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APPLICATION NUMBER:

22-070

MEDICAL REVIEW(S)

CLINICAL REVIEW

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Established Name: Tretinoin 0.05%
(Proposed) Trade Name: Atralin 0.05% gel
Therapeutic Class: Retinoid
Applicant: Coria Laboratories, Ltd.

Priority Designation: S

Formulation: Topical Gel
Dosing Regimen: Once daily application at bedtime
Indication: Acne Vulgaris
Intended Population: 10 years of age and older

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1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends that Atralin Gel 0.05% (tretinoin gel 0.05%) be approved for the topical treatment of acne vulgaris in patients. The applicant has presented adequate evidence from two well-controlled studies in subjects with acne vulgaris, that this product is superior to placebo, when evaluated after 12 weeks of treatment.

The applicant has submitted under section 505(b)(2) and has referenced Retin A Micro 0.1% Gel as the comparator reference product. There are currently no approved tretinoin gel products at the 0.05% concentration.

The first phase 3 study failed to show non-inferiority to Retin A Micro 0.1% Gel, though superiority to vehicle was demonstrated. A second phase 3 study compared tretinoin gel 0.05% to vehicle and again confirmed superiority of the drug product to the vehicle.

The most common adverse events in the phase 3 studies were dry skin, skin exfoliation, erythema, and burning. 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 deaths and no serious adverse events which were considered to be related to tretinoin gel 0.05%.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Risk management will be addressed through labeling. No new safety concerns were evident in the phase 3 studies performed with topical tretinoin gel at the 0.05% concentration as compared to previously approved formulations of topical tretinoin.

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1.2.2 Required Phase 4 Commitments

As discussed during the pre-NDA meeting (June 1, 2006) the sponsor intends to conduct a 90-day dermal dose range-finding study in mice with appropriate toxicokinetics to support a dermal mouse carcinogenicity study with tretinoin gel, 0.05% as a post-marketing commitment.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The applicant conducted two phase 3 studies. The first study (Study 735.126.CL009/01) was a three-arm study comparing tretinoin gel 0.05% to vehicle and to Retin-A Micro Gel 0.1%. The study was conducted from November 2002 to December 2003 and enrolled 936 subjects. This study demonstrated the superiority of tretinoin gel 0.05% to its vehicle, but failed to demonstrate that tretinoin gel 0.05% was non-inferior to Retin-A Micro 0.1% Gel. 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) was a two-arm study comparing tretinoin gel to its vehicle. The study was conducted from June 2005 to February 2006 and enrolled 601 subjects.

1.3.2 Efficacy

The initial study 009 was a randomized, investigator-blind, three-arm study comparing tretinoin gel 0.05% to vehicle and Retin-A Micro 0.1% Gel in subjects age 10 and older. 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%.

The study enrolled 936 subjects (376 tretinoin gel 0.05%, 376 Retin-A Micro, and 185

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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).

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 at least < 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 second study 418, 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 at least 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.

1.3.3 Safety

The applicant conducted seven clinical studies from which adverse event data was collected. Data from three phase 1 trials, two phase 2 trials, and two phase 3 trials were reviewed. 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 by the applicant or by this reviewer to be treatment related.

The most common adverse events in the phase 3 trials were related to local dermatologic

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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.

A novel excipient is included in the drug product formulation, Pancogene® Marin (which contains % collagen derived from teleost fish skin). It is purported to act as a 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. It is recommended that this possibility be handled by stating in the label that the product contains soluble fish proteins and that sensitized or fish-allergic individuals should use with caution.

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A consultation from the Division of Pulmonary and Allergy Products recommended that patients who develop pruritus or urticaria should contact their health care provider. Language to this effect will be incorporated into the label.

1.3.4 Dosing Regimen and Administration

Tretinoin gel 0.05% is to be applied once daily at bedtime to skin where 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.

Dose-ranging studies were not conducted. Currently marketed formulations of tretinoin are dosed once in the evenings. The sponsor based dosing of their product on the dosing of the individually marketed tretinoin products and elected once daily dosing.

1.3.5 Drug-Drug Interactions

Drug-drug interaction studies were not performed.

The tretinoin 0.05% gel labeling includes similar language to the labeling from the comparator product, Retin A Micro 0.1% Gel:

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When treating with Atralin Gel, caution should be exercised with the use of concomitant topical medication, medicated or abrasive soaps and cleansers, products that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices, or lime. Particular caution should be exercised with the concomitant use of topical over-the-counter acne preparations containing benzoyl peroxide, sulfur, resorcinol, or salicylic acid. Allow the effects of such preparations to subside before use of Atralin Gel is begun.

1.3.6 Special Populations

The sponsor presented data to evaluate gender, age, race and ethnicity and the effect on efficacy but the database was not large enough to determine significant differences. There was no evidence of clinically significant effect of any of these parameters on efficacy from the available data.

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 out of 864 pediatric subjects aged 10-16 years.

The reference listed drug, as well as all other topical tretinoin products for acne, is approved for patients 12 years and older.

Since the onset of acne is determined primarily by pubertal age rather than chronological age, a specific lower age limit for the indication is not included in the Indications labeling. There is no evidence that the efficacy or adverse event profile is substantially different at 10 years versus 12 years for pubertally matched subjects.

A waiver is recommended for patients under the age of 10 years, since acne vulgaris does not typically occur in the younger, pre-pubertal age group and no subjects younger than 10 were included in the acne studies.

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.

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2. INTRODUCTION AND BACKGROUND

2.1 Product Information

The applicant has submitted a 0.05% gel formulation of tretinoin, Atralin Gel 0.05%, for daily topical application to skin where acne lesions appear in patients 10 years of age and older.

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.

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%.

Reviewer comment: In some sections of this review, the sponsor's product may still be referred to by the original proposed trade name, _____ in tables copied from the sponsor's clinical study report which employed the name: _____.

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2.2 Currently Available Treatment for Indications

There are a number of products approved for the treatment of acne vulgaris. These treatments include both topical and systemic products. Pharmacologic categories of approved therapies for acne vulgaris include topical antibiotics (e.g. erythromycin, clindamycin), topical retinoids (e.g. tretinoin, tazarotene) and systemic hormonal therapies (e.g. ethinyl estradiol/norgestimate).

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2.3 Availability of Proposed Active Ingredient in the United States

Tretinoin has long been individually marketed in various topical formulations and concentrations for the treatment of acne vulgaris, in concentrations from 0.01% to 0.1%. Tretinoin is thought to have an effect primarily against noninflammatory lesions by normalizing follicular keratinization

Topical retinoids as a class are commonly known to produce some measure of irritancy, particularly in the initial weeks of usage. These effects may include erythema, scaling, itching, and burning. Hypopigmentation may also be seen. Generally, the skin eventually adapts such that the irritancy lessens progressively over time.

Tretinoin is approved as a topical gel product in several concentrations, and one combination product for acne:

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

2.4 Important Issues With Pharmacologically Related Products

Systemic retinoids are teratogens, and the complex regulatory history surrounding this issue is beyond the scope of this document. Topical tretinoin products are categorized in Pregnancy Category C. The labeling for this product will include the following information, as supported by the Pharmacology/Toxicology review by Dr. Merrill:

Pregnancy Category C. There are no well-controlled trials in pregnant women treated with Atralin Gel. Atralin Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Atralin Gel at doses of 0.1, 0.3 and 1 g/kg/day was tested for maternal and developmental toxicity in pregnant Sprague-Dawley rats by dermal application. The dose of 1 g/kg/day was approximately 4 times the clinical dose assuming 100% absorption and based on body surface area comparison. Possible tretinoin-associated teratogenic effects (craniofacial abnormalities (hydrocephaly), asymmetrical thyroids, variations in ossification, and increased supernumerary ribs) were noted in the fetuses of Atralin Gel treated animals. These findings were not observed in control animals. Other maternal and reproductive parameters in the Atralin Gel treated animals were not different from control. For purposes of comparison of the animal exposure to human exposure, the clinical dose is defined as 2 g of Atralin Gel applied daily to a 50 kg person.

Oral tretinoin has been shown to be teratogenic in rats, mice, rabbits, hamsters and nonhuman primates. Tretinoin

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was teratogenic in Wistar rats when given orally in doses greater than 1 mg/kg/day (approximately 8 times the clinical dose based on body surface area comparison). In the cynomolgus monkey, fetal malformations were reported for doses of 10 mg/kg/day, but none were observed at 5 mg/kg/day (approximately 80 times the clinical dose based on body surface area comparison), although increased skeletal variations were observed at all doses. Dose-related increases in embryo/lethality and abortion also were reported. Similar results have also been reported in pigtail macaques.

Topical tretinoin in a different formulation has generated equivocal results in animal teratogenicity tests. There is evidence for teratogenicity (shortened or kinked tail) of topical tretinoin in Wistar rats at doses greater than 1 mg/kg/day (approximately 8 times the clinical dose assuming 100% absorption and based on body surface area comparison). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day (approximately 160 times the clinical dose assuming 100% absorption and based on body surface area comparison) was topically applied. Supernumerary ribs have been a consistent finding in rats when dams were treated topically or orally with retinoids.

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Cases of temporally associated congenital malformations have been reported with use of other topical tretinoin products. The significance of these spontaneous reports in terms of risk to the fetus is not known.

Nonteratogenic effects on fetuses: Oral tretinoin has been shown to be fetotoxic in rats when administered in doses 20 times the clinical dose based on a body surface area comparison. Topical tretinoin has been shown to be fetotoxic in rabbits when administered in doses 8 times the clinical dose based on a body surface area comparison.

2.5 Presubmission Regulatory Activity

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.

Due to changes in Agency recommendations regarding the manner in which lesion counts were calculated, the definition of primary endpoints differs slightly between the two studies. The initial study, 735.126.C1009/01, calculated the percent change in lesion counts, while the second two arm study, 20-CLN-126-0418, calculated the absolute change in lesion counts from baseline as currently recommended. Supportive analyses of both studies are reviewed so that efficacy data for changes in lesion counts can be compared.

2.6 Other Relevant Background Information

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3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The clinical formulation of the product is as follows:

Component	% (w/w)
Tretinoin, USP	0.05
collagen, from Pancogene® Marin	—
Sodium hyaluronate-LP	—
Octoxynol-9	—
Butylated hydroxytoluene, NF	—
Methylparaben, NF	—
Propylparaben, NF	—
Benzyl alcohol, NF	—
Trolamine, NF	—
Glycerin, USP	—
Purified water, USP	—

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Novel Excipient: Pancogene® Marin

The drug product contains one excipient of animal origin, Pancogene Marin, described by the applicant as “soluble collagen”. The origin of the collagen used is fish and is used in the tretinoin gel formulation as a — at a concentration of — %.

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The collagen is derived from the skins of Cynoglossus species (sole), and is extracted and purified. The applicant attests to compliance with microbiological specifications regarding adventitious infectious agents. A certification that the product is not involved with BSE/TSE infectious risk is submitted from Gattefossé, the manufacturer of the Pancogene Marin brand name fish collagen.

Two clinical issues are pertinent to this fish collagen excipient. Despite the low concentration of fish protein in the final formulation, there is the potential risk of allergic reactions in patients with fish protein allergy. In addition, the presence of “soluble collagen” in product labeling must be carefully described in order to minimize the potential of marketing claims for this formulation of tretinoin gel.

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Fish Allergy

The applicant did not address the issue of fish allergy related to the excipient in the drug formulation in the NDA submission.

The prevalence of fish allergy in the general population is estimated to be approximately 0.4% of the overall population. Most literature reports deal with oral ingestion of fish or fish proteins. It is unknown whether this excipient can cause allergic symptoms during topical application. It is also unknown what the dose that might cause allergy symptoms is for this topical product. Fish collagen may be an allergen for at least some fish allergic persons (Hamada, Y, et al., Biosci. Biotechno. Biochem. 65(2), 285-291, 2001.)

The concentration of the fish collagen is estimated to be _____% in the preparation. A recent clinical trial documented that fish gelatin derived from codfish skins would not provoke allergic reactions in cod allergic persons at levels up to 3.61g of cumulative intake (Taylor, SL and Hefle, SL, Can J Allergy, 5:106-110, 2000).

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While the allergy eliciting dose is unknown for this excipient, it seems likely that the topical amounts applied for the treatment of acne will not be sufficient to induce severe allergic symptoms or anaphylaxis. The local symptoms which might occur due to allergy may in fact be indistinguishable from the expected local adverse events of redness, peeling, and swelling, so the true incidence of allergy may never be appreciated clinically.

Thus, the labeling to "Use with caution if allergic to fish" seems more appropriate than completely proscribing the use of this product if patients are allergic or sensitive to fish. A consultation from the Division of Pulmonary and Allergy Products supported this conclusion and recommended that patients who develop pruritus or urticaria should contact their health care provider. Language to this effect will be incorporated into the label.

Collagen Marketing Claims

The manufacturer of Pancogene Marin, the brand name for the fish collagen, describes its product in a Gattefossé company brochure as a "Native marine collagen obtained exclusively from non-endangered warm water fish species. Similar chemical and physical characteristics when compared to bovine collagen (amino acid composition, electrophoresis, electronic microscopy, differential calorimetry). Powerful moisturizing agent, smoothes cutaneous relief, restores skin surface and provide soothing and film-forming properties."

The applicant has not otherwise justified the small amount of this excipient in the formulation other than to characterize it as _____ . The applicant was reminded as far back as 9/26/01 that if any benefit for collagen was to be claimed, 21 CFR 300.50 regulations would need to be addressed. The applicant has made no such claim to date, and

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product labeling should avoid the use of "collagen" to imply any cosmetic claim for this product.

The phrase "soluble collagen" should be avoided in labeling in favor of "soluble fish proteins" so as to avoid unintended validation of this fish collagen as a potentially active (cosmetic) ingredient. In addition, the following statement can be used, "The contribution to efficacy of individual components of the vehicle has not been established."

