

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-070

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

Clinical Pharmacology Review (Addendum)

Submission:	NDA 22-070
Proposed Product Name:	Atralin®
Product:	Tretinoin Gel, 0.05%
Indication:	Treatment of Acne vulgaris
Submission Dates:	09/27/06
Type of Submission:	Original NDA (1S)
Sponsor:	Coria Laboratories, Ltd
OCP Reviewer:	Tapash K. Ghosh, Ph.D. (DCP 3)
OCP Team Leader:	Sue-Chih Lee, Ph.D. (DCP 3)
Medical Officer:	David Kettl, MD (HFD 540, ODE V)

Background:

In this NDA, the applicant has submitted for approval a 0.05% gel formulation of tretinoin, Atralin Gel 0.05%, for daily topical application to skin with acne lesions in patients 10 years of age and older. This NDA is submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, relying on the Agency's safety finding of the previously approved product, Retin-A Micro (NDA 20-475, Johnson & Johnson), and including nonclinical and clinical studies to support the use of a different formulation.

To support this application, the sponsor submitted three Phase 1, two Phase 2 and two Phase 3 studies. The three phase 1 studies included human volunteers and were conducted to evaluate the photoallergic, phototoxic, and contact sensitization potential of tretinoin gel, 0.05% vs. tretinoin gel vehicle vs. white petrolatum.

The two phase 2 studies included subjects with severe acne vulgaris and were performed to assess the systemic exposure of tretinoin and its metabolites following maximal topical application of the proposed drug product and Retin-A Micro.

The original Clinical Pharmacology review of this submission can be found in DFS signed off on July 16, 2007. In that review, mean concentration-time profiles for all three analytes as observed in the two Phase 2 trials were presented for both Atralin Gel 0.05% and Retin-A Micro 0.1% and the statistical analyses to compare AUC of these two products were shown in the section of individual study review. Based on the data, we concluded that the systemic exposure of tretinoin and its two metabolites was comparable between Atralin Gel 0.05% and Retin-A Micro 0.1%.

The purpose of this addendum is to add two tables that list side-by-side summary data for the two products from the two Phase 2 trials. One table relates to the range of concentrations of tretinoin and two of the metabolites and the other relates to the comparison of AUC between the two products. These data are consistent with those presented in the original review and do not change our conclusion.

The ranges of concentration for tretinoin, 13-cis-retinoic acid, and 4-oxo-13-cis-retinoic acid in these two studies at baseline and at the end of Day 14 in patients who applied 4 g (± 0.5 g) of tretinoin gel, 0.05% once daily to face, back and chest are summarized below. The concentration ranges for tretinoin and the two metabolites were similar between Atralin Gel 0.05% and Retin-A Micro 0.1%.

Baseline and final plasma levels of tretinoin and metabolites for Atralin Gel 0.05% and Retin-A Micro 0.1%

Compound	735.126.CL008/01				20.CLN.126.024			
	Tretinoin Gel, 0.05%		Retin-A Micro, 0.1%		Tretinoin Gel, 0.05%		Retin-A Micro, 0.1%	
	Baseline Conc (ng/ml)	Day 14 Conc (ng/ml)	Baseline Conc (ng/ml)	Day 14 Conc (ng/ml)	Baseline Conc (ng/ml)	Day 14 Conc (ng/ml)	Baseline Conc (ng/ml)	Day 14 Conc (ng/ml)
RA	0.9-1.6	0.7-1.7	0.7-1.6	0.7-1.7	0.7-1.5	0.7-2.9	0.8-1.8	0.7-3.3
13-cis	0.8-1.0	0.6-1.2	0.7-1.8	0.5-1.2	0.7-1.5	0.6-2.3	0.8-1.5	0.5-3.2
4-oxo	0.8-2.3	0.6-2.4	1.2-3.6	1.0-3.1	1.7-5.9	1.5-7.0	1.0-3.3	0.6-6.2

Day-14 AUC of tretinoin and metabolites for Atralin Gel 0.05% and Retin-A Micro 0.1%

		735.126.CL008/01			20.CLN.126.024		
		Tretinoin Gel, 0.05%	Retin A Micro	P-Value	Tretinoin Gel, 0.05%	Retin A Micro	P-Value
N		6	6		7	8	
Tretinoin	Mean	27.47	26.22	0.544	32.759	32.675	0.9724
	STD	3.80	3.05		4.234	4.945	
	Range						
13-cis Retinoic Acid	Mean	20.58	19.35	0.475	31.29	33.16	0.6591
	STD	1.94	3.54		5.82	9.43	
	Range						
4-oxo-13 cis Retinoic Acid	Mean	34.19	44.07	0.156	71.81	63.29	0.6227
	STD	11.78	10.47		33.01	32.35	
	Range						

b(4)

In either study, there were no significant differences observed between treatment groups (Atralin Gel 0.05% vs. Retin-A Micro 0.1%) at Day 14 in the area under the concentration time curves for tretinoin, 13-cis-retinoic acid, or 4-oxo-13-cis-retinoic acid. Similarly, there were no significant differences identified between treatment groups in serum level changes from baseline to Day 14 for tretinoin or either of its metabolites.

Conclusion:

The sponsor conducted two head-to-head studies that investigated the systemic exposure under maximal use conditions for Atralin Gel 0.05% versus Retin-A Micro 0.1%. Based on the results, it has been concluded that the systemic exposure of tretinoin and its two metabolites are comparable for the two formulations. As such, the studies establish a clinical bridge for NDA 22-070 (submitted on 9/27/06) to be reviewed as a 505(b)(2) application and the systemic safety of the proposed formulation is expected to be no worse than that for Retin-A Micro 0.1%.

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Pharmacokineticist/DCP III

Team Leader: Sue-Chih Lee, Ph.D. _____

CC: NDA 22-070 (DFS)
HFD-540/Div File
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/s/

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BIOPHARMACEUTICS

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7/26/2007 01:39:06 PM
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Clinical Pharmacology Review

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I. Executive Summary:

In this NDA, the applicant has submitted for approval a 0.05% gel formulation of tretinoin, Atralin Gel 0.05%, for daily topical application to skin with acne lesions in patients 10 years of age and older. This NDA is submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, relying on the Agency's safety finding of the previously approved product, Retin-A Micro (NDA 20-475, Johnson & Johnson), and including nonclinical and clinical studies to support the use of a different formulation.

Retinoids, first shown in the 1970s to be of value for treating acne, are derivatives of vitamin A that prevent comedone formation by normalizing desquamation of follicular epithelium. Tretinoin, a trans-retinoic acid, was the first prescription, retinoid-based therapy available.

To support this application, the sponsor submitted three Phase 1, two Phase 2 and two Phase 3 studies. The three phase 1 studies included human volunteers and were conducted to evaluate the photoallergic, phototoxic, and contact sensitization potential of tretinoin gel, 0.05% vs. tretinoin gel vehicle vs. white petrolatum.

The two phase 2 studies included subjects with severe acne vulgaris and were performed to assess the systemic exposure of tretinoin and its metabolites following maximal topical application of the drug product. These pharmacokinetic studies were similar in design and compared tretinoin (Atralin) gel, 0.05% to tretinoin gel microsphere 0.1% (Retin-A Micro®). The principle difference between the two studies was the age of the enrolled subjects. The population of the first study was restricted to adults, 18 years of age and older; the second study included subjects 13 years of age and older. In both studies, patients with severe acne were randomized to treatment for 14 days with 4 g of either tretinoin gel 0.05% or a microsphere formulation that contained 0.1% tretinoin. Twelve patients (adults, 18 – 37 years of age) were enrolled in the first study, while 16 patients (5 adult patients and 11 pediatric patients aged 13 to 17 years of age) were entered into the second. Blood samples were taken at baseline and immediately prior to treatment on days

1, 5, 10 and 14. On Day 14, the final study day, samples also were taken 1, 2, 4, 6, 8, 10, 12, 16, and 24 hours, post-treatment.

The range of concentration for tretinoin, 13-cis-retinoic acid, or 4-oxo-13-cis-retinoic acid in these two studies at baseline and at the end of Day 14 in patients who applied 4 g (± 0.5 g) of tretinoin gel, 0.05% once daily to face, back and chest are summarized below:

Compound	Study 008		Study 020.CLN.126.024	
	Baseline Conc (ng/ml)	Day 14 Conc (ng/ml)	Baseline Conc (ng/ml)	Day 14 Conc (ng/ml)
RA	0.68-1.62	0.69-1.67	0.74-1.50	0.70-2.88
13-cis	0.67-1.79	0.51-1.24	0.73-1.52	0.61-2.26
4-oxo	0.82-3.62	0.59-3.13	1.66-5.92	1.49-6.96

In either study, there were no significant differences observed between treatment groups at Day 14 in the area under the concentration time curves for tretinoin, 13-cis-retinoic acid, or 4-oxo-13-cis-retinoic acid. Similarly, there were no significant differences identified between treatment groups in serum level changes from baseline to Day 14 for tretinoin or either of its metabolites.

In addition to the two studies described above, blood samples also were collected from all patients at three of 22 investigative centers that participated in study 009. In this 12-week trial, subjects 10 years of age and older with mild to moderate acne were randomized to once daily treatment with approximately 0.5 g of tretinoin gel 0.05%, the vehicle, or a microsphere formulation containing 0.1% tretinoin. Blood samples were obtained at study entry and exit from 89 subjects: 37 patients were treated with tretinoin gel 0.05%; 34 patients received the microsphere formulation; and 18 patients received vehicle. The observed levels of tretinoin and its major metabolites at pre- and post-treatment were in the range reported for endogenous levels of these compounds; however, the sampling times of blood samples were not noted. Therefore, the data are of limited value.

