

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 207955

Name: Tretinoin Gel USP, 0.05%

Sponsor: Mylan Pharmaceuticals Inc.

Approval Date: August 13, 2015

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APPLICATION NUMBER:
ANDA 207955

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APPLICATION NUMBER:

ANDA 207955

APPROVAL LETTER



ANDA 207955

ANDA APPROVAL

Spear Pharmaceuticals
37 Jefferson Landing Circle
Port Jefferson, NY 11777
Attention: David J. Christ

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated September 30, 2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Tretinoin Gel USP, 0.05%.

Reference is also made to your amendments dated October 27, 2014; and January 13, March 17, March 26, June 19, and July 3, 2015.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. **Accordingly the ANDA is approved**, effective on the date of this letter. The Division of Bioequivalence has determined your Tretinoin Gel USP, 0.05% to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug product (RLD), Atralin Gel, 0.05% of Dow Pharmaceutical Sciences (Dow).

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

You have been requested to provide information after the drug application has been approved. Any information submitted to meet the conditions requested in this letter is considered a “Post Approval Commitment Response”. To alert the Office of Generic Drug staff to the fact that you are providing post approval commitment information, please designate your submission in your cover letter as “POST APPROVAL COMMITMENT RESPONSE”.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

William P.

Rickman -S

For Carol A. Holquist, RPh

Acting Deputy Director

Office of Regulatory Operations

Office of Generic Drugs

Center for Drug Evaluation and Research



Digitally signed by William P. Rickman -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People,
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cn=William P. Rickman -S
Date: 2015.08.13 12:14:27 -04'00'

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 207955

LABELING

These highlights do not include all the information needed to use Tretinoin Gel, USP safely and effectively. See full prescribing information for Tretinoin Gel, USP.

**Tretinoin gel, USP 0.05%
For topical use only
Initial U.S. Approval: 1973**

INDICATIONS AND USAGE

Tretinoin gel, USP is a retinoid indicated for topical treatment of acne vulgaris (1)

DOSAGE AND ADMINISTRATION

- Apply a thin layer of tretinoin gel, USP once daily, before bedtime, to skin where lesions occur. Keep away from eyes, mouth, nasal creases, and mucous membranes (2)
- Tretinoin gel, USP is not for oral, ophthalmic, or intravaginal use (2)

DOSAGE FORMS AND STRENGTHS

Gel, 0.05% (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Tretinoin gel, USP should not be used on eczematous or sunburned skin due to potential for severe irritation (5.1)
- Topical over-the-counter acne preparations, concomitant topical medications, medicated cleansers, topical products with alcohol or astringents: Use with caution, irritation may occur. (5.1)
- Avoid unprotected exposure to sunlight including sunlamps (UV light) when using tretinoin gel, USP due to potential for increased photosensitization. Use sunscreen of at least SPF 15 and protective clothing during exposure (5.2)
- Avoid use of tretinoin gel, USP with weather extremes, such as wind or cold due to potential for increased irritation (5.2)
- Use tretinoin gel, USP with caution if allergic to fish due to potential for allergenicity to fish protein. Patients who develop pruritus or urticaria should contact their health care provider. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (incidence \geq 5%) with tretinoin gel, USP are dry skin, peeling/scaling/flaking skin, skin burning sensation, and erythema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Spear Dermatology Products at 1-866-SPEAR-RX (773-2279) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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- DOSAGE AND ADMINISTRATION
- DOSAGE FORMS AND STRENGTHS
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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Tretinoin gel, USP is indicated for topical treatment of acne vulgaris.

2 DOSAGE AND ADMINISTRATION

For topical use only. Not for ophthalmic, oral, or intravaginal use.

Tretinoin gel, USP should be applied once daily, before bedtime, to the skin where acne lesions appear, using a thin layer to cover the entire affected area. Tretinoin gel, USP should be kept away from the eyes, the mouth, paranasal creases, and mucous membranes. Application of excessive amounts of gel will not provide incremental efficacy.

Patients treated with tretinoin gel, USP may use cosmetics, but the areas to be treated should be cleansed thoroughly before the medication is applied.

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

3 DOSAGE FORMS AND STRENGTHS

Gel, 0.05%

Each gram of tretinoin gel, USP contains 0.5 mg (0.05%) tretinoin in a translucent to opaque, pale yellow topical gel.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Skin Irritation

The skin of certain individuals may become dry, red, or exfoliated while using tretinoin gel, USP. If the degree of irritation warrants,

patients should be directed to temporarily reduce the amount or frequency of application of the medication, discontinue use temporarily, or discontinue use all together. Efficacy at reduced frequencies of application has not been established. If a reaction suggesting sensitivity occurs, use of the medication should be discontinued. Mild to moderate skin dryness may also be experienced; if so, use of an appropriate moisturizer during the day may be helpful.

Tretinoin has been reported to cause severe irritation on eczematous or sunburned skin and should be used with utmost caution in patients with these conditions.

To help limit skin irritation, patients must:

- wash the treated skin gently, using a mild, non-medicated soap, and pat it dry
- avoid washing the treated skin too often and scrubbing the affected skin area
- avoid contact with the peels of limes

5.2 Ultraviolet Light and Environmental Exposure

Unprotected exposure to sunlight, including sunlamps, should be minimized during the use of tretinoin gel, USP. Patients who normally experience high levels of sun exposure, and those with inherent sensitivity to sun, should be warned to exercise caution. Use of sunscreen products of at least SPF 15 and protective clothing over treated areas is recommended when exposure cannot be avoided.

Weather extremes, such as wind or cold, also may be irritating to tretinoin-treated skin.

5.3 Fish Allergies

Tretinoin gel, USP contains soluble fish proteins and should be used with caution in patients with known sensitivity or allergy to fish. Patients who develop pruritus or urticaria should contact their health care provider.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under prescribed conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In two randomized, controlled trials, 674 subjects received treatment for up to 12 weeks with tretinoin gel, USP [see *Clinical Trials* (14)]. In these studies, 50% of the subjects who were treated with tretinoin gel, USP reported one or more adverse reactions; 30% of the subjects reported treatment-related adverse reactions. In the vehicle group, 29% of the 487 randomized subjects reported at least one adverse reaction; 5% of the subjects reported events that were treatment-related. There were no serious, treatment-related adverse reactions reported by subjects in any of the treatment groups.

Selected adverse reactions that occurred in at least 1% of subjects in the two studies combined are shown in Table 1 (below). Most skin-related adverse reactions first appear during the first two weeks of treatment with tretinoin gel, USP, and the incidence rate for skin-related reactions peaks around the second and third week of treatment. In some subjects the skin-related adverse reactions persists throughout the treatment period.

Table 1. Number of Subjects with Selected Adverse Reactions (Occurring in At Least 1% of Subjects)

Event	Tretinoin Gel, USP (n = 674)	Vehicle Gel (n = 487)
Dry Skin	109 (16%)	8 (2%)
Peeling/Scaling/Flaking Skin	78 (12%)	7 (1%)
Skin Burning Sensation	53 (8%)	8 (2%)
Erythema	47 (7%)	1 (<1%)
Pruritus	11 (2%)	3 (1%)
Pain of Skin	7 (1%)	0 (0%)
Sunburn	7 (1%)	3 (1%)

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of tretinoin gel, USP. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Temporary hyper- or hypopigmentation has been reported with repeated application of tretinoin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no well-controlled studies in pregnant women treated with tretinoin gel, USP. Tretinoin gel, USP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Tretinoin gel, USP 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 tretinoin gel, USP treated animals. These findings were not observed in control animals. Other maternal and reproductive parameters in the tretinoin gel, USP 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 tretinoin gel, USP applied daily to a 50 kg person.

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



Patient Information Tretinoin Gel, USP 0.05%

For topical use

Important information: Tretinoin gel, USP is for use on skin only. Do not get tretinoin gel, USP in your mouth, eyes, vagina, or the corners of your nose.

What is tretinoin gel, USP?

Tretinoin gel, USP is a prescription medicine used on the skin (topical) to treat acne. Acne is a condition in which the skin has blackheads, whiteheads, and other pimples.

It is not known if tretinoin gel, USP is safe and effective in children under 10 years of age.

What should I tell my healthcare provider before using tretinoin gel, USP?

Before using tretinoin gel, USP, tell your doctor about all of your medical conditions, including if you:

- are allergic to fish. Tretinoin gel, USP contains fish proteins. Tell your healthcare provider if you get hives or itching during treatment with tretinoin gel, USP.
- have a skin condition called eczema
- have a sunburn
- are pregnant or plan to become pregnant. It is not known if tretinoin gel, USP will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if tretinoin gel, USP passes into breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, herbal supplements, and any skin products that you use.

Especially tell your healthcare provider if you use any other medicines to treat your acne, including medicated cleansers or soaps. Using other topical acne products may increase the irritation of your skin when used with tretinoin gel, USP.

How should I use tretinoin gel, USP?

- Use tretinoin gel, USP exactly as your healthcare provider tells you to use it.
- Before you apply tretinoin gel, USP, gently wash the affected skin area with a mild, non-medicated soap. Rinse and pat your skin dry.
- Apply tretinoin gel, USP 1 time a day before bedtime.
- Apply a thin layer of tretinoin gel, USP to cover the affected skin areas. Gently rub tretinoin gel, USP into your skin.
- Do not use more tretinoin gel, USP than you need to cover the affected area and do not apply tretinoin gel, USP more than 1 time a day. Using too much tretinoin gel, USP may irritate or increase the irritation of your skin, and will not give faster or better results.
- You may use moisturizers and cosmetics.

What should I avoid while using tretinoin gel, USP?

- Avoid washing your skin too often and scrubbing the affected skin area.
- You should avoid sunlamps, tanning beds, and ultraviolet light during treatment with tretinoin gel, USP.
- Minimize exposure to sunlight.
- If you have to be in the sunlight or are sensitive to sunlight, use a sunscreen with a SPF (sun protection factor) of 15 or more and wear protective clothing, and a wide brimmed hat to cover the treated areas.
- If you do get sunburned, stop using tretinoin gel, USP until your skin has healed and is back to normal.
- Cold weather and wind may irritate skin treated with tretinoin gel, USP. Skin treated with tretinoin gel, USP may dry out or get wind burned more easily. Talk to your healthcare provider/doctor about ways to manage skin irritation.
- Avoid contact with the peels of limes.

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 fetus: 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.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when tretinoin gel, USP is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in children below the age of 10 have not been established.

A total of 381 pediatric subjects (aged 10 to 16 years), treated with tretinoin gel, USP were enrolled into the two clinical studies. Across these two studies, comparable safety and efficacy were observed between pediatric and adult subjects.

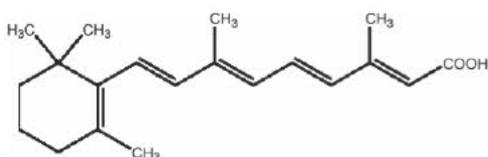
8.5 Geriatric Use

Safety and effectiveness in a geriatric population have not been established. Clinical studies of tretinoin gel, USP did not include any subjects over age 65 to determine whether they respond differently from younger subjects.

11 DESCRIPTION

Tretinoin gel, USP 0.05% is a translucent to opaque, pale yellow topical gel containing 0.05% tretinoin, by weight for topical administration.

Chemically, tretinoin is all-*trans*-retinoic acid, also known as (all-*E*)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid. It is a member of the retinoid class of compounds, and a metabolite of Vitamin A. Tretinoin has a molecular weight of 300.44, a molecular formula of C₂₀H₂₈O₂ and the following structure:



Each gram of tretinoin gel, USP 0.05% contains 0.5 mg of tretinoin.

Other components of this formulation are benzyl alcohol, butyl paraben, butylated hydroxytoluene, carbomer 980, ethyl paraben, fish collagen hydrolyzates, glycerin, iso-butyl paraben, methylparaben, octoxynol 9, phenoxyethanol, propylparaben, purified water, sodium hyaluronate, and trolamine. The contribution to efficacy of individual components of the vehicle has not been evaluated.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tretinoin is a metabolite of Vitamin A that binds with high affinity to specific retinoic acid receptors located in both the cytosol and nucleus, but cutaneous levels of tretinoin in excess of physiologic concentrations occur following application of a tretinoin-containing topical drug product.

Although tretinoin activates three members of the retinoic acid (RAR) nuclear receptors (RAR α , RAR β , and RAR γ) which act to modify gene expression, subsequent protein synthesis, and epithelial cell growth and differentiation, it has not been established whether the clinical effects of tretinoin are mediated through activation of retinoic acid receptors, other mechanisms, or both.

Although the exact mode of action of tretinoin is unknown, current evidence suggests that topical tretinoin decreases cohesiveness of follicular epithelial cells with decreased microcomedo formation. Additionally, tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells causing extrusion of the comedones.

12.3 Pharmacokinetics

In two (2) studies, the plasma levels of tretinoin and its major metabolites (13-*cis*-retinoic acid and 4-*oxo*-13-*cis*-retinoic acid) were investigated in a total of 14 patients (age: 13 – 25 years) with severe acne, who applied 4 g \pm 0.5 g (range 3.5 g – 4.5 g) of tretinoin gel, USP once daily to face, back and chest, as compared to a mean of 0.71 g (range of 0.07 – 3.71 g) applied in the controlled clinical trials. Blood samples were taken at baseline and immediately prior to treatment on days 1, 5, 10 and 14. On Day 14, the final study day, samples also were taken 1, 2, 4, 6, 8, 10, 12, 16, and 24 hours, post-treatment.

The plasma concentrations of tretinoin and its metabolites could be measured (LOQ = 0.5 ng/mL for all three analytes) in all patients at all time points. The range of plasma concentrations of tretinoin and its metabolites, 13-*cis*-retinoic acid and all-*trans*-4-*oxo*-retinoic acid at baseline and after multiple once daily applications of tretinoin gel, USP 0.05% for 14 days are given in Table 2 (below). Although some patients had increased concentrations of tretinoin or its metabolites over baseline values, no consistent increase in these concentrations were observed across patients.

Table 2. Concentrations of active and metabolites at Baseline and at Day 14 after exposure to Tretinoin Gel, USP 0.05%

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year dermal mouse carcinogenicity study was initiated with topical administration of 0.005%, 0.025% and 0.05% tretinoin gel, USP. Although no drug-related tumors were observed in surviving animals, the irritating nature of the drug product precluded daily dosing, confounding data interpretation and reducing the biological significance of these results.

Studies in hairless albino mice with a different formulation suggest that concurrent exposure to tretinoin may enhance the tumorigenic potential of carcinogenic doses of UVB and UVA light from a solar simulator. This effect was confirmed in a later study in pigmented mice, and dark pigmentation did not overcome the enhancement of photocarcinogenesis by 0.05% tretinoin. Although the significance of these studies to humans is not clear, patients should minimize exposure to sunlight or artificial ultraviolet irradiation sources.

The genotoxic potential of tretinoin was evaluated in an *In vitro* bacterial reversion test, an *In vitro* chromosomal aberration assay in human lymphocytes and an *In vivo* rat micronucleus assay. All tests were negative.

In dermal fertility studies of another tretinoin formulation in rats, slight (not statistically significant) decreases in sperm count and motility were seen at 0.5 mg/kg/day (3 mg/m², approximately 4 times the clinical dose based on body surface area comparison), and slight (not statistically significant) increases in the number and percent of nonviable embryos in females treated with 0.25 mg/kg/day and above (1.5 mg/m², approximately 2 times the clinical dose based on body surface area comparison), were observed.

14 CLINICAL TRIALS

The safety and efficacy of tretinoin gel, USP used once daily before bedtime for the treatment of mild to moderate acne vulgaris were assessed in two 12-week prospective, multi-center, randomized, controlled trials. Subjects in these two trials ranged from 10 to 65 years of age, were approximately 52% female, 48% male, and were 74% Caucasian, 15% Black or African American, 3% Asian, and 8% Other.

Efficacy results at Week 12 are presented in Table 3. Success on the 6-point Global Severity Score is defined as a score of 0 (clear) or 1 (very mild). In Trial 2, subjects were also required to have at least two grades reduction from baseline for success. 'Very mild' acne is defined as: *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)*. The database was not large enough to assess whether there were differences in effects in age, gender, or race subgroups.

Table 3. Efficacy Results at Week 12 In Trials 1 and 2

Trial 1	Tretinoin Gel, USP N = 375	Vehicle N = 185
Global Severity Score Success*	78 (21%)	23 (12%)
Non-Inflammatory Facial Lesions		
Mean Baseline Count	50.7	52.4
Mean Absolute Reduction	21.8	10.3
Mean Percent Reduction	43%	21%
Inflammatory Facial Lesions		
Mean Baseline Count	23.4	23.9
Mean Absolute Reduction	9.7	5.8
Mean Percent Reduction	41%	26%
Total Facial Lesions		
Mean Baseline Count	74.1	76.3
Mean Absolute Reduction	31.4	16.1
Mean Percent Reduction	43%	22%
Trial 2	Tretinoin Gel, USP N = 299	Vehicle N = 302
Global Severity Score Success**	69 (23%)	42 (14%)
Non-Inflammatory Facial Lesions		
Mean Baseline Count	51.9	52.7
Mean Absolute Reduction	18.7	10.8
Mean Percent Reduction	37%	20%
Inflammatory Facial Lesions		
Mean Baseline Count	22.9	23.4
Mean Absolute Reduction	7.0	4.0
Mean Percent Reduction	30%	17%
Total Facial Lesions		
Mean Baseline Count	74.8	76.1
Mean Absolute Reduction	25.7	14.7
Mean Percent Reduction	35%	19%

*Success was defined as 0 (clear) or 1 (very mild)

**Success was defined as 0 (clear) or 1 (very mild) with at least 2 grades reduction from baseline

16 HOW SUPPLIED/STORAGE AND HANDLING

Tretinoin Gel, USP 0.05% is a translucent to opaque, pale yellow topical gel and available as:

- 45 g tubes (NDC 66530-262-45)

Storage and Handling: Store at controlled room temperature 20 - 25°C (68 - 77°F) with excursions permitted between 15° - 30°C (59° - 86°F). Protect from freezing. Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information)

Instruct patients to clean the affected areas with an appropriate cleanser before applying tretinoin gel, USP.

Patients may use moisturizers that are non-comedogenic, and should avoid products that could be drying or irritating.

Patients may also wear cosmetics while being treated with tretinoin gel, USP; however, they should be instructed to remove the cosmetics and clean the area thoroughly before applying tretinoin gel, USP.

Warn patients of the drying and irritation effects often seen during treatment. Continue use of the medication if these effects are tolerable.

Caution patients against application of tretinoin gel, USP around the eyes, mouth, paranasal creases, and mucous membranes as this skin is especially prone to irritation.

Minimize exposure to sunlight, including sunlamps. Recommend the use of sunscreen products and protective apparel (e.g., hat) when exposure cannot be avoided.

Rx only

Manufactured by: CCI, Rockledge, FL 32955

Distributed by: Spear Dermatology Products, Randolph, NJ 07869



SPITR05G4

Revised: 03/2015

What are the possible side effects of tretinoin gel, USP?

Tretinoin gel, USP may cause skin irritation, including: skin dryness, burning, redness, excessive flaking or peeling. If you develop these symptoms, your healthcare provider may tell you to stop using tretinoin gel, USP for a while, decrease the number of times you apply tretinoin gel, USP, or completely stop treatment with tretinoin gel, USP. It is not known if tretinoin gel, USP is effective when used less than 1 time a day.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the side effects possible with tretinoin gel, USP.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store tretinoin gel, USP?

- Store tretinoin gel, USP at room temperature, 68° - 77°F (20° - 25°C).
- Protect from freezing.

Keep tretinoin gel, USP and all medicines out of the reach of children.

General information about the safe and effective use of tretinoin gel, USP

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use tretinoin gel, USP for a condition for which it was not prescribed. Do not give tretinoin gel, USP to other people, even if they have the same symptoms you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about tretinoin gel, USP that is written for health professionals.

What are the ingredients of tretinoin gel, USP?

Active ingredient: tretinoin

Inactive ingredients: benzyl alcohol, butyl paraben, butylated hydroxytoluene, carbomer 980, ethyl paraben, fish collagen hydrolyzates, glycerin, iso-butyl paraben, methylparaben, octoxynol 9, phenoxyethanol, propylparaben, purified water, sodium hyaluronate, and trolamine.

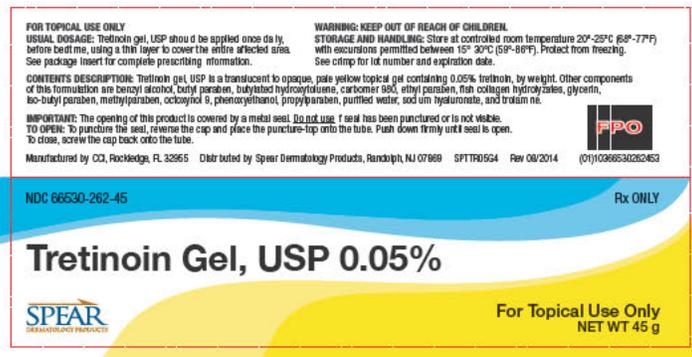
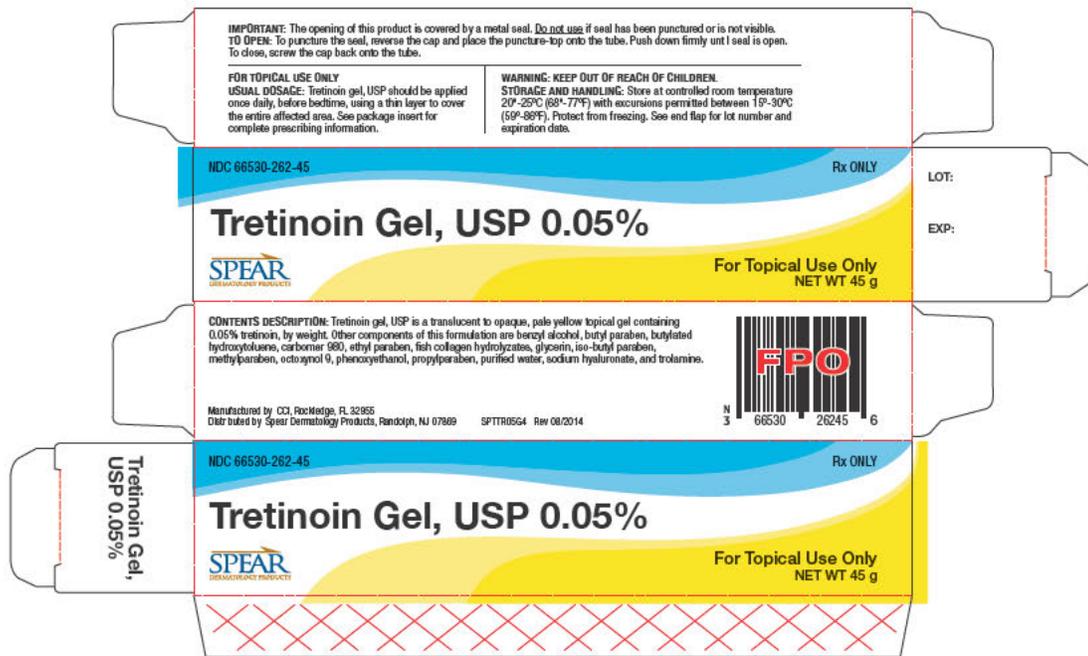
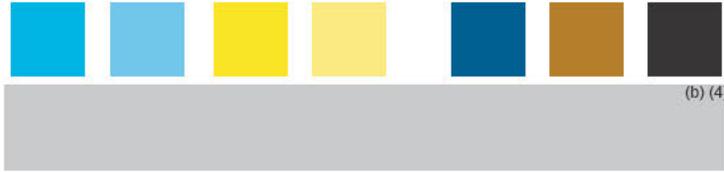
Manufactured by: CCI, Rockledge, FL 32955

Distributed by: Spear Dermatology Products, Randolph, NJ 07869

For more information, call 1-866-SPEAR-RX (773-2279).

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: 03/2015



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 207955

LABELING REVIEWS

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	03/27/2015
ANDA Number	207955
Review Cycle Number	2
Applicant Name	Spear Pharmaceuticals, Inc.
Established Name & Strength(s)	Tretinoin Gel USP, 0.05%
Proposed Proprietary Name	None
Submission Received Date	03/17/2015
Labeling Reviewer	Beverly Weitzman
Acting Labeling Team Leader	Ann Vu
Review Conclusion	
<input type="checkbox"/> ACCEPTABLE – No Comments.	
<input checked="" type="checkbox"/> ACCEPTABLE – Include Post Approval Comments	
<input type="checkbox"/> Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.	
*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.	

LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

NA

1.2 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.

(b) (4)



PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM’S RESPONSE, AND REVIEWER’S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm’s response and reviewer’s assessment. Include the previous review(s) finalized date(s).

Reviewer Comments: There were not previous labeling deficiencies from 10/01/2014 labeling submission. The firm was requested to submit Insert and Patient information Labeling in Final Print.

1.3 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?

NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments: No carton or container labels submitted.

1.4 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s).

Reviewer Comments:

[Click here to enter text.](#)

LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

1.5 REGULATORY INFORMATION

Are there any pending issues in SharePoint Repository files? NO

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

1.6 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check all that apply)

MOST RECENTLY APPROVED MODEL LABELING-NDA

(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)

NDA: 022070/S-003

Supplement Approval Date: 08/29/2014

Proprietary Name: Atralin Gel, 0.05%

Established Name: Tretinoin Gel USP, 0.05%

Description of Supplement: This “Prior Approval” supplemental new drug application provides for incorporation of the findings from the 2 year dermal carcinogenicity study into section 13.1 Mutagenesis, Carcinogenesis, and Impairment of Fertility of the prescribing information.

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check all that apply)

MOST RECENTLY APPROVED MODEL LABELING-ANDA
ANDA#/Supplement# (S-000 if original): Click here to enter text.
Supplement Approval Date: Click here to enter text.
Proprietary Name: Click here to enter text.
Established Name: Click here to enter text.
Description of Supplement: Click here to enter text.

BPCA or PREA TEMPLATE (Describe): Click here to enter text.

OTHER (Describe): Click here to enter text.

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **YES**
 Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#)? **YES**
 Does the Model Labeling have combined insert labeling for multiple dosage forms? **YES**

Reviewer Comments:

Click here to enter text.

1.7 MODEL CONTAINER LABELS

Model labels and carton labeling.

FOR TOPICAL USE ONLY
USUAL DOSAGE: Atralin™ Gel should be applied once daily, before bedtime, using a thin layer to cover the entire affected area. See package insert for complete prescribing information.
WARNING: KEEP OUT OF REACH OF CHILDREN.
STORAGE AND HANDLING: Store at controlled room temperature 20°–25°C (68°–77°F) with excursions permitted between 15°–30°C (59°–86°F). Protect from freezing. See crimp for lot number and expiration date.
CONTENTS DESCRIPTION: Atralin™ Gel is a translucent to opaque, pale yellow liquid gel containing 0.05% tretinoin, by weight. Other components of this formulation are benzyl alcohol, butyl paraben, butylated hydroxytoluene, carbomer 940, ethyl paraben, fish collagen hydrolyzates, glycerin, iso-butyl paraben, methylparaben, octyldecyl 9-phenoxypolysiloxane, polyparaben, purified water, sodium hyaluronate, and toluamide.
IMPORTANT: The opening of this product is covered by a metal seal.
Do not use: if seal has been punctured or is not visible.
TO OPEN: To puncture the seal, reverse the cap and place the puncture-rip into the tube. Push down firmly until seal is open. To close, screw the cap back onto the tube.
REORDER NO.: 13548-070-45

BAR CODE
 13548-070-45

Marketed by:
CORIA™
 CORIA LABORATORIES, LTD.
 Fort Worth, Texas 76107

Manufactured by:
 OPT LABORATORIES, LTD.
 San Antonio, Texas 78215
 Patent No.: 5,670,547
 102738-0707

EXP:

NDC 13548-070-45

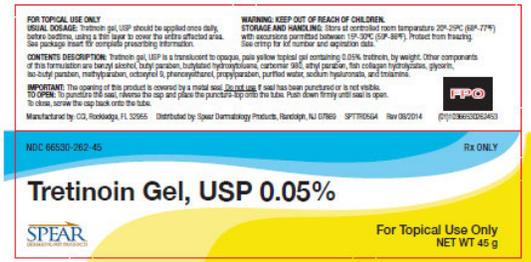
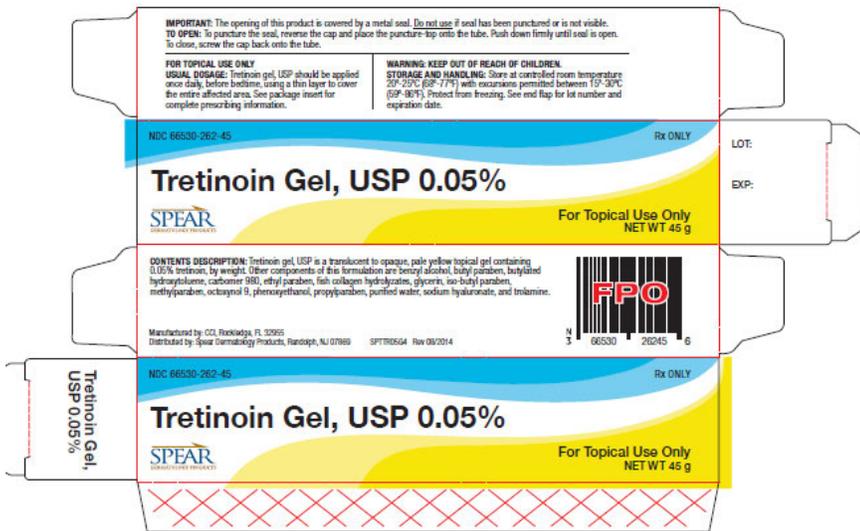
Atralin™
 (tretinoin) gel 0.05%

Rx ONLY

For Topical Use Only
NET WT 45 g



ANDA 207955 Container and Carton Labeling: Satisfactory as of October 01, 2014 electronic submission.



1.8 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	3/27/2015	YES	Tretinoin Gel	Packaging and Storage: Preserve in tight containers, protected from light.
PF	NA	NA	NA	NA

1.9 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 3/27/2015.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
NA	NA	NA	There are no unexpired patents	NA	NA	NA

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

[Click here to enter text.](#)

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
NA	NA	There are no unexpired exclusivities	NA	NA	NA

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

[Click here to enter text.](#)

DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the DESCRIPTION section, HOW SUPPLIED section and manufacturing statements of the Prescribing Information when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section? **NO**

Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED? **NO**

Are there changes to the manufacturing statements? **NO**

If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section		
Previous Labeling Review	Currently Proposed	Assessment

Table 6: Comparison of HOW SUPPLIED Section		
Previously Labeling Review	Currently Proposed	Assessment

Table 7: Manufactured by statement		
Previously Labeling Review	Currently Proposed	Assessment

COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments:

[Click here to enter text.](#)

COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments:

OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for each material analyzed in this review.

If this review is acceptable, then all pertinent labeling pieces must be entered for both tables.

For each row, if you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Date	Recommendation
Container	Final	45 gram tube	October 01, 2014	Satisfactory
Blister	NA			
Carton	Final	1 tube/carton	October 01, 2014	Satisfactory
(Other – specify)	NA			
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Date	Recommendation
Prescribing Information	Final	SPITR05G4 Revised 03/2015	March 26, 2015	Satisfactory
Medication Guide	NA			
Patient Information	Final – 9 point	SPITR05G4 Revised 03/2015	March 26, 2015	Satisfactory
SPL Data Elements		09/2014	October 01, 2014	Data Elements Satisfactory

Attached Labeling:



LABELSA207955N00
DLRRvw2.pdf

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	2/06/2015
ANDA Number	207955
Review Cycle Number	first
Applicant Name	Spear Pharmaceuticals, Inc.
Established Name & Strength(s)	Tretinoin Gel USP, 0.05%
Proposed Proprietary Name	None
Submission Received Date	10/01/2014
Labeling Reviewer	Beverly Weitzman
Labeling Team Leader	John Grace

Review Conclusion

- ACCEPTABLE – No Comments.
- ACCEPTABLE – Include Post Approval Comments
- Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

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1. LABELING COMMENTS

LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

1. CONTAINER LABEL: Satisfactory in Final Print.
2. CARTON LABELING: Satisfactory in Final Print.
3. PRESCRIBING INFORMATION: Satisfactory in DRAFT. Please submit in Final Print.
4. PATIENT INFORMATION: Satisfactory in Draft. However, when submitting in final print, please ensure that the patient insert is provided as a separate labeling piece within the carton or that it may be separated from the professional labeling as a distinct piece. In addition, please ensure that the minimum font size is 8 point type.

Submit your labeling electronically in final print format.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.

(b) (4)



2. LABELING REVIEW INFORMATION

REGULATORY INFORMATION

Acceptable for Filing Date: 10/31/2014
SharePoint Repository files: NO
If Yes, please explain.

MODEL LABELING

2.1.1 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check all that apply)

- MOST RECENTLY APPROVED REFERENCE LISTED DRUG**
NDA: 022070/S-003
Supplement Approval Date: 08/29/2014
Proprietary Name: Atralin Gel, 0.05%
Established Name: Tretinoin Gel USP, 0.05%
Description of Supplement: This "Prior Approval" supplemental new drug application provides for incorporation of the findings from the 2 year dermal carcinogenicity study into section 13.1 Mutagenesis, Carcinogenesis, and Impairment of Fertility of the prescribing information.
- BPCA or PREA TEMPLATE (Describe):** [Click here to enter text.](#)
- OTHER (Describe):** [Click here to enter text.](#)

2.1.2 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: NDA 022070/S-000: Approved 7/26/2007)

The diagram shows a tube with a cap end on the left and an open end on the right. The tube length is labeled as 5 3/4". The label on the tube contains the following information:

FOR TOPICAL USE ONLY
USUAL DOSAGE: Atralin™ Gel should be applied once daily, before bedtime, using a thin layer to cover the entire affected area. See package insert for complete prescribing information.
WARNING, KEEP OUT OF REACH OF CHILDREN.
STORAGE AND HANDLING: Store at controlled room temperature 20° - 25°C (68° - 77°F) with excursions permitted between 15° - 30°C (59° - 86°F). Protect from freezing. See crimp for lot number and expiration date.
CONTENTS DESCRIPTION: Atralin™ Gel is a translucent to opaque, pale yellow topical gel containing 0.05% tretinoin, by weight. Other components of this formulation are benzyl alcohol, butyl paraben, butylated hydroxytoluene, carboxer 940, ethyl paraben, fish collagen hydrolyzates, glycerin, iso-butyl paraben, methylparaben, octylnol 12, phenylethanol, polyparaben, purified water, sodium hyaluronate, and toluene.
IMPORTANT: The opening of this product is covered by a metal seal.
DO NOT USE: If seal has been punctured or is not visible.
TO OPEN: To puncture the seal, reverse the cap and place the puncture tip onto the tube. Push down firmly until seal is open. To close, screw the cap back onto the tube.
REORDER NO.: 13548-070-45

BAR CODE
13548-070-45

Marketed by:
CORIA™
CORIA LABORATORIES, LTD.
Fort Worth, Texas 76107

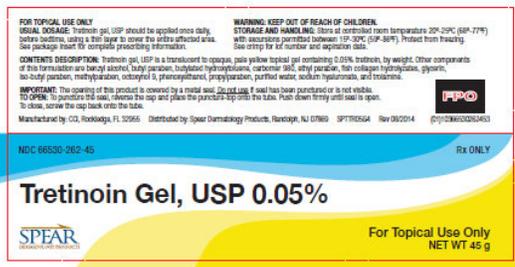
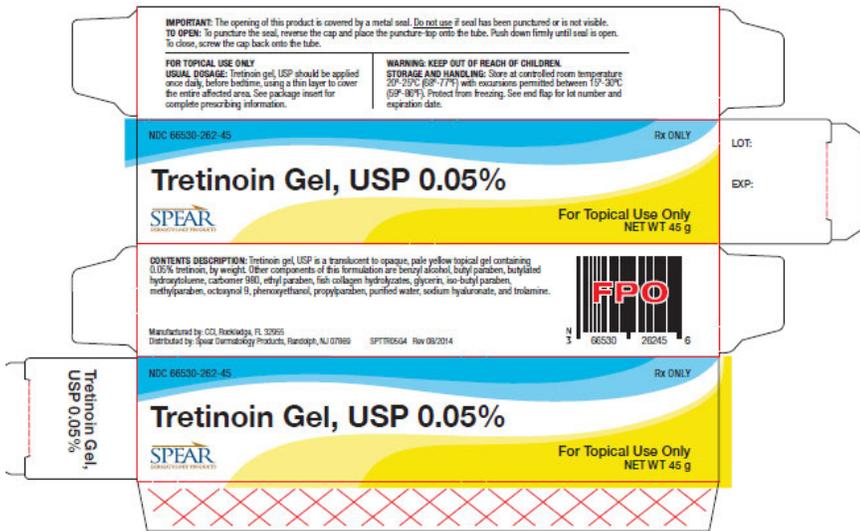
Manufactured by:
DPT LABORATORIES, LTD.
San Antonio, Texas 78215
Patent No.: 5,670,947
102738-0707

EXP:

Label Text:
NDC 13548-070-45
Atralin™
(tretinoin) gel 0.05%
Rx ONLY
For Topical Use Only
NET WT 45 g



ANDA 207955 Container and Carton Labeling: Satisfactory as of October 01, 2014 electronic submission.



UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Labeling Statements (NA if no monograph)
USP	1/29/2015	YES	Tretinoin Gel	Packaging and Storage: Preserve in tight containers, protected from light.
PF	NA	NA	NA	NA

PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 2/6/2015.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications.

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
NA	NA	NA	There are no unexpired patents	NA	NA	NA

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
NA	NA	There are no unexpired exclusivities	NA	NA	NA

MANUFACTURING FACILITY

Table 5 provides a description of the drug product manufacturing facility.