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The CMC review has not been finalized as of the date of this review.

3.2 Animal Pharmacology/Toxicology

The conclusion of the pharmacology/toxicology reviewer is that tretinoin gel, 0.05%, is approvable from a pharmacological/toxicological perspective. However, in addition to the historical teratogenic effects associated with tretinoin, the label should reflect the adverse effects seen in treated animals versus the placebo controls. Recommended labeling is being negotiated with the applicant as of the date of this review.

During the pre-NDA meeting (June 1, 2006), the sponsor agreed to conduct a 90-day dermal dose range-finding study in mice and a subsequent dermal mouse carcinogenicity study as a post-marketing commitment to provide data on long term dermal exposure of Tretinoin Gel, 0.05%.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Sources of clinical data for this review included the original submission for NDA 22-070, and additional efficacy and safety information submitted at the request of the Division during the review process.

The Applicant conducted seven clinical studies from which adverse event and efficacy data was collected: three phase 1 trials; two phase 2 trials; and two phase 3 trials.

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.

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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 Retin-A Micro® (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.

The phase 3 program included subjects 10 years of age and older with mild to moderate acne who were treated with study drug once daily at bedtime for 12-weeks. The first study compared Tretinoin Gel, 0.05% to Retin-A Micro® and Tretinoin Gel Vehicle. In addition to collecting information related to adverse events, a cohort of subjects in this study was investigated to determine systemic exposure potentials for tretinoin and its metabolites following topical application of the study drug. The second study compared tretinoin gel, 0.05% only to its vehicle, and did not include a blood collection. The conditions under which both studies were conducted are considered to be representative of clinical practice. Summaries of the studies are presented in the tables in section 4.2:

4.2 Tables of Clinical Studies

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**Clinical Review Table 1
Phase 1 Studies**

Type of Study	Study Identifier	Objectives of the Study	Study Design and Type of Control	Test Products	Number of Subjects	Diagnosis of Subjects	Duration of Treatment	Safety Data Collection
Safety	735.126.CL005	This standard Phase 1, photolassery study was conducted to ensure the safety of human subjects by evaluating the photolassery potential of the test article.	Single-center, controlled, Investigator/evaluator-blinded, intra-individual comparison of Tretinoin Gel, 0.05% vs. Tretinoin Gel Vehicle vs. White Petrolatum	Tretinoin Gel, 0.05%; Tretinoin Gel Vehicle; White Petrolatum	19 Healthy Volunteers	None	3 week induction phase with test articles; 2 week rest phase (no treatment, no irradiation); 1 week challenge phase	AEs and Irritation Scores
Safety	735.126.CL006	This standard Phase 1, phototoxicity study was conducted to ensure the safety of human subjects by evaluating the phototoxicity potential of the test article.	Single-center, controlled, Investigator/evaluator-blinded, intra-individual comparison of Tretinoin Gel, 0.05% vs. Tretinoin Gel Vehicle vs. White Petrolatum	Tretinoin Gel, 0.05%; Tretinoin Gel Vehicle; White Petrolatum	16 Healthy Volunteers	None	On Day 1, the test article was applied to 2 sets of 3 patch sites, one on each side; Day 2 patches were removed and 1 set of sites irradiated. Sites were evaluated after removal (30 minutes, 24 hours, 48 hours and 72 hours).	AEs and Irritation Scores
Safety	735.126.CL007	To determine the contact sensitization potential of Tretinoin Gel, 0.05%, Tretinoin Gel Vehicle, and White Petrolatum using a standard Draize testing method in healthy subjects.	Single-center, controlled, Investigator/evaluator-blinded, intra-individual comparison of Tretinoin Gel, 0.05% vs. Tretinoin Gel Vehicle vs. White Petrolatum	Tretinoin Gel, 0.05%; Tretinoin Gel Vehicle; White Petrolatum	237 Healthy Volunteers	None	3 week induction phase with test articles; 10-17 day rest phase; single challenge application, repeated if required	AEs and Irritation Scores

**Clinical Review Table 2
Phase 2 Studies**

Type of Study	Study Identifier	Objectives of the Study	Study Design and Type of Control	Test Products	Number of Subjects	Diagnosis of Subjects	Duration of Treatment	Safety Data Collection
Safety	735.126.CL008	To investigate the absorption and safety of Tretinoin Gel, 0.05% compared to Retin-A Micro® following maximum exposure with multiple applications in subjects with moderately severe acne.	Single-center, randomized, parallel group, multiple dose, controlled, investigator-blinded study of Tretinoin Gel, 0.05% vs. Retin-A Micro®	Tretinoin Gel, 0.05% and Retin-A Micro®	12 Subjects	Moderately severe acne	Approx. 4 g of the test article applied daily for 14 days	AEs Concentration Data
Safety	20.CL.N.126.024	To investigate the absorption and safety of Tretinoin Gel, 0.05% compared to Retin-A Micro® following maximum exposure with multiple applications in subjects with moderately severe acne.	Single center randomized, parallel group, multiple dose, controlled, investigator-blinded study of Tretinoin Gel, 0.05% vs. Retin-A Micro®	Tretinoin Gel, 0.05% and Retin-A Micro®	16 Subjects	Moderately severe acne	Approx. 4 g of the test article applied daily for 14 days	AEs Concentration Data

Clinical Review Table 3
Phase 3 Studies

Type of Study	Study Identifier	Objectives of the Study	Study Design and Type of Control	Test Products	Number of Subjects	Diagnosis of Subjects	Duration of Treatment	Safety Data Collection
Safety, Efficacy, and PK	735.126.CL009	<p>Efficacy: To determine if Tretinoin Gel, 0.05% was non-inferior to Retin-A Micro[®], 0.1% and superior to Tretinoin Gel vehicle in treating subjects with mild to moderate acne.</p> <p>Safety: All adverse events that occurred during the study were recorded and evaluated.</p> <p>PK: To determine the plasma concentrations of Tretinoin and its metabolites (13-cis-retinoic acid and 4-oxo-13-cis-retinoic acid).</p>	Controlled, multi-center, investigator-blinded, randomized, 3-arm trial of Tretinoin Gel, 0.05% vs. Retin-A Micro [®] vs. Tretinoin Gel Vehicle	Tretinoin Gel, 0.05%; Retin-A Micro [®] ; Tretinoin Gel Vehicle	936 total: 375 Tretinoin Gel, 0.05%; 376 Retin-A Micro [®] ; 185 Tretinoin Gel Vehicle PK: 110 subjects/ 105 samples	Mild to moderate acne	Once daily application to treated area at bedtime for 12 weeks	Adverse Events Concentration Data
Safety and Efficacy	20.CLIN.126.0418	<p>Efficacy: To determine if Tretinoin Gel, 0.05% was superior to Tretinoin Gel Vehicle in the treatment of mild to moderate acne.</p> <p>Safety: All adverse events that occurred during the study were recorded and evaluated.</p>	Controlled, multi-center, investigator-blinded, randomized trial of Tretinoin Gel, 0.05% vs. Tretinoin Gel Vehicle	Tretinoin Gel, 0.05%; Tretinoin Gel Vehicle	601 total: 299 Tretinoin Gel, 0.05%; 302 Tretinoin Gel Vehicle	Mild to moderate acne	Once daily application to treated area at bedtime for 12 weeks	Adverse Events

4.3 Review Strategy

Adverse event data was reviewed for all seven studies through all three phases of development. Efficacy data was reviewed for the two phase 3 studies.

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4.4 Data Quality and Integrity

No study site investigations by the Division of Scientific Integrity were performed. The applicant's analyses were reviewed, and independent analyses were performed by the Agency biostatistics reviewer.

4.5 Compliance with Good Clinical Practices

The applicant affirmed that the studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP). All subjects were informed about the study and provided the opportunity to ask questions. Subjects, or their legal representatives, read, signed, and dated the IRB-approved consent form before taking part in any study activity. For subjects under the age of 18, an IRB approved assent also was obtained.

4.6 Financial Disclosures

The applicant certified in Form 3454 that they had not entered into any financial arrangements with any of the clinical investigators.

5. CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Three (3) studies investigated the endogenous 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.

In two 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.

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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.

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 who were treated with tretinoin gel 0.05%; 34 who received the microsphere formulation; and 18 who received vehicle. The observed levels of tretinoin and its major metabolites pre- and post-treatment were in the range reported for endogenous levels of these compounds; there were no statistically significant changes from baseline to week 12 in the serum levels of either tretinoin or its major metabolites.

6. INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication sought by the applicant is for topical application in the treatment of acne vulgaris in patients 10 years of age and older.

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6.1.2 General Discussion of Endpoints

Two phase 3 studies were conducted in support of the efficacy of tretinoin 0.05% gel in acne vulgaris treatment. During the product development, the Agency required that the manner in which the change in lesion counts from baseline was calculated be changed from percent change to absolute change. Absolute and percent changes in lesion counts were submitted for both phase 3 studies as requested by the Agency.

The primary efficacy endpoints in study 009 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. A success in the global severity score was defined as reaching a score of 0 (clear), or 1 (very mild).

The primary efficacy endpoints in study 418 were the absolute reduction from baseline to week 12 in inflammatory and non-inflammatory lesion counts, and the inter-group differences in the dichotomized Global Severity assessments at week 12.

The primary safety endpoint in study 009 was the plasma concentration of tretinoin and its metabolites (13-cis-retinoic acid and 4-oxo-13-cis-retinoic acid) at week 12. Blood samples were collected at baseline and week 12 at 3 sites in study 009 to determine plasma concentrations of tretinoin and its metabolites.

6.1.3 Study Design

The clinical efficacy of tretinoin gel 0.05% is based on two phase 3 clinical studies, #009 and #418. The 009 study was designed to demonstrate non-inferiority to an active comparator, Retin A Micro 0.1%, and superiority to tretinoin gel vehicle in the treatment of mild to moderate acne. While tretinoin gel 0.05% was superior to vehicle in all lesion count analyses from baseline to week 12 as well as in global severity scores, tretinoin gel 0.05% was not found to be non-inferior to Retin A Micro gel 0.1%.

The second phase 3 study, #418, was conducted to provide a second adequate and well-controlled study to demonstrate superiority of tretinoin gel 0.05% to vehicle. The Agency agreed with the revised development plan at a guidance meeting on December 2, 2004.

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Study 735.126.CL009/01

This was a controlled, phase 3, multi-center, investigator-blinded, randomized, 3-arm trial in subjects with mild to moderate acne vulgaris. The first subject was enrolled on November 18, 2002 and the final clinical visit of the last subject completing the study was on December 17, 2003. Subjects applied study medication once daily prior at bedtime for 12 weeks. 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.

At baseline, subjects were to have mild (2), mildly moderate (3), or moderate (4) scores on the acne global severity scale, 30 to 125 facial (excluding the nose) non-inflammatory lesions, and 15 to 40 facial (excluding the nose) inflammatory lesions. Subjects were allowed to have up to 3 non-inflamed nodules/cysts that were counted separately.

Subjects were randomized (by randomization code) to one of three treatment groups: tretinoin gel, 0.05% (375 subjects), Retin-A Micro, 0.1% (376 subjects), or tretinoin gel Vehicle (185 subjects). They were evaluated at Baseline, and at Weeks 1, 2, 4, 8, and 12. The primary efficacy endpoints included the percent reduction in at least two of the three lesion groups (inflammatory lesions, non-inflammatory lesions, and total lesion counts) at Week 12 and dichotomized global severity at Week 12.

All clinical evaluations were conducted on the face, even though the subjects enrolled could treat the involved areas of the face, chest, and back.

Subjects were selected based on the following eligibility criteria:

Inclusion Criteria:

- 1) Male or female subjects at least 10 years of age with mild to moderate acne vulgaris;
- 2) Subjects with non-inflammatory facial (excluding the nose) lesion (open and closed comedones) counts no less than 30 but no more than 125;
- 3) Subjects with inflammatory facial (excluding the nose) lesion (papules and pustules) counts no less than 15 but no more than 40. Subjects could have up to 3 non-inflamed nodules/cysts (not part of count);
- 4) Subjects with an Acne Global Severity Grade of 2 through 4;
- 5) Female subjects who had a negative pregnancy test prior to entry and who practiced adequate birth control during the study. Females on birth control pills (other than those approved for treating acne vulgaris; refer to No. 6) must have taken the same type pill for at least 3 months prior to entering the study and could not change type during the study. Those females who had used birth control pills in the past must have stopped usage at least 6 months prior to the start of the study. Any female subjects who were pre-menses at the start of the study and became of childbearing potential during the study must have had a pregnancy test performed at the next visit;

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- 6) Female subjects who took Tri-Cyclen in the past must have discontinued this medication at least 1 year prior to enrollment;
- 7) Female subjects who were on Tri-Cyclen must have been on this medication for at least one year;
- 8) Subjects who were willing and capable of cooperating to the extent and degree specified in the protocol;
- 9) Subjects under the age of 18 years who signed an approved assent form according to the IRB guidelines;
- 10) Subjects (or legal guardians) must have signed an approved informed consent.