Overview of Efficacy: (see clinical review for details). The Applicant conducted seven clinical studies (three phase 1 trials; two phase 2 trials; and two phase 3 trials) from which adverse event and efficacy data were collected.

The applicant initially planned to demonstrate efficacy based on a single 3 arm study using Retin A Micro 0.1% as an active comparator. That study failed to demonstrate an efficacy bridge to Retin A Micro when non-inferiority of tretinoin gel 0.05% was not statistically achieved. The development plan was amended to conduct a second study which compared tretinoin 0.05% gel to vehicle in order to demonstrate efficacy in two adequate and well-controlled studies over vehicle gel.

The first study (Study 735.126.CL009/01) was a randomized, investigator-blind, three-arm study comparing tretinoin gel 0.05% to vehicle and Retin-A Micro 0.1% Gel in subjects aged 10 years and older. The study enrolled 936 subjects (376 tretinoin gel 0.05%, 376 Retin-A Micro, and 185 vehicle gel) at 22 U.S. centers. Subjects applied treatment once per day at bedtime. Subjects were evaluated at baseline and Weeks 1, 2,

4, 8, 12. The primary efficacy endpoints were the percent reduction in lesion counts in two out of three lesion groups (inflammatory, non-inflammatory, and total), and success on the global severity score (clear or very mild). The study was designed to demonstrate the superiority of tretinoin gel 0.05% to its vehicle and to demonstrate the non-inferiority of tretinoin gel 0.05% to Retin-A Micro on both the lesion count and global severity scale endpoints. The pre-specified non-inferiority margin for all endpoints was 10%. Tretinoin gel 0.05% failed to demonstrate non-inferiority to the comparator, Retin-A Micro 0.1% Gel, but demonstrated superiority to vehicle across all primary endpoints. Agency analysis computing both mean absolute reduction to week 12 and mean percent reduction to week 12 showed p-values of < 0.0004 for both inflammatory and non-inflammatory lesions when tretinoin 0.05% gel was compared to its vehicle. Global severity scores that attained "clear" or "very mild" at week 12 showed a p-value of 0.0022. Global severity scores with at least a 2 grade reduction were also significant with a p-value of 0.0002. The Agency and sponsor agreed at a guidance meeting held December 2, 2004 that a second study demonstrating the superiority of tretinoin gel to vehicle would be needed to establish efficacy.

The second study (Study 20.CLN.126.0418), which compared tretinoin 0.05% gel only to its vehicle, was a randomized, investigator-blind, two-arm study comparing tretinoin 0.05% to vehicle in subjects age 10 and older. This study used the following primary efficacy endpoints: the percent reduction in lesion counts in two out of three lesion groups (inflammatory, non-inflammatory, and total), and success on the global severity score (clear or very mild). The study enrolled 601 subjects (299 tretinoin gel 0.05%, and 302 vehicle gel) at 23 U.S. centers. Subjects applied treatment once per day at bedtime. Subjects were evaluated at baseline and Weeks 1, 2, 4, 8, 12. Agency analysis of data comparing tretinoin gel 0.05% to its vehicle demonstrated superiority of tretinoin gel 0.05% to vehicle for both inflammatory and non-inflammatory lesion counts, with p-values of ≤ 0.0015 for both mean percent and mean absolute reduction in lesion to week 12. Superiority to vehicle was shown in 2 grades reduction in global severity score with a p-value of 0.0021.

As such, efficacy for the proposed gel formulation has been demonstrated.

Overview of Safety: (see clinical review for details). Adverse event data was collected from three phase 1 trials, two phase 2 trials, and two phase 3 trials. A total of 960 subjects were exposed to tretinoin gel 0.05% in the course of these trials.

There were no deaths in any of the clinical studies with tretinoin gel 0.05%. The applicant reported eight subjects with serious adverse events: one in a phase 1 study, and seven in phase 3 studies. None of these were considered to be treatment related.

The most common adverse events in the phase 3 trials were related to local dermatologic effects of topical tretinoin gel 0.05%. Skin dryness, burning, redness, peeling and scaly rash were the most common adverse events. The only non-dermatologic commonly reported adverse events $\geq 5\%$ were nasopharyngitis and headache.

The common side effects of skin irritation, dryness, redness, and peeling are predictable with this drug product and labeling is adequate to address these safety concerns. All of these events appear to be related to the dose of tretinoin with Retin-A Micro 0.1% Gel having the highest rates followed by tretinoin gel 0.05% and then by vehicle. There were no significant non-skin related adverse events demonstrated in the development program.

As part of the safety assessment, 3 studies investigated the levels of tretinoin and its major metabolites (13-cis-retinoic acid and 4-oxo-13-cis-retinoic acid) in acne patients who were treated with tretinoin 0.05% gel as described above.

A. Recommendations:

Based on this review, NDA 22-070 is acceptable from a Clinical Pharmacology perspective provided that a mutually satisfactory agreement on the language of the package insert can be reached between the sponsor and the Agency. A review of the PK data in this submission has resulted in certain changes in the appropriate sections of the product label. The suggested changes have been incorporated in the section "Labeling Comments".

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III. Question-Based Review

A. General Attributes

1. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product? What is the proposed mechanism of drug action and therapeutic indications? What is the proposed dosage and route of administration?

Drug substance:

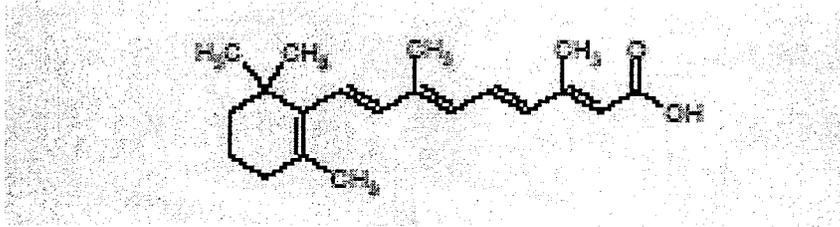
Generic name: Tretinoin, all-trans retinoic acid

Chemical name: 3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid

CAS registry number: 302-79-4

Molecular formula/molecular weight: $C_{20}H_{28}O_2$ / MW=300.44

Structure:



b(4)

Drug Product: (Code name: _____ Gel)

The subject drug product of this application is Tretinoin Gel 0.05% w/w. The product is a topically applied semisolid based on U.S. Patent 5,670,547. Currently, the sponsor has developed only one (1) dosage strength. The active ingredient tretinoin is _____ by Carbomer 940 (trade name _____ collagen and sodium hyaluronate are included as _____. The _____ for the product are Methylparaben, Propylparaben and Benzyl Alcohol. Butylated Hydroxytoluene (BHT) is added as an _____

The following table lists the quantitative composition of the drug product and shows the functions and quality grades of each chemical ingredient.

Composition of Tretinoin Gel 0.05% w/w

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Component	Quality Standard	Function	Grams per tube
Tretinoin	USP	Drug Substance	0.0225
Soluble Collagen (Note 1)	Manufacturer's specification		
Sodium Hyaluronate-LP	Manufacturer's specification		
Octoxynol-9	NF		
Butylated Hydroxytoluene	NF		
Methylparaben	NF		
Propylparaben	NF		
Benzyl Alcohol	NF		
Carbomer 940 (Note 2)	NF, PhEur		
Trolamine	NF		
Glycerin	USP		
Purified Water to	USP		

b(4)

Note 1 - The trade name for Soluble Collagen is Pancogene® Marin. Soluble Collagen contains soluble collagen from marine (non-bovine) sources in an aqueous base. The rate of incorporation given relates to collagen content.

Pancogene Marin also contains preservatives

Note 2 - The trade name for the grade of Carbomer 940 used in Tretinoin Gel, 0.05%, is _____ This grade of Carbomer 940 meets the ICH and PhEur specifications of NMT _____

b(4)

Three ingredients are noncompendial: Pancogene® Marin (which contains _____% collagen derived from teleost fish skin), sodium hyaluronate (which the sponsor stated was a _____ at the pre-IND meeting), and octoxynol-9. The first two are claimed to act as _____ and the third is listed as a _____ The formulation for Pancogene® Marin is not provided. Octoxynol-9 is listed in the National Formulary, but the sponsor previously stated the NF grade material is not commercially available. Sodium hyaluronate is present in the approved drug product Solaraze gel at _____

b(4)

Proposed Dosage and Route of administration: Tretinoin gel 0.05% is to be applied once daily at bedtime to skin where acne lesions appear, using a thin layer to cover the entire affected area. The gel should be kept away from the eyes, mouth, paranasal creases, and mucous membranes.

Mechanism of action: All-*trans*-retinoic acid (tretinoin; vitamin A acid) is a naturally occurring metabolite of vitamin A. The major interest in all-*trans*-retinoic acid in dermatology stems from its important actions in the skin when applied topically as opposed to systemically. It is of particular interest in the topical treatment of acne

vulgaris because of its significant effects on epidermal differentiation, keratin metabolism, repair and inflammatory processes, and its comedolytic activity.