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements		
(b) (4)	Name and Address on ANDA Labels	Name and Address on ANDA Labeling
	Manufactured by: CCI, Rockledge, FL 32955 Distributed by: Spear Dermatology Products, Randolph, NJ 07869	Manufactured by: CCI, Rockledge, FL 32955 Distributed by: Spear Dermatology Products, Randolph, NJ 07869

3. ASSESSMENT OF ANDA LABELING AND LABELS

The results for each material reviewed in this section provide the basis for the labeling comments to the applicant.

Is this product Rx or OTC? Please check one.

- Rx Product (If Rx, complete sections 3.1, 3.3, 3.4 and 3.5.)
 OTC Product (If OTC, complete sections 3.2, 3.3, 3.4 and 3.5.)

Rx (PRESCRIPTION) DRUG PRODUCT

3.1.1 RX: PRESCRIBING INFORMATION

Reviewer Assessment: (If not applicable, enter NA in the “Reviewer Comments” section).

Is the Prescribing Information same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **YES**

Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#)? **YES**

Is the established name for this ANDA acceptable? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Are the required USP recommendations reflected in the labeling? **NA**

Is the applicant’s “patent carve out” acceptable? **NA**

Is the applicant’s “exclusivity carve out” acceptable? **NA**

Is the Manufacturer statement acceptable? **YES**

Reviewer Comments:

3.1.1.1 RX: INACTIVE INGREDIENTS COMPARISON

We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

Table 6: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

Model Labeling Inactive Ingredients	ANDA Labeling Inactive Ingredients
benzyl alcohol, butyl paraben, butylated hydroxytoluene, carbomer 940, ethyl paraben, fish collagen hydrolyzates, glycerin, iso-butyl paraben, methylparaben, octoxynol 9, phenoxyethanol, propylparaben, purified water, sodium hyaluronate, and tromamine.	benzyl alcohol, butyl paraben, butylated hydroxytoluene, carbomer 980, ethyl paraben, fish collagen hydrolyzates, glycerin, iso-butyl paraben, methylparaben, octoxynol 9, phenoxyethanol, propylparaben, purified water, sodium hyaluronate, and tromamine.

Reviewer Assessment:

Is the DESCRIPTION section of the labeling acceptable? **YES**

Are the inactive ingredients information consistent with “Components and Composition” information as provided in Module 3.2.P.1? (Enter NA if the Drug Product Quality Review follows the [Chemistry/Labeling Memorandum of Understanding](#).) **NA**

For products required to be Q1Q2, are the ANDA ingredients consistent with the RLD? **NA**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**

If the labeling includes “Does not contain...” statements, has this statement been verified by chemistry? **NA**

Reviewer Comments: [Click here to enter text.](#)

3.1.1.2 RX: HOW SUPPLIED SECTION

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 7 and will be referred to the appropriate review discipline for evaluation.

Table 7: Comparison of Model Labeling to ANDA Labeling

Model Labeling	Atralin (tretinoin) Gel, 0.05% is a translucent to opaque, pale yellow topical gel and available as 45 g tubes (NDA 13548-070-45)
ANDA Labeling	Tretinoin Gel USP, 0.05% is a translucent to opaque, pale yellow topical gel and available as 45 g tubes (NDA 66530-262-45)

Reviewer Assessment:

Is the description ([scoring](#), color and [imprint](#)) of the finished product in the HOW SUPPLIED section consistent with the information in Module 3.2.P.5.1 for Drug Product Specification? (Enter NA if the Drug Product Quality Review follows the [Chemistry/Labeling Memorandum of Understanding](#).) **NA**

Does the ANDA require the same coloring scheme as the RLD (e.g., warfarin, enoxaparin, levothyroxine)? **NA**

Is there any difference in scoring configuration between the ANDA and the RLD labeling? **NA**

Are the packaging sizes acceptable as compared to the Model Labeling? **YES**

Does the packaging configuration require the addition or deletion of labeling statements based on the comparison to Model Labeling? **NO**

Is the storage or dispensing statement acceptable as compared to the Model Labeling? **YES**

Is the storage or dispensing statement acceptable as compared to the USP? **NA**

Does the temperature statement conform to the OGD format for controlled room temperature? **YES**

Reviewer Comments: [Click here to enter text.](#)

3.1.2 RX: MEDICATION GUIDE

Was Medication Guide submitted? **NA**

Reviewer Assessment:

Is the Medication Guide same as the model labeling, except for allowable differences? **NA**

Does the format meet the requirements of [21 CFR 208.20](#)? **NA**

Has the Applicant committed to provide a sufficient number of medication guides? **NA**

Is the phonetic spelling of the proprietary or established name present? **NA**

Is FDA 1-800-FDA-1088 phone number included? **NA**

Reviewer Comments: [Click here to enter text.](#)

3.1.3 RX: OTHER PATIENT LABELING

Was other patient labeling submitted? **NA**

Reviewer Assessment:

Is the patient labeling the same as the model labeling, except for allowable differences? **NA**

Reviewer Comments:

3.1.4 RX: CONTAINER LABEL

We evaluated the container labels for the inclusion of all required statements and safety considerations.

Reviewer Assessment:

Is the established name acceptable? **YES**

Is title case used in expressing the established name? **YES**

Does labeling comply with Tall Man lettering recommendations found on FDA webpage? **NA**

Does this container meet the “too small” exemption found in [21 CFR 201.10\(i\)](#)? **NA**

Does the following information appear as the most prominent information on the Principal Display Panel?

Proprietary name **NA**
Established name **YES**
Product strength **YES**

Are the following information properly displayed?

Net quantity statement **YES**
Route(s) of administration (other than oral) **YES**
Warnings (if any) or cautionary statements (if any) **YES**
Medication Guide Pharmacist instructions per 21 CFR 208.24(d) **NA**
Controlled substance symbol **NA**
Usual Dosage statement **YES**
Product strength equivalency statement **NA**
NDC **YES**
Bar code per 21 CFR 201.25(c)(2) **YES**

Is the Manufacturer statement acceptable? **YES**

For foreign manufacturers, does the labeling have the country of origin? **NA**

Are the required USP recommendations reflected on the label(s)? **NA**

Is the storage or dispensing statement consistent with the How Supplied section of the insert? **YES**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**

Are all abbreviations acceptable? (e.g., mg, mcg, HCl)? **YES**

Are the recommendations for leading and terminal zeroes, decimals, and commas followed? **YES**

Are multiple strengths differentiated by use of different color or other acceptable means? **NA**

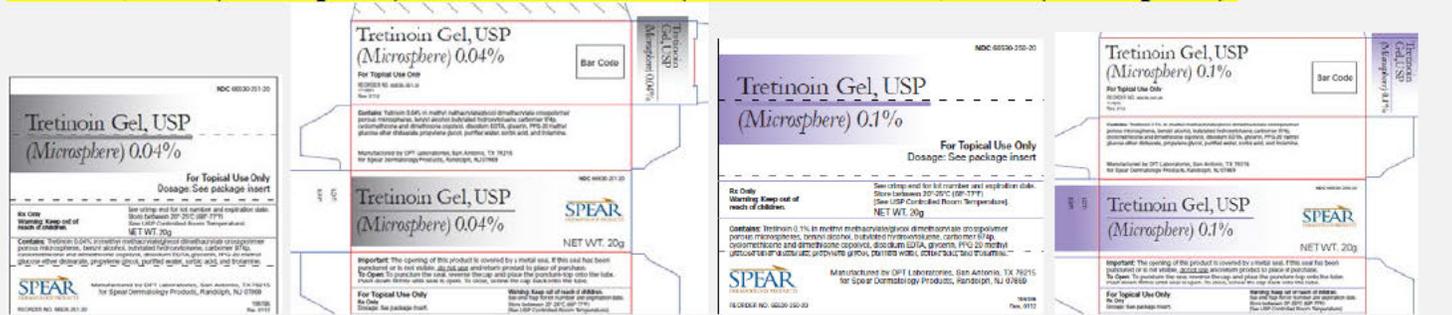
Are the labels of related products differentiated to avoid selection errors? **YES**

Does the ANDA require the same coloring scheme as the RLD (e.g., warfarin, enoxaparin, levothyroxine)? **NA**

Are the requirements of 21 CFR 201.15 met for all required label statements? **YES**

Are the requirements of 21 CFR 201.100 met for all required label statements? **YES**

Reviewer Comments: Related drug products for Spear Pharmaceuticals, Inc.: ANDA 202026 (Tretinoin Gel USP, 0.1% (Microsphere)) and ANDA 202567 (Tretinoin Gel USP, 0.4% (Microsphere)).



3.1.4.1 RX: CONTAINER LABEL FOR SMALL VOLUME PARENTERAL SOLUTIONS

Is container for small volume parenteral solution? **NO**

Reviewer Assessment:

Is the product strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP, General Chapter <1> Injection? **NA**

If volume is less than 1 mL, is strength per fraction of a milliliter the only expression of strength? **NA**

Are inactive ingredients listed on label as required by regulations? **NA**

Reviewer Comments: [Click here to enter text.](#)

3.1.4.2 RX: CONTAINER LABEL FOR STERILE SOLID INJECTABLE

Is container for sterile solid injectable? **NO**

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **NA**

Are instructions for reconstitution and resultant concentration provided, if space permits? **NA**

Are inactive ingredients listed on label as required by regulations? **NA**

Reviewer Comments: [Click here to enter text.](#)

3.1.4.3 RX: CONTAINER LABEL FOR PHARMACY BULK PACKAGE

Is container a Pharmacy Bulk Package (parenteral preparations for admixtures)? **NO**

Reviewer Assessment:

Is there a prominent, boxed declaration reading “Pharmacy Bulk Package – Not for Direct Infusion” on the principal display panel following the expression of strength? **NA**

Does the container label include graduation marks? **NA**

Does label contain the required information on proper aseptic technique including time frame in which the container may be used once it has been entered? **NA**

Are inactive ingredients listed on label as required by regulations? **NA**

Reviewer Comments: [Click here to enter text.](#)

3.1.4.4 RX: UNIT DOSE BLISTER LABEL

Is container a Unit Dose Blister Pack? **NO**

Reviewer Assessment:

Does each blister include only one dosage unit (e.g., one tablet, one capsule)? **NA**

Do proprietary name, established name, strength, bar code, and manufacturer appear on each blister cell?

CLICK HERE

Does the established name describe only one unit (e.g. “tablet” rather than “tablets”)? **NA**

Reviewer Comments: [Click here to enter text.](#)

3.1.5 RX: CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Was carton labeling submitted? **YES**

(If not applicable, enter NA in the “Reviewer Comments” section.)

Reviewer Assessment:

Is the established name acceptable? **YES**

Is title case used in expressing the established name? **YES**

Does labeling comply with Tall Man lettering recommendations found on FDA webpage? **NA**
If container is too small or otherwise unable to accommodate a label with enough space to include all required information, is all required information present on the carton labeling? **NA**

Does the following information appear as the most prominent information on the Principal Display Panel?

Proprietary name **NA**
Established name **YES**
Product strength **YES**

Are the following information properly displayed?

Net quantity statement **YES**
Route(s) of administration (other than oral) **YES**
Warnings (if any) or cautionary statements (if any) **YES**
Medication Guide Pharmacist instructions per 21 CFR 208.24(d) **NA**
[Controlled substance symbol](#) **NA**
Usual Dosage statement **YES**
Product strength equivalency statement **NA**
NDC **YES**
Bar code per [21 CFR 201.25\(c\)\(2\)](#) **YES**

Is the Manufacturer statement acceptable? **YES**

Are the required USP recommendations reflected in the labeling? **NA**

Is the storage or dispensing statement consistent with the How Supplied section of the insert? **YES**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**

Are all abbreviations acceptable? (e.g., mg, mcg, HCl)? **YES**

Are the recommendations for leading and terminal zeroes, decimals, and commas followed? **YES**

Are multiple strengths differentiated by use of different color or other acceptable means? **NA**

Are the labels of related products differentiated to avoid selection errors? **YES**

Does the ANDA require the same coloring scheme as the RLD (e.g., warfarin, enoxaparin, levothyroxine)? **NO**

If country of origin is not on Container, does it appear on outer packaging labeling? **NA**

Are the requirements of [21 CFR 201.15](#) met for all required label statements? **YES**

Are the requirements of [21 CFR 201.100](#) met for all required label statements? **YES**

Reviewer Comments: Refer to 3.1.4 – RX: Container Label

OTC (OVER THE COUNTER) DRUG PRODUCT

3.1.6 OTC: LABELING THAT INCLUDES DRUGS FACTS INFORMATION

Reviewer Assessment:

Is the patient labeling the same as the model labeling, except for allowable differences? **NA**

Is Drug Facts Labeling format acceptable per [21 CFR 201.66](#)? **NA**

Does “Questions?” have a toll-free number no less than 6 pt. font size [per 21 CFR 201.66\(c\)\(9\)](#) or “1-800-FDA-1088” [[21 CFR 201.66 \(c\)\(5\)\(vii\)](#)]? **NA**

Did firm submit a Labeling Format Information Table to evaluate the font size? **NA**

Is the applicant’s “patent carve out” acceptable? **NA**

Is the applicant’s “exclusivity carve out” acceptable? **NA**

Is the established name for this ANDA acceptable? **NA**

Is title case used in expressing the established name? **NA**

Does the following information appear as the most prominent information on the Principal Display Panel?

Proprietary name **NA**
Established name **NA**
Product strength **NA**

Are the following information properly displayed?

Therapeutic category **NA**
Net quantity statement **NA**
Route(s) of administration (other than oral) **NA**
Warnings (if any) or cautionary statements (if any) **NA**
NDC **NA**
Bar code per [21 CFR 201.25\(c\)\(2\)](#) **NA**

Is the Manufacturer statement acceptable? **NA**

For foreign manufacturers, does the labeling have the country of origin? **NA**

Are the required USP recommendations reflected in the labeling? **NA**

Is the storage statement acceptable? **NA**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**

Are all abbreviations acceptable? (e.g., mg, mcg, HCl)? **NA**

Are the recommendations for leading and terminal zeroes, decimals, and commas followed? **NA**

Are multiple strengths differentiated by use of different color or other acceptable means? **NA**

Are the labels of related products differentiated to avoid selection errors? **NA**

Reviewer Comments:

3.1.6.1 OTC: INACTIVE INGREDIENTS COMPARISON

We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

Table 8: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling Inactive Ingredients	ANDA Inactive Ingredients
NA	NA

Reviewer Assessment:

Are the inactive ingredients information consistent with “Components and Composition” information as provided in Module 3.2.P.1? **NA**

For products required to be Q1Q2, are the ANDA ingredients consistent with the RLD? **NA**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**

If the labeling includes “Does not contain...” statements, has this statement been verified by chemistry? **NA**

Reviewer Comments: [Click here to enter text.](#)

3.1.6.2 OTC: HOW SUPPLIED INFORMATION

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 9 and will be referred to the appropriate review discipline for evaluation.

Table 9: Comparison of Model Labeling to ANDA finished product

Model Labeling	NA
ANDA (enter source of information of product description on the right hand column; e.g. chemistry Review & date, Module 3.2.P.5.1)	NA

Reviewer Assessment:

Is the description ([scoring](#), color and [imprint](#)) of the finished product consistent with the Drug Product Quality submission? **NA**

Is there any difference in scoring configuration between the ANDA and the RLD labeling? **NA**

Are the packaging sizes acceptable as compared to the Model Labeling? **NA**

Does the packaging configuration require the addition or deletion of labeling statements based on the comparison to Model Labeling? **NA**

Is the storage or dispensing statement acceptable as compared to the Model Labeling? **NA**

Is the storage or dispensing statement acceptable as compared to the USP? **NA**

Does the temperature statement conform to the OGD format for controlled room temperature? **NA**

Reviewer Comments: [Click here to enter text.](#)

3.1.7 OTC: OTHER PATIENT LABELING

Was other patient labeling submitted? **NA**

Reviewer Assessment:

Is the patient labeling the same as the model labeling, except for allowable differences? **NA**

Reviewer Comments: [Click here to enter text.](#)

CONTAINER/CLOSURE

We evaluated the container/closure system of this product to determine if special child-resistant packaging is required based on packaging configuration. Additionally, we evaluated other aspects of the container closure that relate to the dosage form, product formulation, and product class. Below is a description of the container/closure for the ANDA product.

Reviewer Assessment:

Describe container closure (e.g., 30s CRC, 100s non-CRC) and cite source of information in **Reviewer Comments** text box.

Does the container require a child-resistant closure (CRC) as described in the [Poison Prevention Act and regulations](#)? **NA**

Are the tamper evident requirements met for [OTC](#) and [Controlled Substances](#)? (If quality review follows the chemistry-labeling MOU, obtain answer from Appendix D of chemistry review; if quality review does not follow the MOU, labeling reviewer is responsible for assessing for tamper evidence.) **NA**

For ophthalmic products:

Does this ophthalmic products cap color match [the American Academy of Ophthalmology \(AAO\) packaging color-coding](#) scheme? **NA**

For parenteral products:

Is there text on the cap/ferrule overseal of this injectable product? **NA**

If YES, does text comply with the recommendations in USP General Chapter <1>? **NA**

What is the cap and ferrule color? [Click here to enter text.](#)

CALCULATIONS FOR INACTIVE INGREDIENT CONTENTS IN LABELING

We verified the calculation on the following inactive ingredient content.

Table 10: Inactive Ingredients		
Inactive Ingredient	Stated Content	Location of the Information
NA	NA	NA

(Note: For Rx products, if chemistry review follows the MOU, chemistry reviewer will verify the accuracy of the inactive ingredient amount(s) if information is in the DESCRIPTION or HOW SUPPLIED sections for all products, and additionally, DOSAGE AND ADMINISTRATION section for parenteral products.)

Reviewer Assessment:

Are the stated contents in the table above acceptable? **NA**

(b) (4)

Did the chemistry reviewer verify the (b) (4) content? **NA**

Are the labeling requirements met per 21 CFR 201.323? **NA**

Reviewer Comments: [Click here to enter text.](#)

STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

We evaluated the [SPL data elements](#) to ensure they are consistent with the information submitted in the ANDA.

Table 11: ANDA Tablet/Capsule Size and Imprint	
Tablet/Capsule Strength	ANDA Tablet/Capsule Size (mm) and imprint code from the last chemistry review (Enter NA if not available)
NA	NA
NA	NA

Reviewer Assessment:

Are the data elements consistent with the information submitted in the ANDA labeling? **YES**

Reviewer Comments: [Click here to enter text.](#)

4. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments: NA

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

During the course of this review, was clarification sought on issues to determine if a label or labeling revision is necessary? **NA**

Reviewer Assessment:

Does the response(s) received require a label and/or labeling revision? **CLICK HERE**

Reviewer Comments: [Click here to enter text.](#)

6. SPECIAL CONSIDERATIONS

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 12 and 13 provide a summary of recommendations for each material analyzed in this review.

Table 12: Review Summary of Container Label and Carton Labeling				
	Draft or Final	Packaging Sizes	Submission Date	Recommendation
Container	FPL	45 gram tube	October 01, 2014	Satisfactory
Blister	Click here to enter text.		Click here to enter text.	Click here to enter text.
Carton	FPL	1 tube/carton	October 01, 2014	Satisfactory
(Other – specify)	Click here to enter text.			
Table 13 Review Summary of Prescribing Information and Patient Labeling				
	Draft or Final	Revision Date and/or code	Submission Date	Recommendation
Prescribing Information	Draft	08/2014	October 01, 2014	Submit FPL
Medication Guide	Click here to enter text.			
Patient Information	Draft	08/2014	October 01, 2014	Submit FPL
SPL Data Elements		09/2014	October 01, 2014	Satisfactory

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 207955

MEDICAL REVIEWS

**Addendum to Review of a Clinical Endpoint Bioequivalence Study
Following OSIS Inspection Report**

ANDA number	207955
Drug Product	Tretinoin Topical Gel
Strength(s)	0.05%
Applicant Name	Spear Pharmaceuticals
Chemical Name	(all- <i>E</i>)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen1-yl)-2,4,6,8-nonatetraenoic acid
Treatment Indications	Topical treatment of acne vulgaris
Reference Listed Drug (RLD)	Atralin®
NDA for RLD	NDA 022070 (approved on 7/26/2007)
RLD Applicant Name	Dow Pharmaceutical Sciences Inc
Original Submission Date	10/1/2014
Materials Reviewed	Original submission: 10/1/14 Amendment(s): 10/27/2014 (response to DFR IR), 1/12/2015 (response to DCR ECD for missing dataset) OSIS inspection report by Srinivas Chennamaneni, Ph.D. dated 5/27/2015. FDA Statistical review by Wanjie Sun, Ph.D. completed on 2/20/2015 prior to OSIS inspection result Draft Guidance on Tretinoin Gel/Topical [NDA 022070] (March 2012) DCR original review: 3/19/2015 (recommended approval)
Primary Reviewer	Sarah H. Seung, Pharm.D. Clinical Reviewer Division of Clinical Review (DCR) Office of Bioequivalence (OB) Office of Generic Drugs (OGD)
Secondary Reviewer	Carol Kim, Pharm.D. Acting Team Leader, DCR, OB, OGD
Tertiary Reviewer	Daiva Shetty, M.D. Acting Deputy Director, DCR, OB, OGD
Date of Completion	01/16/2015
DCR Conclusion	DCR recommends approval of this application. Per OSIS recommendation, the clinical data (Study TRET-05) are acceptable.

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Addendum to Review of a Clinical Endpoint Bioequivalence Study for ANDA 207955

1 Executive Summary

1.1 Approval Recommendation

The DCR recommends approval of this application following the Office of Study Integrity and Surveillance (OSIS) inspection report dated 5/27/15.

1.2 Summary of Clinical Findings

Based on the inspection result of the clinical site performed by the FDA's OSIS, the clinical data from the study (TRET-05) are acceptable for the review. This three-center, double-blind, randomized, three-treatment, parallel study (TRET-05) in the treatment of acne vulgaris demonstrates that the Applicant's Tretinoin Topical Gel, 0.05% with the reference listed drug (RLD), Atralin[®], 0.05% (NDA 022070, approved on 7/26/2007).

2 Additional Clinical Review

2.1 Review of the Office of Study Integrity and Surveillance (OSIS) Inspection Report

A For Cause Inspection was requested for all three clinical sites.¹ According to the OSIS inspection report², all three clinical sites were inspected between the period of 2/24/2015 to 3/5/2015. At the conclusion of the inspection, a single item Form FDA-483 was issued to the MOORE Clinical Research, Inc. in Brandon, FL. OSIS did not issue a FDA Form 483 to the other two clinical sites. The OSIS reviewer concluded that "the data from the audited study [TRET-05] were found to be reliable." The OSIS reviewer "recommends that the data be accepted for agency review."

Below is a summary of the OSIS findings during the inspection.

Site number	Site Name and Location	OSIS Findings	Comment
1	MOORE Clinical Research, Inc., Brandon, FL	An investigation was not conducted in accordance with the investigational plan. Specifically, Subject (b) (6) (b) (6) Inclusion criteria #2 of the protocol states that a potential subject must be at least 12 years old in order to participate in the study	VAI (Voluntary Action Indicated)

¹ See ANDA 207955 Clinical Primary Review ("A207955 OSI For Cause Request.doc") by Teena Thomas <https://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880984487>

² See ANDA 207955 Clinical Review Recommendation ("ANDA 207955 MOORE Clan Res Inc-EIR Cover Memo-05272015-S4.pdf") by Srinivas Chennamaneni dated 5/27/2015 <http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880a41ebc>

Site number	Site Name and Location	OSIS Findings	Comment
2	MOORE Clinical Research, Inc., Tampa, FL	None. Form FDA 483 not issued.	NAI (No Action Indicated)
3	MOORE Clinical Research, Inc., Fort Myers, FL	None. Form FDA 483 not issued.	NAI

Reviewer's Comment:

- *Because of questionable site interaction noted from the FDA statistical analysis, a For Cause Inspection was requested for all three sites. For Sites 1 and 3, verification on data accuracy was requested because of different statistical finding at these two sites. For Site 2, verification that subjects received appropriate study medication was requested because of the similar efficacy outcome between the test product and the placebo. The OSIS found no issues, anomalies or discrepancies with the drug accountability, blinding, randomization schedule, Investigator's Global Assessment scale used by the evaluators, evaluator trainings and certifications, and data verification.*
- *For the OSIS finding at Site #1, the clinical site noticed the protocol deviation and reported the deviation to the sponsor and the IRB. Subject (b) (6) (b) (6) This reviewer agrees the OSIS conclusion that "this observation does not impact the data integrity."*
- *This reviewer agrees with the OSIS recommendations that the clinical data are acceptable for review.*

2.2 Review of the FDA Statistical Report

No further subject adjustment or statistical analysis was needed as a result of the OSIS findings.

2.3 Conclusion and Recommendation

2.3.1 Conclusion

Following the OSIS inspection report dated 5/27/15, the clinical data (Study TRET-05) submitted to ANDA 207955 are adequate to demonstrate bioequivalence of the Applicant's Tretinoin Topical Gel, 0.05% with the reference listed drug, Atralin[®], 0.05%.

2.3.2 Recommendation

The DCR recommends approval of this application, contingent on approval recommendations from the other disciplines on the review team.

3 CLINICAL BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

The Division of Clinical Review has no comment at this time.

APPEARS THIS WAY ON
ORIGINAL

Review of a Clinical Endpoint Bioequivalence Study

ANDA number	207955
Drug Product	Tretinoin Topical Gel
Strength(s)	0.05%
Applicant Name	Spear Pharmaceuticals
Chemical Name	(all- <i>E</i>)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen1-yl)-2,4,6,8-nonatetraenoic acid
Treatment Indication	Topical treatment of acne vulgaris
Reference Listed Drug (RLD)	Atralin®
NDA/ANDA number for RLD	NDA 022070 (approved on 7/26/2007)
RLD Applicant Name	Dow Pharmaceutical Sciences Inc
Original Submission Date	10/1/2014
Materials Reviewed	<p>ANDA original submission: 10/1/14 ANDA amendment (s): 10/27/2014 (response to DFR IR), 1/12/2015 (response to DCR ECD for missing dataset) OSI inspection: pending FDA Statistical review by Wanjie Sun, Ph.D. completed on 2/20/2015 Draft Guidance on Tretinoin Gel/Topical [NDA 022070] (March 2012)</p>
Primary Reviewer	<p>Sarah H. Seung, Pharm.D. Clinical Reviewer Division of Clinical Review (DCR) Office of Bioequivalence (OB) Office of Generic Drugs (OGD)</p>
Secondary Reviewer	<p>Carol Kim, Pharm.D. Acting Team Leader, DCR, OB, OGD</p>
Tertiary Reviewer	<p>Daiva Shetty, M.D. Acting Deputy Director, DCR, OB, OGD</p>
Date of Completion	5/26/2018
DCR Conclusion	DCR recommends approval based on clinical data available prior to OSI inspection findings. The clinical endpoint bioequivalence study (TRET-05) in the treatment of acne vulgaris demonstrates that the test product is bioequivalent to the RLD.

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Review of a Clinical Endpoint Bioequivalence Study for ANDA 207955

1 Executive Summary

1.1 Approval Recommendation

The Division of Clinical Review (DCR) recommends approval of this application, pending satisfactory OSI inspection outcome.

1.2 Summary of Clinical Findings

1.2.1 Brief Overview of Clinical Program

This review evaluates the study data submitted in abbreviated new drug application (ANDA) 207955 to determine the bioequivalence of Spear Pharmaceuticals' ("Applicant") Tretinoin Topical Gel, 0.05% with the reference listed drug (RLD), Atralin[®], 0.05% (NDA 022070, approved on 7/26/2007).

On 10/1/2014, the Applicant submitted an ANDA for a generic Tretinoin Topical Gel, 0.05%. In support of an approval for the ANDA, the Applicant conducted a bioequivalence study with clinical endpoint (Study TRET-05) in the treatment of acne vulgaris.

Consistent with the FDA draft guidance on this product, Study TRET-05 was a three-center, double-blind, randomized, three-treatment, parallel study in 574 normal, healthy male and female children and adults (ages 12 to 40 years) with at least Grade 2 (i.e., mild severity) acne vulgaris. Subjects were randomized to receive one of the three treatments. Subjects were treated on the full face once daily for 84 days with the generic Tretinoin Gel 0.05% (Test product), Atralin (RLD) or Gel Vehicle (Placebo). The acne lesions were counted and graded by a single blinded observer at screening, and at study Weeks 0 (baseline), 2, 4, 8, and 12 (\pm 4 days). The two primary endpoints were the percent change from baseline to Week 12 in inflammatory lesion counts and the percent change from baseline to Week 12 in non-inflammatory lesion counts.

1.2.2 Comparative Efficacy

According to the Applicant's and FDA's statistical analyses, the data shows that the test product is bioequivalent to the RLD.

According to the applicant's statistical analysis, the percent reduction in inflammatory lesion count was 41.98% for the test product and 38.90% for the RLD. The percent reduction in non-inflammatory lesion count was 32.3% for the test product and 35.2% for the RLD. The 90% CI of the test/RLD ratio of the mean change from baseline to Week 12 in inflammatory and non-inflammatory lesion counts in the Per-Protocol (PP) population were (0.97, 1.20) and (0.82, 1.02), respectively, both of which are within the bioequivalence limits of [0.80, 1.25]. Both the test product and RLD were shown to be statistically superior to vehicle ($p \leq 0.0008$) in the modified Intent-to-Treat (mITT) population for both co-primary endpoints. A total of 549 subjects were

included in the Applicant's mITT population and 509 were included in the Applicant's PP population.

Based on information available prior to OSI inspection findings, adjustments were made to the Applicant's PP populations. No adjustments were made to the mITT population. A total of 492 were included in the FDA's PP population. According to the FDA's statistical analysis, the percent reduction in inflammatory lesion count was 33.9% for the test product and 36.0% for the RLD. The percent reduction in non-inflammatory lesion count was 29.1% for the test product and 31.7% for the RLD. The 90% CI of the test/RLD ratio of the mean change from baseline to Week 12 in inflammatory and non-inflammatory lesion counts in the FDA Per-Protocol (PP) population were (0.86, 1.03) and (0.83, 1.02), respectively, both of which are within the bioequivalence limits of [0.80, 1.25]. Both the test product and RLD were shown to be statistically superior to vehicle ($p \leq 0.0008$) in the FDA mITT population for both co-primary endpoints.

1.2.3 Comparative Safety

The study showed no clinically significant difference in safety between the test product and the RLD. Of the 549 subjects included in the safety population for Study TRET-05, 121 subjects reported 201 adverse events (AEs). No death or serious adverse event was reported. The number of subjects who experienced an AE during the study was comparable between the test group (n=49; 22.1%) and the RLD group (n=46; 20.9%). Although the number of AEs reported was slightly higher in the test group (n=87) than the RLD group (n=67), the number of treatment-related AE reported was less in the test group (n=3) than the RLD group (n=4). The AE rates were generally comparable between the test group and the RLD group. Majority of the AEs reported in the test group were mild (83 out of 87 AEs) and none were severe. The RLD group experienced more moderate to severe AEs than the test group.

2 Clinical Review

2.1 Introduction and Background

2.1.1 Summary of Drug Information

Reference Listed Drug	Atralin®
RLD Applicant Name	Dow Pharmaceutical Sciences Inc
RLD NDA/ANDA Number	NDA 022070
Date of RLD Approval	7/26/2007
Current Label	http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022070s003lbl.pdf
Approved Indication(s)	Topical treatment of acne vulgaris
Recommended Dose/Administration	<ul style="list-style-type: none"> Apply a thin layer of Atralin Gel once daily, before bedtime, to skin where lesions occur. Keep away from eyes, mouth, nasal creases, and mucous membranes.

	<ul style="list-style-type: none"> • Atralin Gel is not for oral, ophthalmic, or intravaginal use.
Maximal Daily Dose	Same as recommended dose
Boxed Warnings	None
Commonly reported Adverse Events	<ul style="list-style-type: none"> • The most common adverse reactions (incidence $\geq 5\%$) are dry skin, peeling/scaling/flaking skin, skin burning sensation, and erythema. • Most skin-related adverse reactions first appear during the first two weeks of treatment with Atralin Gel, and the incidence rate for skin-related reactions peaks around the second and third week of treatment. In some subjects the skin-related adverse reactions persists throughout the treatment period.
Contraindications	None
Prominent Warnings/Precautions	<ul style="list-style-type: none"> • Should not be used on eczematous or sunburned skin due to potential for severe irritation. • Use with caution with other topical over-the-counter acne preparations, concomitant topical medications, medicated cleansers, topical products with alcohol or astringents. Irritation may occur. • Avoid unprotected exposure to sunlight including sunlamps (UV light) due to potential for increased photosensitization. Use sunscreen of at least SPF 15 and protective clothing during exposure. • Avoid use with weather extremes, such as wind or cold due to potential for increased irritation. • Use with caution if allergic to fish due to potential for allergenicity to fish protein. Patients who develop pruritus or urticaria should contact their health care provider.
Mechanism of Action	<p>Tretinoin is a metabolite of Vitamin A that binds with high affinity to specific retinoic acid receptors located in both the cytosol and nucleus, but cutaneous levels of tretinoin in excess of physiologic concentrations occur following application of a tretinoin-containing topical drug product.</p> <p>Although tretinoin activates three members of the retinoid acid (RAR) nuclear receptors ($RAR\alpha$, $RAR\beta$, and $RAR\gamma$) which act to modify gene expression, subsequent protein synthesis, and epithelial cell growth and differentiation, it has not been established whether the clinical effects of tretinoin are mediated through activation of retinoic acid receptors, other mechanisms, or both.</p> <p>Although the exact mode of action of tretinoin is unknown, current evidence suggests that topical tretinoin decreases</p>

Absorption	cohesiveness of follicular epithelial cells with decreased microcomedo formation. Additionally, tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells causing extrusion of the comedones.
	Very minimal systemic absorption was noted when approximately 5 times the amount (4 g ± 5 g) of Atralin® was applied topically compared to the dose (mean of 0.71 g) applied during controlled clinical trials.

2.1.2 Regulatory Background

2.1.2.1 Guidance on Drug Product

A draft guidance for this drug product is available. Table 2.1 provides a brief overview of the draft guidance recommendations.

Table 2.1: Drug Product Draft Guidance

Draft Guidance	Draft Guidance on Tretinoin Gel/Topical [NDA022070] ¹
Date Posted	March 2012
Recommended Study	Clinical endpoint BE study
Clinical Endpoint Study Recommendations	Randomized, double blind, parallel, placebo controlled, in vivo study. Treatment indication: acne vulgaris Patient population: male or female Study duration: 12 weeks Treatment dosing: once daily in the evening for 12 weeks Inclusion criteria: <ul style="list-style-type: none"> • aged ≥ 12 and ≤ 40 years • on the face: ≤ 25 non-inflammatory lesions (i.e., open and closed comedones) AND ≤ 20 inflammatory lesions (i.e., papules and pustules) AND ≤ 2 nodulocystic lesions (i.e., nodules and cysts) • an Investigator's Global Assessment (IGA) of acne severity grade 2, 3, or 4 (on a 5-point scale)
Primary Endpoint (s)	1. Percent change from baseline to week 12 in the inflammatory (papules and pustules) lesion counts 2. Percent change from baseline to week 12 in the non-inflammatory (open and closed comedones) lesion counts

Reviewer's comments: *The Applicant's study (Study TRET 05) is consistent with the Draft Guidance on Tretinoin. The study protocol referenced the Draft Guidance on Tretinoin.*

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM296997.pdf>

2.1.2.2 Bio-INDs, Protocols, or Control Documents submitted by Applicant

The Applicant did not submit any Bio-IND for this drug product. The Applicant submitted three protocols (Protocols 00-052, 02-069 and 06-091) and three controlled correspondences (Controls 98-063, 99-341, 01-467) for tretinoin topical gel, prior to the posting of any of the Draft Guidance on Tretinoin Gel/Topical. Although the protocols and controlled correspondences were not for the 0.05% strength, comments sent to the Applicant were also consistent with the Draft Guidance on Tretinoin Gel/Topical [NDA22070].

2.1.2.3 Bio-INDs, Protocols, or Control Documents submitted by Other Generic Applicants

No Bio-INDs has been submitted to OGD for this drug product. Several protocols and controlled correspondences were submitted to the OGD for various strengths of generic tretinoin topical gel prior to the posting of the Draft Guidance on Tretinoin Gel/Topical. All protocols and controlled correspondences submitted prior to the posting of the Draft Guidance on Tretinoin have been reviewed and completed. Comments sent to the firms for these protocols and controlled correspondences were consistent with the Draft Guidance on Tretinoin Gel/Topical. There is one controlled correspondence (Control 14-0462) for tretinoin topical gel still open and pending a response to the firm. Control 14-0462 is for the 0.08% strength (RLD is Retin-A Micro/NDA 020475). A Draft Guidance on Tretinoin Gel/Topical [NDA 020475] has not been posted yet.

2.1.2.4 Other ANDA submissions for same or related product

This is a potential first generic application.

There are no approved generic tretinoin topical gel, 0.05%. However, other strengths of generic tretinoin topical gel are available (See Appendix, Table 4.1). The available strengths range from 0.025% to 0.1%. In addition, the cream formulation of tretinoin in various strengths is available as a generic product (See Appendix, Table 4.1). There are no other ANDAs pending review for tretinoin topical gel (See Appendix, Table 4.2).

2.1.3 Other Relevant Information

None

2.2 Description of Clinical Data and Sources

Study No.	TRET-05
CRO	Quartesian, LLC
Study Period	11/20/2013 to 6/20/2014
Study Centers²	3 sites in US (all in FL)
Enrollment	574 subjects

²[\\cdsesub1\evsprod\anda203265\0001\m2\27-clin-sum\271-summary-biopharm\summary-biopharm-pdf.pdf](#), pp. 41 and 43 of 61.

