic Parameters  
A: Isotretinoin Capsules 30 mg, Lot# 27C02 (Cipher Canada Inc.), Fasting

----- Treatment-A -----												
Subject	SEQ	PERIOD	AUC(0-t) (ng.h/mL)	AUC(0-inf) (ng.h/mL)	AUC(0-t) -----(*) AUC(0-inf)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	K <sub>el</sub> (1/h)	T <sub>1/2</sub> (h)	*T <sub>1/2</sub> (h)	**LQCT (h)	***R
01	BA	2	3235.54	3578.00	90.43	255.24	3.00	0.0471	14.71	14.00	48.25	0.9970
02	AB	1	2455.99	2653.81	92.55	252.00	2.00	0.0335	20.68	16.02	72.00	0.9908
03	AB	1	3145.77	3206.63	98.10	261.80	4.50	0.0533	13.01	16.00	72.00	0.9974
04	BA	2	4379.79	4482.44	97.71	309.49	4.00	0.0509	13.62	16.00	72.00	0.9866
05	AB	1	2738.23	3203.11	85.49	205.27	4.50	0.0253	27.38	16.00	72.02	0.9884
06	BA	2	2930.82	3045.91	96.22	231.00	3.00	0.0447	15.52	16.00	72.00	0.9954
08	AB	1	3460.87	3787.22	91.38	249.22	3.00	0.0322	21.51	16.00	72.00	0.9905
10	BA	2	4495.12	4548.02	98.84	429.68	3.50	0.0604	11.48	16.00	72.00	0.9971
11	BA	2	2210.78	2290.00	96.54	177.49	3.50	0.0457	15.15	16.00	72.00	0.9975
12	AB	1	2832.23	2885.50	98.15	211.33	2.00	0.0540	12.84	16.00	72.00	0.9962
13	AB	1	3708.67	3799.96	97.60	373.82	3.50	0.0494	14.04	16.00	72.00	0.9943
14	AB	1	3713.25	3926.53	94.57	366.65	3.00	0.0383	18.09	16.00	72.00	0.9986
15	BA	2	3731.87	4083.36	91.39	204.22	4.00	0.0328	21.14	16.00	72.00	0.9953
16	BA	2	2462.83	2559.56	96.22	219.73	3.50	0.0444	15.62	16.00	72.02	0.9990
18	BA	2	3178.49	3366.77	94.41	225.00	4.50	0.0395	17.56	16.00	72.00	0.9968
19	BA	2	1897.31	1963.84	96.61	148.16	3.00	0.0466	14.88	16.00	72.02	0.9888
MEAN	.	.	3161.10	3336.29	94.76	257.51	3.41	0.0436	16.70	15.88	70.52	0.9950
STD	.	.	735.58	754.35	3.65	76.23	0.78	0.0094	4.16	0.50	5.94	0.0038
CV (%)	.	.	23.27	22.61	3.85	29.60	22.88	21.5378	24.93	3.15	8.42	0.3791

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Summary of Individual Isotretinoin Pharmacokinetic Parameters  
B: Isotretinoin Capsules 30 mg, Lot# 27C02 (Cipher Canada Inc.), Fed

Treatment-B												
Subject	SEQ	PERIOD	AUC(0-t) (ng.h/mL)	AUC(0-inf) (ng.h/mL)	AUC(0-t) -----(% AUC(0-inf)	Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R
01	BA	1	4829.84	5375.20	89.85	225.53	4.50	0.0531	13.06	14.00	48.00	0.9978
02	AB	2	3518.93	3770.39	93.33	294.91	4.50	0.0410	16.90	16.00	72.00	0.9768
03	AB	2	3636.91	3710.51	98.02	471.84	4.00	0.0514	13.49	16.00	72.00	0.9939
04	BA	1	5446.37	5569.38	97.79	439.09	4.50	0.0544	12.73	16.00	72.00	0.9966
05	AB	2	4935.11	5645.51	87.42	435.66	6.00	0.0288	24.07	16.07	72.27	0.9948
06	BA	1	4654.73	4728.21	98.45	574.32	4.50	0.0546	12.70	16.00	72.00	0.9978
08	AB	2	5764.23	5952.89	96.83	346.77	10.00	0.0502	13.81	16.00	72.00	0.9982
10	BA	1	5700.17	5768.56	98.81	708.82	6.03	0.0587	11.81	16.00	72.08	0.9957
11	BA	1	4550.37	4711.36	96.58	351.96	7.00	0.0483	14.34	16.00	72.00	0.9970
12	AB	2	4250.67	4329.22	98.19	396.07	4.50	0.0567	12.24	16.00	72.00	0.9981
13	AB	2	4521.90	4623.34	97.81	423.66	5.00	0.0526	13.17	16.00	72.02	0.9977
14	AB	2	4464.33	4656.37	95.88	457.66	8.00	0.0440	15.74	16.00	72.00	0.9944
15	BA	1	5362.54	5719.24	93.76	778.11	4.50	0.0370	18.71	16.00	72.00	0.9995
16	BA	1	4088.64	4217.21	96.95	167.82	6.00	0.0494	14.04	16.00	72.00	0.9958
18	BA	1	3826.56	3989.94	95.91	525.00	4.50	0.0423	16.39	16.00	72.05	0.9879
19	BA	1	3671.84	3703.39	99.15	399.12	4.50	0.0679	10.20	14.00	72.00	0.9990
MEAN	.	.	4576.45	4779.42	95.92	437.27	5.50	0.0494	14.59	15.75	70.53	0.9951
STD	.	.	729.81	794.78	3.31	158.01	1.63	0.0093	3.30	0.68	6.01	0.0056
CV(%)	.	.	15.95	16.63	3.45	36.14	29.69	18.7797	22.59	4.35	8.52	0.5615

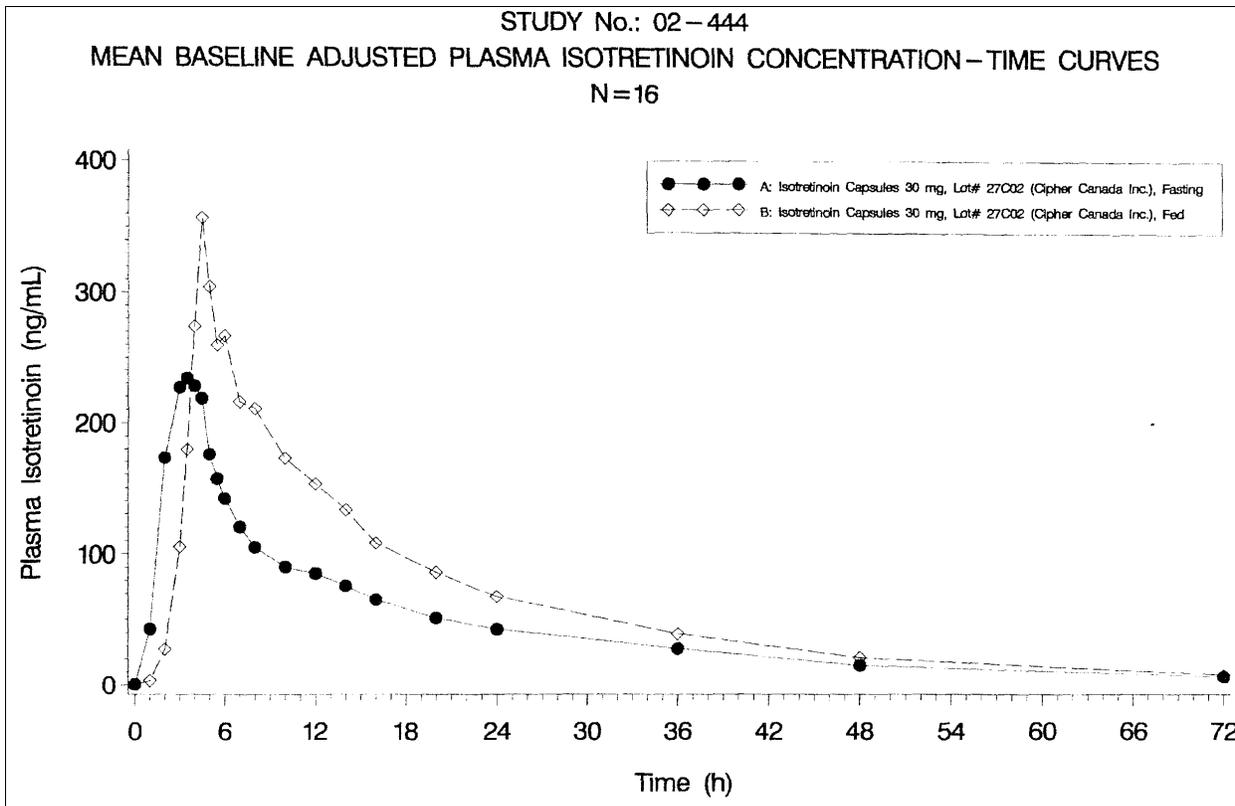
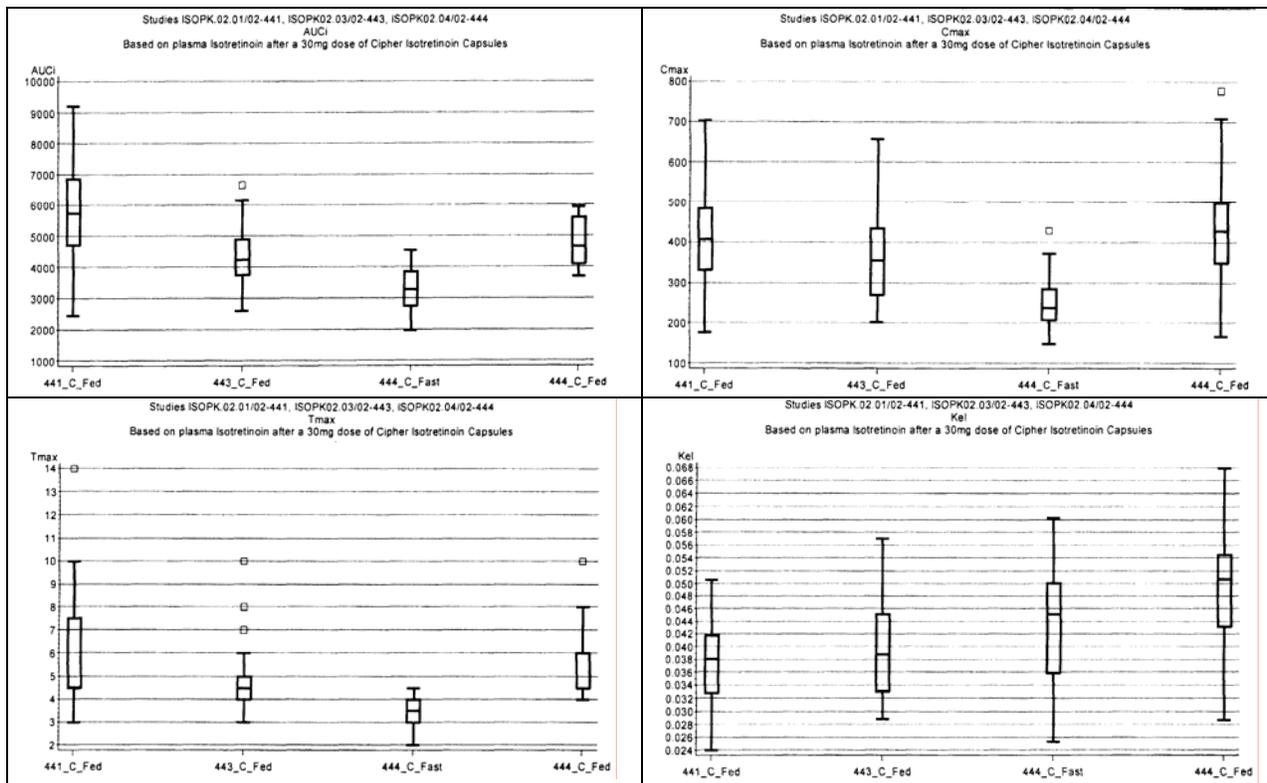
**Analyte: Isotretinoin**

Parameter	Treatment (B)	Treatment (A)	Ratio of Geometric Means (%)	90% Geometric Confidence Interval (%)	Intra- Subject CV (%)
	Geometric Mean Arithmetic Mean CV (%)				
<b>AUCt</b> (ng.h/mL)	4506.68 4576.45 (16)	3083.36 3161.10 (23)	146.16	134.76 – 158.53	13
<b>AUCi</b> (ng.h/mL)	4704.29 4779.42 (17)	3259.24 3336.29 (23)	144.34	133.41 – 156.16	13
<b>Cmax</b> (ng/mL)	408.39 437.27 (36)	250.00 257.51 (30)	163.36	134.95 – 197.75	31
<b>Tmax<sup>a</sup></b> (h)	5.50 (30)	3.41 (23)	-	-	-
<b>Kel<sup>a</sup></b> (h <sup>-1</sup> )	0.0494 (19)	0.0436 (22)	-	-	-
<b>Thalf<sup>a</sup></b> (h)	14.59 (23)	16.70 (25)	-	-	-

<sup>a</sup>Presented as arithmetic mean (CV%) only.

**reatment A:** Isotretinoin 30 mg Capsules (Cipher Canada Inc.); Manufacturer: GALEPHAR P.R. Inc.; Lot # 27C02; Exp. Date: N/A administered following an overnight fast of at least 10 hours.

**Treatment B:** Isotretinoin 30 mg Capsules (Cipher Canada Inc.); Manufacturer: GALEPHAR P.R. Inc.; Lot # 27C02; Exp. Date: N/A taken within 5 minutes after a **high fat, high calorie breakfast**, which was consumed within 25 minutes and served 30 minutes prior to drug administration.



Summary of Individual 4-oxo-isotretinoin Pharmacokinetic Parameters  
A: Isotretinoin Capsules 30 mg, Lot# 27C02 (Cipher Canada Inc.), Fasting

----- Treatment-A -----												
Subject	SEQ	PERIOD	AUC(0-t) (ng·h/mL)	AUC(0-inf) (ng·h/mL)	AUC(0-t) ----- (%) AUC(0-inf)	Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R
01	BA	2	5607.12	9317.85	60.18	159.10	12.00	0.0205	33.89	14.00	48.25	0.9844
02	AB	1	4633.85	5944.89	78.96	108.44	10.00	0.0225	30.81	16.02	72.00	0.9632
03	AB	1	7855.14	10283.93	76.38	211.85	12.00	0.0212	32.66	16.00	72.00	0.9902
04	BA	2	11124.45	14175.82	78.47	231.77	20.00	0.0216	32.16	16.00	72.00	0.9617
05	AB	1	5569.23	13282.02	41.92	108.17	12.00	0.0072	96.56	16.00	72.02	0.7980
06	BA	2	7394.33	9967.19	74.19	173.69	10.00	0.0195	35.46	16.00	72.00	0.9895
08	AB	1	10468.33	20148.90	51.95	216.95	14.00	0.0106	65.18	16.00	72.00	0.9633
10	BA	2	13076.88	16906.33	77.35	283.37	14.00	0.0208	33.28	16.00	72.00	0.9451
11	BA	2	6600.19	7886.03	83.69	144.54	24.00	0.0254	27.30	16.00	72.00	0.9586
12	AB	1	8766.51	11034.03	79.45	203.25	10.00	0.0227	30.49	16.00	72.00	0.9613
13	AB	1	7173.14	8959.00	80.07	186.44	12.00	0.0256	27.06	16.00	72.00	0.9850
14	AB	1	9831.22	14691.81	66.92	227.01	7.00	0.0158	43.98	16.00	72.00	0.9730
15	BA	2	6480.61	9913.83	65.37	141.81	12.00	0.0141	49.26	16.00	72.00	0.9029
16	BA	2	4718.49	9146.53	51.59	100.70	10.00	0.0104	66.57	16.00	72.02	0.9713
18	BA	2	9312.64	12938.01	71.98	198.27	20.00	0.0185	37.47	16.00	72.00	0.9836
19	BA	2	4043.61	5278.51	76.61	88.52	16.00	0.0204	33.94	16.00	72.02	0.9650
MEAN	.	.	7669.67	11242.17	69.69	173.98	13.44	0.0186	42.25	15.88	70.52	0.9560
STD	.	.	2580.42	3928.57	12.30	55.62	4.50	0.0054	18.84	0.50	5.94	0.0472
CV (%)	.	.	33.64	34.94	17.65	31.97	33.50	29.3686	44.59	3.15	8.42	4.9346

Summary of Individual 4-oxo-isotretinoin Pharmacokinetic Parameters  
B: Isotretinoin Capsules 30 mg, Lot# 27C02 (Cipher Canada Inc.), Fed

----- Treatment-B -----												
Subject	SEQ	PERIOD	AUC(0-t) (ng·h/mL)	AUC(0-inf) (ng·h/mL)	AUC(0-t) ----- (%) AUC(0-inf)	Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R
01	BA	1	9169.40	27520.98	33.32	260.08	16.00	0.0095	73.07	14.00	48.00	0.8921
02	AB	2	11667.34	21281.84	54.82	231.82	24.00	0.0112	61.81	16.00	72.00	0.8583
03	AB	2	13576.36	16770.03	80.96	345.44	14.00	0.0239	29.04	16.00	72.00	0.9781
04	BA	1	20036.59	21979.93	91.16	491.76	12.00	0.0346	20.03	16.00	72.00	0.9718
05	AB	2	12884.80	25586.24	50.36	252.07	12.00	0.0100	69.28	16.07	72.27	0.8608
06	BA	1	14927.98	17161.71	86.98	417.75	8.00	0.0295	23.48	16.00	72.00	0.9866
08	AB	2	21691.16	29735.55	72.95	492.87	24.00	0.0199	34.88	16.00	72.00	0.9820
10	BA	1	20271.86	24081.58	84.18	727.07	12.00	0.0263	26.39	16.00	72.08	0.9944
11	BA	1	12460.97	17986.61	69.28	295.27	14.00	0.0172	40.20	16.00	72.00	0.9435
12	AB	2	16858.39	20313.06	82.99	391.61	12.00	0.0257	26.96	16.00	72.00	0.9811
13	AB	2	12011.27	16637.47	72.19	301.60	14.00	0.0194	35.79	16.00	72.02	0.9813
14	AB	2	13382.05	16583.66	80.69	407.42	12.00	0.0259	26.73	16.00	72.00	0.9918
15	BA	1	13412.05	16804.57	79.81	317.73	10.00	0.0235	29.53	16.00	72.00	0.9914
16	BA	1	10849.57	14086.83	77.02	236.73	14.00	0.0209	33.13	16.00	72.00	0.9425
18	BA	1	13623.60	18750.32	72.65	386.19	10.00	0.0195	35.47	16.00	72.05	0.9941
19	BA	1	10178.40	11654.69	87.33	264.36	12.00	0.0293	23.65	14.00	72.00	0.9849
MEAN	.	.	14187.61	19808.44	73.54	363.74	13.75	0.0216	36.84	15.75	70.53	0.9584
STD	.	.	3699.74	4940.91	15.42	128.79	4.43	0.0072	16.49	0.68	6.01	0.0468
CV (%)	.	.	26.08	24.94	20.97	35.41	32.25	33.2737	44.76	4.35	8.52	4.8840

**Analyte: 4-oxo-isotretinoin**

Parameter	Treatment (B)	Treatment (A)	Ratio of Geometric Means (%)	90% Geometric Confidence Interval (%)	Intra- Subject CV (%)
	Geometric Mean Arithmetic Mean CV (%)				
<b>AUCt</b> (ng·h/mL)	13826.52 14187.61 (26)	7294.77 7669.67 (34)	189.54	174.06 – 206.40	14
<b>AUCi</b> (ng·h/mL)	19380.42 19808.44 (25)	10687.14 11242.17 (35)	181.34	158.89 – 206.97	21
<b>Cmax</b> (ng/mL)	344.81 363.74 (35)	165.95 173.98 (32)	207.77	193.21– 223.44	12
<b>Tmax<sup>a</sup></b> (h)	13.75 (32)	13.44 (34)	-	-	-
<b>Kel<sup>a</sup></b> (h <sup>-1</sup> )	0.0216 (33)	0.0186 (29)	-	-	-
<b>Thalf<sup>a</sup></b> (h)	36.84 (45)	42.25 (45)	-	-	-

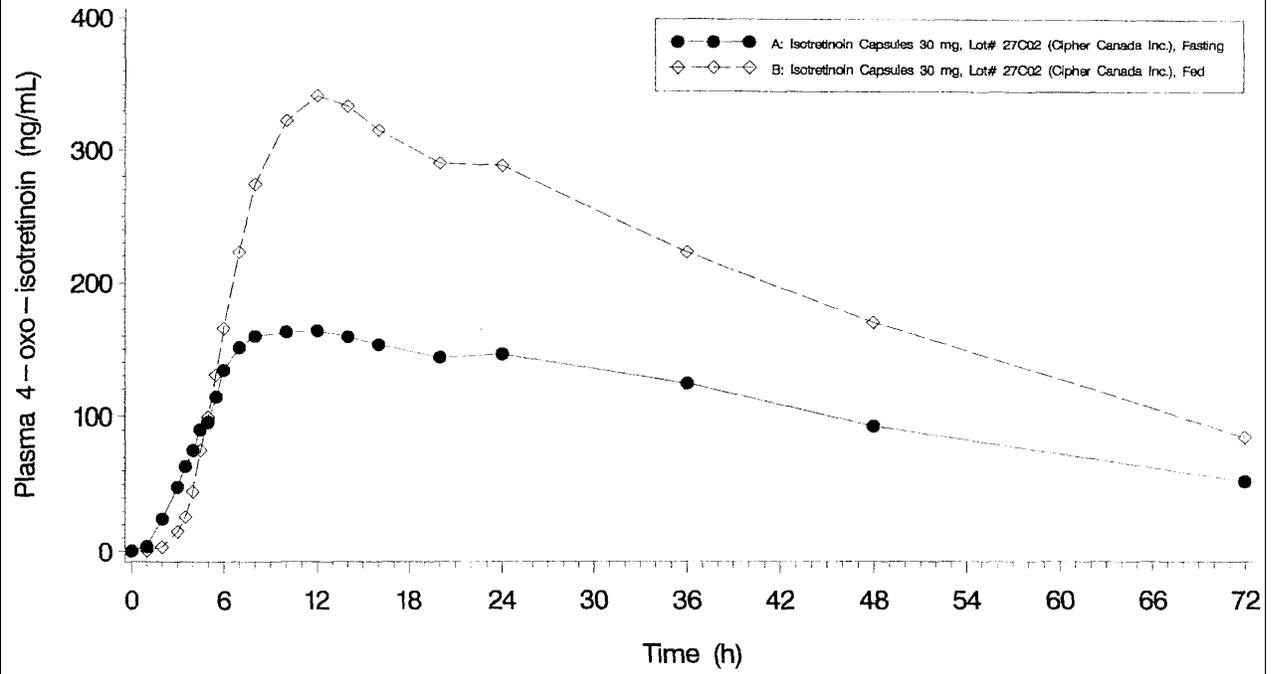
<sup>a</sup>Presented as arithmetic mean (CV%) only.

**reatment A:** Isotretinoin 30 mg Capsules (Cipher Canada Inc.); Manufacturer: GALEPHAR P.R. Inc.; Lot # 27C02; Exp. Date: N/A administered following an overnight fast of at least 10 hours.

**Treatment B:** Isotretinoin 30 mg Capsules (Cipher Canada Inc.); Manufacturer: GALEPHAR P.R. Inc.; Lot # 27C02; Exp. Date: N/A taken within 5 minutes after a **high fat, high calorie breakfast**, which was consumed within 25 minutes and served 30 minutes prior to drug administration.

STUDY No.: 02-444

MEAN BASELINE ADJUSTED PLASMA 4-OXO-ISOTRETINOIN CONCENTRATION-TIME CURVES  
N=16



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Summary of Individual Tretinoin Pharmacokinetic Parameters  
A: Isotretinoin Capsules 30 mg, Lot# 27C02 (Cipher Canada Inc.), Fasting

Treatment=A													
Subject	SEQ	PERIOD	AUC(0-t) (ng.h/mL)	AUC(0-inf) (ng.h/mL)	AUC(0-t) (R)		Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*T1/2IN (h)	**t1/2CT (h)	***R
					AUC(0-t)	AUC(0-inf)							
01	BA	2	59.61	61.42	97.06	6.73	3.00	0.0462	10.16	14.00	48.25	0.9404	
02	AB	1	115.56	-	-	12.55	2.00	-	-	-	72.00	-	
03	AB	1	117.20	128.17	91.50	9.95	4.00	0.0349	19.86	16.00	72.00	0.9234	
04	BA	2	150.59	-	-	6.93	4.00	-	-	-	72.00	-	
05	AB	1	117.34	125.94	93.17	10.94	4.50	0.0383	19.08	16.00	72.00	0.9951	
06	BA	2	49.29	52.01	93.34	6.28	3.00	0.0578	12.00	14.00	48.03	0.9713	
08	AB	1	141.21	146.39	96.46	16.46	3.00	0.0714	9.71	14.00	48.02	0.9666	
10	BA	2	80.17	-	-	9.30	3.50	-	-	-	72.00	-	
11	BA	2	54.31	-	-	4.79	3.50	-	-	-	48.00	-	
12	AB	1	77.52	-	-	7.34	3.00	-	-	-	72.00	-	
13	AB	1	72.81	97.98	74.32	11.11	3.50	0.0379	18.30	14.00	36.00	0.7974	
14	AB	1	69.31	-	-	10.56	3.00	-	-	-	72.00	-	
15	BA	2	156.81	-	-	5.49	3.50	-	-	-	72.00	-	
16	BA	2	173.37	-	-	8.31	10.00	-	-	-	72.02	-	
18	BA	2	74.27	75.37	90.53	6.62	4.50	0.0543	12.76	16.00	72.00	0.9641	
19	BA	2	34.50	36.08	95.60	3.72	3.50	0.0672	10.31	14.00	48.00	0.9713	
MEAN	-	-	97.50	90.52	92.50	8.51	3.84	0.0538	13.90	14.75	62.27	0.9438	
STD	-	-	43.10	45.20	7.70	3.24	1.76	0.0150	4.17	1.04	13.20	0.0436	
CV(%)	-	-	44.29	44.41	8.33	38.02	45.74	27.0391	30.01	7.02	21.33	6.7355	

Summary of Individual Tretinoin Pharmacokinetic Parameters  
B: Isotretinoin Capsules 30 mg, Lot# 27C02 (Cipher Canada Inc.), Fed

Treatment=B													
Subject	SEQ	PERIOD	AUC(0-t) (ng.h/mL)	AUC(0-inf) (ng.h/mL)	AUC(0-t) (R)		Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*T1/2IN (h)	**t1/2CT (h)	***R
					AUC(0-t)	AUC(0-inf)							
01	BA	1	135.30	166.59	91.26	8.69	5.00	0.0391	17.73	14.00	48.00	0.9710	
02	AB	2	148.57	-	-	13.69	4.50	-	-	-	72.00	-	
03	AB	2	143.67	164.66	87.25	19.86	4.00	0.0414	16.73	14.00	48.00	0.9297	
04	BA	1	149.13	-	-	14.04	4.50	-	-	-	72.00	-	
05	AB	2	260.40	295.15	80.25	16.42	6.00	0.0289	23.96	16.07	72.27	0.9765	
06	BA	1	115.46	116.63	99.34	22.26	4.50	0.0645	10.75	16.00	72.00	0.9754	
08	AB	2	204.17	217.73	93.77	13.67	4.50	0.0647	10.72	14.00	48.00	0.9954	
10	BA	1	126.72	133.43	94.98	20.13	6.03	0.0298	23.23	20.00	72.00	0.9841	
11	BA	1	85.02	121.43	70.02	7.43	7.00	0.0346	20.03	12.00	36.00	0.9256	
12	AB	2	81.73	96.61	86.59	11.53	4.50	0.0334	20.77	16.00	48.00	0.9753	
13	AB	2	100.16	126.36	79.27	15.77	5.00	0.0262	26.44	14.00	48.00	0.9223	
14	AB	2	107.89	-	-	12.35	0.00	-	-	-	72.00	-	
15	BA	1	129.45	-	-	15.05	4.50	-	-	-	72.00	-	
16	BA	1	90.85	-	-	4.22	36.00	-	-	-	48.00	-	
18	BA	1	115.05	125.30	91.81	10.97	4.50	0.0292	23.70	16.00	72.00	0.9576	
19	BA	1	84.70	-	-	10.72	4.50	-	-	-	72.00	-	
MEAN	-	-	129.93	156.39	87.05	14.00	7.06	0.0392	19.41	15.21	60.70	0.9613	
STD	-	-	47.54	59.59	9.65	4.81	7.79	0.0142	3.44	2.15	13.51	0.0363	
CV(%)	-	-	36.21	38.11	9.94	34.34	110.31	36.1499	29.01	14.16	22.22	2.7338	

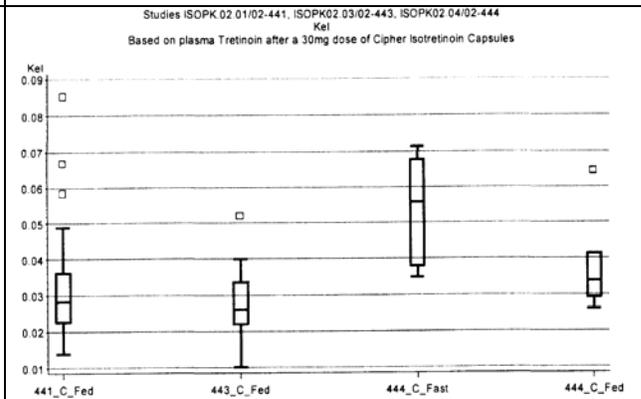
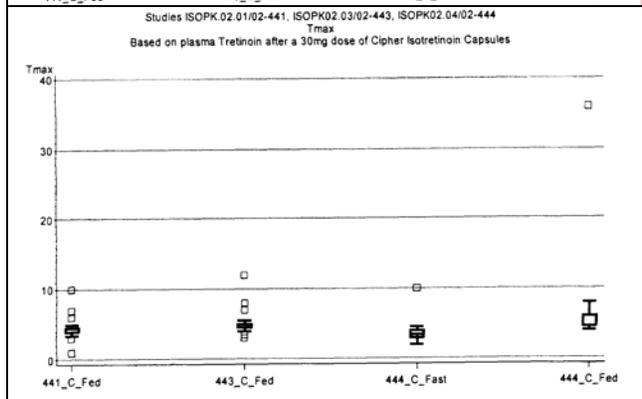
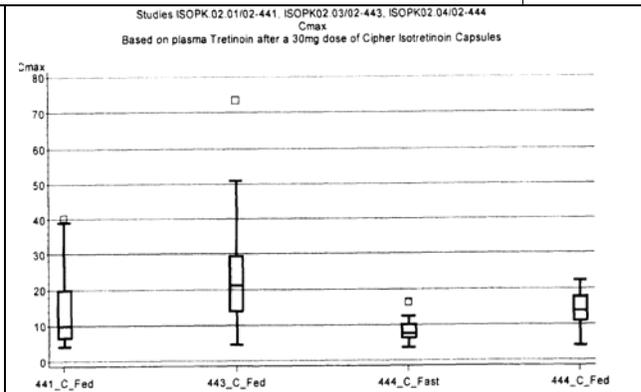
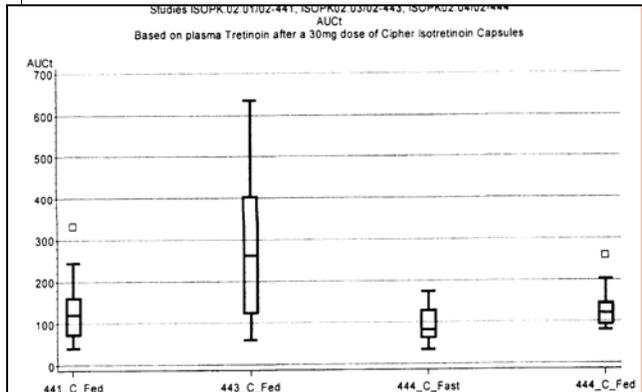
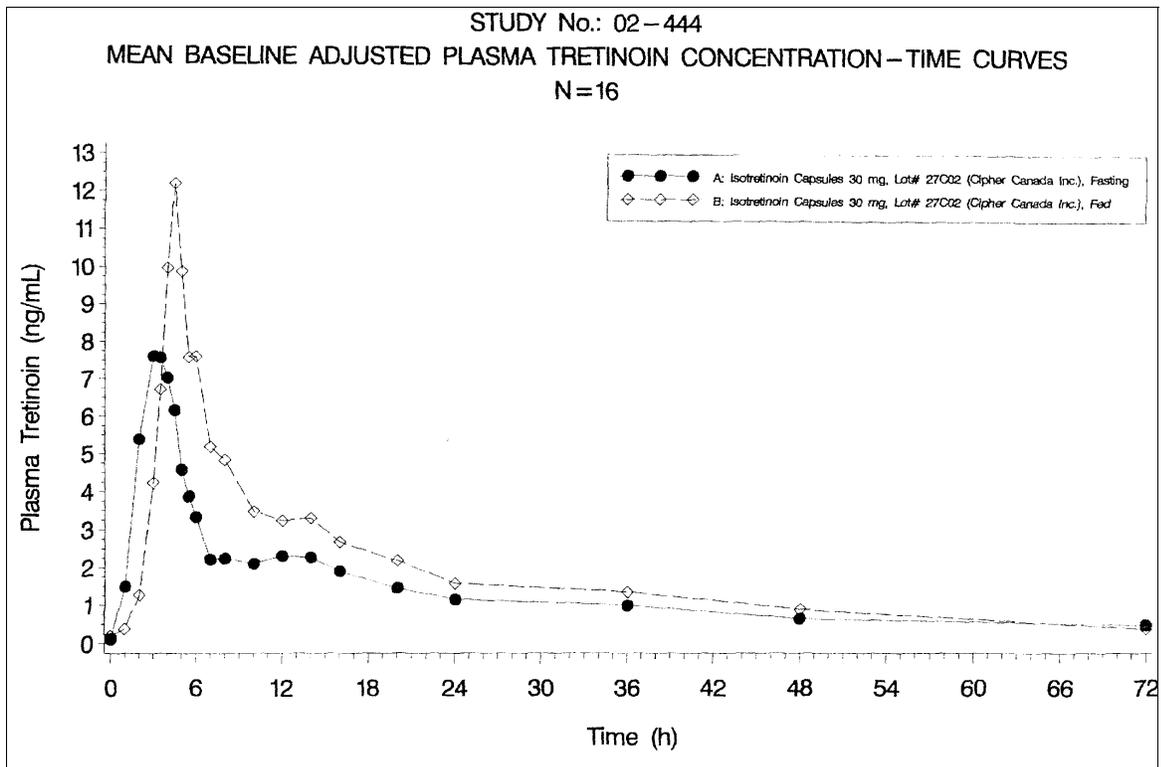
**Analyte: Tretinoin**

Parameter	Treatment (B)	Treatment (A)	Ratio of Geometric Means (%)	90% Geometric Confidence Interval (%)	Intra-Subject CV (%)
	Geometric Mean Arithmetic Mean CV (%)				
<b>AUC<sub>t</sub></b> (ng·h/mL)	125.06 129.93 (36)	89.37 97.50 (44)	139.93	115.70 – 169.24	31
<b>AUC<sub>i</sub></b> (ng·h/mL)	141.78 156.39 (38)	77.63 90.52 (44)	182.63	149.45 – 223.18	19
<b>Cmax</b> (ng/mL)	13.19 14.00 (34)	8.24 8.51 (38)	160.07	129.12 – 198.45	35
<b>Tmax<sup>a</sup></b> (h)	7.06 (110)	3.84 (46)	-	-	-
<b>Kel<sup>a</sup></b> (h <sup>-1</sup> )	0.0392 (36)	0.0538 (28)	-	-	-
<b>T<sub>half</sub><sup>a</sup></b> (h)	19.41 (28)	13.90 (30)	-	-	-

<sup>a</sup>Presented as arithmetic mean (CV%) only.

**reatment A:** Isotretinoin 30 mg Capsules (Cipher Canada Inc.); Manufacturer: GALEPHAR P.R. Inc.; Lot # 27C02; Exp. Date: N/A administered following an overnight fast of at least 10 hours.

**Treatment B:** Isotretinoin 30 mg Capsules (Cipher Canada Inc.); Manufacturer: GALEPHAR P.R. Inc.; Lot # 27C02; Exp. Date: N/A taken within 5 minutes after a **high fat, high calorie breakfast**, which was consumed within 25 minutes and served 30 minutes prior to drug administration.



Summary of Individual 4-oxo-tretinoin Pharmacokinetic Parameters  
A: Isotretinoin Capsules 30 mg, Lot# 27C02 (Cipher Canada Inc.), Fasting

----- Treatment-A -----												
Subject	SEQ	PERIOD	AUC(0-t) (ng.h/mL)	AUC(0-inf) (ng.h/mL)	AUC(0-t) -----(*) AUC(0-inf)	Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R
01	BA	2	76.59	144.62	52.96	2.41	16.00	0.0176	39.29	20.00	48.25	0.9865
02	AB	1	138.98	200.28	69.39	2.93	8.00	0.0186	37.28	20.00	72.00	0.9594
03	AB	1	156.22	258.96	60.32	4.42	14.00	0.0136	50.87	20.00	72.00	0.9906
04	BA	2	148.82	233.29	63.79	3.81	14.00	0.0146	47.60	24.00	72.00	0.8955
05	AB	1	170.84	403.68	42.32	4.10	8.00	0.0079	87.71	20.00	72.00	0.9164
06	BA	2	21.46	.	.	1.36	8.00	.	.	.	24.00	.
08	AB	1	225.95	360.69	62.65	5.87	14.00	0.0145	47.89	20.00	72.00	0.9969
10	BA	2	99.19	159.29	62.27	3.44	12.00	0.0225	30.86	16.00	48.00	0.9800
11	BA	2	0.00	.	.	0.00	0.00	.	.	.	0.00	.
12	AB	1	40.36	.	.	2.95	12.00	.	.	.	24.00	.
13	AB	1	9.83	.	.	1.75	16.00	.	.	.	16.00	.
14	AB	1	69.26	103.35	67.01	2.69	20.00	0.0317	21.88	24.00	48.00	0.9143
15	BA	2	2.93	.	.	1.38	12.00	.	.	.	12.00	.
16	BA	2	0.00	.	.	0.00	0.00	.	.	.	0.00	.
18	BA	2	149.56	252.01	59.34	3.23	10.00	0.0133	52.22	20.00	72.00	0.8441
19	BA	2	0.00	.	.	0.00	0.00	.	.	.	0.00	.
MEAN	.	.	81.87	235.13	60.01	2.52	10.25	0.0171	46.18	20.44	40.77	0.9426
STD	.	.	74.80	96.46	8.11	1.69	6.02	0.0068	18.51	2.40	29.44	0.0527
CV (%)	.	.	91.36	41.87	13.52	67.18	58.70	39.6071	40.08	11.76	72.22	5.5959

Summary of Individual 4-oxo-tretinoin Pharmacokinetic Parameters  
B: Isotretinoin Capsules 30 mg, Lot# 27C02 (Cipher Canada Inc.), Fed

----- Treatment-B -----												
Subject	SEQ	PERIOD	AUC(0-t) (ng.h/mL)	AUC(0-inf) (ng.h/mL)	AUC(0-t) -----(*) AUC(0-inf)	Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R
01	BA	1	129.22	.	.	4.13	16.00	.	.	.	48.00	.
02	AB	2	219.03	.	.	4.53	16.00	.	.	.	72.00	.
03	AB	2	231.32	339.84	68.07	6.82	16.00	0.0166	41.79	24.00	72.00	0.9680
04	BA	1	215.21	259.99	82.78	5.18	8.00	0.0270	25.65	24.00	72.00	0.9879
05	AB	2	457.43	671.40	68.13	9.75	12.00	0.0176	39.34	24.00	72.27	0.9451
06	BA	1	153.57	.	.	5.51	24.00	.	.	.	48.00	.
08	AB	2	426.34	533.16	79.86	11.10	16.00	0.0255	27.22	36.00	72.00	0.9953
10	BA	1	269.78	332.95	81.03	9.80	12.00	0.0323	21.46	16.00	57.23	0.9915
11	BA	1	74.80	113.91	65.66	2.94	14.00	0.0258	26.84	16.00	48.00	0.9400
12	AB	2	159.43	210.05	75.90	4.91	10.00	0.0223	31.05	20.00	72.00	0.9811
13	AB	2	52.33	84.18	62.17	2.55	14.00	0.0339	20.44	20.00	36.00	0.9996
14	AB	2	118.71	178.53	66.49	4.48	12.00	0.0172	40.26	20.00	72.00	0.9495
15	BA	1	148.22	241.15	61.46	4.23	16.00	0.0145	47.71	24.00	72.00	0.9488
16	BA	1	62.68	121.52	51.58	2.49	16.00	0.0194	35.78	20.00	48.00	0.9378
18	BA	1	175.30	272.47	64.34	5.20	14.00	0.0161	43.18	20.03	72.05	0.9055
19	BA	1	26.87	.	.	1.80	12.00	.	.	.	24.00	.
MEAN	.	.	182.52	279.93	68.96	5.34	14.25	0.0224	33.39	22.00	59.85	0.9625
STD	.	.	122.22	173.70	9.29	2.75	3.57	0.0065	9.13	5.26	15.83	0.0291
CV (%)	.	.	66.97	62.05	13.48	51.47	25.04	29.1755	27.33	23.89	26.45	3.0281

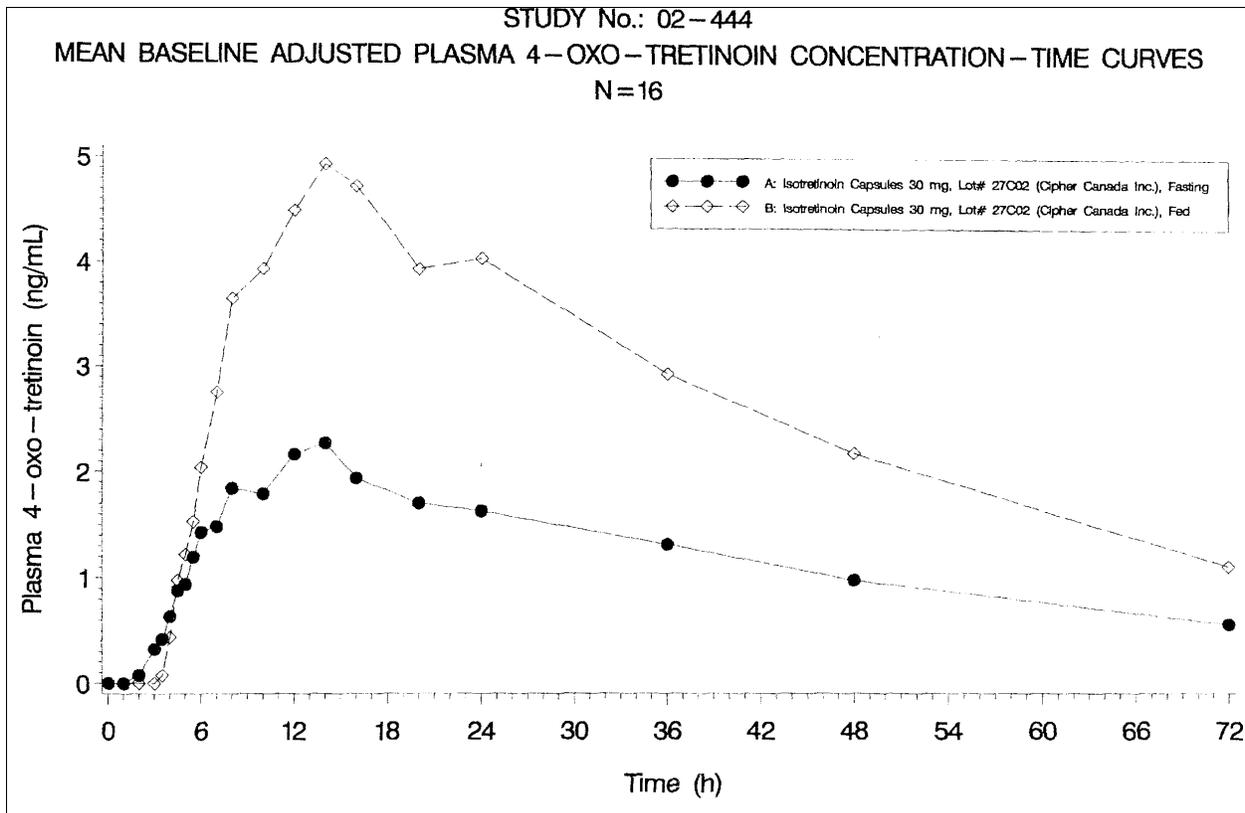
analyte: 4-oxo-tretinoin

Parameter	Treatment (B)	Treatment (A)	Ratio of Geometric Means (%)	90% Geometric Confidence Interval (%)	Intra- Subject CV (%)
	Geometric Mean Arithmetic Mean CV (%)				
<b>AUC<sub>t</sub></b> (ng-h/mL)	149.35 182.52 (67)	50.00 81.87 (91)	298.73	178.55 – 499.79	84
<b>AUC<sub>i</sub></b> (ng-h/mL)	237.63 279.93 (62)	164.35 235.13 (42)	144.58	120.15 – 173.99	18
<b>Cmax</b> (ng/mL)	4.83 5.34 (51)	2.45 2.52 (67)	196.71	167.92 – 230.43	23
<b>Tmax<sup>a</sup></b> (h)	14.25 (25)	10.25 (59)	-	-	-
<b>Kel<sup>a</sup></b> (h <sup>-1</sup> )	0.0224 (29)	0.0171 (40)	-	-	-
<b>Thalf<sup>a</sup></b> (h)	33.39 (27)	46.18 (40)	-	-	-

<sup>a</sup>Presented as arithmetic mean (CV%) only.

**reatment A:** Isotretinoin 30 mg Capsules (Cipher Canada Inc.); Manufacturer: GALEPHAR P.R. Inc.; Lot # 27C02; Exp. Date: N/A administered following an overnight fast of at least 10 hours.

**Treatment B:** Isotretinoin 30 mg Capsules (Cipher Canada Inc.); Manufacturer: GALEPHAR P.R. Inc.; Lot # 27C02; Exp. Date: N/A taken within 5 minutes after a **high fat, high calorie breakfast**, which was consumed within 25 minutes and served 30 minutes prior to drug administration.



### Conclusions

Based on log-transformed data for all 4 analytes (isotretinoin, 4-oxo-isotretinoin, tretinoin and 4-oxo-tretinoin), the extent of absorption of Isotretinoin 30 mg Capsules under fed conditions was between 1.4 to 1.8 times larger than under fasting conditions (144.34, 181.34, 182.63 and 144.58% for isotretinoin, 4-oxo-isotretinoin, tretinoin and 4-oxo-tretinoin, respectively). Similarly, C<sub>max</sub> under fed conditions was between 1.6 to 2.1 times larger than under fasting conditions (163.36, 207.77, 160.07 and 196.71% for isotretinoin, 4-oxo-isotretinoin, tretinoin and 4-oxo-tretinoin, respectively).

Thus, CIP-isotretinoin had a significant food effect per FDA guidance for both AUC and C<sub>max</sub> as well as T<sub>max</sub> for parent and metabolites. The effect here was with a non-standard FDA high fat diet, however, it did approximate the diet in terms of both total calories and composition. Should this product become approvable, then this information regarding the effect of food should be included in the final labeling.

Study PK.04.02 (2004-727)

<b>Title:</b>	A Single-Dose, Comparative Bioavailability Study of Two Formulations of Isotretinoin Capsules 20 mg Under Fed Conditions
<b>Objectives:</b>	The objective of this study was to evaluate the comparative bioavailability between Isotretinoin capsules 20 mg (Cipher Canada Inc., Canada) and Accutane® capsules 20 mg (Roche Laboratories Inc., USA), after a single-dose in healthy subjects under fed conditions
<b>Treatment A: (Test)</b>	Isotretinoin Capsules 20 mg; Lot No.: 28A02, (Cipher Canada Inc., Canada) [20 mg administered after a <b>modified</b> high fat, high calorie breakfast]
<b>Treatment B: (Reference)</b>	ACCUTANE® Capsules 20 mg; Lot No.: U3629, (Roche Laboratories Inc., USA) [20 mg administered after a <b>modified</b> high fat, high calorie breakfast]
<b>Number of Subjects:</b>	Fifty-four (54) [51 male and 3 female] subjects were dosed in Period 1, and 54 subjects completed the entire study. <ul style="list-style-type: none"><li>• Age: 36 ± 9 yrs (18 – 53 yrs)</li><li>• Height: 173.4 ± 7.2 cm (155.0 – 188.5 cm)</li><li>• Weight: 76.5 ± 8.8 kg (54.8 – 92.2 kg)</li></ul>
<b>Sampling Schedule:</b>	Blood samples were obtained at -10, -2 and 0 hours pre-dose, and at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14, 16, 20, 24, 36, 48 and 72 hours following drug administration.
<b>Diet (High Fat Portion):</b>	(1) Regular Bagel with 3 tablespoons of peanut butter (5) Slices of Bacon (1) Dutchie Donut (~230calories, 6gms fat, 40gms carbohydrate- <a href="http://www.timhortons.com">http://www.timhortons.com</a> ) (6) Fluid Ounces of Apple Juice

This study was a single dose relative bioavailability study between Isotretinoin capsules 20 mg (Cipher Canada Inc., Canada) and Accutane® capsules 20 mg (Roche Laboratories Inc., USA), in healthy subjects under fed conditions. Subjects who were selected for the study met the inclusion and exclusion criteria described in the study protocol, and were judged by an investigator to be medically healthy based upon medical history, physical examination, vital signs measurements (blood pressure, heart rate, respiration rate and temperature), 12-lead ECG and clinical laboratory tests.

Because of the known teratogenicity of isotretinoin, a HCG serum pregnancy test was performed for each of the three female subjects during screening (Subjects 03, 04 and 47). The results were negative for pregnancy. As required by the protocol, a second test for HCG, this time in urine, was performed for Subject 03 prior to the first drug administration, 1 day after the start of a menstrual period. This test for HCG in urine prior to dosing was performed at the time of check-in and was not required for Subjects 04 and 47, since they were post-menopausal. However all three female subjects were tested for serum HCG at screening and for urine HCG at check-in, prior to the first drug administration. The result in all cases was negative for pregnancy.

## **Study Procedures**

Subjects were confined to the clinical facility from at least 10.5 hours prior to each drug administration until 24 hours post-dose. All subjects were required to return for the 36-, 48- and 72-hour blood collection. There was a 21 day washout period between the study treatments. Study drugs were administered 30 minutes after the start of a modified high fat and high calorie breakfast. The drug was administered with 240 mL of room temperature water. A mouth check was done immediately after drug administration to ensure that the drug was swallowed.

## **Adverse Events**

Health status monitoring was conducted pre-dose, at approximately 3 and 24 hours post-dose, and at all return blood collections. There were 22 adverse events (AEs) in this study.

Treatment Group	Severity			Relation to the Drug				Intervention	
	Mild	Mod	Severe	Unrelated	Remote	Possible	Probable	Required Drug Therapy	Required Non-Drug Therapy
A (Cipher)	13	0	0	2	0	11	0	0	0
B (Roche)	8	1	0	4	1	4	0	1	0
<b>Total</b>	<b>21</b>	<b>1</b>	<b>0</b>	<b>6</b>	<b>1</b>	<b>15</b>	<b>0</b>	<b>1</b>	<b>0</b>

Subject No.	Period	TRT	Adverse Event	COSTART	Duration (hrs)	Severity	Action Taken	Relationship to the Study Drug
01	1	A	Skin Rash	Rash	4.00	Mild	None	Possible
06	1	A	Headache	Headache	6.00	Mild	None	Possible
15	1	A	Headache	Headache	2.67	Mild	None	Possible
15	1	A	Intermittent Lower Left Chest Pain	Pain Chest	1.00	Mild	None	Possible
15	1	A	Dizziness	Dizziness	6.50	Mild	None	Possible
21	1	A	Nausea	Nausea	37.00	Mild	None	Possible
22	1	A	Generalized Itchiness	Skin Dry	288.00	Mild	None	Possible
22	1	A	Acne on Left Cheek	Acne	456.00	Mild	None	Possible
26	2	A	Epigastric Discomfort	Pain Abdo	0.08	Mild	None	Possible
26	2	A	Vomiting 1 Episode	Vomit	0.03	Mild	None	Possible
26	2	A	Pallor	Pallor	0.23	Mild	None	Possible

Subject No.	Period	TRT	Adverse Event	COSTART	Duration (hrs)	Severity	Action Taken	Relationship to the Study Drug
26	2	A	High Pulse Rate	Tachycardia	0.52	Mild	None	Unrelated
26	2	A	Hypertension	Hypertension	0.52	Mild	None	Unrelated
01	2	B	Back Pain	Pain Back	19.50	Mild	None	Remote
21	2	B	Elevated ALT	SGPT Inc.	12 Days	Mild	None	Possible
22	2	B	Vomiting 5 Episodes	Vomit	14.53	Moderate	Drug Therapy	Possible
26	1	B	Headache	Headache	19.17	Mild	None	Possible
26	1	B	High Pulse Rate	Tachycardia	2.62	Mild	None	Unrelated
26	1	B	Hypertension	Hypertension	0.95	Mild	None	Unrelated
26	1	B	High Pulse Rate	Tachycardia	1.08	Mild	None	Unrelated
26	1	B	High Pulse Rate	Tachycardia	7.77	Mild	None	Unrelated
41	2	B	Drowsiness	Somnolence	3.50	Mild	None	Possible

Of interest in the list of AEs is the listing of hypertension, and it being unrelated to the study drug. This is rather surprising as hypertension is a recognized side effect of retinoids. While it is true that this is rather sudden, still it is not far fetched to consider this to be at least possible and not unrelated as coded here.

## **Results**

Tables of the individual pharmacokinetic profiles, mean plasma level time profiles, box whisker plots, and associated statistical tables are attached.