Although the exact mechanism by which retinoids are beneficial in acne is unknown, current evidence suggests the therapeutic effect of tretinoin relates to its ability to modify abnormal follicular keratinization. Tretinoin is thought to have an effect primarily against noninflammatory lesions by normalizing follicular keratinization. Comedones form in follicles with an excess of keratinized epithelial cells. Tretinoin promotes detachment of cornified cells and the enhanced shedding of corneocytes from the follicle. By increasing the mitotic activity of the follicular epithelia, tretinoin also increases the turnover rate of thin, loosely-adherent corneocytes. Through these actions, the comedo contents are extruded and the formation of the microcomedo, the precursor lesion of acne vulgaris, is reduced.

Electron microscopic evaluations of human skin treated with all-*trans*-retinoic acid have shown a reduction in the keratin precursors, notably the tonofilaments, a reduction in the numbers and size of the desmosomes and an increase in the number of keratinosomes

Topical application of all-*trans*-retinoic acid increases epidermal mitotic activity, reduces the formation of keratins, induces cell differentiation and tissue repair, and is comedolytic in both laboratory animals and man.

B. General Clinical Pharmacology

1. What is the basis for selecting the dose in Tretinoin topical gel?

Dose-ranging studies were not conducted. Various concentrations of tretinoin have been approved in the United States since 1971 in several formulations including creams, liquids, gels, microsponges, and as both a cream and a gel within a liquid polymer matrix.

Tretinoin is currently available as a 0.05% concentration in cream and solution (Retin A, and generics). Tretinoin is available as a gel formulations in concentrations of 0.01%, 0.025%, and in Microsphere products at 0.04% and 0.01%. Tretinoin has long been marketed in various topical formulations and concentrations for the treatment of acne vulgaris, in concentrations from 0.01% to 0.1%. Currently marketed formulations of tretinoin are dosed once daily in the evenings.

Therefore, it appears that the sponsor empirically selected dose and dosing of their product based on the following marketed tretinoin gel products:

Avita Gel 0.025%	NDA 20-400	1/29/1998
Retin A Gel 0.025%	NDA 17-579	4/18/1975
Tretinoin Gel 0.025%	ANDA 75-529	2/22/2000
Retin A Gel 0.01%	NDA 17-955	10/17/1978

Tretinoin Gel 0.01%	ANDA 75-589	6/11/2002
Retin A Micro Gel 0.1%	NDA 20-475	2/1/1997
Retin A Micro Gel 0.04%	NDA 20-475	5/10/2002
Ziana Gel (Clindamycin phosphate 1.2%/tretinoin gel 0.025%)	NDA 50-802	11/7/2006

2. What is the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers measured in clinical studies?

The primary efficacy endpoints were the reduction in lesion counts in two out of three lesion groups (inflammatory, non-inflammatory, and total), and success on the global severity score (clear or very mild).

3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Yes.

4. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

Only one dose and dosing frequency was studied in the clinical trials. No exposure-response relationship was characterized.

5. What are the basic PK parameters?

C_{max} , AUC and $t_{1/2}$ values have been used as basic PK parameters.

6. What was the PK study designs and outcome?

The two phase 2 studies included subjects with moderately severe acne vulgaris and were performed to assess the systemic exposure potential of tretinoin and its metabolites following maximal topical application of the drug product. These pharmacokinetic studies were similar in design and compared tretinoin gel, 0.05% to tretinoin gel microsphere 0.1% (Retin-A Micro®). The principle difference between the two studies was the age of the enrolled subjects. The population of the first study was restricted to adults, 18 years of age and older; the second study included subjects 13 years of age and older. In both studies, patients with severe acne were randomized to treatment for 14 days with 4 g of either tretinoin gel 0.05% or a microsphere formulation that contained 0.1% tretinoin. Twelve patients (adults, 18 – 37 years of age) were enrolled in the first study, while 16 patients (5 adult patients and 11 pediatric patients aged 13 to 17 years of age) were entered into the second. Blood samples were taken at baseline and immediately prior to treatment on days 1, 5, 10 and 14. On Day 14, the final study day, samples also were taken 1, 2, 4, 6, 8, 10, 12, 16, and 24 hours, post-treatment.

The ranges of concentration for tretinoin, 13-cis-retinoic acid, or 4-oxo-13-cis-retinoic acid in these two studies at baseline and at the end of Day 14 in patients who applied

applied 4 g (± 0.5 g) of tretinoin gel, 0.05% once daily to face, back and chest are summarized below:

Compound	Study 008		Study 020.CLN.126.024	
	Baseline Conc (ng/ml)	Day 14 Conc (ng/ml)	Baseline Conc (ng/ml)	Day 14 Conc (ng/ml)
RA	0.684-1.62	0.686-1.67	0.738-1.499	0.696-2.876
13-cis	0.673-1.79	0.507-1.24	0.729-1.517	0.611-2.260
4-oxo	0.817-3.62	0.588-3.13	1.655-5.917	1.489-6.956

Although some patients had increased concentrations of tretinoin or its metabolites over baseline values, no consistent increase in these concentrations were observed across patients.

There were no significant differences observed between treatment groups at Day 14 in the area under the concentration time curves for tretinoin, 13-cis-retinoic acid, or 4-oxo-13-cis-retinoic acid. Similarly, there were no significant differences identified between treatment groups in serum level changes from baseline to Day 14 for tretinoin or either of its metabolites.

C. Intrinsic Factors

1. **What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?**

The sponsor attempted to evaluate gender, age, race and ethnicity effect pertaining to efficacy in the Phase 3 trials. There was no evidence of clinically significant effect of any of these parameters on efficacy.

Subjects 10-65 years of age were enrolled in the pivotal trials, and the mean age of study subjects was approximately 19 years in two phase 3 safety and efficacy studies. The sponsor has requested a waiver for patients under the age of 10 years. Of the 1537 subjects enrolled in the 2 phase 3 studies, there were 14 (1%) 10 year-olds and 32 (2%) 11 year-olds.

A waiver is recommended for patients under the age of 12 years, since acne vulgaris does not typically occur in the younger, pre-pubertal age group. The reference listed drug, as well as all other topical tretinoin products for acne, is all approved for patients 12 years and older.

No subjects older than 65 years of age were included in the phase 3 studies and the labeling acknowledges that safety and effectiveness in a geriatric population have not been established.

D. Extrinsic Factors

1. **What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?**

No pharmacokinetic drug interactions with tretinoin have been identified from review of the published literature. In view of the low absorption of topically applied tretinoin, pharmacokinetic drug interactions are unlikely.

No other interaction study has been performed by the sponsor. However, labeling from the comparator product, Retin A Micro 0.1% Gel includes following drug interactions which is also included in the tretinoin 0.05% gel proposed labeling:

“Concomitant topical medication, medicated or abrasive soaps and cleansers, products that have a strong drying effect, products with high concentrations of alcohol, astringents, or spices should be used with caution because of possible interaction with tretinoin. Particular caution should be exercised with the concomitant use of topical over-the-counter acne preparations containing benzoyl peroxide, sulfur, resorcinol, or salicylic acid with Atralin Gel. It also is advisable to allow the effects of such preparations to subside before use of Atralin Gel is begun.”

b(4) A novel excipient included in the drug product formulation is Pancogene® Marin, which contain: ~~fish~~ collagen derived from teleost fish skin. It is purported to act as a ~~filler~~ in the formulation. This contains fish-derived collagen and individuals with a sensitivity to the proteins present in teleost fish (a large group of fishes with bony skeletons, including most common fishes; distinct from cartilaginous fishes, such as sharks, rays and skates), may be susceptible to sensitization reactions following the use of this product. This possibility may be handled by stating in the label that the product contains fish collagen and that sensitized or fish-allergic individuals should use with caution.

E. Analytical Section

- 1) **How are the active moieties identified and measured in the blood in the clinical pharmacology and biopharmaceutics studies? What bioanalytical methods are used to assess concentrations?**

Human plasma contains retinoids as endogenous compounds at low concentrations (approximately 1.00 – 5.00 ng/mL). Therefore, an assay was developed to monitor systemic exposure of these retinoids both from endogenous and externally applied sources without interfering with each other. Spiked calibration samples were used to calculate retinoid concentrations in unknown study samples.

To that end, human plasma for this assay was stripped or “scrubbed” of endogenous retinoids by a proprietary method. The scrubbed plasma matrix was used as a surrogate to

prepare calibration standards and QC samples in order to investigate the assay for precision, accuracy, and ruggedness. Heparinized human plasma containing RA, 13-cis-RA, 4-oxo-13-cis-RA, and the internal standard, _____ was extracted with an organic solvent mixture. Following centrifugation, transfer of the organic layer, and evaporation, an aliquot of the reconstituted extract was injected onto a _____ LC-MS-MS equipped with an HPLC column. Study samples were assayed without this scrubbing treatment and concentrations calculated directly from the calibration curve. The mean back-calculated concentration of the analytes in blank plasma (before application of study medication) was subtracted from the mean back-calculated concentration of the analytes in corresponding plasma samples (collected following application of study medication).

The method was validated over the range of 0.500 to 20.0ng/mL for all-trans-retinoic acid, 13-cis-retinoic acid, and 4-oxo-13-cis-retinoic acid, based on the analysis of 0.500 mL of plasma. The assay procedure was found to be linear over the range of 0.500 to 20.0 ng/mL for all three analytes.