2.3 Clinical Review Methods

2.3.1 Overview of Materials Consulted in Review

Original Submission	10/1/2014
ANDA Amendments	10/27/2014 (eCTD Sequence 0001): Response to Information Request from Division of Filing Review 1/12/2015 (eCTD Sequence 0002): Response to ECD regarding missing dataset information.
FDA Statistical Review	ANDA 207955 Statistical Primary Review (“207955_Statistical.doc”) by Wanjie Sun, Ph.D., Completed on 2/20/2015 ³

2.3.2 Overview of Methods Used to Evaluate Data Quality and Integrity

Blinding	See Applicant’s Study Report ⁴ , Sections 9.2.4 and 9.4.6 (pp. 21-24 of 267)
Randomization	See Applicant’s Study Report ⁵ , Section 9.4.3 (p. 23 of 267)
Retention of Reserve Samples:	See Applicant’s Study Report ⁶ , Section 9.4 (pp. 20-21 of 267)
Office of Scientific Investigations	A For Cause Inspection was requested for all three sites. ⁷ The results of the inspections are pending at the time of this review.

Reviewer’s comments:

- *Because of questionable site interaction noted from the FDA statistical analysis, a For Cause Inspection was requested for all three sites. For Sites 1 and 3, verification on data accuracy was requested because of different statistical finding at these two sites. For Site 2, verification that subjects received appropriate study medication was requested because of the similar efficacy outcome between the test product and the placebo. OSI inspection results are pending at the time of this review.*
- *The Applicant’s methods for blinding appear appropriate. All tubes (the test product, RLD, and the placebo) were wrapped in a white blind by a third-party, (b) (4). The Applicant states that “Code-breaker envelopes were shipped with the respective clinical supplies to the investigational study locations.” There is no mention in the study report as to whether any of the code-breaker envelopes were opened. However, none of the subjects are noted to have been unblinded during the study.*

³ <https://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880984dd2>

⁴ [\\cdsesub1\evsprod\anda207955\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\tret-05\report-body.pdf](https://cdsesub1\evsprod\anda207955\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\tret-05\report-body.pdf)

⁵ Id.

⁶ Id.

⁷ See ANDA 207955 Clinical Primary Review (“A207955 OSI For Cause Request.doc”) by Teena Thomas <https://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880984487>

- The Applicant states that “an independent third party generated and held the randomization code throughout the conduct of the study in order to minimize bias.”
- The Applicant’s method for selection of reserve samples seems appropriate. OSI inspection results are pending at the time of this review.

2.3.3 Were Trials Conducted in Accordance with Accepted Ethical Standards

Ethical Standards and Compliance with Good Clinical Practices	Reviewer’s Comment: Study TRET 05 appears to have been conducted in accordance with accepted ethical standards. The INTEG Review IRB approved ⁸ the original protocol and the Informed Consent Form prior to the start of the study.
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2.3.4 Evaluation of Financial Disclosure

Financial Disclosure, Form 3454	Reviewer’s Comment: Form FDA 3454 ⁹ is submitted. The Principal Investigator and all sub-investigators are listed.
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2.4 Review of a Clinical Endpoint Bioequivalence Study

2.4.1 Brief Statement of Conclusions

The FDA statistical analysis supports bioequivalence of the test product and the RLD.

2.4.2 General Approach to Review of a Clinical Endpoint Bioequivalence Study

The Applicant’s study (Study TRET-05) was reviewed to evaluate the bioequivalence of the test product and the RLD. The primary parameter was evaluated for bioequivalence.

2.4.3 Detailed Review of a Clinical Endpoint Bioequivalence Study

Applicant’s Study #	TRET-05
Title	Bioequivalence Study of Spear Tretinoin Gel 0.05%, Atralin® (Tretinoin) Gel 0.05%, and Placebo
Objectives	<p>The objectives of this study were to compare the efficacy and safety of Tretinoin Gel 0.05% (Test product) to Atralin (RLD) and the gel vehicle (Placebo) in the treatment of acne.</p> <ol style="list-style-type: none"> 1. The primary objective was to assess the clinical bioequivalence of the RLD and the test product. The primary endpoint was the percent change from baseline in inflammatory and non-inflammatory lesions at Week 12; 2. The secondary objective was to assess the statistical superiority

⁸ [\\cdsesub1\evsprod\anda207955\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\tret-05\iec-irb-consent-form-list.pdf](#), pp. 39-41 of 41

⁹ [\\cdsesub1\evsprod\anda207955\0000\m1\us\financial-certifications.pdf](#)

	<p>of the RLD and the test product to placebo;</p> <p>3. The safety objective was to evaluate the severity of application site reactions. The overall incidence of adverse events (AEs) in treated subjects in the three treatment groups was evaluated.</p>
--	--

2.4.3.1 Protocol Review

Protocol Version	Protocol Date(s)	IRB Approval Date(s)
Original	8/15/2013 & 11/12/2013 ¹⁰	8/21/2013 ¹¹ & 11/18/2013 ¹²
Amendment 1	1/24/2014 ¹³	1/27/2014

Reviewer’s comments:

The protocol amendment, which is dated after study initiation (study period: 11/20/2013 to 6/20/2014), was to change the exclusion criterion regarding "Participation in a clinical study for acne" from "within 4 months preceding study initiation" to "within 2 months preceding study initiation." This change does not impact the outcome of the study. Therefore, it is acceptable that this exclusion criterion was changed after study initiation.

2.4.3.2 Study Design

2.4.3.2.1 Overall Study Design and Plan

Study TRET-05 was a double-blind, randomized, 3 treatment, parallel study in 574 healthy male and female children and adults (ages 12-40 years) with mild to severe acne vulgaris. Table 2.2 outlines the study visits and procedures during each visit.

¹⁰ [\\cdsesub1\evsprod\anda207955\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\tret-05\protocol-or-amendment.pdf](#), pp. 1-29 of 34.

¹¹ [\\cdsesub1\evsprod\anda207955\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\tret-05\iec-irb-consent-form-list.pdf](#), pp. 39-41 of 41

¹² Supra Note 10, p. 31 of 34.

¹³ Id., p. 33 of 34.

Table 2.2: Study Schedule

Action	Visits					
	Screening ^a	Baseline ^a	Week 2	Week 4	Week 8	Week 12
Describe study to candidate and answer any questions	X					
Witness signing of the assent/informed consent statement	X					
Provide copy of the informed consent statement	X					
Conduct urine pregnancy test (if indicated)	X			X	X	X
Collect medical and medication histories	X					
Examine and score facial acne	X	X	X	X	X	X
Determine compliance with inclusion: exclusion criteria		X				
Randomize qualifying candidate to study drug		X				
Dispense study drug and other supplies		X				
Provide diary and instructions		X		X	X	
Review and collect completed 4-week diary and new diary given				X	X	X
Review adverse events		X	X	X	X	X
Review concomitant medications		X	X	X	X	X
Receive used study drug containers				X	X	X
Provide additional study supplies as needed			X	X	X	X

^a The screening and baseline visits were combined if washout was not required.

Reviewer's comments:

- *The study design and procedures are consistent with the Draft Guidance on Tretinoin.*
- *The visit window for each visit was ± 4 days, which is acceptable.*

2.4.3.2.2 Treatment Arms

Treatment Arms	Test	RLD	Placebo
Product Name	Tretinoin	Atralin	Vehicle
Manufacturer	Spear Pharmaceuticals Inc.	Valeant Pharmaceuticals, North America	Spear Pharmaceuticals Inc.
Batch/Lot No.	3G14A	FEBZ	3G12A
Manufacture Date	29 October 2013	n/a	14 November 2013
Expiration Date	(b) (4)	April 2016	December 2015
Strength	0.05%	0.05%	--
Dosage Form	Gel	Gel	Gel
Route of administration	Topical	Topical	Topical
Dose administered	2 pea-sized (½ inch) amount	2 pea-sized (½ inch) amount	2 pea-sized (½ inch) amount
Dosing regimen	QD	QD	QD
Dosing time	evening	evening	evening
Dosing duration	12 weeks (84 days)	12 weeks (84 days)	12 weeks (84 days)
Assignment ratio	2	2	1

Reviewer's comments:

- The treatment administrations are consistent with the approved RLD label and the Draft Guidance on Tretinoin.
- The Applicant made the following statement to confirm that the bio-batches are the same as the commercial batches: "The clinical batch we used for this study was prepared at full commercial scale using all the same ingredients, measures, personnel, test methods, controls and equipment we plan to use subsequent to product approval."¹⁴

2.4.3.2.3 Study Population

This study enrolled healthy subjects, ages 12 to 40 years, with 20-40 inflammatory lesions and 25-60 non-inflammatory lesions with less than 2 nodulocystic lesions and an Investigator's Global Assessment score of 2 to 4. See Applicant's Study Report¹⁵, Section 9.3 (pp. 18-19 of 267) for the full list of the Applicant's inclusion and exclusion criteria.

Reviewer's comments:

- The Applicant's inclusion/exclusion criteria incorporated all the inclusion and exclusion criteria from the Draft Guidance on Tretinoin.
- The Applicant added an additional 4 inclusion criteria and 10 exclusion criteria, all of which are acceptable. To note, the Applicant set an upper limit on the inflammatory lesion count (not more than 40) and on the non-inflammatory lesion count (not more than 60). The Draft

¹⁴ \\cdsesub1\evsprod\anda207955\0000\m3\32-body-data\32p-drug-prod\tretinoin-gel-usp-005\32p2-pharm-dev\pharmaceutical-development.pdf, p. 6 of 81.

¹⁵ Supra Note 4.

Guidance on Tretinoin sets only the lower limit on these lesion counts. Setting an upper limit ensures that the subjects' acne conditions are not worse than severe. Therefore, the applicant's upper limit criteria for baseline lesion counts are acceptable.

Criteria for removal from the study	<p>Participation of a subject in this study could have been discontinued for any of the following reasons:</p> <ul style="list-style-type: none"> • AE necessitating stopping the study • Non-compliance with study requirements • Use of prohibited medications • Decision by the subject not to continue • Judgment by the investigator that it was not in the subject's interest to continue • Lack of treatment effect • Lost to follow-up (documented with at least two phone calls and one certified letter) • Pregnancy
Prior and concomitant therapy	See Applicant's Study Report ¹⁶ , Section 9.4.7 (pp. 24-25 of 267).
Treatment compliance	75% to 125%

Reviewer's comments:

- *The Applicant's criteria for removal of subjects from the study are appropriate.*
- *The Applicant's list of prohibited medications is consistent with the Draft Guidance on Tretinoin except for the use of antibiotics. The Applicant allowed systemic antibiotics used for 10 days or less if the indication was for a medical condition other than acne. Subjects who used antibiotics under these conditions were included in the Applicant's PP population. This reviewer disagrees with the Applicant. If the antibiotic has a known effect on acne, the use of that antibiotic should not be allowed during the study regardless of the duration of use or the indication. This reviewer identified 15 subjects who used antibiotics during the study and were included in the Applicant's PP population. This reviewer recommended that these 15 subjects be excluded from the FDA PP population.*

2.4.3.2.4 Assessments

The following assessments were made during the study:

Assessments	Description
Lesion counts	inflammatory, non-inflammatory and nodulocystic lesions counted

¹⁶ Supra Note 4.

Assessments	Description														
Investigator's Global Assessment	<table border="1"> <thead> <tr> <th>Grade</th> <th>Description</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>Normal, clear skin with no evidence of acne vulgaris</td> </tr> <tr> <td>1</td> <td>Skin almost clear, rare non-inflammatory lesions present, with rare non-inflamed papules (i.e., papules may be hyperpigmented, though not pink-red)</td> </tr> <tr> <td>2</td> <td>Some non-inflammatory lesions are present, with few inflammatory lesions (i.e., papules/pustules only, no nodular lesions)</td> </tr> <tr> <td>3</td> <td>Several comedones and papules/pustules only, and there may or may not be one small nodular lesion. Non-inflammatory lesions predominate, with multiple inflammatory lesions.</td> </tr> <tr> <td>4^a</td> <td>Many inflammatory lesions, up to many comedones and papules/pustules. There may be two nodular lesions.</td> </tr> <tr> <td>5</td> <td>High inflammatory lesions predominate; variable number of comedones, many papules/pustules, and nodular lesions</td> </tr> </tbody> </table>	Grade	Description	0	Normal, clear skin with no evidence of acne vulgaris	1	Skin almost clear, rare non-inflammatory lesions present, with rare non-inflamed papules (i.e., papules may be hyperpigmented, though not pink-red)	2	Some non-inflammatory lesions are present, with few inflammatory lesions (i.e., papules/pustules only, no nodular lesions)	3	Several comedones and papules/pustules only, and there may or may not be one small nodular lesion. Non-inflammatory lesions predominate, with multiple inflammatory lesions.	4 ^a	Many inflammatory lesions, up to many comedones and papules/pustules. There may be two nodular lesions.	5	High inflammatory lesions predominate; variable number of comedones, many papules/pustules, and nodular lesions
	Grade	Description													
	0	Normal, clear skin with no evidence of acne vulgaris													
	1	Skin almost clear, rare non-inflammatory lesions present, with rare non-inflamed papules (i.e., papules may be hyperpigmented, though not pink-red)													
	2	Some non-inflammatory lesions are present, with few inflammatory lesions (i.e., papules/pustules only, no nodular lesions)													
	3	Several comedones and papules/pustules only, and there may or may not be one small nodular lesion. Non-inflammatory lesions predominate, with multiple inflammatory lesions.													
	4 ^a	Many inflammatory lesions, up to many comedones and papules/pustules. There may be two nodular lesions.													
5	High inflammatory lesions predominate; variable number of comedones, many papules/pustules, and nodular lesions														
Application Site Reactions	<p>Signs and Symptoms assessed: erythema/redness, dryness/peeling, burning/stinging, erosion, edema/swelling, pain, and itching</p> <table border="1"> <thead> <tr> <th>Score</th> <th>Description</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>absent</td> </tr> <tr> <td>1</td> <td>mild (slight, barely perceptible)</td> </tr> <tr> <td>2</td> <td>moderate (distinct presence)</td> </tr> <tr> <td>3</td> <td>severe (marked, intense)</td> </tr> </tbody> </table>	Score	Description	0	absent	1	mild (slight, barely perceptible)	2	moderate (distinct presence)	3	severe (marked, intense)				
Score	Description														
0	absent														
1	mild (slight, barely perceptible)														
2	moderate (distinct presence)														
3	severe (marked, intense)														

Reviewer's Comment:

- *The Applicant appropriately did not include nodules and cysts in the inflammatory or non-inflammatory lesion counts.*
- *The Applicant's Investigator's Global Assessment Scale is consistent with the Draft Guidance on Tretinoin. However, the Applicant added one more grade above the scale provided in the Draft Guidance on Tretinoin. The additional grade is a score of 5, which is described as "high inflammatory lesions predominate; variable number of comedones, many papules/pustules, and nodular lesions." This additional upper grade does not change the enrollment criteria as recommended in the Draft Guidance on Tretinoin and does not confound the results of the study. Therefore, this addition is acceptable.*

2.4.3.2.5 Endpoints

Primary Endpoint	Percent change from baseline in inflammatory and non-inflammatory lesions at Week 12
Secondary Endpoint	None

Reviewer's Comment:

The Applicant's primary endpoint is consistent with the Draft Guidance on Tretinoin. A secondary endpoint is not mentioned in the Draft Guidance on Tretinoin.

2.4.3.2.6 Statistical Analysis Plan

See Applicant's Study Report¹⁷, Section 9.7 (pp. 37-46 of 267) and FDA Statistical Review¹⁸, Section 3.4 (pp. 14-15 of 46) for details of the statistical analysis plan.

Reviewer's Comment:

The Applicant's definitions for the safety, modified Intent-to-Treat (mITT), and per-protocol (PP) populations are consistent with the Draft Guidance on Tretinoin. After the posting of the Draft Guidance on Tretinoin, the FDA mITT population definition changed from "mITT population includes all randomized subjects who met the inclusion/exclusion criteria, apply at least one dose of assigned product, and return for at least one post-baseline evaluation visit" to the "mITT population includes all randomized and applied or used at least one dose of assigned product." The FDA statistician used the new FDA mITT population definition.

2.4.3.3 Results

2.4.3.3.1 Subject Disposition

The following table describes the subject disposition at the end of this study.

¹⁷ Supra Note 4.

¹⁸ ANDA 207955 Statistical Primary Review ("207955_Statistical.doc") by Wanjie Sun, Completed on 2/20/2015, <https://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880984dd2>.

Table 2.3: Subject Disposition

Disposition	Tretinoin Gel 0.05% (N = 230) n(%)	Atralin (tretinoin) Gel 0.05% (N = 229) n(%)	Gel Vehicle (N = 115) n(%)	Total (N = 574) n(%)
Enrolled				574
Randomized	230 (100.0%)	229 (100.0%)	115 (100.0%)	574 (100.0%)
Subjects who completed the study	205 (89.1%)	212 (92.6%)	100 (87.0%)	517 (90.1%)
Subjects who discontinued from the study	25 (10.9%)	17 (7.4%)	15 (13.0%)	57 (9.9%)
Reasons for Discontinuation from Study^a				
AE necessitating stopping the study	1 (4.0%)	0	0	1 (1.8%)
Non-compliance with study requirements	0	0	0	0
Use of prohibited medications	3 (12.0%)	1 (5.9%)	0	4 (7.0%)
Decision by the subject not to continue	5 (20.0%)	5 (29.4%)	4 (26.7%)	14 (24.6%)
Judgment by the investigator that it is not in the subject's interest to continue	0	0	0	0
Lack of treatment effect	0	0	1 (6.7%)	1 (1.8%)
Lost to follow-up	14 (56.0%)	10 (58.8%)	10 (66.7%)	34 (59.6%)
Pregnancy	2 (8.0%)	1 (5.9%)	0	3 (5.3%)
Death	0	0	0	0
Other	0	0	0	0

Source: Applicant's Study Report, Table 8 (p. 49 of 267).

Reviewer's comments: Adjustments were made to the Applicant's per-protocol population for the FDA analysis (the FDA PP population)¹⁹. Seventeen subjects were excluded from the PP population for FDA analysis. Sixteen of these were because of prohibited medication use (15 for antibiotic use). The remaining subject was excluded from the FDA PP population because the subject's dose was reported to have been "decreased" on study day 58 because of "erosion on RT cheek" and "skin erosion between eyebrows." Despite the change in the FDA mITT population definition, there were no adjustments needed to the Applicant's mITT population for the FDA analysis. Table 2.4 summarizes the safety, mITT and PP populations for both the Applicant and the FDA analyses.

¹⁹ See ANDA 207955 Clinical Primary Review ("A207955N000DCR_RecStat.doc") by Sarah Seung for a detailed list of the adjustments, <https://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880935807>.

Table 2.4: Number of Subjects in the Applicant and FDA Safety, mITT and PP Populations

	Sponsor				FDA			
	Test	RLD	Vehicle	Total	Test	RLD	Vehicle	Total
Randomized	230	229	115	574				
Total Safety population	222	220	107	549	222	220	107	549
Total exclusion from Safety population	8	9	8	25	8	9	8	25
Reason for exclusion from Safety								
Did not use any study medication	8	9	8	25	8	9	8	25
Total mITT population	222	220	107	549	222	220	107	549
Total exclusion from mITT population	8	9	8	25	8	9	8	25
Reason for exclusion from mITT								
Did not use any study medication	8	9	8	25	8	9	8	25
Total PP population	200	209	100	509	197	199	96	492
Total Exclusion from PP population	30	20	15	65	33	30	19	82
Reason for exclusion from PP								
Did not use any study medication	8	9	8	25	8	9	8	25
Compliance < 75%, Missed applications for >3 consecutive days	1	0	0	1	1	0	0	1
Compliance < 75%, No valid Week 12 visit	1	0	0	1	1	0	0	1
Missed applications for >3 consecutive days, No valid Week 12 visit	3	2	0	5	3	2	0	5
No valid Week 12 visit	12	7	7	26	12	7	7	26
No valid Week 12 visit, Prohibited medication use	3	1	0	4	3	1	0	4
No valid Week 12 visit, Pregnancy	1	0	0	1	1	0	0	1
Prohibited medication use	1	0	0	1	4	9	4	17
Inclusion Criterion 2 violation	0	1	0	1	0	1	0	1
Study medication dose decreased due to AE	0	0	0	0	0	1	0	1

Source: Applicant’s Study Report, Table 9 (p. 51 of 267) and FDA Statistical Review, Table 1.

2.4.3.3.2 Demographics & Baseline Characteristics

The following table provides the demographic and baseline characteristics for the safety population.

Table 2.5: Summary of Demographic and Baseline Characteristics in the Safety Population

Demographic Characteristic	Tretinoin Gel 0.05% (N=222)	Atralin (tretinoin) Gel 0.05% (N=220)	Gel Vehicle (N=107)	Total (N=549)	p-value
Age (years)					
n	222	220	107	549	
Mean (SD)	20.1 (7.06)	20.1 (7.60)	19.6 (7.31)	20.0 (7.32)	0.7595 ^a
Median (Min, Max)	17.0 (12, 40)	17.0 (11, 40)	17.0 (12, 39)	17.0 (11, 40)	
Age Group					
< 18	114 (51.4%)	123 (55.9%)	58 (54.2%)	295 (53.7%)	0.6063 ^b
18 – 40	108 (48.6%)	97 (44.1%)	49 (45.8%)	254 (46.3%)	
Gender					
Male	98 (44.1%)	89 (40.5%)	43 (40.2%)	230 (41.9%)	0.6781 ^b
Female	124 (55.9%)	131 (59.5%)	64 (59.8%)	319 (58.1%)	
Race					
American Indian/Alaska Native	1 (0.5%)	0	0	1 (0.2%)	
Asian	1 (0.5%)	3 (1.4%)	2 (1.9%)	6 (1.1%)	
Black	57 (25.7%)	46 (20.9)	24 (22.4%)	127 (23.1%)	
Native Hawaiian/other Pacific Islander	2 (0.9%)	1 (0.5%)	1 (0.9%)	4 (0.7%)	
Caucasian	111 (50.0%)	109 (49.5%)	61 (57.0%)	281 (51.2%)	
Hispanic	50 (22.5%)	60 (27.3%)	16 (15.0%)	126 (23.0%)	
Other	0 (0%)	1 (0.5%)	3 (2.8%)	4 (0.7%)	
Inflammatory Lesion Count					
n	222	220	107	549	
Mean (SD)	26.2 (4.90)	26.3 (5.01)	27.2 (5.27)	26.4 (5.02)	0.2331 ^a
Median (Min, Max)	25.0 (20, 40)	25.0 (20, 39)	26.0 (20, 39)	25.0 (20, 40)	
Non-Inflammatory Lesion Count					
n	222	220	107	549	
Mean (SD)	34.4 (7.27)	33.8 (7.24)	34.4 (7.21)	34.1 (7.24)	0.6615 ^a
Median (Min, Max)	32.0 (25, 57)	31.5 (25, 58)	33.0 (25, 57)	32.0 (25, 58)	
Nodulocystic Lesion Count					
n	222	220	107	549	
Mean (SD)	0.0 (0.12)	0.0 (0.16)	0.0 (0.00)	0.0 (0.13)	0.4689 ^a

Source: Applicant's Study Report, Table 11 (p. 54 of 267)

For the Safety Population, subjects in the three treatment groups were similar in age (i.e., median 17 years old), ranging from aged 11 years to 40 years. The proportion of males to females was also similar across treatment groups (p = 0.6781). The majority of the subjects were White (281 subjects, 51.2%), followed by Black (127 subjects, 23.1%), and Hispanic (126 subjects, 23.0%). Subjects were distributed similarly across treatment groups for race. For the Safety Population, baseline lesion counts were consistent with study entry criteria and were comparable across treatment groups.

Reviewer’s comments: *Demographics and baseline characteristics were similar between the three treatment groups in the safety, mITT and PP populations. According to both the Applicant’s and FDA’s analyses, there were no statistical difference noted in the baseline characteristics or demographics between the treatment groups.*

2.4.3.3.3 Primary Endpoint Analysis Results

The Applicant and FDA statistician’s analyses results are provided in Table 2.6 and Table 2.7.

Table 2.6: Bioequivalence Analysis for Percent Change from Baseline to Visit 4/Week 12

	Applicant		FDA	
	Test (N=200)	RLD (N=209)	Test (N=197)	RLD (N=199)
Inflammatory				
LS Mean	-41.98	-38.90	-33.9	-36.0
90% CI for Test and RLD	(0.97, 1.20)		(0.86, 1.03)	
Bioequivalence	Pass		Pass	
Non-Inflammatory				
LS Mean	-32.3	-35.2	-29.1	-31.7
90% CI for Test and RLD	(0.82, 1.02)		(0.83, 1.02)	
Bioequivalence	Pass		Pass	

Source: Applicant’s Study Report, Tables 15 & 16 (pp. 62 & 64 of 267) & FDA Statistical Review, Table 7 & 9.

Table 2.7: Superiority Analysis for Percent Change from Baseline to Visit 4/Week 12

	Sponsor				FDA			
	Test (N=222)	Vehicle (N=107)	RLD (N=220)	Vehicle (N=107)	Test (N=222)	Vehicle (N=107)	RLD (N=220)	Vehicle (N=107)
Inflammatory								
LS Mean	-40.2	-28.1	-38.1	-28.0	-32.5	-26.0	-36.2	-26.2
(Test or RLD) vs. Placebo	0.0003		<0.0001		0.007		<0.0001	
Superiority	Pass		Pass		Pass		Pass	
Non-Inflammatory								
LS Mean	-31.8	-23.5	-33.5	-21.6	-28.2	-19.9	-32.2	-20.3
(Test or RLD) vs. Placebo	0.0008		<0.0001		0.0008		<0.0001	
Superiority	Pass		Pass		Pass		Pass	

Source: Applicant’s Study Report, Tables 15 & 16 (pp. 62 & 64 of 267) & FDA Statistical Review, Table 6 & 8.

Reviewer's comments: According to both the Applicant and the FDA statistical analyses, the test product is bioequivalent to the RLD. In addition, both products were statistically superior to vehicle, demonstrating that the study is sensitive enough to detect a difference between products.

2.5 Comparative Review of Safety

2.5.1 Brief Statement of Conclusions

The study showed no clinically significant difference between the test product and the RLD with regard to the adverse events reported.

2.5.2 Description of Adverse Events

Description	Test	RLD	Vehicle	Total
Subjects in Safety Population	222	220	107	549
Number of subjects who had an AEs	49 (22.1%)	46 (20.9%)	26 (24.3%)	121 (22.0%)
Number of AEs reported	87	67	47	201
Number of subjects who had a non-treatment-related AE*	46 (20.7%)	43 (19.5%)	25 (23.4%)	114 (20.8%)
Number of subjects who had a treatment-related AE*	3 (1.4%)	3 (1.4%)	1 (0.9%)	7 (1.3%)
<i>Local swelling</i>	0	1 (0.5%)	0	1 (0.2%)
<i>Edema peripheral</i>	1 (0.5%)	0	0	1 (0.2%)
<i>Headache</i>	1 (0.5%)	0	0	1 (0.2%)
<i>Rash</i>	1 (0.5%)	1 (0.5%)	0	2 (0.4%)
<i>Skin erosion</i>	0	1 (0.5%)	0	1 (0.2%)
<i>Skin mass</i>	0	0	1 (0.9%)	1 (0.2%)
Number of treatment-related AE	3	4	1	8
Severity of AEs				
<i>Mild</i>	83	58	45	186
<i>Moderate</i>	4	9	2	15
<i>Severe</i>	0	1	0	1
Most frequently reported AEs (\geq 1%)*				
<i>Nasopharyngitis</i>	12 (5.4%)	11 (5.0%)	7 (6.5%)	30 (5.5%)
<i>Headache</i>	10 (4.5%)	8 (3.6%)	8 (7.5%)	26 (4.7%)
<i>Dysmenorrhea</i>	4 (1.8%)	2 (0.9%)	2 (1.9%)	8 (1.5%)
<i>Oropharyngeal pain</i>	7 (3.2%)	1 (0.5%)	0	8 (1.5%)
<i>Nasal congestion</i>	6 (2.7%)	0	0	6 (1.1%)
SAE	0	0	0	0
Death	0	0	0	0
Number of subjects discontinued study drug due to AE	3 (1.4%)	1 (0.5%)	1 (0.9%)	5 (0.9%)

Number of AE leading to discontinuation of study drug	3	1	1	5
Clinically significant laboratory findings	0	0	0	0

Source: Applicant's Study Report, Sections 12.2-12.5 (pp. 69-83 of 267) and Tables 19-21 and "ae.xpt" dataset²⁰.
 *Percentages are based on the number of subjects in the Safety population. Subjects are counted once within each AE.

Reviewer's Comment:

- *The number of subjects who experience an AE during the study is comparable between the test group and the RLD group. Although the number of AEs reported is slightly higher in the test group, the number of treatment-related AE reported is less in the test group than the RLD group.*
- *With regard to the severity of AEs, the test group experienced more mild AEs than the RLD group. The RLD group experience more moderate to severe AEs than the test group.*
- *The AE rates were generally comparable between the test group and the RLD group. Oropharyngeal pain and nasal congestion were reported more in the test group than the RLD group. However, all reports of oropharyngeal pain and nasal congestion were unrelated to the study medication. Therefore, it is unlikely that the higher rate of oropharyngeal pain observed in the test group is clinically significant.*

2.6 Relevant Findings From Other Consultant Reviews

2.6.1 Office of Scientific Investigations

A For Cause Inspection was requested for all three sites.²¹ The results of the inspections are pending at the time of this review.

2.6.2 Office of Biostatistics

See FDA Statistical Review²².

Reviewer's comments: *The Office of Biostatistics results are provided in Section 2.4.3.3 "Results" of this review. This reviewer agrees with the Office of Biostatistics results.*

²⁰ [\\cdsesub1\evsprod\anda207955\0000\m5\datasets\tret-05\analysis\adsl.xpt](#)

²¹ Supra Note 7.

²² Supra Note 18.

2.7 Formulation

2.7.1 RLD Formulation

Component	Quality Standard	Function	RLD ²³ Grams per tube		RLD Percent per tube	
			(b) (4)	45g	(b) (4)	45g
Tretinoin	USP	Drug Substance	(b) (4)		(b) (4)	
(b) (4)						
Sodium Hyaluronate-	(b) (4)					
Octoxynol-9						
Butylated Hydroxytoluene						
Methylparaben						
Propylparaben						
Benzyl Alcohol						
Carbomer 940	(b) (4)					
Trolamine						
Glycerin						
Purified Water	(b) (4)					
(b) (4)						

²³NDA 022070/Supplement 1 (eCTD Sequence #0012) dated 8/14/2007, Module 3 Section 3.2.P.1-2

2.7.2 Generic and Vehicle Control (Placebo) Formulations

Ingredient	Function	Test ²⁴ (% w/w)	Vehicle Control ²⁵ (% w/w)
Tretinoin	API		(b) (4)
Purified Water			(b) (4)
(b) (4) (Carbomer 980)			(b) (4)
Sodium Hyaluronate			(b) (4)
Methylparaben ²			(b) (4)
Glycerin			(b) (4)
Benzyl Alcohol			(b) (4)
(b) (4)			(b) (4)
Butylparaben (BP)			(b) (4)
Ethylparaben (EP)			(b) (4)
Isobutylparaben (IBP)			(b) (4)
Methylparaben (MP)			(b) (4)
Propylparaben (PP)			(b) (4)
Phenoxyethanol (Ph)			(b) (4)
(b) (4)			(b) (4)
Butylated Hydroxytoluene			(b) (4)
(b) (4) Fish Collagen			(b) (4)
(b) (4) (Octoxynol 9)			(b) (4)
Trolamine			(b) (4)
(b) (4)			(b) (4)
Total			(b) (4)

Reviewer's comments:

- *The test product is qualitatively and quantitatively different compared to the RLD. The RLD contains (b) (4). However, some of these inactive ingredients differ quantitatively. These qualitative and quantitative differences in inactive ingredients are acceptable at the levels listed from a regulatory perspective, as determined by the filing review from the Division of Filing Review, and the study results show no apparent effect of the formulation differences on product performance or safety.*

²⁴ ANDA 207955 Original Submission, Module 3.2.P.1, p. 1 of 5, [\cdsesub1\evsprod\anda207955\0000\m3\32-body-data\32p-drug-prod\tretinoin-gel-usp-005\32p1-desc-comp\description-and-composition.pdf](#).

²⁵ ANDA 207955 Sequence 0001, Cover Letter, p. 2 of 4, [\cdsesub1\evsprod\anda207955\0001\m1\us\cover-letter.pdf](#).

- *The inactive ingredients in the test product and the placebo formulations are qualitatively and quantitatively the same except for a slight difference in* (b) (4)

The placebo formulation used in Study TRET-05 is acceptable.

2.8 Conclusion and Recommendation

2.8.1 Conclusion

The clinical data submitted to ANDA 207955 are adequate to demonstrate bioequivalence of the Applicant's Tretinoin Topical Gel, 0.05% with the reference listed drug (RLD), Atralin[®], 0.05%. This conclusion is based on information available prior to OSI inspection findings.

2.8.2 Recommendations

DCR recommends approval of this application, contingent on approval recommendations from the other disciplines on the review team and the satisfactory OSI inspection outcome.

3 CLINICAL BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

The Division of Clinical Review has completed its review pending OSI inspection findings and has no comments at this time.

APPEARS THIS WAY ON
ORIGINAL

4 Appendix

Table 4.1: Approved Tretinoin Topical Products

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N020404	AB	No	Tretinoin	Cream;Topical	0.03%	Avita	Mylan Pharms INC
N021108		Yes	Tretinoin	Cream;Topical	0.02%	Renova	Valeant INTL
N019963	AB2	Yes	Tretinoin	Cream;Topical	0.05%	Renova	Valeant INTL
N019049	AB	Yes	Tretinoin	Cream;Topical	0.03%	Retin-A	Valeant Bermuda
N017522	AB1	Yes	Tretinoin	Cream;Topical	0.05%	Retin-A	Valeant Bermuda
N017340	AB	Yes	Tretinoin	Cream;Topical	0.10%	Retin-A	Valeant Bermuda
A075264	AB	No	Tretinoin	Cream;Topical	0.03%	Tretinoin	Matawan Pharms
A075265	AB1	No	Tretinoin	Cream;Topical	0.05%	Tretinoin	Matawan Pharms
A075213	AB	No	Tretinoin	Cream;Topical	0.10%	Tretinoin	Matawan Pharms
A076498	AB2	No	Tretinoin	Cream;Topical	0.05%	Tretinoin	SUNEVA MEDCL
A090098		Yes	Tretinoin	Cream;Topical	0.04%	Tretinoin	Watson Labs INC
A202209		No	Tretinoin	Cream;Topical	0.08%	Tretinoin	Watson Labs INC
N022070		Yes	Tretinoin	Gel;Topical	0.05%	Atralin	Dow Pharm
N020400	BT	No	Tretinoin	Gel;Topical	0.03%	Avita	Mylan
N017955	AB	Yes	Tretinoin	Gel;Topical	0.01%	Retin-A	Valeant INTL
N017579	AB	Yes	Tretinoin	Gel;Topical	0.03%	Retin-A	Valeant INTL
N020475	AB	Yes	Tretinoin	Gel;Topical	0.04%	Retin-A-Micro	Valeant INTL
N020475	AB	Yes	Tretinoin	Gel;Topical	0.10%	Retin-A-Micro	Valeant INTL
N020475		Yes	Tretinoin	Gel;Topical	0.08%	Retin-A-Micro	Valeant INTL
A075589	AB	No	Tretinoin	Gel;Topical	0.01%	Tretinoin	Matawan Pharms
A075529	AB	No	Tretinoin	Gel;Topical	0.03%	Tretinoin	Matawan Pharms
A202567	AB	No	Tretinoin	Gel;Topical	0.04%	Tretinoin	Spear Pharms Inc
A202026	AB	No	Tretinoin	Gel;Topical	0.10%	Tretinoin	Spear Pharms Inc
N016921		Yes	Tretinoin	Solution;Topical	0.05%	Retin-A	Valeant INTL

Source: Search of the Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations by this reviewer on 2/10/2015. Appl No=application number; TE=therapeutic; RLD=reference listed drug.

**Table 4.2: ANDAs Submitted to Office of Generic Drugs for Tretinoin Topical Gel (b) (4)
Approved)**

ANDA NUMBER	DRUG PRODUCT	APPLICANT	CURRENT STATUS
207955	Tretinoin Topical Gel, 0.05%	Spear Pharmaceuticals Inc.	Pending
202567	Tretinoin Topical Gel, 0.04%	Spear Pharmaceuticals Inc.	Approved (7/17/2013)
202026	Tretinoin Topical Gel, 0.1%	Spear Pharmaceuticals Inc.	Approved (7/17/2013)
075529	Tretinoin Topical Gel, 0.03%	Matawan Pharmaceuticals	Approved (2/22/2000)
075589	Tretinoin Topical Gel, 0.01%	Matawan Pharmaceuticals	Approved (6/11/2002)

(b) (4)

Source: Search of DARRTS and GDRP by this reviewer on 2/10/2015.

(b) (4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 207955

CHEMISTRY REVIEWS



Recommendation: Approvable

ANDA 207955 Review # 1

Drug Name/Dosage Form	Tretinoin Gel USP
Strength	0.05%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Spear Pharmaceuticals Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original ANDA	10/01/2014
Quality/Response to Information Request	10/27/2014
Amendment	03/26/2015
Amendment	06/19/2015
Amendment	07/06/2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	David Skanchy	DMF
Drug Product	Richard Chang	B2/ OLDP/Liquid
Process	Vidya Pai	B7/OPF/Div III
Microbiology	N/A	N/A
Facility	Aditi Thakur	B2/OPF/Div V
Biopharmaceutics	N/A	N/A
Project/Business Process Manager	Tania Mazza	B2/OPRO/Div I
Application Technical Lead	Pahala Simamora	B2/OLDP/ Liquid
Laboratory (OTR)	N/A	N/A
ORA Lead	Ann Marie Montemurro	
Environmental Assessment (EA)*	N/A	N/A

* Categorical exclusion per 21 CFR 25.31 (a) (1)

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Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION:

- Reference listed drug (RLD): Atralin (tretinoin) gel, 0.05%
- NDA#:022070
- RLD's Firm's name: Dow Pharm (NDA holder), marketed by Coria Laboratories, a division of Valeant Pharmaceuticals
- Patent (S): There are no unexpired patents. A Paragraph II Certification is provided.
- Exclusivity: There is no unexpired exclusivity for this product.