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**Table 9 - Individual Isotretinoin Pharmacokinetic Parameters**  
 Treatment A: Isotretinoin Capsules 20 mg, Lot No.: 28A02 (Cipher Canada Inc., Canada)  
 Treatment B: ACCUTANE® Capsules 20 mg, Lot No.: U3629 (Roche Laboratories Inc., USA)

Treatment=A													
Subject	SEQ	Period	AUC (0-t) (ng.h/mL)	AUC (0-inf) (ng.h/mL)	AUC (0-t) ----- (%) AUC (0-inf)	Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R	MRTpo (h)
01	AB	1	3382.23	3808.69	88.80	198.79	5.50	0.0314	22.07	16.00	72.00	0.9959	32.92
02	BA	2	4073.97	4660.97	87.41	228.32	12.00	0.0312	22.21	16.00	72.00	0.9930	36.42
03	AB	1	3740.05	4195.97	89.13	243.00	10.00	0.0331	20.93	16.00	72.00	0.9933	34.12
04	BA	2	4985.84	5616.23	88.78	422.60	8.00	0.0309	22.40	16.00	72.07	0.9925	32.28
05	BA	2	1978.16	2078.60	95.17	179.79	4.50	0.0417	16.63	16.00	72.00	0.9987	23.32
06	AB	1	5336.40	6259.82	85.25	228.00	10.00	0.0280	24.71	16.00	72.00	0.9943	39.17
07	AB	1	2489.20	2680.61	92.86	273.61	4.50	0.0359	19.30	16.00	72.00	0.9913	25.15
08	BA	2	2394.32	2791.44	85.77	123.70	5.50	0.0264	26.21	16.00	72.00	0.9947	37.12
09	BA	2	2632.81	2672.47	98.52	217.41	5.00	0.0595	11.65	16.00	72.00	0.9979	19.12
10	BA	2	2451.79	2487.14	98.58	242.45	2.50	0.0560	12.38	16.00	72.00	0.9964	14.04
11	AB	1	2755.68	3188.85	86.42	132.33	4.52	0.0287	24.15	16.00	72.00	0.9939	36.14
12	AB	1	3603.73	3765.87	95.69	222.87	4.50	0.0425	16.31	16.00	73.13	0.9964	24.08
13	AB	1	3898.09	3960.21	98.43	382.65	4.50	0.0586	11.83	16.02	72.00	0.9988	18.75
14	BA	2	2957.17	3136.64	94.28	163.29	8.00	0.0421	16.46	16.00	72.00	0.9911	25.95
15	AB	1	3201.13	3889.76	82.30	185.47	4.50	0.0249	27.79	16.00	72.00	0.9949	41.63
16	BA	2	3185.96			295.93	7.00				72.18		
17	AB	1	4529.78	5323.75	85.09	393.50	5.00	0.0258	26.84	16.00	72.00	0.9877	37.04
18	AB	1	5076.79	5934.90	85.54	245.36	8.00	0.0285	24.32	16.00	72.00	0.9815	37.60
19	BA	2	3881.31	4068.74	95.39	269.22	4.50	0.0439	15.79	16.00	72.00	0.9983	24.60
20	BA	2	3183.13	3284.49	96.91	396.44	4.50	0.0475	14.59	16.00	72.00	0.9959	20.67
21	AB	1	4883.44	6347.76	76.93	129.86	20.00	0.0220	31.56	16.00	72.03	0.9544	51.40
22	AB	1	5047.16	5617.51	89.85	173.44	10.00	0.0343	20.24	16.00	72.00	0.9925	33.55
23	BA	2	4159.98	4460.43	93.26	289.73	5.50	0.0361	19.22	16.00	72.00	0.9930	27.94
24	BA	2	3842.34	4042.26	95.05	240.32	7.00	0.0425	16.32	16.00	72.00	0.9969	24.61
25	AB	1	2988.07	3104.26	96.26	216.86	7.00	0.0477	14.52	16.00	72.00	0.9984	25.04
26	BA	2	3224.09	3545.78	90.93	232.62	2.50	0.0352	19.70	16.00	72.00	0.9917	30.86
27	BA	2	3243.07	3467.89	93.52	184.27	10.00	0.0412	16.80	16.00	72.00	0.9946	28.33
28	AB	1	3519.74	3611.83	97.45	203.59	5.50	0.0543	12.76	16.00	72.00	0.9989	22.10
29	AB	1	3663.91	3788.71	96.71	154.77	3.00	0.0497	13.94	16.00	72.00	0.9960	22.96
30	BA	2	3995.66	4282.59	93.30	194.63	2.50	0.0370	18.72	16.00	72.00	0.9979	26.63
31	AB	1	2271.64	2436.32	93.24	94.40	12.00	0.0404	17.16	16.00	72.00	0.9958	29.41
32	BA	2	3510.00	3603.78	97.40	173.00	14.03	0.0562	12.34	16.00	72.00	0.9980	23.26
33	AB	1	3796.17	4185.54	90.70	215.29	4.50	0.0336	20.62	16.00	72.00	0.9963	30.73

\* TLIN = start time for linear regression  
 \*\* LQCT = last quantifiable concentration time  
 \*\*\* R = correlation coefficient obtained from regression analysis

**Treatment A: Isotretinoin Capsules 20 mg, Lot No.: 28A02 (Cipher Canada Inc., Canada)**  
**Treatment B: ACCUTANE® Capsules 20 mg, Lot No.: U3629 (Roche Laboratories Inc., USA)**

Treatment=A													
Subject	SEQ	Period	AUC (0-t) (ng.h/mL)	AUC (0-inf) (ng.h/mL)	AUC (0-t) ----- (%) AUC (0-inf)	Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R	MRTpo (h)
34	AB	1	3353.11	3681.12	91.09	179.22	5.50	0.0333	20.83	16.00	72.00	0.9965	31.10
35	BA	2	3670.38	4148.54	88.47	314.65	5.00	0.0306	22.63	16.00	72.25	0.9858	32.43
36	BA	2	4064.34	4141.13	98.15	205.00	12.00	0.0629	11.02	16.00	72.00	0.9794	22.74
37	AB	1	3446.31	3706.84	92.97	409.00	4.50	0.0355	19.50	16.00	72.00	0.9979	25.41
38	BA	2	3961.35	4339.72	91.28	185.72	10.00	0.0379	18.31	16.00	72.00	0.9933	31.93
39	BA	2	3979.32	5050.95	78.78	200.41	5.00	0.0219	31.59	16.00	72.00	0.9961	46.75
40	AB	1	3576.35	3863.09	92.58	233.29	4.50	0.0390	17.77	16.00	72.00	0.9859	29.20
41	AB	1	3916.96	4135.46	94.72	205.00	5.50	0.0432	16.04	16.00	72.00	0.9873	26.16
42	BA	2	3103.26	3318.89	93.50	176.00	5.00	0.0404	17.16	16.00	72.00	0.9968	27.40
43	BA	2	3278.13	3535.97	92.71	175.28	8.00	0.0379	18.27	16.00	72.00	0.9939	27.61
44	BA	2	3762.88	3967.60	94.84	202.78	6.00	0.0434	15.99	16.00	72.00	0.9980	25.47
45	BA	2	4498.57	4617.56	97.42	258.71	10.05	0.0514	13.50	16.00	72.00	0.9986	21.50
46	AB	1	3827.42	4670.22	81.95	208.80	8.00	0.0254	27.30	16.00	72.00	0.9879	42.93
47	AB	1	4040.93	4419.30	91.44	347.35	4.50	0.0347	19.95	16.00	72.00	0.9952	29.38
48	BA	2	2991.22	3303.12	90.56	175.67	2.00	0.0317	21.90	16.00	72.00	0.9966	29.88
49	BA	2	3793.83	4111.21	92.28	166.80	5.00	0.0381	18.19	16.00	72.00	0.9989	30.52
50	AB	1	4256.95	4464.29	95.36	424.86	4.50	0.0432	16.04	16.00	72.00	0.9963	23.26
51	AB	1	3571.09	3847.78	92.81	131.87	14.00	0.0411	16.86	16.00	72.00	0.9924	31.26
52	BA	2	3507.55	3967.95	88.40	147.84	10.00	0.0324	21.36	16.00	72.03	0.9872	35.46
53	AB	1	4261.28	4922.09	86.57	164.97	7.00	0.0293	23.65	16.00	72.00	0.9931	37.59
54	BA	2	3160.39	3326.08	95.02	201.67	7.00	0.0436	15.91	16.00	72.00	0.9973	25.54
MEAN	.	.	3627.86	3996.96	91.62	227.08	6.84	0.0386	19.14	16.00	72.03	0.9933	29.63
STD	.	.	725.89	924.25	5.05	79.65	3.45	0.0098	4.88	0.00	0.16	0.0070	7.24
CV (%)	.	.	20.01	23.12	5.51	35.08	50.47	25.4771	25.51	0.01	0.22	0.7062	24.43

\* TLIN = start time for linear regression  
 \*\* LQCT = last quantifiable concentration time  
 \*\*\* R = correlation coefficient obtained from regression analysis

Treatment A: Isotretinoin Capsules 20 mg, Lot No.: 28A02 (Ciphar Canada Inc., Canada)  
 Treatment B: ACCUTANE® Capsules 20 mg, Lot No.: U3629 (Roche Laboratories Inc., USA)

----- Treatment=B -----													
Subject	SEQ	Period	AUC (0-t) (ng.h/mL)	AUC (0-inf) (ng.h/mL)	AUC (0-t) ----- (%) AUC (0-inf)	Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R	MRTpo (h)
01	AB	2	3476.53	4063.36	85.56	355.60	5.50	0.0262	26.41	16.00	72.00	0.9900	36.80
02	BA	1	4152.49	4918.43	84.43	213.91	5.00	0.0283	24.46	16.00	72.00	0.9717	39.86
03	AB	2	4850.95	5780.34	83.92	201.00	10.00	0.0278	24.97	16.00	72.00	0.9356	41.65
04	BA	1	5152.30	5863.51	87.87	360.84	10.00	0.0307	22.57	16.00	72.00	0.9965	35.25
05	BA	1	2798.58	2990.67	93.58	258.83	5.50	0.0374	18.53	16.00	72.00	0.9977	25.48
06	AB	2	5184.79	5794.12	89.48	312.00	7.00	0.0333	20.81	16.00	72.00	0.9942	33.32
07	AB	2	3385.32	3628.48	93.30	359.59	5.50	0.0355	19.52	16.03	72.00	0.9933	25.55
08	BA	1	2422.71	2983.41	81.21	150.56	6.00	0.0238	29.09	16.00	72.00	0.9924	43.01
09	BA	1	2747.23	2882.59	95.30	320.89	4.50	0.0423	16.37	16.00	72.00	0.9869	21.58
10	BA	1	4664.90	4752.60	98.15	649.69	4.50	0.0535	12.96	16.00	72.00	0.9993	17.73
11	AB	2	3961.83	4413.05	89.78	288.68	4.50	0.0316	21.90	16.00	72.00	0.9981	31.68
12	AB	2	3606.92	3878.07	93.01	343.59	6.00	0.0391	17.74	16.00	72.00	0.9941	27.79
13	AB	2	4151.23	4276.37	97.07	245.91	4.00	0.0529	13.11	16.00	72.00	0.9917	21.61
14	BA	1	3439.24	3573.76	96.24	227.74	8.00	0.0474	14.62	16.00	72.00	0.9975	23.88
15	AB	2	4658.90	6474.03	71.96	392.42	5.00	0.0185	37.53	16.00	72.00	0.9758	55.22
16	BA	1	2735.22	.	.	462.77	4.50	.	.	.	72.70	.	.
17	AB	2	4866.37	5817.41	83.65	374.55	6.00	0.0248	28.00	16.00	72.00	0.9890	40.58
18	AB	2	4612.82	5345.84	86.29	201.51	10.00	0.0325	21.34	16.00	72.37	0.9765	39.34
19	BA	1	3937.59	4123.72	95.49	255.91	10.00	0.0449	15.42	16.00	72.02	0.9977	27.36
20	BA	1	3349.12	3442.78	97.28	436.02	5.00	0.0494	14.04	16.00	72.00	0.9971	19.68
21	AB	2	4610.57	5777.03	79.81	164.87	12.00	0.0254	27.34	16.00	72.00	0.9961	47.42
22	AB	2	5533.73	5706.76	96.97	353.28	7.00	0.0353	19.63	16.00	99.70	0.9995	29.90
23	BA	1	3276.28	3577.91	91.57	235.72	2.00	0.0329	21.07	16.00	72.00	0.9912	28.14
24	BA	1	4309.92	4639.31	92.90	267.00	8.00	0.0376	18.41	16.00	72.00	0.9959	29.30
25	AB	2	4153.50	4509.06	92.11	265.87	4.50	0.0354	19.61	16.00	72.00	0.9988	28.51
26	BA	1	4722.01	5120.49	92.22	314.79	4.50	0.0374	18.55	16.00	72.00	0.9964	29.70
27	BA	1	3510.82	3759.57	93.38	179.72	14.00	0.0423	16.38	16.00	72.00	0.9988	31.15
28	AB	2	4787.34	4976.86	96.19	180.73	20.00	0.0503	13.78	16.00	72.00	0.9841	26.99
29	AB	2	4150.31	4310.69	96.28	241.87	4.02	0.0492	14.10	16.00	72.00	0.9997	24.86
30	BA	1	4080.36	4323.86	94.37	232.86	7.00	0.0405	17.12	16.00	72.00	0.9960	26.34
31	AB	2	2610.44	2782.57	93.81	137.00	10.00	0.0420	16.50	16.00	72.00	0.9983	29.21
32	BA	1	3751.44	3839.90	97.70	205.29	6.00	0.0547	12.66	16.00	72.00	0.9978	20.89
33	AB	2	4501.58	4983.45	90.33	247.40	10.00	0.0342	20.24	16.00	72.00	0.9994	32.43

Treatment A: Isotretinoin Capsules 20 mg, Lot No.: 28A02 (Ciphar Canada Inc., Canada)  
 Treatment B: ACCUTANE® Capsules 20 mg, Lot No.: U3629 (Roche Laboratories Inc., USA)

----- Treatment=B -----													
Subject	SEQ	Period	AUC (0-t) (ng.h/mL)	AUC (0-inf) (ng.h/mL)	AUC (0-t) ----- (%) AUC (0-inf)	Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R	MRTpo (h)
34	AB	2	3254.58	3664.04	88.82	197.87	2.50	0.0290	23.90	16.00	72.00	0.9958	31.79
35	BA	1	3593.50	3963.51	90.66	264.24	3.50	0.0333	20.79	16.00	72.00	0.9924	29.67
36	BA	1	4197.55	4255.23	98.64	471.66	10.00	0.0655	10.58	16.00	72.00	0.9961	20.98
37	AB	2	3896.34	4054.11	96.11	629.63	4.50	0.0447	15.52	16.00	72.00	0.9986	21.69
38	BA	1	2513.68	2795.81	89.91	141.53	2.00	0.0310	22.39	16.00	72.00	0.9943	29.04
39	BA	1	4041.13	4874.85	82.90	379.58	4.50	0.0230	30.12	16.00	72.00	0.9973	39.88
40	AB	2	3627.61	3869.84	93.74	268.51	10.00	0.0417	16.61	16.00	72.00	0.9958	28.93
41	AB	2	4781.93	4964.21	96.33	340.00	5.50	0.0507	13.67	16.00	72.25	0.9963	24.41
42	AB	2	3865.86	4193.32	92.19	336.00	5.00	0.0366	18.92	16.00	72.00	0.9978	28.62
43	BA	1	4517.93	4868.12	92.81	350.72	4.50	0.0375	18.51	16.00	72.00	0.9995	28.98
44	BA	1	4109.22	4421.30	92.94	148.87	16.00	0.0429	16.18	16.00	72.00	0.9913	30.26
45	BA	1	4250.73	4418.90	96.19	301.83	10.00	0.0484	14.32	16.00	72.00	0.9934	23.44
46	AB	2	3703.80	4570.48	81.04	212.71	10.00	0.0247	28.06	16.00	72.00	0.9987	44.90
47	AB	2	4682.46	5148.34	90.95	432.51	5.50	0.0337	20.56	16.00	72.00	0.9951	30.56
48	BA	1	3764.04	3997.82	94.15	469.90	4.00	0.0389	17.80	16.00	72.00	0.9969	24.06
49	BA	1	3945.80	4209.84	93.73	197.30	5.50	0.0402	17.26	16.00	72.00	0.9984	28.06
50	AB	2	4605.56	4787.97	96.19	422.57	5.50	0.0455	15.25	16.00	72.00	0.9983	22.15
51	AB	2	3803.02	4034.72	94.26	173.89	4.00	0.0427	16.24	16.00	72.00	0.9962	27.43
52	BA	1	3664.94	4118.37	88.99	139.85	10.00	0.0334	20.75	16.00	72.13	0.9336	35.27
53	AB	2	3404.59	4167.10	81.70	124.92	4.50	0.0238	29.17	16.00	72.00	0.9955	41.58
54	BA	1	4023.89	4188.11	96.08	283.90	10.00	0.0489	14.18	16.00	72.00	0.9934	24.66
MEAN	.	.	3970.40	4393.89	91.31	291.23	6.90	0.0380	19.54	16.00	72.54	0.9921	30.35
STD	.	.	709.86	846.17	5.66	116.27	3.50	0.0097	5.43	0.00	3.77	0.0129	7.73
CV (%)	.	.	17.88	19.26	6.20	39.92	50.77	25.5926	27.79	0.03	5.19	1.3026	25.46

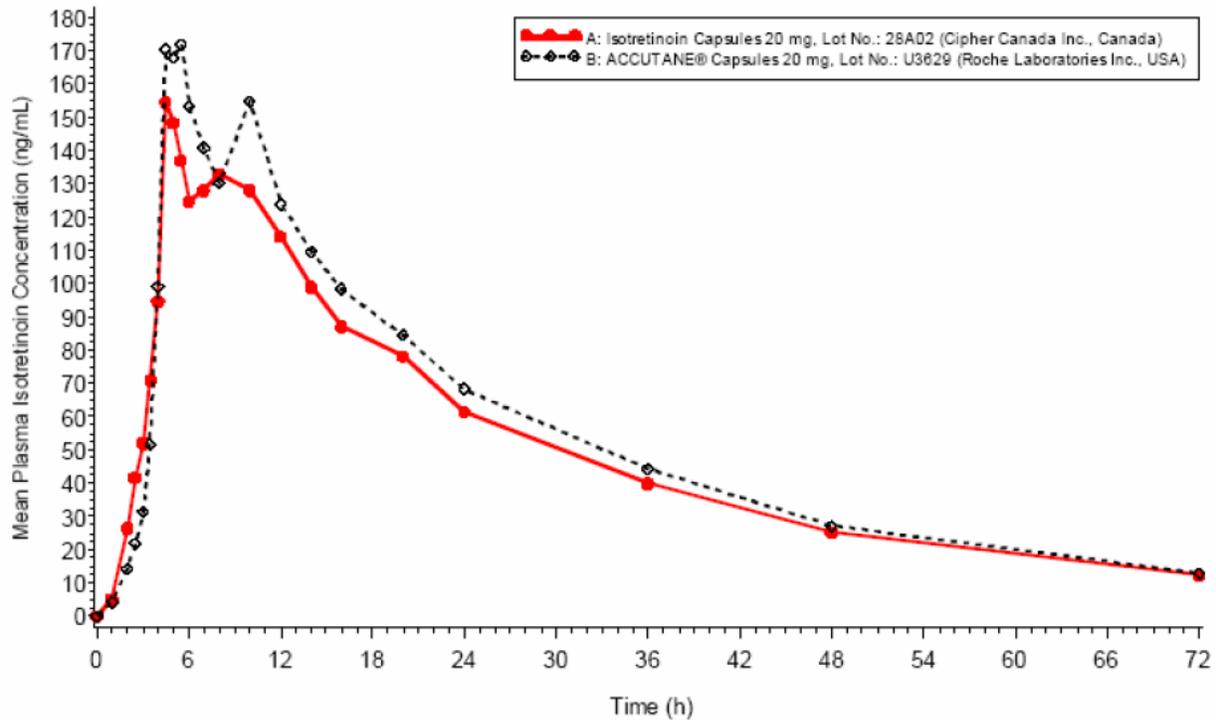
\* TLIN = start time for linear regression  
 \*\* LQCT = last quantifiable concentration time  
 \*\*\* R = correlation coefficient obtained from regression analysis

Summary of Results for Plasma Isotretinoin  
(N = 54)

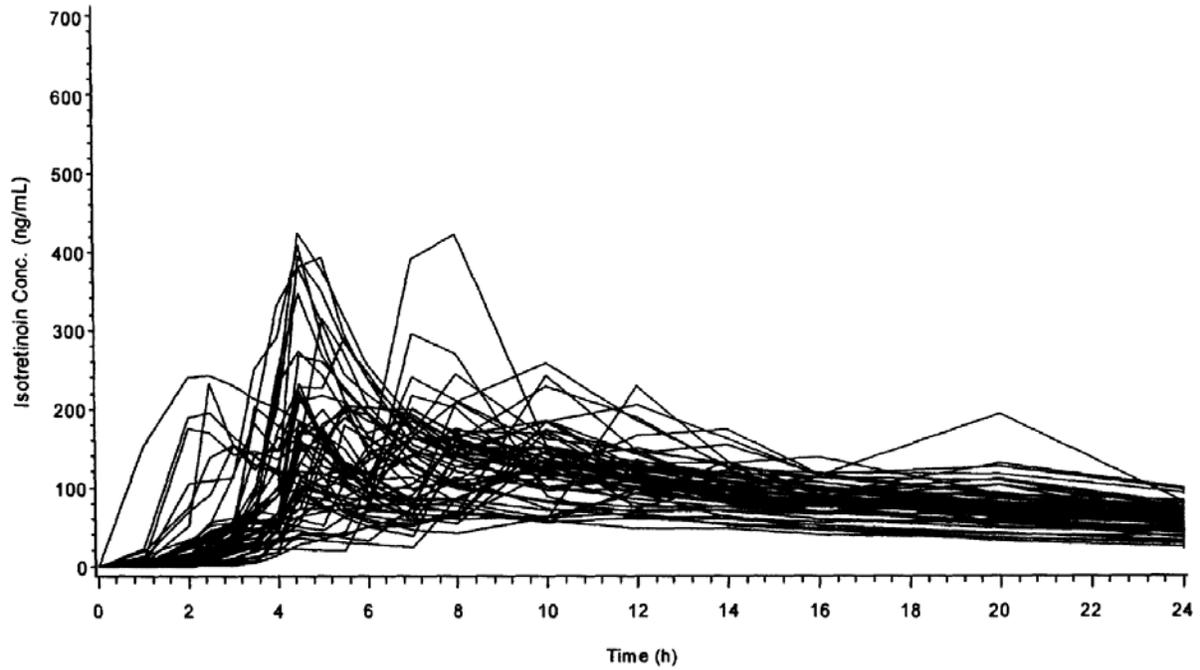
Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra- Subject (CV%)
	Cipher 20mg (FED)	Accutane 20mg (FED)			
AUC <sub>t</sub> (ng*h/mL)	3554.13 3627.86 (20)	3904.04 3970.40 (18)	91.04	87.38 - 94.84	13
AUC <sub>i</sub> (ng*h/mL)	3889.79 3996.96 (23)	4307.77 4393.89 (19)	90.30	86.58 - 94.17	13
C <sub>max</sub> (ng/mL)	214.98 227.08 (35)	270.31 291.23 (40)	79.53	73.54 - 86.02	25
T <sub>max</sub> <sup>a</sup> (h)	6.84 (50)	6.90 (51)	-	-	-
kel <sup>a</sup> (1/h)	0.0386 (25)	0.0380 (26)	-	-	-
Thalf <sup>a</sup> (h)	19.14 (26)	19.54 (28)	-	-	-

<sup>a</sup> Presented as arithmetic mean (CV%) only.

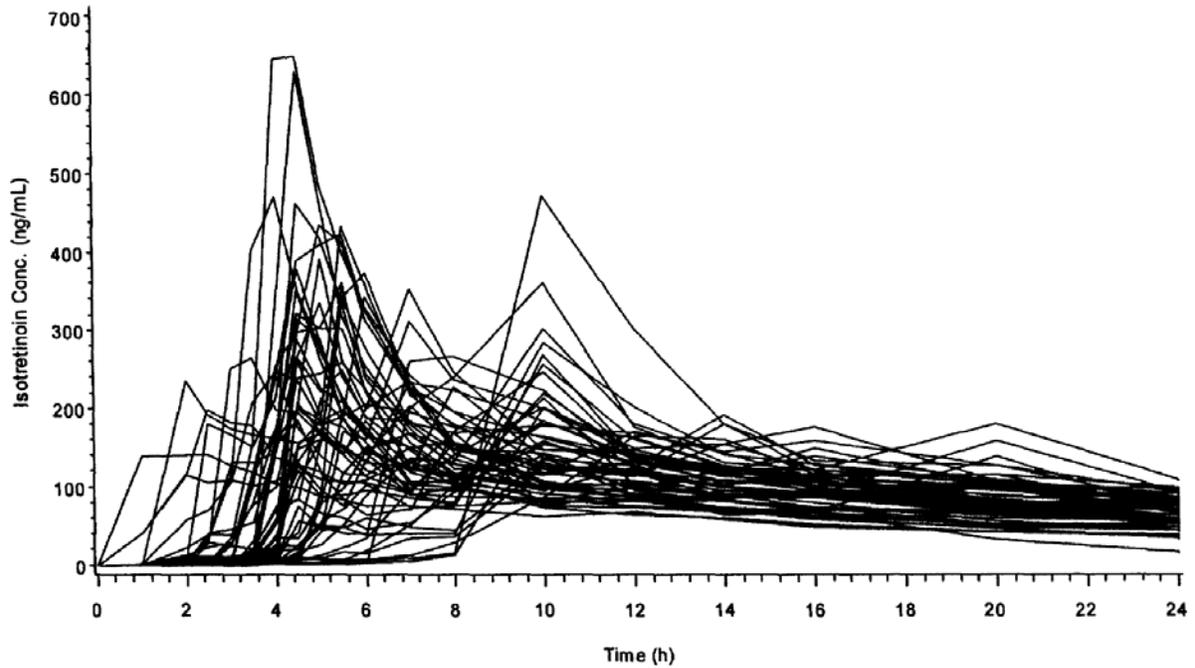
STUDY No.: 2004-727  
MEAN PLASMA ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES  
N=54



STUDY No.: 2004-727  
BASELINE-ADJUSTED PLASMA ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES  
Treatment A: Isotretinoin Capsules 20 mg, Lot No.: 28A02 (Cipher Canada Inc., Canada)  
N=54



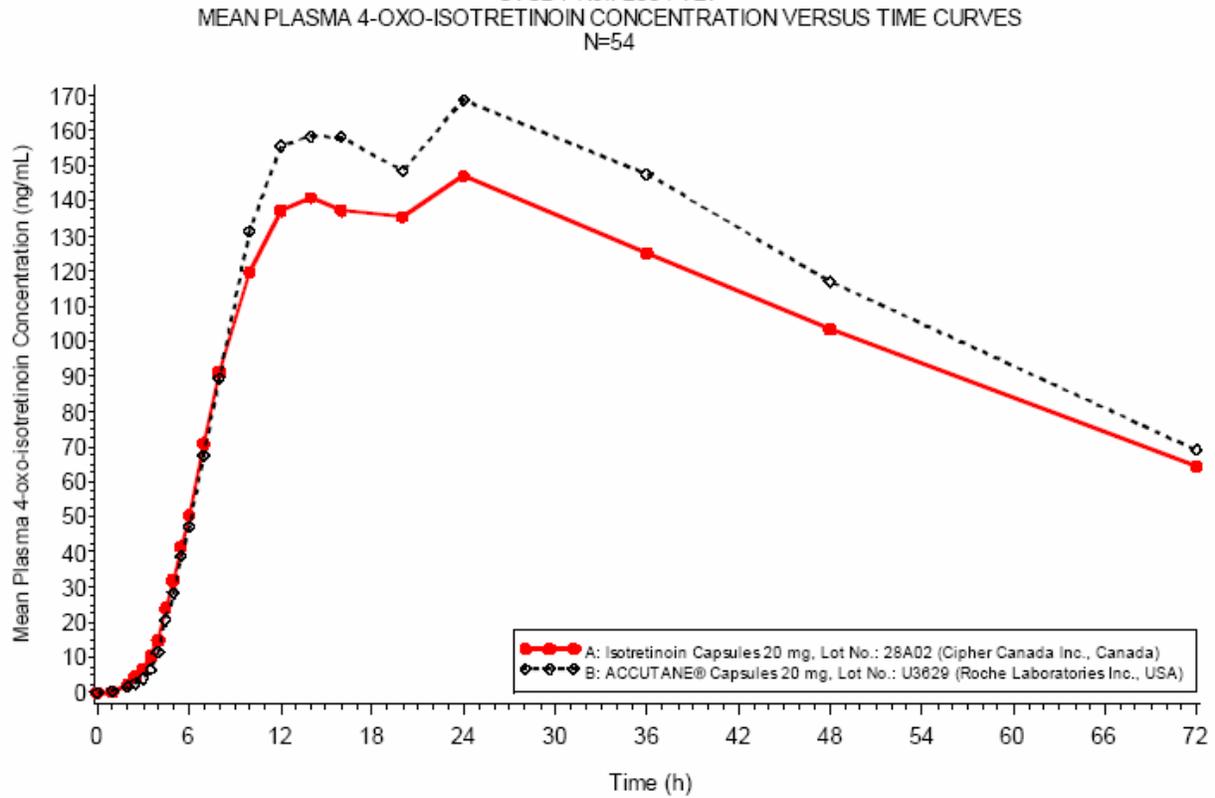
STUDY No.: 2004-727  
BASELINE-ADJUSTED PLASMA ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES  
Treatment B: ACCUTANE® Capsules 20 mg, Lot No.: U3629 (Roche Laboratories Inc., USA)  
N=54



Summary of Results for Plasma 4-oxo-isotretinoin  
(N = 54)

Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra- Subject (CV%)
	Cipher 20mg (FED)	Accutane 20mg (FED)			
AUC <sub>t</sub> (ng*h/mL)	7139.59 7380.60 (26)	8063.62 8343.76 (26)	88.54	84.07 - 93.24	16
AUC <sub>i</sub> (ng*h/mL)	10901.67 11472.21 (30)	12061.26 12347.55 (23)	90.39	85.62 - 95.42	16
C <sub>max</sub> (ng/mL)	156.73 162.81 (28)	177.14 185.87 (31)	88.48	83.26 - 94.02	19
T <sub>max</sub> <sup>a</sup> (h)	17.35 (39)	19.37 (46)	-	-	-
kel <sup>a</sup> (1/h)	0.0185 (35)	0.0193 (33)	-	-	-
Thalf <sup>a</sup> (h)	42.82 (38)	41.14 (43)	-	-	-

<sup>a</sup> Presented as arithmetic mean (CV%) only.

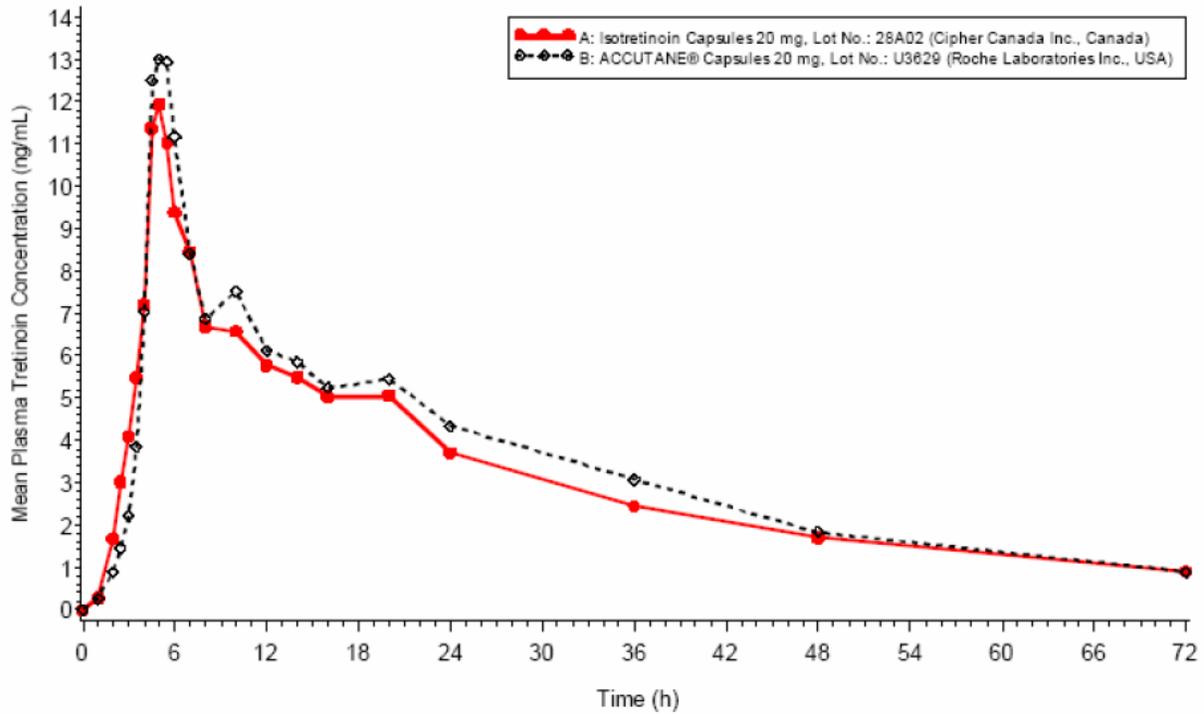


Summary of Results for Plasma Tretinoin  
(N = 54)

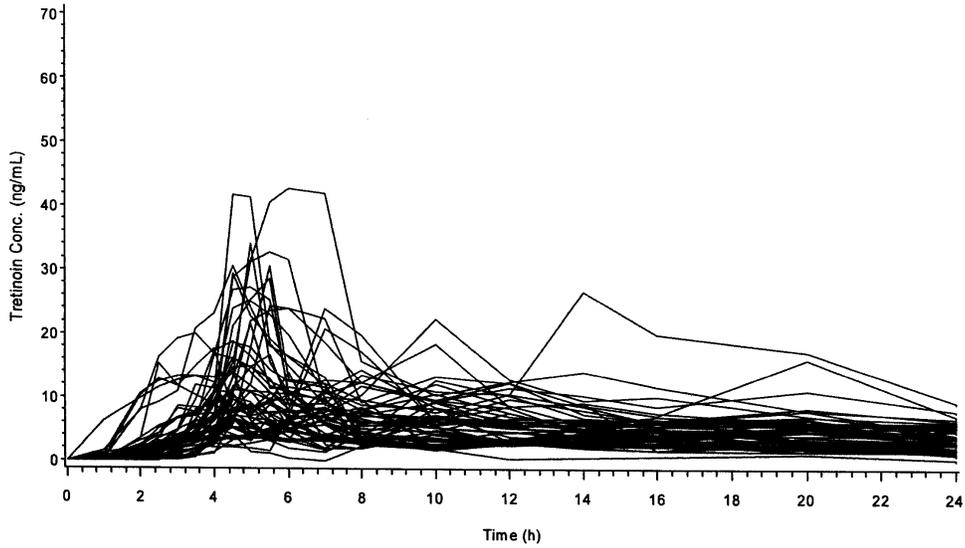
Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra- Subject (CV%)
	Cipher 20mg (FED)	Accutane 20mg (FED)			
AUC <sub>t</sub> (ng*h/mL)	208.80 225.49 (42)	230.55 246.96 (38)	90.57	85.67 - 95.74	17
AUC <sub>i</sub> (ng*h/mL)	246.07 269.23 (39)	266.92 285.76 (37)	92.19	86.67- 98.06	18
C <sub>max</sub> (ng/mL)	15.12 17.17 (53)	18.02 20.45 (55)	83.87	75.53- 93.13	33
T <sub>max</sub> <sup>a</sup> (h)	6.55 (59)	6.77 (54)	-	-	-
kel <sup>a</sup> (1/h)	0.0353 (52)	0.0377 (52)	-	-	-
Thalf <sup>a</sup> (h)	24.25 (44)	23.35 (59)	-	-	-

<sup>a</sup> Presented as arithmetic mean (CV%) only.

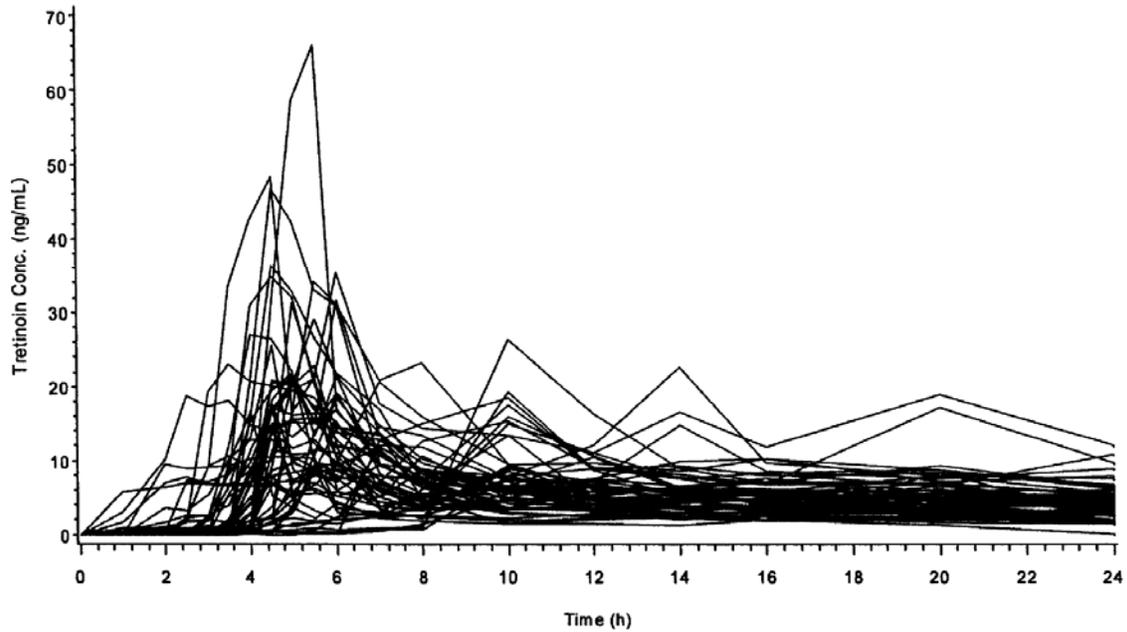
MEAN PLASMA TRETINOIN CONCENTRATION VERSUS TIME CURVES  
N=54



STUDY No.: 2004-727  
BASELINE-ADJUSTED PLASMA TRETINOIN CONCENTRATION VERSUS TIME CURVES  
Treatment A: Isotretinoin Capsules 20 mg, Lot No.: 28A02 (Cipher Canada Inc., Canada)  
N=54



STUDY No.: 2004-727  
BASELINE-ADJUSTED PLASMA TRETINOIN CONCENTRATION VERSUS TIME CURVES  
Treatment B: ACCUTANE® Capsules 20 mg, Lot No.: U3629 (Roche Laboratories Inc., USA)  
N=54

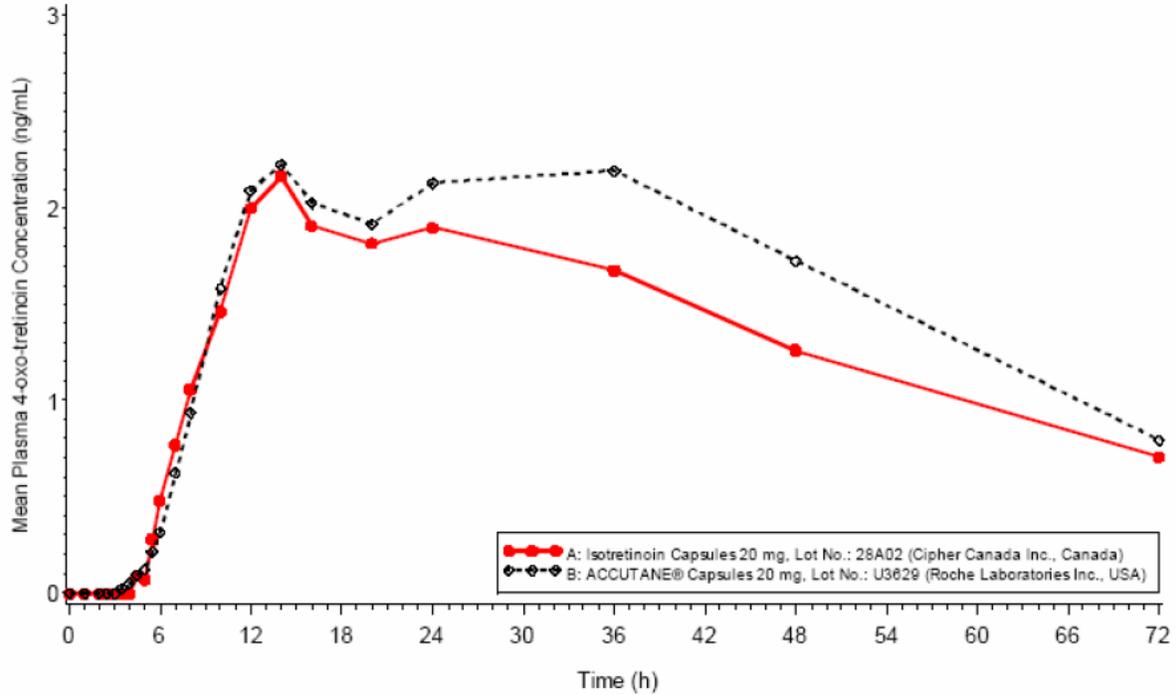


Summary of Results for Plasma 4-oxo-tretinoin  
(N = 54)

Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra- Subject (CV%)
	Treatment A	Treatment B			
AUC <sub>t</sub> (ng*h/mL)	63.60 89.16 (77)	78.86 105.33 (71)	80.65	69.06 - 94.19	50
AUC <sub>i</sub> (ng*h/mL)	179.54 208.77 (55)	188.74 227.26 (37)	95.12	80.17 - 112.86	24
C <sub>max</sub> (ng/mL)	2.46 2.74 (51)	2.70 3.01 (53)	91.26	83.51 - 99.72	27
T <sub>max</sub> <sup>a</sup> (h)	19.33 (64)	25.37 (57)	-	-	-
kel <sup>a</sup> (1/h)	0.0239 (82)	0.0234 (77)	-	-	-
Thalf <sup>a</sup> (h)	38.13 (43)	41.01 (50)	-	-	-

<sup>a</sup> Presented as arithmetic mean (CV%) only.

MEAN PLASMA 4-OXO-TRETINOIN CONCENTRATION VERSUS TIME CURVES  
N=54



## **Conclusion**

Based on isotretinoin results, the 90% confidence intervals of the ratio of geometric means of Treatment A to Treatment B for the AUC<sub>t</sub> and AUC<sub>i</sub> parameters were within the 80-125% range. However, the 90% confidence intervals of the ratio of geometric means of Treatment A to Treatment B for the C<sub>max</sub> parameter was not within the 80-125% range. A similar pattern was seen for tretinoin, while for 4-oxo-isotretinoin AUC and C<sub>max</sub> passed both sets of confidence intervals. T<sub>max</sub> was essentially unchanged for these species.

For 4-oxo-tretinoin, the picture is a bit different with the 90% confidence interval for AUC being outside the interval for AUC<sub>tau</sub> but not AUC<sub>inf</sub>. There was also a 6hr difference in T<sub>max</sub>, suggesting a slower formation of this tertiary metabolite with Accutane™

From a strict bioequivalence standpoint, the CIP-isotretinoin 20 mg capsules are not bioequivalent to Accutane™. The differences in C<sub>max</sub>, following a single dose under the influence of a high fat meal fall below the lower acceptance interval in healthy subjects.

Study PK.04.03 (2004-734)

<b>Title:</b>	A Single-Dose, Food Effect and Fed Comparative Bioavailability Study of Two Formulations of Isotretinoin Capsules 10 mg in Healthy Volunteers
<b>Objectives:</b>	<p>The primary objective of this study is to evaluate the comparative bioavailability between isotretinoin capsules 10 mg (Cipher Canada Inc., Canada) and Accutane® capsules 10 mg (Roche Laboratories Inc., USA), after a single-dose in healthy subjects under fed conditions.</p> <p>The secondary objective of this study is also to evaluate the food effect on isotretinoin capsules 10 mg (Cipher Canada Inc., Canada)</p>
<b>Treatment A: (Test 1)</b>	*Isotretinoin Capsules 10 mg; Lot No.: 16F032, (Cipher Canada Inc., Canada) [10 mg administered after a <b>modified</b> high fat, high calorie breakfast]
<b>Treatment B: (Test 2)</b>	*Isotretinoin Capsules 10 mg; Lot No.: 16F032, (Cipher Canada Inc., Canada) [10 mg administered after an overnight fast of at least 10 hours]
<b>Treatment C: (Reference)</b>	Accutane® Capsules 10 mg; Lot No.: U2624, (Roche Laboratories Inc., USA) [10 mg administered after a <b>modified</b> high fat, high calorie breakfast]
<b>Number of Subjects:</b>	Fifty-Four (54) [40 male and 14 female] subjects were dosed in Period 1, and 51 subjects completed the entire study. <ul style="list-style-type: none"><li>• Age: <math>36 \pm 9</math> yrs (18 – 53 yrs)</li><li>• Height: <math>173.4 \pm 7.2</math> cm (155.0 – 188.5 cm)</li><li>• Weight: <math>76.5 \pm 8.8</math> kg (54.8 – 92.2 kg)</li></ul>
<b>Sampling Schedule:</b>	Blood samples were obtained at -10, -2 and 0 hour pre-dose, and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14, 16, 20, 24, 36, 48 and 72 hours following drug administration.
<b>Diet (High Fat Portion):</b>	(1) Regular Bagel with 3 tablespoons of peanut butter (5) Slices of Bacon (1) Dutchie Donut (~230calories, 6gms fat, 40gms carbohydrate- <a href="http://www.timhortons.com">http://www.timhortons.com</a> ) (6) Fluid Ounces of Apple Juice

As noted above, this study was a single dose comparative bioavailability trial of the CIP-isotretinoin 10mg capsule to the marketed Roche 10mg Accutane™ capsule after a single-dose in healthy subjects under fed conditions. The study itself was an open-label, single-dose, randomized, three-period, six-sequence, three-treatment, crossover study.

Subjects who were selected for the study met the inclusion criteria and did not fulfill any of the exclusion criteria described in the study protocol, and were judged by an investigator to be medically healthy based upon medical history, physical examination, vital signs measurements

(blood pressure, heart rate, respiration rate and temperature), 12-lead ECG and clinical laboratory tests.

Given the teratogenic nature of isotretinoin, a HCG serum pregnancy test was performed for each of the 14 female subjects during screening (Subjects 01 - 12, 20 and 42). The results were negative for pregnancy. However all fourteen female subjects were re-tested for urine HCG at check-in, prior to the first drug administration. The result in all cases was negative for pregnancy.

A total of fifty-Four (54) healthy, non-smoking [40 males and 14 females] subjects were dosed in Period 1 on March 14 , 2004. Subjects 03 and 41 were dismissed from the study after completing Period 1 for not finishing the high fat, high calorie breakfast and drinking a standby's drink, respectively. Subject 47 voluntarily withdrew from study after completing Period 1 due to personal reasons.

### **Study Procedures**

Upon enrollment, subjects were randomly assigned to either sequence ABC, ACB, BAC, BCA, CAB, or CBA, according to a predetermined computer-generated randomization scheme. There was a balanced random allocation of subjects into the six sequences.

Study drugs were administered after an overnight fast of at least 10 hours (Treatment B) or 30 minutes after the start of a modified high-fat and high-calorie breakfast (Treatments A and C). The drug was administered with 240 mL of room temperature potable water. A mouth check was done immediately after drug administration to ensure that the drug was swallowed.

### **Adverse Events**

Health status monitoring was conducted prior to dosing and at approximately 3 and 24 hours post-dose, and at all return blood collections. Individual Safety Assessment forms documenting health status monitoring are included in section 31.4 *Subject CRFs*.

There were 37 adverse events (AEs) in this study.

Treatment Group	Severity			Relation to the Drug				Intervention	
	Mild	Mod	Severe	Unrelated	Remote	Possible	Probable	Required Drug Therapy	Required Non-Drug Therapy
A (Cipher Fed)	10	1	0	0	0	11	0	1	0
B (Cipher Fasted)	16	0	0	1	0	14	1	1	0
C (Roche Fed)	10	0	0	0	1	8	1	1	0
<b>Total</b>	<b>36</b>	<b>1</b>	<b>0</b>	<b>1</b>	<b>1</b>	<b>33</b>	<b>2</b>	<b>3</b>	<b>0</b>

Interestingly, while the study was not powered for safety, it appears from a cursory observation that the fasted Cipher treatment leg produced the most side effects. This is somewhat surprising given that it would be expected to have the lowest plasma levels of any treatment in the study. Again, however, the power of this study precludes any conclusions being drawn from this observation.

Subject No.	Period	TRT	Adverse Event	COSTART	Duration (hrs)	Severity	Action Taken	Relationship to the Study Drug
06	3	A	Headache	Headache	9.00	Mild	None	Possible
08	3	A	Headache	Headache	6.00	Moderate	Drug Therapy	Possible
11	2	A	Abdominal Cramps	Pain Abdo	33.00	Mild	None	Possible
11	2	A	Headache	Headache	35.00	Mild	None	Possible
20	1	A	Dry Skin, Lips and Nose	Skin Dry	28.50	Mild	None	Possible
29	2	A	Dry Throat	Pharyngitis	71.00	Mild	None	Possible
29	2	A	Stomach Pain	Pain Abdo	42.00	Mild	None	Possible
29	2	A	Headache	Headache	13.00	Mild	None	Possible
29	2	A	Dizziness	Dizziness	13.00	Mild	None	Possible
36	2	A	Headache	Headache	52.00	Mild	None	Possible
41	1	A	Headache	Headache	2 50	Mild	None	Possible
08	2	B	Headache	Headache	3 25	Mild	None	Possible
10	3	B	Light Headedness	Dizziness	1.50	Mild	None	Possible
10	3	B	Headache	Headache	15.00	Mild	None	Possible
13	2	B	Stye (Right Upper Eyelid)	Infect	184.00	Mild	None	Unrelated
20	2	B	Dry Skin	Skin Dry	82.50	Mild	None	Possible
21	1	B	Headache	Headache	13.50	Mild	None	Possible
23	3	B	Peeled Skin, Left Arm	Derm Exfol	38.50	Mild	Drug Therapy	Probable
31	2	B	Nausea	Nausea	4.58	Mild	None	Possible
31	2	B	Chilly Sensation	Chills	117.58	Mild	None	Possible
34	3	B	Elevated ALT	SGPT INC	N/A	Mild	None	Possible
36	1	B	Dizziness	Dizziness	0.42	Mild	None	Possible
36	1	B	Dryness of Mouth	Dry Mouth	20.67	Mild	None	Possible
38	2	B	Low Pulse Rate	Bradycardia	0.45	Mild	None	Possible
42	1	B	Rashes on the Face	Rash	24.00	Mild	None	Possible
42	1	B	Headache	Headache	14.00	Mild	None	Possible
43	3	B	Heartburn	Dyspepsia	2.50	Mild	None	Possible
04	1	C	Headache	Headache	66.00	Mild	None	Possible
04	1	C	Nausea	Nausea	3.93	Mild	Drug Therapy	Possible
20	3	C	Headache	Headache	13.67	Mild	None	Possible
25	1	C	Sneezing	Rhinitis	13.50	Mild	None	Remote
37	3	C	Dry Skin on Left Elbow	Skin Dry	21:33	Mild	None	Probable
40	1	C	Cracked Lips	Skin Dry	10.00	Mild	None	Possible
43	2	C	Lower Abdominal Discomfort	Pain Abdo	2.75	Mild	None	Possible
53	2	C	Drowsiness	Somnolence	2.17	Mild	None	Possible

**Results**

Tables of the individual pharmacokinetic profiles, mean plasma level time profiles, box whisker plots, and associated statistical tables are attached.