Exclusion Criteria:

Subjects were excluded from the study if any of the following criteria was satisfied:

- 1) Subjects who had acne conglobata, acne fulminans, secondary acne (as with chlorine), or drug-induced acne (caused by hormone therapy, corticosteroids, anti-epileptic drugs, anti-tuberculosis drugs, lithium, cyclosporine, iodine drugs, or bromine drugs);
- 2) Subjects who had rosacea or atopic dermatitis of the face;
- 3) Subjects who had other underlying disease(s) or some other dermatological condition of the face that required the use of interfering topical or systemic therapy;
- 4) Subjects who had known sensitivities to any of the study preparations as described in the Investigator's Brochure and the Product Package Insert for RETIN-A Micro, 0.1%;
- 5) Subjects who had a beard, which would interfere with the study assessments;
- 6) Subjects who were pregnant and/or nursing or became pregnant during the study;
- 7) Subjects who had not undergone the specified washout period(s) for the following topical preparations or subjects who required the concurrent use of any of the following topical medications:

Corticosteroids on facial area	4 weeks
Antibiotics on the facial area	4 weeks
Anti-inflammatories on the facial area	4 weeks
Other acne treatments (prescription and over the counter, to include Stridex, benzyl peroxide, and salicylic acid)	4 weeks
Retinoids	6 weeks

- 8) Subjects that had not undergone the specified washout period(s) for the following systemic medications or subjects who required the concurrent use of any of the following systemic medications:

Corticosteroids	4 weeks
All Antibiotics	4 weeks
Anti-inflammatories (Rx and acute-mega doses)	4 weeks
Isotretinoin (Accutane)	6 months
Other acne treatments	3 months

- 9) Subjects must have agreed NOT to use potentially irritating over-the-counter (OTC) products that contained ingredients such as alpha-hydroxy acid or glycolic acids;
- 10) Subjects who were on potentially toxic doses of Vitamin A defined by the NIH as anything over

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- 1700 µg/day for ages 9-13,
- 2800 µg/day for ages 14-18, and
- 3000 µg/day for those subjects 19 years of age and older;

11) Subjects who were unable to communicate or cooperate with the Investigator due to language problems, poor mental development, or impaired cerebral function; and

12) Subjects who had participated in another clinical trial within 30 days of enrollment.

Once the subjects had signed the informed consent form, met all of the eligibility criteria, and had been enrolled in the trial, the subjects were then randomized to one of three treatments groups:

- Tretinoin Gel, 0.05%,
- RETIN-A Micro, 0.1%, or
- Tretinoin Gel Vehicle.

Subjects applied study medication once daily prior to bedtime for 12 weeks.

The study drug and vehicle were supplied in identical tubes and labels. The comparator was not transferred into identical tubes, but over-labeled with the same labels used for the other test materials. Although the labels were identical for all three test materials, the tubes were distinguishable by appearance. To maintain blinding of the test materials, someone other than the investigator/evaluator dispensed the tubes and gave instructions for use to the subjects.

Tubes were collected and examined at all visits by designated site personnel (someone other than the Investigator/evaluator). The tubes were weighed before and after use. Subjects were questioned regarding test material application, frequency of application, and use of any other topical or systemic (prescription and OTC) products. Any missed doses were noted on the CRF. A subject was considered compliant with the dosing regimen if the subject did not miss more than 5 consecutive days of dosing and applied 80 to 120% of expected study medication applications (67 to 101 applications).

Study visits and data collection followed the following study flow chart:

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**Clinical Review Table 4
 Study Flow Chart-Study 009**

Parameter	Acne Study					
	BL ¹	Week 1	Week 2 ²	Week 4	Week 8	Week 12
Visit Windows (from BL date)	-	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days
Visit on or between Days		4-10	11-17 ²	25-31	53-59	81-87
Informed Consent/Assent	X					
Inclusion/Exclusion	X					
Demographics	X					
Medical History	X					
Urine Pregnancy Test	X					X ³
Collect Blood Sample ⁵	X					X
Global Severity	X	X	X	X	X	X
Lesion Counts ³	X	X	X	X	X	X
New Tube Weighed and Dispensed	X	Weighed only	X	X	X	
Used Tube Collected and Weighed			X ⁶	X ⁶	X ⁶	X
Adverse Events		X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X
Final Report Form						X ²

b(4)

- ¹ Subjects may also have had a screening visit to determine general eligibility; however, the subjects must have met all entry criteria at the Baseline visit. In addition, all the Investigator evaluations and drug dispensation must have occurred at Baseline.
- ² Completed at Week 12 or upon study discontinuation.
- ³ At least 3 days between Week 1 and Week 2 visit.
- ⁴ Three study centers collected blood samples from all subjects and forwarded to lab for analysis.
- ⁵ Lesion counts of the nose were collected separately from other lesions of the face and were not considered for enrollment.
- ⁶ If the subject had more than half the tube remaining, that tube was re-dispensed.

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 global severity scale is presented below. 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 0.1% on both the lesion count and global severity scale endpoints. The pre-specified non-inferiority margin for all endpoints was 10%.

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Lesion counts and global severity scores were assessed at weeks 1, 2, 4, 8, and 12, and/or upon discontinuation from the study. The global severity score was a static assessment that was independent of the baseline score.

Clinical Review Table 5
Global Severity Grading Scale

GRADE	DESCRIPTION	
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Very Mild	Skin almost clear; rare non-inflammatory lesions present, with rare non-inflamed papules (papules may be hyperpigmented, though not pink-red, less than 4 lesions)
2	Mild	Some non-inflammatory lesions present, with few inflammatory lesions (papules/pustules only, no nodulo-cystic lesions) Less than half of the face involved
3	Mildly Moderate	Non-inflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules only, and there may or may not be 1 small nodulo-cystic lesion. More than half of the face involved.
4	Moderate	Inflammatory lesions are more apparent: many comedones and papules/pustules, there may or may not be a few nodulo-cystic lesions. Entire face involved.
5	Severe	Highly inflammatory lesions predominate: variable number of comedones, many papules/pustules and nodulo-cystic lesions.

Three study centers (Site 10/Jones, Site 17/Beutner, and Site 18/Pariser) were responsible for collecting blood samples from all of their subjects for pharmacokinetic (PK) assays. The blood samples were collected at baseline and week 12 to determine plasma concentrations of tretinoin, 13-cis-retinoic acid, and 4-oxo-13-cis-retinoic acid. Blood samples were not collected from subjects that discontinued prior to the 12-week visit.

Study 20.CLN.126.0418

The objective of study #418 was to determine if tretinoin gel, 0.05% was superior to tretinoin gel vehicle in the treatment of mild to moderate acne vulgaris in subjects age 10 and older. No active comparator arm was included in this second phase 3 study. The study enrolled 601 subjects (299 tretinoin gel 0.05% and 302 vehicle gel) at 23 U.S. centers.

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The study population consisted of male and female subjects, at least 10 years of age with mild to moderate *acne vulgaris* and a Global Severity score of 3 (mildly moderate) to 4 (moderate). Subjects must have had non-inflammatory lesions – facial plus nasal (open and closed comedones) – with counts of not less than 30 but not more than 125, and inflammatory lesions – facial plus nasal (papules and pustules) – with counts of not less than 15 but no more than 40 (subjects may have had up to 3 nodules/cysts).

Inclusion and exclusion criteria were similar to those for study 009 except nasal lesions were included in lesion counts in this study and washout periods for concomitant acne therapy differed slightly.

Subjects meeting all qualifying criteria were enrolled into the study and were randomized to receive either tretinoin gel, 0.05% or tretinoin gel vehicle. Subjects were instructed to apply the study medication once each evening, prior to bedtime throughout the study period (approximately 12 weeks). Subjects also were allowed to apply the study medication to their chests and backs, but these areas were not assessed.

The study drug and its vehicle were supplied in identical packaging. The physical appearance of each test preparation, however, was different. Therefore, the person dispensing the tubes was required to have been different from the person who conducted the clinical evaluations. Both the subject and the person in charge of drug dispensation were instructed not to discuss or show the assigned tube to the investigator or other clinical evaluator.

No direct measures of treatment compliance were conducted. However, subjects were queried at each visit regarding their compliance with the study medication and were asked to report any missed doses.

**Clinical Review Table 6
Study Flow Diagram for Study 20.CLN.126.0418**

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Parameter	BL ^a	Week 1 ± 3 days	Week 3 ± 3 days	Week 4 ± 3 days	Week 8 ± 3 days	Week 12 ± 3 days
Visit Windows (from Scheduled date)	-					
Informed Consent/Assent/Photography Consent	X					
Inclusion/Exclusion	X					
Demographics	X					
Medical History	X					
Physical Examination	X					
Urine Pregnancy Test	X					X ^b
Vital Signs	X					
Acne-QoL Questionnaire	X					X ^b
Global Severity	X	X	X	X	X	X
Photography ^c	X	X	X	X	X	X
Lesion Counts ^d	X	X	X	X	X	X
New Tube Weighed and Dispensed ^e	X	Weighed only	X	X	X	
Used Tube Collected and Weighed			X ^f	X ^f	X ^f	X
Dosing Compliance		X	X	X	X	X
Adverse Events		X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X
Final Report Form						X ^g

^a Subjects may also have had a screening visit to determine general eligibility; however, the subjects must have met all entry criteria at the Baseline visit. In addition, all investigator evaluations and drug dispensations occurred at Baseline.

^b Completed at Week 12 or upon study discontinuation.

^c Six (6) study centers collected photographs of the entire face for marketing purposes only.

^d Lesion counts of the face and nose were collected separately. Any subject who developed a nodule or had an increase in their nodule count that required additional therapy, was discontinued from the study and other treatments were made available to them. Such subjects were considered treatment failures.

^e If the subject had more than half the tube remaining, that tube was re-dispensed.

^f Scales used to weigh medication were calibrated according to appropriate procedures and a calibration log was kept at each site.

Study 418 utilized the same global severity assessment scale as referenced above for study 009 in Clinical Review Table 7, except that it did not include the descriptions “less than half of the face involved”, “more than half of the face involved”, or “entire face involved” for grades 2 – 4.

Lesion count assessments were again made at week 1, 2, 4, 8, and 12, for total, inflammatory and non-inflammatory lesions.

An acne quality of life questionnaire was also used in the study at week 12 as a secondary efficacy variable.

Safety variables included adverse events, concomitant medications, test article compliance, an extent of exposure to study drug.

Unlike study 009, no plasma level measurements of drug concentration were performed during this study 418.

The baseline entry criteria and endpoints in studies 009 and 418 had a number of minor differences, some of which were based on recommendations by the Agency during the review of Protocol 0418. These differences are highlighted in Clinical Review Table

Clinical Review Table 7
Baseline and Endpoint Differences between Study 009 and Study 418

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	Study 009	Study 0418
Global Severity Scale	Included descriptions of facial area involvement	Did not include descriptions of facial are involvement
Baseline GSS	Mild (2), mildly moderate (3), moderate (4)	Mildly moderate (3), moderate (4)
Treatment success	Clear (0) or very mild (1)	Clear (0) or very mild (1) with at least 2 grades reduction
Lesion Counts	Excluded counts on the nose	Included counts on the nose
Baseline lesion counts	30-125 non-inflammatory (excluding the nose) 15-40 inflammatory (excluding the nose)	30-125 non-inflammatory (including the nose) 15-40 inflammatory (including the nose)
Lesion Count Endpoints	Percent reduction in 2 out of 3 counts (inflammatory, non-inflammatory, total)	Absolute reduction in inflammatory and non-inflammatory lesions

Demographics and Baseline Characteristics:

Both studies were similar across treatment arms for all demographic variables. The average age ranged from 18 to 19 in all arms, with about two-thirds of subjects under age 18. The male/female ratio was 47%/53% in the study 009, and 50%/50% in study 418. In study 418, ethnicity was collected separately from race. In study 418, 19% of subjects were Hispanic. The baseline demographic data for the two studies is presented in Clinical Review Tables 8 and 9:

Clinical Review Table 8
Study 009 Demographic Data

	Tretinoin Gel, 0.05%	RETIN-A Micro, 0.1%	Gel Vehicle
Number of Subjects	375	376	185
Age (years)			
Mean	18.2	18.4	19
Range	10-53	10-45	10-49
10 - 17	240 (64%)	232 (62%)	114 (62%)
≥ 18	135 (36%)	144 (38%)	71 (38%)

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Gender			
Male	178 (47%)	167 (44%)	88 (48%)
Female	197 (53%)	209 (56%)	97 (52%)
Race			
Caucasian	258 (69%)	262 (70%)	121 (65%)
Black	57 (15%)	69 (18%)	36 (19%)
Asian	12 (3%)	10 (3%)	5 (3%)
Other	48 (13%)	35 (9%)	23 (12%)

Clinical Review Table 9
Study 418 Demographic Data

	Tretinoin Gel, 0.05%	Gel Vehicle
Number of Subjects	299	302
Age (years)		
Mean (Std)	18.7 (6.9)	19.1 (7.8)
Range	10-52	10-65
10 - 17	200 (67%)	197 (65%)
≥ 18	99 (33%)	105 (35%)
Gender		
Male	149 (50%)	149 (49%)
Female	150 (50%)	153 (51%)
Ethnicity		
Hispanic/Latino	56 (19%)	57 (19%)
Not Hispanic/Latino	243 (81%)	245 (81%)
Race		
White	250 (84%)	248 (82%)
Black or African American	37 (12%)	41 (14%)
Asian	8 (3%)	7 (2%)

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American Indian or Alaska Native	0 (0%)	1 (<1%)
Native Hawaiian or other Pacific Islander	1 (<1%)	0 (0%)
Other	5 (2%)	7 (2%)

Baseline Severity:

Severity measures were fairly balanced across treatment arms in both studies.