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS ¹	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	1	02/04/2015	Reviewed by D. Skanchy (NAI)
	Type III (if applicable)			N/A		
	Type IV (if applicable)					
	Other					

¹ Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: IND, RLD, or sister applications

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22077	Atralin® (Tretinoin Gel 0.05%)

3. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

ANDA is approvable from OPQ perspective based on the following:

- Satisfactory responses to all deficiencies pertaining to the drug substance, drug product and process.
- All drug substance/drug product-related facilities are acceptable

(b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Applicable

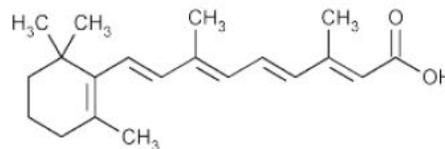
(b) (4)

II. Summary of Quality Assessments

A. Drug Substance [Tretinoin USP] Quality Summary

1. Chemical Name or IUPAC Name/Structure

All-trans-(all-E)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8- nonatetraenoic acid.



2. Properties/CQAs Relevant to Drug Product Quality

Chemically, tretinoin is *all-trans-retinoic acid*. Tretinoin is a yellow to yellow-orange crystalline powder. The melting point is approximately 182°C under decomposition. It should be protected from light and air. It is very sparingly soluble in water, slightly soluble in alcohol and chloroform.

(b) (4)

(b) (4)

(b) (4)

B. Drug Product [Tretinoin Gel USP, 0.05%] Quality Summary

1. Strength: 0.05% w/w
2. Description/Commercial Image:
Tretinoin Gel, 0.05% is a smooth, translucent to opaque, pale yellow topical gel containing 0.05% tretinoin packaged in (b) (4) tube.
3. Summary of Product Design
There is a USP monograph for the drug product. It is formulated as an aqueous gel and packaged in (b) (4) tubes (45g).
4. List of Excipients:
Benzyl alcohol, butyl paraben, butylated hydroxytoluene, carbomer (b) (4) ethyl paraben, fish collagen hydrolyzates, glycerin, iso-butyl paraben, methylparaben, octoxynol 9, phenoxyethanol, propylparaben, purified water, sodium hyaluronate, and trolamine.

(b) (4)

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	N/A
Non Proprietary Name of the Drug Product	Tretinoin Gel, USP
Non Proprietary Name of the Drug Substance	Tretinoin USP
Proposed Indication(s) including Intended Patient Population	Acne Vulgaris
Duration of Treatment	Once daily
Maximum Daily Dose	0.25 mg
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Classification:
 - Drug Substance: N/A
 - Drug Product: N/A

2. Biowaivers/Biostudies
 - Biowaiver Requests: N/A
 - PK studies: Acceptable on 6/2/2015 (Reviewer: Sarah Seung)
 - IVIVC: N/A

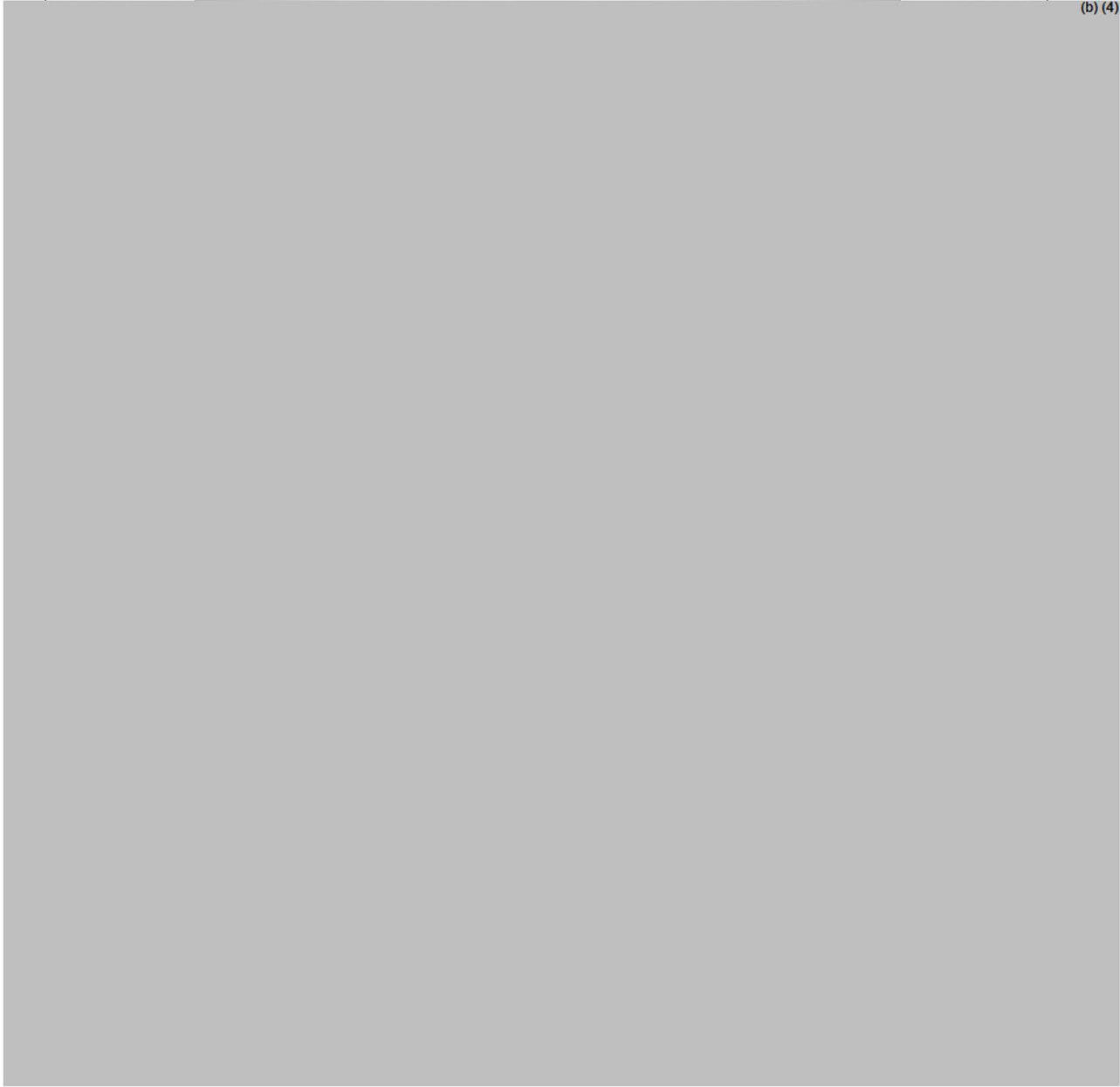
E. Novel Approaches

N/A

F. Any Special Product Quality Labeling Recommendations

N/A

G. Process/Facility Quality Summary (see Attachment A)**H. Life Cycle Knowledge Information (see Attachment B)**



I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

a) DESCRIPTION section

- i) Is the information accurate? Yes No

If "No," explain.

- ii) Is the drug product subject of a USP monograph? Yes No

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

b) HOW SUPPLIED section

- i) Is the information accurate? Yes No
If "No," explain.
- ii) Are the storage conditions acceptable? Yes No
If "No," explain.

c) DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? Yes No N/A
If "No," explain.

d) For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? Yes No
If "No," explain.

The drug product is not an OTC drug and not controlled substance.

e) For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code
0.05%	N/A	N/A

f) Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: N/A

II. List of Deficiencies To Be Communicated

- A. Drug Substance
None
- B. Drug Product
None
- C. Process/Facility
None

- D. Biopharmaceutics
N/A
- E. Microbiology
N/A
- F. Label/Labeling
N/A

IV. Administrative

A. Reviewer's Signature

B. Endorsement Block

Reviewer Name/Date: See review for the primary and secondary reviewers for relevant sections

Application Technical Lead/Date: Pahala Simamora/23-JUL-2015

Project Manager/Date: Tania Mazza/23-JUL-2015

APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207955

STATISTICAL REVIEWS



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

ANDA/Serial Number: 207955

Drug Name: Tretinoin Gel, USP 0.05%

Indication(s): Treatment of acne vulgaris

Reference Listed Drug: Atralin™ (tretinoin) Gel, 0.05%

Applicant: Spear Pharmaceuticals, Inc

Date(s): Submitted on 10/1/2014

Biometrics Division: DBVIII

Statistical Reviewer: Wanjie Sun, Ph.D.

Concurring Reviewers: Fairouz Makhoul, Ph.D., Team Leader

Medical Division: Division of Clinical Review in OGD/OPS/CDER

Clinical Team: Sarah Seung, Pharm.D.

Keywords: inflammatory and non-inflammatory lesion count, , percent change, equivalence

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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

Efficacy

Efficacy was established for both the test product (TEST), Tretinoin Gel 0.05%, and the reference listed product (RLD), Atralin™ (tretinoin) Gel 0.05%, over the vehicle (VEH) for the two co-primary endpoints, i.e., percent change from baseline to Visit 5 (Week 12) in inflammatory and non-inflammatory lesion count, using the FDA's modified intent-to-treat (FDA's mITT) population. However, for inflammatory lesion count, the superiority of TEST over VEH was not consistent across the three sites.

Therefore, we recommend Office of Scientific Investigators (OSI) inspection on the sites.

Equivalence

Equivalence was established between TEST and RLD for both the primary endpoints (percent change in inflammatory and non-inflammatory lesion count from baseline to Visit 5 (Week 12) using the FDA's Per Protocol (FDA's PP) population.

Bioequivalence

Bioequivalence was statistically established between TEST and RLD based on the efficacy and equivalence results (TEST and RLD both superior to VEH in the two co-primary endpoints: TEST and RLD were equivalent in the two co-primary endpoints).

If OSI finds no problem with the sites, the statistical review and evaluation of the current data submitted for ANDA 207955 support approval for bioequivalence.

1.2 STATISTICAL FINDINGS

Efficacy:

The efficacy primary analyses revealed superiority of both TEST and RLD over VEH for both co-primary endpoints of lesion count at the end of treatment Visit 5(Week 12), in the FDA's mITT population. For inflammatory lesion count, the TEST mean percent change from baseline to Visit 5 (Week 12) (-32.5) was significantly higher than that of VEH (-26.0, two-sided p-value = 0.007); likewise, the RLD mean percent change of inflammatory lesion count from baseline to Visit 5 (Week 12) (-36.2) was significantly higher than that of VEH (-26.2, p-value < 0.0001). For non-inflammatory lesion count, the mean percent change from baseline to Visit 5 (Week 12) in TEST (-28.2) was also significantly higher than that of VEH (-19.9, two-sided p-value = 0.0008); Similarly, the RLD mean percent change of non-inflammatory lesion count from baseline to Visit 5 (Week 12) (-32.2) was significantly higher than that of VEH (-20.3, two-sided p-value < 0.0001)

However, for inflammatory lesion count, the superiority of TEST over VEH was not robust in sensitivity analysis. Heterogeneous treatment effect was observed across sites (interaction of treatment and site p-value = 0.01). Site 3 had the best efficacy (TEST: -51.1 vs VEH: -21.9) with the smallest sample size (n = 27 for TEST and VEH), followed by Site 1 (TEST: -13.7 vs VEH: -6.0, n = 182 for TEST and VEH), and Site 2 (TEST: -57.6 vs VEH: -55.8, n = 120 for TEST and VEH). Superiority remained significant

when combining Site 2 and Site 3, however, unadjusted analysis ($p = 0.064$) and adjusted analysis for site and baseline lesion count (and site by treatment group interaction for percent change in inflammatory lesion count) when dropping the 27 subjects at Site 3 (p -value = 0.12) both nullified the superiority.

Furthermore, Site 1 had comparable baseline mean inflammatory lesion counts as Site 2 (Site 1: 26.3 and for Site 2: 27.1, Appendix 6), but much less reduction of lesion count at Visit 5 (Week 12) in both groups (Site 1: -13.7 for TEST and -6 for RLD; Site 2: -57.6 for TEST and -55.8 for RLD), which may be due to inter-rater variability or other reasons.

Therefore, given the heterogeneous treatment effect across sites, we recommend OSI inspection for the three sites.

Equivalence:

Equivalence was established between TEST and RLD for both primary endpoints of the lesion counts using the FDA's PP population. The 90% CI on the mean ratio of TEST to RLD for the percent change in lesion counts from baseline to Visit 5 (Week 12) was (0.86, 1.03) for inflammatory and (0.83, 1.02) for non-inflammatory lesion counts. Both were contained within the FDA's equivalence interval [0.80, 1.25].

Equivalence was reasonably robust in sensitivity analysis. For both endpoints, out of the three sensitivity analyses, equality failed in the unadjusted analysis, but passed in the other two analyses adjusted for site and baseline lesion count when combining Site 2 and Site 3, or dropping Site 3.

2 INTRODUCTION

2.1 OVERVIEW

Introduction

Acne vulgaris is a common skin condition that can affect people of all ages, although teenagers develop acne most often. About 10-20% of adults may continue to experience some form of acne that occurs when there is an increase in sebum release by sebaceous glands. Small cysts or comedones form in hair follicles due to blockage of the follicular orifice by retention of sebum and keratinous material. The clinical hallmark of acne is the comedone, which may be closed (whitehead) or open (blackhead). Closed comedones (contents not easily expressed) are the precursors of inflammatory lesions while open comedones (filled with easily expressible oxidized, darkened, oily debris) rarely result in inflammatory acne lesions. Comedones are usually accompanied by inflammatory lesions: papules, pustules or nodules.

Reference Drug

AtralinTM (tretinoin) Gel (Dow Pharm) 0.05%, NDA 022070, was approved by FDA on July 26, 2007 for the topical treatment of acne vulgaris. Tretinoin Gel 0.05% (Spear Pharmaceuticals, Inc.) is a new prospective generic equivalent of AtralinTM (tretinoin) Gel 0.05.

2.2 DATA SOURCES

The data were submitted electronically. The data files are located in the following directory:
\\cdsesub1\evsprod\ANDA207955\F:\ANDA207955\0000\m5\datasets\12-1001\listings\

3 STATISTICAL EVALUATION

3.1 STUDY DESIGN AND ENDPOINTS

Objective

The objective of this study was to compare the efficacy and safety of the Tretinoin Gel 0.05% (TEST) to the Atralin™ (tretinoin) Gel 0.05% (RLD) and Gel Vehicle (VEH) in the treatment of acne.

The primary objective was to assess the clinical bioequivalence of the Tretinoin Gel 0.05% (TEST) and the Atralin™ (tretinoin) Gel 0.05% (RLD). The secondary objective was to assess the statistical superiority of the Atralin™ (tretinoin) Gel 0.05% (RLD) and the Tretinoin Gel 0.05% (TEST) to Gel VEH.

Study Design

This was a double-blinded, randomized, three-treatment, parallel study conducted in normal, healthy male and female children and adults (i.e. ages 12 to 40 years) with at least Grade 2 (i.e., mild severity) acne vulgaris at three US locations of MOORE Clinical Research, under the supervision of a single investigator. The study enrolled five hundred and seventy four (574) subjects and randomly assigned them in a 2:2:1 ratio to Tretinoin (TEST: n=230), Atralin™ (RLD: n=229), or the Gel vehicle group (VEH: n=115), respectively. The subjects completed five visits: Week 0 or Baseline (Day 0), Week 2 (Day 14 ± 4), Week 4 (28 ± 4), Week 8 (56 ± 4), and Week 12 (84 ± 4). Evaluation of efficacy and equivalence was conducted based on the data at Visit 5 (Week 12).

Treatments

TEST: Tretinoin Gel, USP 0.05% (Spear Pharmaceuticals Inc.)
Lot Number: 3G14A

RLD: Atralin™ (tretinoin) Gel 0.05% (Valeant Pharmaceuticals, North America)
Lot Number: FEBZ

VEH: Tretinoin Gel, USP Placebo (Spear Pharmaceuticals, Inc)
Lot Number: 3G12A

Study Sites

Site 1: MOORSE Clinical Research, Inc. (Brandon, FL)
Site 2: MOORSE Clinical Research Inc. (Tampa, FL)
Site 3: MOORSE Clinical Research Inc. (Fort Myers, FL)

Study Endpoints

Primary endpoints

The co-primary endpoints used in this study were the mean percent change from baseline to Visit 5 (Week 12) in inflammatory (papules and pustules) and non-inflammatory (open and closed comedones) lesion counts.

- The percent change from baseline was calculated as follows:

Let T be the lesion count at Visit 5 (Week 12) and B be the lesion count at Baseline (Week 0), then

$$\text{Percent change from baseline} = 100 * (B - T)/B.$$

Secondary endpoint

This study did not specify a secondary endpoint. The FDA guidance did not recommend one either. The sponsor tabulated the number and percentage of subjects at each Investigator’s Global Assessment (IGA) severity grade by visit. The IGA severity grade was defined as follows:

Investigator's Global Assessment (IGA)

The IGA used the following rating scale.

Grade	Description
0	Clear skin with no inflammatory or noninflammatory lesions
1	Almost clear; rare non-inflammatory lesions present, with no more than one small inflammatory lesion.
2	Mild severity; greater than Grade 1; some noninflammaotry lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)
3	Moderate severity; greater than Grade 2; up to many noninflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion.
4	Severe; greater than Grade 3; up to many noninflammatory lesions and may have some inflammatory lesions, but no more than a few nodular lesions.

The rating scale was static in nature and was performed without reference to any previous assessments for a particular subject.

3.2 SUBJECT DISPOSITION

Study Populations discussed in this review are the modified intent-to-treat (mITT) and per-protocol (PP) populations.

Modified Intent-to-Treat (mITT) Population - The mITT population was used for the efficacy analysis.

The sponsor’s mITT population definition: To be included in the Sponsor’s mITT population, the subjects needed to meet the following criteria:

- Randomized
- Met all inclusion and exclusion criteria
- Applied at least one dose of assigned product
- Returned for at least one post-baseline visit

The FDA's mITT population definition includes subjects who were:

- Randomized
- Applied at least one dose of assigned product

Per-Protocol (PP) Population - The PP population was used for the equivalence analysis. To be included in the PP population, the subjects needed to meet the following criteria:

- Randomized
- Met all inclusion and exclusion criteria
- Applied a pre-specified proportion of the scheduled applications (e.g. 75-125%) of the assigned product for the specified duration of the study
- Did not miss the scheduled applications for more than 3 consecutive days
- Completed the evaluation within the designated visit window (+/- 4 days) with no protocol violations that would affect treatment evaluation,
- Or, discontinued from the study as a treatment failure and do not have any protocol violations that would affect the treatment evaluation.

A total of five hundred and seventy-four (574) subjects were enrolled and randomized at three study sites. Of these, two hundred and thirty (230) (40%) were randomized to TEST, two hundred and twenty-nine (229) (40%) randomized to RLD, and one hundred and fifteen (115) (20%) randomized to VEH, respectively.

According to the study report of the sponsor, five hundred and forty-nine (549) subjects were included the Sponsor's mITT population (25 excluded). Of these, five hundred and nine (509) subjects were included in the PP population (65 excluded). The FDA's mITT population is the same as the Sponsor's mITT . The FDA's PP population consisted of four hundred and ninety-two (492) subjects (82 excluded). Table 1 presents the number of subjects in each population by treatment group and by exclusion reason according to the sponsor and the FDA.

Table 1. Subject Disposition

Source	Population	Total	TEST	RLD	VEH
	Enrollment	574	230	229	115
Sponsor					
	Sponsor's mITT Population				
	Total exclusion from Sponsor's ITT population	25	8	9	8
	Total Sponsor's mITT population (ITT)	549	222	220	107
	Reasons for exclusion of ITT Population				
	Did not take study medication	25	8	9	8
	Sponsor's PP Population				
	Total exclusion from sponsor's PP population	65	30	20	15
	Total Sponsor's PP population (PP)	509	200	209	100
	Reasons for exclusion of PP Population				
	Did not take study medication	25	8	9	8
	Compliance<75%, Miss application for >3 consecutive days	1	1	0	0
	Compliance<75%, No valid Week 12 visit	1	1	0	0
	Miss application for >3 consecutive days, No valid Week 12 visit	5	3	2	0
	No valid Week 12 visit	26	12	7	7
	No valid Week 12 visit, Restricted medication	4	3	1	0
	No valid Week 12 visit, Pregnancy	1	1	0	0
	Restricted medication	1	1	0	0
	Enrolled against inclusion 2	1	0	1	0
FDA					
	FDA's mITT Population				
	Total exclusion from FDA's mITT population	25	8	9	8
	Total FDA's mITT population	549	222	220	107
	Reasons for exclusion from FDA's mITT Population				
	Did not take study medication	25	8	9	8
	FDA's PP Population				
	Total exclusion from FDA's PP population	82	33	30	19
	Total FDA's PP population (FPP)	492	197	199	96
	Did not take study medication	25	8	9	8
	Compliance<75%, Miss application for >3 consecutive days	1	1	0	0
	Compliance<75%, No valid Week 12 visit	1	1	0	0
	Miss application for >3 consecutive days, No valid Week 12 visit	5	3	2	0
	No valid Week 12 visit	26	12	7	7
	No valid Week 12 visit, Restricted medication	4	3	1	0
	No valid Week 12 visit, Pregnancy	1	1	0	0
	Restricted medication*	17	4	9	4
	Enrolled against inclusion 2	1	0	1	0
	Study medication dose decreased due to AE**	1	0	1	0

*Subjects (b) (6) in the TEST group, (b) (6) in the RLD group
and (b) (6) in the VEH group
** Subject (b) (6) in the RLD

The following adjustments to the PP population were made in accordance with the recommendations of the FDA reviewers.

Exclusion from the FDA per Protocol population (FPP):

Seventeen (17) subjects was excluded from the FDA's PP population. Note that subject (b) (6) in the RLD had two reasons to be excluded from the FDA's PP population. Table 2 lists the FDA's adjustment to the Sponsor's PP population.

Table 2. FDA’s PP population adjustment for ANDA 207955

Study #	Change Requested?	Site/Subject number	Treatment	Applicant included/excluded	FDA PP: Included/Excluded	Reason
TRET-05	Yes	(b) (6)	RLD	Included	Exclude	Subject’s study medication dose was “decreased” during the study due to AEs (“Erosion on RT cheek” and “skin erosion between eyebrows”).
			TEST TEST RLD RLD VEH VEH	Included	Exclude	Restricted medication (Took oral amoxicillin during the study)
			VEH	Included	Exclude	Restricted medication (Took oral Augmentin during the study)
			VEH	Included	Exclude	Restricted medication (Receive IM penicillin during the study)
			RLD RLD RLD	Included	Exclude	Restricted medication (Took oral clindamycin during the study)
			RLD	Included	Exclude	Restricted medication (Took oral erythromycin during the study)
			RLD	Included	Exclude	Restricted medication (Took oral Bactrim (trimethoprim-sulfamethoxazole) during the study)
			RLD	Included	Exclude	Restricted medication (Took oral levofloxacin during the study)
			TEST RLD	Included	Exclude	Restricted medication (Took oral ciprofloxacin during the study)
			RLD	Included	Exclude	Restricted medication (Took oral prednisone during the study)

*Subject (b) (6) in the RLD group had two reasons to be excluded from the FDA’s PP population.

3.3 DEMOGRAPHICS AND BASELINE OUTCOMES

Comparability in baseline demographics

Demographic characteristics at baseline by treatment group in the FDA’s mITT and the FDA’s PP population are presented in Table 3. In both populations, there was no statistically significant difference across treatment groups in the demographic characteristics except for ethnicity. The vehicle group has marginally more Hispanic or Latino than the two active treatment groups (TEST and RLD) with p-value=0.045 in the FDA’s mITT population. Stratification by site revealed a similar result.

Table 3. Baseline Demographics by Treatment Group in FDA’s mITT (N=549) or PP population (N=492)

Characteristics	FDA’s mITT Population					FDA’s PP Population				
	Total (N=549)	TEST (N=222)	RLD (N=220)	VEH (N=107)	p-value *	Total (N=492)	TEST (N=197)	RLD (N=199)	VEH (N=96)	p-value*
Age (years)										
Mean (SD)	20.0 (7.3)	20.1 (7.1)	20.1 (7.6)	19.6 (7.3)	0.77	19.9 (7.3)	19.9 (6.8)	20.1 (7.7)	19.6 (7.4)	0.88
Median (Min, Max)	17 (15, 23)	17 (11,40)	17 (12,40)	17(13,38)		17 (12, 40)	17 (12, 40)	17 (12, 40)	17 (12, 39)	
Gender n (%)										
Male	230 (42%)	98 (44%)	89 (41%)	43 (40%)	0.68	216 (44%)	93 (47%)	81 (41%)	42 (44%)	0.43
Female	319 (58%)	124 (56%)	131 (59%)	64 (60%)		276 (56%)	104 (53%)	118 (59%)	54 (56%)	
Race n (%) ~										
Caucasian	394 (72%)	157 (71%)	163 (74%)	74 (69%)	0.13	358 (73%)	142 (72%)	148 (74%)	68 (71%)	0.11
African American	139 (25%)	61 (27%)	52 (24%)	26 (24%)		122 (25%)	52 (26%)	48 (24%)	22 (23%)	
Other	16 (3%)	4 (2%)	5 (2%)	7 (7%)		12 (2%)	3 (2%)	3 (2%)	6 (6%)	
Ethnicity n(%)										
Hispanic or Latino	423 (77%)	172 (77%)	160 (73%)	91 (85%)	0.045	381 (77%)	156 (79%)	144 (72%)	81 (84%)	0.052
Not Hispanic or Latino	126 (23%)	50 (23%)	60 (27%)	16 (15%)		111 (23%)	41 (21%)	55 (28%)	15 (16%)	

* p-values for continuous demographics were derived from a One-way ANOVA model where the respective continuous demographics were the outcome and treatment was the factor. P-values for categorical demographics was calculated from the Pearson Chi-square test.

~ The number of subjects was sparse in American Indian/Alaska native, Asian, native Hawaiian or other pacific islander, and other or mixed. Therefore, these categories are combined into one category as “other.”

^ Subject (b) (6) at baseline. However, as per the clinical reviewer, this subject is still qualified to be included in FDA’s mITT according to the current definition of the FDA’s mITT.

Comparability in Baseline Endpoints

To examine the comparability of the primary endpoints across treatment groups at the baseline visit, the distribution of the inflammatory lesion counts, the non-inflammatory lesion counts, and the IGA scores was compared in both the FDA's mITT and the FDA's PP population. The results are presented in Table 4 below.

ANOVA models showed that in both the FDA's mITT and PP populations, neither the inflammatory nor non-inflammatory lesion counts were significantly different among the three treatment groups (each p-value > 0.05). Adjustment for site in a two-way ANOVA revealed a similar result. Likewise, the IGA score was balanced among the three treatment groups (each p-value > 0.05). Stratified analysis by site showed a similar result.

Table 4. Lesion Count and IGA Score by Treatment Group at Baseline in the FDA's mITT and the FDA's PP populations

	Total	TEST	RLD	VEH	p-value*
FDA's mITT Population					
N	549	222	220	107	
Inflammatory Lesion Count					
Mean (SD)	26.4 (5.0)	26.2 (4.9)	26.3 (5.0)	27.2 (5.3)	0.23
Median (Q1, Q3)	25 (22, 29)	25 (23, 29)	25 (22, 29)	26 (23, 31)	
Non-Inflammatory Lesion Count					
Mean (SD)	34.1 (7.2)	34.4 (7.3)	37.4 (13.0)	36.8 (13.3)	0.66
Median (Q1, Q3)	32 (29, 38)	32 (29, 438)	31.5 (28, 39)	33 (29, 38)	
IGA Score (n (%)) **					
2	50 (9%)	20 (9%)	23 (10%)	7 (7%)	0.74
3	336 (61%)	137 (62%)	135 (61%)	64 (60%)	
4	163(30%)	65 (29%)	62 (28%)	36 (34%)	
FDA's PP Population					
N	492	197	199	96	
Inflammatory Lesion Count					
Mean (SD)	26.5 (5.0)	26.0 (4.9)	26.3 (5.0)	27.3 (5.3)	0.21
Median (Q1, Q3)	25 (22.5, 29)	25 (23, 29)	25 (22, 29)	26.5 (23, 31.5)	
Non-Inflammatory Lesion Count					
Mean (SD)	34.0 (7.1)	34.1 (6.9)	33.6 (7.2)	36.8 (13.3)	0.55
Median (Q1, Q3)	32 (29, 38)	32 (29, 38)	31 (28, 38)	32.5 (29, 38)	
IGA Score (n (%)) **					
2	42 (9%)	16 (8%)	21 (11%)	5 (5%)	0.43
3	304 (62%)	123 (62%)	124 (62%)	57 (59%)	
4	146 (30%)	58 (29%)	54 (27%)	34 (35%)	

* P-values for lesion counts (inflammatory or non-inflammatory) were derived from a One-way ANOVA model where the respective lesion count was the outcome and treatment was the factor. A two-ANOVA model was used to adjust for site as a factor. P-values for the IGA score were calculated using the Pearson Chi-square test. Stratified (by site) analysis was done using the Cochran Mantel Haenszel General Association Test.

** The total percentage may be more or less than 100% due to rounding.

3.4 STATISTICAL METHODOLOGIES

3.4.1 Statistical Analysis Methods

<CONTINUOUS ENDPOINT>

Percent change from baseline to Visit 5 (Week 12) in the inflammatory and non-inflammatory lesion counts were the co-primary endpoints to determine the equivalence between TEST and RLD, and the superiority of active treatments (TEST or RLD) over the vehicle group.

Efficacy/Superiority Analysis

Separate efficacy tests were conducted for superiority of each active treatment (TEST or RLD) over the vehicle in each primary endpoint, at the 5 % significance level for a two-sided test of no difference (or the 2.5% significance level for a one-sided test of superiority). Efficacy analyses used the FDA's mITT population. An analysis of covariance (ANCOVA) model was used in the primary analysis for superiority test, with the respective endpoint as the outcome, treatment, site, and treatment by site if significant as the factors, and the baseline lesion count as the covariate, as the sponsor pre-specified in the protocol. This is also consistent with the ICH E9 guidance, "If one or factors are used to stratify the design, it is appropriate to account for those factors in the analysis." "Special attention should be paid to center effects and to the role of baseline measurements of the primary variable."

The Least squares (LS) mean estimates for each treatment group and the difference between the active treatment and vehicle with its 95% CI were calculated. Given the small number of sites (3) and the large discrepancy in sample size among the three sites for this study, LS means were estimated by assigning each site a weight based on its sample size (i.e., Type 1) rather than an equal weight to each site (i.e., Type 3). Superiority was established if the mean percent change from baseline for each active treatment (TEST or RLD) and each lesion type (inflammatory or non-inflammatory), was statistically greater than that in the vehicle group (at the 5% significance level for a two-sided test of difference or 2.5% level for a one-sided test of superiority).

If the distribution of the residuals from the ANCOVA model departed severely from the normality (Shapiro-Wilks test), a ranked efficacy analysis would be conducted.

Equivalence Analysis

Tests for equivalence between TEST and RLD for each primary endpoint (inflammatory and non-inflammatory lesion count) were conducted separately using the FDA's PP population.

The compound hypothesis tested was:

$$H_0: \mu_T / \mu_R \leq \theta_1 \text{ or } \mu_T / \mu_R \geq \theta_2$$

Versus

$$H_A: \theta_1 < \mu_T / \mu_R < \theta_2$$

Herein, μ_T and μ_R denote the mean values of the outcome for TEST and RLD, respectively

In accordance with the standard in Office of Generic Drug (OGD) for equivalence analyses for continuous endpoints, we use $\alpha=0.05$, and $\theta_1=0.80$ and $\theta_2=1.25$ as the lower and upper equivalence bound. In order to test the clinical equivalence for TEST and RLD in the primary endpoint (e.g. percent change from baseline for the inflammatory or non-inflammatory lesion count), the 90% confidence

interval (corresponding to two one-sided tests each at level $\alpha=0.05$) (Schuirmann 1987) was constructed for the ratio of μ_T/μ_R using Fieller's method (Fieller 1940). The needed statistics for Fieller's method (mean and variance-covariance of the respective primary endpoint for each treatment group) were derived from the least square (LS) mean estimates from the ANOVA model as described in the efficacy/superiority section. For this study, as previously discussed, the LS mean and standard error were estimated by assigning each site a weight based on its sample size (Type 1) rather than an equal weight to each site (Type 3). Equivalence was established (that is, the null hypothesis H_0 is rejected) if the 90% confidence interval for the ratio of μ_T/μ_R based on Fieller's method was contained within the [0.80, 1.25] interval.

3.4.2 Missing Data and Imputation

Among the 574 subjects who were randomized in the study, 57 (9.9%) discontinued from the study. Among the 57 discontinued, 32 were included in the FDA's mITT population, and one was included in the FDA's PP population. Missingness was balanced in general (p-value =0.21) across the TEST (10.9%), RLD (7.4%), and VEH (13.0%) in the randomized subjects.

In the FDA's mITT population, 32 (5.8%) of the 549 subjects did not have Visit 5 (Week 12) measurements. Of these, 17 (7.7%) were from the TEST group, 8 (3.6%) from the RLD group, and 7 (6.5%) from the VEH group. Drop out was balanced across treatment groups (p-value=0.18). The last observation carried forward (LOCF) method was used to impute the missing final measurements for these subjects.

In the FDA's PP population, one subject ^{(b) (6)} from the VEH group was dis-continued due to lack of efficacy. The LOCF method was used to impute the missing primary endpoints (inflammatory or non-inflammatory lesion counts) at Visit 5 (Week 12) for this subject.

Table 5 presents the number of subjects who missed Visit 5 (Week 12) by treatment group among the randomized subjects as well as among the FDA mITT and FDA's PP population.

Table 5. Number of Subjects Who Missed Visit 5 (Week 12) by Treatment Group

	Total	TEST	RLD	VEH	p-value
Randomized					
N	574	230	229	115	
Missed Visit 5, N (%)	57 (9.9%)	25 (10.9%)	17 (7.4%)	15 (13.0%)	0.21
FDA's mITT					
N	549	222	220	107	
Missed Visit 5 (LOCF), N (%)	32 (5.8%)	17 (7.7%)	8 (3.6%)	7 (6.5%)	0.18
FDA's PP					
N	492	197	199	96	
Missed Visit 5 (LOCF), N (%)	1 (0.2%)	0	0	1 (1%)	

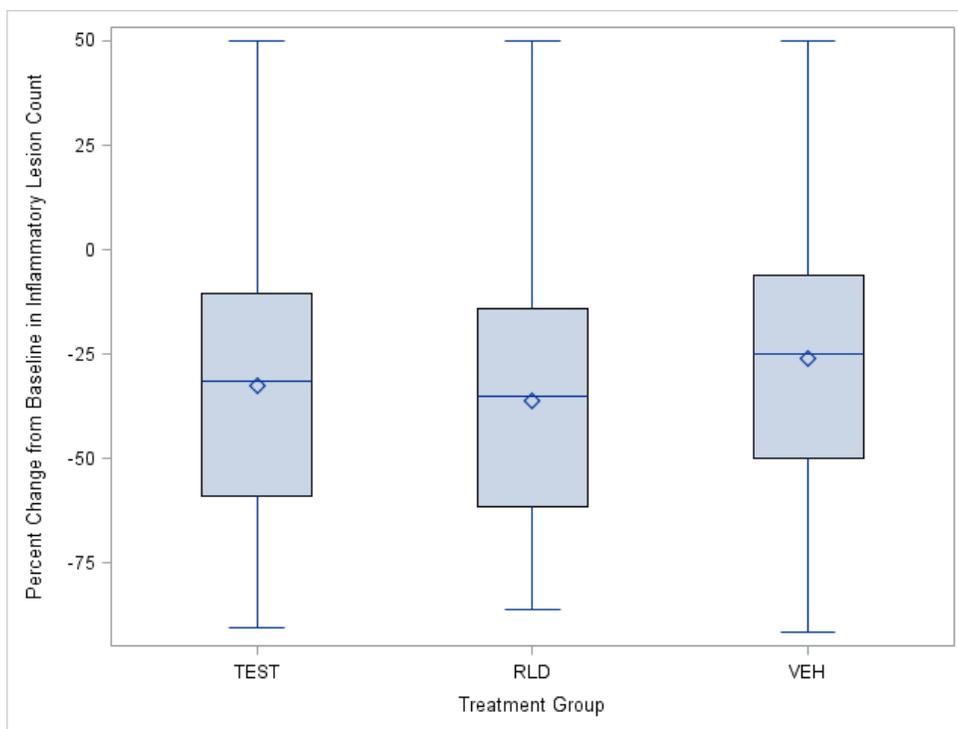
3.5 RESULTS AND CONCLUSIONS

The co-primary endpoints were the mean percent change from baseline to Visit 5 (Week 12) in inflammatory and non-inflammatory lesion counts.

3.5.1 PRIMARY ENDPOINT – Percent Change from Baseline in Inflammatory Lesion Count

The distribution of the percent change from baseline in inflammatory lesion count to Visit 5 (Week 12) by treatment group in the FDA’s mITT population is presented in Figure 1. The data was not skewed (skewness=0.11). TEST had an average of $32.5 \pm 29.4\%$ of reduction in inflammatory lesion count, as compared to $36.3 \pm 28.9\%$ in RLD, and $25.9 \pm 31.9\%$ in VEH.