Summary of Individual Isotretinoin Pharmacokinetic Parameters  
A: Isotretinoin Capsules 30 mg, Lot# 27C02 (Cipher Canada Inc.), Fasting

----- Treatment-A -----												
Subject	SEQ	PERIOD	AUC(0-t) (ng.h/mL)	AUC(0-inf) (ng.h/mL)	AUC(0-t) -----(*) AUC(0-inf)	Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*T1/2 (h)	**LQCT (h)	***R
01	BA	2	3235.54	3578.00	90.43	255.24	3.00	0.0471	14.71	14.00	48.25	0.9970
02	AB	1	2455.99	2653.81	92.55	252.00	2.00	0.0335	20.68	16.02	72.00	0.9908
03	AB	1	3145.77	3206.63	98.10	261.80	4.50	0.0533	13.01	16.00	72.00	0.9974
04	BA	2	4379.79	4482.44	97.71	309.49	4.00	0.0509	13.62	16.00	72.00	0.9866
05	AB	1	2738.23	3203.11	85.49	205.27	4.50	0.0253	27.38	16.00	72.02	0.9984
06	BA	2	2930.82	3045.91	96.22	231.00	3.00	0.0447	15.52	16.00	72.00	0.9954
08	AB	1	3460.87	3787.22	91.38	249.22	3.00	0.0322	21.51	16.00	72.00	0.9905
10	BA	2	4495.12	4548.02	98.84	429.88	3.50	0.0604	11.48	16.00	72.00	0.9971
11	BA	2	2210.78	2290.00	96.54	177.49	3.50	0.0457	15.15	16.00	72.00	0.9975
12	AB	1	2832.23	2885.50	98.15	211.33	2.00	0.0540	12.84	16.00	72.00	0.9962
13	AB	1	3708.67	3799.96	97.60	373.82	3.50	0.0494	14.04	16.00	72.00	0.9943
14	AB	1	3713.25	3926.53	94.57	366.65	3.00	0.0383	18.09	16.00	72.00	0.9986
15	BA	2	3731.87	4083.36	91.39	204.22	4.00	0.0328	21.14	16.00	72.00	0.9953
16	BA	2	2462.83	2559.56	96.22	219.73	3.50	0.0444	15.62	16.00	72.02	0.9990
18	BA	2	3178.49	3366.77	94.41	225.00	4.50	0.0395	17.56	16.00	72.00	0.9968
19	BA	2	1897.31	1963.84	96.61	148.16	3.00	0.0466	14.88	16.00	72.02	0.9888
MEAN	.	.	3161.10	3336.29	94.76	257.51	3.41	0.0436	16.70	15.88	70.52	0.9950
STD	.	.	735.58	754.35	3.65	76.23	0.78	0.0094	4.16	0.50	5.94	0.0038
CV (%)	.	.	23.27	22.61	3.85	29.60	22.88	21.5378	24.93	3.15	8.42	0.3791

**Table 9 - Isotretinoin Pharmacokinetic Parameters**  
 Treatment A: Isotretinoin Capsules 10 mg, Lot No.: 16F032 / Fed (CIPHER Canada Inc., Canada)  
 Treatment B: Isotretinoin Capsules 10 mg, Lot Lot No.: 16F032 / Fasting (CIPHER Canada Inc., Canada)  
 Treatment C: Accutane® Capsules 10 mg, Lot No.: U2624 /Fed (Roche Laboratories Inc., USA)

Treatment=A													
Subject	SEQ	PERIOD	AUC (0-t) (ng.h/mL)	AUC (0-inf) (ng.h/mL)	AUC (0-t) ----- (%) AUC (0-inf)	Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R	MRT (h)
01	ABC	1	1913.45	2028.71	94.32	125.84	10.00	0.0442	15.67	24.00	72.00	0.9998	28.85
02	BCA	3	2201.15	2608.56	84.38	62.47	16.00	0.0314	22.11	24.00	72.00	0.9948	43.05
04	CAB	2	1956.97	2147.54	91.13	116.87	8.07	0.0337	20.56	24.00	72.00	0.9959	31.27
05	BAC	2	2200.14	2759.67	79.72	57.19	20.00	0.0261	26.58	24.00	72.00	0.9933	49.00
06	CBA	3	2677.65	3622.07	73.93	178.00	10.00	0.0201	34.45	24.05	72.07	0.9982	54.55
07	BCA	3	1648.05	1798.33	91.64	115.82	10.00	0.0367	18.87	24.00	72.00	0.9996	31.78
08	CBA	3	2413.43	3093.98	78.00	137.58	8.00	0.0211	32.80	24.00	72.00	0.9718	46.77
09	ABC	1	2575.63	2952.16	87.25	131.33	10.00	0.0314	22.07	24.00	72.00	0.9926	36.85
10	CAB	2	2425.58	2577.83	94.09	138.57	8.00	0.0418	16.58	24.00	72.00	0.9994	28.24
11	BAC	2	1907.47	2113.35	90.26	71.33	12.00	0.0351	19.77	24.00	72.00	0.9999	34.06
12	ACB	1	1900.33	2060.94	92.21	114.71	5.00	0.0350	19.80	24.00	72.00	0.9967	29.20
13	ABC	1	2863.20	3232.92	88.56	133.74	7.00	0.0317	21.83	24.00	72.00	0.9994	34.68
14	ACB	1	1905.89	2073.80	91.90	124.67	8.00	0.0364	19.06	24.00	72.00	0.9985	30.12
15	BCA	3	1978.85	2118.07	93.43	241.00	4.00	0.0371	18.67	24.00	72.00	0.9974	25.49
16	CBA	3	2101.88	2286.93	91.91	127.00	4.52	0.0354	19.58	24.00	72.00	0.9802	28.50
17	CAB	2	1299.66	1490.64	87.19	105.29	3.50	0.0268	25.82	24.00	72.02	0.9808	32.84
18	BAC	2	1879.15	2029.44	92.59	128.86	4.50	0.0355	19.51	24.00	72.00	0.9978	27.96
19	CBA	3	2714.12	2758.86	98.38	276.14	4.50	0.0568	12.19	24.00	72.00	0.9982	18.73
20	ABC	1	2944.75	3141.15	93.75	255.66	8.00	0.0392	17.67	24.00	72.00	0.9958	26.93
21	BAC	2	2021.70	2119.84	95.37	105.88	10.08	0.0444	15.60	24.00	72.00	0.9990	25.78
22	BCA	3	1600.27	1697.24	94.29	148.91	4.50	0.0411	16.85	24.00	72.00	0.9487	26.28
23	ACB	1	1906.34	2057.10	92.67	196.59	4.50	0.0358	19.38	24.00	72.00	0.9971	27.63
24	CAB	2	1976.55	2166.62	91.23	121.00	8.00	0.0359	19.29	24.00	72.00	0.9948	31.10
25	CAB	2	2113.01	2174.47	97.17	97.50	5.00	0.0540	12.83	24.00	72.00	0.9931	22.87
26	ABC	1	1726.28	1975.08	87.40	101.00	10.00	0.0311	22.31	24.00	72.00	0.9939	37.44
27	CBA	3	1891.50	1999.28	94.61	216.73	4.50	0.0387	17.92	24.00	72.02	0.9965	23.49
28	ACB	1	1790.94	1925.27	93.02	126.66	8.00	0.0380	18.22	24.00	72.00	0.9983	28.07
29	BAC	2	2448.34	2557.70	95.72	107.89	8.00	0.0458	15.14	24.00	72.00	0.9997	24.76
30	BCA	3	1687.53	1745.30	96.69	104.77	4.50	0.0484	14.32	24.00	72.00	0.9980	21.67

Treatment A: Isotretinoin Capsules 10 mg, Lot No.: 16F032 / Fed (CIPHER Canada Inc., Canada)  
 Treatment B: Isotretinoin Capsules 10 mg, Lot Lot No.: 16F032 / Fasting (CIPHER Canada Inc., Canada)  
 Treatment C: Accutane® Capsules 10 mg, Lot No.: U2624 /Fed (Roche Laboratories Inc., USA)

Treatment=A (continued)													
Subject	SEQ	PERIOD	AUC (0-t) (ng.h/mL)	AUC (0-inf) (ng.h/mL)	AUC (0-t) ----- (%) AUC (0-inf)	Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R	MRT (h)
31	ABC	1	2271.97	2459.40	92.38	152.70	3.00	0.0354	19.56	24.00	72.00	0.9941	27.85
32	CAB	2	1687.85	1845.43	91.46	85.63	4.50	0.0335	20.69	24.00	72.00	0.9839	29.77
33	CBA	3	2335.94	2727.79	85.63	98.80	10.00	0.0276	25.15	24.00	72.00	0.9969	38.69
34	ACB	1	2287.16	2416.01	94.67	147.00	4.52	0.0413	16.79	24.02	72.07	0.9997	26.11
35	BCA	3	2118.86	2250.99	94.13	180.00	6.00	0.0391	17.71	24.00	72.00	0.9986	25.60
36	BAC	2	2992.32	3080.24	97.15	254.28	10.00	0.0535	12.95	24.02	72.00	0.9984	24.38
37	ABC	1	1905.12	2017.93	94.41	112.66	2.50	0.0382	18.13	24.00	72.00	0.9984	23.37
38	CBA	3	1759.90	1919.78	91.67	126.86	4.50	0.0337	20.55	24.00	72.02	0.9986	29.15
39	BCA	3	2023.70	2114.55	95.70	207.00	4.50	0.0417	16.62	24.00	72.00	0.9990	22.10
40	CAB	2	1356.26	1427.11	95.04	93.47	3.00	0.0405	17.13	24.00	72.00	0.9993	23.16
42	BAC	2	1813.82	2304.58	78.70	58.95	10.00	0.0231	29.97	24.00	72.00	0.9960	47.51
43	ACB	1	1483.74	1512.99	98.07	151.48	5.00	0.0554	12.52	24.00	72.00	0.9970	19.63
44	ABC	1	1656.72	1790.36	92.54	122.88	4.50	0.0348	19.94	24.00	72.00	0.9929	27.34
45	BAC	2	1491.00	1592.84	93.61	150.27	4.50	0.0367	18.87	24.00	72.00	0.9980	25.47
46	CAB	2	2309.85	2434.88	94.87	198.11	4.50	0.0387	17.92	24.00	72.52	0.9971	22.69
48	BCA	3	1490.82	1598.66	93.25	69.65	4.50	0.0395	17.53	24.00	72.00	0.9960	29.57
49	ABC	1	1472.61	1500.77	98.12	98.85	5.00	0.0584	11.88	24.00	72.00	0.9986	21.43
50	CBA	3	2289.97	2442.48	93.76	118.71	4.00	0.0403	17.20	24.00	72.00	0.9993	27.49
51	BAC	2	1756.52	1945.09	90.31	79.92	8.00	0.0341	20.34	23.00	72.00	0.9954	31.83
52	CAB	2	2240.21	2381.48	94.07	81.21	10.00	0.0417	16.63	24.00	72.12	0.9806	30.82
53	BCA	3	2273.57	2514.88	90.40	151.00	4.50	0.0323	21.44	24.00	72.77	0.9971	31.95
54	ACB	1	1411.55	1570.56	89.88	108.29	6.00	0.0288	24.07	24.00	77.38	0.9937	32.61
MEAN	.	.	2021.55	2218.86	91.62	133.66	6.89	0.0376	19.39	23.98	72.14	0.9945	29.93
STD	.	.	410.26	498.22	5.18	51.43	3.39	0.0084	4.65	0.14	0.76	0.0088	7.56
CV (%)	.	.	20.29	22.45	5.65	38.48	49.22	22.3126	23.99	0.59	1.05	0.8801	25.27

\* TLIN = start time for linear regression  
 \*\* LQCT = last quantifiable concentration time  
 \*\*\* R = correlation coefficient obtained from regression analysis

**Table 9 - Isotretinoin Pharmacokinetic Parameters**  
 Treatment A: Isotretinoin Capsules 10 mg, Lot No.: 16F032 / Fed (Cipher Canada Inc., Canada)  
 Treatment B: Isotretinoin Capsules 10 mg, Lot Lot No.: 16F032 / Fasting (Cipher Canada Inc., Canada)  
 Treatment C: Accutane® Capsules 10 mg, Lot No.: U2624 /Fed (Roche Laboratories Inc., USA)

Subject	SEQ	PERIOD	AUC (0-t) (ng.h/mL)	AUC (0-inf) (ng.h/mL)	AUC (0-t)		Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R	MRT (h)
					----- (%)	AUC (0-inf)								
01	ABC	2	1231.27	1398.77	88.03	104.00	1.50	0.0273	25.35	24.00	72.00	0.9996	31.71	
02	BCA	1	1966.21	2180.89	90.16	176.72	2.50	0.0297	23.35	24.02	72.00	0.9949	29.31	
04	CAB	3	1138.70	1240.53	91.79	72.38	4.52	0.0333	20.82	24.00	72.00	0.9947	27.90	
05	BAC	1	708.92	980.31	72.32	30.56	2.00	0.0179	38.79	24.00	72.00	0.9899	55.22	
06	CBA	2	1812.77	2288.45	79.21	98.75	2.50	0.0213	32.47	24.00	72.00	0.9734	44.42	
07	BCA	1	1020.00	1112.69	91.67	69.03	4.50	0.0347	19.95	24.00	72.00	0.9993	29.14	
08	CBA	2	715.11	820.20	87.19	53.97	1.50	0.0273	25.38	24.00	72.00	0.9981	34.04	
09	ABC	2	1785.76	2138.46	83.51	89.36	3.00	0.0239	28.94	24.07	72.00	0.9971	39.45	
10	CAB	3	1145.53	1241.08	92.30	60.10	2.50	0.0359	19.33	24.05	72.00	0.9908	29.15	
11	BAC	1	1174.60	1414.93	83.01	53.56	3.50	0.0236	29.40	24.00	72.00	0.9841	40.04	
12	ACB	3	1322.66	1427.67	92.64	104.64	3.00	0.0339	20.47	24.00	72.10	0.9950	26.24	
13	ABC	2	1880.37	2128.30	88.35	105.82	3.50	0.0293	23.66	24.00	72.00	0.9954	32.98	
14	ACB	3	1564.03	1741.93	89.79	102.66	3.00	0.0306	22.63	24.02	72.38	0.9942	30.07	
15	BCA	1	1073.06	1188.08	90.32	80.82	3.00	0.0311	22.31	24.00	72.00	0.9963	28.79	
16	CBA	2	1182.17	1217.89	97.07	68.45	6.00	0.0484	14.32	24.00	72.00	0.9973	21.59	
17	CAB	3	952.77	1041.44	91.49	55.96	4.00	0.0339	20.46	24.00	72.10	0.9932	28.11	
18	BAC	1	627.89	750.94	86.61	56.63	1.50	0.0221	31.32	24.00	72.00	0.9805	38.14	
19	CBA	2	1365.93	1410.93	96.81	119.65	1.50	0.0433	16.02	24.00	72.00	0.9930	18.85	
20	ABC	2	1431.61	1534.40	93.30	79.45	1.53	0.0366	18.93	24.00	72.00	0.9986	26.08	
21	BAC	1	661.55	710.93	93.06	47.41	2.00	0.0360	19.26	24.00	72.00	1.0000	25.74	
22	BCA	1	1142.19	1240.25	92.09	74.70	3.00	0.0346	20.05	24.00	72.00	0.9934	27.81	
23	ACB	3	850.84	1009.35	84.30	42.40	2.00	0.0249	27.89	24.00	72.00	0.9975	37.72	
24	CAB	3	1980.86	2163.98	91.54	129.00	2.50	0.0343	20.18	24.00	72.00	0.9977	28.80	
25	CAB	3	1247.42	1306.74	95.46	77.90	4.00	0.0428	16.19	24.00	72.00	0.9646	21.45	
26	ABC	2	1159.16	1291.33	89.76	79.71	3.00	0.0305	22.71	24.03	72.00	1.0000	30.19	
27	CBA	2	1142.22	1198.58	95.30	62.49	4.00	0.0421	16.48	24.00	72.00	0.9927	24.23	
28	ACB	3	1289.76	1516.58	85.04	109.00	4.50	0.0236	29.40	24.00	72.00	0.9976	35.34	
29	BAC	1	1092.17	1135.90	96.15	72.33	3.00	0.0444	15.62	24.00	72.00	0.9966	21.50	
30	BCA	1	1335.69	1365.65	97.81	97.56	3.00	0.0548	12.64	24.00	72.00	1.0000	19.44	

Treatment A: Isotretinoin Capsules 10 mg, Lot No.: 16F032 / Fed (Cipher Canada Inc., Canada)  
 Treatment B: Isotretinoin Capsules 10 mg, Lot Lot No.: 16F032 / Fasting (Cipher Canada Inc., Canada)  
 Treatment C: Accutane® Capsules 10 mg, Lot No.: U2624 /Fed (Roche Laboratories Inc., USA)

Subject	SEQ	PERIOD	AUC (0-t) (ng.h/mL)	AUC (0-inf) (ng.h/mL)	AUC (0-t)		Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R	MRT (h)
					----- (%)	AUC (0-inf)								
31	ABC	2	1691.88	1833.44	92.28	98.69	4.00	0.0356	19.48	24.00	72.00	0.9891	27.66	
32	CAB	3	1192.28	1351.03	88.25	44.02	6.00	0.0299	23.21	24.00	72.00	0.9775	34.55	
33	CBA	2	903.87	1018.94	88.71	88.11	3.00	0.0289	23.98	24.00	72.00	0.9980	31.36	
34	ACB	3	945.94	1029.41	91.89	55.70	3.50	0.0341	20.30	24.00	72.48	0.9962	28.04	
35	BCA	1	1173.09	1260.55	93.06	99.65	3.50	0.0348	19.90	24.00	72.00	0.9995	25.47	
36	BAC	1	2032.56	2111.08	96.28	129.27	2.53	0.0432	16.04	24.00	72.00	0.9987	20.29	
37	ABC	2	635.16	649.11	97.85	45.88	2.50	0.0555	12.50	24.00	72.00	0.9957	19.72	
38	CBA	2	1250.55	1393.83	89.72	72.70	4.50	0.0306	22.66	24.00	72.00	0.9998	31.01	
39	BCA	1	841.87	906.93	92.83	56.90	4.00	0.0335	20.69	24.00	72.00	0.9973	24.90	
40	CAB	3	813.68	851.42	95.57	52.40	3.50	0.0426	16.28	24.00	72.00	1.0000	22.64	
42	BAC	1	957.48	1141.45	83.88	89.86	3.00	0.0240	28.94	24.00	72.00	0.9933	37.72	
43	ACB	3	977.29	1003.23	97.41	74.16	3.02	0.0486	14.27	24.00	72.00	0.9873	19.67	
44	ABC	2	706.64	793.82	89.02	47.73	2.00	0.0303	22.86	24.00	72.00	0.9959	31.04	
45	BAC	1	1229.46	1299.87	94.58	109.62	2.00	0.0397	17.47	24.00	72.00	0.9985	24.00	
46	CAB	3	1178.86	1267.61	93.00	67.75	4.00	0.0363	19.11	24.00	72.27	0.9922	26.12	
48	BCA	1	811.27	868.07	93.46	77.59	4.00	0.0391	17.74	24.00	72.00	0.9590	25.17	
49	ABC	2	392.66	471.17	83.34	30.82	1.50	0.0231	29.96	24.00	72.00	0.9401	36.72	
50	CBA	2	1499.00	1655.90	90.53	78.44	4.50	0.0321	21.61	24.00	72.00	0.9977	29.71	
51	BAC	1	1507.04	1641.15	91.83	102.74	4.00	0.0351	19.72	24.00	72.00	0.9912	27.58	
52	CAB	3	1300.59	1405.16	92.56	133.18	2.00	0.0344	20.15	24.00	72.00	0.9958	26.71	
53	BCA	1	1648.66	1874.77	87.94	89.84	4.50	0.0283	24.53	24.00	72.00	0.9999	33.06	
54	ACB	3	1228.42	1371.28	89.58	87.55	2.50	0.0295	23.50	24.00	72.00	0.9975	30.59	
MEAN	.	.	1194.50	1321.50	90.52	80.54	3.14	0.0337	21.75	24.00	72.03	0.9923	29.36	
STD	.	.	380.19	428.32	5.05	28.83	1.10	0.0082	5.37	0.01	0.09	0.0114	6.92	
CV (%)	.	.	31.83	32.41	5.58	35.79	35.17	24.2851	24.68	0.05	0.13	1.1453	23.56	

\* TLIN = start time for linear regression  
 \*\* LQCT = last quantifiable concentration time  
 \*\*\* R = correlation coefficient obtained from regression analysis

**Table 9 - Isotretinoin Pharmacokinetic Parameters**  
 Treatment A: Isotretinoin Capsules 10 mg, Lot No.: 16F032 / Fed (Ciper Canada Inc., Canada)  
 Treatment B: Isotretinoin Capsules 10 mg, Lot Lot No.: 16F032 / Fasting (Ciper Canada Inc., Canada)  
 Treatment C: Accutane® Capsules 10 mg, Lot No.: U2624 /Fed (Roche Laboratories Inc., USA)

Treatment=C													
Subject	SEQ	PERIOD	AUC (0-t) (ng.h/mL)	AUC (0-inf) (ng.h/mL)	AUC (0-t)	Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R	MRT (h)
					----- (%) AUC (0-inf)								
01	ABC	3	2008.43	2274.49	88.30	164.64	10.00	0.0310	22.35	24.03	72.02	0.9942	34.95
02	BCA	2	2729.77	3213.10	84.96	85.27	20.00	0.0301	22.99	24.00	72.00	0.9998	42.28
04	CAB	1	1774.64	1987.37	89.30	87.71	12.07	0.0341	20.34	24.00	72.00	0.9918	34.55
05	BAC	3	2752.70	3732.45	73.75	104.58	16.00	0.0223	31.03	24.00	72.00	0.9910	55.66
06	CBA	1	2280.68	2742.29	83.17	153.21	10.00	0.0262	26.42	24.00	72.02	1.0000	41.84
07	BCA	2	1098.32	1238.39	88.69	37.03	3.00	0.0303	22.90	24.00	72.00	0.9980	33.38
08	CBA	1	2939.63	3288.90	89.38	150.48	8.00	0.0343	20.20	24.00	72.00	0.9944	34.24
09	ABC	3	2440.64	2807.76	86.92	78.71	10.03	0.0322	21.55	24.05	72.02	0.9990	38.97
10	CAB	1	2747.79	2880.08	95.41	130.69	8.00	0.0457	15.18	24.00	72.00	0.9965	27.38
11	BAC	3	2243.32	2517.94	89.09	77.30	20.00	0.0364	19.03	24.00	72.02	0.9987	37.79
12	ACB	2	1942.31	2083.34	93.23	132.60	5.52	0.0387	17.89	24.00	72.00	0.9950	27.50
13	ABC	3	3507.12	3873.12	90.55	182.80	4.50	0.0333	20.79	24.02	72.00	0.9995	31.45
14	ACB	2	2169.31	2350.34	92.30	149.30	5.50	0.0355	19.55	24.00	72.00	0.9995	28.41
15	BCA	2	2101.29	2345.09	89.60	257.00	3.50	0.0304	22.78	24.00	72.00	0.9952	30.15
16	CBA	1	1679.80	1827.10	91.94	159.56	4.50	0.0559	12.41	20.00	48.00	0.9981	20.62
17	CAB	1	1297.89	1410.37	92.02	125.74	4.50	0.0341	20.34	24.00	72.17	0.9987	28.34
18	BAC	3	1854.51	1954.86	94.87	199.25	4.50	0.0414	16.76	24.00	72.00	0.9868	25.09
19	CBA	1	2319.28	2341.74	99.04	178.32	5.00	0.0644	10.76	24.00	72.00	0.9927	17.35
20	ABC	3	3089.10	3284.97	94.04	179.80	10.00	0.0440	15.74	24.00	72.00	0.9847	28.43
21	BAC	3	2027.35	2167.87	93.52	97.46	10.00	0.0386	17.96	24.00	72.00	0.9756	27.22
22	BCA	2	1616.14	1758.71	91.89	225.00	4.03	0.0335	20.72	24.00	72.00	0.9999	27.63
23	ACB	2	1520.50	1673.58	90.85	83.30	4.50	0.0333	20.85	24.00	72.00	0.9807	28.63
24	CAB	1	1916.41	2148.65	89.19	137.00	10.00	0.0335	20.69	24.00	72.00	0.9971	35.01
25	CAB	1	2280.95	2360.15	96.64	138.00	5.50	0.0496	13.97	24.00	72.00	0.9945	23.04
26	ABC	3	2028.16	2269.72	89.36	78.68	12.00	0.0352	19.70	24.00	72.00	0.9930	35.56
27	CBA	1	1304.41	1457.24	89.51	88.26	4.00	0.0289	23.95	24.00	72.00	0.9919	29.27
28	ACB	2	1714.03	1920.20	89.26	150.24	4.50	0.0291	23.82	24.00	72.13	0.9967	30.69
29	BAC	3	2712.05	2927.23	92.65	83.34	16.00	0.0404	17.16	24.00	72.00	0.9996	31.52
30	BCA	2	1286.93	1305.22	98.60	77.05	5.00	0.0647	10.72	24.00	72.00	0.9985	21.67

**Table 9 - Isotretinoin Pharmacokinetic Parameters**  
 Treatment A: Isotretinoin Capsules 10 mg, Lot No.: 16F032 / Fed (Ciper Canada Inc., Canada)  
 Treatment B: Isotretinoin Capsules 10 mg, Lot Lot No.: 16F032 / Fasting (Ciper Canada Inc., Canada)  
 Treatment C: Accutane® Capsules 10 mg, Lot No.: U2624 /Fed (Roche Laboratories Inc., USA)

Treatment=C (continued)													
Subject	SEQ	PERIOD	AUC (0-t) (ng.h/mL)	AUC (0-inf) (ng.h/mL)	AUC (0-t)	Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R	MRT (h)
					----- (%) AUC (0-inf)								
31	ABC	3	2209.14	2370.30	93.20	139.81	6.00	0.0387	17.92	24.00	72.00	0.9897	27.83
32	CAB	1	2003.28	2247.86	89.12	141.76	4.50	0.0310	22.39	24.00	72.00	0.9715	33.21
33	CBA	1	2620.27	2955.56	88.66	126.89	6.00	0.0310	22.36	24.00	72.00	0.9924	33.94
34	ACB	2	2393.81	2514.92	95.18	149.23	8.00	0.0423	16.40	24.02	72.00	0.9956	25.22
35	BCA	2	1948.55	2256.19	86.36	187.00	5.50	0.0426	16.28	20.00	48.00	0.9994	25.11
36	BAC	3	1994.60	2070.52	96.33	169.00	5.50	0.0448	15.48	24.00	72.18	0.9960	21.53
37	ABC	3	2541.29	2640.19	96.25	302.94	4.50	0.0452	15.35	24.00	72.00	0.9992	22.17
38	CBA	1	2083.10	2348.85	88.69	183.00	4.50	0.0296	23.41	24.00	72.00	0.9950	32.48
39	BCA	2	2036.49	2112.28	96.41	150.87	4.50	0.0452	15.35	24.00	72.00	1.0000	21.69
40	CAB	1	1095.28	1191.63	91.91	65.80	2.50	0.0340	20.36	24.00	72.00	0.9937	27.11
42	BAC	3	1725.88	2020.33	85.43	75.28	12.00	0.0298	23.25	24.00	72.05	0.9983	40.64
43	ACB	2	2116.38	2183.01	96.95	147.35	8.02	0.0489	14.18	24.13	72.05	0.9953	22.93
44	ABC	3	1928.70	2135.04	90.34	181.81	4.50	0.0301	22.99	20.00	72.00	0.9836	29.95
45	BAC	3	1259.58	1329.46	94.74	86.42	1.52	0.0387	17.90	24.00	72.00	0.9941	22.99
46	CAB	1	2017.90	2280.39	88.49	125.86	4.50	0.0475	14.61	20.00	48.00	0.9992	24.00
48	BCA	2	1602.65	1839.86	87.11	57.79	20.00	0.0324	21.38	24.00	72.00	0.9999	39.58
49	ABC	3	1737.70	1828.41	95.04	125.69	5.00	0.0424	16.35	24.00	72.00	0.9968	24.59
50	CBA	1	1646.21	1795.44	91.69	100.80	5.50	0.0361	19.20	24.00	72.00	0.9999	30.56
51	BAC	3	1960.70	2181.46	89.88	123.80	8.00	0.0335	20.68	24.00	72.00	0.9967	32.86
52	CAB	1	2243.78	2352.40	95.38	136.91	4.50	0.0393	17.62	24.00	81.17	1.0000	28.43
53	BCA	2	2615.43	2794.52	93.59	251.61	4.50	0.0366	18.95	24.00	72.00	0.9976	25.66
54	ACB	2	1760.10	2050.34	85.84	59.80	5.50	0.0269	25.79	24.00	72.07	0.9976	36.79
MEAN	.	.	2057.34	2267.48	91.07	134.94	7.36	0.0375	19.35	23.69	70.78	0.9948	30.16
STD	.	.	510.51	591.04	4.43	54.37	4.50	0.0088	4.01	1.09	5.89	0.0062	6.91
CV (%)	.	.	24.81	26.07	4.86	40.29	61.12	23.3233	20.72	4.59	8.33	0.6220	22.93

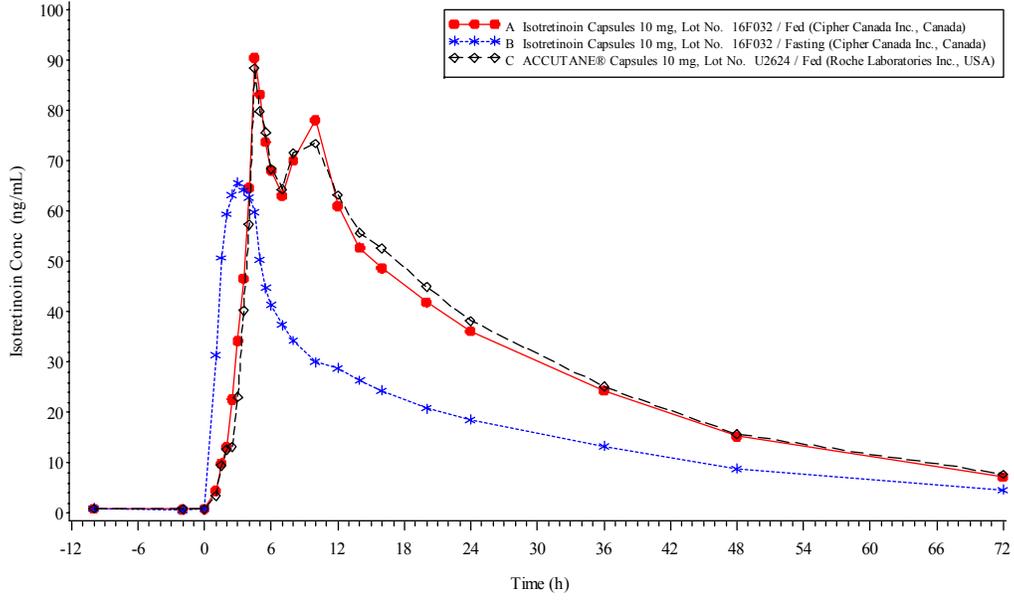
\* TLIN = start time for linear regression  
 \*\* LQCT = last quantifiable concentration time  
 \*\*\* R = correlation coefficient obtained from regression analysis

**Summary of Results for Plasma Isotretinoin**  
(N = 51)

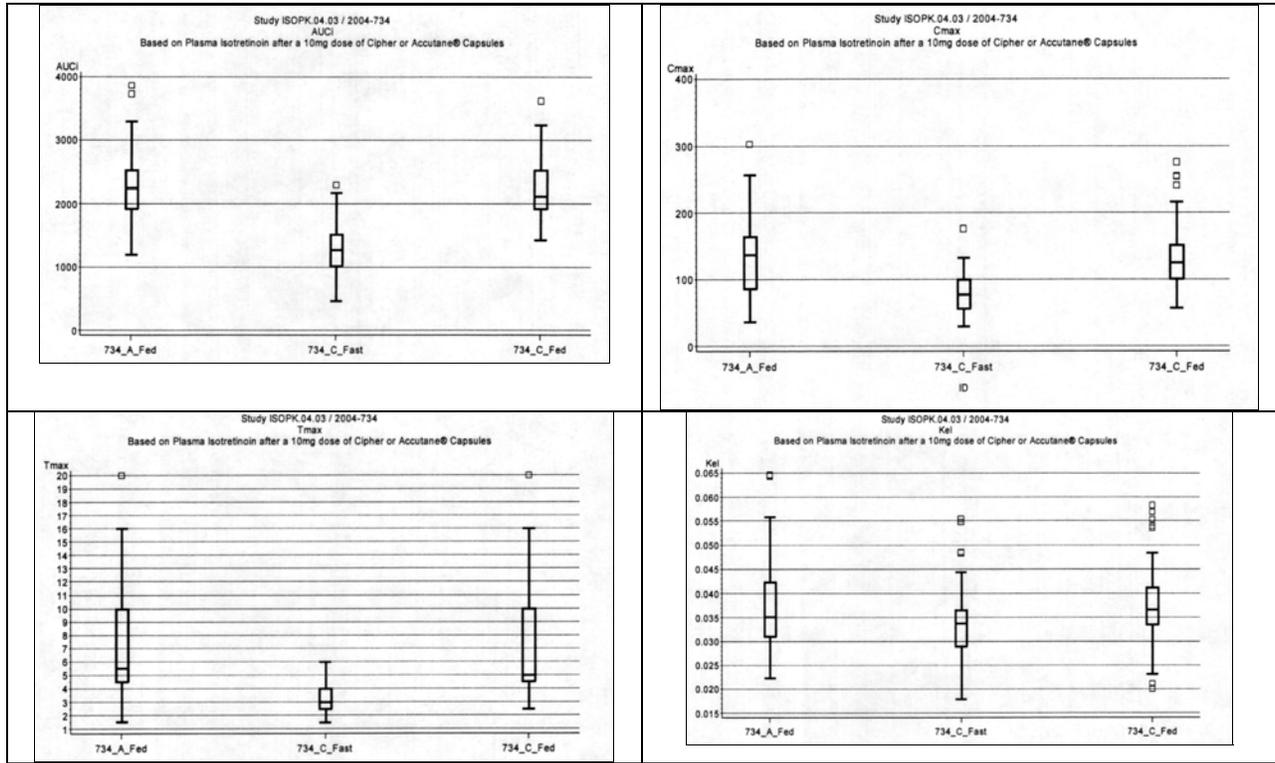
Parameter	Treatment Type	Trt	Means		Type	Code	Contrast Ratio (%)	90% CI (%)	CV%
			Arithmetic (CV%)	Geometric					
AUC <sub>t</sub> (ng·h/mL)	T - Fed	A	2021.55 (20)	1981.20	T/R: Fed	A vs. C	99.52	92.81 – 106.71	21
	T - Fast	B	1194.50 (32)	1133.95	T: Food Effect	A vs. B	174.72	162.94 – 187.34	
	R - Fed	C	2057.34 (25)	1990.81	R/T: Food Effect	C vs. B	175.56	163.73 – 188.25	
AUC <sub>i</sub> (ng·h/mL)	T - Fed	A	2218.86 (22)	2165.84	T/R: Fed	A vs. C	98.96	92.48-105.90	21
	T - Fast	B	1321.50 (32)	1254.78	T: Food Effect	A vs. B	172.61	161.30-184.70	
	R - Fed	C	2267.48 (26)	2188.57	R/T: Food Effect	C vs. B	174.42	163.00-186.64	
C <sub>max</sub> (ng/mL)	T - Fed	A	133.66 (38)	125.57	T/R: Fed	A vs. C	100.99	90.24-113.03	35
	T - Fast	B	80.54 (36)	75.76	T: Food Effect	A vs. B	165.75	148.10-185.51	
	R - Fed	C	134.94 (40)	124.34	R/T: Food Effect	C vs. B	164.13	146.65-183.69	
T <sub>max</sub> (h)	T - Fed	A	6.89 (49)	6.83	T/R: Fed	A vs. C	93.43	-	
	T - Fast	B	3.14 (35)	3.12	T: Food Effect	A vs. B	218.97	-	
	R - Fed	C	7.36 (61)	7.31	R/T: Food Effect	C vs. B	234.37	-	
K <sub>el</sub> (1/h)	T - Fed	A	0.0376 (22)	0.0376	T/R: Fed	A vs. C	100.21	-	
	T - Fast	B	0.0337 (24)	0.0337	T: Food Effect	A vs. B	111.53	-	
	R - Fed	C	0.0375 (23)	0.0375	R/T: Food Effect	C vs. B	111.29	-	
Th <sub>alf</sub> (h)	T - Fed	A	19.39 (24)	19.41	T/R: Fed	A vs. C	100.20	-	
	T - Fast	B	21.75 (25)	21.78	T: Food Effect	A vs. B	89.13	-	
	R - Fed	C	19.35 (21)	19.38	R/T: Food Effect	C vs. B	88.95	-	
MRT <sub>po</sub> (h)	T - Fed	A	29.93 (25)	29.90	T/R: Fed	A vs. C	99.25	-	
	T - Fast	B	29.36 (24)	29.35	T: Food Effect	A vs. B	101.85	-	
	R - Fed	C	30.16 (23)	30.12	R/T: Food Effect	C vs. B	102.62	-	

T = Test : R = Reference

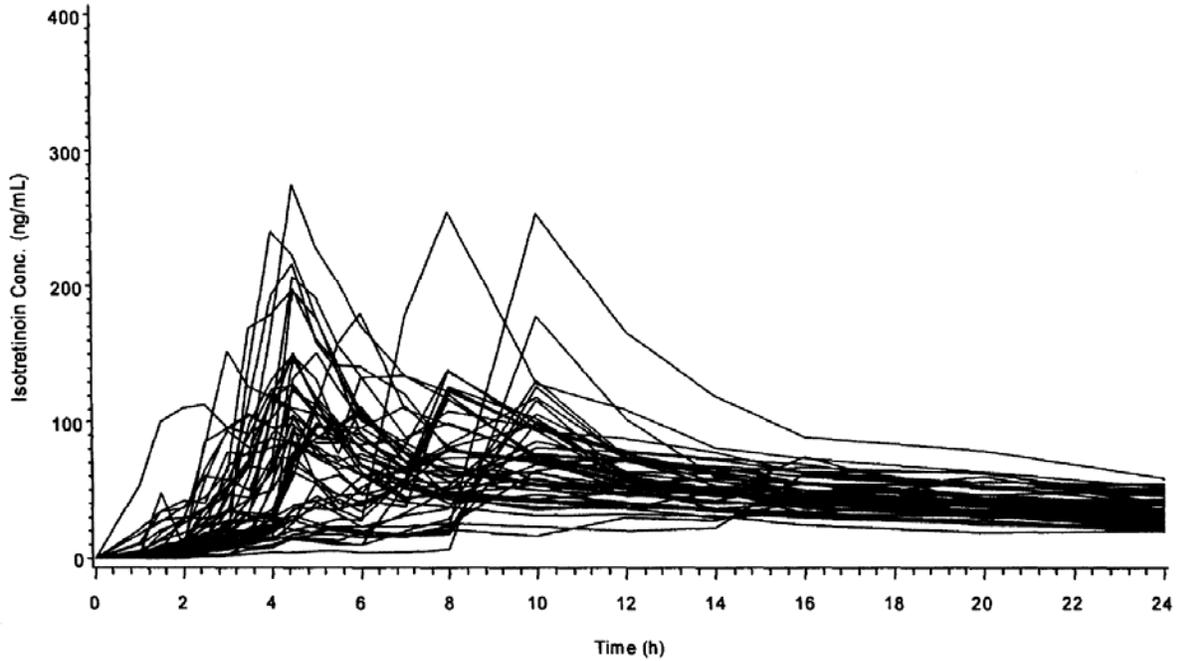
STUDY No : 2004-734  
MEAN MEASURED PLASMA ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES  
N=51



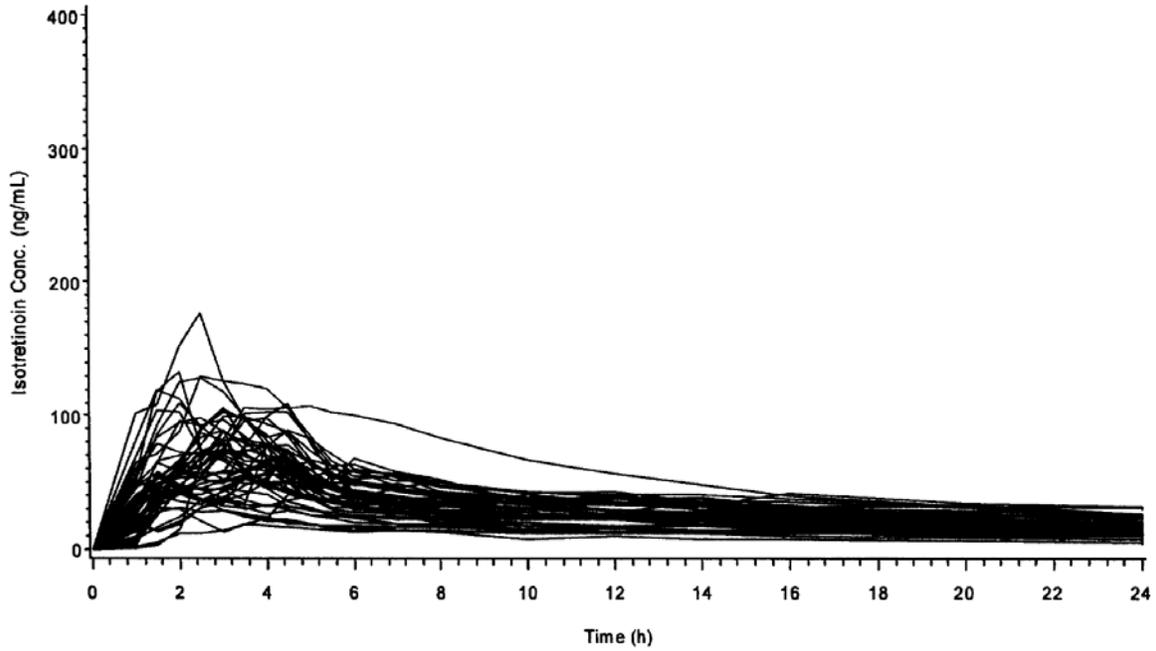
Box-Whisker Plots of Isotretinoin PK Parameters



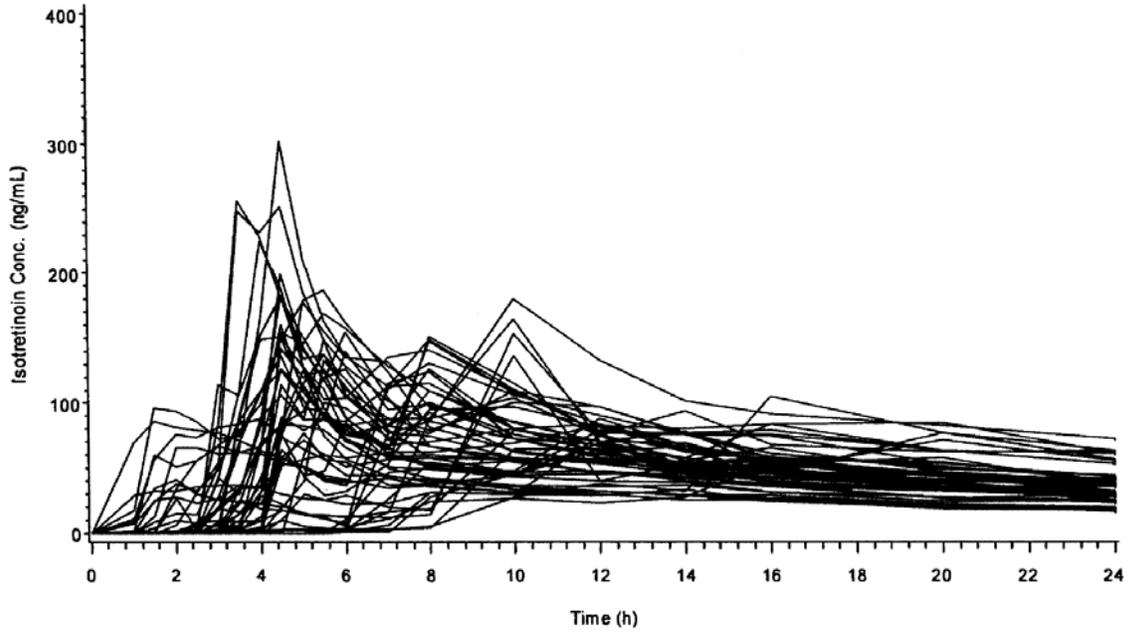
STUDY No.: 2004-734  
 BASELINE-ADJUSTED PLASMA ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES  
 Treatment A: Isotretinoin Capsules 10 mg, Lot No.: 16F032 (CIPHER Canada Inc., Canada) / Fed  
 N=51



STUDY No.: 2004-734  
BASELINE-ADJUSTED PLASMA ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES  
Treatment B: Isotretinoin Capsules 10 mg, Lot No.: 16F032 (Cipher Canada Inc., Canada) / Fast  
N=51



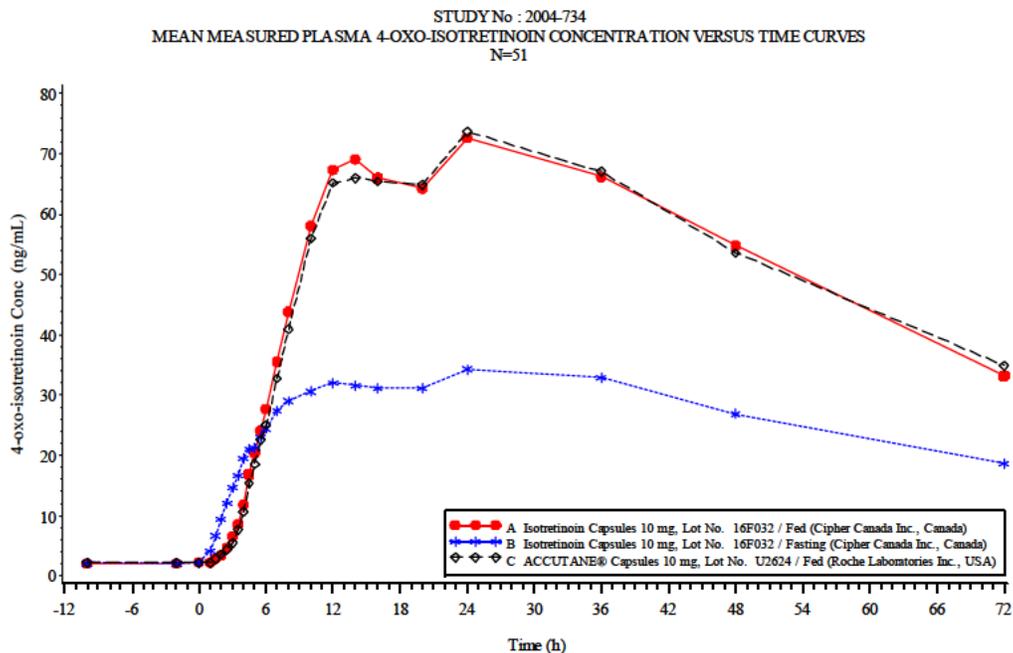
STUDY No.: 2004-734  
BASELINE-ADJUSTED PLASMA ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES  
Treatment C: ACCUTANE® Capsules 10 mg, Lot No.: U2624 (Roche Laboratories Inc., USA) / Fed  
N=51



**Summary of Results for Plasma 4-oxo-isotretinoin**  
(N = 51)

Parameter	Treatment Type	Trt	Means		Type	Code	Contrast Ratio (%)	90% CI (%)	CV%
			Arithmetic (CV%)	Geometric					
AUC <sub>t</sub> (ng·h/mL)	T - Fed	A	3629.66 (21)	3565.86	T/R: Fed	A vs. C	104.02	96.35-112.31	24
	T - Fast	B	1795.30 (34)	1703.40	T: Food Effect	A vs. B	209.34	193.89-226.02	
	R - Fed	C	3563.40 (27)	3427.93	R/T: Food Effect	C vs. B	201.24	186.39-217.28	
AUC <sub>i</sub> (ng·h/mL)	T - Fed	A	5526.55 (28)	5364.16	T/R: Fed	A vs. C	100.91	91.86-110.86	27
	T - Fast	B	3203.40 (44)	2896.28	T: Food Effect	A vs. B	185.21	168.74-203.28	
	R - Fed	C	5669.10 (33)	5315.66	R/T: Food Effect	C vs. B	183.53	167.22-201.44	
C <sub>max</sub> (ng/mL)	T - Fed	A	78.93 (22)	77.35	T/R: Fed	A vs. C	103.31	95.08-112.24	26
	T - Fast	B	34.99 (35)	33.04	T: Food Effect	A vs. B	234.10	215.47-254.35	
	R - Fed	C	78.35 (29)	74.87	R/T: Food Effect	C vs. B	226.61	208.57-246.21	
T <sub>max</sub> (h)	T - Fed	A	19.77 (47)	19.62	T/R: Fed	A vs. C	104.56	-	-
	T - Fast	B	24.77 (44)	24.52	T: Food Effect	A vs. B	80.04	-	
	R - Fed	C	18.96 (51)	18.77	R/T: Food Effect	C vs. B	76.55	-	
K <sub>el</sub> (1/h)	T - Fed	A	0.0187 (30)	0.0184	T/R: Fed	A vs. C	103.17	-	-
	T - Fast	B	0.0155 (42)	0.0155	T: Food Effect	A vs. B	119.09	-	
	R - Fed	C	0.0180 (37)	0.0179	R/T: Food Effect	C vs. B	115.43	-	
T <sub>half</sub> (h)	T - Fed	A	40.67 (33)	41.31	T/R: Fed	A vs. C	96.98	-	-
	T - Fast	B	54.17 (53)	54.05	T: Food Effect	A vs. B	76.43	-	
	R - Fed	C	42.74 (30)	42.59	R/T: Food Effect	C vs. B	78.81	-	
MRT <sub>po</sub> (h)	T - Fed	A	67.53 (28)	68.33	T/R: Fed	A vs. C	96.77	-	-
	T - Fast	B	84.85 (48)	84.65	T: Food Effect	A vs. B	80.72	-	
	R - Fed	C	70.90 (27)	70.61	R/T: Food Effect	C vs. B	83.41	-	

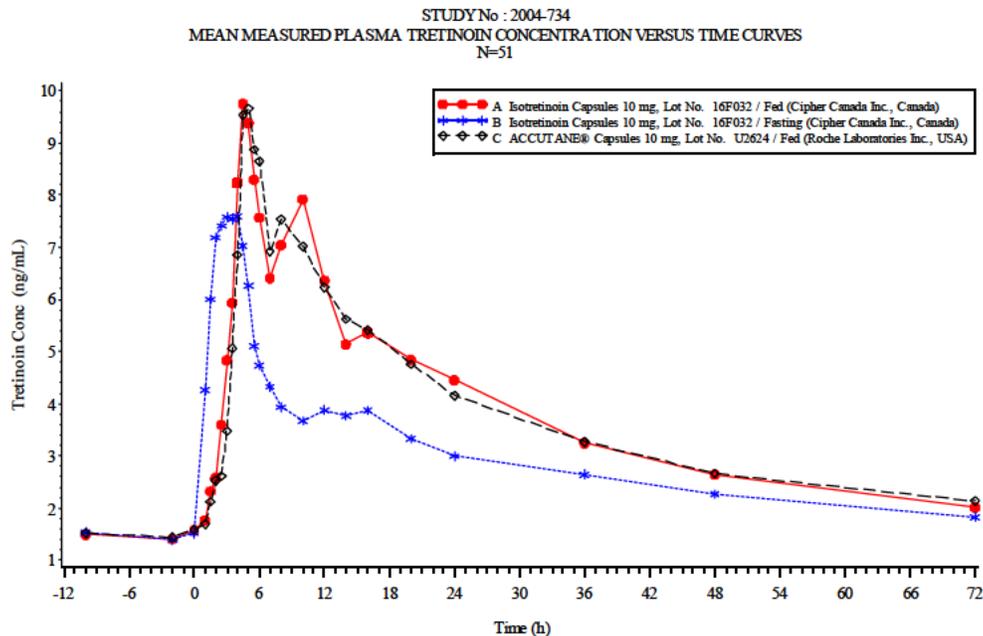
T = Test : R = Reference



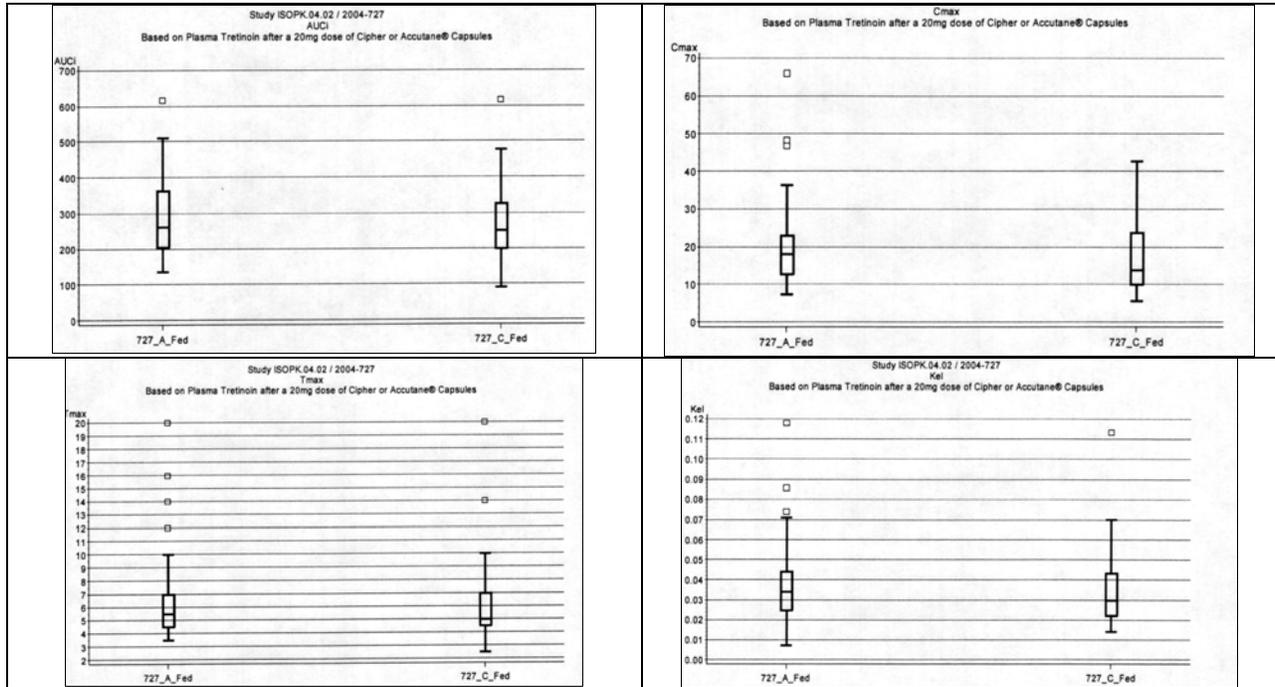
**Summary of Results for Plasma Tretinoin**  
(N = 51)

Parameter	Treatment Type	Trt	Means		Type	Code	Contrast Ratio (%)	90% CI (%)	CV%
			Arithmetic (CV%)	Geometric					
AUC <sub>t</sub> (ng·h/mL)	T - Fed	A	165.40 (50)	147.32	T/R: Fed	A vs. C	101.99	92.57-112.36	30
	T - Fast	B	107.77 (66)	88.38	T: Food Effect	A vs. B	166.70	151.31-183.65	
	R - Fed	C	160.48 (45)	144.45	R/T: Food Effect	C vs. B	163.45	148.36-180.07	
AUC <sub>i</sub> (ng·h/mL)	T - Fed	A	191.05 (50)	172.68	T/R: Fed	A vs. C	98.39	86.21-112.30	33
	T - Fast	B	157.23 (59)	116.64	T: Food Effect	A vs. B	148.05	127.67-171.68	
	R - Fed	C	209.82 (44)	175.50	R/T: Food Effect	C vs. B	150.47	130.70-173.23	
C <sub>max</sub> (ng/mL)	T - Fed	A	13.58 (57)	11.89	T/R: Fed	A vs. C	109.11	96.19-123.77	40
	T - Fast	B	8.19 (57)	7.08	T: Food Effect	A vs. B	167.81	147.94-190.35	
	R - Fed	C	12.77 (60)	10.89	R/T: Food Effect	C vs. B	153.80	135.59-174.46	
T <sub>max</sub> (h)	T - Fed	A	6.78 (46)	6.76	T/R: Fed	A vs. C	103.12	-	
	T - Fast	B	3.27 (36)	3.26	T: Food Effect	A vs. B	207.66	-	
	R - Fed	C	6.61 (54)	6.56	R/T: Food Effect	C vs. B	201.39	-	
K <sub>el</sub> (1/h)	T - Fed	A	0.0439 (54)	0.0433	T/R: Fed	A vs. C	121.20	-	
	T - Fast	B	0.0376 (55)	0.0332	T: Food Effect	A vs. B	130.60	-	
	R - Fed	C	0.0349 (50)	0.0357	R/T: Food Effect	C vs. B	107.76	-	
T <sub>half</sub> (h)	T - Fed	A	20.89 (57)	22.13	T/R: Fed	A vs. C	93.40	-	
	T - Fast	B	24.50 (56)	27.73	T: Food Effect	A vs. B	79.82	-	
	R - Fed	C	24.80 (58)	23.69	R/T: Food Effect	C vs. B	85.46	-	
MRT <sub>po</sub> (h)	T - Fed	A	30.61 (38)	33.06	T/R: Fed	A vs. C	96.18	-	
	T - Fast	B	33.91 (49)	37.40	T: Food Effect	A vs. B	88.37	-	
	R - Fed	C	35.90 (57)	34.37	R/T: Food Effect	C vs. B	91.88	-	

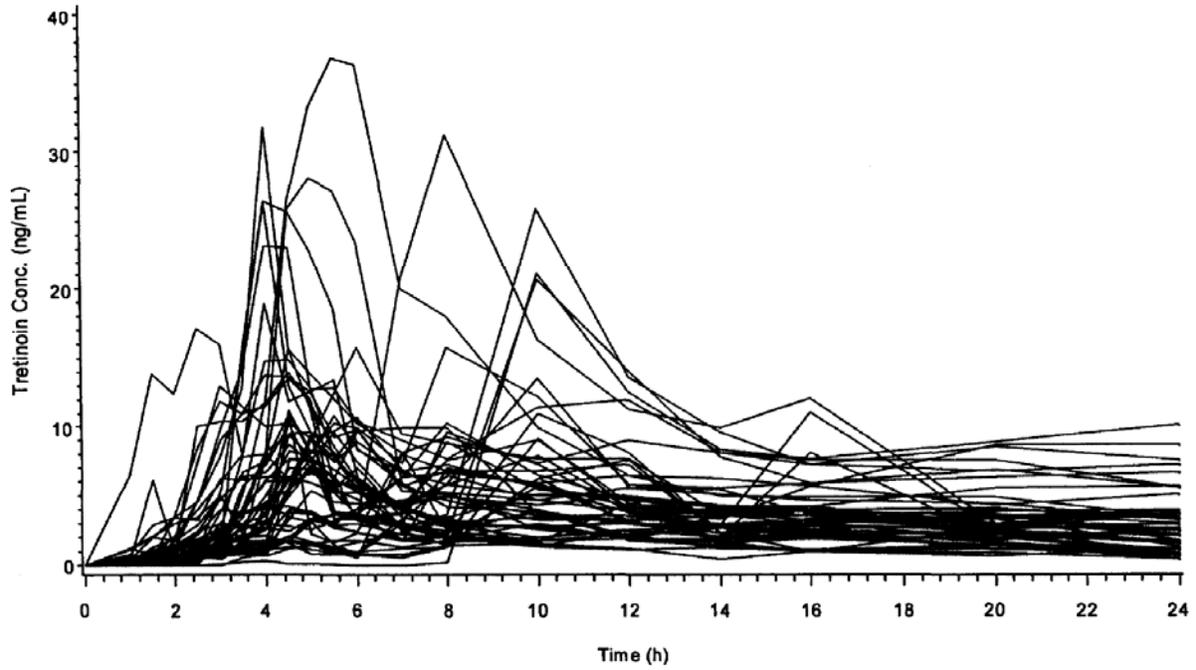
T = Test : R = Reference



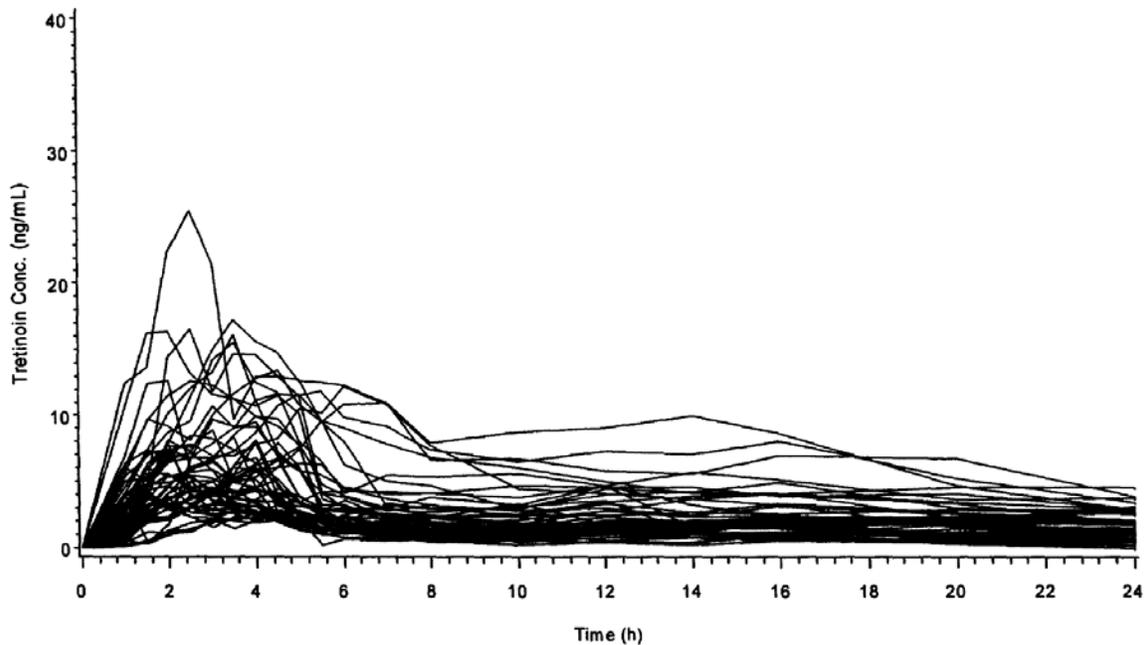
Box-Whisker Plots of Tretinoin PK Parameters



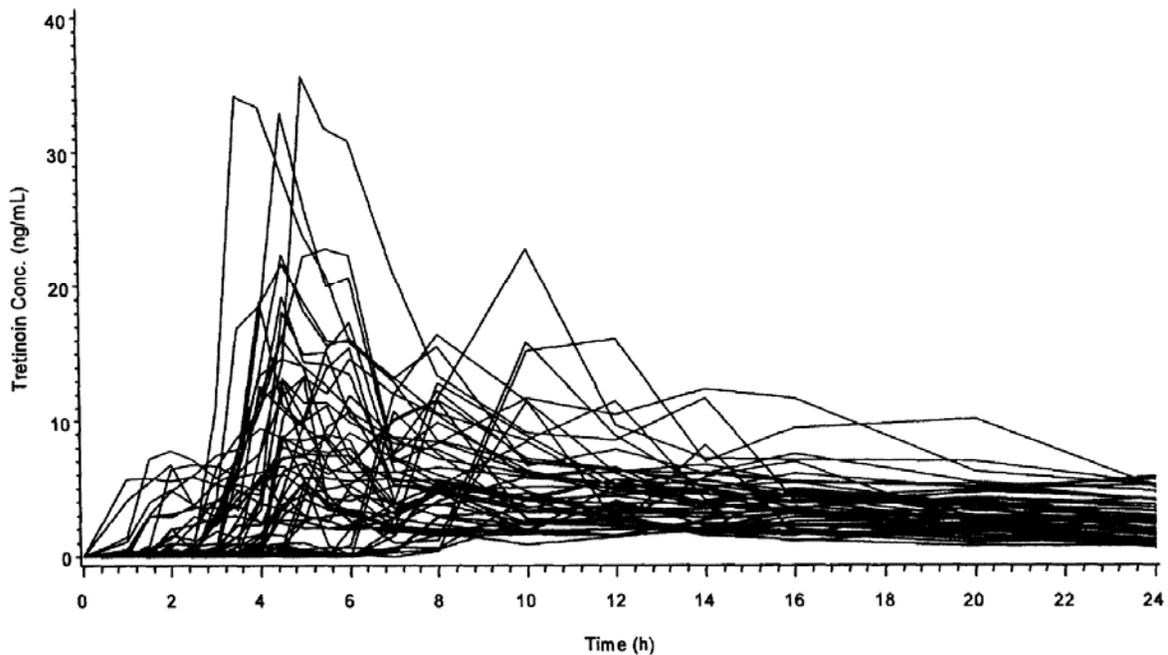
STUDY No.: 2004-734  
BASELINE-ADJUSTED PLASMA TRETINOIN CONCENTRATION VERSUS TIME CURVES  
Treatment A: Isotretinoin Capsules 10 mg, Lot No.: 16F032 (CIPHER Canada Inc., Canada) / Fed  
N=51



STUDY No.: 2004-734  
BASELINE-ADJUSTED PLASMA TRETINOIN CONCENTRATION VERSUS TIME CURVES  
Treatment B: Isotretinoin Capsules 10 mg, Lot No.: 16F032 (Cipher Canada Inc., Canada) / Fast  
N=51



STUDY No.: 2004-734  
BASELINE-ADJUSTED PLASMA TRETINOIN CONCENTRATION VERSUS TIME CURVES  
Treatment C: ACCUTANE® Capsules 10 mg, Lot No.: U2624 (Roche Laboratories Inc., USA) / Fed  
N=51

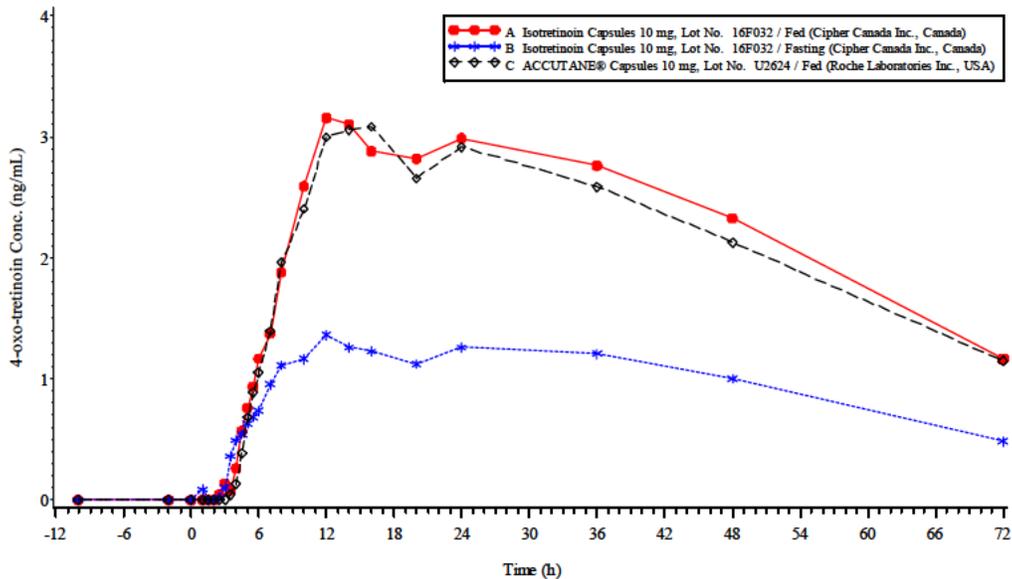


**Summary of Results for Plasma 4-oxo-tretinoin**  
(N = 51)

Parameter	Treatment Type	Trt	Means		Type	Code	Contrast Ratio (%)	90% CI (%)	CV%
			Arithmetic (CV%)	Geometric					
AUC <sub>t</sub> (ng·h/mL)	T - Fed	A	153.87 (78)	110.69	T/R: Fed	A vs. C	119.88	88.73-161.97	114
	T - Fast	B	65.63 (125)	28.10	T: Food Effect	A vs. B	393.90	279.72-554.68	
	R - Fed	C	141.61 (66)	92.33	R/T: Food Effect	C vs. B	328.56	233.44-462.46	
AUC <sub>i</sub> (ng·h/mL)	T - Fed	A	278.81 (65)	228.45	T/R: Fed	A vs. C	88.13	67.39-115.26	46
	T - Fast	B	248.11 (60)	170.39	T: Food Effect	A vs. B	134.08	101.07-117.86	
	R - Fed	C	318.03 (57)	259.21	R/T: Food Effect	C vs. B	152.13	111.75-207.10	
C <sub>max</sub> (ng/mL)	T - Fed	A	3.99 (59)	3.47	T/R: Fed	A vs. C	98.00	86.66-110.81	39
	T - Fast	B	1.83 (94)	1.75	T: Food Effect	A vs. B	197.56	171.78-227.21	
	R - Fed	C	4.14 (60)	3.54	R/T: Food Effect	C vs. B	201.60	175.33-231.81	
T <sub>max</sub> (h)	T - Fed	A	19.83 (62)	19.70	T/R: Fed	A vs. C	107.67	-	
	T - Fast	B	13.88 (94)	13.71	T: Food Effect	A vs. B	143.72	-	
	R - Fed	C	18.45 (55)	18.30	R/T: Food Effect	C vs. B	133.48	-	
K <sub>el</sub> (1/h)	T - Fed	A	0.0259 (71)	0.0245	T/R: Fed	A vs. C	119.31	-	
	T - Fast	B	0.0184 (65)	0.0218	T: Food Effect	A vs. B	112.33	-	
	R - Fed	C	0.0194 (76)	0.0205	R/T: Food Effect	C vs. B	94.15	-	
T <sub>half</sub> (h)	T - Fed	A	43.93 (106)	41.42	T/R: Fed	A vs. C	69.77	-	
	T - Fast	B	56.21 (75)	57.56	T: Food Effect	A vs. B	71.97	-	
	R - Fed	C	54.45 (62)	59.38	R/T: Food Effect	C vs. B	103.16	-	
MRT <sub>po</sub> (h)	T - Fed	A	74.57 (90)	70.92	T/R: Fed	A vs. C	73.89	-	
	T - Fast	B	90.91 (68)	93.93	T: Food Effect	A vs. B	75.51	-	
	R - Fed	C	85.67 (53)	95.99	R/T: Food Effect	C vs. B	102.19	-	

T = Test : R = Reference

STUDY No.: 2004-734  
MEAN MEASURED PLASMA 4-OXO-TRETINOIN CONCENTRATION VERSUS TIME CURVES  
N=51



## **Conclusion**

Unlike the previous study with the 20mg capsules, the 90% confidence intervals for the relative mean plasma isotretinoin, 4-oxo-isotretinoin and tretinoin AUC<sub>t</sub>, AUC<sub>i</sub> and C<sub>max</sub> of test versus reference were within the 80-125% range. Thus, using a high fat diet, the CIP-isotretinoin 10 mg capsule demonstrated equivalent total systemic exposure and equivalent peak exposure to Accutane™ 10 mg Capsules in healthy subjects.