In Study 009, subjects were enrolled with global scores of 2, 3 or 4. Just over half of the subjects were classified as mildly-moderate (3). In Study 0418, subjects were to have global scores of 3 or 4 at baseline, and 61% of subjects were classified as mildly-moderate (3). Subjects in both studies had similar numbers of baseline lesions. Tables for each study are presented below:

Clinical Review Table 10
Study 009 Baseline Severity Characteristics

	Tretinoin Gel, 0.05%	RETIN-A Micro, 0.1%	Gel Vehicle
Number of Subjects	375	376	185
Global Severity Score			
Mild (2)	97 (26%)	90 (24%)	49 (26%)
Mildly-Moderate (3)	211 (56%)	203 (54%)	98 (53%)
Moderate (4)	67 (18%)	82 (22%)	38 (21%)
Non-Inflammatory Lesion Count ¹			
Mean (Std)	50.7 (21.9)	48.2 (19.6)	52.4 (22.5)
Range	30-122	30 -129	30-122
Non-Inflammatory Nasal Count ²			
Mean (Std)	8.4 (10.7)	8.8 (8.5)	9.8 (9.5)
Range	0 - 100	0 - 39	0 - 45
Inflammatory Lesion Count ¹			
Mean (Std)	23.4 (7.2)	23.6 (7)	23.9 (7.2)
Range	15-43	15-46	15-40
Inflammatory Nasal Count ²			
Mean (Std)	1.5 (1.7)	1.7 (2.3)	1.7 (1.9)
Range	0 - 9	0 - 16	0 - 8

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Clinical Review Table 11
 Study 418 Baseline Severity Characteristics

	Tretinoin Gel, 0.05%	Gel Vehicle
Number of Subjects	299	302
Global Severity Score		
Mild (2)	0 (0%)	0 (0%)
Mildly Moderate (3)	189 (63%)	178 (59%)
Moderate (4)	110 (37%)	124 (41%)
Non-Inflammatory Lesion Count ¹		
Mean (Std)	51.9 (21.9)	52.7 (23.3)
Range	25-123	30-186
Inflammatory Lesion Count ¹		
Mean (Std)	22.9 (8)	23.4 (7.3)
Range	15-64	15-40

6.1.4 Efficacy Findings

Studies evaluated inflammatory lesions, non-inflammatory lesions, and global severity; however, the primary analyses differed slightly between the two studies. In study 009, subjects had scores of 2, 3, or 4 at baseline and success on the global severity scale was defined as a score of 0 or 1. In study 418, success on the global was defined as a score of 0 or 1 with at least 2 grades reduction. However, a higher baseline global score was required (3 or 4), so all subjects achieving a score of 0 or 1 would automatically have at least 2 grades reduction. Global success results from study 009 are presented both as defined in the protocol (0 or 1) and as 0 or 1 with at least 2 grades reduction for consistency with study 418.

For lesions counts, the primary endpoints for study 009 were the percent reduction in lesions from baseline to week 12. For a successful study, two out of inflammatory, non-inflammatory, and total were to have been significant. The percent reductions in both inflammatory and non-inflammatory lesions were significant.

Clinical Review Table 12
 Study 009 Efficacy Results at Week 12-Intent to Treat Population (Agency analysis)

Tretinoin Gel 0.05%	RETIN-A Micro, 0.1%	Gel Vehicle	p-value (Tret. vs.	LCB (Tret. –

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	N=375	N=376	N=185	Veh.)	Ret.-A)
Non-Inflammatory Lesions¹					
Mean Baseline	50.7	48.2	52.4		
Mean Absolute Reduction	21.8	24.7	10.3	<0.0001 ³	
Mean Percent Reduction ²	43.3%	51.9%	21.2%	<0.0001 ³	-12.5% ³
Inflammatory Facial Lesions¹					
Mean Baseline	23.4	23.6	23.9		
Mean Absolute Reduction	9.7	11.8	5.8	0.0004 ³	
Mean Percent Reduction ²	40.8%	50.5%	25.6%	<0.0001 ³	-13.1% ³

	Tretinoin Gel 0.05% N=375	RETIN-A Micro, 0.1% N=376	Gel Vehicle N=185	p-value (Tret. vs. Veh.)	LCB (Tret. – Ret.-A)
Global Severity Scale					
Clear or Very Mild ²	78 (20.8%)	120 (31.2%)	23 (12.4%)	0.0022 ⁴	-17.6% ⁵
Clear or Very Mild with at least 2 grades reduction	45 (12%)	71 (18.9%)	6 (3.2%)	0.0002 ⁴	

¹ Excluding the nose

² Primary endpoints

³ P-value and LCB based on ANOVA on the ranks with terms for treatment, pooled investigator, and treatment-by-pooled investigator interaction. Non-inferiority margin was 10%.

⁴ P-value for CMH stratified on pooled investigator

⁵ 97.5% lower confidence bound based on Wald's interval with Yates continuity correction. Non-inferiority margin was 10%.

Lesion counts in study 009 excluded the nose. To see if the exclusion of nasal lesion counts had any impact on the analysis, the lesion count analyses including nasal counts for those subjects with baseline nasal counts were conducted by this reviewer. The results are presented in Clinical Review Table 12. All of the analyses had p-values less than 0.05 except for the absolute reduction in inflammatory lesions (p=0.0687).

Clinical Review Table 12
Study 009 Lesion Analysis Including Nasal Lesions
Among Subjects with Nasal Lesion Counts at Baseline

	Tretinoin Gel 0.05% N=192	RETIN-A Micro, 0.1% N=189	Gel Vehicle N=94	p-value (Tret. vs. Veh.)
Non-Inflammatory Lesions¹				
Mean Baseline	61.6	57.9	66.6	
Mean Absolute Reduction	22.9	28.3	13.2	0.0025
Mean Percent Reduction	36.2%	50.2%	20.1%	0.0002
Inflammatory Facial Lesions¹				
Mean Baseline	25.0	23.9	24.5	
Mean Absolute Reduction	9.5	12.0	5.9	0.0687
Mean Percent Reduction	37.8%	49.7%	24.9%	0.0168

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The efficacy results for study 418 were successful for all three outcome variables:

Clinical Review Table 13
Study 418 Efficacy Results, Intent to Treat Population

	Tretinoin Gel 0.05% N=192	RETIN-A Micro, 0.1% N=189	Gel Vehicle N=94	p-value (Tret. vs. Veh.)
Non-Inflammatory Lesions¹				
Mean Baseline	61.6	57.9	66.6	
Mean Absolute Reduction	22.9	28.3	13.2	0.0025
Mean Percent Reduction	36.2%	50.2%	20.1%	0.0002
Inflammatory Facial Lesions¹				
Mean Baseline	25.0	23.9	24.5	
Mean Absolute Reduction	9.5	12.0	5.9	0.0687
Mean Percent Reduction	37.8%	49.7%	24.9%	0.0168

Study 009 was originally designed to demonstrate that tretinoin gel 0.05% was non-inferior to Retin-A Micro 0.01%. For each endpoint, the sponsor specified a non-inferiority margin of 10%. The applicant failed to meet the non-inferiority criteria for all of the endpoints. Retin-A Micro was superior to tretinoin gel for each endpoint. It is again noted that Retin-A Micro 0.01% has twice the concentration of tretinoin gel 0.05% product. The comparative results are thus not unexpected between the two products. No studies were undertaken to assess the comparability of tretinoin gel 0.05% to Retin A Micro gel 0.04%.

Agency analysis of the per protocol population were similar to the ITT population. All of the global success and lesion count analyses for tretinoin versus vehicle were significant in the per protocol population in both studies.

Clinical Review Table 14
Study 009 Efficacy Results, Per Protocol Population

	Tretinoin Gel 0.05% N=257	RETIN-A Micro, 0.1% N=285	Gel Vehicle N=143	p-value (Tret. vs. Veh.)	LCB (Tret. - Ret.-A)
Non-Inflammatory Lesions¹					
Mean Baseline	51.2	48.7	53.5		
Mean Absolute Reduction	24.3	26.5	11.7	<0.0001	
Mean Percent Reduction ²	47.4%	54.9%	23.1%	<0.0001	-11.2%
Inflammatory Facial Lesions¹					
Mean Baseline	23.5	23.9	24.4		
Mean Absolute Reduction	10.4	12.9	5.1	<0.0001	

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Mean Percent Reduction ²	43.6	54.7	22.4	<0.0001	-12.7%
Global Severity Scale					
Clear or Very Mild ²	63 (24.5%)	101 (35.4%)	20 (14.0%)	0.0188	-18.9%
Clear or Very Mild with at least 2 grades reduction	39 (15.2%)	64 (22.5%)	5 (3.5%)	0.0078	

¹ Excluding the nose

² Primary endpoints

³ P-value for ANOVA on the ranks with terms for treatment, pooled investigator, and treatment-by-pooled investigator interaction

⁴ P-value for CMH stratified on pooled investigator

⁵ 97.5% lower confidence bound based on an analysis of the ranks for lesion endpoints and Wald's interval with Yates continuity correction for GSS. Non-inferiority margin was 10%.

Clinical Review Table 15
Study 418 Efficacy Results, Per Protocol Population

	Tretinoin Gel 0.05% N=197	Gel Vehicle N=226	p-value
Non-Inflammatory Lesions¹			
Mean Baseline	51.4	51.6	
Mean Absolute Reduction to Week 12 ²	20.0	10.6	<0.0001 ³
Mean Percent Reduction to Week 12	38.7%	21.4%	<0.0001 ³
Inflammatory Facial Lesions¹			
Mean Baseline	22.2	23.6	
Mean Absolute Reduction to Week 12 ²	7.5	4.0	0.0041 ³
Mean Percent Reduction to Week 12	31.0%	18.1%	0.0062 ³
Global Severity Scale			
Clear or Very Mild with at least 2 grades reduction ²	50 (25.4%)	34 (15.0%)	0.0120 ⁴

¹ Including the nose

² Primary endpoints

³ P-value for ANOVA on the ranks with terms for treatment, pooled investigator, and treatment-by-pooled investigator interaction

⁴ P-value for CMH stratified on pooled investigator

Effect of Race, Gender, and Age:

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The study database was not large enough to assess whether there were statistical differences in effects among age, gender or race subgroups. There were no trends seen that indicated significant effects of these subgroups on efficacy or adverse events.

Agency analyses of the efficacy results were generally consistent across racial groups, at least among race groups with moderate sample sizes. Most subjects in both studies were Caucasian. Although treatment effects were generally similar, female subjects tended to have slightly better overall results than males. Similarly, adult subjects (18 and older) generally had slightly better results than adolescent subjects (age 10 – 17), although again, the treatment effects were generally similar.

Effect of Baseline Severity:

Baseline severity, as measured by the global scale, does not appear to have much impact on the percent reduction in lesions by Week 12, though there may be a slight trend that subjects with higher baseline global scores have lower percent reductions in inflammatory lesions on average than subjects with lower baseline global scores. The baseline global score however, has a larger impact on the global success rate, as might be expected since the baseline global score impacts how many grades a subject must improve to achieve success (subjects with baseline 2 must improve at least 1 grade, subjects with baseline 3 must improve at least 2 grades, and subjects with baseline of 4 must improve at least 3 grades). Most of the efficacy in Study 009 from subjects with baseline scores of 2 would disappear if the requirement of at least 2 grades reduction were applied.

6.1.5 Clinical Microbiology

The sponsor is not seeking an antimicrobial claim, and no clinical microbiology data was collected in the development program. Tretinoin has no known antimicrobial effects.

6.1.6 Efficacy Conclusions

Tretinoin gel 0.05% demonstrated superiority over placebo in both phase 3 studies across all primary, pre-specified endpoints. Superiority was demonstrated over vehicle for inflammatory lesions, non-inflammatory lesions, and global severity. Findings were robust across all outcomes in both studies.

Study 009 originally had the goal of demonstrating that tretinoin gel 0.05% was non-

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inferior to Retin-A Micro 0.1% Gel. However, non-inferiority could not be established for any of the endpoints. Consequently the applicant conducted the second study, #418, to demonstrate two studies which confirmed superiority to vehicle.

Since the initial 009 study failed to demonstrate non-inferiority to Retin A Micro 0.1% Gel, data for this arm was not recommended for the Clinical Studies section of the product labeling. The applicant has submitted the results of superiority of its product over placebo and that information is recommended to be included in the label. Similarly, the Adverse Reaction section should only include the common, selected adverse events for the tretinoin gel 0.05% product and vehicle. Comparisons to the third arm of the 009 study, which included Retin A Micro gel product at twice the concentration of tretinoin gel 0.05%, would not be informative and allow the applicant to formulate marketing claims that were not assessed in the second phase 3 trial.

7. INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The applicant conducted seven clinical studies from which adverse event data was collected. Data from three phase 1 trials, two phase 2 trials, and two phase 3 trials were reviewed. 960 subjects were exposed to tretinoin gel 0.05% in the course of these trials.

Dosage and disease status varied throughout the development phases:

- The Phase 1 studies used an occluded dose of approximately 0.1 g (gel) in healthy volunteers;
- The Phase 2 studies used a dose of approximately 4 g (gel) in subjects with moderately severe acne, designed to represent a “worst case” for systemic exposure;
- The Phase 3 studies represent the intended clinical application of tretinoin gel, 0.05% and used a dose of approx 0.5 g in subjects with mild to moderate acne.

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7.1.1 Deaths

There were no deaths in any of the clinical studies with tretinoin gel 0.05%.

7.1.2 Other Serious Adverse Events

The applicant reports eight subjects with serious adverse events: one in a phase 1 study, and seven in phase 3 studies. None of these were considered by the applicant to be treatment related. They include: cholelithiasis/gall bladder surgery, dehydration, appendicitis, spinal fusion surgery, bipolar relapse, depression, kidney infection, and jaw surgery. Three of these subjects discontinued due to their adverse effects.

Reviewer comment: This reviewer concurs with the assessment that the relationship of the study drug with the serious adverse events is unlikely.

7.1.3 Dropouts and Other Significant Adverse Events

No subjects withdrew from phase 1 or 2 studies as a result of adverse events. Eleven subjects withdrew from the phase 3 trials as a result of significant adverse events. Eight of the eleven were treated with tretinoin gel 0.05%, and three occurred during treatment with Retin-A Micro 0.1%.

Five of the eight subjects treated with tretinoin 0.05% gel discontinued therapy due to local dermatologic reactions, including burning/stinging, peeling and erythema, which are known adverse effects of topical retinoid therapy. One subject, a 15 year old African American woman, experienced diffuse, extensive hypopigmentation on her face. This resolved with topical Locoid and Loprox twice daily, and this resolved without further treatment. Dropouts were most frequent in the first three weeks of treatment, though two subjects in the tretinoin group discontinued due to local adverse effects at day 87 and day 51.

The remaining three subjects experienced depression, acne cyst development, and a facial burn, all thought to be unrelated to study medication.