Figure 1. Percent Change from Baseline in Inflammatory Lesion Count to Visit 5 (Week 12) by Treatment in the FDA’s mITT Population



3.5.1.1 Superiority/Efficacy of TEST over VEH in Inflammatory Lesion Count

Sponsor’s Result:

The sponsor’s primary analysis was based on an ANCOVA model where the inflammatory lesion count was the outcome, treatment, site, and treatment by site (p-value = 0.01) as the factors, and baseline inflammatory lesion count as the covariate, using the Sponsor’s mITT population. Least squares means were estimated by assigning an equal weight to each site (Type 3 analysis). The sponsor established superiority/efficacy of TEST over VEH based on the analysis results (p-value = 0.0003, Table 6 in this report, also found in the sponsor’s clinical summary Table 15).

FDA’s Result:

FDA’s primary analysis was based on the same ANCOVA model as that used by the sponsor and by using the FDA’s mITT population (which is the same as the sponsor’s mITT). However, as described in Section 3.4.1, the LS means were estimated by assigning each site a weight based on its sample size instead (Type 1). Table 6 shows that the LS mean percent change from baseline was -32.5 (95% CI: -

35.2, -29.8) for TEST and -26.0 (95% CI: -29.9, -22.1) for VEH in the FDA's mITT population. TEST had more percent reduction in inflammatory lesion count than VEH (difference of TEST-VEH: -6.6, 95% CI: -11.3, -1.8, p-value = 0.007). Residuals from the ANCOVA model showed a good model of fit (Appendix 1.1).

Table 6. FDA's and Sponsor's Primary Efficacy Analysis for Percent Change from Baseline to Visit 5 (Week 12) in Inflammatory Lesion Count

Statistics	TEST vs. VEH		RLD vs. VEH	
	TEST (N=222)	VEH (N=107)	RLD (N=220)	VEH (N=107)
FDA's Primary Analysis: Adjusted Model by Site and (Site by Treat) and baseline lesion count, where weight was assigned based on the sample size of each site *				
Least Squares (LS) Mean (95% CI)	-32.5 (-35.2, -29.8)	-26.0 (-29.9, -22.1)	-36.2 (-38.9, -33.6)	-26.2 (-30.0, -22.3)
LSMean Difference (95% CI)	-6.6 (-11.3, -1.8)		-10.1 (-14.7, -5.4)	
2-sided p-value~ (TEST vs. VEH) or (RLD vs. VEH)	0.007		<.0001	
Pass Efficacy: (YES: 2-sided p-value<0.05)	YES		YES	
Sponsor's Primary Analysis: Adjusted Model by Site and (Site by Treat) and baseline lesion count, where an equal weight was assigned to each site ** (Sponsor's Clinical Summary: Table 15)				
Least Squares (LS) Mean (90% CI)	-40.2 (-43.9, -35.4)	-28.1 (-33.4, -22.9)	-38.1 (-41.4, -34.7)	-28.0 (-32.3, -23.7)
LSmean Difference (95% CI)	-12.0 (-18.5, -5.6)		-10.1 (-14.7, -5.4)	
2-sided p-value~ (TEST vs. VEH) or (RLD vs. VEH)	0.0003		<.0001	
Pass Efficacy: (YES: 2-sided p-value<0.05)	YES		YES	

* FDA's primary analysis was based on an ANCOVA model where the inflammatory lesion count was the outcome, treatment and site (and interaction of treatment by site for TEST vs VEH, p-value = 0.01) as the factors, and baseline inflammatory lesion count as the covariate. Weight of each site was assigned based on the sample size at each site.

** Sponsor's primary analysis was based on an ANCOVA model where the inflammatory lesion count was the outcome, treatment and site (and interaction of treatment by site for TEST vs VEH, p-value=0.01) as the factors, and baseline inflammatory lesion count as the covariate. An equal weight was assigned to each site (Type 3 sum of square).

~ The 2-sided p-value was to test whether the LSMean from the two treatment groups were the same, based on the respective model as specified in * and **.

Given that the interaction term between treatment and site was significant (p-value = 0.01), subgroup analysis was conducted to evaluate the heterogeneous treatment effects across sites. Appendix 2.2 shows that Site 3 had the best efficacy (TEST: -51.1 vs VEH: -21.9) with the smallest sample size (n=27 for TEST and VEH), followed by Site 1 (TEST: -13.7 vs VEH: -6.0, n = 182 for TEST and VEH). Site 2 was barely separated in two group means (TEST: -57.6 vs VEH: -55.8, n = 120 for TEST and VEH). Therefore, different sensitivity analyses (Appendix 2) were conducted to test the robustness of the superiority result.

Sensitivity analysis 1: An unadjusted one-way ANOVA model (Appendix 2.4) was employed where the percent change from baseline in inflammatory lesion count was the outcome and the treatment was the factor. The unadjusted model shows that the overall TEST LS mean was higher than the VEH mean, but this superiority didn't reach statistical significance (LS mean difference: -6.6, 90% CI: -13.6, 0.40, p-value = 0.064).

Sensitivity analysis 2: Given the unbalanced sample sizes across the sites, Site 2 and Site 3 were pooled to make a more balanced design across sites. The sponsor's model (as reported in Table 6) was retested using the pooled data with Site 1, and Sites 2 and 3 combined (Appendix 2.4). Superiority remained significant in this sensitivity analysis (LS mean difference: -6.7, 90% CI: -11.6, -1.7, p-value = 0.008).

Sensitivity analysis 3: Since Site 3 had a much higher efficacy and very few subjects (n = 27), the sponsor's model (as reported in Table 6) was tested by dropping Site 3 (Appendix 2.4) to examine the robustness of superiority in the remaining 327 subjects at sites 1 and 2. Appendix 2.4 shows that superiority lost significance (LS mean difference: -4.1, 90% CI: -9.1, 1.0, p-value = 0.12) when Site 3 was dropped.

In summary, superiority of TEST over VEH was established for the percent change from baseline in inflammatory lesion count to Visit 5 (Week 12) in the FDA's mITT population.

However, this superiority was not robust in sensitivity analyses. Heterogeneous treatment effect was observed across sites. Furthermore, Site 1 had comparable baseline inflammatory lesion counts (26.3) as Site 2 (27.1, Appendix 6), but much less reduction at Visit 5 (Week 12) in both groups (Site 1: -13.7 for TEST and -6 for RLD; Site 2: -57.6% for TEST and -55.8% for RLD), which may be due to inter-rater variability or other reasons. Therefore, we recommend OSI inspection on the three sites to verify the data accuracy.

3.5.1.2 Superiority/Efficacy of RLD over VEH in Inflammatory Lesion Count

Sponsor's Result:

The sponsor's primary analysis was based on an ANCOVA model where the inflammatory lesion count was the outcome, treatment and site as the factors, and baseline inflammatory lesion count as the covariate, using the Sponsor's mITT population. Least squares means were estimated by assigning an equal weight to each site (Type 3 analysis). The sponsor established superiority/efficacy of RLD over VEH results (p-value < 0.0001, Table 6 in this report, also found in the sponsor's clinical summary Table 15).

FDA's Result:

FDA's primary analysis was based on the same ANCOVA model as the sponsor's and using the FDA's mITT population (which is the same as the Sponsor's mITT), except that the LS means were estimated by assigning each site a weight based on its sample size. Table 6 shows that the LS mean percent change was -36.2% (95% CI: -38.9, -33.6%) for the RLD and -26.2 (95% CI: -30.0, -22.3%) for the VEH in the FDA's mITT population. TEST had significantly higher percent reduction in inflammatory lesion count than VEH (difference of RLD-VEH: -10.1, 95% CI: -14.7, -5.4, p-value < 0.0001). Residuals from the ANCOVA model showed a good model of fit (Appendix 1.2).

Supportive analyses (Appendix 2.4) employing an unadjusted one-way ANOVA (where no factor or covariate was adjusted), the same ANCOVA model as the sponsor's (as reported in Table 6) but pooling sites 2 and 3 (Appendix 2.4), or dropping site 3 (Appendix 2.4), all revealed a similar result as the primary analysis. RLD had significantly higher percent reduction in inflammatory lesion count than VEH in all three sensitivity analyses (each p-value ≤ 0.003). Therefore, the superiority of RLD over VEH was robust.

In summary, superiority of RLD over VEH was established in the primary end-point: percent change from baseline in inflammatory lesion count at Visit 5 (Week 12), among the mITT population. This superiority was robust in sensitivity analyses.

3.5.1.3 Equivalence of TEST vs. RLD in Inflammatory Lesion Count

Sponsor's Result:

The sponsor's primary analysis was based on Fieller's confidence interval using the Sponsor's PP population. The LS mean and standard error estimate for each treatment group were estimated from an ANCOVA model, where the inflammatory lesion count was the outcome, treatment, site, and treatment by site as the factors, and baseline inflammatory lesion count as the covariate. Least squares means were estimated by assigning an equal weight to each site (Type 3 analysis). The sponsor established equivalence of TEST and RLD based on the 90% CI of the mean ratio (Mean ratio: 1.08, 90% CI: (0.97, 1.20), see Table 7 in this report, also reported in the sponsor's clinical summary Table 15).

FDA's Result:

The FDA's primary analysis was based on Fieller's confidence interval using the FDA's PP population, where the LS mean and standard error estimates of the percent change in inflammatory lesion count were derived from the same ANCOVA model as the sponsor's. The LS means were estimated by assigning each site a weight based on its sample size rather than an equal weight. Table 7 shows that the TEST mean percent change from baseline (-33.9 ± 1.38) was equivalent to the RLD mean (-36.0 ± 1.37), because the 90% CI of the mean ratio (0.86, 1.03) was contained within the FDA's equivalence interval [0.80, 1.25].

Given that the interaction term between treatment and site was significant (p-value=0.008), subgroup analysis was conducted to evaluate the heterogeneous treatment effects across sites. Appendix 3.1 shows that at Sites 1 and 2, TEST had less reduction than RLD (Site 1: -14.3 vs -19.0, n=226 for TEST and RLD ; Site 2: -62.0 vs. -64.9, n=135 for TEST and RLD) while at Site 3, TEST had more reduction than RLD (-52.3 vs. -35.2, n=35 for TEST and RLD). Therefore, different sensitivity analyses (Appendix 3.2) were conducted to test the robustness of the equivalence result.

Sensitivity analysis 1: An unadjusted one-way ANOVA model (Appendix 3.2) was employed where the percent change from baseline in inflammatory lesion count was the outcome and the treatment was the factor. The unadjusted model shows that TEST was not equivalent (inferior) to RLD (mean ratio: 0.89, 90% CI: 0.77, 1.02). The 90% CI is outside of the FDA's equivalence boundary.

Sensitivity analysis 2: Given the unbalanced sample sizes across the sites, Site 2 and Site 3 were pooled to make a more balanced design across sites. The sponsor's model (as reported in Table 7) was retested using the pooled data with Site 1, and Sites 2 and 3 combined (Appendix 3.2). TEST was equivalent to RLD (mean ratio: 0.95, 90% CI: 0.87, 1.04).

Sensitivity analysis 3: Since Site 3 had a different direction from the other two sites, the sponsor's model (as reported in Table 7) was retested by dropping site 3 (Appendix 3.2). TEST was equivalent to RLD (mean ratio: 0.91, 90% CI: 0.83, 0.99).

In summary, equivalence of TEST and RLD was established in the primary end-point: percent change from baseline to Visit 5 (Week 12) in inflammatory lesion count among the FDA's PP population. This equivalence was reasonably robust in sensitivity analyses.

Table 7. FDA’s and Sponsor’s Primary Equivalence Analysis for Percent Change from Baseline to Visit 5 (Week 12) for the Inflammatory Lesion Count

Statistics	TEST vs. RLD	
	TEST	RLD
FDA’s Primary Analysis: Adjusted by Site, Site*Treat, Baseline Inflammatory Lesion Count where weight was assigned based on the sample size at each site *		
N of FDA’s PP Population	197	199
LSMean (StdErr)	-33.9 (1.38)	-36.0 (1.37)
Mean Ratio	0.94	
90% CI of Mean Ratio	(0.86, 1.03)	
Equivalence: 90% CI within [0.80, 1.25]	YES	
Sponsor’s Primary Analysis: Adjusted by Site, Site*Treat, Baseline Inflammatory Lesion Count where an equal weight was assigned to each site** (Sponsor’s Clinical Summary: Table 15)		
N of Sponsor’s PP Population	200	209
LSMean	-41.98(1.84)	-38.90 (1.77)
Mean Ratio	1.08	
90% CI of Mean Ratio	(0.97, 1.20)	
Equivalence: 90% CI within [0.80, 1.25]	YES	

*FDA’s primary analysis: The 90% Fieller’s CI of mean ratio was based on the mean and standard error estimation from an ANCOVA model with the lesion count as the outcome, treatment, site, and treatment by site as the factors, and baseline lesion count as the covariate, where the weight of each site was assigned based on its sample size.

** Sponsor’s adjusted 90% Fieller’s CI of mean ratio was based on an ANCOVA model with the lesion count as the outcome, treatment, site, and treatment by site as the factors, and baseline lesion count as the covariate, where an equal weight was assigned to each site.

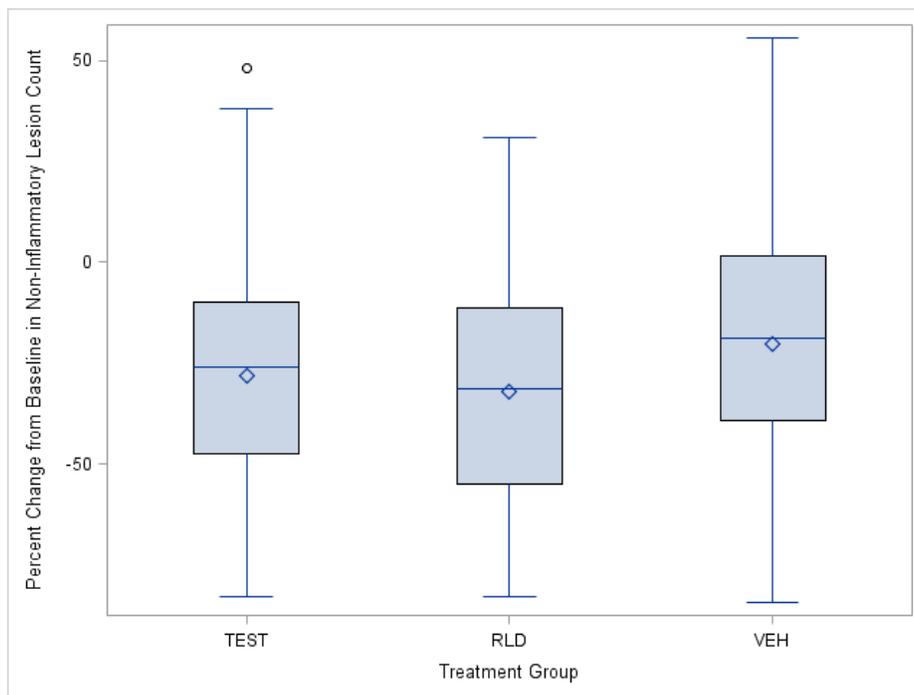
3.5.1.4 Bioequivalence in Inflammatory Lesion Count

In summary, based on the efficacy result (TEST and RLD were both superior to VEH in the FDA’s mITT population) and equivalence result (TEST and RLD were equivalent in the FDA’s PP population), TEST and RLD were bioequivalent in the primary end-point: percent change from baseline to Visit 5 (Week 12) in inflammatory lesion count.

3.5.2 CO-PRIMARY ENDPOINT – Percent Change in Non-Inflammatory Lesion Count

The distribution of the percent change from baseline to Visit 5 (Week 12) in the non-inflammatory lesion count by treatment group in the mITT population is presented in Figure 2. TEST had an average of -28.1 ± -25.9 of percent reduction in non-inflammatory lesion count, as compared to -32.2 ± -25.4in RLD, and -20.2 ± -28.2 in VEH. This data was not skewed (skewness=0.10).

Figure 2. Percent Change from Baseline in Non-Inflammatory Lesion Count to Visit 5 (Week 12) by Treatment in the FDA’s mITT Population



3.5.2.1 Superiority/Efficacy of TEST over VEH in Non-Inflammatory Lesion Count

Sponsor’s Result:

The sponsor’s primary analysis was based on an ANCOVA model where the non-inflammatory lesion count was the outcome, treatment and site as the factors, and baseline non-inflammatory lesion count as the covariate, using the Sponsor’s mITT population. Least squares means were estimated by assigning an equal weight to each site (Type 3 analysis). The sponsor established superiority/efficacy of TEST over VEH (p-value = 0.0008, see Table 8 in this report, also found in the sponsor’s clinical summary Table 15).

FDA’s Result:

FDA’s primary analysis was based on the same ANCOVA model as the sponsor’s and using the FDA’s mITT population (FDA’s mITT is the same as the Sponsor’s mITT). However, as described in Section 3.4.1, the LS means were estimated by assigning each site a weight based on its sample size. Table 8 shows that the LS mean of the percent change of the non-inflammatory lesion count was -28.2% (95% CI: -31.0, -25.5) for TEST and -19.9 (95% CI: -23.8, -15.9) for VEH in the FDA’s mITT population. TEST had higher percent reduction in non-inflammatory lesion count than VEH (difference of TEST-VEH: -8.3, 95% CI: -13.2, -3.5, p-value = 0.0008). Residuals from the ANCOVA model showed a good model of fit (Appendix 1.3).

Table 8. FDA’s and Sponsor’s Efficacy Analysis for Percent Change from Baseline to Visit 5 (Week 12) in Non-Inflammatory Lesion Count

Statistics	TEST vs. VEH		RLD vs. VEH	
	TEST (N=222)	VEH (N=107)	RLD (N=220)	VEH (N=107)
FDA’s Primary Analysis: Adjusted Model by Site and baseline lesion count, where weight was assigned based on the sample size of each site *				
Least Squares (LS) Mean (95% CI)	-28.2 (-31.0, -25.5)	-19.9 (-23.8, -15.9)	-32.2 (-34.7, -29.6)	-20.3 (-24.0, -16.6)
LSMean Difference (95% CI)	-8.3 (-13.2, -3.5)		-11.9 (-16.4, -7.4)	
2-sided p-value (TEST vs. VEH) or (RLD vs. VEH)	0.0008		<.0001	
Pass Efficacy: (YES: 2-sided p-value < 0.05)	YES		YES	
Sponsor’s Primary Analysis: Adjusted Model by Site and (Site by Treat) and baseline lesion count, where an equal weight was assigned to each Site ** (Sponsor’s Clinical Summary: Table 15)				
Least Squares (LS) Mean (90% CI)	-31.8 (-35.3, -28.4)	-23.5 (-28.0, -19.0)	-33.5 (-36.7, -30.2)	-21.6 (-25.7, -17.4)
LSmean Difference (95% CI)	-8.4 (-13.2, -3.5)		-11.9 (-16.4, -7.4)	
2-sided p-value (TEST vs. VEH) or (RLD vs. VEH)	0.0008		<.0001	
Pass Efficacy: (YES: 2-sided p-value < 0.05)	YES		YES	

* FDA’s primary analysis was based on an ANCOVA model where the non-inflammatory lesion count was the outcome, treatment and site as the factors, and baseline non-inflammatory lesion count as the covariate. Weight of each site was assigned based on the sample size at each site.

** Sponsor’s primary analysis was based on an ANCOVA model where the non-inflammatory lesion count was the outcome, treatment and site as the factors, and baseline non-inflammatory lesion count as the covariate. An equal weight was assigned to each site (Type 3 sum of square).

Supportive analyses (Appendix 4.3) employing an unadjusted one-way ANOVA (where no factor or covariate was adjusted), the same ANCOVA model as the sponsor’s (as reported in Table 8) but pooling sites 2 and 3 (Appendix 4.3), or dropping site 3 (Appendix 4.3), all revealed a similar result as the primary analysis. TEST had significantly higher percent reduction in percent change of the non-inflammatory lesion count than VEH in all three sensitivity analyses (each p-value ≤ 0.013).

In summary, TEST was superior to VEH in the co-primary end-point: percent change from baseline to Visit 5 (Week 12) in non-inflammatory lesion count, in the FDA’s mITT population. This superiority was robust in sensitivity analyses.

3.5.2.2 Superiority/Efficacy of RLD over VEH in Non-inflammatory Lesion Count

Sponsor’s Result:

The sponsor’s primary analysis was based on an ANCOVA model where the non-inflammatory lesion count was the outcome, treatment, and site as the factors, and baseline non-inflammatory

lesion count as the covariate, using the Sponsor’s mITT population. Least square mean was estimated by assigning an equal weight to each site (Type 3 analysis). The sponsor established superiority/efficacy of

RLD over VEH based on the analysis results (p-value < 0.0001, see Table 8 in this report, also reported in the sponsor's clinical summary Table 15).

FDA's Result:

FDA's primary analysis was based on the same ANCOVA model as the sponsor's and using the FDA's mITT population (FDA's mITT is the same as the Sponsor's mITT). However, as described in Section 3.4.1, the LS means were estimated by assigning each site a weight based on its sample size. Table 8 shows that the LS mean percent change was -32.2% (95% CI: -34.7, -29.6) for RLD and -20.3 (95% CI: -24.0, -16.6) for VEH in the FDA's mITT population. RLD had higher percent reduction in non-inflammatory lesion count than VEH (difference of TEST-VEH: -11.9, 95% CI: -16.4, -7.4, p-value < 0.0001). Residuals from the ANCOVA showed a good model of fit (Appendix 1.4).

Supportive analyses (Appendix 4.3) employing an unadjusted one-way ANOVA (where no factor or covariate was adjusted), the same ANCOVA model as the sponsor's (as reported in Table 8) but pooling sites 2 and 3 (Appendix 4.3), or dropping site 3 (Appendix 4.3), all revealed a similar result as the primary analysis. RLD had significantly higher percent reduction in non-inflammatory lesion count than VEH in all three sensitivity analyses (each p-value \leq 0.0001).

In summary, RLD was superior to VEH in the co-primary end-point: percent change from baseline to Visit 5 (Week 12) in non-inflammatory lesion count, among the mITT population. This superiority was robust in sensitivity analyses.

3.5.2.3 Equivalence of TEST vs. RLD in Non-inflammatory Lesion Count

Sponsor's Result:

The sponsor's primary analysis was based on Fieller's confidence interval using the sponsor's PP population. The LS mean and standard error estimate for each treatment group were estimated from an ANCOVA model, where the non-inflammatory lesion count was the outcome, treatment and site as the factors, and baseline non-inflammatory lesion count as the covariate. Least squares means were estimated by assigning an equal weight to each site (Type 3 analysis). The sponsor established equivalence of TEST and RLD based on the 90% CI of the mean ratio (Mean ratio: 0.92, 90% CI: 0.84, 1.01, Table 9 in this report, also seen the sponsor's clinical summary Table 15).

FDA's Result:

The FDA's primary analysis was based on Fieller's confidence interval using the FDA's PP population. The LS mean and standard error estimates of the percent change in non-inflammatory lesion count were derived from an ANCOVA model where the non-inflammatory lesion count was the outcome, treatment, site, and treatment by site (p-value = 0.008) as the factors, and baseline non-inflammatory lesion count as a covariate. The LS means were estimated by assigning each site a weight based on its sample size rather than an equal weight. Table 9 shows that the TEST mean percent change from baseline (-29.1 ± 1.4) was equivalent to the RLD mean (-31.7 ± 1.4), because the 90% CI of the mean ratio (0.83, 1.02) was contained within the FDA's equivalence interval [0.80, 1.25].

Given that the interaction term between treatment and site was significant (p-value = 0.008), subgroup analysis was conducted to evaluate the heterogeneous treatment effects across sites. Appendix 5.1 shows that at Site 1 and Site 2, TEST had less reduction than RLD (Site 1: -14.1 vs -18.0, n = 226 for TEST and RLD; Site 2: -52.2 vs. -56.3, n = 135 for TEST and RLD) while at Site 3, TEST had more reduction than RLD (-36.3 vs. -26.9, n = 35 for TEST and RLD). Therefore, different Sensitivity analyses (Appendix 5.2) were conducted to test the robustness of the superiority result.

Sensitivity analysis 1: An unadjusted one-way ANOVA model (Appendix 5.2) was employed where the percent change from baseline in non-inflammatory lesion count was the outcome and the treatment was the factor. The unadjusted model shows that TEST was not equivalent (inferior) to RLD (mean ratio: 0.86, 90% CI: 0.74, 1.00). The 90% CI is outside of the FDA's equivalence boundary.

Sensitivity analysis 2: Given the unbalanced sample sizes across the sites, Sites 2 and 3 were pooled to make a more balanced design across sites. The sponsor's model (as reported in Table 9) was retested using the pooled data with Site 1, and Sites 2 and 3 combined (Appendix 5.2). TEST was equivalent to RLD (mean ratio: 0.92, 90% CI: 0.83, 1.02).

Sensitivity analysis 3: Since Site 3 had a different direction from the other two sites, the sponsor's model (as reported in Table 9) was retested but dropping site 3 (n = 35, Appendix 5.2) to test the robustness of equivalence in the rest 361 subjects. TEST was equivalent to RLD (mean ratio: 0.90, 90% CI: 0.81, 0.99).

In summary, equivalence of TEST and RLD was established in the co-primary end-point: percent change from baseline in non-inflammatory lesion count at Visit 5 (Week 12), among the FDA's PP population. This equivalence was reasonably robust in sensitivity analyses.

Table 9. FDA’s and Sponsor’s Primary Equivalence Analysis for Percent Change from Baseline to Visit 5 (Week 12) in Non-Inflammatory Lesion Count

Statistics	TEST vs. RLD	
	TEST	RLD
FDA’s Primary Analysis: Adjusted by Site, Site*Treat, Baseline Non-Inflammatory Lesion Count where weight was assigned based on the sample size at each site*		
N of FDA’s PP Population	197	199
LSMean (StdErr)	-29.1 (1.4)	-31.7 (1.4)
Mean Ratio	0.92	
90% CI of Mean Ratio	(0.83, 1.02)	
Equivalence: 90% CI within [0.80, 1.25]	YES	
Sponsor’s Primary Analysis: Adjusted by Site, Baseline Non-Inflammatory Lesion Count where an equal weight was assigned to each site** (Sponsor’s Clinical Summary: Table 15)		
N of Sponsor’s PP Population	200	209
LSMean	-32.3 (1.6)	-35.2 (1.5)
Mean Ratio	0.92	
90% CI of Mean Ratio	(0.84, 1.01)	
Equivalence: 90% CI within [0.80, 1.25]	YES	

*FDA’s primary analysis: The 90% Fieller’s CI of mean ratio was based on the mean and standard error estimation from an ANCOVA model with the lesion count as the outcome, treatment, site, and treatment by site as the factors, and baseline lesion count as the covariate, where the weight of each site was assigned based on its sample size.

** Sponsor’s adjusted 90% Fieller’s CI of mean ratio was based on an ANCOVA model with the lesion count as the outcome, treatment and site as the factors, and baseline lesion count as the covariate, where an equal weight was assigned to each site.

3.5.2.4 Bioequivalence in Non-inflammatory Lesion Count

Based on the efficacy result (TEST and RLD were both superior to VEH in the FDA’s mITT population) and equivalence result (TEST and RLD were equivalent in the FDA’s PP population), TEST and RLD were bioequivalent in the co-primary end-point: percent change from baseline to Visit 5 (Week 12) in the non-inflammatory lesion count.

3.5.3 Other Endpoint – IGA

Appendix 7 reports the frequency of IGA at Visit 5 (Week 12) among the FDA’s PP population and FDA’s mITT population by treatment group.

4 SUMMMARY AND CONCLUSIONS

4.1 STATISTICAL FINDINGS AND COLLECTIVE EVIDENCE

Efficacy:

The efficacy primary analyses revealed superiority of both TEST and RLD over VEH for both co-primary endpoints of lesion count at the end of treatment Visit 5(Week 12), in the FDA's mITT population. For inflammatory lesion count, the TEST mean percent changefrom baseline to Visit 5 (Week 12) (-32.5) was significantly larger than that of VEH (-26.0, two-sided p-value = 0.007); Likewise, the RLD mean percent change of inflammatory lesion count from baseline to Visit 5 (Week 12) (-36.2) was significantly higher than that of VEH (-26.2, p-value < 0.0001). For non-inflammatory lesion count, the mean percent change from baseline to Visit 5 (Week 12) in TEST (-28.2) was also significantly more than that of VEH (-19.9, two-sided p-value = 0.0008); Similarly, the RLD mean percent change of non-inflammatory lesion count from baseline to Visit 5 (Week 12) (-32.2) was significantly higher than that of VEH (-20.3, two-sided p-value < .0001)

However, for inflammatory lesion count, the superiority of TEST over VEH, was not robust in sensitivity analysis. Heterogeneous treatment effect was observed across sites (p-value = 0.01). Site 3 had the best efficacy (TEST: -51.1 vs VEH: -21.9) with the least sample size (n=27 for TEST and VEH), followed by Site 1 (TEST: -13.7 vs VEH: -6.0, n = 182 for TEST and VEH), and Site 2 (TEST: -57.6 vs VEH: -55.8, n = 120 for TEST and VEH). Superiority remained significant when combing sites 2 and 3, however, unadjusted analysis (p-value = 0.064) and adjusted analysis for site and baseline lesion count (and site by treatment group interaction for percent change in inflammatory lesion count) but dropping the 27 subjects at site 3 (p-value = 0.12) both nullified the superiority.

Furthermore, Site 1 had comparable baseline mean inflammatory lesion counts as Site 2 (Site 1: 26.3 and for Site 2: 27.1, Appendix 6), but much less reduction in lesion count at Visit 5 (Week 12) in both groups (Site 1: -13.7 for TEST and -6 for RLD; Site 2: -57.6 for TEST and -55.8 for RLD), which may be due to inter-rater variability or other reasons.

Therefore, given the heterogeneous treatment effect across sites, we recommend OSI inspection for the three sites.

Equivalence:

Equivalence was established between TEST and RLD for both primary endpoints of the lesion counts using the FDA's PP population. The 90% CI on the mean ratio of TEST to RLD for the percent change in lesion counts from baseline to Visit 5 (Week 12) was (0.86, 1.03) for inflammatory and (0.83, 1.02) for non-inflammatory lesion counts. Both were contained within the FDA's equivalence interval [0.80, 1.25].

Equivalence was reasonably robust in sensitivity analysis. For both endpoints, out of the three sensitivity analyses, equality failed in the unadjusted analysis, but passed in the other two analyses adjusted for site and baseline lesion count when combining Site 2 and Site 3, or dropping Site 3.

4.2 STATISTICAL ISSUES

The sponsor followed the statistical analysis plan pre-specified in the protocol. The FDA statistical reviewer's comments on the sponsor's statistical analyses are summarized as follows.

- Type 3 analysis

The sponsor pre-specified an ANCOVA model to adjust for site and baseline inflammatory lesion count in the protocol, and followed the protocol in the final analysis. Least squares means were estimated by assigning an equal weight to each site (i.e., the Type 3 analysis). For this study, however, the number of sites is very small (3), and the sample size has a very high imbalance across sites (the total number of subjects combining three treatment groups is 302 for Site 1, 201 for Site 2, and 58 for Site 3). Assigning an equal weight to each site would down weigh the impact of Sites 1 and 2 and increase the impact of Site 3 greatly. Therefore, the FDA statistical reviewer changed the weight from an equal weight for each site to assigning weights based on each site's sample size.

4.3 CONCLUSIONS AND RECOMMENDATIONS

Efficacy

Efficacy was established for both the test product (TEST), Tretinoin Gel 0.05%, and the reference listed product (RLD), Atralin™ (tretinoin) Gel 0.05%, over the vehicle (VEH) for the two co-primary endpoints, i.e., percent change from baseline to Visit 5 (Week 12) in inflammatory and non-inflammatory lesion count, using the FDA's modified intent-to-treat (mITT) population. However, for inflammatory lesion count, the superiority of TEST over VEH was not consistent across the three sites.

Therefore, we recommend Office of Scientific Investigators (OSI) inspection on the sites.

Equivalence

Equivalence was established between TEST and RLD for both the primary endpoints (percent change in inflammatory and non-inflammatory lesion count from baseline to Visit 5 (Week 12) using the FDA's Per Protocol (PP) population.

Bioequivalence

Bioequivalence was statistically established between TEST and RLD based on the efficacy and equivalence results (TEST and RLD both superior to VEH in the two co-primary endpoints; TEST and RLD were equivalent in the two co-primary endpoints).

If OSI finds no problem with the sites, the statistical review and evaluation of the current data submitted for ANDA 207955 support approval for bioequivalence.

5 REFERENCES

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Franz, Volker H. "Ratios: A short guide to confidence limits and proper use." *arXiv preprint arXiv:0710.2024* (2007).

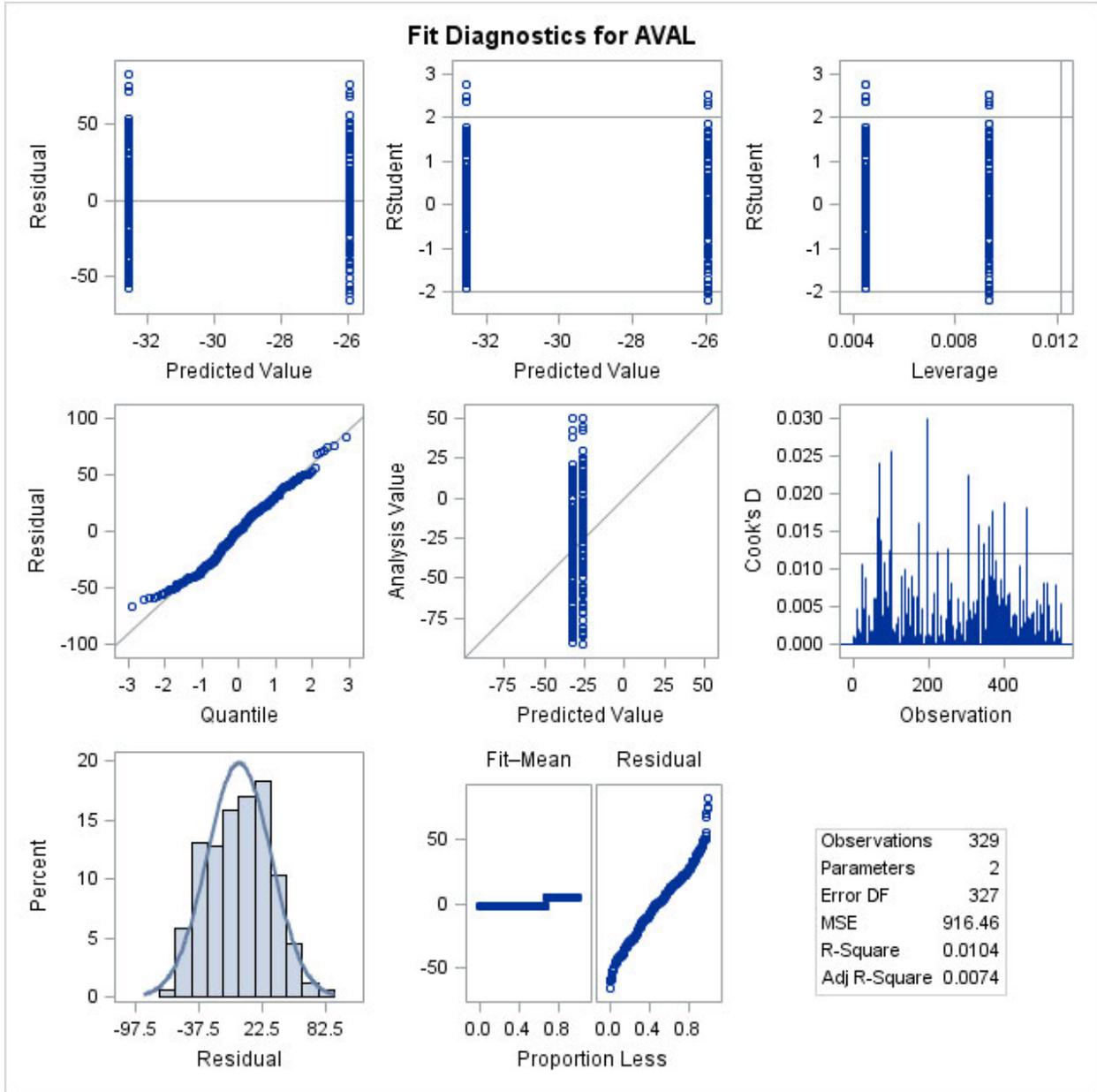
Levene, H. "Robust tests for equality of variances 1." *Contrib Prob Stat: Essays Honor Harold Hotel 2* (1960): 278.

Schirmann, Donald J. "A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability." *Journal of pharmacokinetics and biopharmaceutics* 15.6 (1987): 657-680.