Precision and accuracy at the LLOQ were verified by analyzing at least three samples at the lowest standard concentration (0.500 ng/mL for all three analytes) on each day of validation. Interday precision for 13-cis-RA was out of the 20% LLOQ acceptance criteria at _____. Absolute deviation was 3.1%. Three out of four validation were within acceptance criteria of _____ for intraday precision and accuracy. This suggests that the LLOQ is acceptable over multiple runs using a wider acceptance criteria. The wider acceptance criteria was approved by the Laboratory Director. The intraday precision and accuracy at the LLOQ were verified by analyzing six samples at the lowest standard concentration during four separate days of validation. Intraday precision for RA in one run was outside the acceptance criteria of _____ However, intraday precision for the other three days was within 15%. Intraday accuracy for 13-cis-RA was 31.9% in one run. However, intraday accuracy for the other three days was less than 15%. A wider acceptance criteria was approved by the Laboratory Director, due to the technical difficulty of this assay.

b(4)

At least three samples from each QC pool (high, medium, and low) were processed on each day of validation. The interday and intraday precision and accuracy were all within acceptance criteria.

Benchmark, freeze/thaw, and extract stability studies in heparinized human plasma were performed. Three replicates from high (16.0 ng/mL for all three analytes), medium (8.00 ng/ml for all three analytes) and low (1.50 ng/mL for all three analytes) QC pools were tested. At least two-thirds of the stability samples in each pool were within $\pm 15\%$ of their theoretical concentrations. Based on these findings, it is concluded that RA, 13-cis-RA, and 4-Oxo-13-cis-RA are stable under these operating conditions. Average recovery data of the internal standard, _____ was 82.4%.

b(4)

OCPB labeling recommendations

The following changes are suggested. ABC suggests deletion of text and ABC suggests insertion of new text:

12.1 Pharmacokinetics

In two (2) studies, the plasma levels of tretinoin and its major metabolites (13-cis-retinoic acid and 4-oxo-13-cis-retinoic acid) were investigated in a total of 14 patients (age: 13 – 25 years) with severe acne who applied 4 g (± 0.5 g) of TRADENAME Gel once daily to face, back and chest. Blood samples were taken at baseline and immediately prior to treatment on days 1, 5, 10 and 14. On Day 14, the final study day, samples also were taken 1, 2, 4, 6, 8, 10, 12, 16, and 24 hours, post-treatment.

b(4)

The plasma concentrations of tretinoin and its metabolites could be measured (LOQ = 0.5 ng/mL for all three analytes) in all patients at all time points. The range of plasma concentrations of tretinoin and its metabolites, 13-cis-retinoic acid and all-trans-4-oxo-retinoic acid at baseline and after multiple once daily applications of TRADENAME Gel, 0.05% for 14 days are given in the table below. Although some patients had increased concentrations of tretinoin or its metabolites over baseline values, no consistent increase in these concentrations were observed across patients.

b(4)

Compound	Baseline Concentration Range (ng/ml)	Day 14 Concentration Range (ng/ml)
Tretinoin	0.68-1.62	0.69-2.88
13-cis-retinoic acid	0.67-1.79	0.51-2.26
4-oxo-13-cis-retinoic acid	0.82-5.92	0.59-6.96

b(4)

VI. Appendices

- A. Package Insert (annotated)
 - B. Clinical Pharmacology Individual Study Reviews
 - C. Cover Sheet and OCP Filing/Review Form
-

Tapash K. Ghosh, Ph.D.
Pharmacokineticist/DCP III

Team Leader: Sue-Chih Lee, Ph.D. _____

CC: NDA 22-070 (DFS)
HFD-540/Div File
HFD-540/CSO/Baurlein

3 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Appendix B

NDA: 22-070/Study 735.126.CL008/01

Study Dates: Nov, 01 – Dec, 01

b(4)

Absorption Evaluation of _____^M (Tretinoin) Gel, 0.05% and RETIN-A[®] (Tretinoin) Micro, 0.1% Following Maximum Exposure with Multiple Applications in Subjects with Acne Vulgaris

Objectives: To investigate the absorption and safety of this new formulation of tretinoin, _____^M (Tretinoin) Gel, 0.05% compared to RETIN-A[®] (Tretinoin) Micro, 0.1% following maximum exposure with multiple applications in subjects with more severely involved acne vulgaris.

b(4)

Study Design: This study was conducted as a single-center, multiple-dose, randomized, controlled, investigator- blinded, study to assess absorption and safety of _____^A (Tretinoin) Gel, 0.05%. The two test groups as described below were involved:

	_____ ^A	RETIN-A [®]
Number of Subjects	6	6
Age (Years)		
Mean	19.35	22.80
STD	0.82	7.50
Range		
Gender		
Male	3 (50%)	4 (67%)
Female	3 (50%)	2 (33%)

b(4)

Study medication was applied by a gloved clinic staff technician once daily for 14 days to the entire face including the nose and chest, back, and neck and excluding the eyelids and lips by “rubbing” the material in until the test article has “disappeared”. A once-daily application of the test articles was chosen based on the approved labeling for RETIN-A[®] (Tretinoin) Micro, 0.1% for the treatment of acne vulgaris. One application consisted of an average of 4 g of test article, determined by weighing to be within a range of 3.5 g – 4.5 g. A 4 g application was selected based on surface area of the face, back and chest. It is estimated that these areas equal about 1000 to 2500 cm² and to cover these areas entirely, approximately 4 g ± 0.5 g is needed. Blood samples were collected prior to study medication administration at baseline, and days 1, 5, 10, and 14 to determine plasma concentrations of tretinoin and metabolites. After the final dose on Day 14, blood samples were collected at 1, 2, 4, 6, 8, 10, 12, 16, and 24 hours post dosing.

Analytical Method

Human plasma contains retinoids as endogenous compounds at low concentrations (approximately 1.00 – 5.00 ng/mL). Therefore, an assay was developed to monitor systemic exposure of these retinoids both from endogenous and externally applied sources without interfering with each other. Spiked calibration samples were used to calculate retinoid concentrations in unknown study samples.

To that end, human plasma for this assay was stripped or “scrubbed” of endogenous retinoids by a proprietary method. The scrubbed plasma matrix was used as a surrogate to prepare calibration standards and QC samples in order to interrogate the assay for precision, accuracy, and ruggedness. Heparinized human plasma containing RA, 13-cis-RA, 4-oxo-13-cis-RA, and the internal standard, [redacted], was extracted with an organic solvent mixture. Following centrifugation, transfer of the organic layer, and evaporation, an aliquot of the reconstituted extract was injected onto a [redacted] LC-MS-MS equipped with an HPLC column. Study samples were assayed without this scrubbing treatment and concentrations calculated directly from the calibration curve. The mean back-calculated concentration of the analytes in blank plasma (before application of study medication) was subtracted from the mean back-calculated concentration of the analytes in corresponding plasma samples (collected following application of study medication).

b(4)

The method was validated for a range of 0.500 to 20.0ng/mL for all-trans-retinoic acid, 13-cis-retinoic acid, and 4-oxo-13-cis-retinoic acid, based on the analysis of 0.500 mL of plasma. The assay procedure was found to be linear over the range of 0.500 to 20.0 ng/mL for all three analytes.

Results: The range of concentration of for tretinoin, 13-cis-retinoic acid, or 4-oxo-13-cis-retinoic acid at baseline and at the end of Day 14 in patients who applied applied 4 g (± 0.5 g) of tretinoin gel, 0.05% once daily to face, back and chest are summarized below:

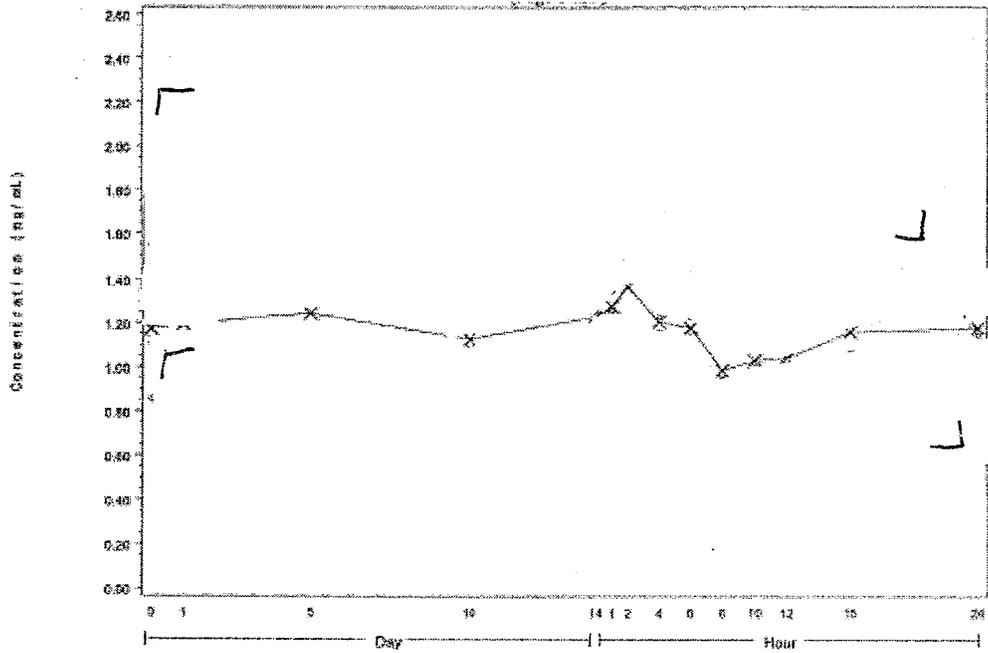
Compound	Study 008	
	Baseline Conc (ng/ml)	Day 14 Conc (ng/ml)
RA	0.684-1.62	0.686-1.67
13-cis	0.673-1.79	0.507-1.24
4-oxo	0.817-3.62	0.588-3.13

Tretinoin Concentration Levels:

Individual and Mean Tretinoin Concentration Levels (ng/ml) from [redacted] (Tretinoin) Gel, 0.05% and RETIN-A[®] (Tretinoin) Micro, 0.1% are presented in the following Figures 008.1 and 008.2 respectively. The repeated measures analysis of variance resulted in an insignificant overall treatment effect ($p=0.238$) and an insignificant

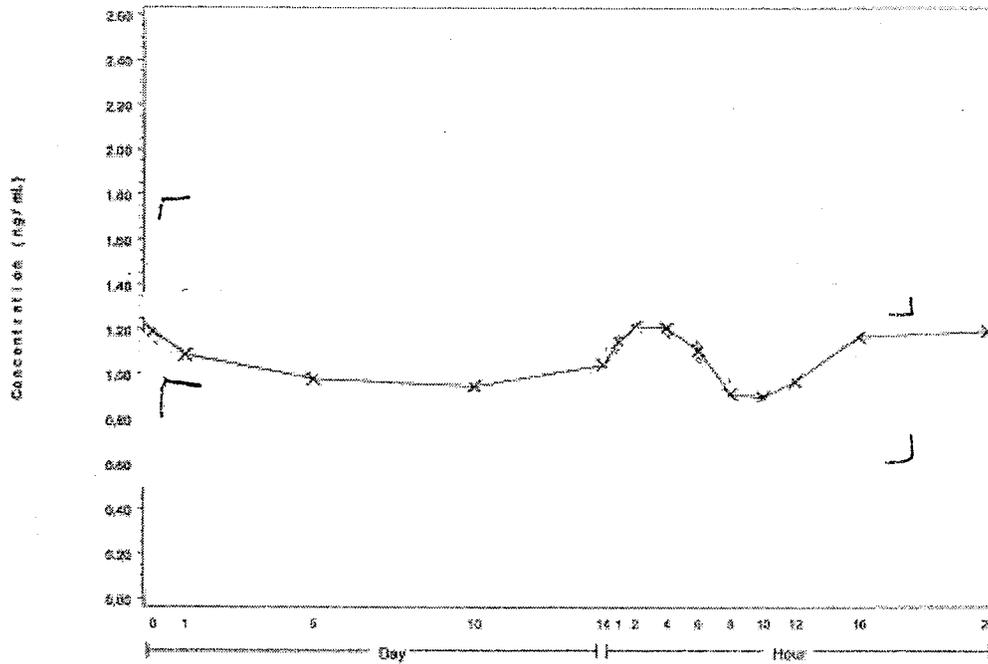
b(4)

treatment-by-time interaction ($p=0.755$). At each time interval, there was not a significant difference between treatment groups in average concentration levels ($p>0.084$).



b(4)

Figure 008.1: Individual and Mean Tretinoin Concentration Levels (ng/ml): Treatment:
 ——— M (Tretinoin) Gel, 0.05%



b(4)

Figure 008.2: Individual and Mean **Tretinoin** Concentration Levels (ng/ml): Treatment: *RETIN-A[®] (Tretinoin) Micro, 0.1%*

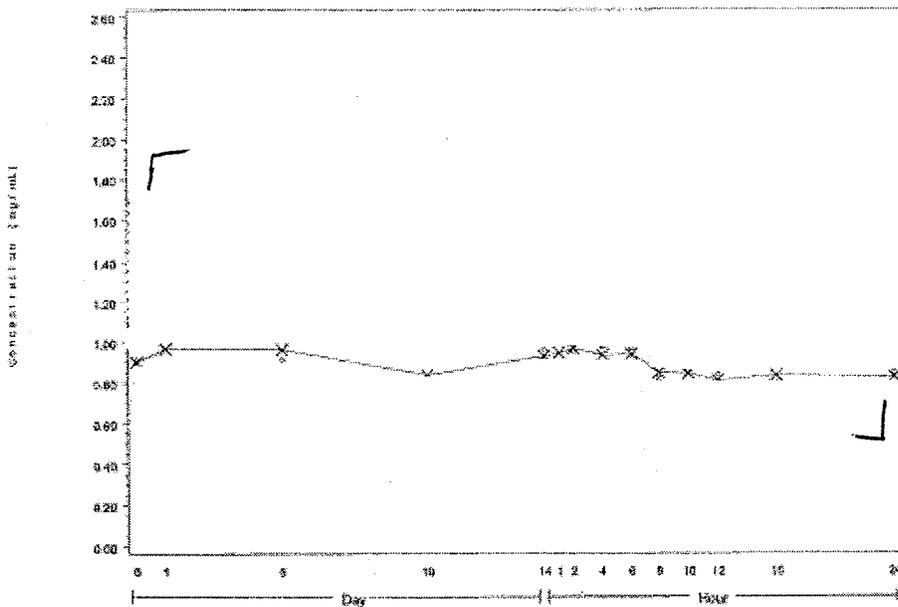
b(4)

Within the *(Tretinoin) Gel, 0.05%* treatment group, concentration levels ranged from ~ 10 ng/mL across timepoints. Within the *RETIN-A[®] (Tretinoin) Micro, 0.1%* treatment group, concentration levels range from 0.5 to 1.7 ng/mL across timepoints. No effect of treatment on circulating levels of Tretinoin were found.

13-Cis-Retinoic Acid Concentration Levels

Individual and Mean 13-Cis-Retinoic Acid Concentration Levels (ng/ml) from *(Tretinoin) Gel, 0.05%* and *RETIN-A[®] (Tretinoin) Micro, 0.1%* are presented in the following Figures 008. 3 and 008.4 respectively. The repeated measures analysis of variance resulted in an insignificant overall treatment effect ($p=0.626$) and an insignificant treatment-by-time interaction ($p=0.797$). At each time interval, there was not a significant difference between treatment groups in average concentration levels ($p>0.107$).

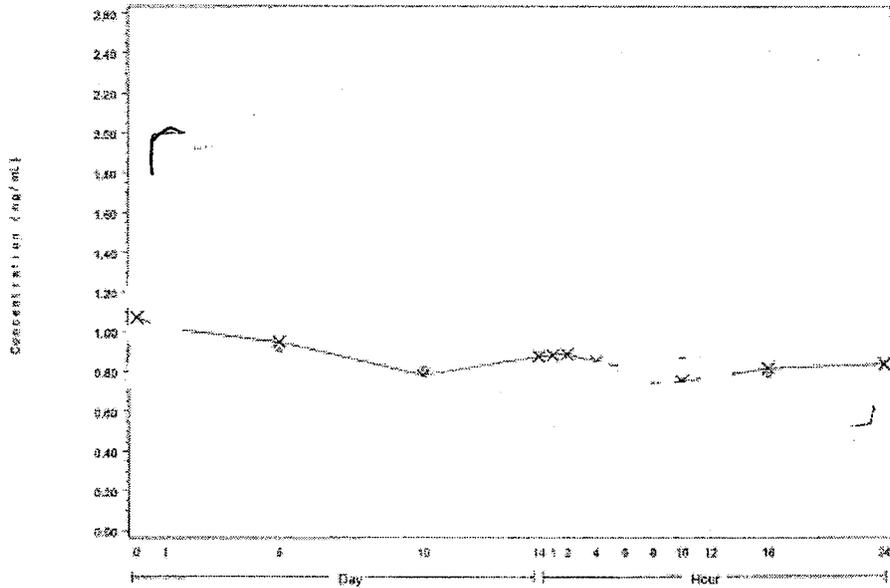
b(4)



b(4)

Figure 008.3: Individual and Mean **13-Cis-Retinoic Acid** Concentration Levels (ng/ml): Treatment: *(Tretinoin) Gel, 0.05%*

b(4)



b(4)

Figure 008.4: Individual and Mean 13-Cis-Retinoic Acid Concentration Levels (ng/ml): Treatment: RETIN-A[®] (Tretinoin) Micro, 0.1%

Within the 10^{-5} M (Tretinoin) Gel, 0.05% treatment group, concentration levels ranged from 10^{-4} to 10^{-3} ng/mL across time points. Within the RETIN-A[®] (Tretinoin) Micro, 0.1% treatment group, concentration levels ranged from 0.5 to 1.8 ng/mL across timepoints. No effect of treatment on circulating levels of 13-Cis-Retinoic Acid were found.

b(4)

4-Oxo 13-Cis-Retinoic Acid Concentration Levels

Individual and Mean 4-Oxo-13-Cis-Retinoic Acid Concentration Levels (ng/ml) from 10^{-5} M (Tretinoin) Gel, 0.05% and RETIN-A[®] (Tretinoin) Micro, 0.1% are presented in the following Figures 008.5 and 008.6 respectively. The repeated measures analysis of variance resulted in an insignificant overall treatment effect ($p=0.150$) and an insignificant treatment-by-time interaction ($p=0.067$). With the exception of baseline, there was not a significant difference between treatment groups in average concentration levels ($p>0.071$) at each time interval. At baseline, there was a significantly higher mean concentration in the RETIN-A[®] (Tretinoin) Micro, 0.1% treatment group compared to 10^{-5} M (Tretinoin) Gel, 0.05% ($p=0.031$).

b(4)