Clinical Table 16

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Significant Adverse Events Resulting in Discontinuation from Study

Phase / Study	Treatment Group/ Subject Number	Age (yrs)/Sex	Adverse Event (Primary Term)	Study Day of Onset	Severity	Relationship to Study Drug	Duration of Event (Days)	Outcome
III / 735.126.CL009	Tretinoin Gel, 0.05% / 167	23/F	Dermatitis exfoliative; Skin burning sensation	Day 2	Moderate	Possibly	9	Resolved without treatment;
				Day 2	Moderate	Possibly	9	Resolved without treatment. (Discontinued)
III / 735.126.CL009	Tretinoin Gel, 0.05% / 348	29/F	Dermatitis exfoliative; Skin burning sensation	Day 5	Mild	Related	10	Resolved with treatment;
				Day 11	Severe	Related	3	Resolved without treatment; (Discontinued)
III / 735.126.CL009	Tretinoin Gel, 0.05% / 377	12/M	Depression	Day 8	Mild	Unrelated	10	Resolved without treatment. (Discontinued)
III / 735.126.CL009	Tretinoin Gel, 0.05% / 1037	45/F	Acne	Day 11	Moderate	Unlikely	No recorded resolution	Continuing with treatment. (Discontinued)
III / 20.CLN.126.0418	Tretinoin Gel, 0.05% / 1097	15/F	Diffuse, Extensive Hypopigmentation on Face	Day 18	Moderate	Possibly	30	Resolved with treatment (Discontinued)

Phase / Study	Treatment Group/ Subject Number	Age (yrs)/Sex	Adverse Event (Primary Term)	Study Day of Onset	Severity	Relationship to Study Drug	Duration of Event (Days)	Outcome
III / 20.CLN.126.0418	Tretinoin Gel, 0.05% / 1151	14/M	Burns First Degree	Day 2	Mild	Not Related	No recorded resolution	Continuing with Treatment (Discontinued)
III / 20.CLN.126.0418	Tretinoin Gel, 0.05% / 1265+	22/F	Skin Burning Sensation;	Day 8	Mild	Probably	15	Both resolved without treatment. (Discontinued)
			Skin Exfoliation	Day 8	Mild	Probably	15	
III / 20.CLN.126.0418	Tretinoin Gel, 0.05% / 1598	14/F	Erythema	Day 51	Moderate	Definitely	No recorded resolution	Continuing with Treatment (Discontinued)
III / 735.126.CL009	Retin-A Micro® / 494	29/F	Pruritis; Skin burning sensation	Day 5	Moderate	Possibly	4	Resolved without treatment;
					Moderate	Possibly	4	Resolved without treatment. (Discontinued)
III / 735.126.CL009	Retin-A Micro® / 525	17/F	Acne	Day 21	Moderate	Unlikely	No recorded resolution	Continuing with treatment at study end. (Discontinued)
III / 735.126.CL009	Retin-A Micro® / 967	36/F	Dermatitis exfoliative; Dry Skin	Day 2	Moderate	Probably	60	Resolved with treatment;
				Day 30	Severe	Probably	32	Resolved with treatment. (Discontinued)

7.1.3.1 Overall profile of dropouts

Study 009

Approximately 14% of subjects in Study 009 discontinued early. The discontinuation rate was higher in the tretinoin and vehicle arms than in the Retin-A arm. The most common

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reason for discontinuation was loss to follow-up, and the loss to follow-up rate was twice as high in the tretinoin gel arm (8%) as it was in either the Retin-A arm or the vehicle arm (3-4%). The next most common reason for discontinuation was “subject request unrelated to an AE” (4%) and the rate was similar among all three arms. The subject disposition in Study 009 is presented in Clinical Review Table 17

Clinical Review Table 17
Study 009 Subject Disposition

	Tretinoin Gel, 0.05%	RETIN-A Micro, 0.1%	Gel Vehicle
Number of Subjects	375	376	185
Subjects with Normal Study Completion	311 (83%)	338 (90%)	156 (84%)
Reasons for Study Discontinuation			
Adverse Reaction or Event	4 (1%)	3 (1%)	0 (0%)
Lost to Follow-Up	30 (8%)	12 (3%)	8 (4%)
Subject Request Unrelated to an AE	15 (4%)	11 (3%)	8 (4%)
Interfering Therapy	5 (1%)	4 (1%)	5 (3%)
Treatment Failure	1 (<1%)	0 (0%)	2 (1%)
Noncompliance	8 (2%)	8 (2%)	4 (2%)
Incl/Excl Discrepancy/Violation	0 (0%)	0 (0%)	1 (<1%)
Other	1 ^a (<1%)	0 (0%)	1 ^b (<1%)

^a Subject dropped in error

^b Subject wanted to try other treatment

Study 418

Approximately 13% of subjects in Study 418 discontinued early. The discontinuation rate was slightly higher in the tretinoin than the vehicle arm. The most common reason for discontinuation was “subject request unrelated to an AE”, and the rate was higher in the tretinoin gel arm (8%) than it was in the vehicle arm (5%). The next most common reason for discontinuation was “lost to follow-up” and the rate was slightly higher on the tretinoin arm than the vehicle arm (5% vs. 3%). The subject disposition for Study 418 is presented in Clinical Review Table 18:

Clinical Review Table 18

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Study 418 Subject Disposition

	Tretinoin Gel, 0.05%	Gel Vehicle
Number of Subjects	299	302
Subjects with Normal Study Completion	253 (85%)	269 (89%)
Reasons for Study Discontinuation		
Adverse Reaction or Event	4 ^a (1%)	0 (0%)
Lost to Follow-Up	15 (5%)	9 (3%)
Subject Request Unrelated to an AE	23 (8%)	16 (5%)
Interfering Therapy	0 (0%)	0 (0%)
Treatment Failure	0 (0%)	4 (1%)
Noncompliance	4 (1%)	2 (<1%)
Inclusion/Exclusion Discrepancy/Violation	0 (0%)	1 (<1%)
Other	0 (0%)	1 ^b (<1%)

^a One tretinoin subject who discontinued due to an adverse reaction (facial burning and peeling) was found to be pregnant at the exit visit.

^b Investigator's decision

Six of the eight dropouts who discontinued due to adverse events in the tretinoin group were female, and two were male.

7.1.5 Common Adverse Events

Analyses of common adverse events were not conducted for phase 1 and 2 trials because the application of medication was not typical of the intended clinical use. Only the two phase 3 trials will be discussed in this section.

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 incidence of treatment related adverse events was highest in the Retin-A Micro 0.1% group (65%), as compared to the tretinoin gel 0.05% group (50%). The Retin-A Micro group had more subjects with treatment related (judged by investigator) adverse events than the tretinoin gel 0.05% group (52% vs. 30%).

The only non-dermatologic commonly reported adverse events $\geq 5\%$ were nasopharyngitis and headache.

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Clinical Review Table 19
Adverse Events Occurring at ≥ 1% Frequency in Phase 3 Studies

Preferred Term	No. of Subjects Reporting One or More Events					
	Tretinoin Gel, 0.05% (N=674)		Retin-A Micro [®] (N=370)		Tretinoin Gel Vehicle (N=487)	
Dry skin	109	16%	112	30%	8	2%
Skin burning sensation	53	8%	57	15%	8	2%
Erythema	47	7%	67	18%	1	<1%
Dermatitis exfoliative	37	5%	80	21%	4	1%
Nasopharyngitis	35	5%	29	8%	23	5%
Headache	29	4%	22	6%	16	3%
Rash scaly	14	2%	29	8%	1	<1%

Reviewer comment: The most common adverse events were not unexpected and have been previously reported with topical tretinoin formulations. Reports of nasopharyngitis and headache are considered unrelated to study drug.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The coding differed between studies 009 and 418. In particular, investigator verbatim terms for 'peeling', 'scaling', and 'flaking' were coded differently for the two studies. In Study 009 verbatim terms including 'peeling' were coded as 'dermatitis exfoliative', verbatim terms including 'scaling' were coded as 'rash scaly', and verbatim terms including 'flaking' were coded as 'skin desquamation'. In study 418, the verbatim terms for 'peeling', 'scaling', and 'flaking' were all coded as 'skin exfoliation'.

7.1.5.4 Common adverse event tables

Clinical Review Table 20
Adverse Events Occurring in Phase 3 Studies > 1% Frequency

Clinical Review
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Preferred Term	No. of Subjects Reporting One or More Events					
	Tretinoin Gel, 0.05% (N=674)		Retin-A Micro® (N=376)		Tretinoin Gel Vehicle (N=487)	
Dry skin	109	16%	112	30%	8	2%
Skin burning sensation	53	8%	57	15%	8	2%
Erythema	47	7%	67	18%	1	<1%
Dermatitis exfoliative	37	5%	80	21%	4	1%
Nasopharyngitis	35	5%	29	8%	23	5%
Headache	29	4%	22	6%	16	3%
Skin exfoliation	25	4%	0	0%	2	<1%
Pharyngolaryngeal pain	19	3%	5	1%	8	2%
Upper respiratory tract infection	17	3%	3	1%	14	3%
Rash scaly	14	2%	29	8%	1	<1%
Influenza	12	2%	8	2%	8	2%
Pruritus	11	2%	11	3%	3	1%
Cough	10	1%	8	2%	3	1%
Sinus congestion	9	1%	8	2%	3	1%
Sinusitis	8	1%	4	1%	2	<1%
Sunburn	7	1%	5	1%	3	1%
Pain of skin	7	1%	3	1%	0	0%
Gastroenteritis viral	7	1%	1	<1%	6	1%
Dermatitis contact	6	1%	4	1%	1	<1%
Bronchitis	4	1%	2	1%	5	1%
Skin desquamation	3	<1%	5	1%	0	0%
Gingival pain	2	<1%	4	1%	2	<1%
Nausea	2	<1%	3	1%	5	1%
Seasonal allergy	1	<1%	4	1%	0	0%
Respiratory tract congestion	0	0%	4	1%	2	<1%

Clinical Review Table 21
Adverse Events ≥ 1% Frequency by System Organ Class

Clinical Review
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System Organ Class/ Preferred Term	No. of Subjects Reporting One or More Events					
	Tretinoin Gel, 0.05% (N=674)		Retin-A Micro® (N=376)		Tretinoin Gel Vehicle (N=487)	
Eye disorders	5	1%	5	1%	1	<1%
Gastrointestinal disorders	18	3%	16	4%	18	4%
Gingival pain	2	<1%	4	1%	2	<1%
Nausea	2	<1%	3	1%	5	1%
General disorders and administration site conditions	14	2%	6	2%	7	1%
Immune system disorders	5	1%	4	1%	0	0%
Seasonal allergy	1	<1%	4	1%	0	0%
Infections and infestations	96	14%	58	15%	70	14%
Bronchitis	4	1%	2	1%	5	1%
Gastroenteritis viral	7	1%	1	<1%	6	1%
Influenza	12	2%	8	2%	8	2%
Nasopharyngitis	35	5%	29	8%	23	5%
Sinusitis	8	1%	4	1%	2	<1%
Upper respiratory tract infection	17	3%	3	1%	14	3%
Injury, poisoning and procedural complications	26	4%	15	4%	11	2%
Sunburn	7	1%	5	1%	3	1%
Musculoskeletal and connective tissue disorders	10	1%	7	2%	6	1%
Nervous system disorders	33	5%	26	7%	18	4%
Headache	29	4%	22	6%	16	3%
Reproductive system and breast disorders	6	1%	2	1%	7	1%
Respiratory, thoracic and mediastinal disorders	43	6%	25	7%	22	5%
Cough	10	1%	8	2%	3	1%
Pharyngolaryngeal pain	19	3%	5	1%	8	2%
Respiratory tract congestion	0	0%	4	1%	2	<1%
Sinus congestion	9	1%	8	2%	3	1%
Skin and subcutaneous tissue disorders	208	31%	196	52%	25	5%
Dermatitis contact	6	1%	4	1%	1	<1%
Dermatitis exfoliative	37	5%	80	21%	4	1%
Dry skin	109	16%	112	30%	8	2%
Erythema	47	7%	67	18%	1	<1%
Pain of skin	7	1%	3	1%	0	0%
Pruritus	11	2%	11	3%	3	1%
Rash scaly	14	2%	29	8%	1	<1%
Skin burning sensation	53	8%	57	15%	8	2%
Skin desquamation	3	<1%	5	1%	0	0%
Skin exfoliation	25	4%	0	0%	2	<1%

7.1.5.5 Identifying common and drug-related adverse events

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Local, cutaneous adverse events were likely related to application of the study drug product.

The incidence of treatment-related AEs was highest in the Retin-A Micro 0.1% Gel group (N=245; 65%) as compared with the tretinoin gel, 0.05% group (N=199; 53%). Both of these incidence rates were significantly greater than the incidence rate for the tretinoin gel vehicle group (N=69, 37%; $P<0.001$).

No comparison was attempted to compare the tretinoin 0.05% gel product to the Retin-A Micro 0.04% Gel product, which more closely approximates the active drug concentration. It is reasonable to expect that the adverse events for the 0.04% concentration would more closely approximate those of the tretinoin 0.05% gel than the 0.1% concentration of Retin-A Micro gel which was used in the first three arm trial.

Reviewer comment: The applicant should compare the tretinoin 0.05% gel product to the Retin-A Micro 0.04% Gel before making any comparative claims regarding differences in formulation and its relationship to relative safety and efficacy.

7.1.5.6 Additional analyses and explorations

Effect of Gender on Adverse Event Reporting

The proportion of female subjects reporting one or more adverse events and skin events in particular was higher than the males across all treatment groups. The number of events was not great enough to demonstrate any marked differences in safety between subjects when evaluated by gender, but the applicant does not characterize or explain the gender differences further.