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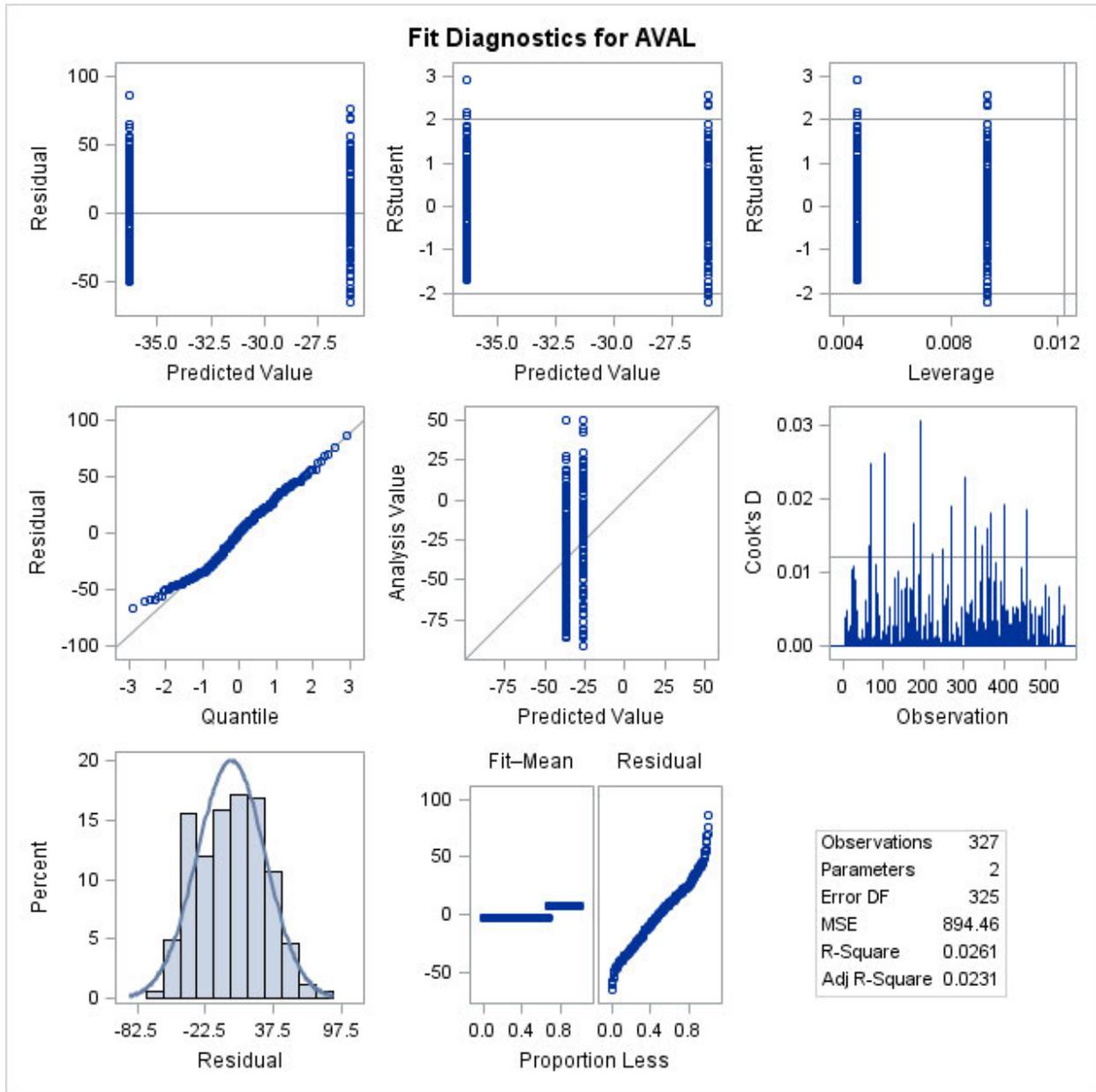
6 APPENDIX

Appendix 1.1 ANCOVA Model Diagnosis for Superiority of TEST vs VEH in Percent Change from Baseline for the Inflammatory Lesion Count

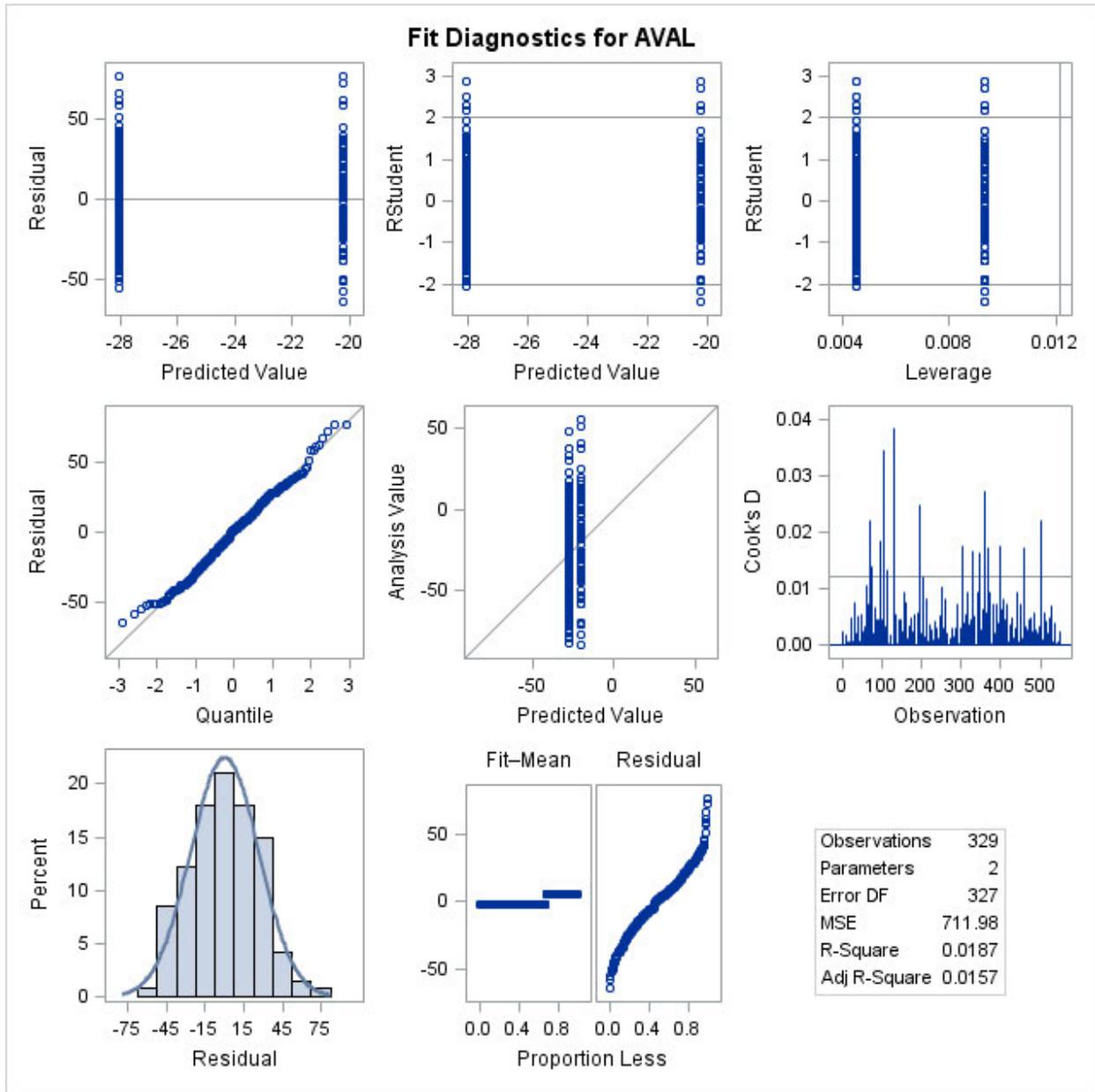


Appendix 1.2

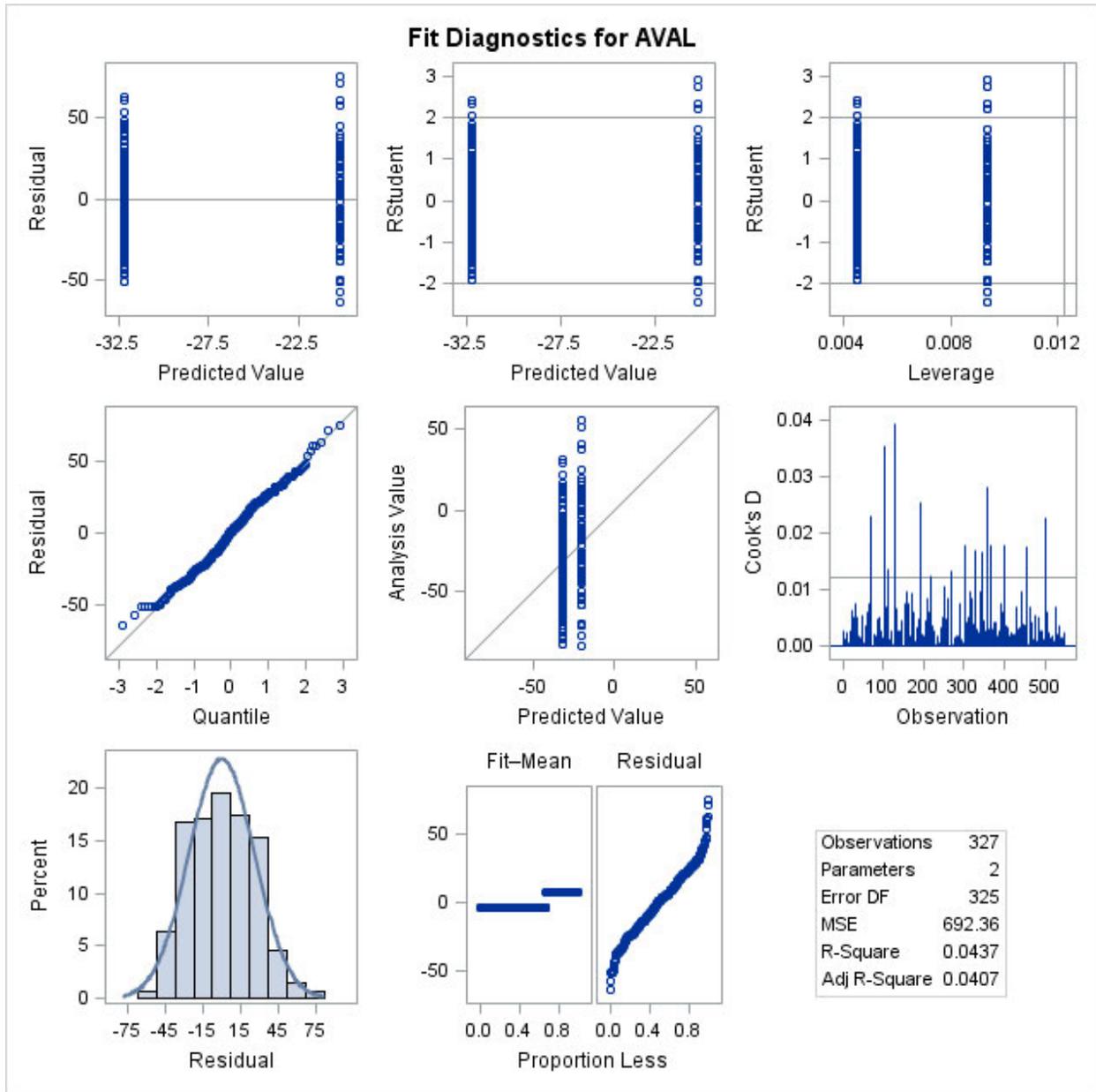
ANCOVA Model Diagnosis for Superiority of RLD vs VEH in Percent Change from Baseline for the Inflammatory Lesion Count



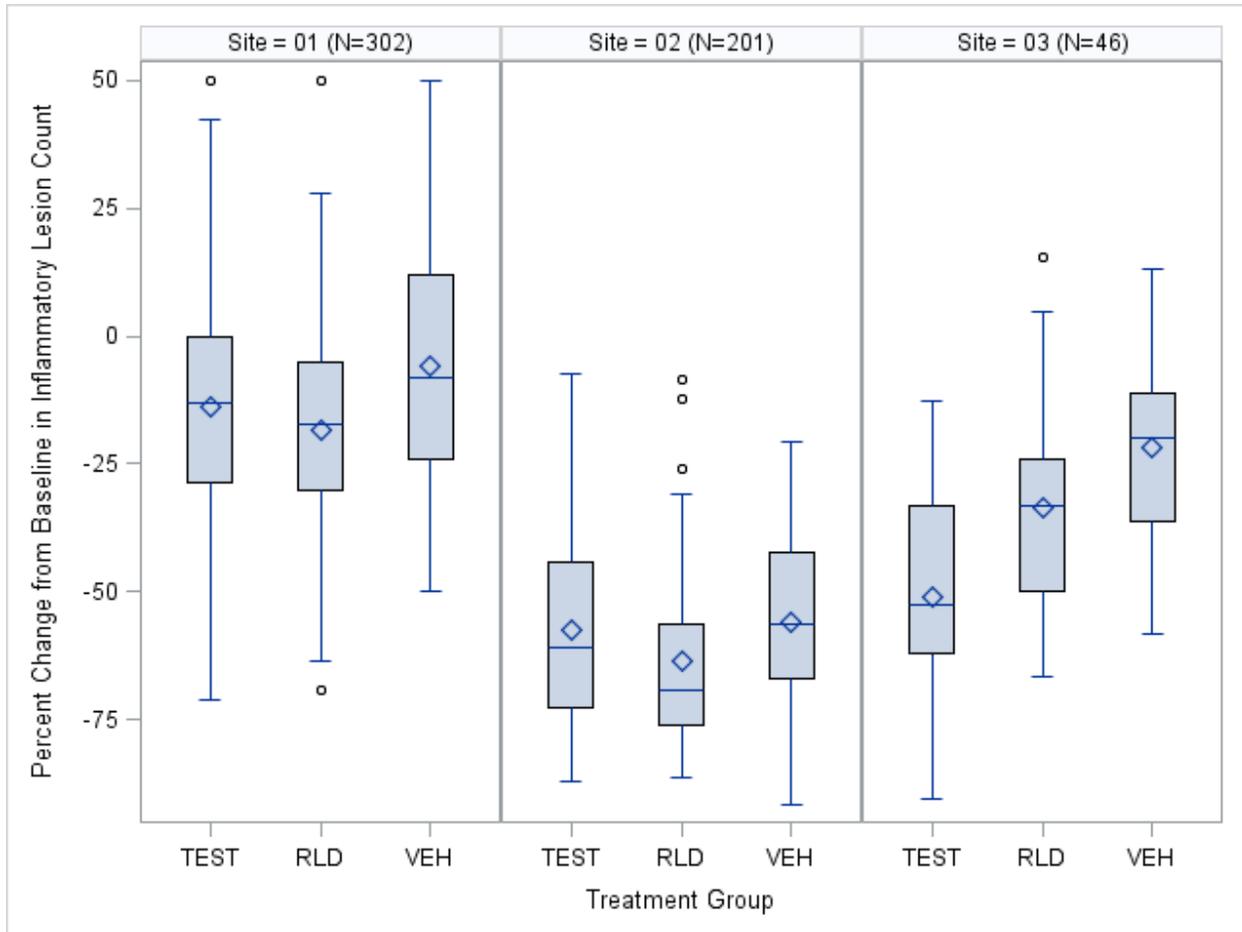
Appendix 1.3
ANCOVA Model Diagnosis for Superiority of TEST vs VEH
in Percent Change from Baseline for the Non-Inflammatory Lesion Count



Appendix 1.4
ANCOVA Model Diagnosis for Superiority of RLD vs VEH
in Percent Change from Baseline for the Non-Inflammatory Lesion Count



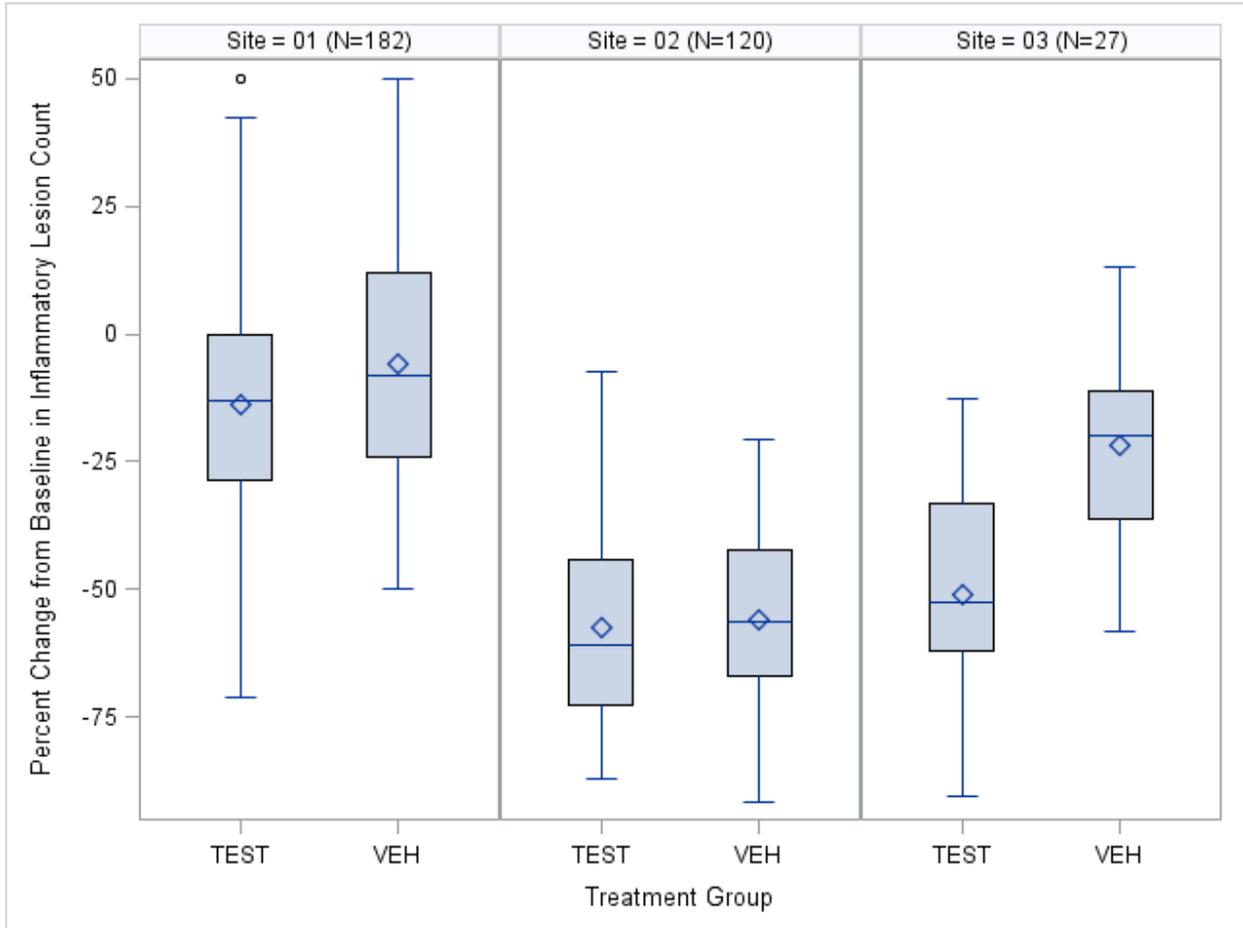
Appendix 2.1
Subgroup Efficacy Analysis: Percent Change from Baseline to Visit 5 (Week12) in the
Inflammatory Lesion Count
For TEST, RLD, and VEH by Site among the FDA's mITT



	Total N	TEST Percent Change in Inflammatory Lesion Count (n=222) Mean (SD)	RLD Percent Change in Inflammatory Lesion Count (n=220) Mean (SD)	VEH Percent Change in Inflammatory Lesion Count (n=107) Mean (SD)
Site 1	302	n=124 -13.7 (20.6)	n=120 -18.4 (20.86)	n=58 -6.0 (23.7)
Site 2	201	n=80 -57.6 (19.7)	n=81 -63.6 (17.2)	n=40 -55.8 (18.7)
Site 3	46	n=18 -51.1 (21.4)	n=19 -33.5 (22.3)	n=9 -21.9 (20.6)

Appendix 2.2

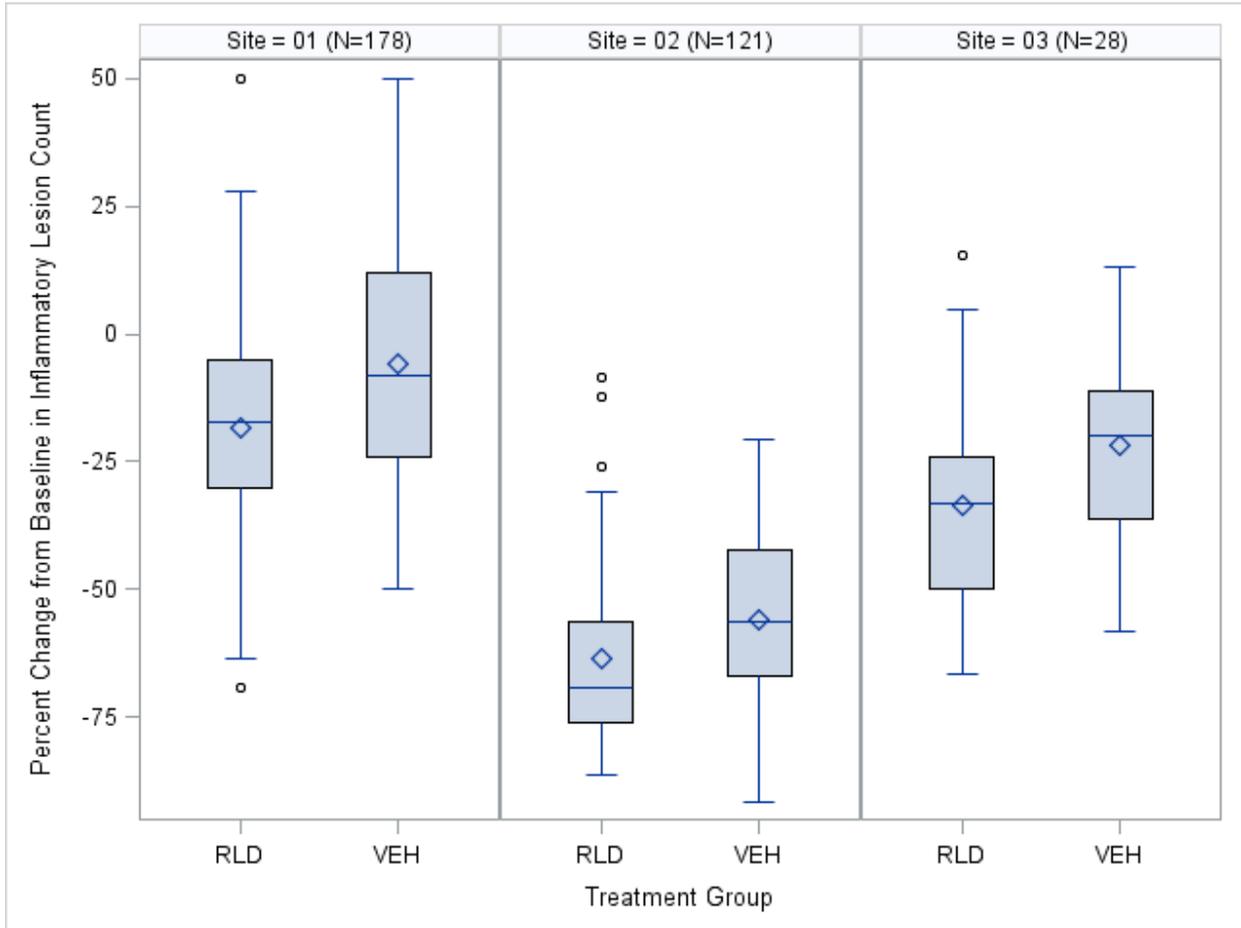
Subgroup Efficacy Analysis: Percent Change from Baseline to Visit 5 (Week 12) in the Inflammatory Lesion Count For TEST and VEH by Site among the FDA's mITT



	Total N	TEST Percent Change in Inflammatory Lesion Count (n=222) Mean (SD)	VEH Percent Change in Inflammatory Lesion Count (n=107) Mean (SD)
Site 1	182	n=124 -13.7 (20.6)	n=58 -6.0 (23.7)
Site 2	120	n=80 -57.6 (19.7)	n=40 -55.8 (18.7)
Site 3	27	n=18 -51.1 (21.4)	n=9 -21.9 (20.6)

Appendix 2.3

Subgroup Efficacy Analysis: Percent Change from Baseline to Visit 5 (Week 12) in the Inflammatory Lesion Count for RLD and VEH by Site among the FDA's mITT



	Total N	RLD Percent Change in Inflammatory Lesion Count (n=220) Mean (SD)	VEH Percent Change in Inflammatory Lesion Count (n=107) Mean (SD)
Site 1	178	n=120 -18.4 (20.8)	n=58 -6.0 (23.7)
Site 2	121	n=81 -63.4 (17.2)	n=40 -55.8 (18.7)
Site 3	28	n=19 -33.5 (22.3)	n=9 -21.9 (20.6)

Appendix 2.4

Supportive and Sensitivity Analysis of Superiority/Efficacy Tests in Percent Change from Baseline to Visit 5 (Week 12) for the Inflammatory Lesion Count in the FDA's mITT

Statistics	TEST vs. VEH		RLD vs. VEH	
	TEST (N=222)	VEH (N=107)	RLD (N=220)	VEH (N=107)
Sensitivity Analysis 1: Unadjusted Model *				
Least Squares (LS) Mean (95% CI)	-32.6 (-36.6, -28.6)	-25.9 (-31.7, -20.2)	-36.3 (-40.3, -32.4)	-25.9 (-31.6, -20.3)
LSMean Difference (95% CI)	-6.6 (-13.6, 0.40)		-10.4 (-17.3, -3.5)	
2-sided p-value ¹ (TEST vs. VEH) or (RLD vs. VEH)	0.064		0.003	
Pass Efficacy: (YES: 2-sided p-value<0.05)	NO		YES	
Sensitivity Analysis 2: Sponsor's model but Combining Site 2 and 3 **				
Least Squares (LS) Mean (95% CI)	-34.9 (-37.7, -32.1)	-28.2 (-32.2, 024.2)	-38.1 (-41.0, -35.2)	-27.9 (-32.1, -23.7)
LSmean Difference (95% CI)	-6.7 (-11.6, -1.7)		-10.2 (-15.3, -5.1)	
2-sided p=value (TEST vs. VEH) or (RLD vs. VEH)	0.008		<.0001	
Pass Efficacy: (YES: 2-sided p-value<0.05)	YES		YES	
Sensitivity Analysis 3: Sponsor's model but dropping Site 3 (N=27) and using Site 2 and 3 (N=302) Only***				
Least Squares (LS) Mean (95% CI)	-35.5 (-38.4, -32.6)	-31.4 (-35.6, -27.2)	-41.0 (-43.8, -38.2)	-31.1 (-35.1, -27.1)
LSmean Difference (95% CI)	-4.1 (-9.1, 1.0)		-10.0 (-14.8, -5.1)	
2-sided pvalue (TEST vs. VEH) or (RLD vs. VEH)	0.12		<.0001	
Pass Efficacy: (YES: 2-sided p-value<0.05)	NO		YES	

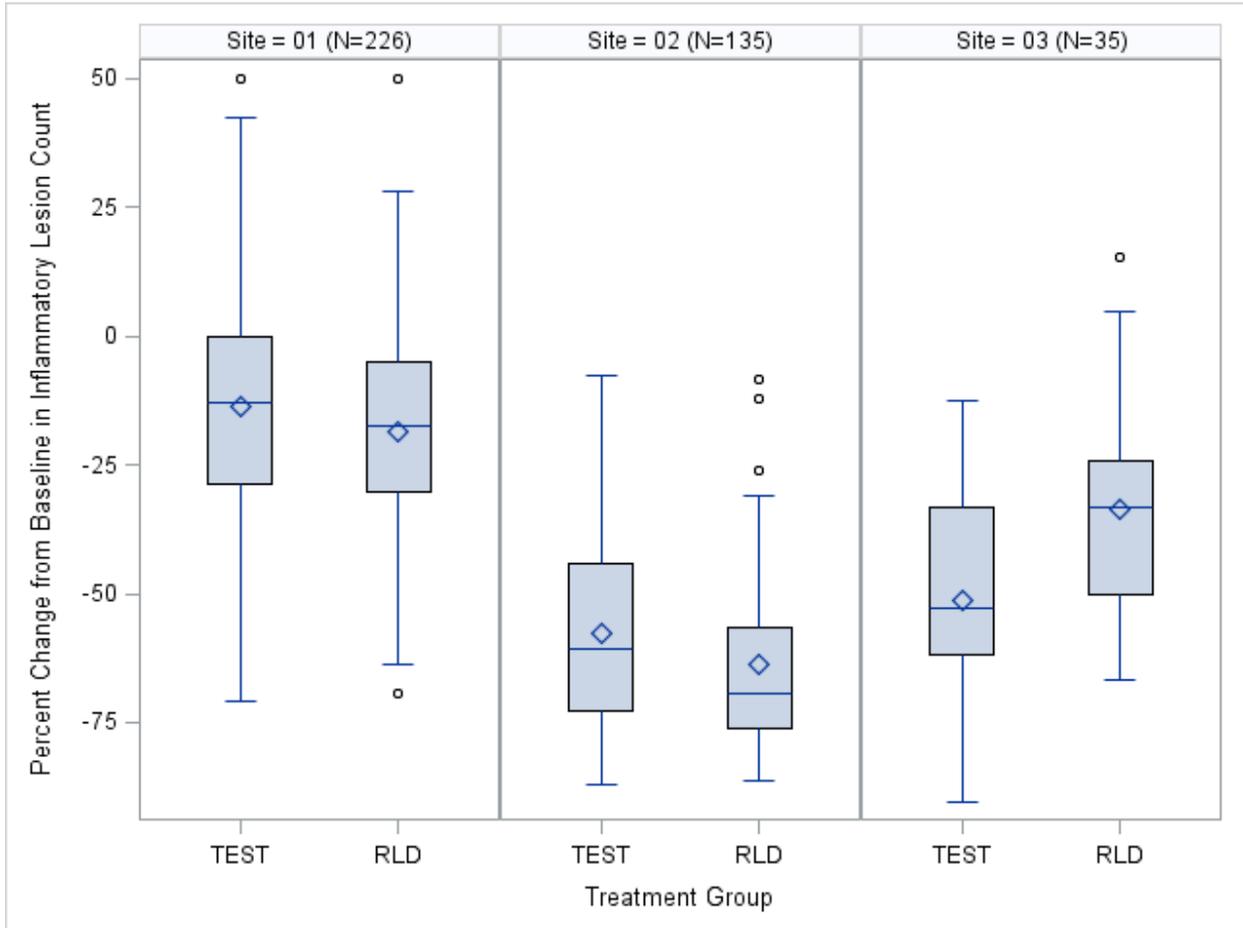
*Sensitivity analysis 1 was an unadjusted one-way ANOVA where the percent change from baseline in lesion count was the outcome and treatment group was the factor.

**Sensitivity analysis 2 was the same as the sponsor's ANCOVA model, where the percent change from baseline in lesion count was the outcome, treatment, site, and treatment by site as the factors, and baseline lesion count as the covariate. An equal weight was assigned to each site. Sites 2 and 3 were pooled to make more balanced sample sizes across sites.

***Sensitivity analysis 3 was the same as the sponsor's ANCOVA model, where the percent change from baseline lesion count was the outcome, treatment, site, and treatment by site as the factors, and baseline lesion count as the covariate. An equal weight was assigned to each site. Sites 3 (n=27) was dropped to test the sensitivity of equivalence in the remaining 327 subjects at sites 1 and 2.

Appendix 3.1

Subgroup Equivalence Analysis: Boxplot of the Percent Change from Baseline to Visit 5 (Week 12) for the Inflammatory Lesion Count in TEST and RLD by Site in the FDA's PP



	N	TEST Percent Change in Inflammatory Lesion Count (n=197) Mean (SD)	RLD Percent Change in Inflammatory Lesion Count (n=199) Mean (SD)
Site 1	226	n=117 -14.3 (20.2)	n=109 -19.0 (21.0)
Site 2	135	n=63 -62.0 (18.6)	n=72 -64.9 (15.6)
Site 3	35	n=17 -52.3 (21.5)	n=18 -35.2 (21.7)

**Appendix 3.2. Sensitivity Equivalence Analysis for Percent Change from Baseline to Visit 5
(Week 12) for the Inflammatory Lesion Count in FDA's PP**

Statistics	TEST vs. RLD	
	TEST	RLD
Sensitivity Analysis 1: Unadjusted*		
N of FDA's PP Population	197	199
LSMean (StdErr)	-32.8 (2.1)	-37.1 (2.1)
Mean Ratio	0.89	
90% CI of Mean Ratio	(0.77, 1.02)	
Equivalence: 90% CI within [0.80, 1.25]	NO	
Sensitivity Analysis 2: Sponsor's model but Combining Site 2 and 3 **		
N of FDA's PP Population	197	199
LSMean	-37.1 (1.47)	-39.0 (1.45)
Mean Ratio	0.95	
90% CI of Mean Ratio	(0.87, 1.04)	
Equivalence: 90% CI within [0.80, 1.25]	YES	
Sensitivity Analysis 3: Sponsor's model but dropping Site 3 ***		
N of FDA's PP Population	197	199
LSMean	-38.2 (1.50)	-42.1 (1.45)
Mean Ratio	0.91	
90% CI of Mean Ratio	(0.83, 0.99)	
Equivalence: 90% CI within [0.80, 1.25]	YES	

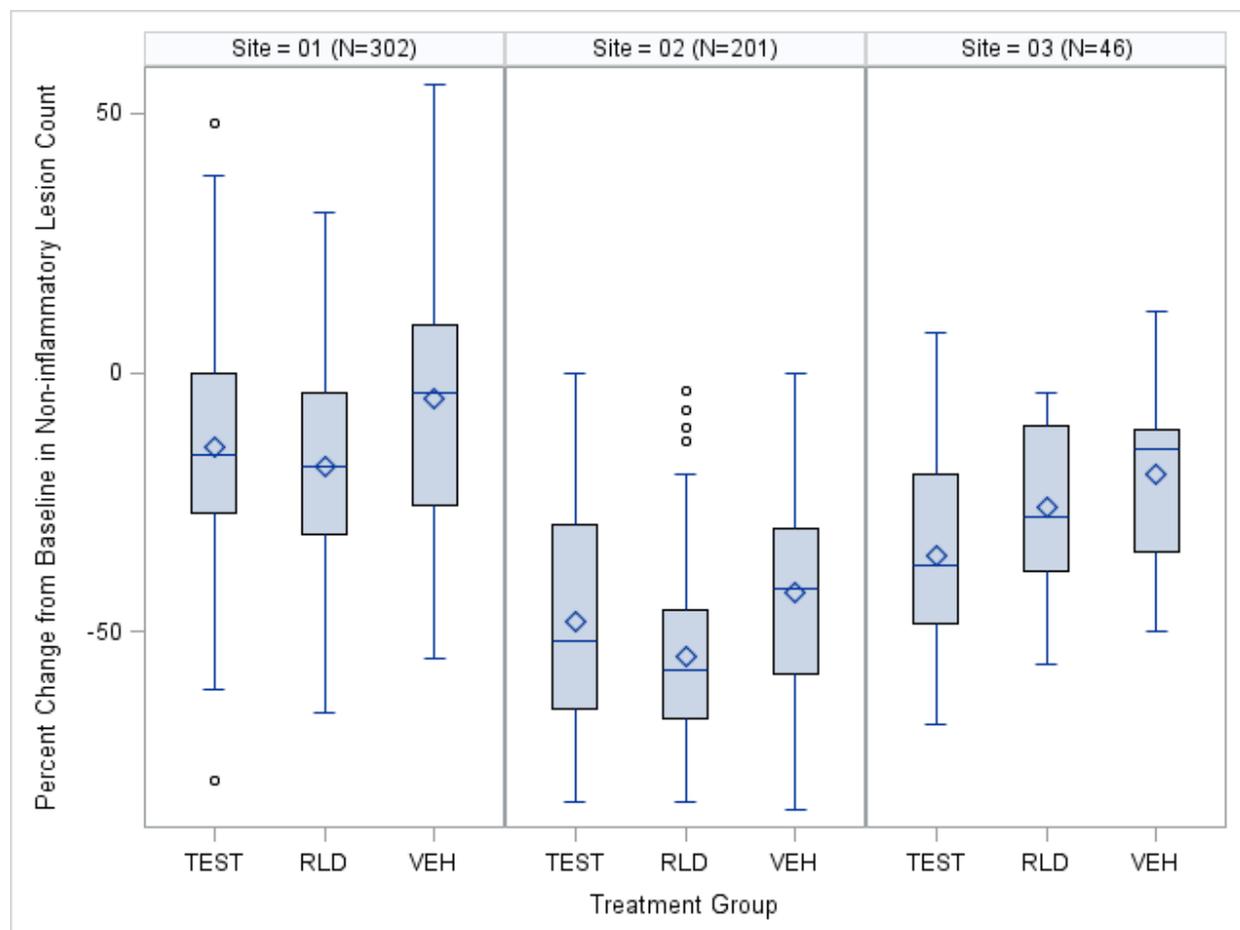
*Sensitivity analysis 1: The unadjusted 90% Fieller's CI of mean ratio was based on the mean and standard error estimation from a one-way ANOVA with the percent change from baseline in lesion count as the outcome and treatment group as the factor.

**Sensitivity analysis 2: The adjusted 90% Fieller's CI of mean ratio was based on an ANCOVA model with the percent change from baseline in lesion count as the outcome, treatment, site, and treatment by site as the factors, and baseline lesion count as the covariate, where an equal weight was assigned to each site. Sites 2 and 3 were pooled to make more balanced sample sizes across sites.

** Sensitivity analysis 3: The adjusted 90% Fieller's CI of mean ratio was based on an ANCOVA model with the percent change from baseline in lesion count as the outcome, treatment, site, and treatment by site as the factors, and baseline lesion count as the covariate, where an equal weight was assigned to each site. Sites 3 (n=27) was dropped to test the sensitivity of equivalence in the remaining 327 subjects at sites 1 and 2.