As with previous trials, the administration of the CIP-isotretinoin capsules with food increased the bioavailability of the drug by approximately 75% for AUC<sub>t</sub> and 66% for C<sub>max</sub>. Food also almost doubled the time to maximum concentrations, relative to the fasted state. There were no significant changes in the half-life of isotretinoin.

With regards to the predominant circulating species, 4-oxo-isotretinoin, the mean plasma AUC<sub>t</sub> increased by 109% and C<sub>max</sub> by 134%. There was an observed difference of 5 hours in the mean T<sub>max</sub> between the fasting and fed conditions for 4-oxo-isotretinoin. A similar trend to isotretinoin was observed for tretinoin: a 67% increase in mean AUC<sub>t</sub>, 68% increase in mean C<sub>max</sub> and 108% increase in mean T<sub>max</sub>.

Study PK.03.04 (2003-627)

- Title:** An Open Label, Single-Dose, Four-Way, Randomized, Crossover Comparative Bioavailability Of Two Formulations of Isotretinoin Capsules In Healthy Volunteers Under Fed and Fasting Conditions
- Objective:** To evaluate the comparative bioavailability between Isotretinoin 2 x 20 mg capsules (Manufactured for Cipher Pharmaceuticals Limited, Barbados by Galephar, P.R. Inc.) and Accutane® 40 mg capsules (Roche Laboratories Inc., U.S.A.) in healthy, male and female volunteers under fasting and fed conditions.
- Treatment A: (Test)** Isotretinoin 20 mg Capsules (Manufactured for Cipher Pharmaceuticals Limited, Barbados by Galephar, P.R. Inc.); Lot No.: 12B02; Expiration Date: N/A [40 mg administered after an overnight fast of at least 10 hours]
- Treatment B: (Test)** Isotretinoin 20 mg Capsules (Manufactured for Cipher Pharmaceuticals Limited, Barbados by Galephar, P.R. Inc.); Lot No.: 12B02; Expiration Date: N/A [40 mg administered after a modified high fat, high calorie breakfast]
- Treatment C: (Reference)** Accutane® 40 mg Capsules (Roche Laboratories Inc., Nutley, New Jersey); Lot No.: U0622; Expiration Date: 10 2004 [40 mg administered after an overnight fast of at least 10 hours]
- Treatment D: (Reference)** Accutane® 40 mg Capsules (Roche Laboratories Inc., Nutley, New Jersey); Lot No.: U0622; Expiration Date: 10 2004 [40 mg administered after a modified high fat, high calorie breakfast]
- Number of Subjects:** Sixty (60) [male (40) and female (20)] subjects were dosed in Period 1, and 57 subjects completed the entire study.
- Age:  $36 \pm 9$  yrs (21 – 55 yrs)
  - Height:  $169.7 \pm 8.7$  cm (150.0 – 188.0 cm)
  - Weight:  $71.5 \pm 9.1$  kg (49.8 – 86.4 kg)
- Sampling Schedule:** Blood samples were obtained at -10, -2, 0, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14, 16, 20, 24, 36, 48 and 72 hours following drug administration.
- Diet (High Fat Portion):** (1) Regular Bagel with 3 tablespoons of peanut butter  
(5) Slices of Bacon  
(1) Dutchie Donut (~230calories, 6gms fat, 40gms carbohydrate-<http://www.timhortons.com>)  
(6) Fluid Ounces of Apple Juice

This study is considered by this reviewer to be the pivotal study in the application. It is the only study that utilizes a head to head comparison of the Cipher product to Accutane™ under both fed and fasted conditions in healthy, male and female volunteers. One limitation of the trial is, however, the use of multiple dosage units (i.e., 2x20mg capsules) rather than a single capsule. This resulted in “double-peaking” which does tend to obscure a true dosage unit assessment between the two products.

All subjects who were selected for the study met the inclusion and exclusion criteria described in the study protocol, and were judged by an Investigator to be medically healthy, based upon medical history, physical examination, vital signs measurements, 12-lead ECG, and clinical laboratory tests.

A serum HCG pregnancy test was performed on all female subjects during screening. In addition, urine HCG pregnancy tests were performed prior to drug administration for female subjects who were not post-menopausal nor who have had a hysterectomy.

Three (3) subjects did not complete Period 2 of the study. Subject 23 withdrew from the study after Period 2 check-in for personal reasons. Subjects 31 and 39 were dismissed due to non-compliance.

### **Study Procedures**

As noted above, this study was an open-label, single-dose, randomized, four-period, twelve-sequence, four-treatment, crossover comparative bioavailability study. Subjects were randomly assigned to one of 12 sequences according to a predetermined computer-generated randomization scheme. There was a balanced random allocation of subjects into the twelve sequences.

Subjects were confined to the clinical facility [REDACTED] (b) (4) from at least 10.5 hours prior to each drug administration until 48 hours post-dose. The drug was administered with 240 ml of room temperature water. A mouth check was done immediately following drug administration to ensure that each capsule was swallowed. The washout period between the successive drug administrations was 21 days.

For Treatments A and C, the drug products were administered after an overnight fast of at least 10 hours. For Treatments B and D, the drug products were administered after an overnight fast of at least 10 hours and after consumption of a modified high fat, high calorie breakfast with reduced vitamin A content.

### **Adverse Events**

In each period, health status monitoring was conducted at pre-dose and at approximately 6, 24, 48, and 72 hours post-dose. There were 55 adverse events involving 25 subjects in the study (see following table).

Treatment Group	Severity			Relation to the Drug				Intervention	
	Mild	Moderate	Severe	Unrelated	Remote	Possible	Probable	Required Drug Therapy	Required Non-Drug Therapy
A (Cipher fasted)	17	0	1	0	4	14	0	1	4
B (Cipher fed)	4	5	0	0	0	9	0	4	0
C (Roche fasted)	7	0	0	1	0	6	0	0	0
D (Roche fed)	20	1	0	1	0	20	0	2	0
<b>Total</b>	<b>48</b>	<b>6</b>	<b>1</b>	<b>2</b>	<b>4</b>	<b>49</b>	<b>0</b>	<b>7</b>	<b>4</b>

Subject No.	Period	TRT	Adverse Event	COSTART Term	Duration (hrs)	Severity	Action Taken	Relationship to the Study Drug
06	4	A	Elevated AST	SGOT INC	69 days	Mild	None	Possible
06	4	A	Elevated ALT	SGPT INC	69 days	Mild	None	Possible
07	3	A	Lightheadedness	Dizziness	0.17	Mild	Non-Drug Therapy	Remote
07	3	A	Pallor	Pallor	0.17	Mild	Non-Drug Therapy	Remote
07	3	A	Cold	Chills	0.17	Mild	Non-Drug Therapy	Remote
07	3	A	Clammy	Sweat	0.17	Mild	Non-Drug Therapy	Remote
08	1	A	Headache	Headache	13.33	Severe	Drug Therapy	Possible
09	1	A	Headache	Headache	2.50	Mild	None	Possible
24	3	A	Headache	Headache	8.00	Mild	None	Possible
29	4	A	Elevated ALT	SGPT INC	148 days	Mild	None	Possible
46	4	A	Tiredness	Asthenia	5.50	Mild	None	Possible
49	4	A	Headache	Headache	30.50	Mild	None	Possible
49	4	A	Nausea	Nausea	27.75	Mild	None	Possible
50	1	A	Hot Flush	Vasodilat	0.67	Mild	None	Possible
50	1	A	Lightheadedness	Dizziness	13.50	Mild	None	Possible
52	2	A	Headache	Headache	19.75	Mild	None	Possible
56	3	A	Stiff Neck	Neck Rigid	70.00	Mild	None	Possible
57	4	A	Sleepiness	Somnolence	3.00	Mild	None	Possible
09	3	B	Headache	Headache	36.00	Mild	None	Possible
16	1	B	Headache	Headache	54.00	Moderate	Drug Therapy	Possible
16	1	B	Nausea	Nausea	54.00	Moderate	None	Possible
24	1	B	Headache	Headache	0.83	Mild	None	Possible
24	1	B	Headache	Headache	16.50	Moderate	Drug Therapy	Possible
50	3	B	Headache	Headache	51.00	Moderate	Drug Therapy	Possible
58	4	B	Sleepiness	Somnolence	5.00	Mild	None	Possible
58	4	B	Headache	Headache	16.00	Moderate	Drug Therapy	Possible
60	3	B	Headache	Headache	28.50	Mild	None	Possible

Subject No.	Period	TRT	Adverse Event	COSTART Term	Duration (hrs)	Severity	Action Taken	Relationship to the Study Drug
16	3	C	Headache	Headache	18.00	Mild	None	Possible
34	4	C	Elevated Blood Pressure	Hypertens	Unknown	Mild	None	Possible
37	1	C	Pimple	Acne	56.00	Mild	None	Possible
47	4	C	Tiredness	Asthenia	7.00	Mild	None	Possible
50	2	C	Disoriented	Confus	47.03	Mild	None	Possible
50	2	C	Headache	Headache	24.50	Mild	None	Possible
56	4	C	Left Leg Toe Pain	Pain	6.00	Mild	None	Unrelated
09	4	D	Headache	Headache	30.00	Mild	None	Possible
10	3	D	Headache	Headache	8.00	Mild	None	Possible
16	4	D	Headache	Headache	15.83	Mild	None	Possible
24	2	D	Tiredness	Asthenia	13.50	Mild	None	Possible
25	4	D	Diarrhea (1 episode)	Diarrhea	0.08	Mild	None	Possible
35	3	D	Headache	Headache	15.50	Mild	None	Possible
41	1	D	Bruise on Right Elbow and Forearm	Ecchymosis	100.00	Mild	None	Unrelated
43	2	D	Nausea	Nausea	3.67	Mild	None	Possible
43	2	D	Dizziness	Dizziness	3.67	Mild	None	Possible
48	1	D	Headache	Headache	19.88	Mild	None	Possible
49	1	D	Headache	Headache	22.00	Mild	None	Possible
49	1	D	Hot Flush	Vasodilat	14.00	Mild	None	Possible
49	1	D	Nausea	Nausea	14.00	Mild	None	Possible
50	4	D	Headache	Headache	58.50	Moderate	Drug Therapy	Possible
50	4	D	Back Ache	Pain Back	15.50	Mild	None	Possible
51	2	D	Hot Flashes	Vasodilat	38.00	Mild	None	Possible
52	3	D	Tiredness	Asthenia	24.50	Mild	None	Possible
58	1	D	Headache	Headache	22.50	Mild	Drug Therapy	Possible
60	1	D	Headache	Headache	24.00	Mild	None	Possible
60	1	D	Dizziness	Dizziness	0.83	Mild	None	Possible
60	1	D	Vomit (1 episode)	Vomit	0.08	Mild	None	Possible

A physical examination was performed on all subjects upon study completion or upon removal from the study. All subjects were discharged in good physical condition, however, the total cholesterol and triglycerides tests were not performed for Subject 39, and the triglycerides test result was not reported for Subject 23.

It is interesting to note that in this study the elevated diastolic blood pressure experienced by Subject 34 was deemed by the Principal Investigator to be a mild adverse event possibly

related to the reference drug product. Interesting in that when hypertension was seen previously in study 727 (page 15 of the appendix), it was coded as not related. Hypertension is a recognized adverse event of retinoid/isotretinoin use.

## **Results**

Tables of the individual pharmacokinetic profiles, mean plasma level time profiles, box whisker plots, and associated statistical tables are attached.

**Summary of Individual Isotretinoin Pharmacokinetic Parameters**  
**A: Isotretinoin 2 x 20 mg Capsules, Lot No.: 28A02 (Cipher Pharmaceuticals Ltd., Barbados), Fast**

Subject	SEQ	Period	AUC (0-t) (ng.h/mL)	AUC (0-inf) (ng.h/mL)	AUC (0-t)		Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R	MRTpo (h)
					-----(% AUC (0-inf)									
01	BACD	2	3690.68	3929.82	93.91	383.67	2.00	0.0359	19.30	16.00	72.00	0.9972	22.64	
02	BCDA	4	3866.25	3960.00	97.63	554.86	3.00	0.0470	14.75	16.00	72.00	0.9964	15.51	
03	BDAC	3	4639.97	4915.08	94.40	421.31	3.50	0.0375	18.50	16.00	72.00	0.9984	22.31	
04	DBCA	4	4879.06	5176.92	94.25	408.73	3.00	0.0384	18.07	16.00	72.00	0.9872	22.10	
05	CBAD	3	4874.50	5267.56	92.54	298.03	3.50	0.0362	19.15	16.00	72.00	0.9889	28.61	
06	CDBA	4	3875.46	4189.51	92.50	295.67	4.00	0.0343	20.22	16.00	72.38	0.9985	26.53	
07	DCAB	3	4136.15	4490.26	92.11	161.29	12.00	0.0384	18.06	16.00	72.00	0.9976	30.86	
08	ADCB	1	5186.30	5453.40	95.10	383.90	4.50	0.0404	17.14	16.00	72.03	0.9991	22.97	
09	ACBD	1	6237.95	6675.66	93.44	380.56	3.50	0.0376	18.44	16.00	72.00	0.9886	24.23	
10	CADB	2	3833.14	4341.86	88.28	240.00	3.00	0.0289	23.99	16.00	72.00	0.9965	31.48	
11	ABDC	1	4286.25	4576.13	93.67	308.00	3.00	0.0383	18.10	16.00	72.00	0.9916	24.68	
12	DABC	2	4787.42	4913.23	97.44	552.82	2.00	0.0467	14.85	16.00	72.00	0.9889	16.83	
13	ADCB	1	4227.37	4481.05	94.34	328.00	3.00	0.0383	18.11	16.00	72.00	0.9928	23.93	
14	CADB	2	2732.32	2972.51	91.92	155.55	4.50	0.0354	19.56	16.00	72.00	0.9883	28.72	
15	ACBD	1	3860.53	4264.91	90.52	303.62	3.50	0.0310	22.39	16.00	72.00	0.9966	27.90	
16	BACD	2	1457.49	1570.08	92.83	103.00	4.00	0.0361	19.22	16.00	72.00	0.9777	25.05	
17	BCDA	4	4028.74	4166.05	96.70	638.17	2.00	0.0413	16.78	16.00	72.00	0.9987	16.80	
18	DBCA	4	2856.28	3138.16	91.02	237.00	4.00	0.0324	21.38	16.00	72.00	0.9992	28.32	
19	CDBA	4	4662.49	4863.59	95.87	463.80	3.50	0.0415	16.72	16.00	72.00	0.9762	20.80	
20	CBAD	3	5003.05	5518.68	90.66	373.00	3.50	0.0308	22.48	16.00	72.00	0.9992	28.12	
21	DABC	2	3919.75	4407.33	88.94	287.25	3.00	0.0307	22.61	16.00	72.08	0.9759	30.41	
22	ABDC	1	3751.65	4036.78	92.94	204.80	4.00	0.0361	19.18	16.00	72.00	0.9985	26.01	
24	BDAC	3	4215.35	4416.26	95.45	230.98	1.00	0.0387	17.91	16.00	72.00	0.9667	24.22	
25	CBAD	3	4196.49	4442.51	94.46	398.62	3.00	0.0383	18.11	16.00	72.00	0.9919	21.81	
26	ADCB	1	3511.08	3767.93	93.18	342.28	3.50	0.0347	19.96	16.00	72.02	0.9951	23.46	
27	BACD	2	2251.16	2283.85	98.57	337.91	2.00	0.0553	12.54	16.00	72.00	0.9899	14.03	
28	ACBD	1	2175.81	2511.33	86.64	192.00	2.00	0.0246	28.22	16.00	72.18	0.9912	33.64	
29	CDBA	4	6291.15	7168.97	87.76	308.65	10.00	0.0309	22.41	16.00	72.00	0.9804	34.31	
30	DBCA	4	5226.81	5769.25	90.60	363.20	3.00	0.0321	21.61	16.00	72.00	0.9924	28.86	
32	BDAC	3	4250.68	4629.84	91.81	433.65	2.50	0.0334	20.78	16.00	72.00	0.9827	24.86	
33	ABDC	1	4749.86	5063.44	93.81	346.30	4.50	0.0370	18.74	16.00	72.47	0.9925	23.50	

Subject	SEQ	Period	AUC (0-t) (ng.h/mL)	AUC (0-inf) (ng.h/mL)	AUC (0-t)		Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R	MRTpo (h)
					-----(% AUC (0-inf)									
34	DABC	2	5932.98	6351.38	93.41	438.52	4.50	0.0369	18.81	16.00	72.00	0.9983	25.29	
35	BCDA	4	5922.30	6717.96	88.16	324.66	4.00	0.0285	24.34	16.02	72.02	0.9971	32.47	
36	DCAB	3	3076.34	3108.46	98.97	307.69	4.50	0.0607	11.42	16.00	72.03	0.9936	16.01	
37	CADB	2	5094.56	5500.20	92.63	477.31	3.00	0.0345	20.07	16.00	72.00	0.9920	25.73	
38	BACD	2	2835.11	2881.50	98.39	275.81	2.00	0.0569	12.18	16.00	72.00	0.9942	15.32	
40	DABC	2	7299.07	7553.37	96.63	503.30	4.00	0.0460	15.06	16.00	72.00	0.9929	19.29	
41	DCAB	3	4153.29	4983.77	83.34	263.27	2.00	0.0233	29.71	16.00	72.00	0.9924	39.38	
42	CBAD	3	4822.49	5334.39	90.40	310.86	4.50	0.0316	21.96	16.00	72.05	0.9536	27.90	
43	BDAC	3	4950.46	5187.64	95.43	616.00	3.00	0.0402	17.25	16.00	72.00	0.9922	20.02	
44	ADCB	1	6335.56	6688.33	94.73	472.63	3.50	0.0412	16.83	16.00	72.00	0.9857	23.86	
45	CDBA	4	5664.87	6291.65	90.04	329.62	4.00	0.0300	23.08	16.00	72.00	0.9942	30.41	
46	BCDA	4	2679.50	3071.82	87.23	294.00	2.02	0.0257	26.93	16.00	72.00	0.9985	31.97	
47	ABDC	1	3914.10	4306.48	90.89	240.00	3.50	0.0329	21.08	16.00	72.00	0.9932	28.54	
48	DBCA	4	4311.30	4561.87	94.51	282.68	3.00	0.0378	18.33	16.00	72.63	0.9975	23.48	
49	BDCA	4	3029.33	3256.63	93.02	278.00	2.00	0.0338	20.51	16.03	72.00	0.9968	24.41	
50	ACBD	1	4036.97	4705.25	85.80	229.64	4.50	0.0263	26.40	16.00	72.00	0.9280	34.66	
51	ADCB	1	4935.66	5304.30	93.05	313.00	3.50	0.0372	18.65	16.00	72.00	0.9603	23.99	
52	CADB	2	3696.85	4048.45	91.32	240.00	4.00	0.0338	20.48	16.00	72.00	0.9897	27.22	
53	CDBA	4	6628.14	7379.36	89.82	526.42	2.50	0.0305	22.71	16.00	72.00	0.9827	28.44	
54	BACD	2	4716.40	4866.71	96.91	655.90	2.00	0.0462	15.01	16.00	72.00	0.9875	17.16	
55	ABDC	1	3774.35	4091.58	92.25	336.00	3.00	0.0328	21.14	16.00	72.00	0.9933	24.51	
56	BDAC	3	3570.87	4073.81	87.65	257.49	2.00	0.0282	24.56	16.00	72.00	0.9927	32.81	
57	BCDA	4	2760.04	3287.91	83.95	183.62	2.00	0.0233	29.69	16.00	72.00	0.9535	38.05	
58	DCAB	3	2662.54	3338.91	79.74	315.81	2.00	0.0204	33.96	16.00	72.00	0.9573	41.79	
59	CBAD	3	7186.60	7776.00	92.42	546.31	4.00	0.0355	19.53	16.00	72.00	0.9880	25.31	
60	DABC	2	3891.77	4506.72	86.35	324.00	1.00	0.0257	26.98	16.00	72.12	0.9935	33.91	
MEAN	.	.	4307.77	4676.08	92.11	347.00	3.40	0.0358	20.28	16.00	72.04	0.9880	26.06	
STD	.	.	1234.59	1324.86	3.95	122.55	1.74	0.0079	4.37	0.00	0.12	0.0139	6.04	
CV(%)	.	.	28.66	28.33	4.28	35.32	51.29	21.9667	21.57	0.03	0.16	1.4048	23.19	

\* TLIN = start time for linear regression  
\*\* LQCT = last quantifiable concentration time  
\*\*\* R = correlation coefficient obtained from regression analysis

**Summary of Individual Isotretinoin Pharmacokinetic Parameters**  
**B: Isotretinoin 2 x 20 mg Capsules, Lot No.: 28A02 (Cipher Pharmaceuticals Ltd., Barbados), Fed**

Subject	SEQ	Period	AUC (0-t) (ng.h/mL)	AUC (0-inf) (ng.h/mL)	AUC (0-t) ----- (%)		Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R	MRTpo (h)
					AUC (0-inf)	AUC (0-inf)								
01	BACD	1	5743.09	6079.43	94.47	298.00	4.50	0.0416	16.65	16.07	72.00	0.9945	24.56	
02	BCDA	1	4715.95	4952.49	95.22	622.84	4.50	0.0429	16.17	16.00	72.00	0.9819	21.82	
03	BDAC	1	6904.49	7465.55	92.48	337.89	5.50	0.0372	18.62	16.00	72.00	0.9903	28.36	
04	DBCA	2	6388.89	6659.81	95.93	537.23	10.00	0.0470	14.76	16.00	72.18	0.9641	21.61	
05	CBAD	2	7171.00	7682.76	93.34	409.00	7.03	0.0397	17.47	16.00	72.02	0.9772	27.59	
06	CDBA	3	5876.13	6040.62	97.28	583.00	3.50	0.0496	13.97	16.00	72.00	0.9936	19.27	
07	DCAB	4	6801.61	7149.44	95.13	423.65	4.50	0.0416	16.68	16.00	72.00	0.9975	24.70	
08	ADCB	4	7504.28	8030.94	93.44	364.04	8.00	0.0407	17.02	16.00	72.00	0.9920	27.60	
09	ACBD	3	6160.51	6448.55	95.53	239.60	7.00	0.0458	15.13	16.00	72.00	0.9973	26.12	
10	CADB	4	5266.25	5936.41	88.71	327.00	3.50	0.0300	23.11	16.00	72.00	0.9917	31.06	
11	ABDC	2	6965.30	7210.80	96.60	489.77	3.00	0.0459	15.09	16.00	72.00	0.9912	21.52	
12	DABC	3	6229.57	6332.71	98.37	584.32	5.50	0.0546	12.71	16.00	72.00	0.9932	16.89	
13	ADCB	4	5518.00	5956.40	92.64	483.00	4.50	0.0349	19.86	16.00	72.00	0.9977	26.17	
14	CADB	4	6785.71	7772.57	87.30	666.38	4.50	0.0281	24.71	16.00	72.00	0.9912	33.89	
15	ACBD	3	6524.01	6959.71	93.74	405.44	4.50	0.0430	16.11	16.00	72.00	0.9844	27.65	
16	BACD	1	5588.73	5862.09	95.34	356.00	3.50	0.0439	15.79	16.00	73.60	0.9696	23.27	
17	BCDA	1	7584.36	7819.76	96.99	538.64	12.00	0.0512	13.55	16.00	72.00	0.9953	22.83	
18	DBCA	2	7887.70	8384.27	94.08	310.00	10.00	0.0429	16.16	16.00	72.00	0.9808	28.08	
19	CDBA	3	7208.93	7411.69	97.26	663.50	4.50	0.0493	14.06	16.00	72.00	0.9946	21.25	
20	CBAD	2	6981.24	7589.05	91.99	393.94	10.00	0.0366	18.94	16.00	72.00	0.9958	29.76	
21	DABC	3	5411.51	6006.88	90.09	453.54	8.00	0.0328	21.12	16.00	72.00	0.9315	31.16	
22	ABDC	2	5282.41	5658.50	93.35	405.54	10.00	0.0384	18.05	16.00	72.00	0.9931	26.98	
24	BDAC	1	6791.17	7200.59	94.31	413.64	10.00	0.0441	15.73	16.00	72.00	0.9919	26.84	
25	CBAD	2	6468.82	6824.59	94.79	259.23	16.00	0.0470	14.74	16.00	72.00	0.9897	27.30	
26	ADCB	4	5214.14	5512.04	94.60	563.64	4.50	0.0387	17.89	16.03	72.12	0.9929	23.83	
27	BACD	1	4750.36	4876.16	97.42	375.62	10.00	0.0512	13.55	16.00	72.00	0.9916	21.03	
28	ACBD	3	5704.64	5957.64	95.75	862.31	4.50	0.0419	16.53	16.00	72.30	0.9945	21.08	
29	CDBA	3	4162.60	5183.72	80.30	286.63	2.50	0.0204	33.98	16.00	72.00	0.9897	43.74	
30	DBCA	2	8448.64	9765.18	86.52	319.65	4.50	0.0308	22.51	16.00	72.47	0.9859	36.53	
32	BDAC	1	5954.49	6395.46	93.10	205.00	5.00	0.0447	15.52	24.00	72.00	0.9784	30.01	
33	ABDC	2	6105.27	6408.70	95.27	540.22	4.50	0.0426	16.28	16.00	72.00	0.9925	23.10	

**B: Isotretinoin 2 x 20 mg Capsules, Lot No.: 28A02 (Cipher Pharmaceuticals Ltd., Barbados), Fed**

Subject	SEQ	Period	AUC (0-t) (ng.h/mL)	AUC (0-inf) (ng.h/mL)	AUC (0-t) ----- (%)		Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R	MRTpo (h)
					AUC (0-inf)	AUC (0-inf)								
34	DABC	3	7726.51	8323.37	92.83	396.76	10.00	0.0386	17.94	16.00	72.00	0.9979	30.02	
35	BCDA	1	8470.01	9447.35	89.65	701.90	10.00	0.0319	21.71	16.00	72.52	0.9965	32.43	
36	DCAB	4	4080.16	4130.10	98.79	646.71	4.50	0.0586	11.83	16.00	72.00	0.9949	17.05	
37	CADB	4	5989.01	6489.82	92.28	374.32	4.50	0.0366	18.95	16.00	72.00	0.9904	27.02	
38	BACD	1	5882.11	5994.22	98.13	357.63	10.00	0.0598	11.60	16.00	72.00	0.9949	20.31	
40	DABC	3	6992.70	7289.61	95.93	698.91	8.00	0.0458	15.12	16.00	72.00	0.9869	22.50	
41	DCAB	4	6107.85	6736.21	90.67	394.81	8.00	0.0352	19.70	16.00	72.00	0.9915	31.14	
42	CBAD	2	8329.20	8908.46	93.50	463.75	10.00	0.0403	17.19	16.00	72.00	0.9902	27.59	
43	BDAC	1	7016.91	7289.34	96.26	524.65	8.00	0.0483	14.36	16.00	72.00	0.9957	23.23	
44	ADCB	4	7239.28	7809.30	92.70	748.61	10.00	0.0388	17.87	16.00	72.00	0.9946	29.11	
45	CDBA	3	9567.82	10563.40	90.58	604.62	10.00	0.0322	21.55	16.00	72.00	0.9972	31.37	
46	BCDA	1	7298.18	8348.81	87.42	562.40	4.50	0.0265	26.20	16.00	72.00	0.9957	34.19	
47	ADCB	2	5761.25	6130.46	93.98	316.00	4.50	0.0420	16.51	16.00	72.03	0.9835	25.83	
48	DBCA	2	6104.22	6395.12	95.45	773.96	4.50	0.0421	16.45	16.00	72.00	0.9968	21.95	
49	DBCA	2	4048.35	4340.56	93.27	146.00	4.00	0.0411	16.88	16.00	72.00	0.9972	29.38	
50	ACBD	3	5977.81	6596.64	90.62	263.83	4.50	0.0337	20.59	16.00	72.00	0.9963	31.00	
51	ADCB	4	6753.77	7148.27	94.48	395.26	10.00	0.0443	15.66	16.00	72.00	0.9801	25.10	
52	CADB	4	4821.03	5080.66	94.89	354.00	7.00	0.0412	16.82	16.00	72.00	0.9987	24.88	
53	CDBA	3	10521.48	11270.66	93.35	1128.45	4.50	0.0378	18.32	16.00	72.00	0.9944	25.41	
54	BACD	1	6399.06	6695.66	95.57	506.32	8.00	0.0452	15.32	16.00	72.00	0.9922	24.40	
55	ABDC	2	4591.65	4835.21	94.96	454.00	4.50	0.0431	16.08	16.00	72.00	0.9907	24.16	
56	BDAC	1	4628.31	4945.81	93.58	286.65	10.00	0.0420	16.49	16.00	72.00	0.9950	28.79	
57	BCDA	1	6563.21	7342.63	89.39	437.51	8.00	0.0338	20.53	16.00	72.03	0.9688	31.53	
58	DCAB	4	5927.46	6345.94	93.41	428.32	8.00	0.0385	18.00	16.00	72.02	0.9911	26.42	
59	CBAD	2	7642.25	8047.04	94.97	505.64	8.00	0.0433	16.00	16.00	72.00	0.9903	24.24	
60	DABC	3	6262.85	6906.71	90.68	397.00	8.00	0.0334	20.76	16.00	72.00	0.9960	31.00	
MEAN	.	.	6400.04	6858.70	93.49	466.43	6.85	0.0409	17.56	16.14	72.06	0.9895	26.59	
STD	.	.	1282.67	1428.64	3.28	174.94	2.83	0.0074	3.72	1.06	0.23	0.0108	4.85	
CV (%)	.	.	20.04	20.83	3.51	37.51	41.37	18.0731	21.16	6.56	0.32	1.0931	18.23	

\* TLIN = start time for linear regression  
\*\* LQCT = last quantifiable concentration time  
\*\*\* R = correlation coefficient obtained from regression analysis

**Summary of Individual Isotretinoin Pharmacokinetic Parameters**  
**C: ACCUTANE® 40 mg Capsules, Lot No.: U0622 (Roche Laboratories Inc., USA), Fast**

Subject	SEQ	Period	AUC (0-t) (ng.h/mL)	AUC (0-inf) (ng.h/mL)	AUC (0-t)	Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R	MRTpo (h)
					----- (%) AUC (0-inf)								
01	BACD	3	2046.11	2167.86	94.38	165.82	1.00	0.0370	18.71	16.00	72.00	0.9973	23.25
02	BCDA	2	1763.50	1831.90	96.27	120.75	4.50	0.0453	15.31	16.00	72.00	0.9983	21.59
03	BDAC	4	2708.67	3000.75	90.27	198.00	3.50	0.0308	22.47	16.00	72.00	0.9940	28.57
04	DBCA	3	1587.38	1759.00	90.24	113.70	4.50	0.0333	20.81	16.00	72.00	0.9680	28.66
05	CBAD	1	2729.02	3037.67	89.84	169.84	3.00	0.0316	21.96	16.00	72.00	0.9979	30.58
06	CDBA	1	2715.36	2862.69	94.85	222.28	4.50	0.0411	16.88	16.00	72.00	0.9877	22.89
07	DCAB	2	2405.19	2645.80	90.91	120.65	4.00	0.0326	21.26	16.00	72.00	0.9949	29.41
08	ADCB	3	3775.07	4181.15	90.29	184.00	4.00	0.0335	20.70	16.00	72.00	0.9929	31.06
09	ACBD	2	2304.99	2519.22	91.50	150.51	3.50	0.0334	20.74	16.00	72.00	0.9966	28.06
10	CADB	1	1678.43	1977.16	84.89	126.00	1.00	0.0251	27.61	16.00	72.00	0.9900	36.12
11	ABDC	4	2004.81	2279.29	87.96	150.32	2.00	0.0266	26.06	16.00	72.00	0.9952	30.23
12	DABC	4	2143.74	2223.02	96.43	156.88	1.00	0.0431	16.08	16.00	72.00	0.9952	20.39
13	ADCB	3	2499.39	3061.42	81.64	126.96	2.50	0.0238	29.17	16.00	72.12	0.9653	39.86
14	CADB	1	3736.47	4479.71	83.41	179.67	4.50	0.0240	28.83	16.00	72.00	0.9916	38.38
15	ACBD	2	1709.99	1985.18	86.14	163.66	1.00	0.0250	27.70	16.00	72.00	0.9884	33.26
16	BACD	3	1461.44	1525.21	95.82	134.00	2.50	0.0434	15.96	16.00	72.00	0.9788	20.72
17	BCDA	2	1794.59	1877.42	95.59	214.00	2.50	0.0402	17.24	16.00	72.00	0.9944	19.50
18	DBCA	3	1985.56	2125.91	93.40	155.74	3.50	0.0399	17.35	16.00	72.00	0.9929	27.19
19	CDBA	1	2591.62	2775.33	93.38	122.70	3.50	0.0405	17.13	16.00	72.00	0.9756	25.20
20	CBAD	1	1994.28	2362.21	84.42	162.67	2.50	0.0245	28.25	16.00	72.00	0.9867	37.28
21	DABC	4	2636.78	3160.84	83.42	169.86	3.00	0.0240	28.91	16.00	72.00	0.9869	38.71
22	ABDC	4	2149.24	2392.19	89.84	166.60	4.50	0.0290	23.90	16.00	72.00	0.9527	28.07
24	BDAC	4	1943.75	2057.15	94.49	161.64	3.50	0.0421	16.46	16.00	72.00	0.9974	26.28
25	CBAD	1	2400.02	2637.94	90.98	151.48	1.00	0.0315	21.98	16.00	72.00	0.9945	27.07
26	ADCB	3	2159.88	2325.94	92.86	147.23	4.00	0.0355	19.51	16.00	72.37	0.9929	26.11
27	BACD	3	2144.26	2177.77	98.46	193.79	1.00	0.0539	12.86	16.00	72.87	0.9963	15.93
28	ACBD	2	1346.79	1517.39	86.76	92.70	2.00	0.0284	24.38	16.00	72.12	0.9943	30.98
29	CDBA	1	2729.98	3286.87	83.06	211.00	2.00	0.0235	29.47	16.00	72.00	0.9908	38.53
30	DBCA	3	2314.36	2794.38	82.82	161.56	3.50	0.0212	32.75	16.00	72.00	0.9737	39.72
32	BDAC	4	2452.06	2647.55	92.62	186.65	1.00	0.0360	19.23	16.00	72.00	0.9779	24.23
33	ABDC	4	3338.05	3630.81	91.94	261.73	3.50	0.0329	21.06	16.00	72.00	0.9943	26.99

**C: ACCUTANE® 40 mg Capsules, Lot No.: U0622 (Roche Laboratories Inc., USA), Fast**

Subject	SEQ	Period	AUC (0-t) (ng.h/mL)	AUC (0-inf) (ng.h/mL)	AUC (0-t)	Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R	MRTpo (h)
					----- (%) AUC (0-inf)								
34	DABC	4	2591.47	2893.45	89.56	159.59	2.00	0.0317	21.83	16.00	72.00	0.9797	28.85
35	BCDA	2	3072.90	3544.42	86.70	195.13	3.00	0.0261	26.51	16.00	72.70	0.9932	34.60
36	DCAB	2	1828.14	2205.08	82.91	142.30	2.50	0.0263	26.38	16.00	72.00	0.8644	35.65
37	CADB	1	2731.47	2950.62	92.57	164.63	3.50	0.0344	20.17	16.00	72.00	0.9804	27.08
38	BACD	3	1217.19	1244.18	97.83	158.89	3.50	0.0515	13.46	16.00	72.00	0.9967	17.11
40	DABC	4	3538.92	3761.83	94.07	305.92	2.00	0.0358	19.34	16.00	72.05	0.9982	22.75
41	DCAB	2	2689.07	3149.57	85.38	103.30	12.00	0.0302	22.97	16.00	72.00	0.9866	39.69
42	CBAD	1	2733.61	3106.70	87.99	145.00	3.50	0.0300	23.09	16.00	71.55	0.9595	31.45
43	BDAC	4	1908.12	1987.48	96.01	215.00	2.00	0.0418	16.57	16.00	72.30	0.9866	20.23
44	ADCB	3	3306.54	3617.59	91.40	285.74	2.50	0.0323	21.47	16.00	72.00	0.9907	27.45
45	CDBA	1	3227.65	3542.48	91.11	170.71	1.03	0.0331	20.96	16.00	72.00	0.9976	28.38
46	BCDA	2	2966.93	3439.21	86.27	197.56	1.00	0.0270	25.65	16.00	72.00	0.9657	35.57
47	ABDC	4	1591.28	1795.24	88.64	130.00	4.00	0.0292	23.72	16.00	72.17	0.9805	33.84
48	DBCA	3	2396.76	2543.20	94.24	180.66	2.00	0.0373	18.57	16.00	72.18	0.9980	23.00
49	DBCA	3	1532.42	1802.34	85.02	120.00	1.00	0.0249	27.88	16.05	72.00	0.9918	35.90
50	ACBD	2	2461.20	2642.85	93.13	160.14	2.00	0.0356	19.46	16.00	72.00	0.9947	26.80
51	ADCB	3	3524.09	4035.78	87.32	290.15	4.50	0.0275	25.24	16.00	72.00	0.9611	32.54
52	CADB	1	1648.07	1821.35	90.49	107.00	3.00	0.0313	22.16	16.00	72.13	0.9910	28.56
53	CDBA	1	2549.94	2861.47	89.11	197.48	3.00	0.0298	23.27	16.00	72.00	0.9967	31.41
54	BACD	3	2344.81	2467.51	95.03	250.74	1.00	0.0425	16.29	16.00	72.00	0.9740	20.42
55	ABDC	4	1349.86	1422.78	94.87	103.29	2.00	0.0390	17.76	16.00	72.00	0.9944	23.95
56	BDAC	4	2233.94	2512.03	88.93	199.78	3.50	0.0303	22.86	16.00	72.02	0.9863	33.14
57	BCDA	2	980.71	1199.14	81.78	68.74	4.50	0.0229	30.26	16.00	72.00	0.9880	41.66
58	DCAB	2	2437.77	2804.31	86.93	144.66	4.50	0.0269	25.77	16.00	72.00	0.9905	33.01
59	CBAD	1	3956.62	4402.34	89.88	247.32	4.00	0.0301	23.02	16.00	72.00	0.9921	28.86
60	DABC	4	1836.68	2237.98	82.07	144.65	2.00	0.0232	29.86	16.00	72.00	0.9867	40.24
MEAN	.	.	2349.24	2619.26	90.00	169.66	2.94	0.0327	22.20	16.00	72.05	0.9852	29.42
STD	.	.	674.53	774.82	4.51	49.01	1.70	0.0073	4.69	0.01	0.17	0.0196	6.40
CV (%)	.	.	28.71	29.58	5.01	28.89	57.85	22.3725	21.14	0.04	0.24	1.9906	21.75

\* TLIN = start time for linear regression  
\*\* LQCT = last quantifiable concentration time  
\*\*\* R = correlation coefficient obtained from regression analysis

**Summary of Individual Isotretinoin Pharmacokinetic Parameters**  
**D: ACCUTANE® 40 mg Capsules, Lot No.: U0622 (Roche Laboratories Inc., USA), Fed**

Subject	SEQ	Period	AUC(0-t) (ng.h/mL)	AUC(0-inf) (ng.h/mL)	AUC(0-t) ----- (%) AUC(0-inf)	Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R	MRTpo (h)
01	BACD	4	5232.25	5623.92	93.04	317.86	4.50	0.0385	18.02	16.00	72.00	0.9945	27.17
02	BCDA	3	5105.56	5238.79	97.46	730.84	4.50	0.0495	14.01	16.00	72.00	0.9984	19.64
03	BDCB	2	6605.68	6988.22	94.53	312.28	10.00	0.0441	15.71	16.00	73.50	0.9882	26.96
04	DBCA	1	3520.10	3687.77	95.45	245.92	8.00	0.0472	14.70	16.00	72.07	0.9877	24.86
05	CBAD	4	7289.07	8027.16	90.81	458.68	2.50	0.0344	20.16	16.00	72.17	0.9671	31.16
06	CDBA	2	7044.38	7250.06	97.16	519.67	10.00	0.0538	12.88	16.00	72.00	0.9955	23.01
07	DCAB	1	5354.06	5625.46	95.18	417.77	2.00	0.0401	17.31	16.00	72.00	0.9988	22.48
08	ADCB	2	10235.09	10881.04	94.06	699.82	10.00	0.0387	17.90	16.00	72.00	0.9358	26.19
09	ACBD	4	7059.64	7535.88	93.68	227.59	10.00	0.0420	16.51	16.00	72.00	0.9989	29.24
10	CADB	3	5957.98	6392.25	93.21	257.00	10.00	0.0375	18.47	16.00	72.00	0.9121	29.03
11	ABDC	3	3229.78	3464.51	93.22	264.63	2.00	0.0338	20.50	16.00	72.00	0.9894	25.54
12	DABC	1	5008.70	5097.26	98.26	415.93	4.50	0.0530	13.08	16.00	72.00	0.9951	16.74
13	ADCB	2	6383.65	6741.47	94.69	447.00	5.00	0.0408	16.99	16.00	72.00	0.9962	25.24
14	CADB	3	9298.01	9943.25	93.51	545.75	4.50	0.0408	16.97	16.00	72.00	0.9779	28.63
15	ACBD	4	5272.03	5634.79	93.56	375.58	4.50	0.0366	18.94	16.00	72.00	0.9913	25.54
16	BACD	4	5487.81	5757.03	95.32	532.62	3.00	0.0409	16.94	16.00	72.00	0.9955	21.03
17	BCDA	3	8382.15	8610.95	97.34	576.00	12.00	0.0520	13.33	16.00	72.00	0.9956	22.76
18	DBCA	1	5074.45	5372.50	94.45	279.00	2.50	0.0406	17.07	16.00	72.00	0.9955	23.73
19	CDBA	2	8279.17	8511.51	97.27	700.56	3.50	0.0510	13.58	16.00	72.00	0.9922	20.65
20	CBAD	4	6140.84	6646.19	92.40	677.00	8.00	0.0356	19.46	16.00	72.00	0.9980	27.84
21	DABC	1	4961.89	5654.61	87.75	236.21	14.00	0.0312	22.22	16.00	72.00	0.9742	37.74
22	ABDC	3	4419.97	4812.32	91.85	381.73	10.00	0.0370	18.72	16.00	72.00	0.9937	30.35
24	BDCB	2	6797.31	7106.08	95.65	438.61	2.50	0.0447	15.50	16.03	72.00	0.9872	22.90
25	CBAD	4	3850.73	4056.22	94.93	238.45	3.50	0.0410	16.92	16.00	72.00	0.9929	21.96
26	ADCB	2	5553.99	5819.97	95.43	626.89	4.50	0.0421	16.47	16.00	72.33	0.9904	22.18
27	BACD	4	5687.36	5766.11	98.63	344.89	10.00	0.0615	11.28	16.00	72.00	0.9957	19.41
28	ACBD	4	5893.28	6129.13	96.15	654.00	4.00	0.0419	16.55	16.00	72.02	0.9978	20.49
29	CDBA	2	6157.92	7193.39	85.61	422.37	8.00	0.0288	24.11	16.00	72.00	0.9880	37.99
30	DBCA	1	7895.76	8628.48	91.51	523.88	10.00	0.0367	18.90	16.00	72.05	0.9957	31.79
32	BDCB	2	6916.14	7276.10	95.05	502.00	20.00	0.0497	13.94	24.00	73.07	0.9963	31.90
33	ABDC	3	7084.60	7429.69	95.36	732.55	8.00	0.0428	16.21	16.00	72.00	0.9930	23.85

**D: ACCUTANE® 40 mg Capsules, Lot No.: U0622 (Roche Laboratories Inc., USA), Fed**

Subject	SEQ	Period	AUC(0-t) (ng.h/mL)	AUC(0-inf) (ng.h/mL)	AUC(0-t) ----- (%) AUC(0-inf)	Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R	MRTpo (h)
34	DABC	1	6822.46	7290.12	93.59	420.76	5.00	0.0395	17.56	16.00	72.00	0.9899	26.52
35	BCDA	3	5964.02	6685.63	89.21	277.84	2.50	0.0299	23.22	16.00	72.07	0.9989	31.68
36	DCAB	1	4144.23	4383.54	94.54	500.74	4.50	0.0420	16.52	16.00	72.00	0.9368	20.40
37	CADB	3	5778.38	6019.38	96.00	490.85	4.00	0.0446	15.53	16.00	72.00	0.9722	21.50
38	BACD	4	2809.94	2881.18	97.53	252.00	1.00	0.0501	13.83	16.00	72.00	0.9969	17.56
40	DABC	1	6140.52	6462.39	95.02	730.82	7.03	0.0436	15.91	16.03	72.00	0.9819	23.41
41	DCAB	1	4433.26	5095.77	87.00	269.87	10.00	0.0304	22.76	16.00	72.00	0.9934	36.54
42	CBAD	4	5508.23	5966.49	92.32	290.02	10.00	0.0404	17.15	16.00	72.00	0.9863	30.51
43	BDCB	2	6878.63	7198.10	95.56	471.31	10.00	0.0482	14.37	16.00	72.00	0.9760	25.25
44	ADCB	2	9625.06	10603.52	90.77	916.28	7.00	0.0365	19.01	16.00	72.00	0.9776	30.20
45	CDBA	2	8626.10	9254.61	93.21	609.46	8.00	0.0381	18.18	16.00	72.00	0.9954	28.37
46	BCDA	3	7844.96	8584.56	91.38	716.76	4.50	0.0336	20.62	16.00	72.00	0.9671	29.80
47	ABDC	3	5526.21	5830.81	94.78	394.00	10.00	0.0463	14.97	16.00	72.00	0.9941	27.60
48	DBCA	1	6784.11	7046.69	96.27	1018.84	4.50	0.0443	15.64	16.00	72.00	0.9938	20.27
49	DBCA	1	5862.01	6157.27	95.20	296.00	10.00	0.0474	14.62	16.00	72.00	0.9936	26.78
50	ACBD	4	8355.12	9256.83	90.26	683.57	4.50	0.0314	22.11	16.00	72.00	0.9885	32.74
51	ADCB	2	4748.50	5183.63	91.61	445.20	1.00	0.0349	19.84	16.00	72.00	0.9687	25.80
52	CADB	3	3105.25	3302.08	94.04	221.00	1.00	0.0370	18.71	16.00	72.05	0.9963	24.79
53	CDBA	2	6900.55	7372.59	93.60	823.67	4.00	0.0376	18.41	16.00	72.00	0.9951	25.25
54	BACD	4	7036.05	7220.27	97.45	594.00	8.07	0.0541	12.82	16.00	72.00	0.9905	21.18
55	ABDC	3	4527.68	4742.22	95.48	381.85	4.50	0.0436	15.90	16.00	72.00	0.9891	22.71
56	BDCB	2	6093.68	6500.65	93.74	371.55	10.00	0.0431	16.07	16.00	72.00	0.9361	31.28
57	BCDA	3	6487.79	7320.48	88.63	369.52	10.00	0.0343	20.24	16.03	72.00	0.9921	35.70
58	DCAB	1	6571.87	7441.78	88.31	218.25	10.00	0.0336	20.62	16.00	72.00	0.9773	36.37
59	CBAD	4	7162.11	7517.85	95.27	665.00	8.00	0.0458	15.13	16.00	72.00	0.9764	23.56
60	DABC	1	5395.36	5792.00	93.15	333.00	10.00	0.0429	16.17	16.00	71.00	0.9888	28.60
MEAN	.	.	6145.81	6561.62	93.80	471.32	6.75	0.0414	17.18	16.14	72.04	0.9853	26.36
STD	.	.	1580.49	1710.32	2.85	191.08	3.74	0.0068	2.83	1.06	0.28	0.0177	5.09
CV(%)	.	.	25.72	26.07	3.04	40.54	55.41	16.5303	16.45	6.56	0.39	1.7930	19.30

\* TLIN = start time for linear regression  
 \*\* LQCT = last quantifiable concentration time  
 \*\*\* R = correlation coefficient obtained from regression analysis