Clinical Review Table 22
Number and Percentage of Subjects Reporting One or More Events
By Gender and Treatment

Gender	Tretinoin Gel, 0.05% n/N (%)	Retin-A Micro [®] n/N (%)	Tretinoin Gel Vehicle n/N (%)
Male	151/327 (22%)	99/167 (26%)	61/237 (13%)
Female	185/347 (27%)	146/209 (39%)	80/250 (16%)
Total	336/674 (50%)	245/376 (65%)	141/487 (29%)

Clinical Review Table 23
Number and Percentage of Subjects Reporting One or More Skin and

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Subcutaneous Disorder Events by Gender and Treatment

Gender	Tretinoin Gel, 0.05% n / N (%)	Retin-A Micro® n / N (%)	Tretinoin Gel Vehicle n / N (%)
Male	89/327 (13%)	81/167 (22%)	15/237 (3%)
Female	119/347 (18%)	115/209 (31%)	10/250 (2%)
Total	208/674 (31%)	196/376 (52%)	25/487 (5%)

Effect of Age on Adverse Event Reporting:

Slightly more adverse events were reported by older subjects (≥ 16) than by younger ones in the two phase 3 studies combined. The differences are minor, and were consistent across the three treatment groups.

**Clinical Review Table 24
 Number and Percentage of Subjects Reporting One or More Events
 By Age and Treatment**

Age Group	Tretinoin Gel, 0.05% n / N (%)	Retin-A Micro® n / N (%)	Tretinoin Gel Vehicle n / N (%)
Age < 16	161/304 (24%)	106/161 (28%)	63/218 (13%)
Age ≥ 16	175/370 (26%)	139/215 (37%)	78/269 (16%)
Total	336/674 (50%)	245/376 (65%)	141/487 (29%)

**Clinical Review Table 25
 Number and Percentage of Subjects Reporting One or More Skin and
 Subcutaneous Disorder Events by Gender and Treatment**

	Tretinoin Gel, 0.05% n / N (%)	Retin-A Micro® n / N (%)	Tretinoin Gel Vehicle n / N (%)
Age < 16	91/304 (14%)	91/161 (24%)	14/218 (3%)
Age ≥ 16	117/370 (17%)	105/215 (28%)	11/269 (2%)
Total	208/674 (31%)	196/376 (52%)	25/487 (5%)

Incidence of Adverse Events Over Time

Clinical Review Table 26 presents a week-by-week graph of percent of subjects experiencing new incidences of adverse events for the Skin and Subcutaneous Tissue organ

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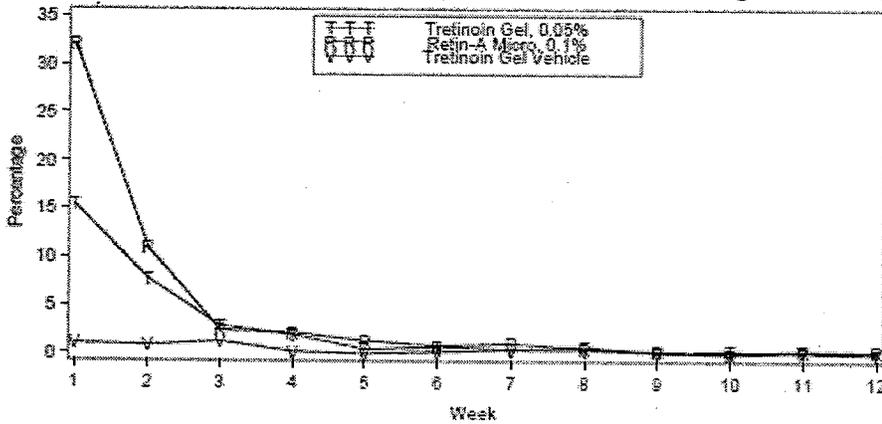
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class during the two phase 3 studies. These events included rash, skin burning, peeling, irritation, pruritus, hypopigmentation, swelling, tightness, skin ulcer, urticaria and seborrheic dermatitis. The events were counted once (even if continued into subsequent weeks) and were attributed to the week in which it began.

New events for the two treatment groups declined close to vehicle levels by week 3 and were consistently at or below 1% by week 5. Tretinoin gel 0.05% subjects had less than half the adverse event incidence at week 1 than Retin-A Micro 0.1% (15% vs. 32%).

Clinical Review Table 26
Percentage of Subjects Experiencing New Incidences of Adverse Events
Relating to Skin and Subcutaneous Tissue Disorders Organ Class by Week



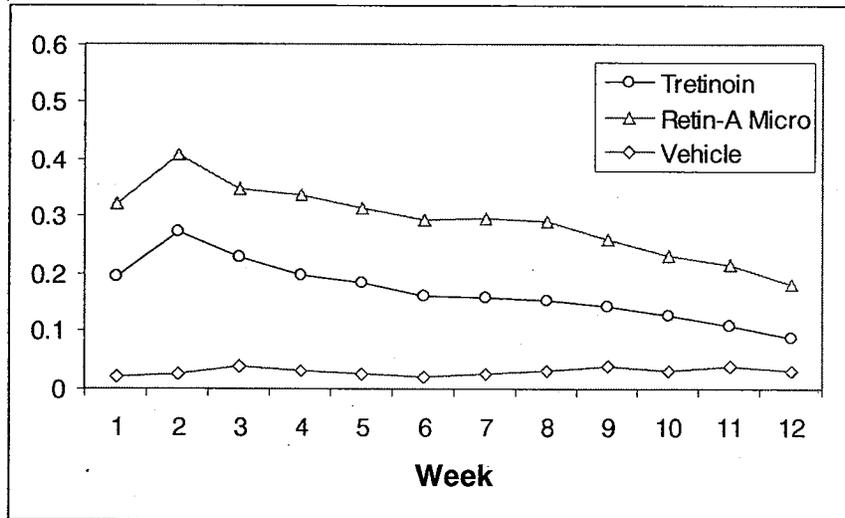
	<u>Week 1</u>	<u>Week 2</u>	<u>Week 3</u>	<u>Week 4</u>	<u>Week 5</u>	<u>Week 6</u>
Tretinoin Gel, 0.05% (N=674)	104 (15%)	52 (8%)	19 (3%)	13 (2%)	3 (<1%)	5 (1%)
Retin-A Micro®, 0.1% (N=376)	121 (32%)	41 (11%)	9 (2%)	8 (2%)	5 (1%)	3 (1%)
Tretinoin Gel Vehicle (N=487)	5 (1%)	4 (1%)	5 (1%)	1 (<1%)	0 (0%)	1 (<1%)
	<u>Week 7</u>	<u>Week 8</u>	<u>Week 9</u>	<u>Week 10</u>	<u>Week 11</u>	<u>Week 12</u>
Tretinoin Gel, 0.05% (N=674)	3 (<1%)	5 (1%)	1 (<1%)	2 (<1%)	1 (<1%)	0 (0%)
Retin-A Micro®, 0.1% (N=376)	4 (1%)	2 (1%)	1 (<1%)	0 (0%)	1 (<1%)	1 (<1%)
Tretinoin Gel Vehicle (N=487)	2 (<1%)	2 (<1%)	1 (<1%)	0 (0%)	2 (<1%)	1 (<1%)

Agency analysis of adverse events which looked at new or continuing skin related adverse events by study week are presented below for each study. To evaluate the time course of skin-related adverse events, all events in the 'skin and subcutaneous tissue disorders' were pooled together. Time was categorized into one-week intervals. Subjects were counted as having a skin event for a particular week if any skin-related adverse event had been reported as starting before or during the given week and stopping during or after the given week (7-day interval). Many events did not list stopping dates and were marked as 'continuing'. In these cases, the event was considered to have continued until the subject left the trial (date of last visit). The skin events were most common during the first three weeks of the studies, however, many subjects had events that continued throughout the course of the trial, and the incidence rate of subjects experiencing an event declined only slightly over time. The incidence of skin-related adverse events was higher on Retin-A

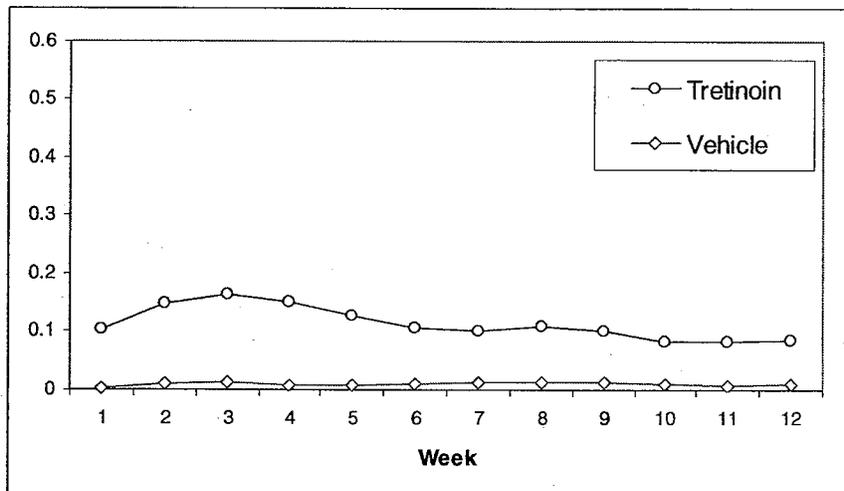
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Micro than tretinoin, and the vehicle rate was very low.

Clinical Review Table 27
Proportion of Subjects Experiencing a New or Continuing Skin-Related Adverse Event by Study Week (Study 009)



Clinical Review Table 28
Proportion of Subjects Experiencing a New or Continuing Skin-related Adverse Event by Study Week (Study 418)



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7.1.7 Laboratory Findings

No laboratory studies were performed during the phase 3 trials.

Both of the phase 2 trials included laboratory evaluations for hematology, serum chemistry and urinalysis. These studies included only 28 subjects in total and study duration was only 14 days. No clinically significant changes in laboratory parameters were identified in either study with this limited clinical laboratory examination.

Routine pregnancy testing was not performed during the phase 3 trials. Three subjects (two in the 009 study and one in the 418 study) were found to be pregnant at their exit visits. They are further discussed in section 7.1.14.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital sign data was collected in the two phase 2 trials only. A total of 28 subjects were followed for 14 days. There were no clinically relevant differences between the treatment groups.

7.1.9 Electrocardiograms (ECGs)

No electrocardiogram data was collected during any phase of drug development.

Reviewer comment: EKG assessments were not needed for this topical product.

7.1.12 Special Safety Studies

The applicant conducted several dermal safety studies to support labeling.

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Study 735.126.CL007/01 assessed the contact irritation potential of repeated applications of tretinoin 0.05% gel to the skin of healthy volunteer subjects. Nine occlusive test patches were applied containing approximately 0.1 ml of each test article over a 21 day period. Skin reactions were recorded approximately 48-72 hours after each induction application. 237 subjects were enrolled and 215 subjects completed the study. The conclusion of the study was that tretinoin 0.05% gel is irritating under occlusive conditions. One subject developed contact sensitization during the challenge phase. One subject had a serious adverse event (cholelithiasis) which was considered by the applicant to be unrelated to the study drug product.

Study 735.126.CL006/01 assessed the phototoxicity potential following application to the skin of healthy volunteer subjects. 16 subjects were enrolled, and all 16 completed the study. No erythema reactions greater than a score of 2 (moderate erythema) were observed. The applicant concluded that no subjects were considered to have had a phototoxic reaction to the study drug. There were no serious adverse events reported. No adverse event was considered related to the study drug.

Study 735.126.CL005 evaluated the photo-allergenic potential of tretinoin 0.05% gel following repeated applications to the skin of healthy volunteer subjects. 19 subjects were enrolled, and 15 completed the study. No suspected or proven cases of photo-allergenic contact dermatitis were seen in the 15 evaluable subjects. No serious adverse events were reported. Nine subjects reported 13 adverse reactions. Two were considered by the applicant to be possibly related to the study medication. These were complaints of headache. No adverse event was considered clinically significant.

Reviewer comment: It is unclear why two of six adverse events of headache were presumed to be study related and the other four were not considered to be related. Four subjects of 19 failed to complete the study (two subjects withdrew, one was deemed ineligible, and one was unable to make the scheduled visits).

In addition, the photoallergy study included 15 subjects in place of the Agency suggested 50. The phototoxicity study included only 16 subjects instead of the recommended 30 subjects.

Nonetheless, the labeling which is agreed to by the applicant is similar to the Retin A Micro 0.1% Gel labeling regarding sunlight, weather extremes, and the general Precaution regarding dry, red, swollen or blistered skin. The labeling is appropriate for the topical tretinoin class and is supported by the clinical studies submitted by the applicant.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No reports of withdrawal or rebound phenomena were received in the clinical trials for

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tretinoin gel 0.05%.

7.1.14 Human Reproduction and Pregnancy Data

All clinical studies excluded pregnant women and required that women of child bearing potential use an acceptable method of birth control throughout the studies. However, three subjects became pregnant in the phase 3 studies.

Clinical Review Table 29
Subjects Who Became Pregnant During the Phase 3 Studies

Phase / Study	Treatment Group/ Subject Number	Age(yrs)	Date of Study Entry	Date of Study Exit	Pregnancy Outcome
III/ 735.126.CL009	Tretinoin Gel, 0.05% / 185	26	March 28, 2003	April 25, 2003	Noncompliant; lost to follow- up
III/ 735.126.CL009	Tretinoin Gel, 0.05% / 1034	23	April 3, 2003	April 3, 2003	Miscarriage+
III/ 20.CLN.126.0418	Tretinoin Gel, 0.05% / 1265	22	August 16, 2005	October 11, 2005	Successful Childbirth

+ Follow-up information from the investigator indicated that she miscarried on August 19, 2003; the subject was noted to have had a history of "female problems" as defined by the investigator.

Subject 185 applied the tretinoin gel 0.05% for one month before discontinuing from the study. She was lost to follow-up and no pregnancy outcome is available.