Appendix 4.1

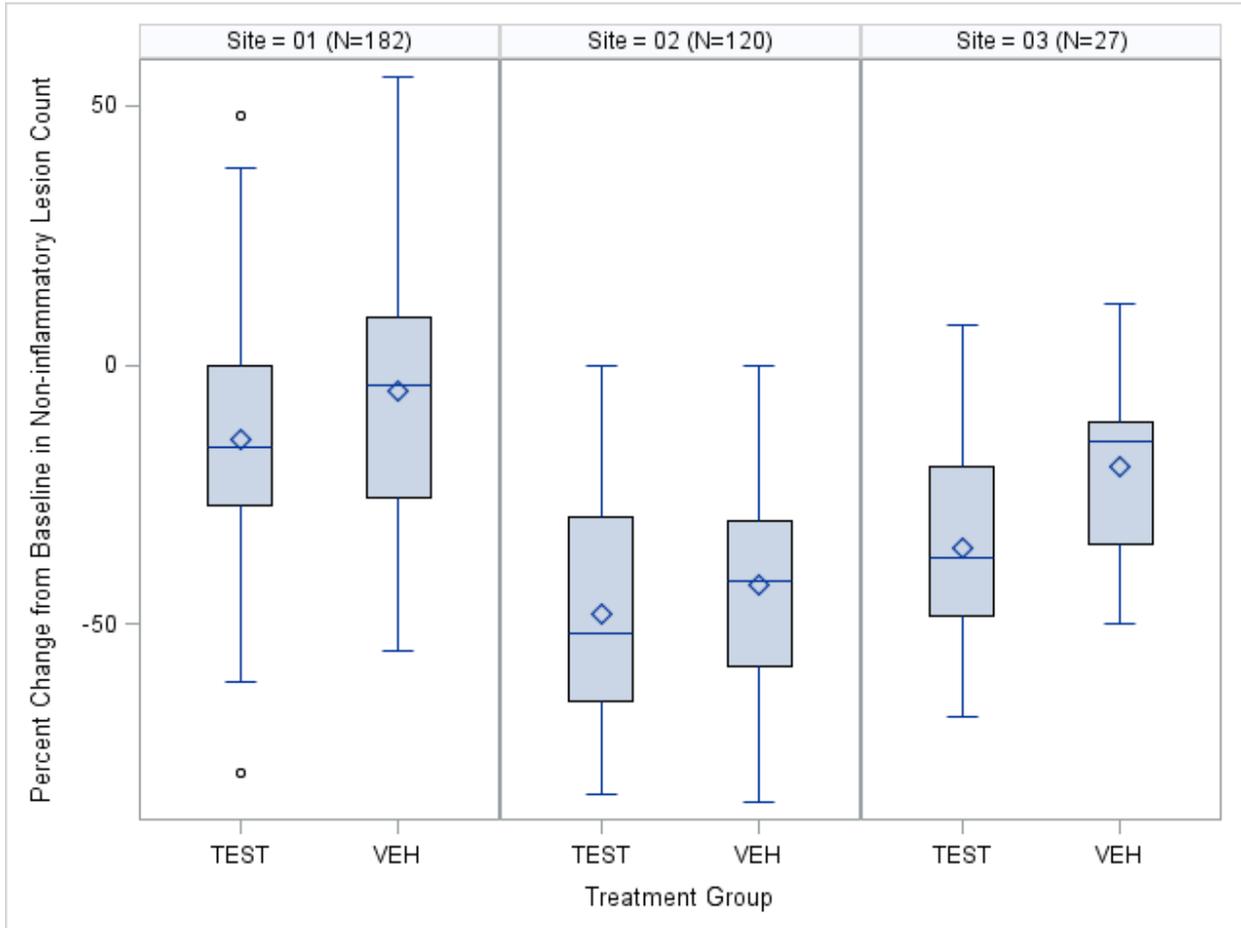
Subgroup Efficacy Analysis: Boxplot of the Percent Change from Baseline to Visit 5 (Week 12) in the Non-Inflammatory Lesion Count for TEST, RLD, and VEH by Site in the FDA's mITT



	Total N	TEST Percent Change in Non- Inflammatory Lesion Count (n=222) Mean (SD)	RLD Percent Change in Non- Inflammatory Lesion Count (n=220) Mean (SD)	VEH Percent Change in Non-Inflammatory Lesion Count (n=107) Mean (SD)
Site 1	302	n=124 -14.2 (20.8)	n=120 -17.9 (19.6)	n=58 -4.9 (23.2)
Site 2	201	n=80 -47.8 (20.3)	n=81 -54.8 (17.3)	n=40 -42.5 (20.8)
Site 3	46	n=18 -35.3 (20.4)	n=19 -25.8 (16.4)	n=9 -19.6 (20.3)

Appendix 4.2

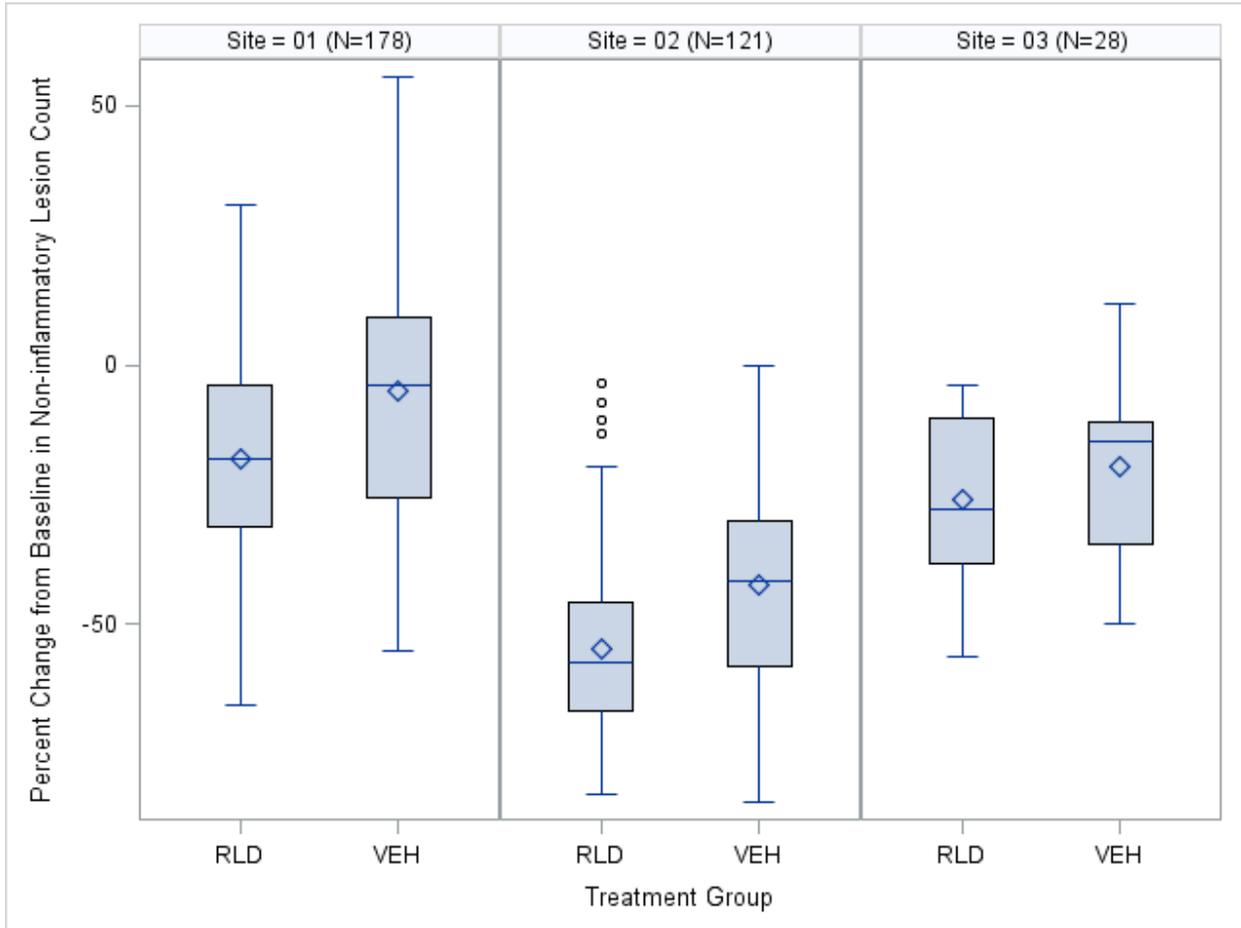
Subgroup Efficacy Analysis: Percent Change from Baseline to Visit 5 (Week 12) in the Non-Inflammatory Lesion Count for TEST and VEH by Site among the FDA's mITT



	N	TEST Percent Change in Non- Inflammatory Lesion Count (N=222) Mean (SD)	VEH Percent Change in Non- Inflammatory Lesion Count (N=107) Mean (SD)
Site 1	182	n=124 -14.2 (20.8)	n=58 -4.9 (23.2)
Site 2	120	n=80 -47.8 (20.3)	n=40 -42.5 (20.8)
Site 3	27	n=18 -35.3 (20.4)	n=9 -19.6 (20.3)

Appendix 4.3

Subgroup Efficacy Analysis: Percent Change from Baseline to Visit 5 (Week 12) in the Non-Inflammatory Lesion Count For RLD and VEH by Site in the FDA's mITT



	Total N	RLD Percent Change in Non-Inflammatory Lesion Count (n=220) Mean (SD)	VEH Percent Change in Non-Inflammatory Lesion Count (n=107) Mean (SD)
Site 1	178	n=120 -17.9 (19.6)	n=58 -4.9 (23.2)
Site 2	121	n=81 -54.8 (17.3)	n=40 -42.5 (20.8)
Site 3	28	n=19 -25.8 (16.4)	n=9 -19.6 (20.3)

Appendix 4.4
Supportive and Sensitivity Analysis of Superiority/Efficacy Tests
in the Percent Change from Baseline to Visit 5 (Week 12) in the Non-Inflammatory Lesion
Count in the FDA's mITT

Statistics	TEST vs. VEH		RLD vs. VEH	
	TEST (N=222)	VEH (N=107)	RLD (N=220)	VEH (N=107)
Sensitivity Analysis 1: Unadjusted Model *				
Least Squares (LS) Mean (95% CI)	-28.1 (-31.6, -24.5)	-20.2 (-25.3, -15.1)	-32.2 (-35.7, -28.7)	-20.2 (-25.2, -15.2)
LSMean Difference (95% CI)	-7.8 (-14.0, -1.7)		-11.9 (-18.0, -5.8)	
2-sided p-value (TEST vs. VEH) or (RLD vs. VEH)	0.013		0.0001	
Pass Efficacy: (YES: 2-sided p-value<0.05)	YES		YES	
Sensitivity Analysis 2: Sponsor's model but Combining Site 2 and 3 **				
Least Squares (LS) Mean (95% CI)	-30.0 (-32.7, -27.1)	-21.6 (-25.6, -17.5)	-33.5 (-36.3, -30.8)	-21.8 (-25.7, -17.8)
LSmean Difference (95% CI)	-8.3 (-13.3, -3.4)		-11.8 (-16.6, -7.0)	
2-sided p-value (TEST vs. VEH) or (RLD vs. VEH)	0.001		<.0001	
Pass Efficacy: (YES: 2-sided p-value<0.05)	YES		YES	
Sensitivity Analysis 3: Sponsor's model but dropping Site 3 ***				
Least Squares (LS) Mean (95% CI)	-31.1 (-34.1, -28.2)	-23.4 (-27.6, -19.2)	-36.2 (-39.0, -33.5)	-23.9 (-27.8, -19.9)
LSmean Difference (95% CI)	-7.7 (-12.8, -2.7)		-12.3 (-17.1, -7.6)	
2-sided p-value (TEST vs. VEH) or (RLD vs. VEH)	0.003		<.0001	
Pass Efficacy: (YES: 2-sided p-value<0.05)	YES		YES	

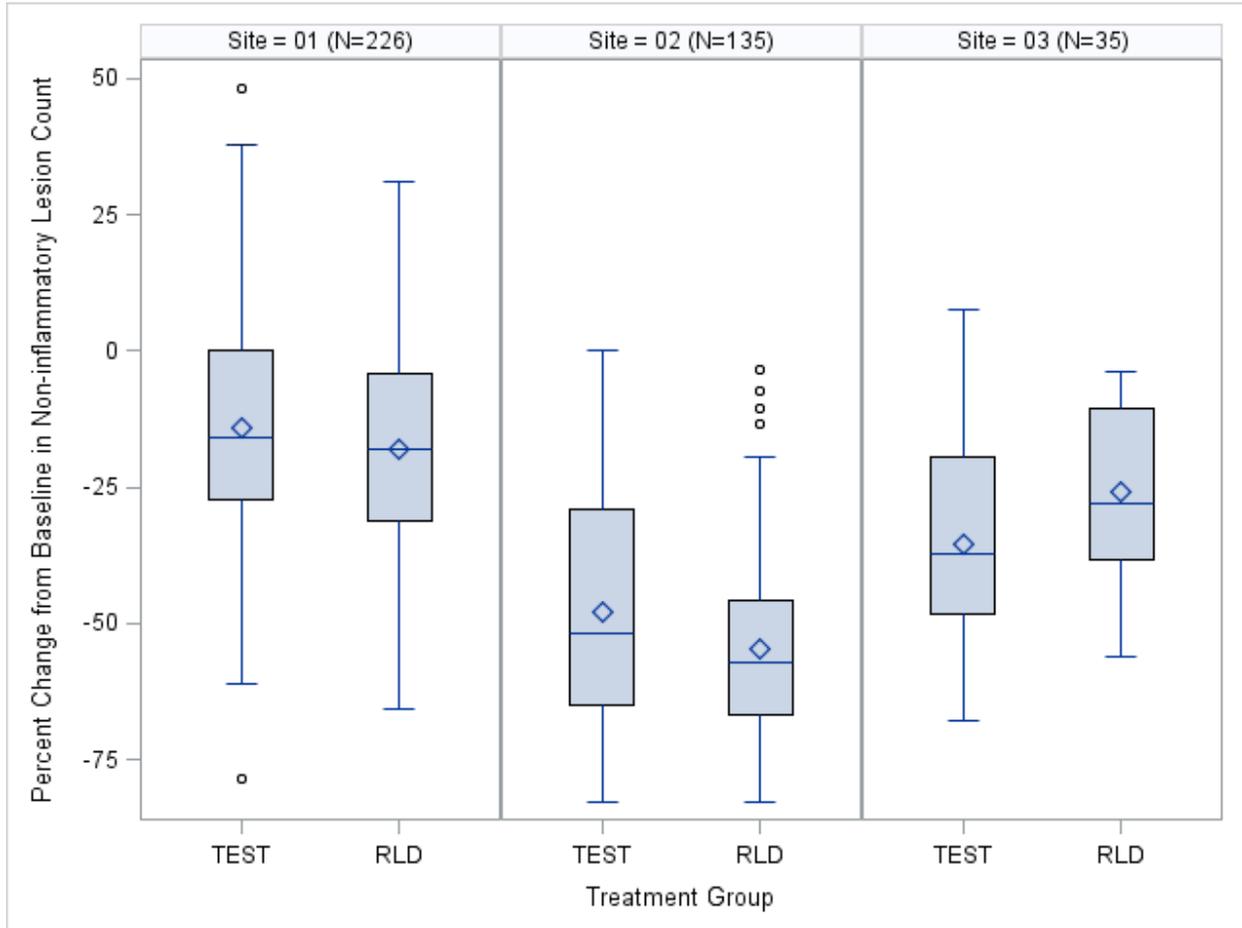
*Sensitivity analysis 1 was an unadjusted one-way ANOVA where the percent change from baseline in lesion count was the outcome and treatment group was the factor.

**Sensitivity analysis 2 was the same as the sponsor's ANCOVA model, where the percent change from baseline in lesion count was the outcome, treatment and site as the factors, and baseline lesion count as the covariate. An equal weight was assigned to each site. Sites 2 and 3 were pooled to make more balanced sample sizes across sites.

*** Sensitivity analysis 3 was the same as the sponsor's ANCOVA model, where the percent change from baseline lesion count was the outcome, treatment and site as the factors, and baseline lesion count as the covariate. An equal weight was assigned to each site. Sites 3 (n=27) was dropped to test the sensitivity of equivalence in the remaining 327 subjects at sites 1 and 2.

Appendix 5.1

Subgroup Equivalence Analysis: Percent Change from Baseline to Visit 5 (Week 12) in the Non-Inflammatory Lesion Count in TEST and RLD by Site in the FDA's PP Population



	Total N	TEST Percent Change in Non- Inflammatory Lesion Count (n=197) Mean (SD)	RLD Percent Change in Non- Inflammatory Lesion Count (n=199) Mean (SD)
Site 1	226	n=117 -14.1 (20.9)	n=109 -18.0 (20.0)
Site 2	135	n=63 -52.2 (19.2)	n=72 -56.3 (15.7)
Site 3	35	n=17 -36.3 (20.6)	n=18 -26.9 (16.1)

Appendix 5.2

Sensitivity Equivalence Analysis for Percent Change from Baseline to Visit 5 (Week 12) in Non-Inflammatory Lesion Count in the FDA's PP Population

Statistics	TEST vs. RLD	
	TEST	RLD
Sensitivity Analysis 1: Unadjusted*		
N of FDA's PP Population	197	199
LSMean (StdErr)	-28.2 (1.9)	-32.7 (1.9)
Mean Ratio	0.86	
90% CI of Mean Ratio	(0.74, 1.00)	
Equivalence: 90% CI within [0.80, 1.25]	NO	
Sensitivity Analysis 2: Sponsor's model but Combining Site 2 and 3 **		
N of FDA's PP Population	197	199
LSMean	-31.4 (1.4)	-34.2 (1.4)
Mean Ratio	0.92	
90% CI of Mean Ratio	(0.83, 1.02)	
Equivalence: 90% CI within [0.80, 1.25]	YES	
Sensitivity Analysis 3: Sponsor's model but dropping Site 3 ***		
N of FDA's PP Population	197	199
LSMean	-33.3 (1.5)	-37.0 (1.4)
Mean Ratio	0.90	
90% CI of Mean Ratio	(0.81, 0.99)	
Equivalence: 90% CI within [0.80, 1.25]	YES	

*Sensitivity analysis 1: The unadjusted 90% Fieller's CI of mean ratio was based on the mean and standard error estimation from a one-way ANOVA with the percent change from baseline in lesion count as the outcome and treatment group as the factor.

**Sensitivity analysis 2: The adjusted 90% Fieller's CI of mean ratio was based on an ANCOVA model with the percent change from baseline in lesion count as the outcome, treatment and site as the factors, and baseline lesion count as the covariate, where an equal weight was assigned to each site. Sites 2 and 3 were pooled to make more balanced sample sizes across sites.

***Sensitivity analysis 3: The adjusted 90% Fieller's CI of mean ratio was based on an ANCOVA model with the percent change from baseline in lesion count as the outcome, treatment and site as the factors, and baseline lesion count as the covariate, where an equal weight was assigned to each site. Sites 3 (n=35) was dropped to test the sensitivity of equivalence in the remaining 361 subjects at sites 1 and 2.

Appendix 6
Baseline Lesion Count and Demographics by Site and by Site and Treatment Group in the mITT Population

Characteristics	Total				by Treatment Group									
	Site 1	Site 2	Site 3	p-value*	Site 1			Site 2			Site 3			p-value**
					TEST	RLD	VEH	TEST	RLD	VEH	TEST	RLD	VEH	
N	302	201	46		124	120	58	80	81	40	18	19	9	
Age (years)														
Mean (SD)	19.4 (7.2)	21.1 (7.5)	19.6 (6.6)	.029	19.4 (6.8)	19.3 (7.7)	19.4 (7.2)	21.3 (7.6)	21.6 (7.6)	19.7 (7.1)	20.1 (6.1)	18.8 (5.7)	20.2 (9.4)	0.77
Gender n (%)														
Male	42.7	38.3	52.2	.21	37.5	47.6	43.1	39.5	38.8	35.0	63.2	44.4	44.4	.87
Race n (%) ~														
Caucasian	72.5	65.7	93.5	.003	75.8	70.2	70.7	66.7	67.5	60.0	94.7	88.9	100	.49
African American	23.8	31.8	6.5		20.8	27.4	22.4	1.2	31.3	32.5	5.3	11.1	0	
Other	3.6	2.5	0		3.3	2.4	6.9	32.1	1.3	7.5	0	0	0	
Ethnicity:														
Hispanic or Latino	18.5	30.9	17.4	.004	18.3	20.2	15.5	43.2	25.0	17.5	15.7	27.8	0	0.013
Not Hispanic or Latino	81.5	69.2	82.6		81.6	79.8	84.5	56.8	75.0	82.5	84.2	72.2	100	
Inflammatory Lesion Count at Baseline														
Mean (SD)	26.3 (4.8)	27.1 (5.2)	24.5 (5.2)	.004	26.3 (4.5)	25.9 (4.8)	27.0 (5.5)	26.6 (5.5)	27.4 (5.2)	27.8 (4.5)	24.3 (4.9)	24.2 (4.8)	25.7 (6.9)	.23
Non-Inflammatory Lesion Count at Baseline														
Mean (SD)	34.4 (7.6)	33.6 (6.6)	35.0 (7.5)	.34	34.7 (7.3)	33.6 (7.7)	35.3 (8.2)	34.0 (7.5)	33.6 (6.3)	32.8 (5.0)	33.9 (6.7)	35.9 (8.1)	35.0 (8.4)	.66

* p-values were for the site effect. For continuous demographics/lesion count, a One-way ANOVA model was used where the respective continuous demographics/lesion counts were the outcome and site was the factor. P-values for categorical demographics were calculated from the Pearson Chi-square test.

**p-values were for treatment effect adjusted by site. A two-way ANOVA model was used for continuous variables, where the respective continuous demographics were the outcome, and treatment and site were the factors. P-values for categorical demographics were derived from the Cochran Mantel Haenszel General Association Test stratified by site.

Appendix 7

IGA Score at Visit 5 (Week 12) by Treatment Group in the FDA's PP Population and FDA's mITT Population

	TEST	RLD	VEH
FDA's PP Population			
N	197	199	96
IGA Score (n (%))			
1	48 (24.4)	57 (28.6)	20 (20.8)
2	65 (33.0)	78 (39.2)	30 (31.3)
3	55 (27.9)	44 (22.1)	26 (27.1)
4	29 (14.7)	20 (10.1)	20 (20.8)
FDA's ITT Population			
N	222	220	107
IGA Score (n (%))			
1	51 (23.0)	62 (28.2)	23 (21.5)
2	80 (36.0)	85 (38.6)	32 (29.9)
3	57 (25.7)	49 (22.3)	30 (28.0)
4	34 (15.3)	24 (10.9)	22 (20.6)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 207955

OTHER REVIEWS

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: May 27, 2015

TO: John Peters, M.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

FROM: Srinivas R. Chennamaneni, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Office of Translational Sciences

THROUGH: Charles R. Bonapace, Pharm.D.
Director (Acting)
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Office of Translational Sciences

SUBJECT: Review of EIR covering ANDA 207955, Tretinoin Topical Gel, 0.05%, from Spear Pharmaceuticals

At the request of the Office of Generic Drugs (OGD), the Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the following clinical endpoint bioequivalence study.

TRET-05: "Bioequivalence Study of Spear Tretinoin Gel 0.05%, Atralin® (Tretinoin) Gel 0.05%, and Placebo"

Clinical Site 1: MOORE Clinical Research, Inc.
1170 Nikki View Drive
Brandon, FL 33511

of enrolled Subjects: 314

Clinical Site 2: MOORE Clinical Research, Inc.
4257 West Kennedy Boulevard
Tampa, FL 33609

of enrolled Subjects: 212

Clinical Site 3: MOORE Clinical Research, Inc.
8931 Conference Drive, Unit 5
Fort Myers, FL 33919

of enrolled Subjects: 48

Principal

Investigator (for all three sites): Susan Barker, M.D.

This memo provides a review of the data audit conducted for the three clinical sites listed above. The study records from all three sites were stored at Extra Space Storage, 707 Providence Road, Brandon, FL. MOORE Clinical Research, Inc., Fort Myers, FL closed prior to the inspection.

The data audit was performed by Gene R. Gunn (ORA, Florida District Office) at MOORE Clinical Research, Inc., Brandon, FL, from February 24 to March 05, 2015. The audit covered a thorough review of the source records, evaluation of primary and secondary efficacy endpoints, adverse events reporting, concomitant medications, and adherence to protocol and protocol deviations. The inspection also covered 100% review of Informed Consent Forms, regulatory documentation, monitoring practices, study medication accountability, delegation of authority, employee training, examination of facilities and equipment, and interviews and discussions with the firm's management and staff.

At the conclusion of the inspection, a single item Form FDA-483 was issued to the MOORE Clinical Research, Inc. Brandon, FL (Attachment 1). The observation, the firm's response to Form FDA 483 dated 03/12/2015, and our evaluation follow.

OBSERVATION 1:

An investigation was not conducted in accordance with the investigational plan. Specifically,

Subject [REDACTED] (b) (6)

Inclusion criteria #2 of the protocol states that a potential subject must be at least 12 years old in order to participate in the study (Attachment 1).

Firm's response:

The firm acknowledged the observation and stated that subject [REDACTED] (b) (6)

(b) (6)

(b) (4) The site noticed this protocol deviation on Mar 31, 2014 during an internal quality control process. Dr. Barker contacted the sponsor and reported this protocol deviation to the IRB. The site re-consented the subject on (b) (4) and received the acknowledgement from the IRB. Dr. Baker stated the site updated their SOP for subject identification to avoid this error in the future (Attachment 2).

Reviewer's Evaluation:

The investigator reported the protocol deviation to the sponsor and re-consented the subject into the study (b) (6). (b) (6) This observation does not impact the data integrity.

OGD's concerns:

Prior to the inspection, OGD requested OSIS to investigate potential site interactions, since the efficacy (e.g., percent change from baseline at visit 5) was grossly different between the sites and treatments. In addition, OSIS was requested to verify whether subjects received their protocol-specified treatments at site #2 because comparable efficacy was observed for the test (-57.6%) and vehicle (-55.8%) groups. Specific issues to be addressed during the inspection consisted of the following:

- Site #3 was the only site that the test article was more efficacious than reference.
- The test article was the most efficacious compared to vehicle at site #3
- The efficacy of test, reference, and vehicle were greatest at site #2, even though baseline mean inflammatory lesion counts was similar to site #1.
- Site #2 had similar efficacy results between the test and vehicle groups.

Key study aspects addressed during this inspection:

- Drug accountability: There were no issues in the drug accountability records and reconciliation. The study records were properly maintained to document which kits were dispensed to which subjects. Three sets of reserve samples [placebo (Lot#3G12A), test (Lot#3G14A) and reference (FEBZ)] were collected from each site during the

inspection and shipped to the Division of Pharmaceutical Analysis (DPA), St. Louis, MO for evaluation.

- Blinding: All blinding codes remained intact. The inspection verified that no dosing records were unblinded at any site.
- Randomization schedule: The ORA investigator noticed that the Master Randomization Schedule envelopes could be opened and resealed without any noticeable damage to the seal or the envelope. However, he observed that the document inside the envelope was in a tear away-envelope and any attempt to reveal the randomization code would have been readily apparent. No anomalies were observed.
- Investigator's Global Assessment (IGA): IGA scale used by the acne rater was validated using the site's SOP (Attachment 3).
- Evaluator: All acne lesion scorers were trained, tested, and certified as acne raters (Attachment 3). However, training was limited, which may have contributed to inter-rater variability (Attachment 4). There was a one rater and a backup at each site. The same blinded raters at each site did all of the acne ratings in the records that were audited except one occasion where the back-up rater was utilized. All raters were validated and certified by the PI.
- Data verification: There were no discrepancies between the primary endpoint scores in the source documents at the site and the data that were submitted to the agency.
- Please note that in the reference listing 16.2.6.1 (individual subject raw data), the headers for nodulocystic lesions and non-inflammatory lesions are switched. However, the efficacy responses for % Change Non-Inflammatory Lesions were calculated appropriately and correct results are presented in the summary tables 14.2.1.1 to 14.2.5.2 in the study report.

Conclusions:

- Although there was a protocol deviation at site #1 (MOORE Clinical Research, Inc. Brandon, FL), it is unlikely that this deviation had a negative impact on the data integrity.
- The inspection did not identify any anomalies or assignable causes that may have contributed to the observed differences in efficacy OGD noted between the study sites and treatments.

Recommendations:

After evaluating the EIR and supporting documents, the data from the audited study were found to be reliable. Therefore, this reviewer recommends that the data be accepted for agency review.

Srinivas Rao Chennamaneni, Ph.D.
DNDBE Branch, OSIS, OTS

Final Classification:

VAI: MOORE Clinical Research, Inc., Brandon, FL
FEI: 3007748961

NAI: MOORE Clinical Research, Inc., Tampa, FL
FEI: 3010556211

NAI: MOORE Clinical Research, Inc., Fort Myers, FL
FEI: NA

Attachments:

Attachment 1: Form FDA 483

Attachment 2: Response to Form FDA 483 from MOORE Clinical Research, Inc.

Attachment 3: Validation of Acne raters [REDACTED] (b) (4) and Acne validation results across all raters

Attachment 4: Acne Rater Training, Certificate of Completion

CC:

OTS/OSIS/Taylor/Dejernett/Nkah/Fenty-Stewart/Johnson/Kadavil
OTS/OSIS/Chennamaneni/Cho/Choi/Dasgupta/Skelly/Haidar
/Bonapace
CDER/OGD/DCR/Furlong/Teena
ORA/FLA BIMO/Gunn/Barido

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/MOORE Clinical Research, Inc., Brandon, FL
MOORE Clinical Research, Inc., Tampa, FL
MOORE Clinical Research, Inc., Fort Myers, FL

Draft: SRC 05/03/2015

Edit: JC 05/12/2015; 05/21/2015

OSI: BE6769

FACTS: 11485925

Srinivas Rao
Chennamaneni -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=2001584247,
cn=Srinivas Rao Chennamaneni -S
Date: 2015.05.27 10:36:34 -04'00'

Seongeun
N. Cho -S

Digitally signed by Seongeun N. Cho -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=200033697
8, cn=Seongeun N. Cho -S
Date: 2015.05.27 15:12:30 -04'00'

Charles R. Bonapace -S

Digitally signed by Charles R. Bonapace -S
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0.9.2342.19200300.100.1.1=1300156609, cn=Charles R. Bonapace -
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Date: 2015.05.27 15:36:40 -04'00'

Attachment 1

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 555 Winderley Place, Suite 200 Maitland, FL 32751 (407) 475-4700 Fax: (407) 475-4768 Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION 02/24/2015 - 03/05/2015
	FEI NUMBER 3007748961

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
TO: Susan M. Barker, MD, Principal Investigator

FIRM NAME Moore Clinical Research Inc.	STREET ADDRESS 1171 Nikki View Drive
CITY, STATE, ZIP CODE, COUNTRY Brandon, FL 33511	TYPE ESTABLISHMENT INSPECTED Biopharmaceutics Clinical Facility

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

OBSERVATION 1

An investigation was not conducted in accordance with the investigational plan.

Specifically,

Subject [REDACTED] (b) (4)

AMENDMENT 1

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Gene R. Gunn, Investigator <i>ARG</i>	DATE ISSUED 04/08/2015

Following this page, 24 Pages Withheld in Full as (b)(4) and (b)(6)

OSI Consult Request for Biopharmaceutical Inspections

Date	2/19/15
Subject	For Cause inspection request
To	William H. Taylor, Ph.D. Director (Acting), Office of Study Integrity and Surveillance (OSIS), Office of Translational Sciences (OTS)
Consulting Office/Division	OGD/Division of Clinical Review/ANDA Team
Project Manager	Teena Thomas
Application Type	ANDA
ANDA number	207955
Drug Product	Tretinoin Topical Gel, 0.05%
Applicant Name	Spear Pharmaceuticals
Applicant Address	37 Jefferson Landing Circle, Port Jefferson NY 11777
Original Submission Date	10/1/2014
GDUFA Due Date	12/31/2015
Target Action Date	07/27/2015
OSI Review Requested by	Lesley-Anne Furlong, MD, Acting Director, Division Of Clinical Review

Inspection Request Detail	
Study Number	TRET-05
Study Title	Bioequivalence Study of Spear Tretinoin Gel 0.05%, Atralin® (Tretinoin) Gel 0.05%, and Placebo
Study Type	In Vivo Clinical Endpoint BE study
Inspection Request Site	Clinical Sites

Specific Items To Be Addressed During the Inspection

- This is first GDUFA year 3 ANDA.
- For Cause inspection is requested based on preliminary statistical analysis with a significant site interaction.
- Concern from clinical perspective: site # 2 had similar efficacy outcome between test and placebo group (percent change in inflammatory lesion counts: -55.6 in test vs. -55.8 in placebo group). We need to verify whether these subjects received appropriate study drugs as specified in the submission.
- Concern from statistical perspective: site #3 and site #1 had different preliminary statistical findings so we need to verify the accuracy of data at sites 1 and 3.
- See below for details on site 1 and 3.

Concern:

Based on preliminary statistical analysis, we note questionable site interaction. Particularly, the study outcome was grossly different from site to site.

Concerns for Site 3:

Superiority of TEST over VEH (Figure 1): For percent change from baseline in inflammatory lesion count, Site 3 had the best efficacy (TEST: -51.1 vs VEH: -21.9) with the smallest sample size (n = 27 for TEST and VEH), followed by Site 1 (TEST: -13.7 vs VEH: -6.0, n = 182 for TEST and VEH), and Site 2 (TEST: -57.6 vs VEH: -55.8, n = 120 for TEST and VEH). If we drop Site 3 (n=27) from the analysis, superiority of TEST over VEH is no longer significant (p-value=0.12). Therefore, the superiority of TEST over VEH is largely driven by the 27 subjects at Site 3 (<10% of the total subjects in TEST and VEH).

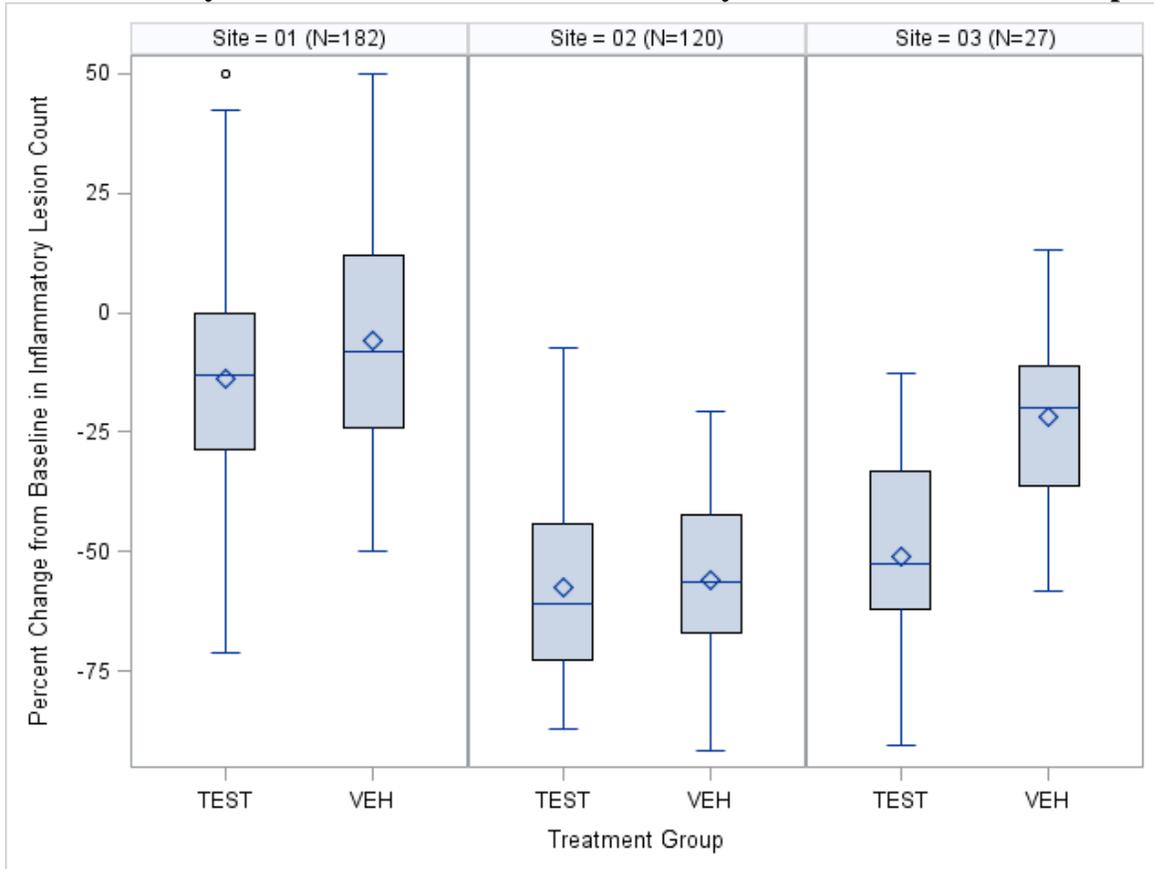
Equivalence of TEST and RLD (Figure 2): for percent change from baseline in inflammatory lesion count, Site 3 has contradictory direction in terms of equivalence between TEST and RLD. At Sites 1 and 2, TEST had less reduction than RLD (Site 1: -14.3 vs -19.0, n=226 for TEST and RLD ; Site 2: -62.0 vs. -64.9, n=135 for TEST and RLD) while at Site 3, TEST had more reduction than RLD (-52.3 vs. -35.2, n=35 for TEST and RLD).

Therefore, considering the heterogeneous treatment effect at Site 3 from that at Site 1 and Site 2 and the small sample size at Site 3, we would like to verify the accuracy of the data at Site 3.