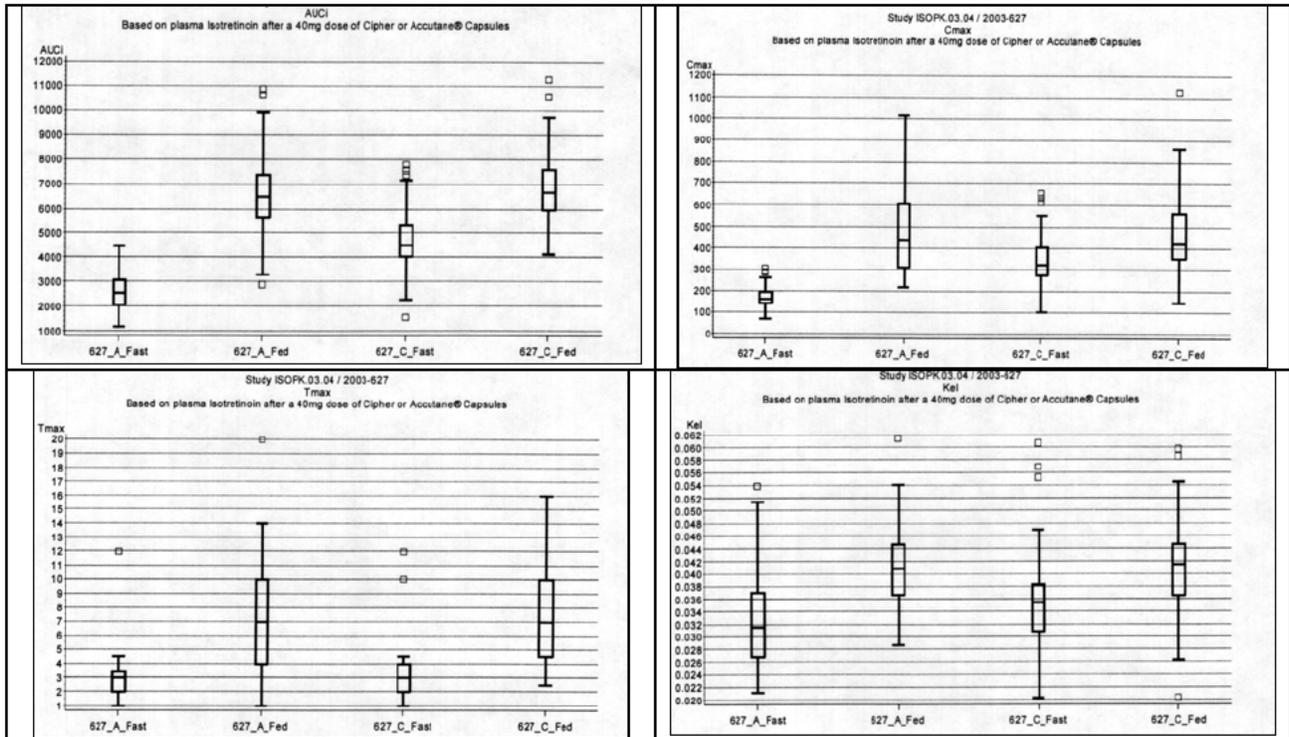
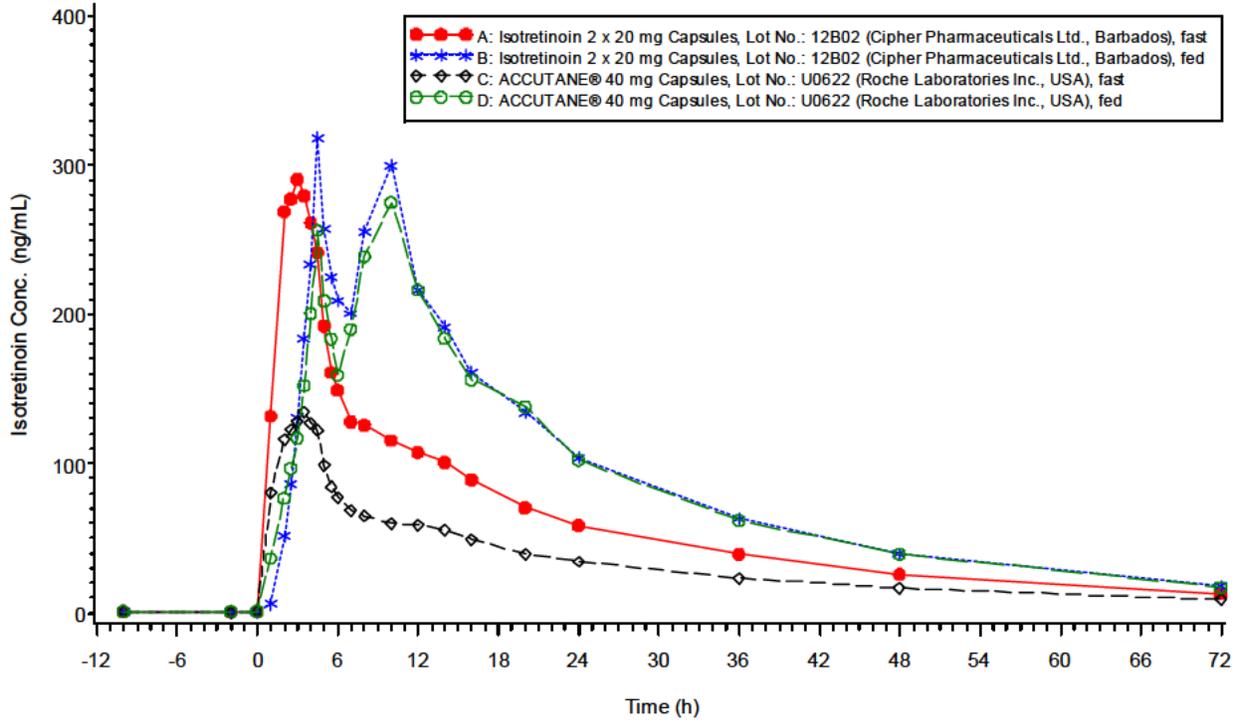
**Summary of Study Results**  
(Based on Baseline-adjusted Plasma Isotretinoin Parameters)

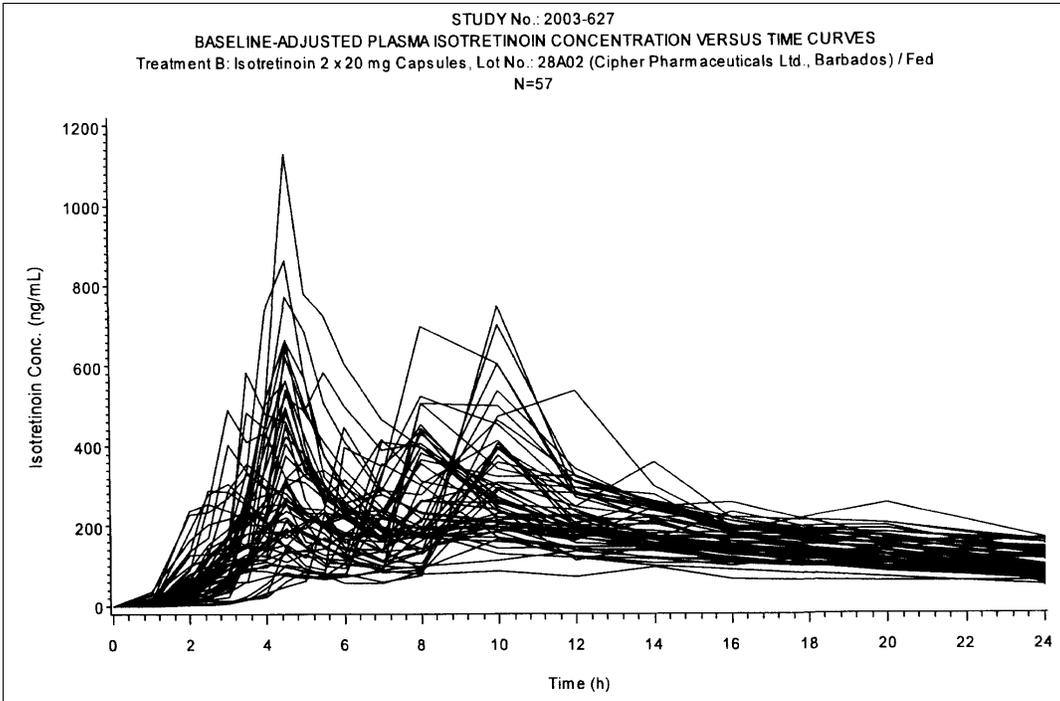
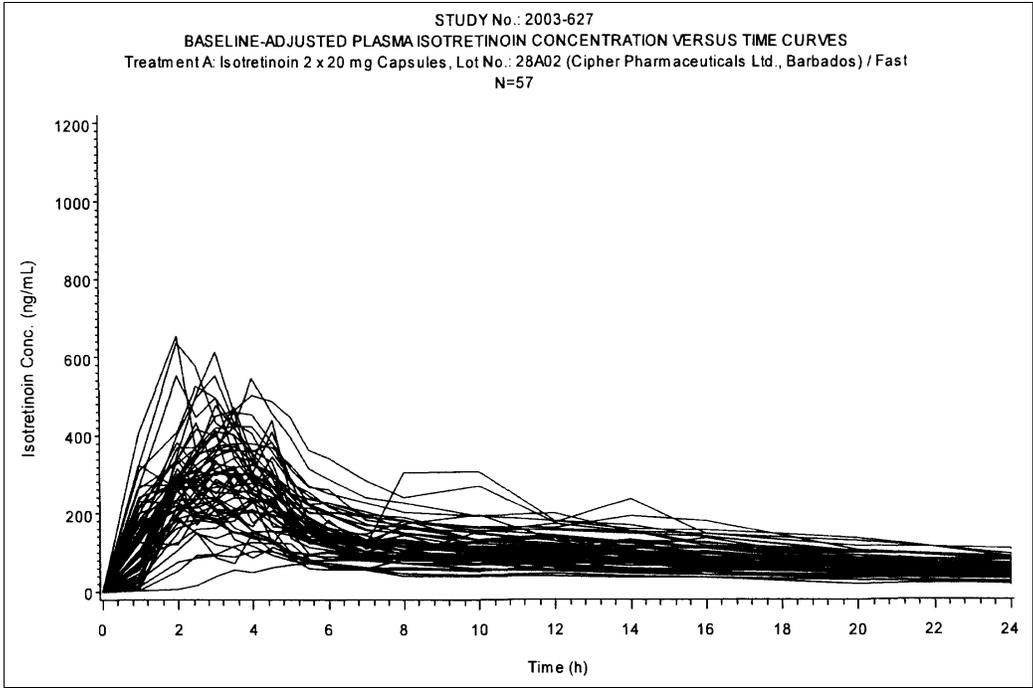
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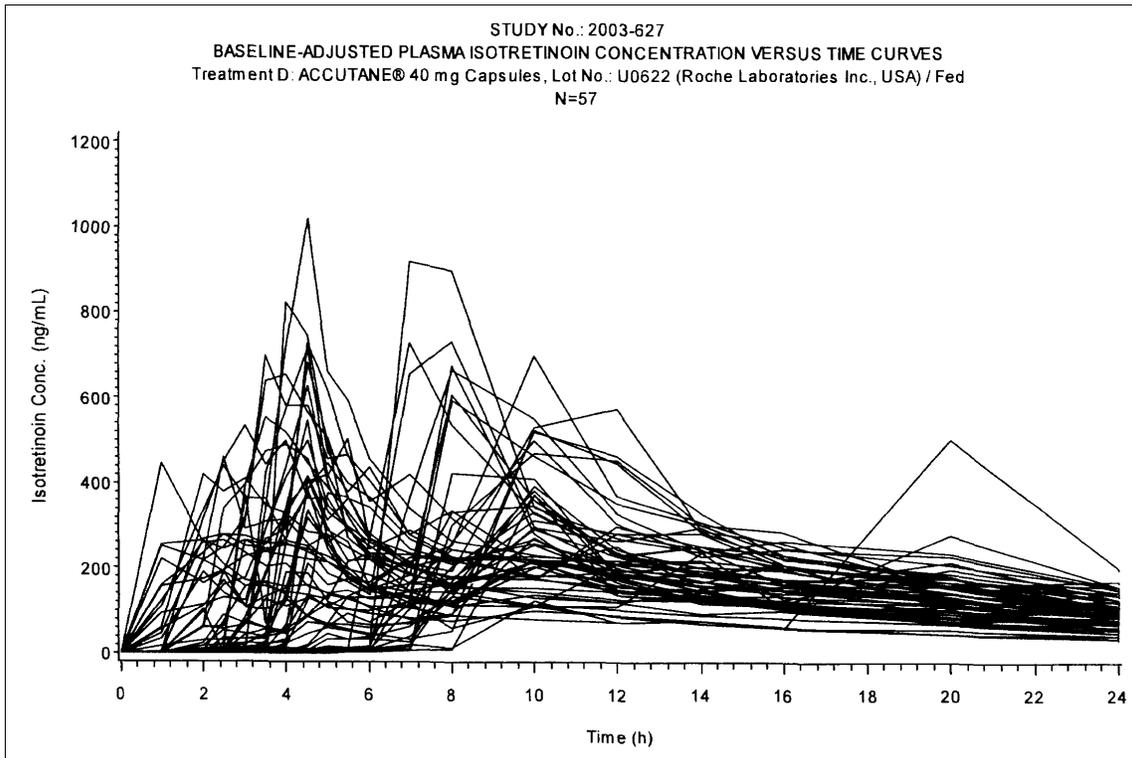
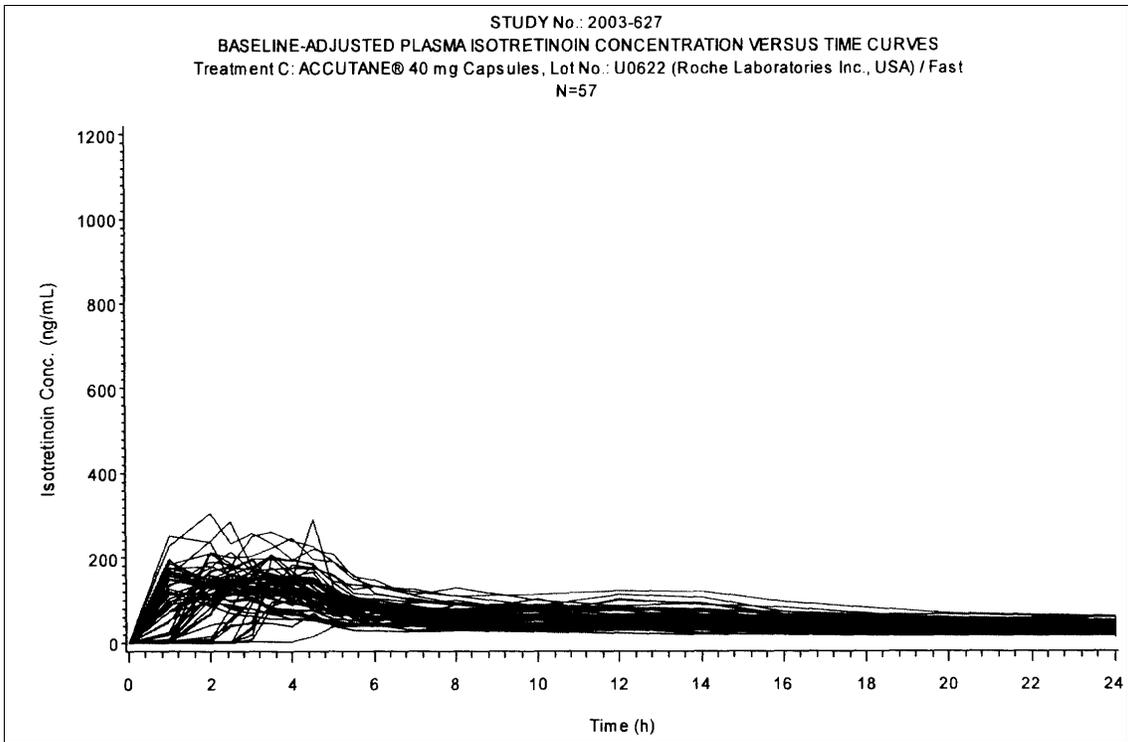
Parameter	Treatment		Means		Type	Code	Contrast Ratio (%)	90% CI (%)	CV%
	Type	Trt	Arithmetic (CV%)	Geometric					
AUC <sub>t</sub> (ng·h/mL)	T - Fast	A	4307.77 (29)	4110.64	T: Food Effect	B vs. A	152.07	142.49 – 162.29	21
	T - Fed	B	6400.04 (20)	6251.05	R: Food Effect	D vs. C	263.46	246.86 – 281.17	
	R - Fast	C	2349.24 (29)	2245.49	T/R - Fast	A vs. C	183.06	171.53 – 195.37	
	R - Fed	D	6145.81 (26)	5915.87	T/R - Fed	B vs. D	105.67	99.01 – 112.77	
AUC <sub>i</sub> (ng·h/mL)	T - Fast	A	4676.08 (28)	4470.45	T: Food Effect	B vs. A	149.78	140.52 – 159.66	21
	T - Fed	B	6858.70 (21)	6695.87	R: Food Effect	D vs. C	252.60	236.98 – 269.26	
	R - Fast	C	2619.26 (30)	2500.01	T/R - Fast	A vs. C	178.82	167.76 – 190.60	
	R - Fed	D	6561.62 (26)	6315.15	T/R - Fed	B vs. D	106.03	99.47 – 113.02	
C <sub>max</sub> (ng/mL)	T - Fast	A	347.00 (35)	323.18	T: Food Effect	B vs. A	134.39	122.60 – 147.32	30
	T - Fed	B	466.43 (38)	434.33	R: Food Effect	D vs. C	267.53	244.05 – 293.28	
	R - Fast	C	169.66 (29)	161.43	T/R - Fast	A vs. C	200.20	182.63 – 219.46	
	R - Fed	D	471.32 (41)	431.88	T/R - Fed	B vs. D	100.57	91.74 – 110.24	
T <sub>max</sub> (h)	T - Fast	A	3.40 (51)	-	T: Food Effect	B vs. A	201.19	-	
	T - Fed	B	6.85 (41)	-	R: Food Effect	D vs. C	228.40	-	
	R - Fast	C	2.94 (58)	-	T/R - Fast	A vs. C	115.06	-	
	R - Fed	D	6.75 (55)	-	T/R - Fed	B vs. D	101.35	-	
K <sub>el</sub> (1/h)	T - Fast	A	0.0358 (22)	-	T: Food Effect	B vs. A	114.45	-	
	T - Fed	B	0.0409 (18)	-	R: Food Effect	D vs. C	126.68	-	
	R - Fast	C	0.0327 (22)	-	T/R - Fast	A vs. C	109.33	-	
	R - Fed	D	0.0414 (17)	-	T/R - Fed	B vs. D	98.78	-	
T <sub>half</sub> (h)	T - Fast	A	20.28 (22)	-	T: Food Effect	B vs. A	86.69	-	
	T - Fed	B	17.56 (21)	-	R: Food Effect	D vs. C	77.55	-	
	R - Fast	C	22.20 (21)	-	T/R - Fast	A vs. C	91.43	-	
	R - Fed	D	17.18 (16)	-	T/R - Fed	B vs. D	102.21	-	
MRT <sub>po</sub> (h)	T - Fast	A	26.06 (23)	-	T: Food Effect	B vs. A	101.95	-	
	T - Fed	B	26.59 (18)	-	R: Food Effect	D vs. C	89.60	-	
	R - Fast	C	29.42 (22)	-	T/R - Fast	A vs. C	88.62	-	
	R - Fed	D	26.36 (19)	-	T/R - Fed	B vs. D	100.83	-	

T = Test  
R = Reference

STUDY No.: 2003-627  
 MEAN MEASURED PLASMA ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES  
 N=57







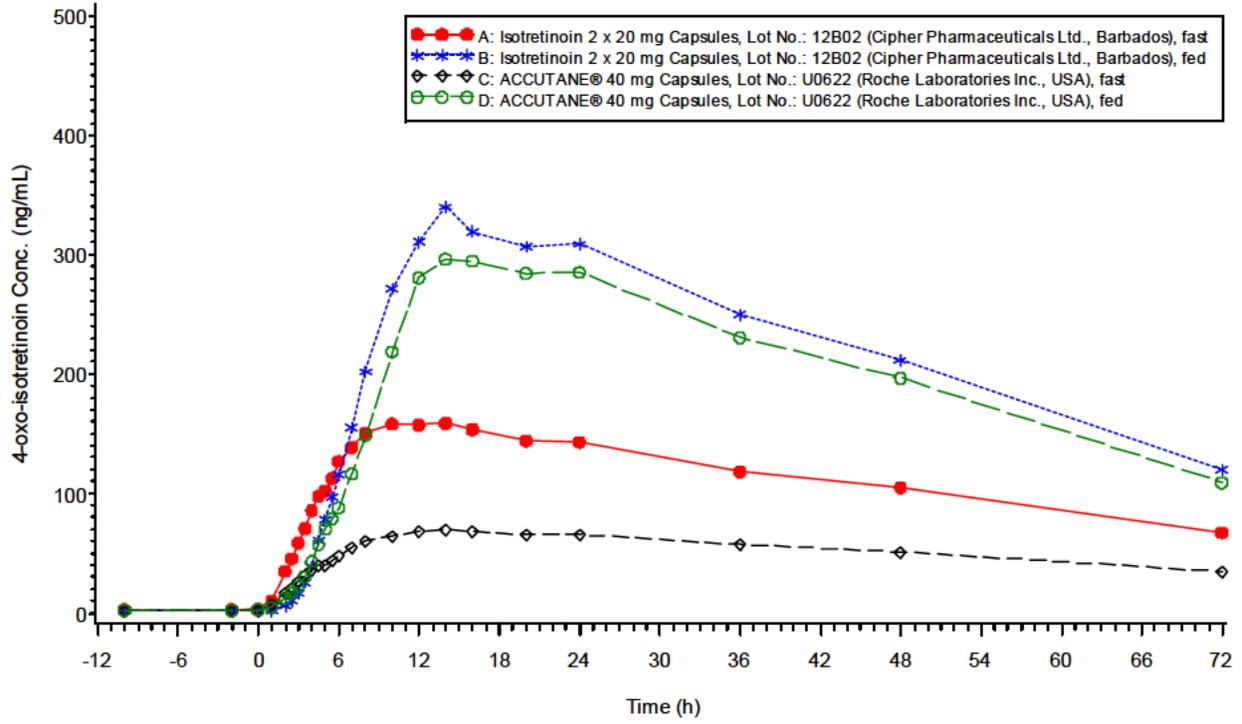
**Summary of Study Results**  
(Based on Baseline-adjusted Plasma 4-oxo-isotretinoin Parameters)

(N = 57)

Parameter	Treatment		Means		Type	Code	Contrast Ratio (%)	90% CI (%)	CV%
	Type	Trt	Arithmetic (CV%)	Geometric					
AUC <sub>t</sub> (ng·h/mL)	T - Fast	A	7843.81 (33)	7383.24	T: Food Effect	B vs. A	200.02	183.85 – 217.63	28
	T - Fed	B	15318.97(25)	14768.25	R: Food Effect	D vs. C	387.61	356.25 – 421.72	
	R - Fast	C	3581.28 (33)	3371.19	T/R - Fast	A vs. C	219.01	201.30 – 238.28	
	R - Fed	D	13919.06 (33)	13066.91	T/R - Fed	B vs. D	113.02	103.88 – 122.96	
AUC <sub>i</sub> (ng·h/mL)	T - Fast	A	12962.12 (43)	11865.08	T: Food Effect	B vs. A	178.01	162.09 – 195.50	31
	T - Fed	B	22080.03 (31)	21121.13	R: Food Effect	D vs. C	312.59	284.63 – 343.30	
	R - Fast	C	6667.38 (46)	6049.60	T/R - Fast	A vs. C	196.13	178.59 – 215.39	
	R - Fed	D	20485.24 (39)	18910.45	T/R - Fed	B vs. D	111.69	101.70 – 122.66	
C <sub>max</sub> (ng/mL)	T - Fast	A	177.23 (39)	163.73	T: Food Effect	B vs. A	215.24	196.12 – 236.23	31
	T - Fed	B	368.76 (28)	352.42	R: Food Effect	D vs. C	439.82	400.75 – 482.71	
	R - Fast	C	75.61 (35)	70.55	T/R - Fast	A vs. C	232.09	211.48 – 254.71	
	R - Fed	D	336.61 (38)	310.28	T/R - Fed	B vs. D	113.58	103.49 – 124.65	
T <sub>max</sub> (h)	T - Fast	A	13.89 (46)	-	T: Food Effect	B vs. A	114.64	-	
	T - Fed	B	15.90 (33)	-	R: Food Effect	D vs. C	114.80	-	
	R - Fast	C	14.93 (40)	-	T/R - Fast	A vs. C	93.08	-	
	R - Fed	D	17.13 (37)	-	T/R - Fed	B vs. D	92.94	-	
K <sub>el</sub> (1/h)	T - Fast	A	0.0163 (38)	-	T: Food Effect	B vs. A	122.88	-	
	T - Fed	B	0.0201 (30)	-	R: Food Effect	D vs. C	144.15	-	
	R - Fast	C	0.0142 (44)	-	T/R - Fast	A vs. C	115.17	-	
	R - Fed	D	0.0205 (34)	-	T/R - Fed	B vs. D	98.18	-	
Th <sub>alf</sub> (h)	T - Fast	A	50.66 (51)	-	T: Food Effect	B vs. A	75.05	-	
	T - Fed	B	37.84 (33)	-	R: Food Effect	D vs. C	62.09	-	
	R - Fast	C	62.97 (71)	-	T/R - Fast	A vs. C	80.56	-	
	R - Fed	D	38.96 (44)	-	T/R - Fed	B vs. D	97.37	-	
MRT <sub>po</sub> (h)	T - Fast	A	77.61 (48)	-	T: Food Effect	B vs. A	80.59	-	
	T - Fed	B	62.34 (27)	-	R: Food Effect	D vs. C	67.44	-	
	R - Fast	C	95.75 (66)	-	T/R - Fast	A vs. C	81.14	-	
	R - Fed	D	64.41 (38)	-	T/R - Fed	B vs. D	96.95	-	

T = Test  
R = Reference

STUDY No.: 2003-627  
MEAN MEASURED PLASMA 4-OXO-ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES  
N=57



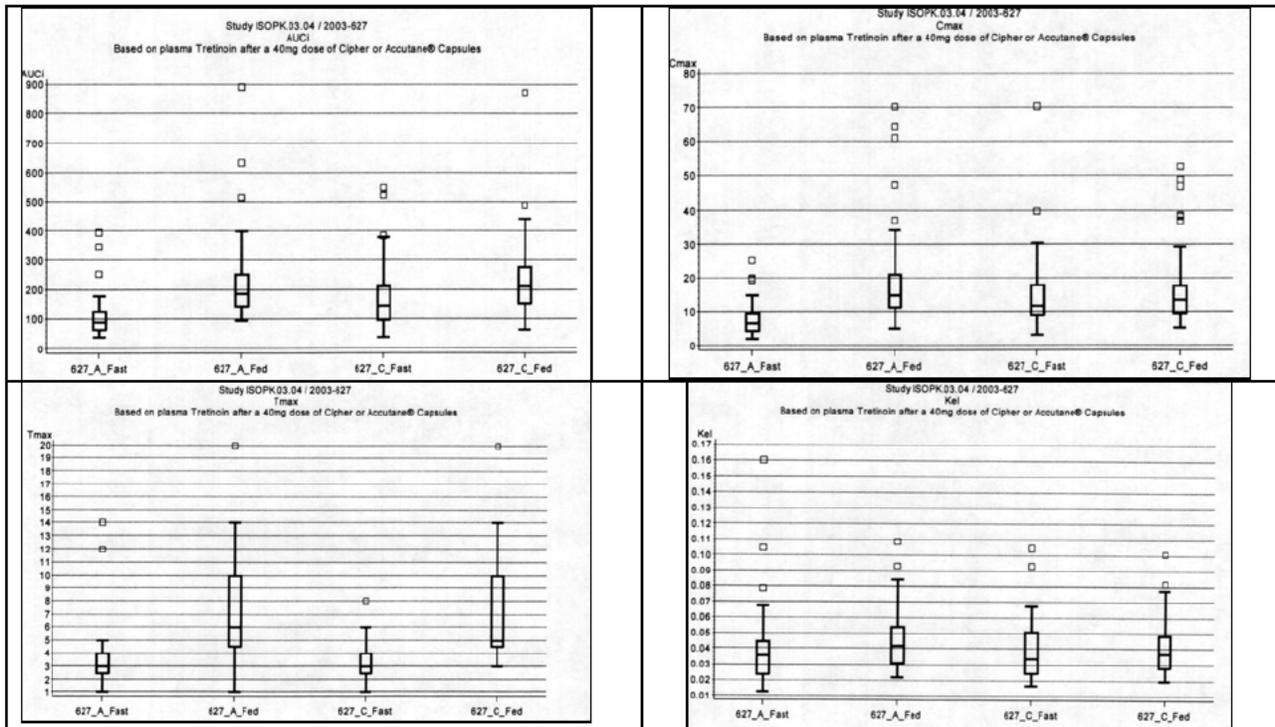
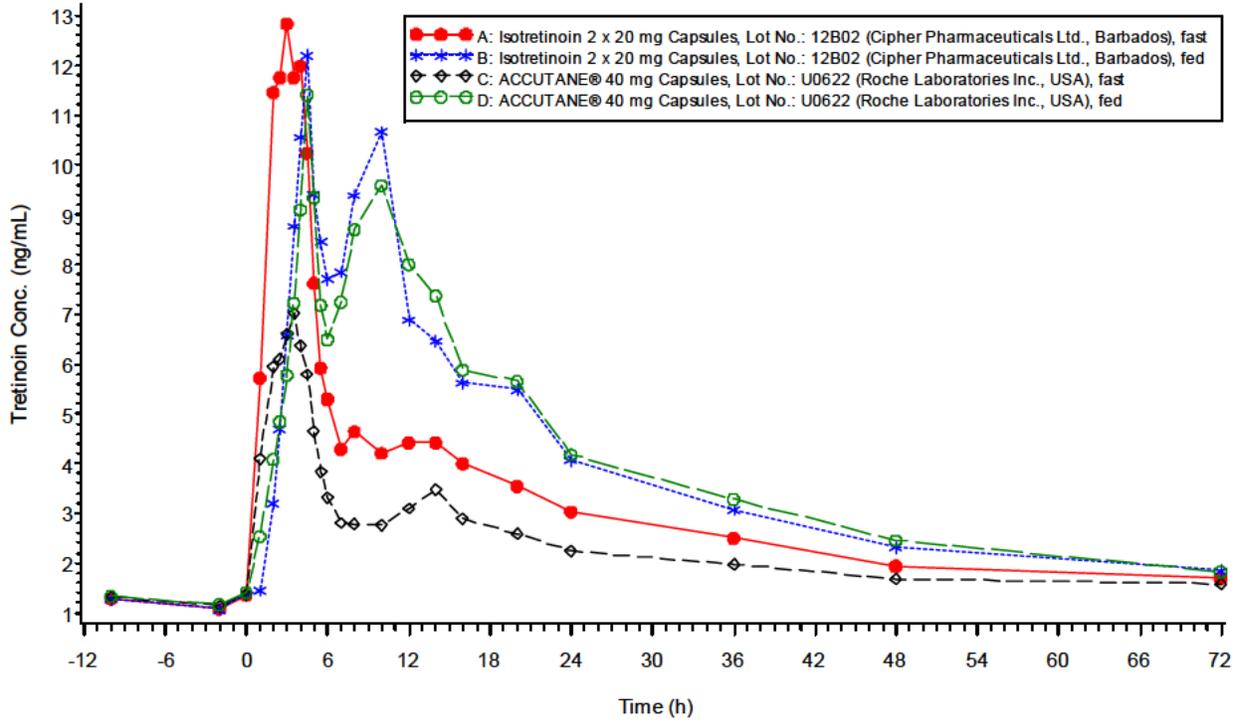
**Summary of Study Results**  
(Based on Baseline-adjusted Plasma Tretinoin Parameters)

(N = 57)

Parameter	Treatment		Means		Type	Code	Contrast Ratio (%)	90% CI (%)	CV%
	Type	Trt	Arithmetic (CV%)	Geometric					
AUC <sub>t</sub> (ng·h/mL)	T - Fast	A	139.51 (68)	116.65	T: Food Effect	B vs. A	143.51	129.88 – 158.57	33
	T - Fed	B	193.13 (62)	167.41	R: Food Effect	D vs. C	251.62	227.72 – 278.01	
	R - Fast	C	77.65 (67)	66.41	T/R - Fast	A vs. C	175.67	158.99 – 194.09	
	R - Fed	D	193.53 (67)	167.09	T/R - Fed	B vs. D	100.19	90.68 – 110.70	
AUC <sub>i</sub> (ng·h/mL)	T - Fast	A	177.07 (68)	143.95	T: Food Effect	B vs. A	130.92	115.62 – 148.24	34
	T - Fed	B	232.06 (60)	188.46	R: Food Effect	D vs. C	230.88	203.63 – 261.78	
	R - Fast	C	108.29 (69)	82.40	T/R - Fast	A vs. C	174.69	152.89 – 199.59	
	R - Fed	D	229.24 (62)	190.25	T/R - Fed	B vs. D	99.05	87.92 – 111.60	
C <sub>max</sub> (ng/mL)	T - Fast	A	14.84 (69)	12.65	T: Food Effect	B vs. A	113.14	99.91 – 128.12	42
	T - Fed	B	16.91 (66)	14.31	R: Food Effect	D vs. C	237.92	210.10 – 269.42	
	R - Fast	C	7.66 (60)	6.50	T/R - Fast	A vs. C	194.64	171.89 – 220.40	
	R - Fed	D	18.82 (74)	15.46	T/R - Fed	B vs. D	92.56	81.74 – 104.81	
T <sub>max</sub> (h)	T - Fast	A	3.23 (36)	-	T: Food Effect	B vs. A	209.56	-	
	T - Fed	B	6.75 (49)	-	R: Food Effect	D vs. C	199.25	-	
	R - Fast	C	3.45 (62)	-	T/R - Fast	A vs. C	93.19	-	
	R - Fed	D	6.88 (54)	-	T/R - Fed	B vs. D	98.01	-	
K <sub>el</sub> (1/h)	T - Fast	A	0.0396 (49)	-	T: Food Effect	B vs. A	104.45	-	
	T - Fed	B	0.0420 (43)	-	R: Food Effect	D vs. C	114.51	-	
	R - Fast	C	0.0403 (67)	-	T/R - Fast	A vs. C	101.62	-	
	R - Fed	D	0.0450 (41)	-	T/R - Fed	B vs. D	92.69	-	
Thalf (h)	T - Fast	A	21.27 (42)	-	T: Food Effect	B vs. A	92.33	-	
	T - Fed	B	19.38 (39)	-	R: Food Effect	D vs. C	72.46	-	
	R - Fast	C	23.16 (53)	-	T/R - Fast	A vs. C	90.38	-	
	R - Fed	D	17.70 (36)	-	T/R - Fed	B vs. D	115.17	-	
MRT <sub>po</sub> (h)	T - Fast	A	27.27 (41)	-	T: Food Effect	B vs. A	103.17	-	
	T - Fed	B	27.97 (35)	-	R: Food Effect	D vs. C	80.35	-	
	R - Fast	C	31.71 (51)	-	T/R - Fast	A vs. C	85.41	-	
	R - Fed	D	26.82 (30)	-	T/R - Fed	B vs. D	109.66	-	

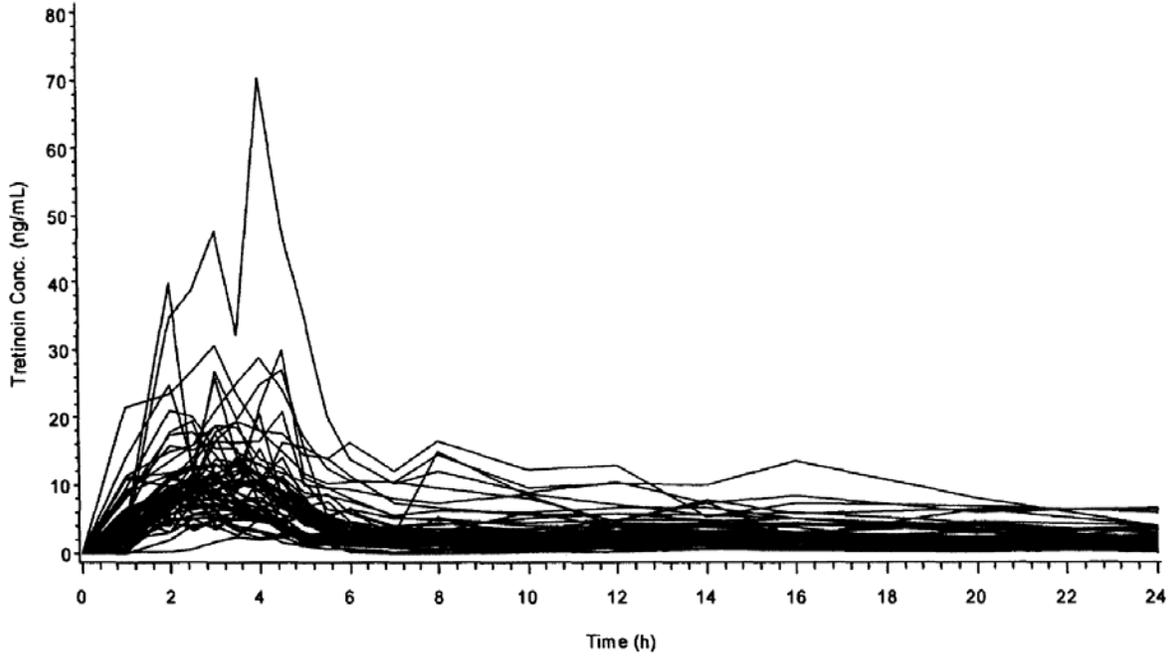
T = Test  
R = Reference

STUDY No.: 2003-627  
 MEAN MEASURED PLASMA TRETINOIN CONCENTRATION VERSUS TIME CURVES  
 N=57

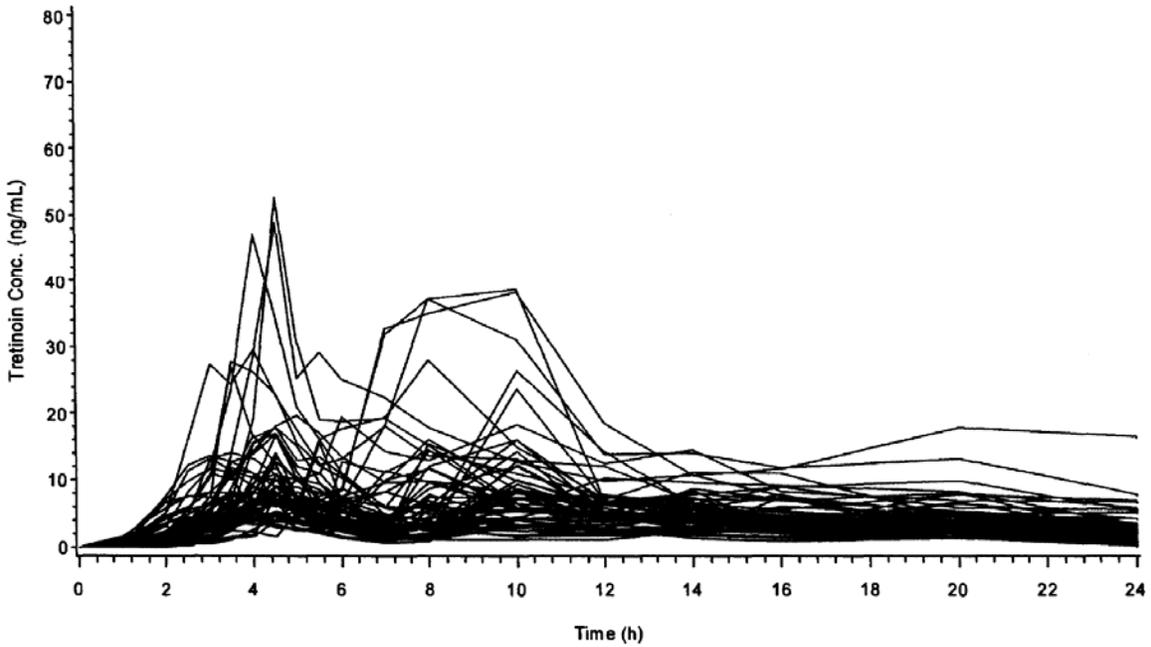


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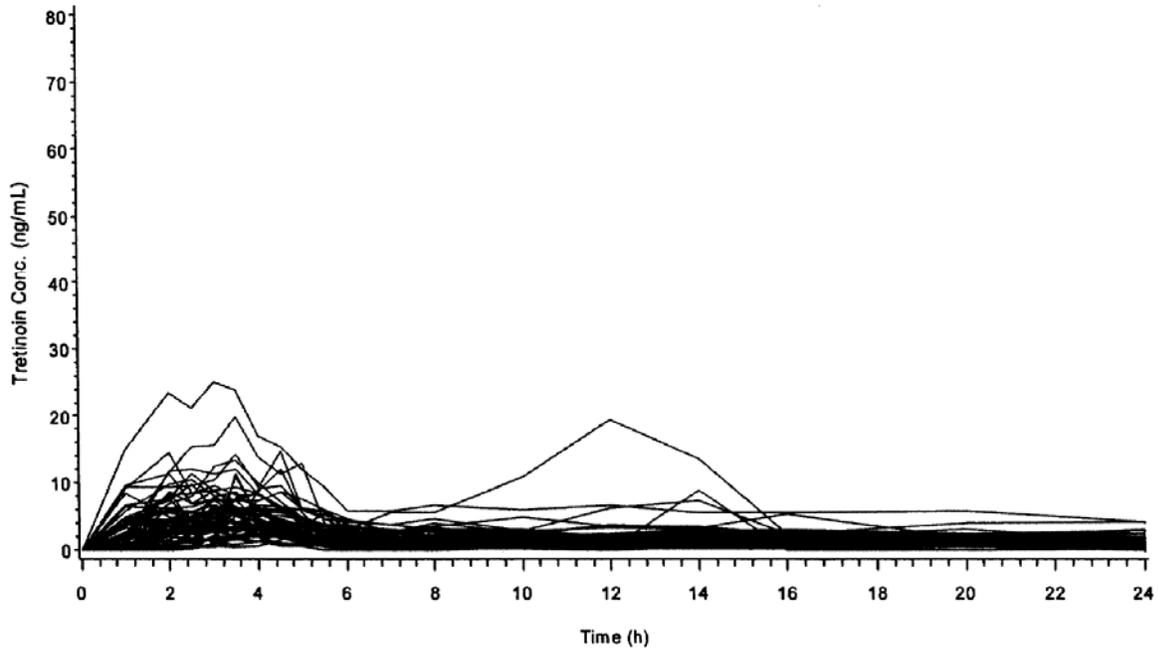
STUDY No.: 2003-627  
BASELINE-ADJUSTED PLASMA TRETINOIN CONCENTRATION VERSUS TIME CURVES  
Treatment A: Isotretinoin 2 x 20 mg Capsules, Lot No.: 28A02 (Cipher Pharmaceuticals Ltd., Barbados) / Fast  
N=57



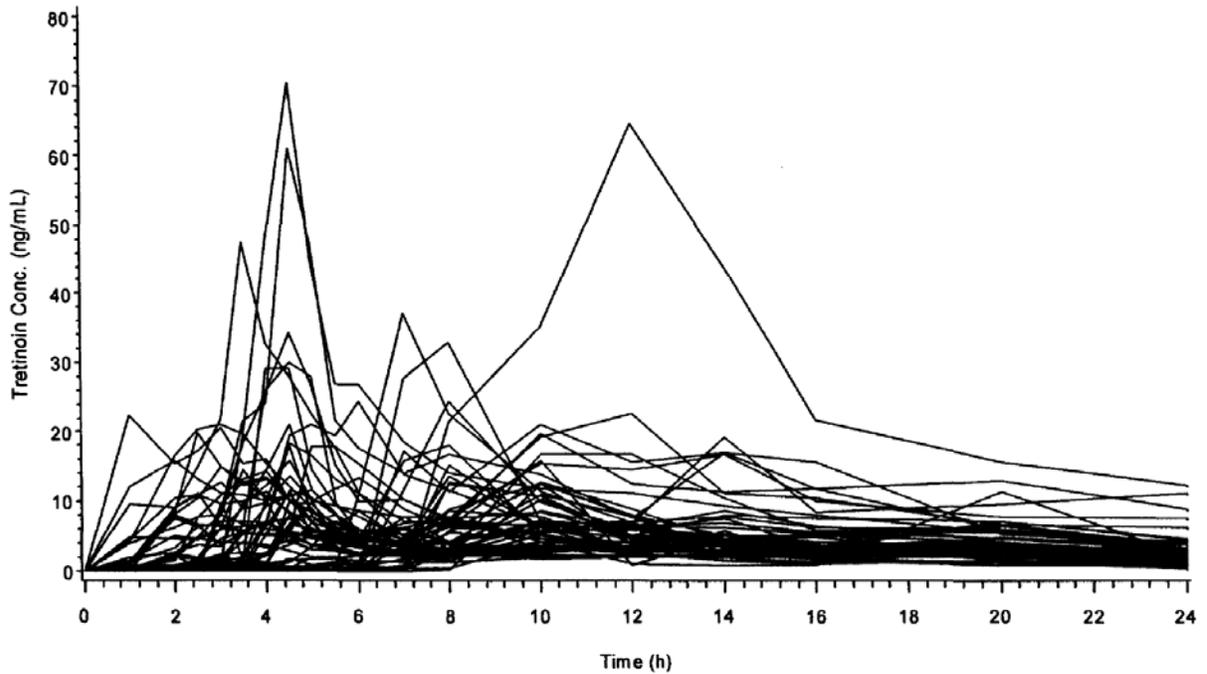
STUDY No.: 2003-627  
BASELINE-ADJUSTED PLASMA TRETINOIN CONCENTRATION VERSUS TIME CURVES  
Treatment B: Isotretinoin 2 x 20 mg Capsules, Lot No.: 28A02 (Cipher Pharmaceuticals Ltd., Barbados) / Fed  
N=57



STUDY No.: 2003-627  
BASELINE-ADJUSTED PLASMA TRETINOIN CONCENTRATION VERSUS TIME CURVES  
Treatment C: ACCUTANE® 40 mg Capsules, Lot No.: U0622 (Roche Laboratories Inc., USA) / Fast  
N=57



STUDY No.: 2003-627  
BASELINE-ADJUSTED PLASMA TRETINOIN CONCENTRATION VERSUS TIME CURVES  
Treatment D: ACCUTANE® 40 mg Capsules, Lot No.: U0622 (Roche Laboratories Inc., USA) / Fed  
N=57



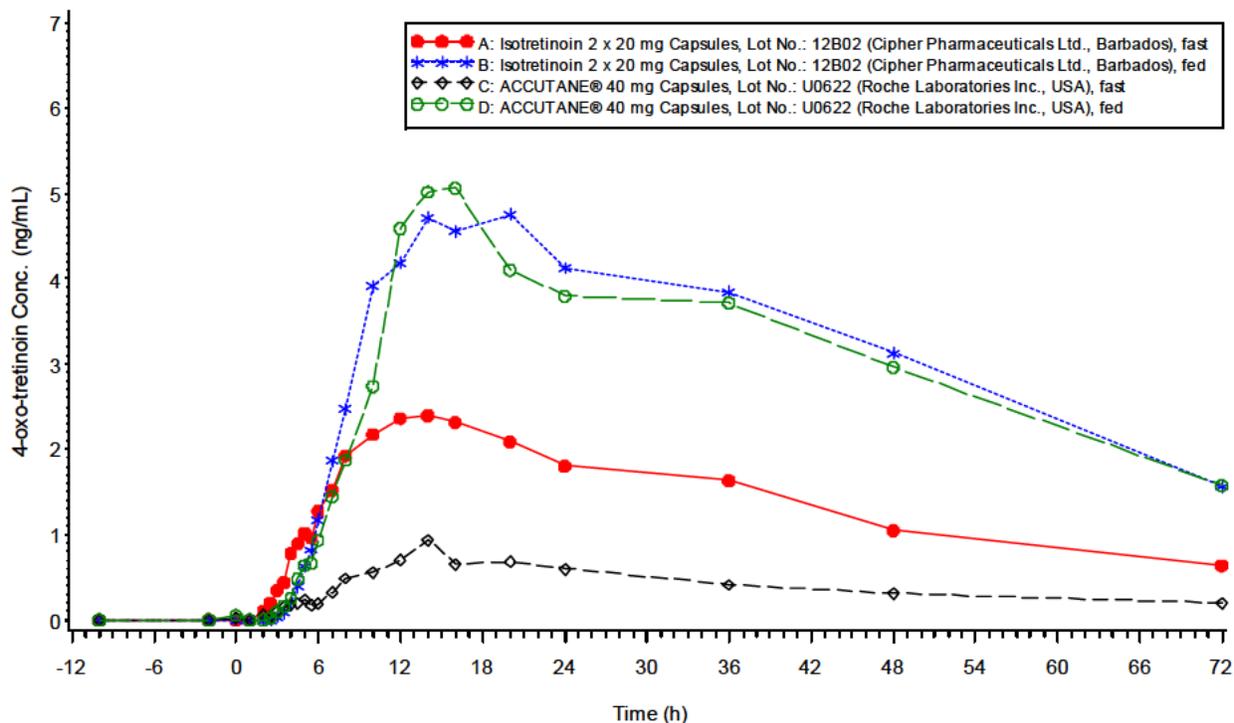
**Summary of Study Results**  
(Based on Baseline-adjusted Plasma 4-oxo-tretinoin Parameters)

(N = 55)

Parameter	Treatment		Means		Type	Code	Contrast Ratio (%)	90% CI (%)	CV%
	Type	Trt	Arithmetic (CV%)	Geometric					
AUC <sub>t</sub> (ng·h/mL)	T - Fast	A	87.52 (153)	46.40	T: Food Effect	B vs. A	327.66	244.02 – 439.96	110
	T - Fed	B	204.68 (127)	152.04	R: Food Effect	D vs. C	1222.42	857.05 – 1743.54	
	R - Fast	C	28.39 (231)	10.85	T/R - Fast	A vs. C	427.80	298.48 – 613.16	
	R - Fed	D	197.31 (120)	132.59	T/R - Fed	B vs. D	114.67	86.49 – 152.04	
AUC <sub>i</sub> (ng·h/mL)	T - Fast	A	205.37 (75)	155.80	T: Food Effect	B vs. A	182.80	138.94 – 240.50	42
	T - Fed	B	382.39 (105)	284.80	R: Food Effect	D vs. C	258.01	164.99 – 403.48	
	R - Fast	C	310.29 (109)	102.68	T/R - Fast	A vs. C	151.73	95.11 – 242.05	
	R - Fed	D	350.01 (153)	264.93	T/R - Fed	B vs. D	107.50	89.71 – 128.82	
C <sub>max</sub> (ng/mL)	T - Fast	A	3.12 (109)	2.63	T: Food Effect	B vs. A	189.84	163.08 – 221.00	49
	T - Fed	B	6.35 (105)	4.99	R: Food Effect	D vs. C	290.51	241.90 – 348.88	
	R - Fast	C	1.41 (150)	1.62	T/R - Fast	A vs. C	161.96	134.52 – 194.99	
	R - Fed	D	6.21 (116)	4.71	T/R - Fed	B vs. D	105.84	91.51 – 122.41	
T <sub>max</sub> (h)	T - Fast	A	14.51 (68)	-	T: Food Effect	B vs. A	114.65	-	
	T - Fed	B	16.63 (63)	-	R: Food Effect	D vs. C	216.64	-	
	R - Fast	C	8.60 (118)	-	T/R - Fast	A vs. C	169.88	-	
	R - Fed	D	18.48 (62)	-	T/R - Fed	B vs. D	89.91	-	
K <sub>el</sub> (1/h)	T - Fast	A	0.0244 (90)	-	T: Food Effect	B vs. A	76.24	-	
	T - Fed	B	0.0182 (48)	-	R: Food Effect	D vs. C	97.63	-	
	R - Fast	C	0.0226 (52)	-	T/R - Fast	A vs. C	103.19	-	
	R - Fed	D	0.0221 (38)	-	T/R - Fed	B vs. D	80.59	-	
T <sub>half</sub> (h)	T - Fast	A	41.02 (48)	-	T: Food Effect	B vs. A	112.54	-	
	T - Fed	B	49.03 (59)	-	R: Food Effect	D vs. C	76.96	-	
	R - Fast	C	43.76 (81)	-	T/R - Fast	A vs. C	88.28	-	
	R - Fed	D	37.27 (49)	-	T/R - Fed	B vs. D	129.09	-	
MRT <sub>po</sub> (h)	T - Fast	A	65.36 (41)	-	T: Food Effect	B vs. A	111.79	-	
	T - Fed	B	78.00 (50)	-	R: Food Effect	D vs. C	77.96	-	
	R - Fast	C	74.00 (68)	-	T/R - Fast	A vs. C	85.63	-	
	R - Fed	D	63.48 (38)	-	T/R - Fed	B vs. D	122.79	-	

T = Test  
R = Reference

STUDY No.: 2003-627  
MEAN MEASURED PLASMA 4-OXO-TRETINOIN CONCENTRATION VERSUS TIME CURVES  
N=55



## Conclusion

### Effect of Food

The effect of food was substantially larger on the Accutane® formulation than on the CIPHER formulation, however, there was still a significant food effect with the CIP-isotretinoin capsules. In the presence of food, the systemic exposure to isotretinoin increased on average 1.5 times for the CIPHER (test) formulation and approximately 2.5 times for the Accutane® (reference) formulation. The peak exposure to isotretinoin increased under fed conditions 1.3 times and 2.7 times for the CIPHER and Accutane® formulations, respectively.

With respect to the primary circulating metabolite, 4-oxo-isotretinoin, the food effect on the CIPHER formulation translated to an increase of approximately 2 times in the systemic exposure and peak exposure, while Accutane® exhibited between a 3 to 4 fold increase in the systemic exposure and a 4 fold increase in the peak exposure due to the presence of food.

The 90% confidence intervals of the ratios of geometric means of the test to reference products conducted under fed conditions (B vs. D) for AUC<sub>t</sub>, AUC<sub>i</sub> and C<sub>max</sub> were within the 80-125% range for isotretinoin, 4-oxo-isotretinoin and tretinoin.

## Effect of Fasting

There was a difference between the two isotretinoin formulations under fasting conditions. The Cipher formulation delivered approximately twice as much isotretinoin and 4-oxo-isotretinoin (systemic exposure and peak exposure) when compared to Accutane® when the drug products were administered after an overnight fast. What is unclear is whether or not this difference, ie. higher levels under fasted conditions, will translate into a safety concern when the drug is administered under real world conditions where diet is in a daily flux. As it is the diet used here is an unrealistic diet for the average population, albeit a possible diet for some, it seems unreasonable to base equivalence solely on the fed performance with such a test. This reviewer notes that currently the Office of Generic Drugs is requiring the equivalence under both fed and fasted conditions. Without a demonstration that the expected alteration in plasma levels has no impact on safety, it seems imprudent to allow this product to be used in an uncontrolled dietary setting.

PK.03.02 (2003-666)

Title:	An Open-Label, Multiple-Dose, Randomized, Two-Way Crossover, Relative Bioavailability Study of Cipher Isotretinoin Capsules (2 x 20 mg) versus Accutane® (40 mg) Administered as a 40 mg Dose Twice a Day, in Healthy Subjects, Under Fed Conditions
Objectives:	The objective of this study is to evaluate the comparative bioavailability between isotretinoin capsules 2 x 20 mg (Cipher Canada Inc., Canada) and Accutane® capsules 40 mg (Roche Laboratories Inc., USA), after multiple 40 mg doses in healthy male and female subjects under fed conditions at steady-state.
Treatment A: (Test)	*Isotretinoin Capsules 20 mg; Lot No.: 28A02, (Cipher Canada Inc., Canada) [2 x 20 mg administered twice a day (q12h) after a high fat, high calorie meal for 11 days- <i>See Diet Sub-section below</i> ] *Isotretinoin Capsules 20 mg refers to CIP-Isotretinoin Capsules 20 mg
Treatment B: (Reference)	Accutane® Capsules 40 mg; Lot No.: U0625 50, (Roche Laboratories Inc., USA) [1 x 40 mg administered twice a day (q12h) after a high fat, high calorie meal for 11 days- <i>See Diet Sub-section below</i> ]
Number of Subjects:	Forty-seven (47) [45 male and 2 female] subjects were dosed in Period 1, and 40 subjects completed the entire study.  Age: 36 ± 8 yrs (19 – 49 yrs) Height: 174.1 ± 6.0 cm (162.0 – 184.0 cm) Weight: 79.3 ± 8.3 kg (61.3 – 97.9 kg)
Sampling Schedule:	Blood samples were obtained prior to drug administration (at approximately -10, -2 and 0 hours) on Day 1 and prior to the morning and evening drug administrations on Days 9 and 10. On Day 11, blood samples were obtained pre-dose and at 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 13, 14, 15, 15.5, 16, 16.5, 17, 17.5, 18, 19, 20, 22 and 24 hours following the morning dose.
Diet	Due to the nature of this study, a varied high fat diet was utilized. Two breakfast options were given on alternate days throughout the 11 days of dosing, beginning and ending with Option 1. Similarly, the three dinner options were given in an alternating sequence, beginning with Option 1 and ending with Option 2. The same breakfast and dinner sequences were followed for both periods of the study.