Subject 1034 completed the 12 week study and became aware that she was pregnant at her final week 12 study visit following the routine pregnancy test that was scheduled in the study protocol. She subsequently miscarried, _____, eight weeks after study product use. She had a history of uterine fibroids.

b(6)

Subject 1265 used tretinoin gel 0.05% gel for 7 days and discontinued treatment due to facial burning and peeling. At her exit visit, she stated she was pregnant. She reported a successful childbirth.

The pharmacology/toxicology review of this product by Dr. Merrill notes that:

"Tretinoin, like other retinoids, is teratogenic and embryotoxic in multiple species when administered at sufficient doses and at the vulnerable gestational time period. Doses of tretinoin that do not cause morphological changes in offspring may cause behavioral effects in the developing animals. Topical application of tretinoin appears to be less likely to result in teratogenic or other effects probably due to lower systemic and embryo exposure to tretinoin by the topical route than by the oral route."

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The inadvertent pregnancy experience in this application does not present any information to support any change in the labeling utilized for Retin-A products; nor does the applicant propose any such change. The final label carries a pregnancy category of C and language similar to the Retin A Micro labeling:

“With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Cases of temporally associated congenital malformations have been reported with use of other topical tretinoin products. The significance of these spontaneous reports in terms of risk to the fetus is not known.

There are no well-controlled studies in pregnant women. Atralin Gel. Atralin Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.”

7.1.16 Overdose Experience

No reports of drug overdose were received for clinical trials for tretinoin gel 0.05%. No literature reports of intentional or accidental overdosage or oral ingestion were found. No overdosage section is recommended in labeling for this topical product.

7.1.17 Postmarketing Experience

Tretinoin gel 0.05% is not marketed in any country to date. There is extensive experience related to topical tretinoin gels since 1975 in eight different gel formulations.

		<u>Approval Date</u>
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

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7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1.2 Demographics

Clinical Review Table 30
Demographic Information for Phase 1 and 2 Studies

Treatment	Phase I			Phase II			
	735.126.CL005	735.126.CL006	735.126.CL007	735.126.CL008		20.CLN.126.024	
	Tretinoin Gel, 0.05%; Tretinoin Gel, Vehicle; W. Petrolatum	Tretinoin Gel, 0.05%; Tretinoin Gel, Vehicle; W. Petrolatum	Tretinoin Gel, 0.05%; Tretinoin Gel, Vehicle; W. Petrolatum	Tretinoin Gel, 0.05%	Retin-A Micro®	Tretinoin Gel, 0.05%	Retin-A Micro®
	n=19	n=16	n=237	n=6	n=6	n=8	n=8
Age (years)							
Mean	22.63	30.50	22.89	19.33	22.00	18.63	19.38
Std	6.46	13.10	8.29	0.82	7.40	4.63	7.07
Range	18-45	20-71	17-61	18.0-20.0	18.0-37.0	13-25	14-33
< 16	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (25%)	3 (38%)
≥ 16	19 (100%)	16 (100%)	237 (100%)	6 (100%)	6 (100%)	6 (75%)	5 (63%)
Gender							
Male	3 (16%)	3 (19%)	76 (32%)	3 (50%)	4 (67%)	6 (75%)	4 (50%)
Female	16 (84%)	13 (81%)	161 (68%)	3 (50%)	2 (33%)	2 (25%)	4 (50%)
Race							
Caucasian	18 (95%)	14 (88%)	No data	3 (50%)	1 (17%)	8 (100%)	5 (63%)
Black	0 (0%)	0 (0%)	No data	2 (33%)	2 (33%)	0 (0%)	2 (25%)
Asian	0 (0%)	1 (6%)	No data	1 (17%)+	2 (33%)+	0 (0%)	0 (0%)
Other	1 (5%)†	1 (6%)	No data	0 (0%)	1 (17%)†	0 (0%)	1 (13%)†
Skin Phototype							
I	0 (0%)	0 (0%)	No data	No data	No data	No data	No data
II	1 (5%)	6 (38%)	No data	No data	No data	No data	No data
III	18 (95%)	9 (56%)	No data	No data	No data	No data	No data
IV	0 (0%)	1 (6%)	No data	No data	No data	No data	No data
V	0 (0%)	0 (0%)	No data	No data	No data	No data	No data
VI	0 (0%)	0 (0%)	No data	No data	No data	No data	No data

+Asian / Pacific Islander

†Hispanic / Latino

Due to rounding, the percentages may not add to 100%.

Clinical Review Table 31
Demographic Information for Phase 3 Studies

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Treatment	Phase III				
	735.126.CL009			20.CLN.126.0418	
	Tretinoin Gel, 0.05%	Retin-A Micro®	Tretinoin Gel Vehicle	Tretinoin Gel, 0.05%	Tretinoin Gel Vehicle
	n=375	n=376	n=185	n=299	n=302
Age (years)					
Mean	18.18	18.4	19.04	18.7	19.1
Std	6.89	6.65	8.09	6.9	7.8
Range	10-53	10-45	10-49	10-52	10-65
< 16	172 (46%)	161 (43%)	86 (46%)	132 (44%)	132 (44%)
≥ 16	203 (54%)	215 (57%)	99 (54%)	167 (56%)	170 (56%)
Gender					
Male	178 (47%)	167 (44%)	88 (48%)	149 (50%)	149 (49%)
Female	197 (53%)	209 (56%)	97 (52%)	150 (50%)	153 (51%)
Race					
Caucasian	258 (69%)	262 (70%)	121 (65%)	250 (84%)	248 (82%)
Black	57 (15%)	69 (18%)	36 (19%)	37 (12%)	41 (14%)
Asian	12 (3%)	10 (3%)	5 (3%)	8 (3%)	7 (2%)
Other	48 (13%)	35 (9%)	23 (12%)	6 (2%)§	8 (2%)‡
Skin Phototype					
I	16 (4%)	16 (4%)	10 (5%)	10 (3%)	11 (4%)
II	88 (23%)	83 (22%)	40 (22%)	46 (15%)	41 (14%)
III	141 (38%)	136 (36%)	68 (37%)	101 (34%)	92 (30%)
IV	130 (35%)	140 (37%)	67 (36%)	85 (28%)	95 (31%)
V	No data	No data	No data	30 (10%)	35 (12%)
VI	No data	No data	No data	27 (9%)	28 (9%)

‡American Indian / Alaskan Native

§Hawaiian / Pacific Islander

The skin phototype scale used in the two Phase III studies differed between studies and therefore was not pooled. Study 735.126.CL009 used a scale that ranged from phototype I to IV and was based solely on sunburn/tanning history. Study 20.CLN.126.0418 used the Fitzpatrick scale with categorizations ranging from I to VI that included both skin color and sunburn/tanning history.

The n for Skin Phototype for Retin-A Micro® adds to 375 because Subject 318 had missing baseline data. Due to rounding, the percentages may not add to 100%.

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7.2.2.2 Postmarketing experience

The proposed product is not yet marketed in any country.

7.2.3 Adequacy of Overall Clinical Experience

The overall exposure in terms of numbers of subjects and duration of exposure is acceptable to assess the safety of the product for its intended use. The designs of the studies were adequate to address safety concerns. Topical safety was adequately assessed in the development program.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The pharmacology/toxicology review by Dr. Merrill concludes:

“No specific safety pharmacology studies have been undertaken with Tretinoin Gel, 0.05%. Topical tretinoin has been in extensive clinical usage for many years and no toxicologically important safety pharmacology issues have been identified. The absence of specific safety pharmacology data for this formulation is considered to be fully justified since preclinical and clinical pharmacokinetic exposure at large multiples of the therapeutic dose does not result in alteration of circulating levels of endogenous tretinoin or its metabolites.”

During the pre-NDA meeting (June 1, 2006), the sponsor agreed to conduct a 90-day dermal dose range-finding study in mice and a subsequent dermal mouse carcinogenicity study as a post-marketing commitment to provide data on long term dermal exposure of tretinoin gel, 0.05%.

7.2.5 Adequacy of Routine Clinical Testing

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The studies conducted for this application are adequate to support an approval action for this application. No new safety issues were identified and there is extensive clinical experience for topical tretinoin formulations at various concentrations above and below the dose for this product.

Limitations of comparison claims by the applicant should be considered for any claims related to the comparator product, Retin-A Micro Gel 0.1%. The tretinoin 0.05% gel failed to demonstrate non-inferiority and although the safety profile was better than the comparator in the first study 418, the concentrations of tretinoin are different enough that no claims for improved tolerability should be allowed.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Two Phase 2 and one Phase 3 clinical trials included evaluations of blood samples that were collected both before and after subject treatment with Tretinoin Gel, 0.05% at levels that were considered to be either maximal (high concentrations) or "normal" concentrations anticipated from product use under usual treatment conditions).

The results of the pharmacokinetic analyses conducted in these three trials demonstrated that use of tretinoin gel, 0.05% has no effect on the circulating levels of either tretinoin or its relevant metabolites (13-cis-RA and 4-oxo-13-cis-RA). No differences between treatment groups were observed in concentrations of tretinoin or its metabolites for subjects who were randomized to tretinoin gel, 0.05%, Retin-A Micro 0.1%, and/or the tretinoin gel vehicle.

The findings from these studies demonstrated that Tretinoin Gel, 0.05% does not result in measurably increased systemic exposure to either tretinoin or its relevant metabolites.

7.2.9 Additional Submissions, Including Safety Update

The applicant, Coria Laboratories, Ltd., submitted a four month safety update on February 12, 2007. They reported that "There is no new safety information to submit to this application. No new studies have been initiated since the submission of this application."

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7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Tretinoin is a well established molecular entity and its adverse event profile is reasonably well understood. The common side effects of skin irritation, dryness, redness, and peeling are predictable and labeling is adequate to address these safety concerns. There were no significant non-skin related adverse events demonstrated in the development program.

No conclusions can be drawn from the inadvertent pregnancy experience in the phase 3 studies. Labeling similar to other formulations of tretinoin topical products is recommended and should be adequate to communicate the potential risk to exposed pregnant women.

7.4 General Methodology

7.4.3 Causality Determination

It is likely that the local dermatologic adverse events of skin dryness, burning, redness, and peeling were causally related to the studied product, tretinoin gel 0.05%. The other reported adverse events which occurred at a frequency $\geq 1\%$ are unlikely to be causally related to the tretinoin gel 0.05%. These included nasopharyngitis (5%), headache (4%), and rash (2%).

8. ADDITIONAL CLINICAL ISSUES

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8.1 Dosing Regimen and Administration

Dose-ranging studies were not conducted. Currently marketed formulations of tretinoin are dosed once in the evening. Rather than conduct dose-ranging studies, the applicant based their dosing regimen on those for the individually marketed tretinoin products electing once daily dosing.

Dosing at bedtime may have a beneficial effect since the product may cause heightened susceptibility to sun exposure. The comparator product, Retin-A Micro 0.01% Gel, carries similar dosing instruction.

8.2 Drug-Drug Interactions

No drug-drug interactions were analyzed. The applicant has submitted similar labeling for drug interactions as for Retin A Micro 0.1% Gel which has been agreed to by the Agency:

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.

8.3 Special Populations

The applicant's efforts to evaluate the effects of age, gender or skin type/race and ethnicity on efficacy were adequate. There was no evidence of clinically significant effect of any of these parameters on efficacy.

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8.4 Pediatrics

The applicant has requested a partial waiver in order to exclude the requirements for conducting pediatric assessments in subjects under the age of 10 years. The applicant asserts that studies within this age group are either impossible or highly impractical to conduct, and thus the statutory reasons for waiver of pediatric studies has been met as per Section 505B(a)(4)(B)(i) of the Food, Drug and Cosmetic Act.

The applicant contends that the indication, acne vulgaris, has extremely limited applicability to pediatric patients under the age of 10 years because the disease is manifested predominantly during puberty with a typical age onset of 12-13 years. The mean age of subjects of the phase 3 clinical studies was approximately 19 years.

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 10 years, since acne vulgaris does not typically occur in the younger, pre-pubertal age group and subjects younger than 10 were not included in the phase 3 trials.

The reference listed drug, as well as all other topical tretinoin products for acne, is approved for patients 12 years and older.

Since the onset of acne is determined primarily by pubertal age rather than chronological age, a specific lower age limit for the indication is not included in the Indications labeling for this product. There is no evidence that the efficacy or adverse event profile is substantially different at 10 years versus 12 years for pubertally matched subjects.

8.7 Postmarketing Risk Management Plan

During the pre-NDA meeting (June 1, 2006), the sponsor agreed to conduct a

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Clinical Review

David Kettl, MD

NDA 22-070

Atralin Gel 0.05% (tretinoin gel 0.05%)

dermal dose range-finding study in mice and a subsequent dermal mouse carcinogenicity study as a post-marketing commitment to provide data on long term dermal exposure of tretinoin gel, 0.05%.

9. OVERALL ASSESSMENT

9.1 Conclusions

This reviewer recommends that Atralin Gel 0.05% (tretinoin gel 0.05%) be approved for the topical treatment of acne vulgaris. The applicant has presented adequate evidence from two well-controlled studies that the proposed concentration of this product is superior to placebo in the treatment of acne for 12 weeks.

The most common adverse events in the phase 3 studies were dry skin, skin exfoliation, erythema, and burning. 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 deaths and no serious adverse events which were considered to be related to tretinoin gel 0.05%.

9.2 Recommendation on Regulatory Action

Approval is recommended for NDA 22-070, Atralin gel 0.05% (tretinoin gel 0.05%) for the indication of acne vulgaris. The data submitted in this application show efficacy over placebo in two studies across all efficacy endpoints. Safety data reviewed to date indicate that the safety population was adequate and the safety profile of tretinoin gel 0.05% is acceptable.

The applicant has submitted under section 505(b)(2) and has referenced Retin A Micro

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0.1% Gel as the comparator product. There are currently no approved tretinoin gel products at the 0.05% concentration.