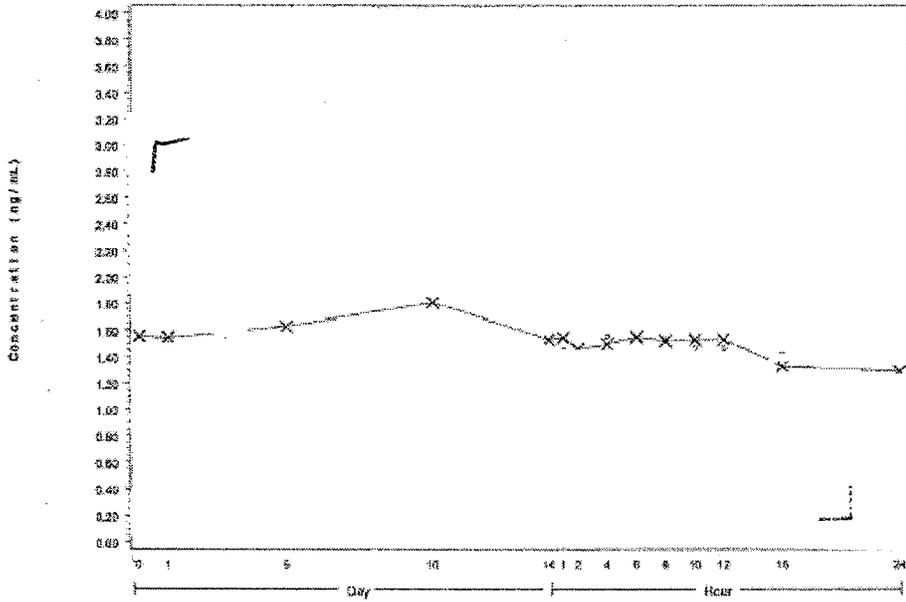


Figure 008.5: Individual and Mean 4-Oxo-13-Cis-Retinoic Acid Concentration Levels (ng/ml): Treatment: ---^{TM} (Tretinoin) Gel, 0.05%

b(4)

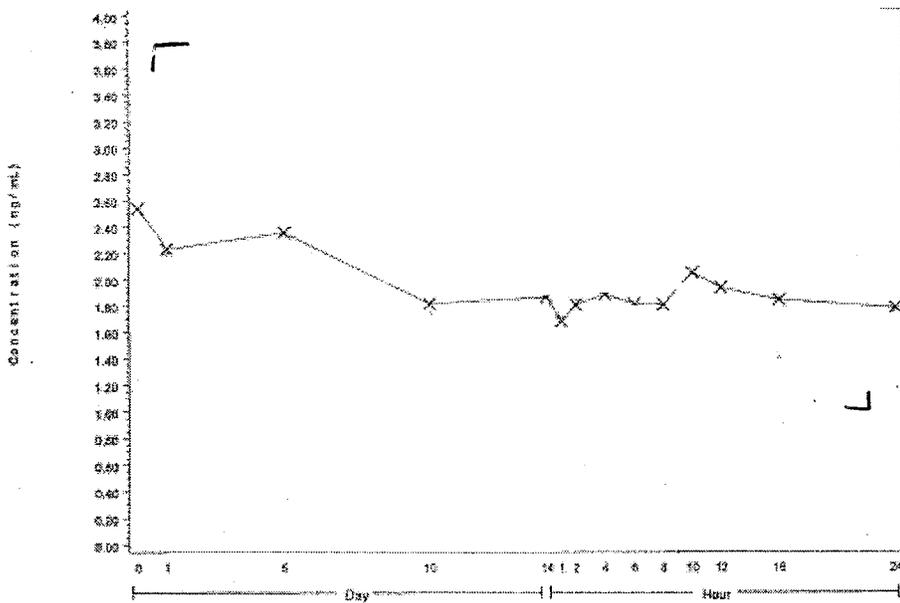


Figure 008.6: Individual and Mean 4-Oxo-13-Cis-Retinoic Acid Concentration Levels (ng/ml): Treatment: RETIN-A[®] (Tretinoin) Micro, 0.1%

b(4)

Within the ---^{A} (Tretinoin) Gel, 0.05% treatment group, concentration levels ranged from --- to --- ng/mL across timepoints. Within the RETIN-A[®] (Tretinoin) Micro, 0.1% treatment group, concentration levels ranged from 1.0 to 3.8 ng/mL across

timepoints. No effect of treatment on circulating levels of 4-Oxo 13-Cis-Retinoic were found.

Day 14 Area Under the Concentration Time Curve

Table 008.1 summarizes the analysis of the Day 14 area under the concentration time curve (AUC) for Tretinoin, 13-Cis-Retinoic Acid, and 4-Oxo 13-Cis-Retinoic Acid. There was not a significant difference between groups for any of the metabolites (p>0.156).

Table 008.1: Analysis of Day 14 Area Under the Concentration Time Curve (ng/ml. hours) (All Subjects)

		RETIN-A [®]	P-Value ^a
Number of Subjects	6	6	
Tretinoin			
Mean	27.47	26.22	0.544
STD	3.80	3.05	
Range			
13 Cis-Retinoic Acid			
Mean	20.38	19.35	0.475
STD	1.94	3.54	
Range			
4 Oxo 13 Cis-Retinoic Acid			
Mean	34.18	44.07	0.156
STD	11.78	10.47	
Range			

^a P-value from a one-way analysis of variance with factor of treatment.

b(4)

CONCLUSIONS

This study measured the concentration levels of tretinoin and relevant metabolites in subjects treated with [™](Tretinoin) Gel, 0.05% or RETIN-A[®] (Tretinoin) Micro, 0.1%. The observed levels of tretinoin and relevant metabolites noted before and after treatment were in the range reported (1 – 5 ng/ml) for endogenous levels of these compounds. Levels achieved with [™](Tretinoin) Gel, 0.05% were no greater than levels noted with RETIN-A[®] (Tretinoin) Micro, 0.1%.

b(4)

NDA: 22-070/Study 20.CLN.126.024

Study Dates: Aug, 02 – Feb, 03

Absorption Evaluation of ~~_____~~^M (Tretinoin) Gel, 0.05% and RETIN-A[®] (Tretinoin) Micro, 0.1% Following Maximum Exposure with Multiple Applications in Subjects with Acne Vulgaris

b(4)

Objectives: To investigate the absorption and safety of this new formulation of tretinoin, ~~_____~~^M (Tretinoin) Gel, 0.05% compared to RETIN-A[®] (Tretinoin) Micro, 0.1% following maximum exposure with multiple applications in subjects with more severely involved acne vulgaris.

b(4)

Study Design: This study was conducted as a single-center, multiple-dose, randomized, controlled, investigator- blinded, study to assess absorption and safety of ~~_____~~TM (Tretinoin) Gel, 0.05%. The two test groups as described below were involved:

b(4)

Characteristic	Statistic	_____	RETIN-A*	Total
Number of Subjects		8	8	16
Age (Years)	Number of Subjects	8	8	16
	Mean	18.63	19.38	19.00
	Median	16.50	16.50	16.50
	Standard Dev.	4.63	7.07	5.79
	Range			
Gender	Number of Subjects n(%)	8	8	16
	Female	2 (25.0)	4 (50.0)	6 (37.5)
	Male	6 (75.0)	4 (50.0)	10 (62.5)

Study medication was applied by a gloved clinic staff technician once daily for 14 days to the entire face including the nose and chest, back, and neck and excluding the eyelids and lips by "rubbing" the material in until the test article has "disappeared". A once-daily application of the test articles was chosen based on the approved labeling for RETIN-A[®] (Tretinoin) Micro, 0.1% for the treatment of acne vulgaris. One application consisted of an average of 4 g of test article, determined by weighing to be within a range of 3.5 g – 4.5 g. A 4 g application was selected based on surface area of the face, back and chest. It is estimated that these areas equal about 1000 to 2500 cm² and to cover these areas entirely, approximately 4 g ± 0.5 g is needed. Blood samples were collected prior to study medication administration at baseline, and days 1, 5, 10, and 14 to determine plasma

concentrations of tretinoin and metabolites. After the final dose on Day 14, blood samples were collected at 1, 2, 4, 6, 8, 10, 12, 16, and 24 hours post dosing. Samples were assayed using the method described in Study CL008.01

Results: The range of concentration of for tretinoin, 13-cis-retinoic acid, or 4-oxo-13-cis-retinoic acid at baseline and at the end of Day 14 in patients who applied applied 4 g (± 0.5 g) of tretinoin gel, 0.05% once daily to face, back and chest are summarized below:

Compound	Study 20.CLN.126.024	
	Baseline Conc (ng/ml)	Day 14 Conc (ng/ml)
RA	0.738-1.499	0.696-2.876
13-cis	0.729-1.517	0.611-2.260
4-oxo	1.655-5.917	1.489-6.956

Tretinoin Concentration Levels:

Individual and Mean Tretinoin Concentration Levels (ng/ml) from  (Tretinoin) Gel, 0.05% and RETIN-A[®] (Tretinoin) Micro, 0.1% are presented in the following Figure 024.1. The repeated measures analysis of variance resulted in an insignificant overall treatment effect ($p=0.3850$) and an insignificant treatment-by-time interaction ($p=0.7099$). At each time interval, there was not a significant difference between treatment groups in average concentration levels ($p>0.1097$).

b(4)