The menus for each of the meals are summarized below:

**Breakfast:**

**Option 1**

<b>Item Description</b>	<b>Quantity</b>	<b>Fat (grams)</b>	<b>Carbohydrates (grams)</b>	<b>Calories</b>
Bagel	1 unit	2	56	297
Peanut Butter	3 tablespoons	25.1	8.8	288
Bacon	5 slices	14	0.4	185
Dutchie Donut	1 unit	13	42	308
Apple Juice	200 mL	0.23	24.4	97
<b>TOTAL</b>		<b>54.33</b>	<b>131.6</b>	<b>1175</b>

**Option 2**

<b>Item Description</b>	<b>Quantity</b>	<b>Fat (grams)</b>	<b>Carbohydrates (grams)</b>	<b>Calories</b>
Pancakes	2 units	5.6	30	171
Skillet Sausage	4 strips	23.4	0.6	242
Sugar Twist Donut	1 unit	10	29	221
Syrup (pancake)	42.5 mL	0	34.8	133
Whole Almonds	32 grams	16.2	6.32	185
Apple Juice	200 mL	0.23	24.4	97
<b>TOTAL</b>		<b>55.43</b>	<b>125.12</b>	<b>1049</b>

**Dinner:****Option 1**

Item Description	Quantity	Fat (grams)	Carbohydrates (grams)	Calories
Rotini Noodles	10 oz	1.9	81	402
Tomato Sauce	250 mL	0.5	18	90
Italian Meatballs	6 oz	14.4	16	224
Dinner Roll	1 unit	2	14	84
Vanilla Pudding	99 grams	3.6	21.9	129
Sprite (Day 1) /	355 mL /	0 / 0.27	38.27 / 38.25	147 /
Grape Juice (Days 4, 7 and 10)	300 mL			153
<b>TOTAL</b>		22.4 / 22.67	189.17 / 189.15	1076 / 1082

**Option 2**

Item Description	Quantity	Fat (grams)	Carbohydrates (grams)	Calories
Chicken	half	23	3	456
Rice	1.5 cups	0.7	64.9	299
Garlic Sauce	2 oz	19.64	14.5	229
Pita Bread	1 unit	0.72	33.42	165
Grilled Tomato	1 unit	0.14	5	22
Banana	1 unit	0.4	27	105
Ginger Ale (Day 2) /	355 mL /			124 /
Grape Juice (Days 5, 8 and 11)	300 mL	0 / 0.27	31.8 / 38.25	153
<b>TOTAL</b>		44.6 / 44.87	179.62 / 186.07	1400 / 1429

**Option 3**

Item Description	Quantity	Fat (grams)	Carbohydrates (grams)	Calories
Beef Kebob	300 grams	19.65	0	513
French Fries	200 grams	9.4	39.6	280
Garden Salad	100 grams	0.1	3.2	16
Pita Bread	1 unit	0.72	33.42	165
Pear	1 unit	0.2	25.7	96
Salad Dressing	1 oz	16	0.8	144
Strawberry Fruitopia (Days 3 and 9) /	341 mL /	0	42.9 / 31.8	172 / 124
Ginger Ale (Day 6)	355 mL			
<b>TOTAL</b>		46.07	145.62 / 134.52	1386 / 1338

This study was a comparative bioavailability study between CIP-isotretinoin capsules 2 x 20 mg and Accutane® capsules 40 mg, after multiple 40 mg doses in healthy male and female subjects under fed conditions at steady-state. Subjects who were selected for the study met the inclusion and exclusion criteria described in the study protocol, and were judged by an investigator to be medically healthy based upon medical history, physical and psychiatric examination, vital signs measurements (blood pressure, heart rate, respiration rate and temperature), 12-lead ECG and clinical laboratory tests.

Due to the known teratogenic potential of isotretinoin, an HCG serum pregnancy test as well as a urine HCG pregnancy test were performed for both female subjects (47 and 48) prior to the first drug administration, as required by the protocol.

Forty-eight (48) subjects were enrolled into the study; however, several tentative subjects withdrew prior to dosing. Therefore, 47 healthy, non-smoking subjects [45 male and 2 female (non-pregnant and non-lactating)] were dosed in Period 1. During Period 1, Subject 15 was dismissed on Day 7 after the morning drug administration due to emesis and Subject 37 withdrew prior to the morning dosing on Day 2 due to adverse events. In addition, Subject 12 withdrew from the study prior to Period 2 check-in for personal reasons.

Forty-four (44) subjects were dosed in Period 2. During Period 2, four subjects were dismissed from the study due to adverse events. Subjects 02 and 36 were dismissed prior to the morning drug administration on Days 7 and 10, respectively, and Subjects 26 and 41 were both dismissed prior to the evening drug administration on Days 4 and 6.

### **Study Procedures**

Subjects were confined to the clinical facility for at least 10.5 hours prior to the first drug administration in each period until 24 hours following the morning dose on Day 11, thus they were confined for the entire dosing interval of 11 days. Upon entry they were randomly assigned to either sequence AB or BA, according to a predetermined computer-generated randomization scheme.

Because of the nature of the trial and the concern of contamination with extraneous sources of vitamin A, prescription, over-the-counter medications, herbal products or vitamins were restricted for 14 days preceding the first drug administration until completion of the entire study. An exception was made for oral or implanted contraceptives for the two women in the trial. In addition, subjects were prohibited from bringing any facial cream, lip balm or moisturizer to the study. Even with this instruction, during Period 1, various types of Vaseline®, lip balms, petroleum jellies, creams, body lotions and moisturizers were confiscated from Subjects 01, 03, 04, 06, 07, 08, 14, 18, 20, 21, 22, 23, 28, 29, 32, 35, 37, 38, 39, 40, 41, 44, 47 and 48.

In each period, an optional pre-study snack was provided to each subject after check-in and prior to fasting. The study drug was administered twice daily (2 x 40 mg) 30 minutes after the start of a high fat and high calorie breakfast and dinner. The drug was administered with 240 mL of room temperature water. A mouth check was done immediately after drug administration to ensure that the drug was swallowed.

On each of the 11 dosing days, subjects fasted overnight for at least 9 hours prior to a high fat, high calorie breakfast and for at least 5 hours following the morning drug

administration. In addition, subjects fasted for 5 hours prior to the consumption of a high fat, high calorie dinner and for 2 hours following the evening drug administration.

Standardized xanthine-free meals with a reduced vitamin A content, as well as caffeine-free beverages, were provided to subjects 5.5 hours following the morning dose and 2 hours following the evening dose. Other than the protocol specified meals, subjects were not allowed any other food or drink while confined in the clinic. Each breakfast option was given on alternate days throughout the 11 days of dosing, beginning and ending with Option 1. Similarly, the three dinner options were given in an alternating sequence, beginning with Option 1 and ending with Option 2. The same breakfast and dinner sequences were followed for both periods of the study. The interval between the last dose of Period 1 and the first dose of Period 2 was approximately 22.5 days.

### **Adverse Events**

Health status monitoring was conducted daily prior to each drug administration and at approximately 3 hours following each dose. Health monitoring was not conducted for the following subjects:

<b>Subject</b>	<b>Period</b>	<b>Day</b>	<b>Time Point (hours)</b>
13	1	7	3
24	2	2	15
35	1	7	15
43	2	3	15
44	2	3	11

There were 302 adverse events (AEs) in this study.

Treatment Group	Severity			Relation to the Drug				Intervention		
	Mild	Mod	Severe	Unrelated	Remote	Possible	Probable	Required Drug Therapy	Required Non-Drug Therapy	N/A*
A (Cipher 2x20mg)	128	0	0	4	1	123	0	1	26	2
B (Roche 2x20mg)	168	6	0	7	1	165	1	4	29	1
<b>Total</b>	<b>296</b>	<b>6</b>	<b>0</b>	<b>11</b>	<b>2</b>	<b>288</b>	<b>1</b>	<b>5</b>	<b>55</b>	<b>3</b>

\* action taken unknown for these adverse events

Given the large number of adverse events over the 22 days of this trial, the AE data will not be broken out by treatment and patient, as has been presented previously but only by treatment and event.

<b>Observed AEs (# of observations)</b>	
<b>Treatment A-CIP-isotretinoin</b>	<b>Treatment B-Accutane™</b>
dry lips (26)	headache (36)
headache (25)	dry lips (31)
dry skin (9)	dry skin (13)

diarrhea (7)	metallic taste in mouth (6)
dry skin on face (4)	elevated ALT (6)
nose bleed (4)	elevated AST (5)
elevated blood pressure (3)	elevated blood pressure (4)
sore throat (3)	eye irritation (4)
dry and cracked lips (2)	elevated gamma GT (3)
flatulence (2)	diarrhea (3)
frequent micturition/urination (2)	acne (3)
chest pain (2)	red eyes (3)
back pain (2)	cracked lips (2)
nausea (2)	elevated pulse rate (2)
stomach pain (2)	constipation (2)
upset stomach (2)	decreased platelet count (2)
cracked lips (1)	frequent urination (2)
indigestion (1)	shoulder discomfort/sore (2)
neck stiffness (1)	stiff neck (2)
conjunctivitis (1)	facial rash (2)
drowsiness (1)	back pain (2)
left ear pain (1)	dry mouth (2)
urgency of urination (1)	platelets reduced (2)
strong urine smell (1)	itchy skin (1)
pain in both shoulders (1)	dry skin (facial) (1)
pain on both knees (1)	dry, cracked lips (1)
lower back pain (1)	dry, itchy skin (1)
dry throat (1)	dry eyes (1)
razor bumps (acne) (1)	ear pain (1)
red eyes (1)	headache (with photophobia) (1)
cracked tongue (1)	loose stool (1)
tiredness (1)	elevated LD (1)
painful left eye (1)	knee and elbow joint pain (1)
heartburn (1)	stomach pain (1)
lightheaded (1)	heartburn (1)
tingling feet (1)	lightheadedness (1)
dry scalp (1)	sore tongue (1)
dysphagia (1)	elevated triglycerides (1)
neck pain (1)	dry throat (1)

elevated triglycerides (1)	skin lesion (1)
itchy red eyes (1)	blurred vision (1)
pinched nerve (in neck) (1)	numbness in left elbow (1)
dizziness (1)	vomiting (1)
constipation (1)	scaling (lower half of face) (1)
acne (on face) (1)	abdominal pain (1)
dry, tired eyes (1)	tired (1)
sinus headache (1)	itchy scalp (1)
	flushed face (1)
	tingling in both arms (1)
	nose bleeding (1)
	swelling of eyelids (itchy and red) (1)
	dizziness (1)
	decreased pulse rate (1)
	dryness of hands (1)
	dry face (1)
	chapped lips (1)
	(pimple like) rash (1)
	dry sinuses (1)

Most of these AEs are typical retinoid side effects that are currently reflected in the Accutane™ package insert. They are manifestations of hypervitaminosis A and are typical during retinoid therapy.

## **Results**

Tables of the individual pharmacokinetic profiles, mean plasma level time profiles, box whisker plots, and associated statistical tables are attached.

**Summary of Individual Isotretinoin Pharmacokinetic Parameters (Evening-dose Interval)**  
**A: Isotretinoin Capsules 2 x 20 mg, Lot No.: 28A02 (Cipher Canada Inc., Canada)**

Subject	SEQ	Period	AUCtau (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	Cmin (ng/mL)	Cav (ng/mL)	DF (%)
01	AB	1	5219.93	746.13	6.00	200.13	434.994	125.52
03	AB	1	3360.11	440.20	10.02	192.20	280.009	88.57
04	BA	2	3192.27	388.90	4.50	137.90	266.032	94.35
05	BA	2	3101.24	465.70	4.00	89.80	258.437	145.45
06	AB	1	3810.41	521.90	10.00	193.90	317.534	103.30
07	BA	2	4692.82	560.61	8.00	263.61	391.068	75.95
08	AB	1	5166.76	634.69	4.00	226.69	430.564	94.76
09	BA	2	3528.13	676.52	5.57	159.52	294.011	175.84
10	AB	1	4957.88	600.63	4.50	200.63	413.157	96.82
11	AB	1	3093.02	592.59	5.00	159.59	257.732	167.99
13	AB	1	4170.41	798.16	6.00	130.16	347.534	182.21
14	AB	1	3565.11	417.61	10.00	158.61	297.093	87.18
16	BA	2	3138.13	433.82	7.00	170.82	261.511	100.57
17	AB	1	2896.66	395.51	8.00	152.51	241.388	100.67
18	BA	2	3195.66	513.68	3.00	146.68	266.305	137.81
19	BA	2	3177.95	479.68	8.00	137.68	264.829	129.14
20	AB	1	3561.84	398.82	5.00	200.82	296.820	66.71
21	AB	1	4350.35	666.38	8.00	189.38	362.529	131.58
22	AB	1	3484.88	474.67	5.50	173.67	290.407	103.65
23	BA	2	4313.41	814.79	7.00	141.79	359.451	187.23
24	BA	2	6302.62	624.48	10.00	381.48	525.218	46.27
25	AB	1	3968.13	514.52	6.00	228.52	330.677	86.49
27	BA	2	3720.94	487.08	5.00	190.08	310.078	95.78
28	AB	1	3682.31	457.68	12.00	250.68	306.859	67.46
29	BA	2	4878.61	601.10	10.00	283.10	406.531	78.22
30	BA	2	4467.76	534.65	5.50	230.65	372.313	81.65
32	AB	1	3208.92	346.91	2.00	130.91	267.410	80.77
33	AB	1	3334.32	421.69	8.00	190.69	277.860	83.14
34	BA	2	2847.94	361.62	10.00	115.62	237.328	103.65
35	AB	1	4100.72	794.89	7.00	142.89	341.727	190.80
38	AB	1	2940.04	412.75	10.00	139.75	245.003	111.43
39	AB	1	3358.61	480.86	5.00	162.86	279.884	113.62
40	BA	2	4130.53	524.11	5.50	262.11	344.211	76.12
42	AB	1	3850.25	522.00	5.00	182.00	320.854	105.97
43	BA	2	4718.90	588.00	4.00	257.00	393.242	84.17
44	BA	2	2695.67	345.67	8.00	149.67	224.639	87.25
45	AB	1	2973.96	438.58	5.00	111.58	247.830	131.95
46	AB	1	2472.70	336.00	10.00	96.70	206.058	116.13
47	BA	2	6237.62	918.59	7.00	284.59	519.802	121.97
48	BA	2	3600.50	636.67	8.00	111.67	300.042	174.98
MEAN	.	.	3836.70	534.22	6.80	183.22	319.725	111.08
STD	.	.	899.20	141.62	2.37	60.21	74.934	36.60
CV (%)	.	.	23.44	26.51	34.82	32.86	23.437	32.95

**Summary of Individual Isotretinoin Pharmacokinetic Parameters (Morning-dose Interval)**  
**A: Isotretinoin Capsules 2 x 20 mg, Lot No.: 28A02 (Cipher Canada Inc., Canada)**

Subject	SEQ	Period	AUCtau (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	Cmin (ng/mL)	Cav (ng/mL)	DF (%)
01	AB	1	5063.77	998.13	4.50	200.13	421.981	189.11
03	AB	1	4148.44	724.20	6.00	232.20	345.703	142.32
04	BA	2	2819.52	625.90	6.00	147.90	234.960	203.44
05	BA	2	2450.29	330.70	3.50	89.80	204.191	117.98
06	AB	1	4477.76	843.90	6.00	254.90	373.147	157.85
07	BA	2	4243.57	499.61	6.00	258.61	353.631	68.15
08	AB	1	4175.03	545.69	5.50	226.69	347.919	91.69
09	BA	2	4117.55	897.52	4.00	159.52	343.129	215.08
10	AB	1	4664.85	925.63	6.00	224.63	388.738	180.33
11	AB	1	4554.62	998.59	5.00	178.59	379.552	216.04
13	AB	1	3843.32	681.16	3.50	140.16	320.277	168.92
14	AB	1	4311.09	799.61	4.50	205.61	359.258	165.34
16	BA	2	4694.63	881.82	5.00	198.82	331.219	174.58
17	AB	1	3270.66	700.51	5.00	147.51	272.555	202.89
18	BA	2	3697.16	614.68	4.50	149.68	308.097	150.93
19	BA	2	2863.20	428.68	6.00	133.68	238.600	123.64
20	AB	1	4101.84	761.82	3.50	215.82	341.820	159.73
21	AB	1	4402.14	947.38	5.00	213.38	366.845	200.08
22	AB	1	3227.25	366.67	3.50	173.67	268.937	71.76
23	BA	2	3730.44	524.79	3.00	141.79	310.870	123.20
24	BA	2	6031.47	656.48	7.00	393.48	502.623	52.33
25	AB	1	4848.70	697.52	2.00	238.52	404.058	113.60
27	BA	2	3295.50	434.08	6.00	170.08	274.625	96.13
28	AB	1	3540.46	469.68	6.00	207.68	295.038	88.80
29	BA	2	4890.24	763.10	6.00	290.10	407.520	116.07
30	BA	2	5277.76	934.65	5.50	261.65	439.813	153.02
32	AB	1	3236.17	540.91	4.00	140.91	269.681	148.32
33	AB	1	3719.82	693.69	3.50	181.69	309.985	165.17
34	BA	2	2796.44	587.62	5.00	124.62	233.037	198.68
35	AB	1	4256.97	964.89	5.00	155.89	354.748	228.05
38	AB	1	3462.04	692.75	6.00	126.75	288.503	196.18
39	AB	1	3170.11	607.86	6.00	168.86	264.176	166.18
40	BA	2	4233.28	670.11	6.00	265.11	352.773	114.80
42	AB	1	4007.25	805.00	4.00	151.00	333.938	195.85
43	BA	2	4115.99	571.00	5.00	232.00	342.999	98.83
44	BA	2	3162.12	422.67	3.50	157.67	263.510	100.57
45	AB	1	2553.71	461.58	5.00	113.58	212.809	163.53
46	AB	1	2545.25	368.00	5.50	90.50	212.104	130.83
47	BA	2	7039.47	1038.59	4.50	411.59	586.623	106.88
48	BA	2	2812.19	446.67	3.50	138.67	234.349	131.43
MEAN	.	.	3946.30	673.10	4.88	192.84	328.858	147.21
STD	.	.	961.28	199.36	1.12	69.53	80.107	45.26
CV (%)	.	.	24.36	29.62	22.96	36.06	24.359	30.75

**Summary of Individual Isotretinoin Pharmacokinetic Parameters (Morning-dose Interval)**  
**B: Accutane® Capsules 1 x 40 mg, Lot No.: U0625 50 (Roche Laboratories Inc., USA)**

Subject	SEQ	Period	AUCtau (ng.h/mL)	Cmax (ng/mL)	Tmax (h)	Cmin (ng/mL)	Cav (ng/mL)	DF(%)
01	AB	2	5525.05	894.86	5.50	275.86	460.421	134.44
03	AB	2	3706.92	725.33	5.50	193.33	308.910	172.22
04	BA	1	3279.78	765.82	5.50	146.82	273.315	226.48
05	BA	1	2287.45	314.75	1.00	98.75	190.621	113.31
06	AB	2	4955.19	1188.62	6.00	198.62	412.933	239.75
07	BA	1	3505.40	851.82	6.00	141.82	292.116	246.48
08	AB	2	5969.58	853.51	5.50	279.51	497.465	115.39
09	BA	1	4051.17	1000.00	4.00	136.00	336.431	255.30
10	AB	2	5272.60	726.52	10.00	246.52	439.383	109.24
11	AB	2	4457.72	1120.00	4.50	208.00	371.476	245.51
13	AB	2	5302.39	1378.55	4.50	164.55	441.866	274.74
14	AB	2	3531.32	731.69	4.50	182.69	294.277	186.56
16	BA	1	3825.00	1140.00	4.00	145.00	318.750	312.16
17	AB	2	3384.46	761.06	5.52	149.06	282.039	216.99
18	BA	1	3591.80	702.65	4.50	141.65	239.317	187.43
19	BA	1	2827.95	580.85	6.00	134.85	218.996	203.66
20	AB	2	4862.24	969.47	4.50	245.47	405.187	178.68
21	AB	2	4412.32	942.03	6.00	196.03	367.693	202.89
22	AB	2	4118.93	713.86	6.00	193.86	343.244	151.50
23	BA	1	5073.58	707.67	5.50	155.67	422.798	130.56
24	BA	1	6418.90	1449.62	6.00	196.62	534.908	234.25
25	AB	2	4907.43	916.67	5.50	225.67	408.952	168.97
27	BA	1	3776.00	1130.00	5.50	165.00	314.667	306.36
28	AB	2	4002.75	612.84	7.02	182.84	333.563	128.91
29	BA	1	4649.50	937.00	4.00	206.00	387.458	188.67
30	BA	1	5809.10	1138.72	4.00	221.72	484.092	189.43
32	AB	2	4384.64	825.72	5.50	170.72	365.387	179.26
33	AB	2	3887.97	780.81	3.50	172.81	323.998	187.66
34	BA	1	2321.70	534.00	5.50	98.40	193.475	225.15
35	AB	2	4456.55	1229.15	5.00	125.15	371.379	297.27
38	AB	2	2865.11	445.11	3.50	124.11	238.759	134.45
39	AB	2	3308.33	465.92	8.00	153.92	275.694	113.17
40	BA	1	4096.17	547.91	6.00	234.91	341.348	191.70
42	AB	2	4651.47	904.64	4.50	168.64	387.623	189.88
43	BA	1	3000.08	452.00	5.52	138.00	250.007	125.60
44	BA	1	3204.91	469.87	4.00	111.87	267.076	134.04
45	AB	2	3425.84	526.68	4.50	170.68	285.487	124.70
46	AB	2	2764.32	388.59	3.00	139.59	230.360	108.09
47	BA	1	5553.84	829.65	5.00	236.65	462.820	128.13
48	BA	1	3587.45	1019.60	5.50	143.60	298.954	293.02
MEAN	.	.	4120.57	817.09	5.14	175.55	343.381	186.30
STD	.	.	1018.84	274.01	1.42	45.51	84.904	61.48
CV(%)	.	.	24.73	33.53	27.61	25.93	24.726	33.00

**Summary of Individual Isotretinoin Pharmacokinetic Parameters (Evening-dose Interval)**  
**B: Accutane® Capsules 1 x 40 mg, Lot No.: U0625 50 (Roche Laboratories Inc., USA)**

Subject	SEQ	Period	AUCtau (ng.h/mL)	Cmax (ng/mL)	Tmax (h)	Cmin (ng/mL)	Cav (ng/mL)	DF(%)
01	AB	2	4636.18	599.86	3.50	232.86	386.348	94.99
03	AB	2	4094.72	687.33	8.02	135.33	341.227	161.77
04	BA	1	3509.34	613.82	8.00	149.82	292.445	158.66
05	BA	1	2966.21	427.75	4.00	98.75	247.184	133.10
06	AB	2	5459.41	987.62	8.00	208.62	454.951	171.23
07	BA	1	3760.88	463.82	10.00	162.82	313.407	96.04
08	AB	2	5843.58	738.51	2.00	323.51	486.965	85.22
09	BA	1	3385.75	534.00	7.00	129.00	282.146	143.54
10	AB	2	5450.75	704.52	2.00	336.52	454.229	81.02
11	AB	2	3325.50	505.00	2.00	193.00	277.125	112.58
13	AB	2	4323.64	587.55	2.00	200.55	360.303	107.41
14	AB	2	3228.07	567.69	7.00	165.69	310.673	129.40
16	BA	1	4984.25	959.00	7.00	171.00	415.354	189.72
17	AB	2	3158.08	498.06	8.00	140.06	263.173	136.03
18	BA	1	3661.05	587.65	2.00	153.65	305.088	142.25
19	BA	1	3022.95	538.85	2.00	136.85	251.912	159.58
20	AB	2	4720.60	757.47	2.00	233.47	393.383	133.20
21	AB	2	4115.32	570.03	10.00	165.03	342.943	118.10
22	AB	2	4040.24	441.86	7.00	223.86	336.686	76.63
23	BA	1	3454.33	445.67	1.00	162.67	287.861	98.31
24	BA	1	5947.90	735.52	8.00	344.62	487.325	80.23
25	AB	2	3927.25	540.67	12.00	265.67	327.271	84.03
27	BA	1	2861.75	445.00	1.00	142.00	240.146	126.17
28	AB	2	4105.83	494.84	7.00	230.84	342.153	77.16
29	BA	1	3620.00	455.00	1.00	207.00	301.667	82.21
30	BA	1	5223.60	777.72	3.00	260.72	435.300	118.77
32	AB	2	4645.52	619.72	6.02	207.72	387.126	106.43
33	AB	2	4145.57	589.81	2.00	231.81	345.465	103.63
34	BA	1	3165.47	506.00	10.02	98.60	263.789	154.44
35	AB	2	3476.80	819.15	10.00	108.15	289.733	245.40
38	AB	2	3889.94	797.11	7.00	105.11	324.162	213.47
39	AB	2	3668.83	490.92	2.00	184.92	305.736	100.09
40	BA	1	4679.42	553.91	6.00	304.91	389.952	63.85
42	AB	2	4129.72	512.64	8.00	193.64	344.143	92.69
43	BA	1	3624.24	525.00	5.00	169.00	302.020	117.87
44	BA	1	3305.06	465.87	8.00	158.87	275.421	111.47
45	AB	2	3242.61	450.68	3.00	144.68	270.218	113.24
46	AB	2	3289.04	727.59	7.05	102.59	274.087	228.03
47	BA	1	6667.35	847.65	4.50	279.65	505.613	112.34
48	BA	1	3460.03	417.60	2.00	169.60	288.336	86.01
MEAN	.	.	4050.92	600.71	5.38	190.83	337.577	123.66
STD	.	.	854.85	146.92	3.15	65.43	71.238	42.24
CV(%)	.	.	21.10	24.46	58.53	34.29	21.103	34.16

**Summary of Individual Isotretinoin Pharmacokinetic Parameters (24-hour Interval)  
A: Isotretinoin Capsules 2 x 20 mg, Lot No.: 28A02 (Cipher Canada Inc., Canada)**

Subject	SEQ	Period	AUC24 (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	Cmin (ng/mL)	Cav (ng/mL)	DF (%)
01	AB	1	10283.70	998.13	4.50	200.13	428.487	186.24
03	AB	1	7508.55	724.20	6.00	192.20	312.856	170.05
04	BA	2	6002.26	625.90	6.00	137.90	250.094	195.13
05	BA	2	5551.53	465.70	16.00	89.80	231.314	162.51
06	AB	1	8288.17	843.90	6.00	193.90	345.340	188.22
07	BA	2	8936.39	560.61	20.00	258.61	372.350	81.11
08	AB	1	9341.79	634.69	16.00	226.69	389.241	104.82
09	BA	2	7632.35	897.52	4.00	159.52	318.014	232.06
10	AB	1	9622.73	925.63	6.00	200.63	400.947	180.82
11	AB	1	7647.64	998.59	5.00	159.59	318.652	263.30
13	AB	1	8013.73	798.16	18.00	130.16	333.905	200.06
14	BA	2	7876.20	799.61	4.50	158.61	328.175	195.32
16	BA	2	7832.76	881.82	5.00	170.82	326.365	217.85
17	AB	1	6167.32	700.51	5.00	147.51	256.972	215.20
18	BA	2	6892.82	614.68	4.50	146.68	287.201	162.95
19	BA	2	6041.15	479.68	20.00	133.68	251.715	137.46
20	AB	1	7663.68	761.82	3.50	200.82	319.320	175.69
21	AB	1	8752.49	947.38	5.00	189.38	364.687	207.85
22	BA	2	6712.13	474.67	17.50	173.67	279.672	107.63
23	BA	2	8043.85	814.79	19.00	141.79	335.160	200.80
24	BA	2	12334.09	656.48	7.00	381.48	513.920	53.51
25	AB	1	8816.83	697.52	2.00	228.52	367.368	127.66
27	BA	2	7016.44	487.08	17.00	170.08	292.352	108.43
28	AB	1	7222.77	469.68	6.00	207.68	300.949	87.06
29	BA	2	9768.85	783.10	6.00	283.10	407.035	117.93
30	BA	2	9745.52	934.65	5.50	230.65	406.063	173.37
32	AB	1	6445.09	540.91	4.00	130.91	268.545	152.67
33	AB	1	7054.14	693.69	3.50	181.69	293.923	174.20
34	BA	2	5644.38	587.82	5.00	115.62	235.182	200.70
35	AB	1	8357.69	984.89	5.00	142.89	348.237	236.05
38	AB	1	6402.08	692.75	6.00	126.75	266.753	212.18
39	AB	1	6528.72	607.86	6.00	162.86	272.030	163.58
40	BA	2	8363.81	670.11	6.00	262.11	348.492	117.08
42	AB	1	7857.50	805.00	4.00	151.00	327.396	199.76
43	BA	2	8834.89	588.00	16.00	232.00	368.120	96.71
44	BA	2	5854.68	422.67	3.50	149.67	243.945	111.91
45	AB	1	5527.67	461.58	5.00	111.58	230.320	151.96
46	AB	1	5017.95	368.00	5.50	90.50	209.081	132.72
47	BA	2	13277.09	1038.59	4.50	284.59	553.212	136.29
48	BA	2	6412.69	636.67	20.00	111.67	267.195	196.49
MEAN	.	.	7782.35	700.87	8.23	179.19	324.265	163.38
STD	.	.	1766.76	180.73	5.82	59.31	73.615	47.99
CV (%)	.	.	22.70	25.79	70.75	33.10	22.702	29.37

**Summary of Individual Isotretinoin Pharmacokinetic Parameters (24-hour Interval)  
B: Accutane® Capsules 1 x 40 mg, Lot No.: U0625 50 (Roche Laboratories Inc., USA)**

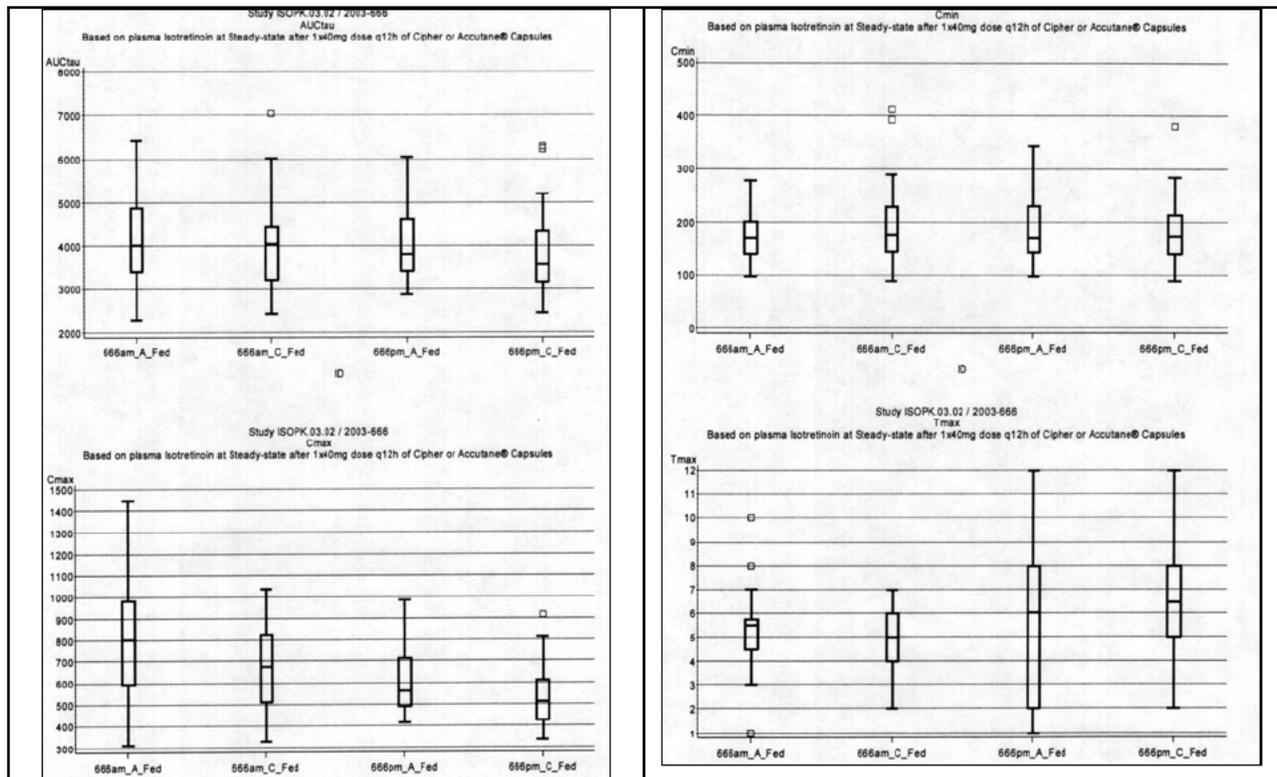
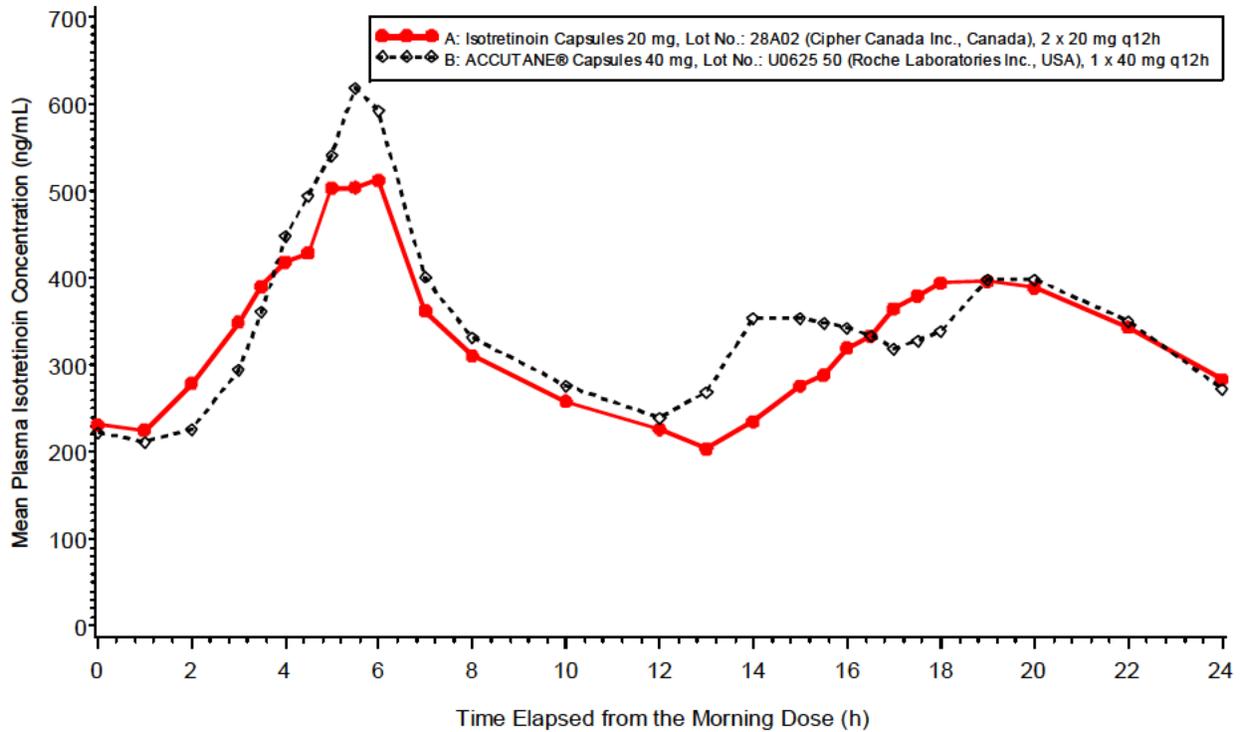
Subject	SEQ	Period	AUC24 (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	Cmin (ng/mL)	Cav (ng/mL)	DF (%)
01	AB	2	10161.23	894.86	5.50	232.86	423.384	156.36
03	AB	2	7801.64	725.33	5.50	135.33	325.068	181.90
04	BA	1	6789.12	765.82	5.50	146.82	282.880	218.82
05	BA	1	5253.66	427.75	16.00	98.75	218.903	150.30
06	AB	2	10414.60	1188.62	6.00	198.62	433.942	228.14
07	BA	1	7266.28	861.82	6.00	141.82	302.762	237.81
08	AB	2	11813.16	853.51	5.50	279.51	492.215	116.82
09	BA	1	7446.92	1000.00	4.03	129.00	310.288	280.71
10	AB	2	10723.32	726.52	10.00	246.52	446.806	107.43
11	AB	2	7783.22	1120.00	4.50	193.00	324.301	285.85
13	AB	2	9826.03	1378.55	4.50	164.55	401.085	302.68
14	AB	2	7259.39	731.69	4.50	165.69	302.475	187.12
16	BA	1	8809.25	1140.00	4.00	145.00	367.052	271.08
17	AB	2	6942.54	761.06	5.52	140.06	272.606	227.80
18	BA	1	7252.85	702.65	4.50	141.65	302.202	185.64
19	BA	1	5850.90	580.85	6.00	134.85	235.454	189.42
20	AB	2	9582.84	962.47	4.50	233.47	399.285	184.33
21	AB	2	8527.64	942.03	6.00	165.03	355.318	218.68
22	AB	2	8159.16	713.86	6.00	193.86	339.965	182.96
23	BA	1	8527.91	707.67	5.50	155.67	355.330	155.35
24	BA	1	12266.80	1449.62	6.00	196.62	511.117	245.15
25	AB	2	8829.98	916.67	5.50	225.67	367.916	187.81
27	BA	1	6657.75	1130.00	5.50	142.00	277.406	356.16
28	AB	2	8103.99	612.84	7.02	182.84	337.666	127.34
29	BA	1	8269.50	937.00	4.00	206.00	344.563	212.15
30	BA	1	11032.70	1138.72	4.00	221.72	459.696	199.48
32	AB	2	9030.16	825.72	5.50	170.72	376.256	174.08
33	AB	2	8033.54	780.81	3.50	172.81	334.731	181.64
34	BA	1	5487.17	534.00	5.50	98.40	228.632	190.52
35	AB	2	6755.05	797.11	19.00	105.11	281.461	245.86
39	AB	2	6977.16	490.92	14.00	153.92	290.715	115.92
40	BA	1	8775.59	553.91	18.00	234.91	365.650	87.24
42	AB	2	8781.19	904.64	4.50	168.64	365.883	201.16
43	BA	1	6624.33	525.00	17.00	138.00	276.014	140.21
44	BA	1	6509.96	469.87	4.00	111.87	271.248	131.98
45	AB	2	6668.45	526.68	4.50	144.68	277.852	137.48
46	AB	2	6053.36	727.59	19.05	102.59	252.223	247.80
47	BA	1	11621.20	847.65	16.50	236.65	484.216	126.18
48	BA	1	7047.48	1019.60	5.50	143.60	293.645	298.32
MEAN	.	.	8171.26	840.24	7.33	167.67	340.469	199.61
STD	.	.	1763.02	249.36	4.72	45.79	73.459	64.49
CV (%)	.	.	21.58	29.68	64.48	27.31	21.576	32.31

**Summary of Results for Plasma Isotretinoin**  
(N = 40)

Parameter	Interval (hours)	Geometric Means		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
		Arithmetic Means (CV%)				
		20mg CIPHER	20mg Accutane			
AUC <sub>tau</sub> (ng*h/mL)	0 – 12	3839.63 3946.30 (24)	3974.46 4120.57 (25)	96.61	92.56 – 100.84	11
	12 – 24	3755.33 3836.70 (23)	3955.89 4050.92 (21)	94.93	90.72 – 99.34	12
AUC <sub>24</sub> (ng*h/mL)	0 – 24	7616.47 7782.35 (23)	7958.80 8171.26 (22)	95.70	92.81 – 98.68	8
C <sub>max</sub> (ng/mL)	0 – 12	639.11 673.10 (30)	768.57 817.09 (34)	83.16	76.38 – 90.53	23
	12 – 24	518.95 534.22 (27)	582.09 600.71 (24)	89.15	81.71 – 97.28	23
	0 – 24	675.12 700.87 (26)	801.75 840.24 (30)	84.21	78.36 – 90.48	19
C <sub>min</sub> (ng/mL)	0 – 12	182.87 192.84 (36)	168.33 175.55 (26)	108.64	102.45 – 115.21	16
	12 – 24	175.02 183.22 (33)	179.77 190.83 (34)	97.36	91.47 – 103.63	17
	0 – 24	171.31 179.19 (33)	160.76 167.67 (27)	106.57	100.72 – 112.75	15
T <sub>max</sub> <sup>a</sup> (h)	0 – 12	4.88 (23)	5.14 (28)			
	12 – 24	6.80 (35)	5.38 (59)	-	-	-
	0 – 24	8.23 (71)	7.33 (64)			
DF <sup>a</sup> (%)	0 – 12	147.21 (31)	186.30 (33)			
	12 – 24	111.08 (33)	123.66 (34)	-	-	-
	0 – 24	163.38 (29)	199.61 (32)			

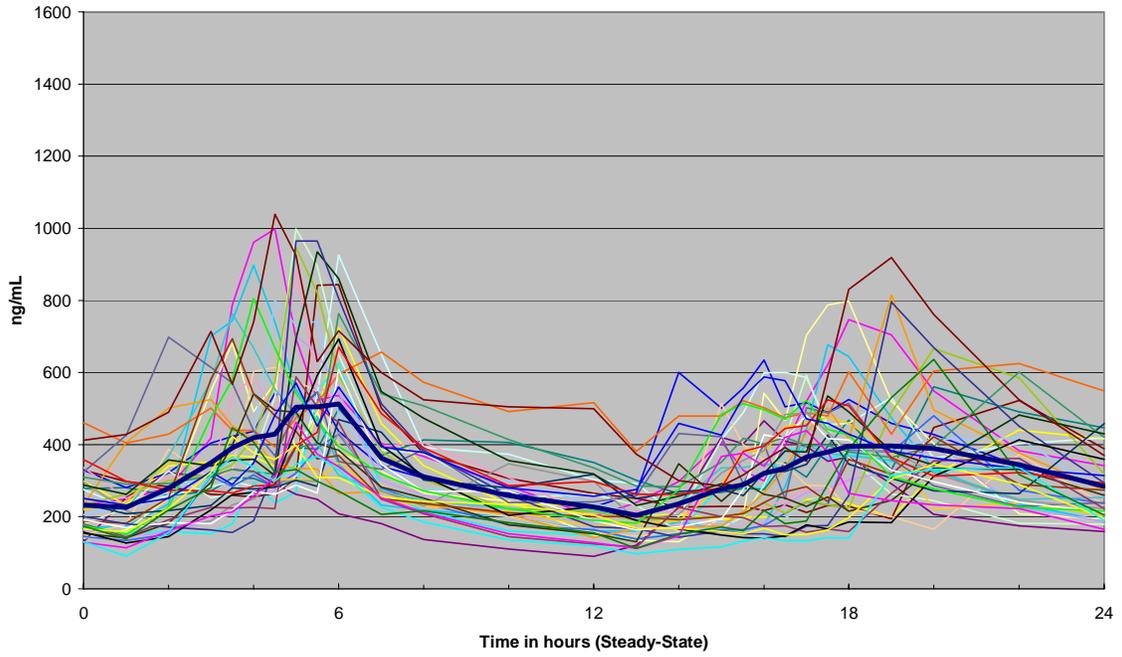
<sup>a</sup> Presented as arithmetic mean (CV%) only.

STUDY No.: 2003-666  
 MEAN MEASURED PLASMA ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES (DAY 11)  
 N=40

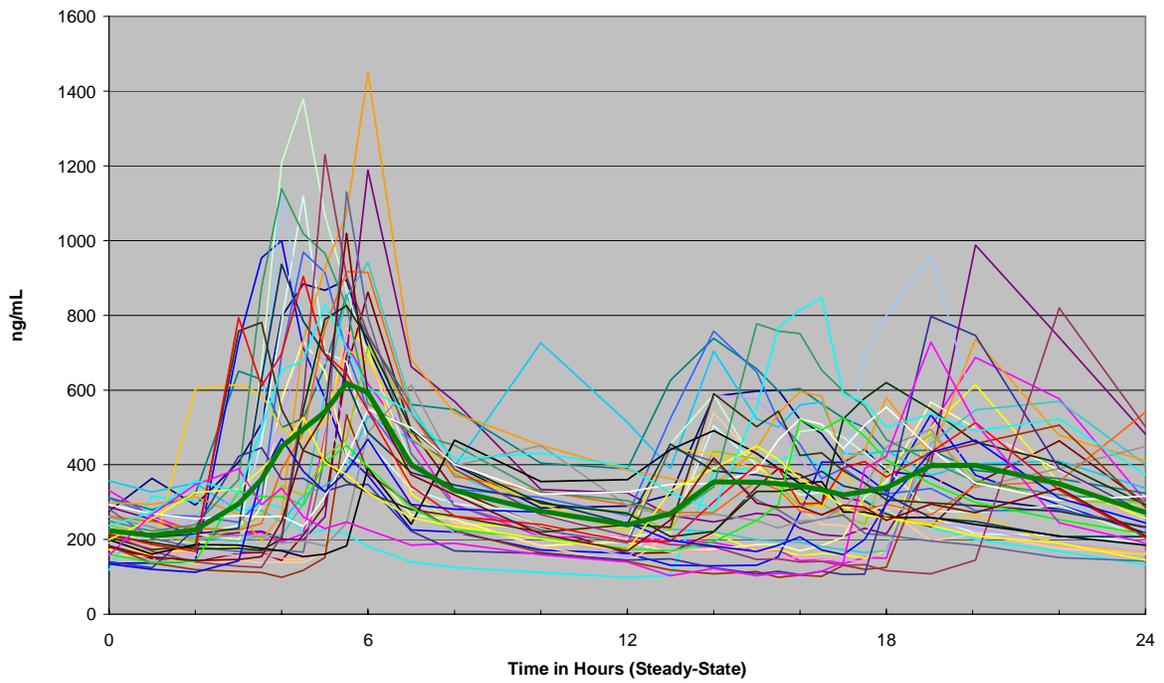


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Individual Plasma Concentrations-Cipher  
Study 203-666



Individual Plasma Concentrations-Accutane  
Study 203-666

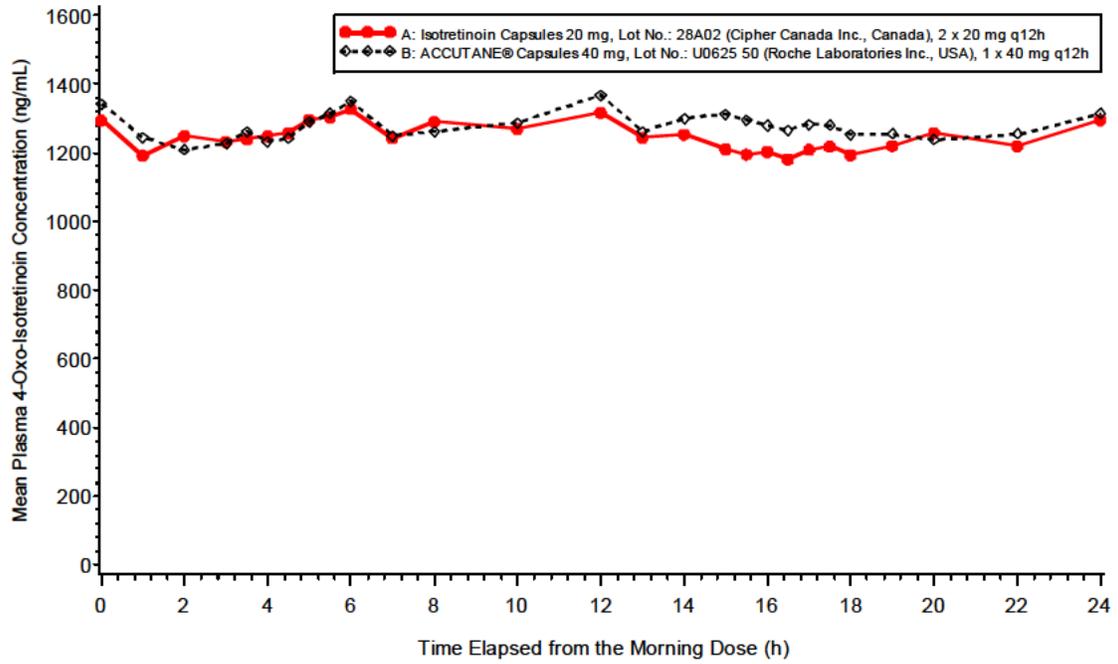


**Summary of Results for Plasma 4-oxo-isotretinoin**  
(N = 40)

Parameter	Interval (hours)	Geometric Means		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
		Arithmetic Means (CV%)				
		20mg CIPHER	20mg Accutane			
AUC <sub>tau</sub> (ng*h/mL)	0 – 12	14857.03 15183.59 (19)	14851.50 15274.71 (20)	100.04	96.92 – 103.26	8
	12 – 24	14365.06 14775.67 (20)	14796.89 15270.58 (22)	97.08	92.80 – 101.56	12
AUC <sub>24</sub> (ng*h/mL)	0 – 24	29243.07 29954.25 (19)	29675.46 30543.94 (21)	98.54	95.05 – 102.16	10
	0 – 12	1428.76 1462.06 (19)	1433.72 1477.25 (21)	99.65	96.57 – 102.83	8
C <sub>max</sub> (ng/mL)	12 – 24	1397.11 1440.56 (21)	1451.21 1496.52 (22)	96.27	92.14 – 100.59	12
	0 – 24	1464.25 1501.63 (20)	1496.85 1538.17 (20)	97.82	94.03 – 101.77	10
C <sub>min</sub> (ng/mL)	0 – 12	1061.86 1085.43 (19)	1059.61 1090.05 (20)	100.21	96.26 – 104.33	11
	12 – 24	1032.11 1062.21 (22)	1043.72 1081.57 (24)	98.89	93.84 – 104.21	14
	0 – 24	1003.26 1029.73 (21)	999.57 1030.00 (21)	100.37	96.10 – 104.83	12
T <sub>max</sub> <sup>a</sup> (h)	0 – 12	5.04 (83)	6.00 (66)			
	12 – 24	4.56 (96)	5.23 (82)	-	-	-
	0 – 24	9.23 (82)	12.21 (57)			
DF <sup>a</sup> (%)	0 – 12	29.69 (33)	30.28 (28)			
	12 – 24	31.04 (36)	33.04 (40)	-	-	-
	0 – 24	38.20 (33)	40.20 (31)			

<sup>a</sup> Presented as arithmetic mean (CV%) only.

STUDY No.: 2003-666  
MEAN MEASURED PLASMA 4-OXO-ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES (DAY 11)  
N=40

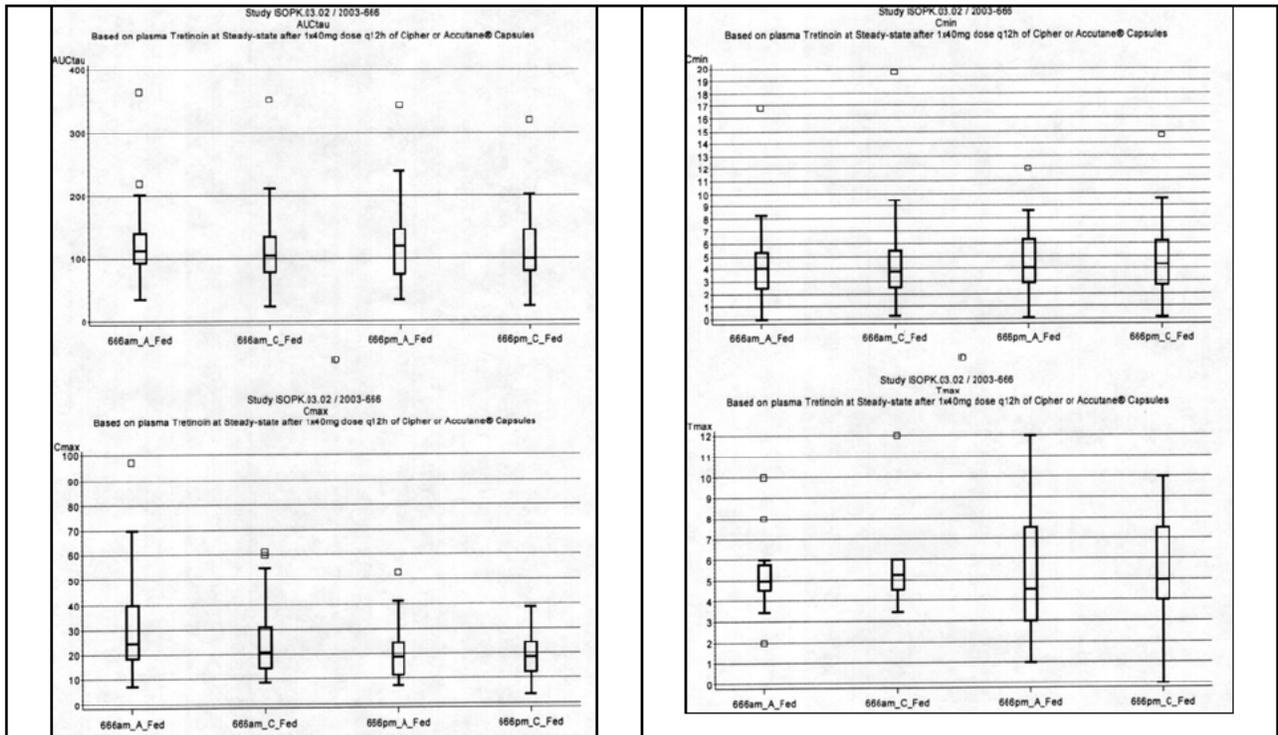
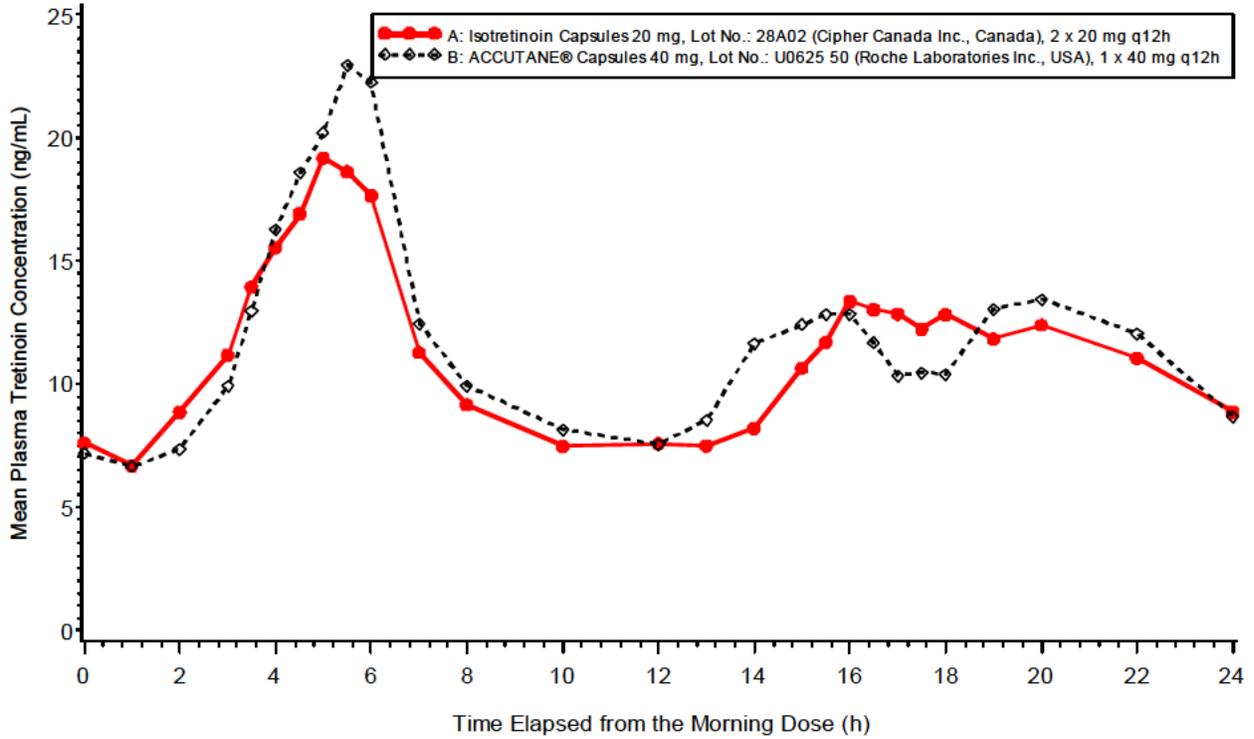


**Summary of Results for Plasma Tretinoin**  
(N = 40)

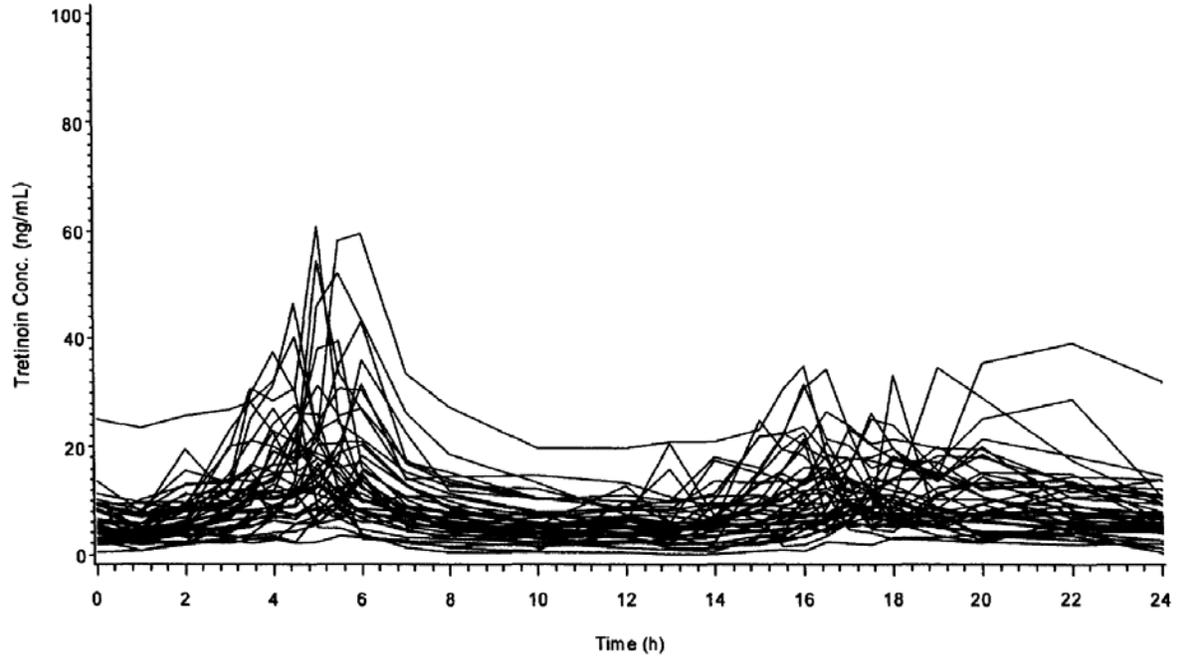
Parameter	Interval (hours)	Geometric Means		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
		Arithmetic Means (CV%)				
		20mg CIPHER	20mg Accutane			
AUC <sub>tau</sub> (ng*h/mL)	0 – 12	101.89 114.66 (52)	111.46 122.33 (47)	91.41	86.02 – 97.14	16
	12 – 24	102.50 114.11 (49)	106.14 120.03 (51)	96.58	88.93 – 104.88	22
AUC <sub>24</sub> (ng*h/mL)	0 – 24	205.50 228.74 (50)	219.18 242.36 (47)	93.75	88.79 – 99.00	14
C <sub>max</sub> (ng/mL)	0 – 12	21.95 25.27 (56)	27.14 31.51 (60)	80.87	71.62 – 91.31	33
	12 – 24	17.50 19.21 (43)	17.83 20.37 (54)	98.16	85.97 – 112.08	36
	0 – 24	24.13 26.95 (49)	28.74 32.83 (56)	83.95	76.69 – 91.90	24
C <sub>min</sub> (ng/mL)	0 – 12	3.57 4.46 (75)	3.52 4.30 (66)	101.52	90.89 – 113.38	29
	12 – 24	3.82 4.77 (63)	3.61 4.52 (55)	105.82	93.87 – 119.29	32
	0 – 24	3.33 4.20 (68)	3.12 3.86 (60)	106.59	94.62 – 120.07	32
T <sub>max</sub> <sup>a</sup> (h)	0 – 12	5.20 (27)	5.18 (31)			
	12 – 24	5.61 (44)	5.25 (54)	-	-	-
	0 – 24	7.74 (66)	8.60 (69)			
DF <sup>a</sup> (%)	0 – 12	224.59 (37)	268.12 (41)			
	12 – 24	166.17 (43)	160.96 (33)	-	-	-
	0 – 24	252.87 (37)	298.78 (43)			

<sup>a</sup> Presented as arithmetic mean (CV%) only.