The first phase 3 study failed to show non-inferiority to Retin A Micro 0.1% Gel, though superiority to vehicle was demonstrated. A second phase 3 study compared tretinoin gel 0.05% to vehicle and again confirmed superiority of the drug product to the vehicle.

The most common adverse events in the phase 3 studies were dry skin, skin exfoliation, erythema, and burning. 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 deaths and no serious adverse events which were considered to be related to tretinoin gel 0.05%.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Risk management will be addressed through labeling, which is similar to other existing topical tretinoin products. The expected risks of tretinoin gel are local, dermatologic effects. The safety data reported in the studies in this application did not identify any other safety concerns beyond those expected local adverse events.

9.3.2 Required Phase 4 Commitments

During the pre-NDA meeting (June 1, 2006), the sponsor agreed to conduct a ——— dermal dose range-finding study in mice and a subsequent dermal mouse carcinogenicity study as a post-marketing commitment to provide data on long term dermal exposure of tretinoin gel, 0.05%.

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No additional phase 4 commitments are required from the clinical perspective.

9.3.3 Other Phase 4 Requests

There are no other phase 4 requests.

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9.4 Labeling Review

Labeling negotiations are ongoing at the time of closure of this clinical review.

9.5 Comments to Applicant

From the pharmacology/toxicology review by Dr. Merrill:

Please submit a timeline for the mouse dermal carcinogenicity study which was agreed to be conducted as a phase 4 study commitment. This should include dates of submission for the _____ dose range-finding study report, study protocol submission, study start date and date of final report submission.

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Clinical Review
David Kettl, MD
NDA 22-070
Atralin Gel 0.05% (tretinoin gel 0.05%)

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/s/

David Kettl
7/11/2007 01:14:47 PM
MEDICAL OFFICER

Markham Luke
7/13/2007 01:39:20 PM
MEDICAL OFFICER
Clinical Review - labeling in PLR format under discussion
with sponsor. Concur with approval recommendation. See also
TL interdisciplinary review to follow.

Susan Walker
7/27/2007 03:30:18 PM
DIRECTOR

Medical Officer Review of NDA 22-070
Clinical Review Addendum

NDA: 22-070
Serial Number: 000
RPM: Bauerlien

Correspondence Date: September 28, 2007
CDER Stamp Date: September 29, 2007
Review Date: July 26, 2007
Clinical: Kettl/Luke

Sponsor: Coria Laboratories, Ltd.

Drug: Atralin (tretinoin gel) 0.05%

Pharmacologic Category: Retinoid

Indication: Acne vulgaris

Dosage Form and Route of Administration: Topical gel

Regulatory Summary:

The applicant has submitted a 0.05% gel formulation of tretinoin, Atralin Gel 0.05%, for daily topical application for the treatment of acne vulgaris. This review is an addendum to the clinical review dated July 15, 2007, and will elaborate on several issues which arose during the final review process prior to an action decision by the Division. The issues of the status of the 505(b)(2) clinical bridge and dermal safety studies will be discussed.

The applicant has submitted under section 505(b)(2) and has referenced Retin A Micro 0.1% Gel as the comparator reference product. There are currently no approved tretinoin gel products at the 0.05% concentration.

The sponsor's original development plan for tretinoin gel 0.05% in the treatment of acne vulgaris was to conduct one three-arm study to support a 505(b)(2) application with listed drug Retin-A Micro Gel (tretinoin) 0.1% (Study 009). The study demonstrated that tretinoin gel was superior to vehicle but could not demonstrate that tretinoin gel was non-inferior to Retin-A Micro Gel 0.1%.

After meeting with the Agency (December 2, 2004), the sponsor agreed to revise their development plan and conduct a second study so that the efficacy assessment could be based on two studies with vehicle control arms with the Retin-A Micro arm of the first study providing a bridge to the Agency's findings of safety for the listed product.

During the December 2, 2004 Guidance meeting, the applicant was informed that:

If the sponsor submits a 505(b)(2) NDA with an adequate clinical bridge to Retin-A Micro Gel 0.1% then the Agency will be able to use its finding of safety for Retin-A Micro Gel 0.1% to help support the safety of the sponsor's product. In that case, no additional nonclinical studies would be recommended to support the active ingredient, tretinoin. However, adequate data to support the new excipients should be submitted.

The sponsor then completed a second phase 3 study which compared tretinoin gel 0.05% to vehicle and again confirmed superiority of the drug product to the vehicle. Thus efficacy was established with two adequate clinical phase 3 trials demonstrating efficacy to placebo.

The applicant has established a clinical bridge for both systemic and local safety with the reference comparator product, Retin A Micro Gel 0.1%.

Systemic safety was demonstrated in 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%. These phase 2 studies, 735.126.CL008, and 20.CLN.126.024, included 12 and 16 subjects, respectively. 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). 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. The clinical pharmacology review concluded that the systemic exposure of tretinoin and its two metabolites are comparable for the two tretinoin formulations, and the systemic safety of the proposed Atralin product is expected to be no worse than Retin A Micro Gel 0.1%.

Baseline and final plasma levels for tretinoin and metabolites

Compound	735.126.CL008/01				20.CLN.126.024			
	Tretinoin Gel, 0.05%		RETIN-A Micro		Tretinoin Gel, 0.05%		RETIN-A Micro	
	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	1.6-3.6	1.0-3.1	1.7-5.9	1.5-7.0	1.0-3.3	0.6-6.2

Day-14 AUC for tretinoin and metabolites

	735.126.CL007/01			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	0.544	32.750	32.675	0.9724
	STD	3.80		4.234	4.945	
	Range	21.9-32.0	31.9-31.3	27.5-37.8	26.7-40.8	
13-cis Retinoic Acid	Mean	20.58	0.475	31.20	33.16	0.6591
	STD	1.94		5.82	9.43	
	Range	16.9-22.0	13.4-24.2	24.4-41.4	21.3-47.3	
4-oxo-13 cis Retinoic Acid	Mean	34.19	0.156	71.81	63.29	0.6227
	STD	11.78		33.01	32.35	
	Range	18.2-50.4	31.7-56.4	49.0-138.2	24.3-112.3	

Local safety was assessed throughout development by the assessment of adverse event data from three phase 1 trials, two phase 2 trials, and two phase 3 trials. 960 subjects were exposed to tretinoin gel 0.05% in the course of these trials. In the two phase 2 trials already referenced above, as well as the initial phase 3 trial which compared Atralin Gel 0.05% to its vehicle and to the reference product, Retin A Micro Gel 0.1%, local safety was assessed and compared.

Local safety adverse events were less than the comparator product. However, it should again be noted that the concentration of the Retin A Gel product is twice that of the proposed Atralin product. These results were not unexpected, but they again help to bridge the local safety to the comparator product in support of a 505(b)(2) application.

This reviewer concludes that the studies which included Retin A Micro Gel 0.1% have adequately established a clinical bridge for the application of Atralin Gel 0.05% and the systemic and local safety of the proposed Atralin gel is expected to be no worse than the profile of Retin A Micro Gel 0.1%.

Dermal Safety Studies:

The applicant conducted several dermal safety studies to support labeling.

Study 735.126.CL007/01 assessed the contact irritation potential of repeated applications of tretinoin 0.05% gel to the skin of healthy volunteer subjects. Nine occlusive test patches were applied containing approximately 0.1 ml of each test article over a 21 day period. Skin reactions were recorded approximately 48-72 hours after each induction application. 237 subjects were enrolled and 215 subjects completed the study. The

conclusion of the study was that tretinoin 0.05% gel is irritating under occlusive conditions. One subject developed contact sensitization during the challenge phase. One subject had a serious adverse event (cholelithiasis) which was considered by the applicant to be unrelated to the study drug product.

Study 735.126.CL006/01 assessed the phototoxicity potential following application to the skin of healthy volunteer subjects. 16 subjects were enrolled, and all 16 completed the study. No erythema reactions greater than a score of 2 (moderate erythema) were observed. The applicant concluded that no subjects were considered to have had a phototoxic reaction to the study drug. There were no serious adverse events reported. No adverse event was considered related to the study drug.

Study 735.126.CL005 evaluated the photo-allergenic potential of tretinoin 0.05% gel following repeated applications to the skin of healthy volunteer subjects. 19 subjects were enrolled, and 15 completed the study. No suspected or proven cases of photo-allergenic contact dermatitis were seen in the 15 evaluable subjects. No serious adverse events were reported. Nine subjects reported 13 adverse reactions. Two were considered by the applicant to be possibly related to the study medication. These were complaints of headache. No adverse event was considered clinically significant.

During discussions with the applicant in the review of the application since the original clinical review was filed, it was concluded that the dermal safety studies which were conducted were inadequate in terms of the numbers of subjects included. The photoallergy study included 15 subjects in place of the Agency suggested 50. The phototoxicity study included only 16 subjects instead of the recommended 30 subjects. The cumulative irritation assessed in the 007 protocol did not apply sufficient exposures of the product.

The applicant submitted in serial number 049 of IND 63,067 a protocol for the assessment of 21 day cumulative irritation. This study included 32 evaluable subjects instead of the suggested 35 subjects, and a final report will be submitted by the applicant by 12/31/07. This is acceptable to this reviewer as a phase 4 post-marketing commitment.

The applicant has agreed to complete phototoxicity and photoallergenicity protocols with adequate numbers of evaluable subjects as an additional post-marketing commitment. The final study reports are to be submitted by June 30, 2008.

Recommendation:

This reviewer again recommends approval of Atralin Gel 0.05% for the treatment of acne vulgaris. The applicant has presented adequate evidence from two adequate and well-controlled studies in subjects with acne vulgaris, that this product is superior to placebo, when evaluated after 12 weeks of treatment.

Systemic and local safety relative to the reference listed product, Retin A Micro Gel 0.1% in two phase 2 pharmacokinetic studies as well as the phase 3 three arm study, 009. This clinical bridge to Retin A Micro Gel 0.1% is sufficient to support approval for a 505(b)(2) application.

While this reviewer anticipates no issues of local dermal safety beyond those seen in the phase 3 efficacy trials, the applicant has agreed to conduct more adequate dermal safety studies to ensure that no signals related to differences in formulation are identified. These phase 4 post-marketing commitments are expected to be completed by June 30, 2008.

David Kettl, MD
Medical Officer

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/s/

David Kettl
7/26/2007 12:03:19 PM
MEDICAL OFFICER

Susan Walker
7/26/2007 02:25:54 PM
DIRECTOR

DIVISION OF PULMONARY AND ALLERGY PRODUCTS
MEDICAL OFFICER CONSULTATION

Date: June 20, 2007
To: Melinda Bauerlien, Project Manager, Division of Dermatology and
Dental Products (DDDP)
From: Susan Limb, MD, Medical Officer
Through: Sally Seymour, MD, Medical Team Leader
Through: Badrul Chowdhury, MD, PhD, Division Director
Subject: NDA 22-090 Tretinoin Gel 0.05% and Fish Allergy

General Information

NDA/IND#: NDA 22-070
Sponsor: Coria
Drug Product: Tretinoin Gel 0.05%
Protocol: Not applicable
Request From: Melinda Bauerlien, Project Manager, DDDP
Date of Request: June 12, 2007
Date Received: June 12, 2007
Materials: Literature reference, proposed tretinoin 0.05% gel package insert
Reviewed:

Executive Summary

This is a medical officer consultation in response to a consultation request from the Division of Dermatology and Dental Products regarding potential hypersensitivity reactions in a new topical drug product, tretinoin 0.05% gel, that contains collagen derived from a fish source (Pancogene Marin). Pancogene Marin is included as a _____ at a concentration of _____%. The proposed indication for tretinoin 0.05% gel is the treatment of acne vulgaris. Adverse reactions associated with tretinoin include redness, burning, stinging, peeling, and itching. The issue of potential fish allergy was not addressed in the clinical trials submitted under the NDA. DDDP has asked for input regarding potential allergy concerns and relevant labeling recommendations. b(4)

Division Response

Parvalbumin is generally considered the major fish allergen. While the reference provided suggests that collagen may also be a significant allergen, the supportive literature is quite limited and originates from Japan and Scandinavia, two specific regions of the world where fish consumption is particularly high and fish allergy is far more prevalent. Based on current evidence, it is unlikely that fish collagen is a significant allergen in the US population.

Although the risk of contamination of the collagen preparation with other allergenic proteins like parvalbumin remains, the likelihood of an allergic reaction from topical application and at such a low concentration is very low. Although application to a compromised skin barrier may increase the risk of sensitization or allergic reaction, a systemic reaction, including generalized urticaria or anaphylaxis, is highly unlikely in the absence of ingestion or direct inhalation. If any immediate allergic reaction is observed, it would probably be limited to local pruritus and erythema, possibly accompanied by a wheal reaction.

In the United States, the estimated prevalence of fish allergy is ~0.4% of the general population (Sicherer SH et al. *J Allergy Clin Immunol*, 2004 Jul; 114(1): 159-65). Although this estimate may seem high, this figure is based on a telephone survey of US households randomly selected and may well be an overestimate as the reliability of self-reported food allergy is often questionable. In many patients with self-reported fish allergy, the symptoms do not appear to have an IgE-mediated etiology upon skin/RAST testing or may be attributable to cross-contamination from other foods, particularly shellfish.

Given the route and negligible amount of expected exposure, combined with the presumed modest allergenic potential of fish collagen, the risk to fish-allergic patients using the tretinoin 0.05% gel product seems very low. Patients who do develop pruritus or urticaria should be advised to stop the medication and contact their health care provider. The inclusion of fish allergy in the Warnings and Precautions is appropriate as the risk for an allergic reaction remains a possibility, but a more stringent warning does not seem indicated in the absence of a safety signal from the clinical experience.

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/s/

Susan L Limb
6/26/2007 03:06:32 PM
MEDICAL OFFICER

Sally Seymour
6/26/2007 03:11:31 PM
MEDICAL OFFICER
I concur.

Badrul Chowdhury
6/26/2007 03:28:35 PM
MEDICAL OFFICER
I concur