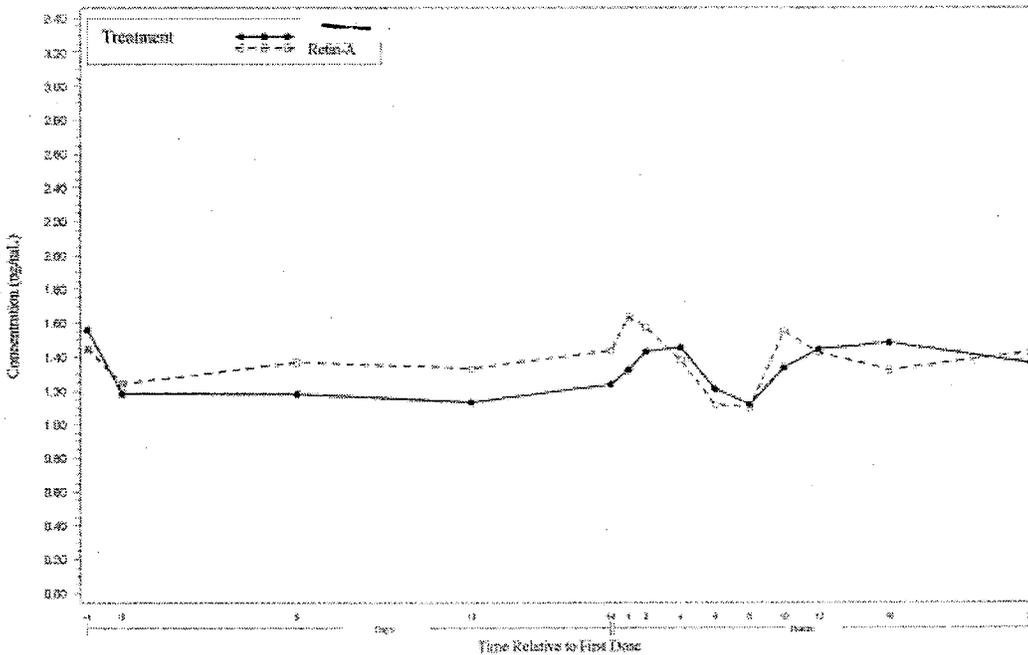


Figure 024.1 Mean RA Trough Concentration Levels (ng/mL)

Within the _____TM (Tretinoin) Gel, 0.05% treatment group, concentration levels ranged from _____ ng/mL across timepoints. Within the RETIN-A[®] (Tretinoin) Micro, 0.1% treatment group, concentration levels range from _____ ng/mL across timepoints. No effect of treatment on circulating levels of Tretinoin were found.

b(4)

13-Cis-Retinoic Acid Concentration Levels

Individual and Mean 13-Cis-Retinoic Acid Concentration Levels (ng/ml) from _____TM (Tretinoin) Gel, 0.05% and RETIN-A[®] (Tretinoin) Micro, 0.1% are presented in the following Figure 024.2. The repeated measures analysis of variance resulted in an insignificant overall treatment effect ($p=0.7506$) and an insignificant treatment-by-time interaction ($p=0.7284$). At each time interval, there was not a significant difference between treatment groups in average concentration levels ($p>0.107$).

b(4)

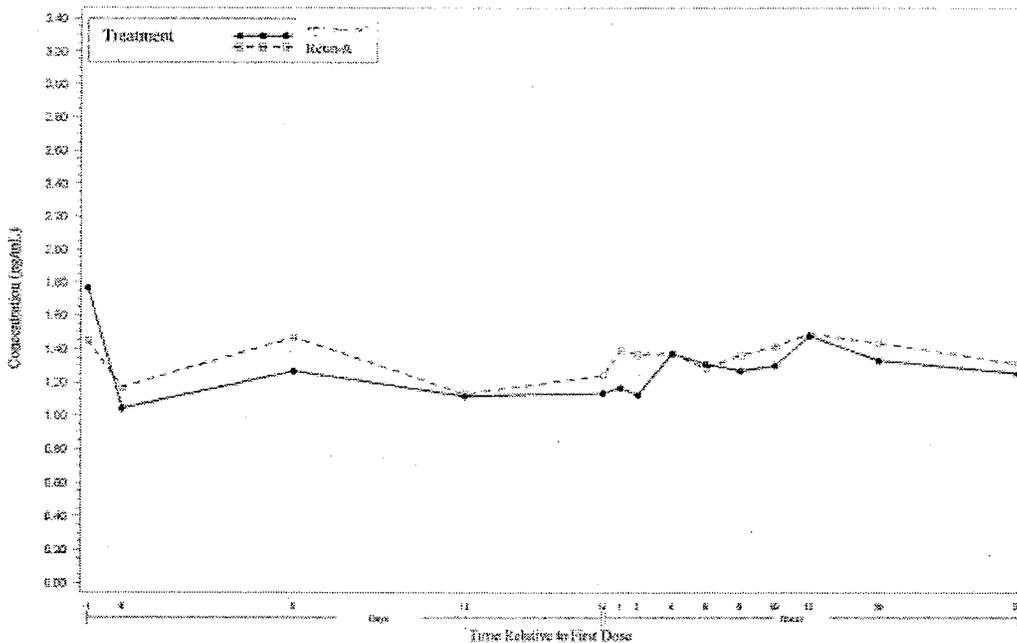


Figure 024.2 Mean 13-cis-Retinoic Acid Trough Concentration Levels (ng/mL)

Within the _____TM (Tretinoin) Gel, 0.05% treatment group, concentration levels ranged from _____ ng/mL across timepoints. Within the RETIN-A[®] (Tretinoin) Micro, 0.1% treatment group, concentration levels ranged from _____ ng/mL across timepoints. No effect of treatment on circulating levels of 13-Cis-Retinoic Acid were found.

b(4)

4-Oxo 13-Cis-Retinoic Acid Concentration Levels

Individual and Mean 4-Oxo-13-Cis-Retinoic Acid Concentration Levels (ng/ml) from (Tretinoin) Gel, 0.05% and RETIN-A® (Tretinoin) Micro, 0.1% are presented in the following Figure 024.3. The repeated measures analysis of variance resulted in an insignificant overall treatment effect (p=0.7342) and an insignificant treatment-by-time interaction (p=0.2272). With the exception of baseline, there was not a significant difference between treatment groups in average concentration levels (p>0.195) at each time interval.

b(4)

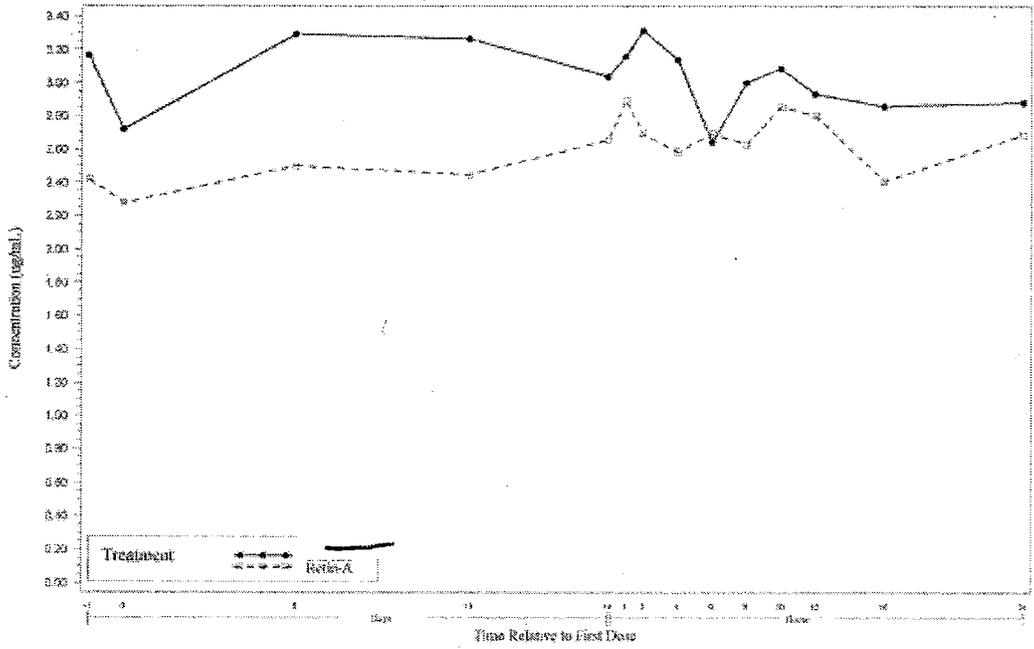


Figure 024.3 Mean 4-Oxo-13-cis-Retinoic Acid Trough Concentration Levels (ng/mL)

b(4)

Within the (Tretinoin) Gel, 0.05% treatment group, concentration levels ranged from ng/mL across timepoints. Within the RETIN-A® (Tretinoin) Micro, 0.1% treatment group, concentration levels ranged from ng/mL across timepoints. No effect of treatment on circulating levels of 4-Oxo 13-Cis-Retinoic were found.

Day 14 Area Under the Concentration Time Curve

Table 024.1 summarizes the analysis of the Day 14 area under the concentration time curve (AUC) for Tretinoin, 13-Cis-Retinoic Acid, and 4-Oxo 13-Cis-Retinoic Acid. There was not a significant difference between groups for any of the metabolites (p>0.5057).

Table 024.1: Analysis of Day 14 Area Under the Concentration Time Curve (ng/ml. hours) (All Subjects)

	— ¹	RETIN-A [®]	Degrees of Freedom ²	p-value ³
RA				
N	7	8	13	0.9449
Mean	3.4819	3.4768		
Standard Deviation	0.1303	0.1487		
Range				
13-cis-Retinoic Acid				
N	7	8	13	0.7734
Mean	3.4290	3.4659		
Standard Deviation	0.1824	0.2843		
Range				
4-Oxo-13-cis-Retinoic Acid				
N	7	8	13	0.5057
Mean	4.1966	4.0235		
Standard Deviation	0.4109	0.5463		
Range				

¹ln(AUC) = Log-transformed AUC.