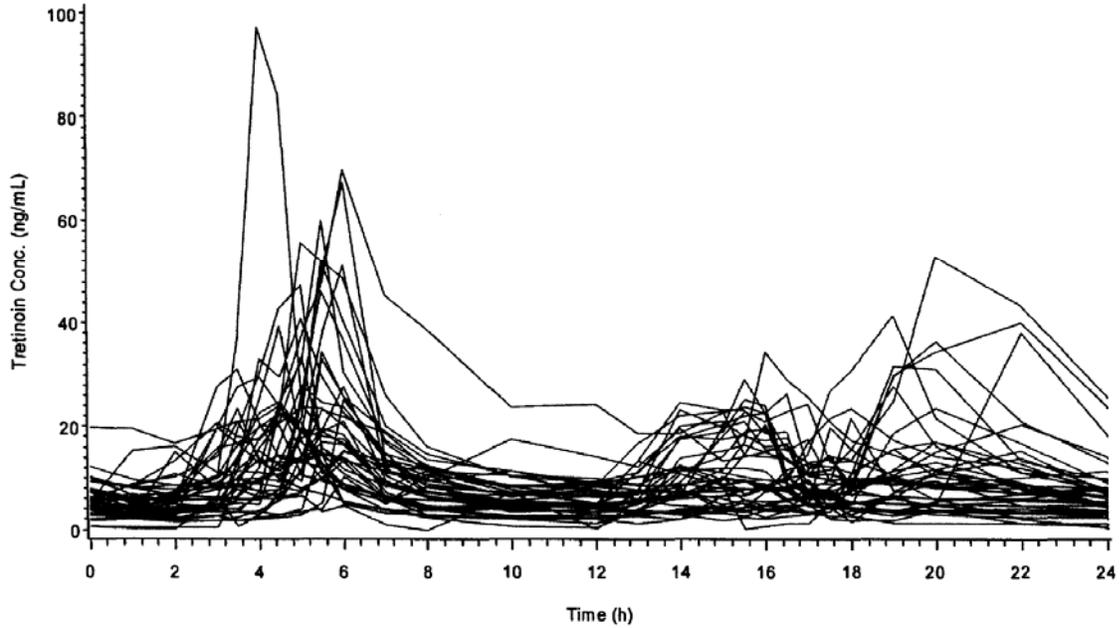
STUDY No.: 2003-666  
 MEAN MEASURED PLASMA TRETINOIN CONCENTRATION VERSUS TIME CURVES (DAY 11)  
 N=40



STUDY No.: 2003-666  
MEASURED STEADY-STATE PLASMA TRETINOIN CONCENTRATION VERSUS TIME CURVES (DAY 11)  
Treatment A: Isotretinoin Capsules 20 mg, Lot No.: 28A02 (Cipher Canada Inc., Canada), 2 x 20 mg q12h  
N=57



STUDY No.: 2003-666  
MEASURED STEADY-STATE PLASMA TRETINOIN CONCENTRATION VERSUS TIME CURVES (DAY 11)  
Treatment B: ACCUTANE® Capsules 40 mg, Lot No.: U0625 50 (Roche Laboratories Inc., USA), 1 x 40 mg q12h  
N=57

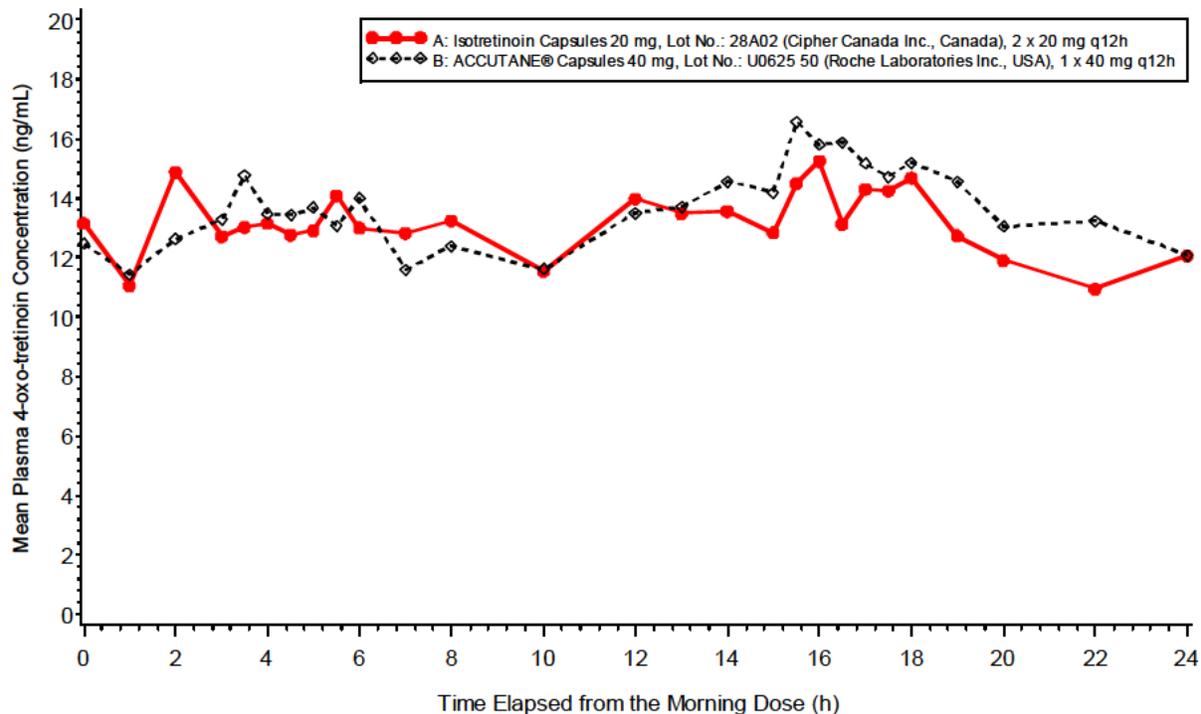


**Summary of Results for Plasma 4-oxo-tretinoin**  
(N = 40)

Parameter	Interval (hours)	Geometric Means		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
		Arithmetic Means (CV%)				
		20mg CIPHER	20mg Accutane			
AUC <sub>tau</sub> (ng*h/mL)	0 – 12	140.93 154.58 (41)	135.42 151.89 (43)	104.08	97.27 – 111.36	18
	12 – 24	141.48 154.98 (39)	150.18 168.78 (43)	94.20	88.79 – 99.95	16
AUC <sub>24</sub> (ng*h/mL)	0 – 24	283.07 309.47 (39)	286.47 320.65 (42)	98.81	93.43 – 104.51	15
C <sub>max</sub> (ng/mL)	0 – 12	17.87 21.14 (66)	16.94 19.26 (45)	105.51	93.42 – 119.17	33
	12 – 24	18.76 21.35 (48)	18.37 20.65 (42)	102.12	93.35 – 111.71	24
	0 – 24	20.60 24.24 (60)	20.04 22.57 (41)	102.78	91.85 – 115.00	30
C <sub>min</sub> (ng/mL)	0 – 12	7.80 8.44 (40)	7.90 8.93 (44)	98.75	92.24 – 105.71	18
	12 – 24	8.27 9.07 (40)	8.45 9.78 (49)	97.83	91.61 – 104.48	17
	0 – 24	7.37 7.99 (40)	7.52 8.53 (45)	98.10	93.06 – 103.42	14
T <sub>max</sub> <sup>a</sup> (h)	0 – 12	5.15 (64)	5.04 (59)			
	12 – 24	4.04 (68)	4.65 (51)	-	-	-
	0 – 24	11.55 (55)	13.24 (44)			
DF <sup>a</sup> (%)	0 – 12	91.64 (66)	82.57 (44)			
	12 – 24	92.54 (48)	80.03 (34)	-	-	-
	0 – 24	120.25 (61)	107.72 (36)			

<sup>a</sup> Presented as arithmetic mean (CV%) only.

STUDY No.: 2003-666  
 MEAN MEASURED PLASMA 4-OXO-TRETINOIN CONCENTRATION VERSUS TIME CURVES (DAY 11)  
 N=40



### Conclusion

The 90% confidence intervals of the ratios of geometric means of Treatment A to Treatment B for the AUC<sub>tau</sub> and AUC<sub>24</sub> parameters were within the 80-125% range for all three time intervals (0-12 hours, 12-24 hours and 0-24 hours) and for all analytes (isotretinoin, 4-oxo-isotretinoin, tretinoin and 4-oxo-tretinoin).

The relative mean C<sub>max</sub> parameter was within the 80-125% range for all analytes over the 0-12, 12-24 and 0-24 intervals. However, for isotretinoin and tretinoin, the lower limits of the 90% confidence intervals for the C<sub>max</sub> parameter were slightly out of range for the interval following the morning drug administration and for the 24-hour dosing interval. That is the C<sub>max</sub> values for the CIP-isotretinoin capsules were lower than those from Accutane™.

For both treatments, but especially for the Roche product, there is a significant amount of variability in the data both for C<sub>max</sub> and T<sub>max</sub>. As these two parameters are more closely related to absorption rate than AUC is, this difference is felt to be due to the relatively poor solubility of isotretinoin in gastric fluid. In addition the use of multiple dosage units in the CIP-isotretinoin arm added to the observed variability.

What this study does not address is the impact of uncontrolled diet on the absorption of the drug product. Isotretinoin is very sensitive to meals and their timing. There has been suggestion in the literature that isotretinoin undergoes entero-hepatic re-cycling. Under the controlled conditions of this trial the sponsor came very close to establishing strict bioequivalence between the two products, however, from study 627 we know that the fasted bioavailability is markedly different. How this will play out from a safety aspect is unknown.

## Study PK.02.01 (02-441)

- Title:** An Open-Label, Single-Dose, Randomized, Three-Way Crossover, Relative Bioavailability Study of Cipher Isotretinoin Capsules (30 mg) Versus Accutane<sup>®</sup> (40 mg) In Healthy Subjects, Under Fasting and Fed Conditions
- Objective:** To define pharmacokinetics and to determine relative bioavailability of Isotretinoin 30 mg Capsules (Manufacturer: GALEPHAR P.R. Inc.) against Accutane<sup>®</sup> 40 mg Capsules, (Manufacturer: Roche Laboratories Inc.) in healthy, male and female subjects, under fed and fasting conditions.
- Treatment A:** A single dose of Isotretinoin 30 mg Capsules (Cipher Canada Inc.; Manufacturer: GALEPHAR P.R. Inc.; Manufacturing Date: Not specified; Lot # 27C02; Exp. Date: N/A) was administered within 5 minutes of completion of the modified high fat, high calorie breakfast.
- Treatment B:** A single dose of Accutane<sup>®</sup> 40 mg Capsules (Manufacturer: ROCHE LABORATORIES INC.; Manufacturing Date: Not specified; Lot # U0605; Exp. Date: 03 2004; NDC: 0004-0156-49) was administered within 5 minutes of completion of the modified high fat, high calorie breakfast.
- Treatment C:** A single dose of Accutane<sup>®</sup> 40 mg Capsules (Manufacturer: ROCHE LABORATORIES INC.; Manufacturing Date: Not specified; Lot # U0605; Exp. Date: 03 2004; NDC: 0004-0156-49) was administered after an overnight fast of at least 10.5 hours.
- Number of Subjects:** Thirty-six (36) male and female subjects were dosed in the first period. Thirty-three (33) subjects completed two periods of the study and 29 subjects completed the entire study. Data from 32 subjects were included in the final data set.
- Age:  $35 \pm 9$  yrs (18 – 50 yrs)
  - Height:  $172.5 \pm 8.3$  cm (156.2 – 186.5 cm)
  - Weight:  $72.4 \pm 10.5$  kg (52.4 – 97.4 kg)
- Subjects who completed 2 periods of the study were included in the final data. Subjects #05, 14, 21, 34 and 37 were dosed in Period II, but did not finish the study. Out of these 5 subjects, Subject #21 did not complete Period II. Subject #37 was dosed improperly in Period II (see Section 5.3). As a consequence, 32 subjects were included in the final data set.
- Sampling Schedule** Blood samples were collected at –10 (2 x 7 mL), -2 and 0 hours pre-dose and 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14, 16, 20, 24, 36, 48 and 72 hours post-dose (1 x 7 mL) (23 time points).

As in the previous studies a non FDA High Fat breakfast was served to subjects in this study. It consisted of:

<b>Item Description</b>	<b>Quantity</b>	<b>Fat (grams)</b>	<b>Carbohydrates (grams)</b>	<b>Calories</b>
Bagel	1 unit	2	56	297
Peanut Butter	3 tablespoons	25.1	8.8	288
Bacon	5 slices	14	0.4	185
Dutchie Donut	1 unit	13	42	308
Apple Juice	200 mL	0.23	24.4	97
<b>TOTAL</b>		<b>54.33</b>	<b>131.6</b>	<b>1175</b>

This study was another single dose evaluation of the Cipher product under fed conditions, relative to that of Accutane™ under both fed and fasted conditions in healthy, male and female subjects. To better define the pharmacokinetics and relative bioavailability of the CIP-isotretinoin capsules the sponsor should have included a fasted treatment leg for the Cipher product.

## STUDY DESIGN

All subjects who were selected for the study met the inclusion and exclusion criteria described in the study protocol, and were judged by an Investigator to be medically healthy based on medical history, physical examination, vital signs measurements, 12-lead ECG, and clinical laboratory tests, including a pre-Period III hematology evaluation.

Thirty-six (36) healthy, non-smoking, male and female subjects were dosed in Period I. Subject #05 withdrew prior to Period III due to personal reasons. Subject #11 was dismissed post-dose of Period I due to an adverse event (rash). Subject #13 withdrew prior to Period II check-in due to personal reasons. Subject #14 was dismissed pre-dose of Period III due to a positive urine test (opiates/morphine test). Subject #21 withdrew approximately 6.5 hours post-dose of Period II due to a family emergency. Subject #34 withdrew prior to Period III check-in due to health problems. Subject #37 was dismissed prior to Period III due to non-compliance. Therefore, 29 subjects were dosed in Period III on August 21, 2002 and completed the study.

## **Study Procedures**

The study was designed as an open-label, single-dose, randomized, three-treatment, six sequence, three-period, crossover bioavailability study. Each subject was randomly assigned to the 6 possible sequences according to a predetermined computer-generated randomization scheme.

Subjects were to refrain from taking any prescription or over-the-counter medications, herbal products and vitamins, with the exception of oral or implanted contraceptives, for 14 days preceding the first drug administration and until completion of the entire study. One (1) unknown capsule was confiscated from Subject #33 during Period I check-in. Subjects abstained from ingesting foods and beverages containing alcohol, caffeine, or xanthine-containing products

for 48 hours prior to each drug administration and until after the last sample collection in each period. Subjects limited the intake of foods which had a high content of vitamin A for 72 hours prior to each drug administration and until after the last sample collection in each period. Subjects were dosed at one-minute intervals and remained seated or in a semi-reclined position for 4 hours following drug administration, unless required to ambulate for study specific procedures, and resumed normal activity thereafter.

All subjects, except Subject #37 in Treatments A and B fasted for at least 10 hours prior to consumption of the high fat, high calorie breakfast and for at least 4 hours following drug administration. The drugs were then administered with 240 mL of room temperature water within 5 minutes of completing the modified high fat, high calorie breakfast that restricts vitamin A content. Subjects were required to complete the entire meal within 25 minutes of being served. All subjects in Treatment C fasted for at least 10.5 hours prior to drug administration and for at least 4 hours following drug administration. The washout period between each drug administration was 21 days.

In order to maintain the largest possible sample size, at the sponsor's request, subjects who completed 2 periods of the study were included in the final data. Subjects #05, 14, 21, 34 and 37 were dosed in Period II, but did not finish the study. Out of these 5 subjects, Subject #21 did not complete Period II. Subject #37 was dosed improperly in Period II (see Section 5.3). As a consequence, 32 subjects were included in the final data set: Subjects #01-02, 04-10, 12, 14-20, 22-30, 32-36 and 38. Thus the trial does have some incomplete blocks in the dataset, resulting in an imbalance in treatments, but not to the level where one would suspect a bias in the data.

### **Adverse Events**

Throughout the study there were a total of 26 adverse events in 13 individual subjects.

#### **Listing of Adverse Events by Period and Treatment**

<b>Subject No.</b>	<b>Period/ A, B, C, PC</b>	<b>Adverse Event (COSTART)</b>	<b>Duration</b>	<b>Severity</b>	<b>Action Taken</b>	<b>Relationship to the Study Drug</b>
02	I/A	Tiredness (Asthenia)	21 hrs 30min	Mild	None	Possible
23	III/A	Nausea (Nausea)	3 hrs	Mild	None	Probable
23	III/A	Lightheadedness (Dizziness)	3 hrs	Mild	None	Possible
28	II/A	Sleepiness (Somnolence)	30 hrs	Mild	None	Possible
32	I/A	Lump right earlobe (Abnormal mass)	Unknown	Mild	None	Unrelated
33	II/A	Headache (Headache)	30 hrs 30 min	Mild	Non-drug therapy	Probable

Subject No.	Period/ A, B, C, PC	Adverse Event (COSTART)	Duration	Severity	Action Taken	Relationship to the Study Drug
13	I/B	Abrasions on face (cheeks, nose and forehead) (Injury intent)	1511 hrs	Mild	Subject consulted physician	Unrelated
13	I/B	Headache (Headache, injury intent)	20 hrs	Mild	Subject consulted physician	Unrelated
13	I/B	Vomit (Vomit, injury intent)	2 min	Mild	Subject consulted physician	Unrelated
13	I/B	Nostril bleeding (Epistaxis, injury intent)	3 min	Mild	Subject consulted physician	Unrelated
13	I/B	Abrasion on buccal surface of both lips (Injury intent)	162 hrs	Mild	Subject consulted physician	Unrelated
25	III/B	Dizziness (Dizziness)	11 hrs 30 min	Mild	None	Possible
34	II/B	Headache intermittent (Headache intermittent)	Unknown	Mild	None	Possible
34	II/B	Lung Infection (Infect)	Unknown	Mild	None	Unrelated
10	II/C	Elevated blood pressure (Hypertension)	5 hrs 41 min	Mild	None	Possible
11	I/C	Hives (Urticaria)	22 hrs 10 min	Moderate	Drug therapy	Probable
11	I/C	Rash (Rash)	72 hrs 10 min	Moderate	Drug therapy	Probable
11	I/C	Itchiness (Pruritis)	72 hrs 10 min	Moderate	Drug therapy	Probable
11	I/C	Tightness in chest (Pain chest)	1 hrs	Moderate	None	Possible
22	I/C	Elevated blood pressure (Hypertension)	1 hr 10 min	Mild	None	Unrelated
27	I/C	Headache intermittent (Headache intermittent)	25 hrs 30 min	Mild	None	Probable

<b>Subject No.</b>	<b>Period/ A, B, C, PC</b>	<b>Adverse Event (COSTART)</b>	<b>Duration</b>	<b>Severity</b>	<b>Action Taken</b>	<b>Relationship to the Study Drug</b>
27	I/C	Nausea (Nausea)	11 hrs	Mild	None	Probable
27	I/C	Burning Sensation in upper arm and chest (Pain Chest)	7 hrs	Mild	None	Probable
33	I/C	Headache (Headache)	19 hrs	Mild	None	Probable

#### **POST STUDY AEs**

<b>Subject No.</b>	<b>Period/ A, B, C, PC</b>	<b>Adverse Event (COSTART)</b>	<b>Duration</b>	<b>Severity</b>	<b>Action Taken</b>	<b>Relationship to the Study Drug</b>
11	PC	Elevated Urea, AST, ALT and LD (Lab Test Abnorm)	Unknown	Mild	Lost to follow-up	Possible
37	PC	Elevated potassium (Hyperkalemia)	Unknown	Mild	Lost to follow-up	Remote

The AE reports are interesting for two reasons, 1.) the sponsor is again coding hypertension inconsistently, in one case it is not related, in the other it is possible. As hypertension is a recognized adverse effect of isotretinoin it should be considered as at least possible if not related. Also it is a bit concerning that one subject (#13) is coded as having “injury intent”. Given the concern of the psychiatric effect of isotretinoin, it is puzzling that this event is coded as unrelated to the study drug. A case report form for this subject could not be located. While this does not have a direct bearing on the CIP-isotretinoin capsule as it occurred during treatment with Accutane™, it does demonstrate a disturbing trend as to how safety is being monitored in these trials, both the inconsistent coding and lack of association of known isotretinoin AEs. While the issue with subject #13 is at best ambiguous, it is incumbent upon the sponsor to address these findings in their materials.

## **Results**

Tables of the individual pharmacokinetic profiles, mean plasma level time profiles, box whisker plots, and associated statistical tables are attached.

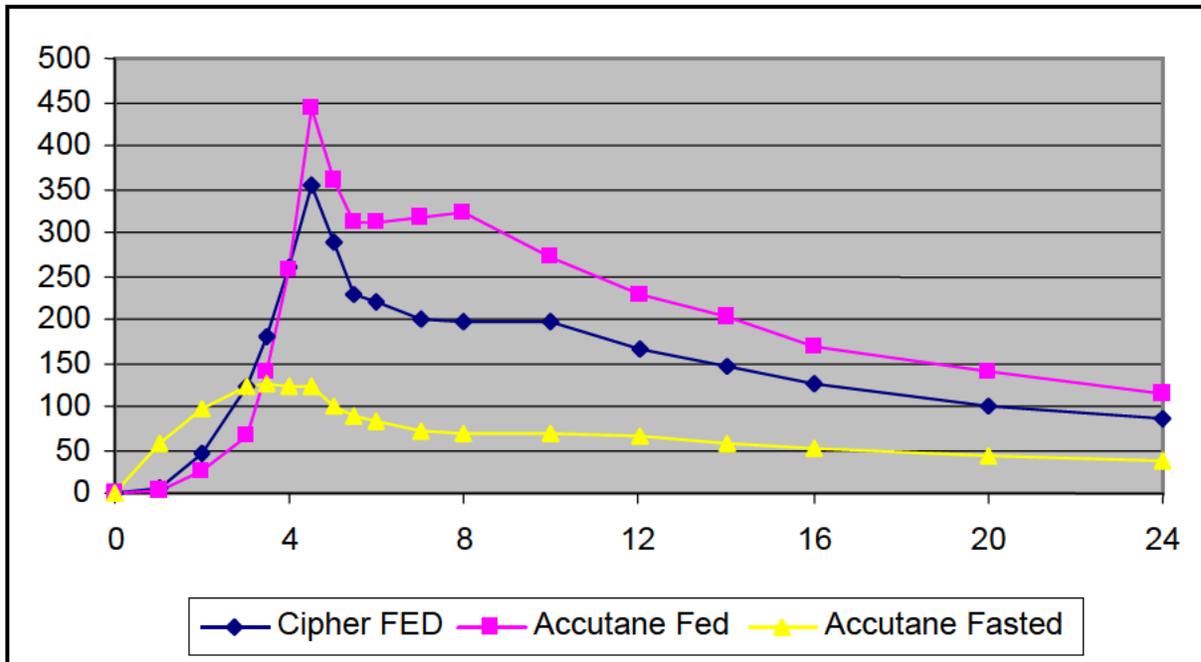
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Summary of Individual Isotretinoin Pharmacokinetic Parameters  
 A: Fed: Isotretinoin Capsules 30 mg, Lot# 27C02 (Cipher Canada Inc.)

Treatment-A

Subject	SEQ	PERIOD	AUC(0-t) (ng.h/mL)	AUC(0-inf) (ng.h/mL)	AUC(0-t) -----(*) AUC(0-inf)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	K <sub>el</sub> (1/h)	T <sub>1/2</sub> (h)	*TLIN (h)	**LQCT (h)	***R
01	CBA	3	6462.30	6930.78	93.24	470.05	4.50	0.0364	19.05	24.00	72.00	0.9972
02	ABC	1	4123.13	4390.99	93.90	658.77	4.00	0.0506	13.69	20.00	48.00	0.9922
04	CAB	2	4704.77	4828.29	97.44	703.92	4.50	0.0495	14.01	24.00	72.00	0.9981
05	BAC	2	3687.75	4055.11	90.94	449.55	5.00	0.0322	21.49	24.00	72.00	0.9897
06	ACB	1	6386.18	6823.29	93.59	398.61	5.00	0.0380	18.24	24.00	72.00	0.9996
07	BAC	2	4663.64	5655.34	82.46	415.65	4.00	0.0315	22.00	20.00	48.35	0.9809
08	ABC	1	4472.78	4650.04	96.19	633.19	4.50	0.0425	16.32	24.00	72.00	0.9988
09	CBA	3	8332.06	9218.13	90.39	446.26	3.00	0.0322	21.51	24.02	72.00	0.9987
10	BCA	3	6685.78	8214.70	81.39	263.71	10.00	0.0240	28.87	24.00	72.00	0.9837
12	ACB	1	6149.40	6551.58	93.86	417.10	4.50	0.0375	18.47	24.00	72.00	0.9965
14	BAC	2	4618.89	5090.03	90.74	553.72	4.00	0.0310	22.34	24.00	72.00	0.9992
15	ABC	1	4692.78	5050.71	92.91	215.64	14.00	0.0381	18.19	24.00	72.00	0.9997
16	ACB	1	5792.65	6066.50	95.49	316.67	8.00	0.0441	15.73	24.00	72.00	0.9975
17	CBA	3	3423.59	3498.84	97.85	481.52	4.50	0.0497	13.95	24.00	72.22	0.9909
18	CAB	2	2397.25	2479.72	96.67	222.66	4.50	0.0459	15.11	24.00	72.00	0.9994
19	BCA	3	6183.13	6519.04	94.85	380.47	4.50	0.0413	16.79	24.00	73.42	0.9948
20	ACB	1	3547.29	3753.57	94.50	350.67	4.00	0.0366	18.92	24.00	72.00	0.9998
22	CAB	2	5195.41	5480.19	94.80	548.25	4.50	0.0395	17.55	24.00	72.00	0.9909
23	CBA	3	6618.36	7265.43	91.09	361.00	6.00	0.0340	20.39	24.00	72.00	0.9971
24	ABC	1	7984.33	8617.03	92.66	490.24	7.00	0.0356	19.45	24.00	72.00	0.9928
25	ACB	1	4412.68	4933.88	89.44	569.30	4.50	0.0301	23.02	24.02	72.00	0.9992
26	CBA	3	6846.88	7668.19	89.29	663.76	4.50	0.0294	23.56	24.00	72.00	0.9970
27	CAB	2	7160.88	7925.06	90.36	349.49	8.12	0.0336	20.62	24.00	72.00	0.9990
28	BAC	2	6095.42	6518.59	93.51	365.23	10.00	0.0409	16.93	24.00	72.00	0.9998
29	ABC	1	5859.20	6211.10	94.33	424.38	10.00	0.0414	16.73	24.02	72.00	0.9980
30	BCA	3	7467.10	8085.75	92.35	420.54	6.00	0.0374	18.53	24.00	72.03	0.9811
32	ACB	1	5036.92	5218.78	96.52	417.90	4.50	0.0471	14.70	24.00	72.00	0.9992
33	CAB	2	4743.33	5287.55	89.71	212.29	8.00	0.0314	22.07	24.00	72.00	0.9965
34	ABC	1	2502.43	2647.48	94.52	178.31	4.53	0.0410	16.90	24.03	72.12	0.9811
35	BCA	3	2685.12	2837.85	94.62	186.64	8.00	0.0414	16.72	24.00	72.00	0.9936
36	CBA	3	5580.54	5853.86	95.33	358.17	5.00	0.0420	16.52	24.00	72.00	0.9987
38	BAC	2	5868.52	6154.49	95.35	380.65	7.00	0.0411	16.87	24.00	72.00	0.9995
MEAN	-	-	5324.39	5765.06	92.82	411.38	5.94	0.0384	18.60	23.75	70.57	0.9950
STD	-	-	1538.05	1742.61	3.70	141.81	2.44	0.0064	3.33	0.98	5.88	0.0059
CV(%)	-	-	28.89	30.23	3.98	34.47	41.14	16.7857	17.93	4.14	8.33	0.5914

\* TLIN = start time for Linear regression  
 \*\* LQCT = last quantifiable concentration time  
 \*\*\* R = correlation coefficient obtained from regression analysis



**Summary of Study Results for Comparative Bioavailability under Fed Conditions**  
**(Treatment A Data Adjusted to the 40 mg Dose)**  
**(N = 32)**

Parameter	Cipher 30mg (dose normalized to 40mg) Geometric Mean	Accutane 40mg	Ratio of Geometric Means (%)	90% Geometric Confidence Interval (%)
<b>Analyte: Isotretinoin</b>				
<b>AUC<sub>t</sub></b> (ng h/mL)	6770.35	6781.76	99.83	90.90 – 109.64
<b>AUC<sub>i</sub></b> (ng h/mL)	7319.17	7300.88	100.25	91.12 – 110.30
<b>C<sub>max</sub></b> (ng/mL)	512.29	624.47	82.04	71.90 – 93.60
<b>Analyte: 4-oxo-isotretinoin</b>				
<b>AUC<sub>t</sub></b> (ng h/mL)	20702.91	21609.95	95.80	86.12 – 106.57
<b>AUC<sub>i</sub></b> (ng h/mL)	31192.09	33950.26	91.88	77.51 – 108.91
<b>C<sub>max</sub></b> (ng/mL)	486.10	525.72	92.46	82.76 – 103.31
<b>Analyte: Tretinoin</b>				
<b>AUC<sub>t</sub></b> (ng h/mL)	147.28	136.04	108.26	90.96 – 128.85
<b>AUC<sub>i</sub></b> (ng h/mL)	165.66	164.09	100.95	79.89 – 127.57
<b>C<sub>max</sub></b> (ng/mL)	15.01	16.11	93.18	76.58 – 113.39
<b>Analyte: 4-oxo-tretinoin</b>				
<b>AUC<sub>t</sub></b> (ng h/mL)	233.48	243.28	95.97	74.33 – 123.91
<b>AUC<sub>i</sub></b> (ng h/mL)	417.99	412.88	101.24	83.11 – 123.32
<b>C<sub>max</sub></b> (ng/mL)	6.97	6.92	100.80	85.24 – 119.20

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Summary of Individual Isotretinoin Pharmacokinetic Parameters  
B: Fed: Accutane® Capsules 40 mg, Lot# U0605 (ROCHE LABORATORIES INC.)

Treatment-B												
Subject	SEQ	PERIOD	AUC(0-t) (ng.h/mL)	AUC(0-inf) (ng.h/mL)	AUC(0-t) -----(*) AUC(0-inf)	Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R
01	CBA	2	7148.45	7589.12	94.19	553.63	4.50	0.0398	17.42	24.00	72.00	0.9915
02	ABC	2	5620.24	5714.41	98.35	988.74	4.50	0.0532	13.04	24.00	72.00	0.9918
04	CAB	3	5647.81	5805.02	97.29	863.91	4.50	0.0470	14.76	24.00	72.00	0.9950
05	BAC	1	6563.34	6860.76	95.66	538.22	10.00	0.0444	15.59	24.00	72.00	0.9955
06	ACB	3	8155.90	8588.15	94.97	743.44	4.50	0.0406	17.08	24.00	72.00	0.9951
07	BAC	1	5858.51	6960.08	84.17	252.65	10.00	0.0399	17.37	20.00	48.00	0.9805
08	ABC	2	5499.80	9804.45	96.91	718.60	4.00	0.0478	14.49	24.00	72.00	0.9920
09	CBA	2	7489.91	7944.67	94.28	753.23	4.50	0.0405	17.10	24.00	72.00	0.9991
10	BCA	1	8270.09	9804.45	84.35	648.89	5.00	0.0260	26.66	24.00	72.00	0.9911
12	ACB	3	5427.87	5812.10	93.39	284.71	4.50	0.0380	18.23	24.00	72.18	0.9982
14	BAC	1	7480.56	8103.50	92.31	1008.74	4.00	0.0343	20.24	24.00	72.00	0.9976
15	ABC	2	4960.33	5221.97	94.99	482.66	8.00	0.0426	16.26	24.00	72.00	0.9874
16	ACB	3	8769.16	9016.63	97.26	672.94	10.00	0.0515	13.46	24.00	72.00	0.9908
17	CBA	2	4977.42	5136.68	96.90	498.58	3.50	0.0459	15.09	24.00	72.00	0.9983
18	CAB	3	5468.36	5581.75	97.97	496.65	4.00	0.0528	13.12	24.00	72.00	0.9956
19	BCA	1	7339.15	7644.29	96.01	618.56	4.50	0.0448	15.48	24.00	72.00	0.9982
20	ACB	3	7521.32	7990.89	94.12	823.89	4.50	0.0370	18.72	24.00	72.00	0.9981
22	CAB	3	5442.52	5696.91	95.53	868.46	4.50	0.0431	16.09	24.00	72.02	0.9949
23	CBA	2	6630.38	7187.17	92.25	483.31	8.00	0.0356	19.48	24.00	72.00	0.9966
24	ABC	2	7340.14	7640.21	96.07	1043.30	4.50	0.0447	15.52	24.00	72.07	0.9969
25	ACB	3	5580.66	6379.42	87.48	524.66	7.02	0.0285	24.33	24.00	72.05	0.9937
26	CBA	2	8825.67	9432.94	93.56	1336.00	4.50	0.0351	19.76	24.00	72.00	0.9908
27	CAB	3	8308.66	9240.29	89.92	778.81	8.00	0.0314	22.11	24.02	72.00	0.9926
28	BAC	1	8457.52	8936.03	94.65	441.19	12.00	0.0485	14.30	24.00	72.00	0.9972
29	ABC	2	5724.77	6438.23	88.92	492.49	8.03	0.0485	14.30	20.00	48.00	0.9985
30	BCA	1	8913.35	9593.20	92.91	439.82	7.00	0.0402	17.25	24.00	72.00	0.9973
32	ACB	3	8019.73	8224.99	97.50	648.89	5.00	0.0526	13.18	24.00	72.00	0.9977
33	CAB	3	7695.17	8103.76	94.96	729.18	6.00	0.0435	15.93	24.05	72.02	0.9993
34	ABC	2	4689.83	5215.47	89.92	351.00	10.00	0.0580	11.95	20.00	48.05	0.9753
35	BCA	1	7536.45	7988.68	94.34	978.85	7.00	0.0386	17.96	24.00	72.00	0.9979
36	CBA	2	7908.19	8729.27	90.59	758.80	4.50	0.0482	14.37	24.00	48.00	0.9969
38	BAC	1	6085.68	7651.10	79.54	609.30	8.00	0.0500	13.86	16.00	36.00	0.9881
MEAN	-	-	6854.90	7372.10	93.17	669.75	6.20	0.0429	16.70	23.25	67.89	0.9940
STD	-	-	1304.94	1429.42	4.40	239.83	2.34	0.0075	3.31	1.88	9.93	0.0054
CV(%)	-	-	19.04	19.39	4.72	35.81	37.64	17.4225	19.80	8.11	14.63	0.5410

\* TLIN = start time for Linear regression  
 \*\* LQCT = last quantifiable concentration time  
 \*\*\* R = correlation coefficient obtained from regression analysis

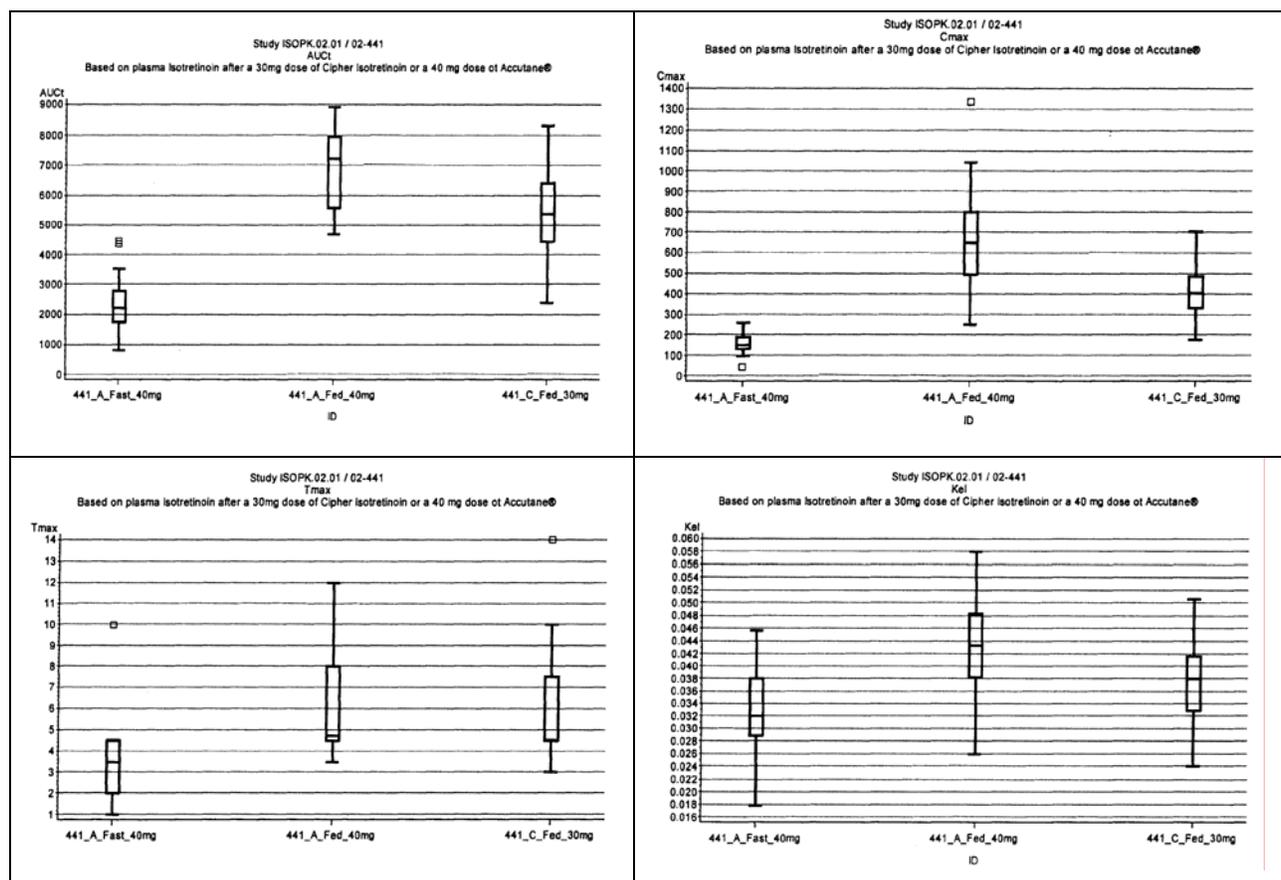
Summary of Individual Isotretinoin Pharmacokinetic Parameters  
C: Fasting: Accutane® Capsules 40 mg, Lot# U0605 (ROCHE LABORATORIES INC.)

Treatment-C												
Subject	SEQ	PERIOD	AUC(0-t) (ng.h/mL)	AUC(0-inf) (ng.h/mL)	AUC(0-t) -----(*) AUC(0-inf)	Cmax (ng/mL)	Tmax (h)	Kel (1/h)	T_half (h)	*TLIN (h)	**LQCT (h)	***R
01	CBA	1	3313.52	3547.79	93.40	237.17	4.00	0.0356	19.47	24.00	72.00	0.9978
02	ABC	3	1510.49	1576.13	95.84	131.61	2.00	0.0410	16.89	24.00	72.00	0.9966
04	CAB	1	2629.64	2752.02	95.55	138.00	3.50	0.0415	16.70	24.00	72.00	0.9985
05	BAC	3	-	-	-	-	-	-	-	-	-	-
06	ACB	2	2940.39	3237.40	90.83	152.32	3.00	0.0321	21.63	24.00	72.00	0.9993
07	BAC	3	825.86	919.53	89.81	39.40	4.50	0.0302	22.94	24.00	75.35	0.9853
08	ABC	3	2642.73	2756.96	95.86	196.43	2.00	0.0439	15.79	24.00	72.00	0.9956
09	CBA	1	2135.60	2305.20	92.64	151.16	1.00	0.0358	19.36	24.00	72.00	0.9964
10	BCA	2	2000.37	2563.20	78.04	143.63	3.50	0.0199	34.75	24.00	72.10	0.9718
12	ACB	2	1618.95	2044.25	79.20	113.44	3.00	0.0288	24.08	20.00	48.00	0.9855
14	BAC	3	-	-	-	-	-	-	-	-	-	-
15	ABC	3	1506.52	1621.87	92.89	129.58	3.50	0.0375	18.49	24.00	72.00	0.9938
16	ACB	2	2040.90	2299.92	88.74	191.00	2.00	0.0394	17.60	16.00	48.00	0.9967
17	CBA	1	1747.44	1866.96	93.60	154.84	3.00	0.0351	19.73	24.00	72.00	0.9849
18	CAB	1	1299.06	1375.28	94.46	111.75	2.00	0.0373	18.58	24.00	72.00	0.9970
19	BCA	2	2347.00	2502.46	93.79	142.16	4.50	0.0380	18.24	24.00	72.00	0.9991
20	ACB	2	1748.26	1871.85	93.40	192.30	3.00	0.0349	19.86	24.00	72.00	0.9899
22	CAB	1	1806.54	1873.26	96.44	223.09	2.00	0.0457	15.18	24.00	72.00	0.9980
23	CBA	1	3496.19	4035.18	86.64	182.00	4.50	0.0267	25.94	24.00	72.00	0.9966
24	ABC	3	1671.50	1919.00	87.10	108.33	3.00	0.0272	25.50	24.00	72.02	0.9930
25	ACB	2	1752.13	2030.05	86.31	97.73	4.50	0.0280	24.73	24.00	72.00	0.9958
26	CBA	1	3229.83	3795.12	85.10	179.62	2.00	0.0244	28.35	24.00	72.00	0.9943
27	CAB	1	2793.07	3137.50	89.02	135.70	3.50	0.0299	23.19	24.00	72.00	0.9987
28	BAC	3	4457.82	4745.19	93.94	258.97	10.00	0.0430	16.10	24.02	72.02	0.9928
29	ABC	3	2217.43	2455.27	90.31	107.35	2.00	0.0320	21.63	24.00	72.00	0.9954
30	BCA	2	2665.32	3661.07	72.80	162.22	4.50	0.0178	38.95	24.00	72.00	0.9598
32	ACB	2	3522.85	3700.92	95.19	230.67	4.50	0.0417	16.63	24.00	72.00	0.9982
33	CAB	1	2550.79	2880.95	88.54	140.74	3.50	0.0289	23.99	24.00	72.00	0.9990
35	BCA	2	2154.85	2689.72	80.11	143.28	4.50	0.0318	21.83	20.00	48.00	0.9888
36	CBA	1	4365.89	4858.27	89.87	255.26	4.52	0.0320	21.65	24.00	72.00	0.9983
38	BAC	3	2467.08	2760.18	89.38	173.92	2.00	0.0289	23.99	24.00	72.00	0.9951
MEAN	-	-	2395.10	2682.15	89.61	159.44	3.43	0.0334	21.79	23.45	69.64	0.9932
STD	-	-	870.91	969.47	5.92	50.27	1.65	0.0070	5.42	1.76	7.51	0.0088
CV(%)	-	-	36.36	36.15	6.60	31.53	47.98	20.8585	24.88	7.53	10.78	0.8832

\* TLIN = start time for Linear regression  
 \*\* LQCT = last quantifiable concentration time  
 \*\*\* R = correlation coefficient obtained from regression analysis

**Summary of Study Results for Comparative Bioavailability  
under Fed and Fasted Conditions for Accutane**

Parameter	Accutane 40mg (fed) Geometric Mean	Accutane 40mg (fasted) Geometric Mean	Ratio of Geometric Means (%)	90% Geometric Confidence Interval (%)
<b>Analyte: Isotretinoin</b>				
AUC <sub>t</sub> (ng.h/mL)	6781.76	2188.46	309.89	281.09 – 341.63
AUC <sub>i</sub> (ng.h/mL)	7300.88	2452.56	297.68	269.51 – 328.81
C <sub>max</sub> (ng/mL)	624.47 669.75 (36)	147.61 159.44 (32)	423.05	368.78 – 485.29
<b>Analyte: 4-oxo-isotretinoin</b>				
AUC <sub>t</sub> (ng.h/mL)	21609.95	5100.04	423.72	379.27 – 473.39
AUC <sub>i</sub> (ng.h/mL)	33950.26	10016.11	338.96	283.97 – 404.59
C <sub>max</sub> (ng/mL)	525.72	106.84	492.05	438.41 – 552.26
<b>Analyte: Tretinoin</b>				
AUC <sub>t</sub> (ng.h/mL)	136.04	54.74	248.51	207.33 – 297.87
AUC <sub>i</sub> (ng.h/mL)	164.09	72.46	226.45	163.63 – 313.39
C <sub>max</sub> (ng/mL)	16.11	5.25	306.59	249.95 – 376.06
<b>Analyte: 4-oxo-tretinoin</b>				
AUC <sub>t</sub> (ng.h/mL)	243.28	55.53	438.11	320.96 – 598.01
AUC <sub>i</sub> (ng.h/mL)	412.88	221.65	186.28	138.75 – 250.08
C <sub>max</sub> (ng/mL)	6.92	2.47	279.95	228.25 – 343.37



### Study Conclusions:

#### Comparative Bioavailability Study (A vs B)

Without normalizing the doses, the CIP-isotretinoin arm (Trt A, 1 x 30 mg dose) exhibited approximately 75% of the extent of absorption of Accutane™ (Trt B, 1 x 40 mg dose): 75.19, 68.91, 75.72 and 75.93% for isotretinoin, 4-oxo-isotretinoin, tretinoin and 4-oxo-tretinoin respectively. These percentages closely resemble the ratio of the drug contents of the 2 formulations (30/40) and respectively of the administered doses.

According to the sponsor, the use a dose-adjusted analysis, both AUCs and Cmax of Trt A and the original AUCs and Cmax of Treatment B led to ratios of geometric means being contained within the 80-125% range (e.g. for AUCinf isotretinoin - 100.25%, 4-oxo-isotretinoin - 91.88%, tretinoin - 100.95% and 4-oxo-tretinoin - 101.24%). What the sponsor has evidently decided to overlook is the fact that the observed confidence interval itself falls outside of the 80-125% interval for a number of these comparisons. The standard is **NOT** that the point estimate/ratio be contained in the interval, but that the entire interval be within the 80-125% range. It is *possible*, that given the observed variability in the data a larger sample size would have been necessary to generate narrower confidence intervals.

The sponsor's consultant concluded that an equal strength formulation would likely prove to be "bioequivalent" to Accutane<sup>®</sup> 40 mg capsules. This statement by the consultant presupposes that one is using the fed treatment as the standard of comparison.

#### Food Effect Study (B vs C)

Based on log-transformed data for all 4 analytes (isotretinoin, 4-oxo-isotretinoin, tretinoin and 4-oxo-tretinoin), the extent of absorption of Accutane<sup>®</sup> under fed conditions (Treatment B) was between 1.9 to 3.4 times larger than under fasting conditions (Treatment C): 297.68, 338.96, 226.45 and 186.28% for isotretinoin, 4-oxo-isotretinoin, tretinoin and 4-oxo-tretinoin respectively.

Similarly, C<sub>max</sub> under fed conditions was between 2.8 to 4.9 times larger than under fasting conditions (423.05, 492.05, 306.59 and 279.95% for isotretinoin, 4-oxo-isotretinoin, tretinoin and 4-oxo-tretinoin respectively).

These findings are well known for Accutane<sup>™</sup> and are not germane to the approval of the CIPHER product, as approval will not be made on the basis of Accutane's<sup>™</sup> performance but on the performance of the CIP-isotretinoin product alone.

Study 442 An Open-Label, Multiple-Dose, Randomized, Two-Way Crossover, Relative Bioavailability Study of Cipher Isotretinoin Capsules (30 mg) Versus Accutane<sup>®</sup> (40 mg) In Healthy Subjects, Under Fed Conditions

**Sponsor:** Cipher Canada Inc.  
6560 Kennedy Road  
Mississauga, Ontario  
Canada L5T 2X4

**Treatment A:** A single dose of Isotretinoin 30 mg Capsules (Cipher Canada Inc.; Manufacturer: GALEPHAR P.R. Inc.; Manufacturing Date: Not specified; Lot 27C02; Exp. Date: N/A) was administered once a day for 11 days **within 5 minutes of completion of the modified high fat, high calorie breakfast.**

**Treatment B:** A single dose of Accutane<sup>®</sup> 40 mg Capsules (Manufacturer: ROCHE LABORATORIES INC.; Manufacturing Date: Not specified; Lot U0605; Exp. Date: 03 2004; NDC: 0004-0156-49) was administered once a day for 11 days **within 5 minutes of completion of the modified high fat, high calorie breakfast.**

**Number of Subjects:** Thirty-six (36) male and female subjects were dosed in Period I. Twenty-eight (28) subjects completed the study.

**Study (Dosing) Dates:** Period I: July 11, 2002 – July 21, 2002  
Period II: August 11, 2002 – August 21, 2002

**Blood Sampling Times:** Blood samples were collected at –10 (2 x 7 mL), -2 and 0 hours on Day 1 and pre-dose (0-hour) on days 8, 9, 10 and 11 (1 x 7 mL). On Day 11, blood was drawn at 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14, 16, 20 and 24 hours post-dose (1 x 7 mL) (24 time points).

This study was designed to establish the multiple dose performance of the CIP-isotretinoin product relative to Accutane<sup>®</sup> given once a day, in healthy, male and female subjects, under fed conditions. It should be noted that currently Accutane<sup>™</sup> is not labeled for once daily dosing.

All subjects who were selected for the study met the inclusion and exclusion criteria described in the study protocol, and were judged by an Investigator to be medically healthy based on medical history, physical examination, vital signs measurements, 12-lead ECG, clinical laboratory tests, and  $\beta$ -hCG Pregnancy Test (only for female subjects). Thirty-six (36) healthy, non-smoking, male and female subjects were dosed in Period I.

Throughout this study a number of subjects dropped out of the trial for a variety of reasons:

Subject #	Reason for Dismissal
Subject #02	withdrew prior to Period II check-in due to personal reasons
Subject #06	dismissed prior to dosing on Day 4, during Period II due to an adverse event. On the night of (b) (6) the subject was driven to (b) (6) Hospital for swollen hands and abrasions, after he repeatedly punched a wall. An X-ray was conducted, and no bone fractures were observed. The subject went back to the clinic and was examined by the PI the next morning. The subject was dismissed from the study, but stayed in the clinic for safety measures. On (b) (6) the subject saw a psychiatrist and was considered fine. He was then released from the clinic.
Subject #10	dismissed prior to dosing on Day 6, during Period II due to an adverse event. On August 15, 2002 the subject complained of diarrhea and abdominal cramps. The PI saw the subject, and dismissed him from the study. The subject stayed in the clinic for safety measures, until the last day of the study.
Subject #13	dismissed after dosing on Day 2, during Period II due to an adverse event. On August 12, 2002, the subject complained of irritation and of a momentary desire to hurt people. The PI saw the subject, and dismissed her from the study, but she was kept in the clinic for safety measures. On August 13, 2002 the subject left the clinic, against the medical advice given by the Study Director and Study Coordinator.
Subject #19	did not check-in for Period II
Subject #20	dismissed after dosing on Day 1, during Period II due to an adverse event. The subjects' health status and meal records were monitored for safety measures until the subject left the clinic on August 14, 2002.
Subject #26	dismissed prior to dosing on Day 8, during Period I due to non-compliance. The subject was suspected of hiding his breakfast meal and was asked by the Study Coordinator to empty his pockets. The subject was offered a replacement for the food he hid in his pocket in order to complete his meal, but he refused. He became agitated and threw his food in the garbage. The incident was reported by the Study Coordinator to the Study Director of the clinic, and it was decided not to dose the subject and to dismiss him from the study.
Subject #32	disqualified prior to drug administration in Period I, due to increased blood pressure, he was then replaced by Subject #39 (ZI16664)
Subject #39	did not show for Period II

## **Study Procedures**

This was an open-label, multiple-dose, randomized, two-treatment, two sequence, two-period, crossover relative bioavailability study. A single dose of isotretinoin (1 x 30 mg or 1 x 40 mg) was administered according to the dosage regimen beginning at 07:01am. Subjects were dosed at one-minute intervals and remained seated or in a semi-reclined position for 4 hours following drug administration, unless required to ambulate for study specific procedures, and resumed normal activity thereafter. Subjects were to be confined to the clinical facility of from at least 10 hours prior to drug administration on Day 1 until 24 hours following drug administration on Day 11 (a total of 12 nights in the clinic). The washout period between the last dose of Period I and the first dose of Period II was 21 days.

Subjects were instructed to refrain from taking any prescription or over-the-counter medications, herbal products and vitamins, with the exception of oral or implanted contraceptives, for 14 days preceding the first drug administration and until completion of the entire study. Subjects abstained from ingesting foods and beverages containing alcohol, caffeine, or xanthine-containing products for 48 hours prior to each study period and until after the last sample collection in each period. Subjects limited the intake of foods which had a high content of vitamin A, for 72 hours prior to each study period and until after the last sample collection in each period. At check-in of each period, subjects were questioned concerning adherence to these restrictions and their responses were noted on subject

The menu for the modified high fat, high calorie breakfast was as follows:

- 1 regular bagel
- 3 tablespoons of peanut butter
- 5 slices of bacon
- 6 fl oz of apple juice
- 1 dutchie donut

Modified xanthine-free and low vitamin A content meals were provided with caffeine-free beverages at approximately 4, 9 and 14 hours post-dose on each study day in each period. Other than the prescribed meals, subjects were not allowed any food while confined in the clinic. Any subject who did not complete the entire breakfast was dismissed from the study prior to drug administration.

## **Adverse Events**

Adverse events were monitored throughout the study. There were 253 adverse events reported by 29 different subjects in this study.

<b>TRT A-Cipher</b>	<b>TRT B-Accutane™</b>
<b>One hundred and twenty-seven</b>	<b>One hundred and twenty-six (126)</b>

<b>(127) adverse events were associated with Treatment A, 102 were mild, 24 were moderate and 1 was severe</b>	<b>adverse events were associated with Treatment B, 110 were mild and 16 were moderate</b>
headache (11) dry skin (10) pruritus (9) dry mouth (7) rash (6) asthenia (6) headache intermittent (4) acne (3) conjunctivitis (3) nose bleed (3) <b>euphoria (3)</b> back pain (3) eye pain (3) constipation (3) <b>agitation (2)</b> chills (2) dry eye (2) insomnia (2) heart burn (2) gingivitis (2) pain (2) abdomen pain (2) chest pain (2) <b>nervousness (2)</b> vomiting (2) increased pulse (2) <b>antisocial (1)</b> <b>anxiety (1)</b> joint pain (1) cough (1) diarrhea (1 episode) (1) diarrhea intermittent (1) dizziness (1)	headache (10) pain (8) dry mouth (8) rash (9) pruritus (5) dry skin (4) asthenia (4) insomnia (4) conjunctivitis (4) constipation (3) dry eye (3) headache intermittent (3) eye pain (3) rhinitis (3) pharyngitis (4) acne (2) <b>anxiety (2)</b> gingivitis (2) <b>nervousness (2)</b> abdomen pain (1) back pain (2) tachycardia (2) hypertension (2) chest pain (2) neck pain (2) abscess periodontal (1) <b>agitation (1)</b> anorexia (1) arthralgia (1) chills (1) cough (1) dizziness (1) dyspepsia (1)

menstrual cramps (1) discomfort on swallowing food (1) inflamed and swollen hands (1) guilty isolated (1) euphoria intermittent (1) hostility (1) increased blood pressure (1) injury (1) muscle ache intermittent (1) nausea (1) nervousness intermittent (1) back pain intermittent (1) pain intermittent (1) neck pain (1) pimple like rash on the face (1) red spots on arms and face (1) rhinitis (1) elevated ALT (1) somnolence (1) stomatitis (1) thirsty (1) urine frequency (1)	emotion labile (1) euphoria (1) glossitis (1) hem eye (1) hem gum (1) hypesthesia (1) injury (1) myalgia (1) nausea intermittent (1) nervousness intermittent (1) back pain intermittent (1) ear pain (1) paresthesia (1) papular rash (1) 4 blisters on lips (1) thirsty (1) urine frequency (1) depression (1) vasodilation (1) skin dry intermittent (1) pain abdominal intermittent (1) bruise (1) urticaria (1) altered voice (1)
All were judged possibly (60), probably (66) and unrelated (1), to the study drugs by the Principal Investigator	All were judged possibly (73), unrelated (1), and probably (52) related to the study drugs by the Principal Investigator.

Throughout the study there were a number of adverse events that are consistent with the psychiatric issues with isotretinoin that are presented in the label for Accutane™. The reports of both euphoria and depression, along with hostile thoughts are especially disturbing for such a small study of very limited duration. This data has been shared with the reviewing medical officer for their evaluation, although the very small sample size and limited duration, relative to normal dosing with isotretinoin (20 weeks) is a limiting factor. The highlighted fields above indicate those AEs that appear to be related to psychiatric findings.

## Results

Tables of the individual pharmacokinetic profiles, mean plasma level time profiles, box whisker plots, and associated statistical tables are attached.

### Summary of Study Results for Comparative Bioavailability under Fed Conditions

(Treatment A Data Adjusted to the 40 mg Dose)

(N = 28)

Parameter	Treatment (A)	Treatment (B)	Ratio of Geometric Means (%)	90% Geometric Confidence Interval (%)
	Geometric Mean			
<b>Analyte: Isotretinoin</b>				
AUC <sub>tau</sub> (ng h/mL)	4416.2	4307.3	102.53	96.82 – 108.58
C <sub>max</sub> (ng/mL)	504.1	530.3	95.05	84.64 – 106.75
C <sub>min</sub> (ng/mL)	89.6	73.5	121.99	112.78 – 131.94
<b>Analyte: 4-oxo-isotretinoin</b>				
AUC <sub>tau</sub> (ng h/mL)	16603.0	16033.5	103.55	96.44 – 111.19
C <sub>max</sub> (ng/mL)	895.7	844.5	106.07	99.07 – 113.56
C <sub>min</sub> (ng/mL)	527.9	484.8	108.90	101.65 – 116.66
<b>Analyte: Tretinoin</b>				
AUC <sub>tau</sub> (ng h/mL)	206.20	195.29	105.58	97.71 – 114.09
C <sub>max</sub> (ng/mL)	27.04	26.32	102.70	88.87 – 118.68
C <sub>min</sub> (ng/mL)	3.64	3.03	119.98	104.13 – 138.25
<b>Analyte: 4-oxo-tretinoin</b>				
AUC <sub>tau</sub> (ng h/mL)	416.5	382.3	108.96	98.19 – 120.92
C <sub>max</sub> (ng/mL)	26.2	24.6	106.23	95.87 – 117.71
C <sub>min</sub> (ng/mL)	9.1	8.5	108.03	97.65 – 119.50

Treatment A (Test):

A single dose of Isotretinoin 30 mg Capsules (Cipher Canada Inc; Manufacturer: GALEPHAR P.R. Inc; Manufacturing Date: Not specified; Lot 27C02; Exp Date: N/A) was administered once a day for 11 days within 5 minutes of completion of the modified high fat, high calorie breakfast.

Treatment B (Reference):

A single dose of Accutane® 40 mg Capsules (Manufacturer: ROCHE LABORATORIES INC; Manufacturing Date: Not specified; Lot U0605; Exp Date: 03 2004; NDC: 0004-0156-49) was administered once a day for 11 days within 5 minutes of completion of the modified high fat, high calorie breakfast.

**Summary of Individual Isotretinoin Pharmacokinetic Parameters  
A: Isotretinoin Capsules, 30 mg o.d., Lot 27C02 (Cipher Canada Inc.)**

----- Treatment=A -----

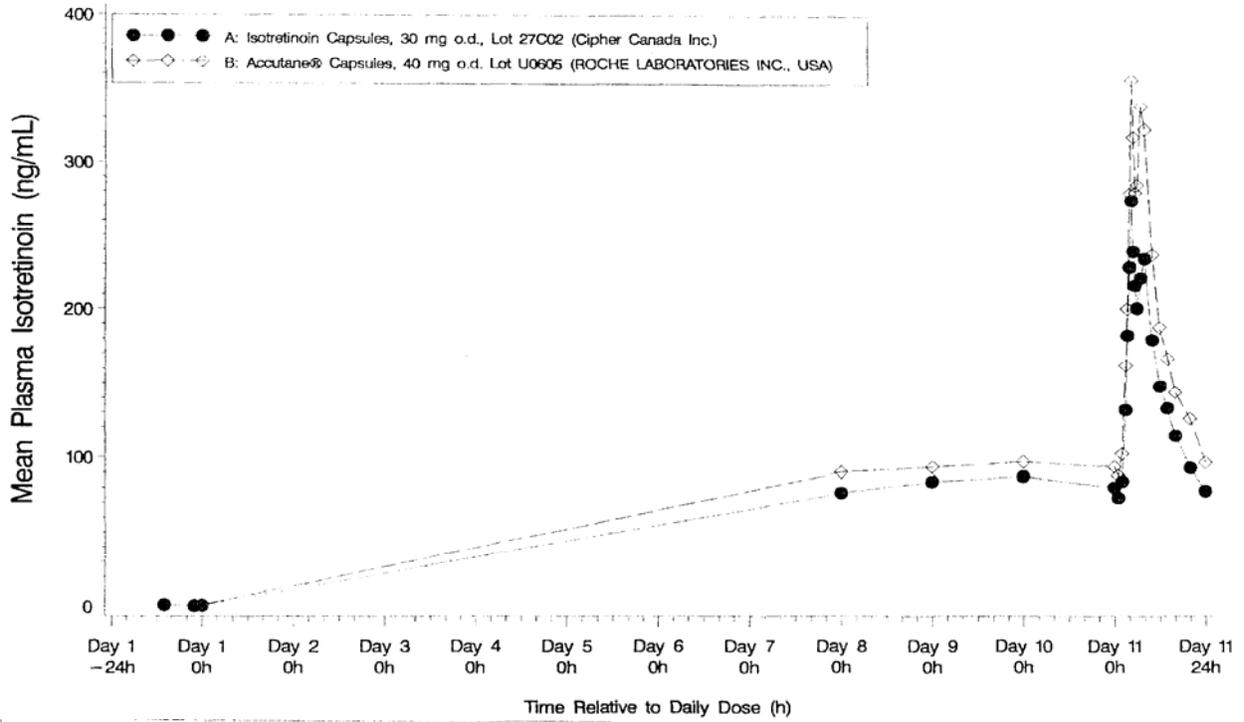
Subject	SEQ	PERIOD	AUCtau (ng.h/mL)	Cmax (ng/mL)	Tmax (h)	Cmin (ng/mL)	Cavg (ng/mL)	DF (%)	Swing (%)
01	BA	2	3010.9	428.0	4.00	39.0	125.5	310.07	997.44
03	AB	1	4000.1	373.7	10.00	80.5	166.7	175.91	364.19
04	AB	1	3846.6	381.8	7.00	94.9	160.3	179.01	302.23
05	BA	2	2650.9	295.0	6.00	60.9	110.5	211.94	384.40
07	AB	1	3558.9	345.6	4.00	77.8	148.3	180.60	344.38
08	AB	1	3608.3	559.8	4.52	53.0	150.3	337.09	955.57
09	AB	1	2828.7	193.0	14.00	62.0	117.9	111.15	211.29
11	BA	2	3201.6	310.7	8.00	57.3	133.4	189.96	442.62
12	AB	1	3371.9	359.0	4.00	59.7	140.5	213.03	501.34
14	BA	2	3855.2	417.6	5.50	79.3	160.6	210.60	426.54
15	AB	1	2803.9	379.6	4.00	59.9	116.8	273.65	534.02
16	AB	1	4924.8	466.7	4.50	122.7	205.2	167.64	280.38
17	BA	2	3684.4	443.9	7.00	75.0	153.5	240.30	492.17
18	AB	1	2801.4	320.9	4.50	40.7	116.7	240.05	688.17
21	BA	2	3341.5	366.0	6.00	78.9	139.2	206.21	363.88
22	BA	2	4385.1	586.2	7.00	80.4	182.7	276.83	628.74
23	AB	1	3044.9	363.0	8.00	70.6	126.9	230.47	414.16
24	AB	1	2643.9	383.7	5.00	48.3	110.2	304.46	694.99
25	AB	1	2654.3	400.3	4.50	48.0	110.6	318.55	734.52
27	BA	2	3235.4	656.9	4.50	68.4	134.8	436.54	860.51
28	BA	2	2633.1	182.0	8.00	67.8	109.7	104.09	168.44
29	BA	2	2281.4	268.0	5.00	38.8	95.1	241.12	590.72
30	AB	1	2573.8	294.6	8.02	61.0	107.2	217.83	382.99
31	BA	2	2889.5	465.7	4.50	64.4	120.4	333.32	623.49
33	AB	1	4491.3	365.0	4.50	114.0	187.1	134.13	220.18
34	BA	2	3569.1	288.6	10.00	87.9	148.7	134.96	228.26
35	AB	1	4524.8	652.7	8.00	80.4	188.5	303.55	712.02
36	BA	2	4354.6	514.3	4.50	91.0	181.4	233.30	465.35
MEAN	.	.	3384.6	395.1	6.23	70.1	141.0	232.73	500.46
STD	.	.	706.1	118.8	2.39	20.5	29.4	76.40	222.60
CV (%)	.	.	20.9	30.1	38.28	29.3	20.9	32.83	44.48

**Summary of Individual Isotretinoin Pharmacokinetic Parameters  
B: Accutane® Capsules, 40 mg o.d., Lot U0605 (ROCHE LABORATORIES INC., USA)**

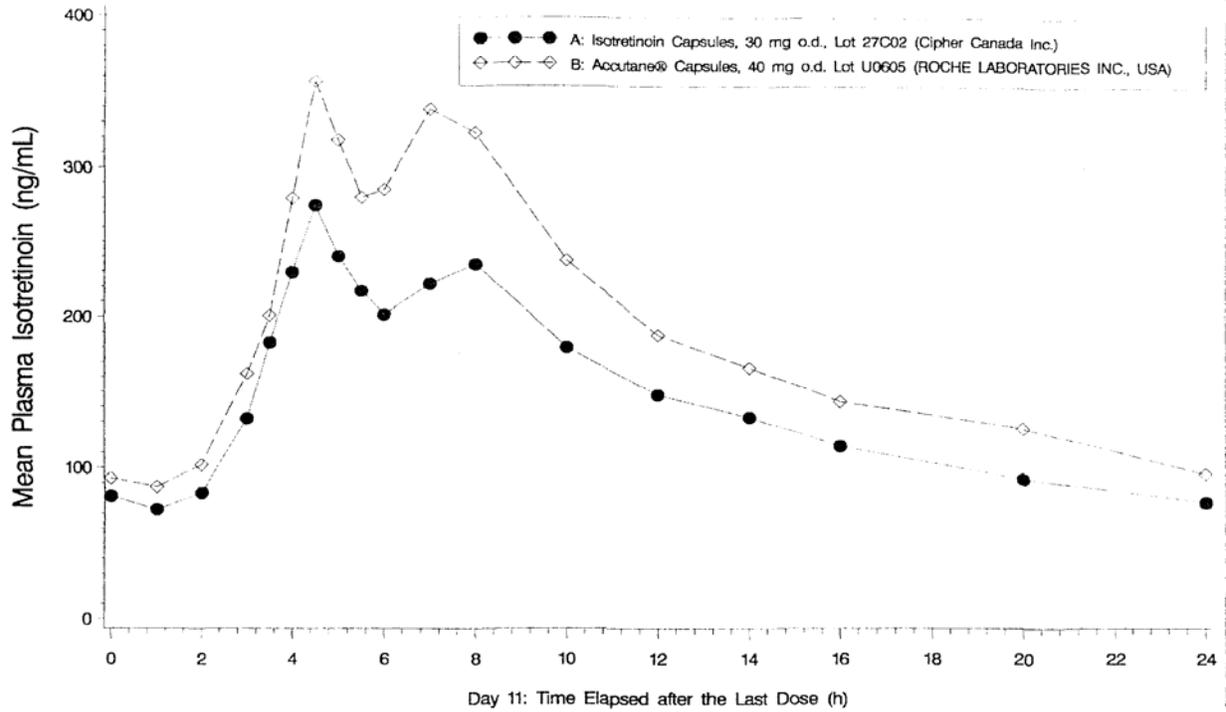
----- Treatment=B -----

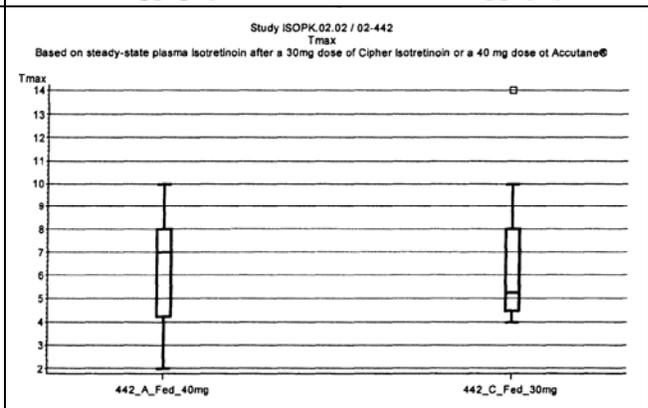
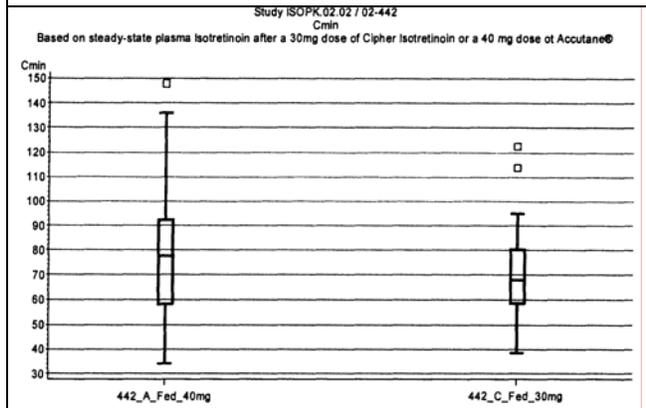
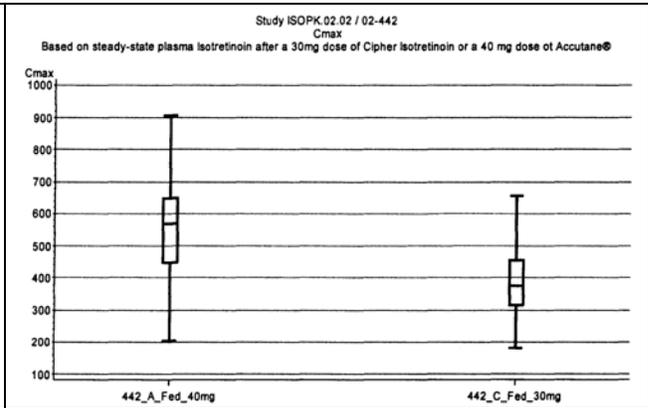
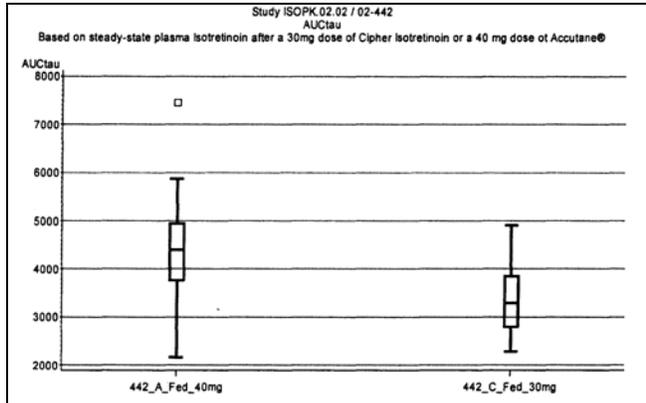
Subject	SEQ	PERIOD	AUCtau (ng.h/mL)	Cmax (ng/mL)	Tmax (h)	Cmin (ng/mL)	Cavg (ng/mL)	DF (%)	Swing (%)
01	BA	1	3813.0	623.0	4.00	41.4	158.9	366.07	1404.83
03	AB	2	4737.0	673.8	7.00	101.8	197.4	289.80	562.07
04	AB	2	5789.4	866.6	7.00	93.3	241.2	320.57	828.65
05	BA	1	3756.6	816.0	4.50	73.8	156.5	474.18	1005.69
07	AB	2	5402.0	624.8	4.00	86.8	225.1	239.02	620.10
08	AB	2	3407.6	481.8	4.50	50.5	142.0	303.77	853.95
09	AB	2	5110.8	458.0	10.00	98.2	212.9	168.96	366.40
11	BA	1	3741.5	563.8	7.00	55.6	155.9	325.99	914.80
12	AB	2	5105.2	469.0	8.02	91.2	212.7	177.61	414.25
14	BA	1	4521.3	321.0	3.00	136.0	188.4	98.20	136.03
15	AB	2	3884.6	440.5	4.00	72.7	161.9	227.24	506.05
16	AB	2	7461.8	595.9	8.00	147.9	310.9	144.09	302.93
17	BA	1	4899.9	726.8	8.00	70.0	204.2	321.70	938.29
18	AB	2	4210.1	607.6	4.50	34.3	175.4	326.81	1670.29
21	BA	1	4120.9	713.0	4.50	82.2	171.7	367.38	767.40
22	BA	1	4993.9	613.0	7.00	78.8	208.1	256.73	678.32
23	AB	2	4371.1	391.0	8.00	85.5	182.1	167.74	357.31
24	AB	2	3578.8	325.6	7.00	58.8	149.1	178.92	453.41
25	AB	2	3779.7	576.0	3.50	70.9	157.5	320.72	712.41
27	BA	1	4924.5	906.9	5.00	78.0	205.2	403.97	1062.06
28	BA	1	2884.6	303.3	2.00	68.6	120.2	195.27	342.05
29	BA	1	3511.2	585.0	5.50	38.1	146.3	373.82	1435.43
30	AB	2	2171.8	203.7	10.00	38.0	90.5	183.11	436.44
31	BA	1	4084.5	485.3	4.00	77.6	170.2	239.56	525.32
33	AB	2	4653.4	525.6	7.00	78.1	193.9	230.80	572.81
34	BA	1	4764.1	421.0	10.00	112.0	198.5	155.66	275.89
35	AB	2	4423.5	725.0	7.00	57.7	184.3	362.05	1156.50
36	BA	1	5884.6	530.7	8.00	111.7	245.2	170.89	374.99
MEAN	.	.	4428.1	556.2	6.14	78.2	184.5	263.95	702.67
STD	.	.	1026.7	170.6	2.21	27.8	42.8	93.61	384.90
CV (%)	.	.	23.2	30.7	35.99	35.5	23.2	35.47	54.78

STUDY No.: 02-442  
 MEAN MEASURED PLASMA ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES  
 N=28



STUDY No.: 02-442  
 MEAN BASELINE-ADJUSTED PLASMA ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES  
 N=28





## Summary of Individual 4-oxo-isotretinoin Pharmacokinetic Parameters

### A: Isotretinoin Capsules, 30 mg o.d., Lot 27C02 (Cipher Canada Inc.)

Treatment=A

Subject	SEQ	PERIOD	AUCtau (ng.h/mL)	Cmax (ng/mL)	Tmax (h)	Cmin (ng/mL)	Cavg (ng/mL)	DF (%)	Swing (%)
01	BA	2	9716.0	586.3	8.00	255.3	404.8	81.76	129.63
03	AB	1	15738.3	923.0	12.00	441.0	655.8	73.50	109.30
04	AB	1	10830.2	691.6	12.00	357.6	451.3	74.02	93.41
05	BA	2	11669.5	664.0	7.00	391.0	486.2	56.15	69.83
07	AB	1	14754.8	750.8	8.00	473.8	614.8	45.06	58.46
08	AB	1	16378.2	821.0	12.00	476.0	682.4	50.55	72.48
09	AB	1	10606.9	488.9	16.00	389.9	442.0	22.40	25.39
11	BA	2	12474.9	713.5	14.00	356.5	519.8	68.68	100.15
12	AB	1	12893.3	738.5	4.00	473.5	537.2	49.33	55.97
14	BA	2	12702.1	706.3	12.00	379.3	529.3	61.78	86.22
15	AB	1	9599.9	465.8	7.00	314.8	400.0	37.75	47.97
16	AB	1	12092.2	622.0	10.00	435.0	503.8	37.11	42.99
17	BA	2	15088.1	854.5	8.00	410.5	628.7	70.63	108.17
18	AB	1	14630.2	772.6	4.00	563.6	609.6	34.29	37.08
21	BA	2	12552.0	659.1	10.00	421.1	523.0	45.51	56.52
22	BA	2	11517.4	615.7	12.00	314.7	479.9	62.72	95.63
23	AB	1	12967.9	666.0	14.00	413.0	540.3	46.82	61.26
24	AB	1	10704.4	532.2	10.00	371.2	446.0	36.10	43.37
25	AB	1	14623.2	786.5	0.00	466.5	609.3	52.52	68.59
27	BA	2	13646.2	812.7	6.00	456.7	568.6	62.61	77.95
28	BA	2	10361.9	563.5	12.00	331.5	431.7	53.74	69.98
29	BA	2	8229.2	461.6	8.00	245.6	342.9	63.00	87.96
30	AB	1	11278.4	620.8	12.07	301.8	469.9	67.88	105.71
31	BA	2	10772.6	558.1	10.00	336.1	448.9	49.46	66.04
33	AB	1	12716.9	619.5	0.00	491.5	529.9	24.16	26.04
34	BA	2	13001.6	699.3	14.00	450.3	541.7	45.96	55.30
35	AB	1	18020.4	982.6	14.00	516.6	750.9	62.06	90.21
36	BA	2	15750.0	801.0	14.00	546.0	656.3	38.86	46.70
MEAN	.	.	12689.9	684.9	9.65	406.4	528.7	52.66	71.01
STD	.	.	2303.6	131.6	4.14	82.1	96.0	15.21	26.72
CV(%)	.	.	18.2	19.2	42.92	20.2	18.2	28.89	37.63

## Summary of Individual 4-oxo-isotretinoin Pharmacokinetic Parameters

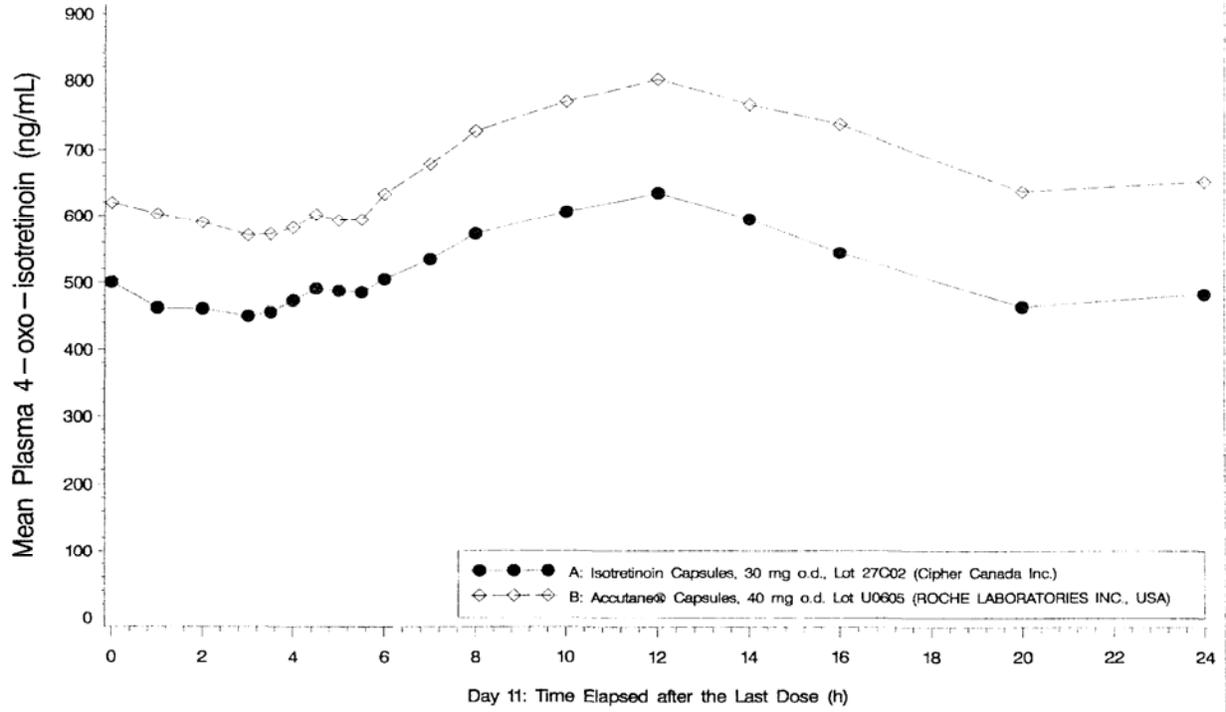
### B: Accutane® Capsules, 40 mg o.d., Lot U0605 (ROCHE LABORATORIES INC., USA)

Treatment=B

Subject	SEQ	PERIOD	AUCtau (ng.h/mL)	Cmax (ng/mL)	Tmax (h)	Cmin (ng/mL)	Cavg (ng/mL)	DF (%)	Swing (%)
01	BA	1	13373.0	679.7	7.00	413.7	557.2	47.74	64.30
03	AB	2	20000.5	984.6	12.00	573.6	833.4	49.32	71.65
04	AB	2	20042.7	1057.8	12.00	466.8	835.1	70.77	126.62
05	BA	1	20482.8	1048.6	8.00	625.6	853.4	49.56	67.62
07	AB	2	22326.2	1157.9	6.00	750.9	930.3	43.75	54.20
08	AB	2	14526.4	850.8	10.00	520.8	605.3	54.52	63.36
09	AB	2	13331.8	658.6	12.00	435.6	555.5	40.14	51.20
11	BA	1	15084.3	814.7	14.00	343.7	628.5	74.94	137.05
12	AB	2	21433.0	985.0	16.00	724.0	893.0	29.23	36.05
14	BA	1	18496.4	911.7	24.00	583.7	770.7	42.56	56.19
15	AB	2	12159.8	716.5	12.00	339.5	506.7	74.41	111.05
16	AB	2	19317.1	975.8	8.00	552.8	804.9	52.55	76.52
17	BA	1	16596.0	907.8	12.00	428.8	691.5	69.27	111.71
18	AB	2	17705.7	944.4	8.00	535.4	737.7	55.44	76.40
21	BA	1	13013.9	655.9	8.00	473.9	542.2	33.56	38.41
22	BA	1	14722.3	895.8	12.00	427.8	613.4	76.29	109.40
23	AB	2	15151.1	842.8	14.00	409.8	631.3	68.59	105.66
24	AB	2	17144.0	944.0	14.00	527.0	714.3	58.38	79.13
25	AB	2	18330.6	998.5	5.00	682.5	763.8	41.37	46.30
27	BA	1	19219.0	935.1	10.00	716.1	800.8	27.35	30.58
28	BA	1	11759.6	559.6	12.00	445.6	490.0	23.27	25.58
29	BA	1	13653.6	729.7	10.00	338.7	568.9	68.73	115.44
30	AB	2	8668.6	439.5	16.00	240.5	361.2	55.10	82.74
31	BA	1	15261.5	789.6	8.00	433.6	635.9	55.98	82.09
33	AB	2	12698.7	709.5	12.00	430.5	529.1	52.73	64.81
34	BA	1	13236.6	752.5	24.00	390.5	551.5	65.64	92.71
35	AB	2	17608.4	981.8	10.00	457.8	733.7	71.42	114.46
36	BA	1	26113.6	1337.2	12.00	839.2	1088.1	45.77	59.34
MEAN	.	.	16480.6	866.6	11.71	503.9	686.7	53.51	76.81
STD	.	.	3836.2	188.1	4.45	141.7	159.8	15.13	30.39
CV(%)	.	.	23.3	21.7	38.02	28.1	23.3	28.27	39.57

STUDY No.: 02-442

MEAN BASELINE-ADJUSTED PLASMA 4-OXO-ISOTRETINOIN CONCENTRATION VERSUS TIME CURVES  
N=28



**Summary of Individual Tretinoin Pharmacokinetic Parameters  
A: Isotretinoin Capsules, 30 mg o.d., Lot 27C02 (Cipher Canada Inc.)**

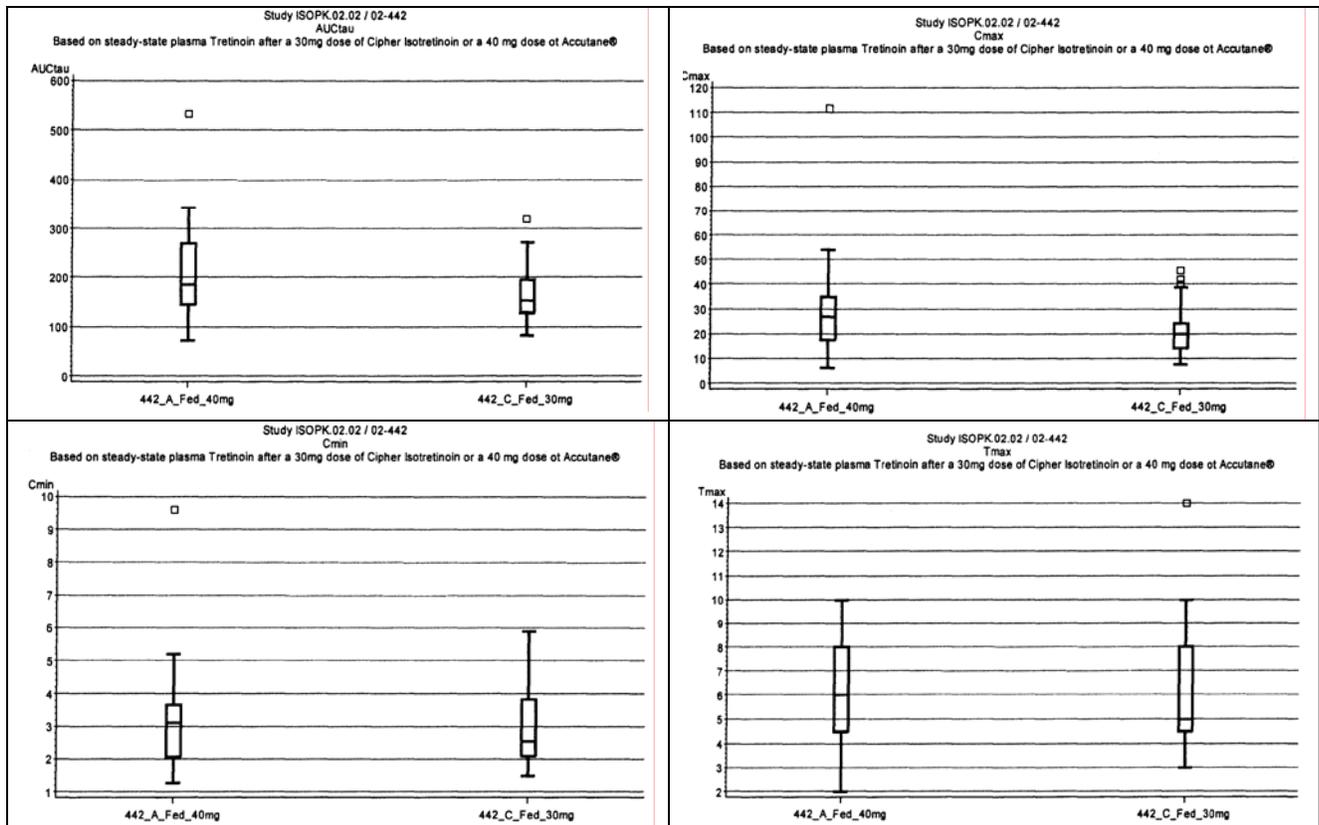
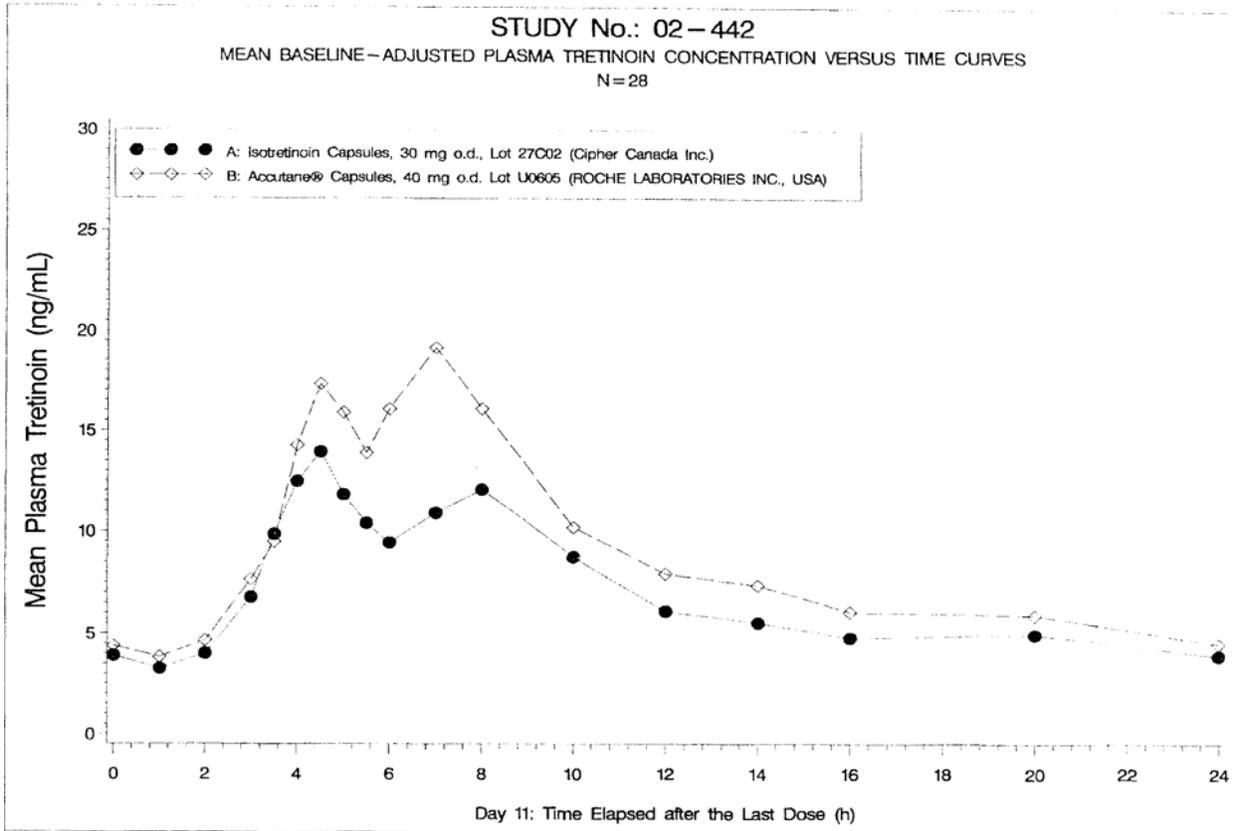
----- Treatment=A -----

Subject	SEQ	PERIOD	AUCtau (ng.h/mL)	Cmax (ng/mL)	Tmax (h)	Cmin (ng/mL)	Cavg (ng/mL)	DF (%)	Swing (%)
01	BA	2	197.47	41.89	4.00	2.97	8.23	473.04	1310.44
03	AB	1	135.15	13.03	10.00	2.56	5.63	185.92	408.45
04	AB	1	152.59	14.40	7.00	3.99	6.36	163.73	260.90
07	AB	1	227.87	23.14	4.00	4.06	9.49	200.96	469.57
08	AB	1	183.38	40.00	4.52	2.85	7.64	486.19	1303.51
09	AB	1	164.19	11.00	14.00	2.34	6.84	126.58	370.09
11	BA	2	320.42	38.90	8.00	5.89	13.35	247.25	560.44
12	AB	1	202.78	24.12	3.00	4.96	8.45	226.77	386.03
14	BA	2	175.18	24.21	5.00	2.16	7.30	302.10	1019.26
15	AB	1	92.32	16.61	4.00	2.04	3.85	378.76	713.05
16	AB	1	127.44	14.12	4.50	3.38	5.31	202.26	317.75
17	BA	2	155.20	20.10	7.00	2.34	6.47	274.65	758.97
18	AB	1	131.01	18.24	4.00	1.69	5.46	303.19	981.23
21	BA	2	271.67	28.66	7.00	4.86	11.32	210.25	489.38
22	BA	2	260.01	45.96	7.00	3.83	10.83	388.88	1100.00
23	AB	1	179.99	21.10	8.00	3.72	7.50	231.75	467.62
24	AB	1	131.35	23.86	4.50	2.13	5.47	397.04	1018.59
25	AB	1	85.44	13.11	4.50	1.59	3.56	323.59	724.53
27	BA	2	102.27	20.47	4.00	1.51	4.26	444.95	1258.41
28	BA	2	106.85	7.60	5.50	1.96	4.45	126.68	287.76
29	BA	2	150.04	16.37	5.00	2.42	6.25	223.14	575.65
30	AB	1	83.26	13.01	8.02	1.78	3.47	323.70	632.08
31	BA	2	181.06	25.90	4.50	2.96	7.54	304.08	775.00
33	AB	1	196.56	15.86	4.50	3.98	8.19	145.06	298.24
34	BA	2	132.90	19.10	10.00	2.55	5.54	298.88	649.02
35	AB	1	143.35	22.90	8.00	2.09	5.97	348.41	995.69
36	BA	2	101.49	16.50	4.50	2.13	4.23	339.81	674.65
MEAN	.	.	162.64	21.86	6.08	2.92	6.78	284.36	696.53
STD	.	.	58.50	9.81	2.50	1.14	2.44	101.92	324.93
CV(%)	.	.	35.97	44.86	41.20	39.21	35.97	35.84	46.65

**Summary of Individual Tretinoin Pharmacokinetic Parameters  
B: Accutane® Capsules, 40 mg o.d., Lot U0605 (ROCHE LABORATORIES INC., USA)**

----- Treatment=B -----

Subject	SEQ	PERIOD	AUCtau (ng.h/mL)	Cmax (ng/mL)	Tmax (h)	Cmin (ng/mL)	Cavg (ng/mL)	DF (%)	Swing (%)
01	BA	1	265.91	43.45	4.00	3.26	11.08	362.75	1231.56
03	AB	2	161.30	26.81	7.00	3.11	6.72	352.63	762.88
04	AB	2	186.00	30.47	7.00	2.39	7.75	362.32	1174.90
07	AB	2	284.93	32.67	5.00	3.62	11.87	244.70	801.75
08	AB	2	143.75	21.53	4.50	1.85	5.99	328.58	1063.78
09	AB	2	280.53	26.70	10.00	4.99	11.69	185.73	435.07
11	BA	1	534.64	111.62	7.00	4.77	22.28	479.65	2241.61
12	AB	2	270.02	29.93	8.02	4.30	11.25	227.81	596.51
14	BA	1	290.40	30.41	4.50	9.61	12.10	171.90	216.37
15	AB	2	93.41	16.99	4.00	2.17	3.89	380.79	684.00
16	AB	2	179.81	17.67	8.00	3.59	7.49	187.93	392.20
17	BA	1	185.26	28.14	8.00	2.82	7.72	328.02	897.87
18	AB	2	188.70	34.70	4.50	1.28	7.86	425.06	2610.94
21	BA	1	343.47	54.02	5.00	5.21	14.31	341.06	936.85
22	BA	1	293.56	43.20	7.00	3.20	12.23	327.02	1250.00
23	AB	2	231.91	19.60	8.00	3.65	9.66	165.07	436.59
24	AB	2	186.63	17.56	3.50	2.25	7.78	196.88	680.44
25	AB	2	116.72	17.91	4.50	1.87	4.86	329.81	856.23
27	BA	1	170.60	39.42	4.50	3.12	7.11	510.66	1163.46
28	BA	1	118.16	13.01	2.00	3.05	4.92	202.31	326.20
29	BA	1	235.19	37.07	6.00	2.08	9.80	357.06	1682.21
30	AB	2	73.07	6.48	10.00	1.66	3.04	158.31	290.36
31	BA	1	189.65	31.78	4.50	3.34	7.90	359.91	851.50
33	AB	2	124.80	14.92	7.00	1.53	5.20	257.51	877.07
34	BA	1	187.09	16.60	10.00	4.72	7.80	152.40	251.69
35	AB	2	135.66	25.90	7.00	1.94	5.65	423.88	1235.05
36	BA	1	178.22	16.09	4.00	3.11	7.43	174.79	417.81
MEAN	.	.	209.24	29.80	6.09	3.28	8.72	296.09	902.40
STD	.	.	94.20	19.66	2.14	1.67	3.92	104.54	574.69
CV(%)	.	.	45.02	65.97	35.20	51.07	45.02	35.30	63.68



**Summary of Individual 4-oxo-tretinoin Pharmacokinetic Parameters  
A: Isotretinoin Capsules, 30 mg o.d., Lot 27C02 (Cipher Canada Inc.)**

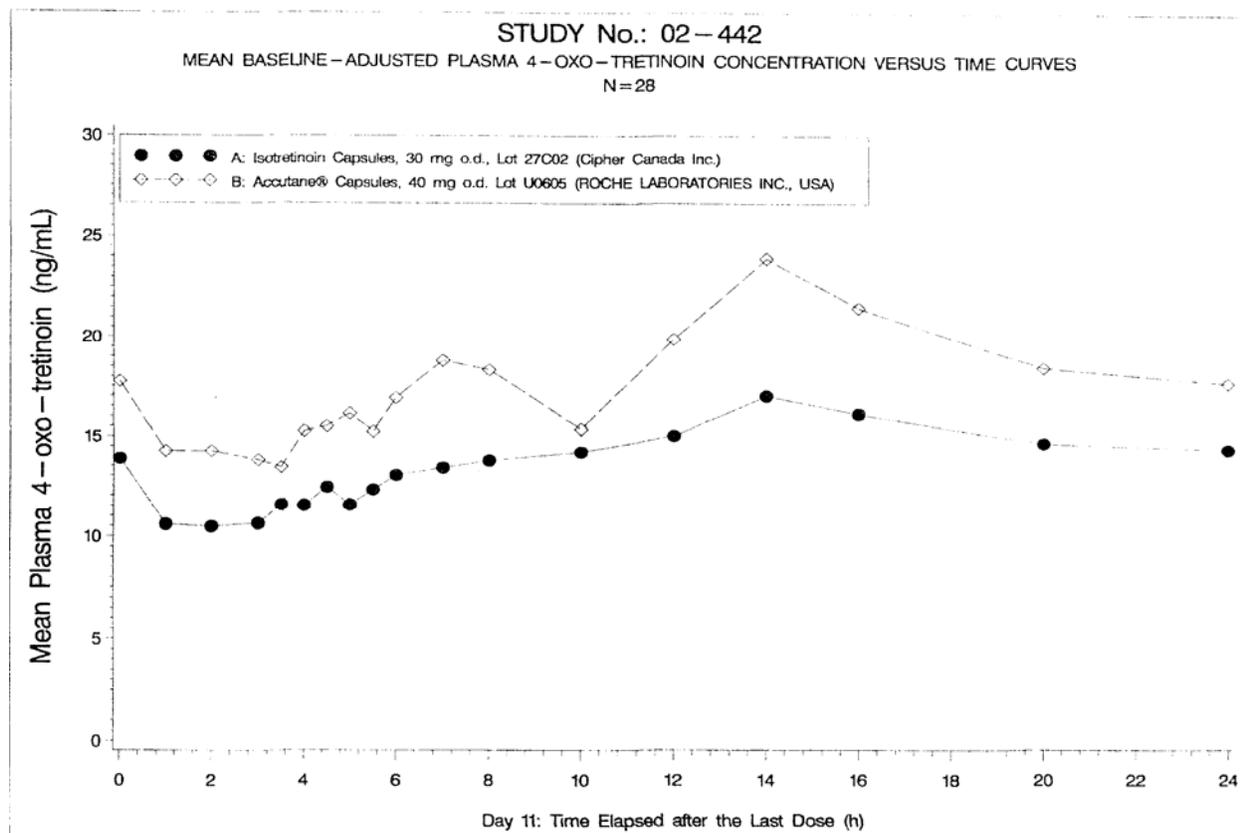
----- Treatment=A -----

Subject	SEQ	PERIOD	AUCtau (ng.h/mL)	Cmax (ng/mL)	Tmax (h)	Cmin (ng/mL)	Cavg (ng/mL)	DF (%)	Swing (%)
01	BA	2	296.73	16.00	14.00	6.32	12.36	78.29	153.16
03	AB	1	468.55	28.70	14.00	10.10	19.52	95.27	184.16
04	AB	1	291.62	17.10	12.00	9.32	12.15	64.03	83.48
07	AB	1	648.05	37.40	7.00	21.80	27.00	57.77	71.56
08	AB	1	497.00	26.30	4.52	10.60	20.71	75.81	148.11
09	AB	1	376.73	23.20	10.00	7.07	15.70	102.76	228.15
11	BA	2	610.40	40.10	10.00	10.60	25.43	115.99	278.30
12	AB	1	439.19	31.20	6.00	20.30	18.30	59.56	53.69
14	BA	2	381.24	35.40	3.50	5.78	15.88	186.47	512.46
15	AB	1	151.21	10.40	24.00	3.36	6.30	111.74	209.52
16	AB	1	200.48	16.00	24.00	5.28	8.35	128.33	203.03
17	BA	2	280.71	16.30	16.00	5.88	11.70	89.09	177.21
18	AB	1	291.58	17.10	16.00	8.43	12.15	71.36	102.85
21	BA	2	466.75	24.00	16.00	7.06	19.45	87.10	239.94
22	BA	2	299.44	16.50	0.00	5.49	12.48	88.24	200.55
23	AB	1	314.17	16.10	24.00	8.89	13.09	55.08	81.10
24	AB	1	360.81	20.30	14.00	6.97	15.03	88.67	191.25
25	AB	1	396.24	22.20	14.00	9.46	16.51	77.16	134.67
27	BA	2	348.05	21.00	16.00	6.88	14.50	97.37	205.23
28	BA	2	261.14	19.70	14.00	4.33	10.88	141.26	354.97
29	BA	2	376.56	22.70	16.00	6.44	15.69	103.63	252.48
30	AB	1	160.51	9.49	14.00	3.70	6.69	86.57	156.49
31	BA	2	342.14	22.80	16.00	5.48	14.26	121.50	316.06
33	AB	1	281.03	20.70	20.00	7.61	11.71	111.79	172.01
34	BA	2	173.03	12.30	10.00	4.01	7.21	114.99	206.73
35	AB	1	256.86	16.40	16.00	6.13	10.70	95.96	167.54
36	BA	2	129.85	8.95	14.00	3.54	5.41	99.99	152.82
MEAN	.	.	337.04	21.05	13.52	7.81	14.04	96.51	193.98
STD	.	.	128.79	8.06	5.95	4.36	5.37	28.28	95.39
CV(%)	.	.	38.21	38.30	43.98	55.89	38.21	29.31	49.18

**Summary of Individual 4-oxo-tretinoin Pharmacokinetic Parameters  
B: Accutane® Capsules, 40 mg o.d., Lot U0605 (ROCHE LABORATORIES INC., USA)**

----- Treatment=B -----

Subject	SEQ	PERIOD	AUCtau (ng.h/mL)	Cmax (ng/mL)	Tmax (h)	Cmin (ng/mL)	Cavg (ng/mL)	DF (%)	Swing (%)
01	BA	1	404.43	23.70	14.00	11.50	16.85	72.40	106.09
03	AB	2	704.93	44.00	20.00	16.60	29.37	93.29	165.06
04	AB	2	413.69	25.40	12.00	11.60	17.24	80.06	118.97
07	AB	2	700.62	44.60	12.00	18.20	29.19	90.43	145.05
08	AB	2	434.23	29.10	10.00	6.63	18.09	124.19	338.91
09	AB	2	576.82	33.20	12.00	11.30	24.03	91.12	193.81
11	BA	1	987.04	73.47	16.00	13.37	41.13	146.13	449.40
12	AB	2	802.51	58.60	14.00	16.00	33.44	127.40	266.25
14	BA	1	824.48	65.60	4.50	13.30	34.35	152.24	393.23
15	AB	2	176.92	11.90	14.00	3.70	7.37	111.24	221.62
16	AB	2	352.21	22.50	8.00	7.45	14.68	102.55	202.01
17	BA	1	278.34	16.70	14.00	7.85	11.60	76.31	112.74
18	AB	2	372.08	27.10	14.00	7.19	15.50	128.43	276.91
21	BA	1	511.53	29.40	24.00	13.60	21.31	74.13	116.18
22	BA	1	309.05	17.80	14.00	5.50	12.88	95.52	223.64
23	AB	2	315.06	17.20	16.00	9.62	13.13	57.74	78.79
24	AB	2	593.63	37.50	16.00	10.50	24.73	109.16	257.14
25	AB	2	425.35	23.80	14.00	7.87	17.72	89.88	202.41
27	BA	1	336.49	30.70	12.00	8.68	14.02	157.06	253.69
28	BA	1	278.19	16.60	16.00	7.24	11.59	80.75	129.28
29	BA	1	605.28	42.10	16.00	10.50	25.22	125.30	300.95
30	AB	2	108.30	7.87	16.00	2.56	4.51	117.67	207.42
31	BA	1	424.05	24.20	14.00	10.10	17.67	79.80	139.60
33	AB	2	186.89	11.70	24.00	5.57	7.79	78.72	110.05
34	BA	1	163.00	10.90	24.00	4.20	6.79	98.65	159.52
35	AB	2	208.08	13.90	20.00	4.24	8.67	111.42	227.83
36	BA	1	263.00	14.60	14.00	6.99	10.96	69.44	108.87
MEAN	.	.	435.41	28.67	14.98	9.33	18.14	101.52	203.91
STD	.	.	224.17	16.91	4.51	4.08	9.34	26.44	92.53
CV(%)	.	.	51.48	58.96	30.09	43.70	51.48	26.04	45.38



### Study Conclusions

Focusing on the dose adjusted data analysis the sponsor makes the claim that their product meets the bioequivalence criteria for the ratios of geometric means and 90% confidence intervals for AUC<sub>tau</sub> and C<sub>max</sub> parameters. They go on to state that the relative mean C<sub>min</sub> was also contained within the 80-125% range-this is incorrect, only the point estimate/ratio is within the 80-125% confidence interval. For C<sub>min</sub> the upper limit of the 90% CI was 131.9%, indicating that even under these controlled dosing conditions that there is a difference in the absorption of isotretinoin such that the levels with repeated dosing of CIP-isotretinoin are different from that seen with Accutane™. The significance of this finding cuts two ways, 1) as Accutane™ is not labeled for once daily use, it suggests that the finding is not relevant or 2) it provides a signal to what might happen under real world dosing conditions of an uncontrolled diet, that is higher levels throughout the dosing interval due to the diminished negative impact on absorption of fasting. Thus, it does not appear that the data as presented is sufficient to address the linkage of the CIP-isotretinoin product back to the Accutane™ safety database, but ultimately that is a medical issue. In addition the relative imbalance of psychiatric side effects in this study is worrisome and suggests again that these two products may indeed be different. The differentiation of whether or not the increased C<sub>min</sub> values play a role in this was not an objective of this trial, but it is again a worrisome finding.

# Proposed Annotated Package Insert

32 Pages of Draft Labeling have been Withheld  
in Full as B4 (CCI/TS) Immediately Following  
this Page

*Office of Clinical Pharmacology and Biopharmaceutics*  
*New Drug Application Filing and Review Form*

General Information About the Submission

	Information		Information
NDA Number	21-951	Brand Name	CIP-Isotretinoin
OCPB Division (I, II, III)	III	Generic Name	Isotretinoin
Medical Division	HFD-540	Drug Class	Retinoid
OCPB Reviewer	Bashaw	Indication(s)	(b) (4)
OCPB Team Leader	Selen	Dosage Form	Capsule
		Dosing Regimen	40mg qd/20mg bid
Date of Submission	7/5/2005	Route of Administration	Oral
Estimated Due Date of OCPB Review		Sponsor	Cipher
PDUFA Due Date	5/5/06	Priority Classification	1-S
Division Due Date			

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.				Very poor index, volumes only no specifics.
Tabular Listing of All Human Studies				Not contained in 1.1
HPK Summary				Unable to locate
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) -				
<b>Healthy Volunteers-</b>				
single dose:	X	6		
multiple dose:	X	2		
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:	X	6		
fasting / non-fasting multiple dose:	X	1		
<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:	X			
<b>Population Analyses -</b>				
Data rich:				

Data sparse:				
<b>II. Biopharmaceutics</b>				
Absolute bioavailability:				
Relative bioavailability -				
Marketed Product as reference:		3		
alternate formulation as reference:		3		
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	2		
Dissolution:	X			
(IVIVC):	X			
<b>Bio-wavier request based on BCS</b>				
BCS class				
<b>III. Other CPB Studies</b>				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		8		
<b>Filability and QBR comments</b>				
	"X" if yes	Comments		
Application filable ?		While the information for an in vivo biopharmaceutic review is present, the larger issues as proposed below (QBR section) remain. The NDA is poorly organized and lacks sufficient indexing to allow for ready review. The electronic dataset appears to be complete in terms of data, no text files were provided electronically		
Comments sent to firm ?				
QBR questions (key issues to be considered)		1.) Have sufficient studies been done to allow for dosing to be extrapolated from the Accutane experience to this new product in terms of both safety and efficacy? 2.) Does the change in bioavailability re:food effect provide sufficient evidence of a safety benefit as claimed by the sponsor?		
Other comments or information not included above		The NDA itself is poorly organized and not readily reviewable as submitted		
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 21-951, HFD-850(P. Lee), HFD-860 (M. Mehta), HFD-540(CSO), HFD-880(Lazor, Selen), CDR

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

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Dennis Bashaw  
4/19/2006 01:31:35 PM  
BIOPHARMACEUTICS

John P. Hunt  
4/19/2006 03:02:19 PM  
BIOPHARMACEUTICS