²Treatments are compared using SAS PROC TTEST. Satterthwaite's method of computing the degrees of freedom is used when an F-test indicates that the treatments have different standard deviations at the 5% level. When the standard deviations are equal, the standard pooled degrees of freedom are used.

³The p-value is from a two-sample t-test.

CONCLUSIONS

There was no significant differences in the pharmacokinetic parameters for each of the treatments. There were no treatment related differences with respect to AUC, ln(AUC), Cmax, and ln(Cmax) for tretinoin or any of the metabolites. However, the sample size was small. It is noted that the concentrations of the parent compound and the two metabolites observed with the proposed formulation were within the range seen with the reference product.

NDA: 22-070/Study 735.126.CL009/01

Study Dates: Nov, 02 – Dec, 03

Safety and Efficacy Evaluation of Tretinoin Gel, 0.05% versus RETIN-A® Micro, 0.1% and Tretinoin Gel Vehicle, in the Treatment of Mild to Moderate Acne Vulgaris

Objectives: To determine if Tretinoin Gel, 0.05% is non-inferior to RETIN-A Micro, 0.1% and superior to Tretinoin Gel vehicle in treating subjects with mild to moderate acne vulgaris.

Study Design: This was a controlled, phase III, multi-center, investigator-blinded, randomized, 3-arm trial in subjects with mild to moderate acne vulgaris. Male and female subjects at least 10 years of age (see the following demography) with mild to moderate acne vulgaris of the face were eligible. Subjects were required to have no less than 30 and no more than 125 non-inflammatory lesions, and 15 to 40 inflammatory lesions. Subjects applied study medication once daily prior to bedtime for 12 weeks.

	<u>Tretinoin Gel 0.05%</u>	<u>RETIN-A Micro 0.1%</u>	<u>Tretinoin Vehicle</u>
Number of Subjects	257	285	143
Age (years)			
Mean	13.30	13.11	13.59
Std	7.97	6.46	7.96
Range			
Gender			
Male	132 (51%)	135 (47%)	71 (50%)
Female	125 (48%)	150 (53%)	72 (50%)

Twenty-two (22) Investigators enrolled 936 subjects (ranging from 6 to 141 subjects at each site), at least 10 years of age and older, with mild to moderate acne vulgaris of the face. Subjects were randomized in a ratio of 2:2:1 to one of three groups: 375 subjects were randomized to Tretinoin Gel, 0.05%, 376 subjects were randomized to RETIN-A Micro, 0.1%, and 185 subjects were randomized to Tretinoin Gel Vehicle. A total of 22 study centers participated in this trial. Subjects were evaluated at Baseline, and at Weeks 1, 2, 4, 8, and 12.

Study medication was applied once daily for 14 days to the face with mild to moderate acne vulgaris prior to bedtime. Three study centers (Site 10/Jones, Site 17/Beutner, and Site 18/Pariser; 110 subjects enrolled, samples collected from 105 subjects) also collected blood samples from each subject, at Baseline (prior to treatment), and at Week 12, to assess plasma concentrations of Tretinoin and its metabolites (13-cis-retinoic acid and 4-oxo-13-cis-retinoic acid). Samples were assayed using the method described in Study CL008.01

Primary Efficacy Variables: The primary efficacy endpoints in this study were the percent reduction in at least two of the three lesions groups (inflammatory lesions, non-

inflammatory lesions, and total lesions) at Week 12 and dichotomized global severity at Week 12.

Primary Safety Variable: The primary safety endpoint was the plasma concentration of Tretinoin and its metabolites (13-cis-retinoic acid and 4-oxo-13-cis-retinoic acid) at Week 12.

Results:

Primary Safety Endpoint: Of 199 samples received, 194 were analyzed. Four were not properly identified and one was mislabeled; none of these samples were analyzed or reported. The observed levels of tretinoin and relevant metabolites noted before and after treatment were in the range reported^{3,4,5} for endogenous levels of these compounds.

Tables 009.1 displays the descriptive statistics for plasma concentrations of tretinoin, 13-cis-retinoic acid, and 4-oxo-13-cis-retinoic acid by treatment group for the ITT population. The change from Baseline to Week 12 was calculated for those subjects with both samples collected. A negative value indicates a decrease in the level. Changes in the concentrations of tretinoin and its metabolites over the duration of the study were analyzed in plasma samples received from three study centers. The levels of tretinoin and its metabolites before and after 12 weeks of treatment were in the range reported for the endogenous levels of these compounds. The changes in concentration from Baseline to Week 12 were not statistically significant in any of the treatment groups for the comparison of tretinoin ($P=0.792$), 13-cis-retinoic acid ($P=0.827$), or 4-oxo-13-cis-retinoic acid ($P=0.666$).

Table 009.1: Summary of Change from Baseline of Tretinoin, 13-Cis-Retinoic Acid, and 4-Oxo-13-Cis-Retinoic Acid Plasma Concentrations (ng/mL) (ITT Population)

	Tretinoin Gel 0.05%			EBTDS-A Micro 0.1%			Tretinoin Gel Vehicle		
	Baseline	Week 12	Change	Baseline	Week 12	Change	Baseline	Week 12	Change
Tretinoin									
N	37	37	37	34	34	34	18	18	18
Mean	1.31	1.24	-0.07	1.28	1.28	-0.01	1.27	1.25	-0.02
STD	0.30	0.29	0.33	0.32	0.29	0.41	0.25	0.20	0.23
Minimum									
Maximum									
Overall P Value*	0.792								
13-Cis-Retinoic Acid									
N	37	37	37	34	34	34	18	18	18
Mean	0.97	0.91	-0.06	1.01	0.99	-0.03	0.91	0.92	0.01
STD	0.33	0.32	0.49	0.41	0.36	0.37	0.40	0.39	0.39
Minimum									
Maximum									
Overall P Value*	0.827								
4-Oxo-13-Cis-Retinoic Acid									
N	34	34	34	33	33	33	17	17	17
Mean	2.03	2.16	0.13	2.06	2.13	0.07	2.07	2.34	0.28
STD	0.68	0.97	0.82	0.74	0.70	0.53	1.10	1.15	0.64
Minimum									
Maximum									
Overall P Value*	0.666								

b(4)

* P value on change from Baseline from a two-way ANOVA with factors of treatment group and analysis site. Subjects with data points below detectable limits are recorded as 0.000 for analysis purposes.

CONCLUSIONS

The objective of this study was to determine if the newly formulated Tretinoin Gel, 0.05% is non-inferior to a reference drug and superior to its vehicle in treating subjects with mild to moderate acne vulgaris. The study did not show non-inferiority of Tretinoin Gel, 0.05% to RETIN-A Micro, 0.1%. This result may reflect the fact that the reference product contains 0.1% w/w volume of tretinoin as compared to 0.05% w/w tretinoin in the investigational drug and also the narrow 10% range that was set for the non-inferiority margin. With regard to superiority, Tretinoin Gel, 0.05% demonstrated superiority over Tretinoin Gel Vehicle for percent change from Baseline to Week 12 in all three lesion count analyses (inflammatory, non-inflammatory, and total lesions) and the analysis of dichotomized global severity.

In conclusion, although the clinical study failed to show non-inferiority of Tretinoin Gel, 0.05% to RETIN-A Micro, 0.1%, Tretinoin Gel, 0.05% was clearly superior to its vehicle for all three lesion count analyses (Week 12 percent change from baseline in inflammatory, noninflammatory, and total lesions) as well as the dichotomized global severity. Additionally, Tretinoin Gel, 0.05% clearly demonstrated a superior and clinically relevant local tolerance profile resulting in less irritation as compared with RETIN-A Micro® (tretinoin) Gel, 0.1% in the topical treatment of mild to moderate acne vulgaris.

Comments: The sponsor did not record the exact timing of blood samples at week 12. Diurnal and nutritional factors are known to influence plasma levels of endogenous retinoids to a greater extent than topical administration of tretinoin at doses used for acne therapy. The levels of tretinoin and its metabolites before and after 12 weeks of treatment were in the range reported for the endogenous levels of these compounds. While these results are reassuring of not having any unwanted systemic exposures of tretinoin and its metabolites under clinical usage condition, inclusion of summary statistics of this study in the label is unnecessary.

Appendix C

OCP Filing Form

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-070	Brand Name	Atralin® Gel
OCPB Division (I, II, III)	III	Generic Name	Tretinoin 0.05%Gel
Medical Division	540	Drug Class	Retinoids
OCPB Reviewer	Tapash K. Ghosh	Indication(s)	Acne
OCPB Team Leader	Edward D. Bashaw	Dosage Form	Topical gel
		Dosing Regimen	qd
Date of Submission	9/27/06	Route of Administration	Topical
Estimated Due Date of OCPB Review	06/27/07	Sponsor	Coria Lab.
PDUFA Due Date	7/27/07	Priority Classification	3S
Division Due Date	06/30/07		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X	2	2	
Phase 3:		1	1	
PK/PD:				
Phase 1 and/or 2, proof of concept:				

Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		3		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	Does Atralin® gel have adequate systemic safety?			
Other comments or information not included above				
Primary reviewer Signature and Date	<i>Tapash Ghosh</i>			
Secondary reviewer Signature and Date	<i>Dennis Bashaw</i>			

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

/s/

Tapash Ghosh
7/16/2007 04:32:27 PM
BIOPHARMACEUTICS

Sue Chih Lee
7/16/2007 04:40:58 PM
BIOPHARMACEUTICS