Concern for Site 1:

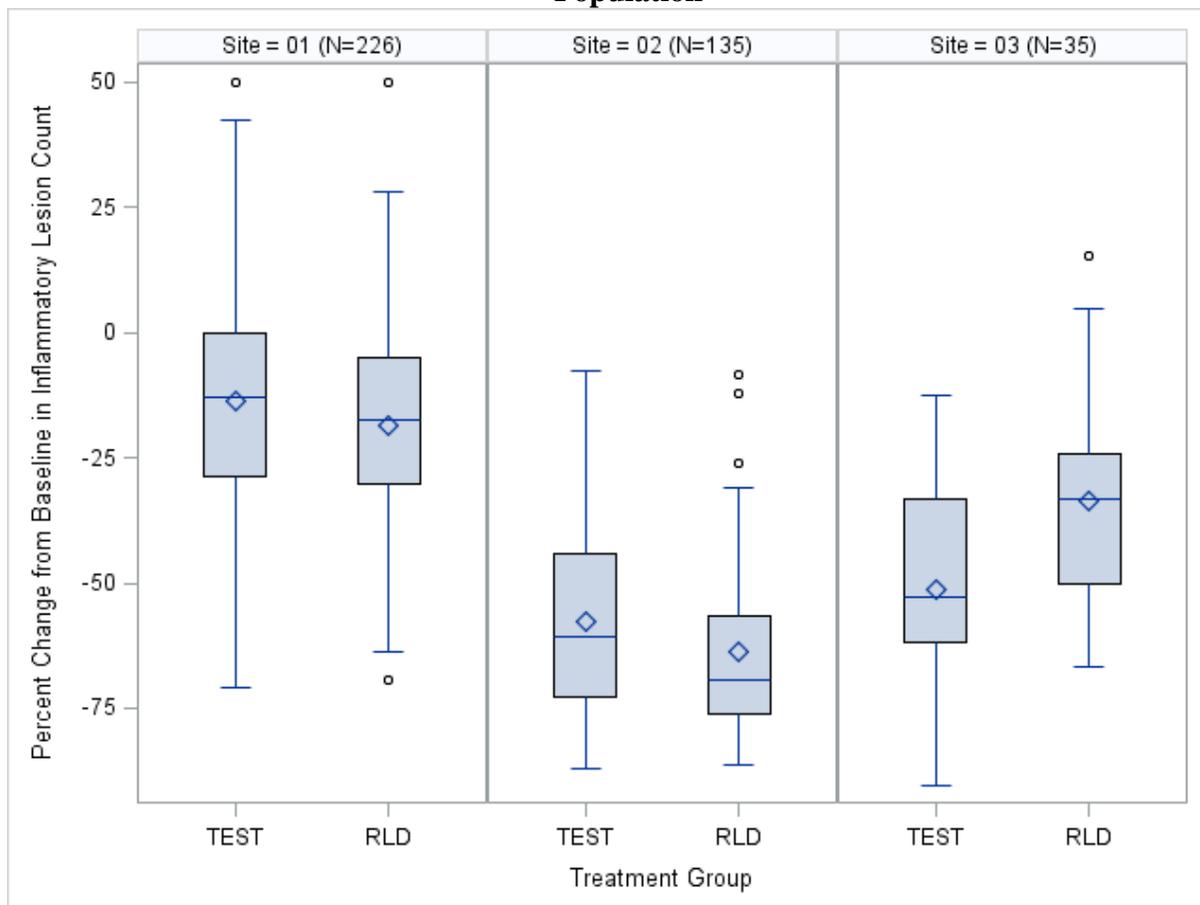
For percent change from baseline in inflammatory lesion count (Figure 3), Site 1 had comparable baseline mean inflammatory lesion counts as Site 2 (Site 1: 26.3 and for Site 2: 27.1), but much less reduction of lesion count at Visit 5 (Week 12) in both groups (Site 1: -13.7 for TEST and -6 for RLD; Site 2: -57.6 for TEST and -55.8 for RLD), which may be due to inter-rater variability or other reasons. Therefore, we would like to verify the data accuracy at Site 1.

Figure 1
Subgroup Efficacy Analysis: Percent Change from Baseline to Visit 5 (Week 12) in the Inflammatory Lesion Count For TEST and VEH by Site in the FDA's mITT Population



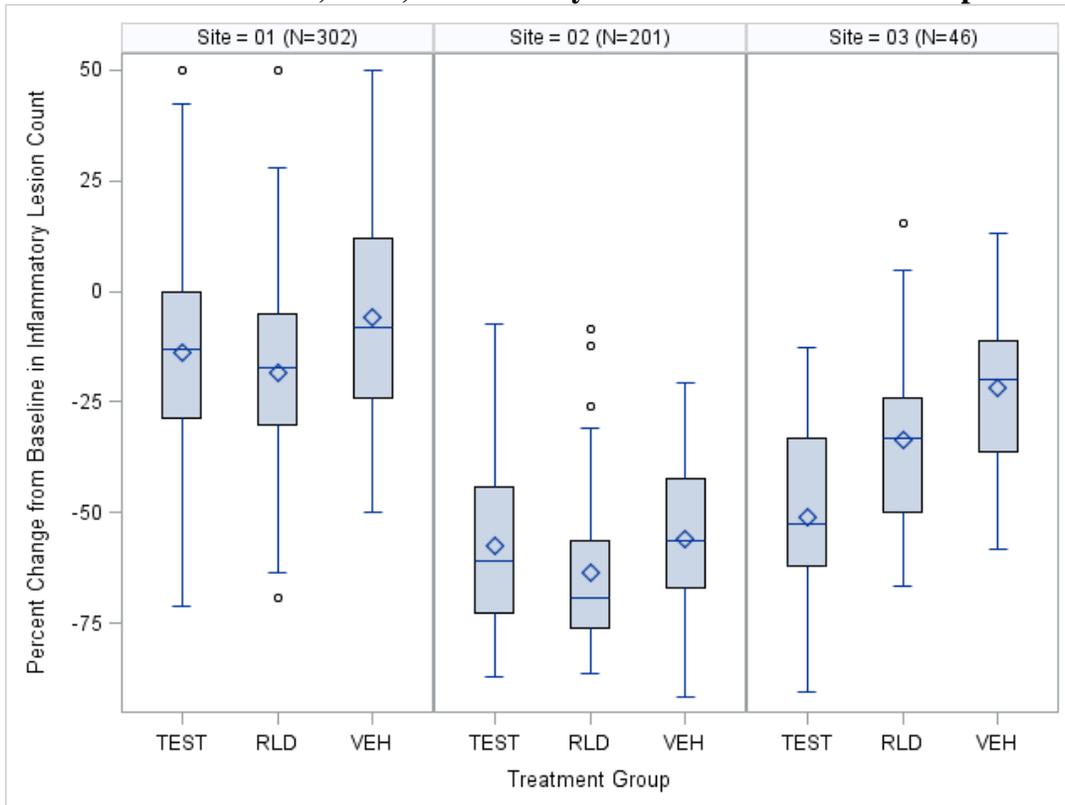
	Total N	TEST Percent Change in Inflammatory Lesion Count (n=222) Mean (SD)	VEH Percent Change in Inflammatory Lesion Count (n=107) Mean (SD)
Site 1	182	n=124 -13.7 (20.6)	n=58 -6.0 (23.7)
Site 2	120	n=80 -57.6 (19.7)	n=40 -55.8 (18.7)
Site 3	27	n=18 -51.1 (21.4)	n=9 -21.9 (20.6)

Figure 2.
Subgroup Equivalence Analysis: Boxplot of the Percent Change from Baseline to Visit 5 (Week 12) for the Inflammatory Lesion Count in TEST and RLD by Site in the FDA's PP Population



	N	TEST Percent Change in Inflammatory Lesion Count (n=197) Mean (SD)	RLD Percent Change in Inflammatory Lesion Count (n=199) Mean (SD)
Site 1	226	n=117 -14.3 (20.2)	n=109 -19.0 (21.0)
Site 2	135	n=63 -62.0 (18.6)	n=72 -64.9 (15.6)
Site 3	35	n=17 -52.3 (21.5)	n=18 -35.2 (21.7)

Figure 3
Subgroup Efficacy Analysis: Percent Change from Baseline to Visit 5 (Week12) in the
Inflammatory Lesion Count
For TEST, RLD, and VEH by Site in the FDA's mITT Population



	Total N	TEST Percent Change in Inflammatory Lesion Count (n=222) Mean (SD)	RLD Percent Change in Inflammatory Lesion Count (n=220) Mean (SD)	VEH Percent Change in Inflammatory Lesion Count (n=107) Mean (SD)
Site 1	302	n=124 -13.7 (20.6)	n=120 -18.4 (20.86)	n=58 -6.0 (23.7)
Site 2	201	n=80 -57.6 (19.7)	n=81 -63.6 (17.2)	n=40 -55.8 (18.7)
Site 3	46	n=18 -51.1 (21.4)	n=19 -33.5 (22.3)	n=9 -21.9 (20.6)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 7 November 2014

TO: Office of Bioequivalence

FROM: Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: ANDA 207955 – MOORE Clinical Research, Inc (4257 West Kennedy Blvd., Tampa, FL) – Clinical Endpoint

The Division of Bioequivalence and GLP Compliance (DBGLPC) recommends accepting data without on-site inspection. The rationale for this decision is noted below.

OSI inspected the site(s) within the last four years. The inspectional outcome from the inspection(s) was classified as No Action Indicated (NAI).

Nicola M.
Nicol -S

 Digitally signed by Nicola M. Nicol -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2001347020,
cn=Nicola M. Nicol -S
Date: 2014.11.07 08:14:26 -05'00'

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 207955

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

Approval Type: <input checked="" type="checkbox"/> FULL APPROVAL <input type="checkbox"/> TENTATIVE APPROVAL <input type="checkbox"/> SUPPLEMENTAL APPROVAL (NEW STRENGTH)		
RPM: Ashley Burns Team: Bic Nguyen		Approval Date: 8/13/2015
<input type="checkbox"/> PI <input checked="" type="checkbox"/> PII <input type="checkbox"/> PIII <input type="checkbox"/> PIV (eligible for 180 day exclusivity) <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> MOU <input checked="" type="checkbox"/> RX or <input type="checkbox"/> OTC		
ANDA #: 207955 Applicant: Spear Pharmaceuticals		Established Product Name: Tretinoin Gel USP, 0.05%
Basis of Submission (RLD): Atralin Gel, 0.05% / NDA 022070 / Dow Pharmaceutical Sciences (Dow) (Is ANDA based on an approved Suitability Petition? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No)		
Does the ANDA contain REMS? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No (If YES, initiate approval action 6 weeks prior to target action date)		
Regulatory Project Manager Evaluation:		Date: 8/5/2015
<input type="checkbox"/> Date last Complete Response (CR) letter was issued -- Date N/A		
<input type="checkbox"/> Previously reviewed and tentatively approved (if applicable) --- Date N/A		
Date of Application 9/30/2014		Original Received Date 10/1/2014
Date Acceptable for Filing 10/1/2014		
YES	NO	
<input checked="" type="checkbox"/>	<input type="checkbox"/>	All submissions have been reviewed and relevant disciplines are adequate and finalized in the platform (Date or N/A) Date of Acceptable Quality 7/24/2015 Date of Acceptable Dissolution N/A Date of Acceptable Bioequivalence N/A Date of Acceptable Labeling 3/27/2015
		If applicable: Date of Acceptable Microbiology N/A Date of Acceptable Clinical Review 6/2/2015 Date of Acceptable REMS N/A
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Are consults pending for any discipline?
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Has there been an amendment providing for a major change in formulation or new strength since filing? If YES → Verify a second filing review was completed and that all disciplines completed new reviews <input type="checkbox"/>
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Is there a pending Citizen Petition (CP)?
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Overall OC Recommendation is acceptable (EES is acceptable) Date Acceptable: 8/3/2015 Re-evaluation Date: 12/31/2015
<input checked="" type="checkbox"/>	<input type="checkbox"/>	OSI Clinical Endpoint and Bioequivalence Site Inspections are acceptable
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Is ANDA a Priority Approval (First generic, drug shortage, PEPFAR, other OGD Communications priorities)? If YES → Email OGD Communications Staff (OGDREQUEST) 30 to 60 days prior to approval, Date emailed 8/5/2015
Draft Approval/Tentative Approval Letter		
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Approval/Tentative Approval letter is drafted and uploaded to the Final Decision task
Review Discipline/Division Endorsements		
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Division of Legal and Regulatory Support Endorsement completed, Date 8/6/2015
<input type="checkbox"/>	<input type="checkbox"/>	Paragraph IV Evaluation completed (if applicable), Date N/A
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Quality Endorsement completed, Date 8/11/2015
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Bioequivalence Endorsement completed, Date 8/6/2015
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Labeling Endorsement completed, Date 8/6/2015
<input type="checkbox"/>	<input type="checkbox"/>	REMS Endorsement (if applicable), Date N/A
RPM Team Leader Endorsement and Action Package Verification		
<input checked="" type="checkbox"/>	<input type="checkbox"/>	RPM Team Leader Endorsement completed, Date 8/13/2015
Final Decision and Letter Sign-off		
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Final Decision recommending approval/tentative approval completed, Date 8/13/2015
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Approval/Tentative Approval letter electronically signed, Date: 8/13/2015
Project Close-Out		
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Notify applicant of approval and provide a courtesy copy of the electronically signed letter
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Is there a Post Marketing Agreement (PMA)? IF YES → Send email to PMA coordinator, Date emailed N/A
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Email OGD Approval distribution list (CDER-OGDAPPROVALS) with approval information

This page to be completed by the RPM

Lead Division: Program Management **Effective Date:** 10/1/2014 **Page 1 of 8**

Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

Please ensure you are using the most current version of this Form. It is available at:
[OGD QMS Approved Documents](#)



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 8/6/2015
Name/Title: MHS

Contains GDEA certification: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> (required if sub after 6/1/92)	Pediatric Exclusivity System RLD = _____ NDA# _____ Date Checked _____ Nothing Submitted <input type="checkbox"/> Written request issued <input type="checkbox"/> Study Submitted <input type="checkbox"/>
Patent/Exclusivity Certification: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes <input type="checkbox"/> No <input type="checkbox"/> Was applicant sued w/in 45 days: Yes <input type="checkbox"/> No <input type="checkbox"/> Has case been settled: Yes <input type="checkbox"/> No <input type="checkbox"/> Date settled: Is applicant eligible for 180 day Is a forfeiture memo needed: Yes <input type="checkbox"/> No <input type="checkbox"/> If yes, has it been completed	
Generic Drugs Exclusivity for each strength: Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	
Date of latest Labeling Review/Approval Summary	
Any filing status changes requiring addition Labeling Review Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	
Type of Letter: <input checked="" type="checkbox"/> APPROVAL <input type="checkbox"/> TENTATIVE APPROVAL <input type="checkbox"/> SUPPLEMENTAL APPROVAL (NEW STRENGTH) <input type="checkbox"/> OTHER:	
Comments: ANDA submitted on 10/1/2014, BOS=Atralin NDA 22070, PII cert provided('547 patent had expired on 9/23/2014). ANDA ack for filing on October 1, 2014(LO dated 10/31/2014). There are no unexpired patents or exclusivities that will preclude approval of this ANDA. Application is eligible for immediate Full Approval.	

Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

2. **Paragraph IV Evaluation (for ANDAs with PIV certifications or other controversial regulatory issues)**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

3. **Quality Endorsement by the Office of Pharmaceutical Science**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

4. **Bioequivalence Endorsement**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

5. **Labeling Endorsement**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

6. **REMS Endorsement**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

7. **RPM Team Leader Endorsement**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

8. Final Decision

Date: 8/13/2015
Name/Title: wpr

Para.IV Patent Cert: Yes No
Pending Legal Action: Yes No
Petition: Yes No
Entered to APTrack database
GDUFA User Fee Obligation Status Met Unmet
Press Release Acceptable
First Generic Approval
PD or Clinical for BE
Special Scientific or Reg. Issue

Date PETS checked for first generic drug _____

Comments:

BOS=Atralin NDA 22070. Spear provided a PII patent certification ('547 patent had expired on 9/23/2014). There are no unexpired patents or exclusivities that block approval of this ANDA. Chemistry acceptable 7/24/2015. QE 8/11/2015. Clinical acceptable 6/2/2015. Stats acceptable pending OSI inspection 2/20/2015. OSI inspection results okay see memo dated 6/3/2015. Labeling acceptable 3/27/2015. Inspection report acceptable 12/31/2015. This is a 1st generic approval. Application is eligible for immediate Full Approval.



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

Orange Book Report:
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APPEARS THIS WAY ON
ORIGINAL

Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

Please ensure you are using the most current version of this Form. It is available at:
[OGD QMS Approved Documents](#)



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

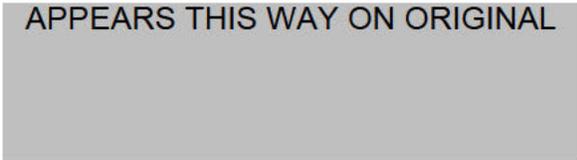
REFERENCES / ASSOCIATED DOCUMENTS

4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA

REVISION HISTORY

Version	Effective date	Name	Role	Summary of changes
01	10/1/2014	Heather Strandberg	Author	New Form

APPEARS THIS WAY ON ORIGINAL



CHECKLIST FOR THE CHEMISTRY REVIEW:

ANDA 207955, Tretinoin Gel 0.05%

Function	Performed By (Initial and Date)	Check appropriate box
Is this package for new strength PAS?	PQRPM	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
DMF adequate?	PQRPM	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No *(see comments)
Any outstanding consults?	PQRPM	<input type="checkbox"/> Yes *(see comments) <input checked="" type="checkbox"/> No
Final recommended dissolution method/specification acknowledged by Firm?	DD, DDD or designee	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
Are all facility inspections acceptable?	PQRPM	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Is microbiology recommendation adequate for sterile products?	PQRPM	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
Chemistry Post Marketing Agreement (PMA)?	PQRPM	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
If PMA is yes, was OGD informed?	PQRPM	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
If USP monograph exists, do the specifications conform to the current USP?	DD, DDD or designee	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No *(see comments) <input type="checkbox"/> N/A
Is the final review uploaded into the current IT platform?	PQRPM	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Division	Signature	Date
DLBP	Pahala Simamora -A <small>Signature of the Designee of the Applicant Pahala Simamora -A Pahala Simamora -A</small>	



ANDA 207955

INFORMATION REQUEST

Spear Pharmaceuticals
Attention: David J Christ,
VP Regulatory
37 Jefferson Landing Circle
Port Jefferson, NY 11777

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated October 1, 2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Tretinoin Gel USP 0.05%.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than June 21, 2015, in order to continue our evaluation of your ANDA.

List of the deficiencies:

Drug product:



(b) (4)

(b) (4)

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4. Please provide your updated long term stability data, if available.

Manufacturing process:

(b) (4)

A very large rectangular area of the document is redacted with a solid grey fill, covering the entire lower half of the page.

If you do not submit a complete response by June 21, 2015, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

Please note, if information or data submitted exceeds the data requested in the IR/ECD this may result in conversion to a Tier 2 Unsolicited Amendment (i.e., an amendment with information not requested by FDA).

If the submitted data is determined to be a tier 2 unsolicited amendment, this may affect the goal date.

Send your submission through the Electronic Submission Gateway <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm>. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**INFORMATION REQUEST
QUALITY
REFERENCE # 115081**

If you have any questions, please contact Tania Mazza, Regulatory Business Project Manager, at (240) 402-9013.

Sincerely,

{See appended electronic signature page}

Tania Mazza
Regulatory Business Project Manager
Office of Program and Regulatory Operations Office
of Pharmaceutical Quality
Center for Drug Evaluation and Research

**Tania B.
Mazza -S**

Digitally signed by Tania B. Mazza -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Tania B. Mazza
-S,
0.9.2342.19200300.100.1.1=2001169109
Date: 2015.05.21 15:48:46 -04'00'



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 207955

EASILY CORRECTABLE DEFICIENCY

Please see the attached pdf for labeling deficiencies.

Provide a complete response to these deficiencies by March 24, 2015. We will not process or review a partial response. Facsimile or e-mail responses will not be accepted.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY

LABELING

REFERENCE # 85972

If you do not submit a complete response by March 24, 2015, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence. For more information, please refer to the guidance for industry, ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA, available on FDA's website.

If you have any questions, contact Julie Call, Labeling Project Manager at 240-402-8598.

Sincerely,

OFFICE OF GENERIC DRUGS

Center for Drug Evaluation and Research

U.S. Food and Drug Administration



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Hi,

Attached please find IR letter for ANDA 207955. Please respond to the letter within 30 days.

Please confirm the receipt of this letter.

Thank,

Tania Mazza

OFFICE OF GENERIC DRUGS EXPEDITED REVIEW REQUESTED

ANDA#/SUPPLEMENT#: 207955
 DRUG: Tretinoin Gel USP, 0.05%

APPLICANT: Spear Pharmaceuticals
 DATE OF SUBMISSION: 09/30/2014

The Office of Generic Drugs may grant expedited review status to either an Original or Supplemental abbreviated new drug application for the following reasons (MaPP 5240.1, MaPP 5240.3 & GDUFA). At least one of the criteria must be met to receive Expedited Review Status:

1. **PUBLIC HEALTH NEED.** Events that affect the availability of a drug for which there is no alternative

2. **EXTRAORDINARY HARDSHIP ON THE APPLICANT.**
 - a) Catastrophic events such as explosion, fire storms damage.

 - b) Events that could not have been reasonably foreseen and for which the applicant could not plan. Examples include:
 - ◆ Abrupt discontinuation of supply of active ingredient, packaging material, or container closure; and
 - ◆ Relocation of a facility or change in an existing facility because of a catastrophic event(see item 2.a)

3. **AGENCY NEED.**
 - a) Matters regarding the government's drug purchase program, upon request from the appropriate FDA office.
 - b) Federal or state legal/regulatory actions, including mandated formation changes or labeling changes if it is in the Agency's best interest.
 - c) Expiration-date extension or packaging change when the drug product is the subject of a government contract award.
 - d) Request for approval of a strength that was previously tentatively approved (To be used in those cases where 180-day generic drug exclusivity prevented full approval of all strengths).
 - e) MaPP 5240.3 conditions.

4. **GDUFA.** Year one and year two cohort PIV 180-day eligibility (First Generic)

RECOMMENDATIONS:

DISCIPLINE	STATUS	SIGNATURE/DATE
Team Project Manager (PM must Endorse)	Grant <input type="checkbox"/> Deny <input type="checkbox"/>	
Chemistry Team Leader (sign as needed)	Grant <input type="checkbox"/> Deny <input type="checkbox"/>	
Micro Team Leader (sign as needed)	Grant <input type="checkbox"/> Deny <input type="checkbox"/>	
Labeling Team Leader (sign as needed)	Grant <input type="checkbox"/> Deny <input type="checkbox"/>	
Chem. Div./Deputy Director (DO must Endorse)	Grant <input type="checkbox"/> Deny <input type="checkbox"/>	
Office Director/Deputy Director (email concurrence) (Original ANDAs)	Grant <input checked="" type="checkbox"/> Deny <input type="checkbox"/>	10/31/14

RETURN TO PROJECT MANAGER CHEMISTRY TEAM: SELECT TEAM #42

ENTER FORM INTO DAARTS

DATE: 10/31/14

Paste Email Copy Below:



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 207955

[EASILY CORRECTABLE DEFICIENCY]

Original ANDA

Spear Pharmaceuticals INC.
15016 Pratolino Way,
Naples, FL 34110

Attention: David J Christ, VP Regulatory

Dear Mr.Christ:

Please refer to your Abbreviated New Drug Application (ANDA) submitted on October 01, 2014 under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Tretinoin Gel, 0.05%.

For Study TRET-05 submitted under ANDA 207955, we request the following additional information:

1.We note that all the prior medications listed in the “cm.xpt” file and Listing 16.2.9.3 are marked as “ongoing” during the study. No prior medications which were stopped prior to the baseline visit are included. Your Clinical Study Report (CSR) Section 9.5.1.3 states that during the Baseline Visit, a “complete list of current and past (i.e., within the previous 30 days) concomitant medications was obtained for each subject.”

a.Please confirm if all the subjects did not use any other prior medications which were stopped within 30 days of the baseline visit.

b.If subjects did use other prior medications which were stopped within 30 days of the baseline visit, please add those medications to the “cm.xpt” file and resubmit the “cm.xpt” file.

2.Provide the following additional medical history information:

a.For Subject (b) (6) specify the type and location of dermatitis.

- b. For Subjects [REDACTED] (b) (6) specify the medication allergy.
- c. For Subject [REDACTED] (b) (6) specify the food allergy.
- d. For Subject [REDACTED] specify the location of keratosis pilaris.

3. In the “ADSL.xpt” file, the reasons for exclusion from the Safety Population are not included. There are 25 subjects marked as “N” for the “SAFFL” variable. In your CSR Table 9, 25 subjects are excluded from the Safety Population because “Did not use any study drug”.

- a. Please confirm that the 25 subjects marked as “N” for “SAFFL” in the “ADSL.xpt” file are the same 25 subjects excluded from the Safety Population as mentioned in your CSR Table 9.
- b. If those 25 subjects are not the same, please add the reason for exclusion from Safety Population in the “ADSL.xpt” file and resubmit the “ADSL.xpt” file with a revised “define” file.
- c. We note that these same 25 subjects do not have values for the “infil”, “noninfil” and “nodulcsl” variables in the “ADSL.xpt” file. In the “QS.xpt” file, values are entered in the “qsorres” variable for Visit 1. Please explain.
- d. In addition, please update the “ADSL.xpt” file with values for the “infil”, “noninfil” and “nodulcsl” variables for these 25 subjects and resubmit the “ADSL.xpt” file with a revised “define” file.

Provide a complete response to these deficiencies by January 15, 2015. We will not process or review a partial response. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
DIVISION OF CLINICAL REVIEW
REFERENCE # 60312

If you do not submit a complete response by January 15, 2015, the review will be closed and the listed deficiencies will be incorporated in a **COMPLETE RESPONSE** correspondence. For more information, please refer to the guidance for industry, **ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA**, available on FDA’s website.

If you have any questions, contact Ashley Burns, Regulatory Project Manager at 240-402-7111.

Sincerely,

Ashley Burns, Regulatory Project Manager

Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 207955

ANDA ACKNOWLEDGEMENT

Spear Pharmaceuticals
15016 Pratolino Way
Naples, FL 34110
Attention: David J. Christ

Dear David J. Christ:

This email is for your records for ANDA 207955.

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

The acknowledgment letter is attached to this correspondence. This electronic mail is in lieu of a fax.

Reply to this correspondence in acknowledgment.

Sincerely,

Rebekah Granger
Team Leader (Acting)
Division of Filing Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 207955

ANDA ACKNOWLEDGEMENT

Spear Pharmaceuticals
15016 Pratolino Way
Naples, FL 34110
Attention: David J. Christ

Dear David J. Christ:

This email is for your records for ANDA 207955.

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

The acknowledgment letter is attached to this correspondence. This electronic mail is in lieu of a fax.

Reply to this correspondence in acknowledgment.

Sincerely,

Rebekah Granger
Team Leader (Acting)
Division of Filing Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

**DIVISION OF CLINICAL REVIEW FILING REVIEW DETERMINATION
FOR APPLICATION COMPLETENESS
(CLINICAL ENDPOINT STUDY)**

ANDA#	207955
DRUG NAME	Tretinoin Topical Gel, 0.05%
DOSAGE FORM	Gel
APPLICANT NAME	Spears Pharmaceuticals
REFERENCE LISTED DRUG (RLD) #	NDA 022070
DRUG NAME	Atralin (tretinoin) gel, 0.05%
DOSAGE FORM	Gel
APPLICANT	Dow Pharmaceutical Sciences Inc
APPROVAL DATE	7/26/2007
PRIMARY REVIEWER	Sarah H. Seung, Pharm.D. Clinical Reviewer Division of Clinical Review Office of Bioequivalence Office of Generic Drugs
SECONDARY REVIEWER	Carol Y. Kim, Pharm.D. Acting Team Leader, ANDA Team Division of Clinical Review Office of Bioequivalence Office of Generic Drugs
REQUESTED BY	Julia Lee Division of Filing Review Office of Generic Drugs
REQUESTED DATE	10/2/2014
GOAL DATE FOR FILING REVIEW	10/31/2014

**Summary of Findings by Division of Clinical Review
(By Both DCR and Statistical Reviewers)**

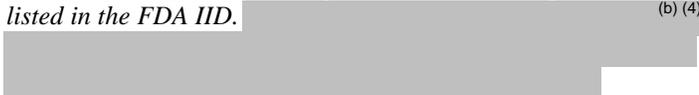
Clinical Endpoint Study:	¹ From DCR perspective, the clinical endpoint BE study (TRET-05) data are acceptable for filing. Please see comments to be conveyed to the applicant.
Clinical Section ___ Complete X Incomplete	

RECOMMENDATION FROM DCR PERSPECTIVE:

__X__ ACCEPTABLE ___ NOT ACCEPTABLE

¹ Any filing deficiencies to be communicated to the applicant will be listed under appropriate heading at the end of the review.

Item Verified:	YES	NO	Comments
Protocol (original and amendments)	x		\\cdsesub1\evsprod\anda207955\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\tret-05\protocol-or-amendment.pdf Original Protocol (dated 11/12/2013): pp. 1-29 Amendment 1 summary (dated 1/24/2014): p. 33
Study Report	x		\\cdsesub1\evsprod\anda207955\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\tret-05\report-body.pdf
Clinical Site (s) and study investigator (s)	x		\\cdsesub1\evsprod\anda207955\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\tret-05\list-description-investigator-site.pdf p.1
Reasons for discontinuation from the study if discontinued (SAS .xpt)	x		\\cdsesub1\evsprod\anda207955\0000\m5\datasets\tret-05\analysis\adsl.xpt
Adverse Events (SAS.xpt)	x		\\cdsesub1\evsprod\anda207955\0000\m5\datasets\tret-05\listings\ae.xpt
Concomitant Medications (SAS.xpt)	x		\\cdsesub1\evsprod\anda207955\0000\m5\datasets\tret-05\listings\cm.xpt
Individual subject's scores/data per visit (SAS.xpt)	x		\\cdsesub1\evsprod\anda207955\0000\m5\datasets\tret-05\listings\qs.xpt
Pre-screening of Patients	x		\\cdsesub1\evsprod\anda207955\0000\m5\datasets\tret-05\listings\blankcrf.pdf
IRB Approval (Approval letters for protocol and consent/assent forms)	x		\\cdsesub1\evsprod\anda207955\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\tret-05\iec-irb-consent-form-list.pdf pp. 39-41
Consent Forms	x		\\cdsesub1\evsprod\anda207955\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\tret-05\iec-irb-consent-form-list.pdf pp. 6-38
Protocol Deviations	x		\\cdsesub1\evsprod\anda207955\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\tret-05\protocol-deviations.pdf \\cdsesub1\evsprod\anda207955\0000\m5\datasets\tret-05\listings\dv.xpt
All Case Report Forms	x		\\cdsesub1\evsprod\anda207955\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\tret-05\crf 137 CRFs for all subjects who had SAE, death, protocol violation/deviations, and excluded from analysis populations. Plus 10% (41 CRFs) random selection of remaining subjects.
Clinical Raw Data/ Medical Records	x		Provided in CRFs

Item Verified:	YES	NO	Comments
Primary data in SAS .xpt file	x		\\cdsesub1\evsprod\anda207955\0000\m5\datasets\tret-05\listings\qs.xpt See FDA statistical filing review "Stat Nontransdermal Filing Review 207955 Elena(f).doc" Version 1.0, uploaded on 10/14/2014 for details.
Financial Disclosure	x		\\cdsesub1\evsprod\anda207955\0000\m1\us\financial-certifications.pdf
Formulation	x		\\cdsesub1\evsprod\anda207955\0000\m2\23-qos\drug-product-tretinoin.pdf p. 1 \\cdsesub1\evsprod\anda207955\0000\m3\32-body-data\32p-drug-prod\tretinoin-gel-usp-005\32p1-desc-comp\description-and-composition.pdf
Placebo formulation		x	The applicant should provide this information.
All inactive ingredients below IID limits		x	\\cdsesub1\evsprod\anda207955\0000\m2\23-qos\drug-product-tretinoin.pdf p. 2-3 Reviewer's Comments: Ethylparaben and isobutylparaben are not listed in the FDA IID. (b) (4) 
Evidence provided by the sponsor to demonstrate that the difference in such inactive ingredients do not affect the safety and efficacy of the proposed drug product. (e.g., pharm/tox data, copy of references)	x		\\cdsesub1\evsprod\anda207955\0000\m2\23-qos\drug-product-tretinoin.pdf p. 3, table footnote #3
BioStudy Lot Numbers and date of manufacture	x		\\cdsesub1\evsprod\anda207955\0000\m2\27-clin-sum\summary-biopharm.pdf p.6
Exp. Date of RLD	x		\\cdsesub1\evsprod\anda207955\0000\m2\27-clin-sum\summary-biopharm.pdf p.6
Waiver requests for other strengths		x	Not applicable
Supporting data		x	Not applicable
Draft/final guidance (include posted date)	x		http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM296997.pdf (March 2012)
Sponsor's study design consistent with the FDA Guidance. (e.g., treatment indication, patient population, dose, frequency, primary endpoint, application site)	x		\\cdsesub1\evsprod\anda207955\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\tret-05\report-body.pdf p. 17 (treatment indication, dose, frequency, & application site); p. 35 (primary endpoint); p. 39 (patient population).
Primary endpoint defined (within BE limits)	x		\\cdsesub1\evsprod\anda207955\0000\m2\27-clin-sum\summary-biopharm.pdf p. 16 & 18-20
Primary endpoint: superiority over placebo	x		\\cdsesub1\evsprod\anda207955\0000\m2\27-clin-sum\summary-biopharm.pdf p. 16 & 18-20

Item Verified:	YES	NO	Comments
Secondary endpoint defined (within BE limits)		x	Both the applicant and Draft Guidance on Tretinoin do not define a secondary endpoint.
Secondary endpoint: superiority over placebo		x	Both the applicant and Draft Guidance on Tretinoin do not define a secondary endpoint.
Does the RLD have a REMS?		x	
If the RLD has a REMS, has the applicant provided a REMS?		x	Not applicable

Comments to be conveyed to the applicant:

<p>From Both DCR and STAT perspectives, comments to be conveyed to the applicant:</p>	<p>Your clinical endpoint BE study is acceptable for receiving your ANDA.</p> <p>The following additional information is requested for the review of the study TRET-05:</p> <ol style="list-style-type: none"> 1. Provide the Vehicle Control formulation description and composition. If the inactive ingredients in the Vehicle Control are different from those in your proposed test formulation: <ol style="list-style-type: none"> a. Provide justification for the differences b. Explain how the use of different inactive ingredients in the Vehicle Control would not affect the study outcome compared to using a Vehicle Control with the the same inactive ingredients as the test formulation. 2. Please submit the randomization schedule file in .xpt format. 3. ITT flag (variable name: ITTFL) and reasons for exclusion (variable name: ITTEXRSN) are included in ADSL.XPT file. However, for all subjects excluded from ITT, the values for ITTEXRSN are missing. Please clarify and/or provide the information of reasons for exclusion from ITT. 4. PP flag (variable name: PPROTFL) and reasons for exclusion (variable name: PPEXRSN) are included in ADSL.XPT file. However, for some subjects excluded from PP, the values for PPEXRSN are missing. Please clarify and/or provide the information of reasons for exclusion from PP. 5. Please submit all SAS programs for efficacy endpoints derivation and efficacy analyses.
--	--

**STATISTICAL REVIEW CHECKLIST FOR ANDA
FOR APPLICATION COMPLETENESS AT FILING
(Non-transdermal)**

ANDA	207955
DRUG NAME	Tretinoin Gel USP 0.05%
APPLICANT NAME	Spear Pharmaceuticals, Inc.
REFERENCE LISTED DRUG (RLD)	Atralin (tretinoin) Gel 0.05%
<i>Primary</i> REVIEWER	Elena Rantou, Ph.D.
<i>Secondary</i> REVIEWER	Jingyu (Julia) Luan, Ph.D.
DATE	Date of Receipt of ANDA: 10/1/2014 Date of Assignment: 10/6/2014 Date of Primary Review Completion: 10/9/2014

RECOMMENDATION TO DCR FROM A STATISTICAL PERSPECTIVE	
ACCEPTABLE	X
NOT ACCEPTABLE	

Reviewed by:

Primary Reviewer Generic Team, DBVI/OB/OTS/CDER

Secondary Reviewer Generic Team, DBVI/OB/OTS/CDER

Comments to the DCR filing reviewer:

If guidance was available, did the sponsor use the OGD recommended statistical methods for the primary endpoint(s)?	YES	
---	-----	--

In agreement with the guidance, the sponsor used two primary endpoints, the percent change from baseline to Visit 5 in Inflammatory lesion counts and the percent change from baseline to Visit 5 in Non-Inflammatory lesion counts.

Statistical Requests (see DCR filing review for final comments to be transmitted to the sponsor):

- Please submit the randomization schedule file in .xpt form.
- ITT flag (variable name: ITTFL) and reasons for exclusion (variable name: ITTEXRSN) are included in ADSL.XPT file. However, for all subjects excluded from ITT, the values for ITTEXRSN are missing. Please clarify and/or provide the information of reasons for exclusion from ITT.
- PP flag (variable name: PPROTFL) and reasons for exclusion (variable name: PPEXRSN) are included in ADSL.XPT file. However, for some subjects excluded from PP, the values for PPEXRSN are missing. Please clarify and/or provide the information of reasons for exclusion from PP.
- Please submit all SAS programs for efficacy endpoints derivation and efficacy analyses.

Checklist (Study Identifier):

Item included and appears adequate:	YES	NO	Comments
FDA Guidance for this product is available	X		http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM296997.pdf
Data definition file (describes the variables in each data set)	X		The file \\cdsesub1\evsprod\ANDA207955\0000\m5\datasets\tret-05\analysis\define.xml is a web page file. It would be helpful if this was also provided in a .pdf or .xls form
Randomization Schedule Format: SAS .xpt file		X	The randomization scheme and code are included in the file: \\cdsesub1\evsprod\anda207955\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\tret-05\randomization-scheme.pdf
Demographic Data Format: SAS .xpt file	X		Demographic data is included in the .xpt file: \\cdsesub1\evsprod\anda207955\0000\m5\datasets\tret-05\listings\dm.xpt
Summary Data Format: SAS .xpt file	X		Data file ADSL.XPT \\cdsesub1\evsprod\anda207955\0000\m5\datasets\tret-05\analysis\adsl.xpt
Identification of mITT Population/ Reasons for Exclusion Format: SAS .xpt file	X		Intent to Treat population flag variable ITTFL is found in data set ADSL.XPT. Variable ITTEXRSN for reasons of exclusion, is also found in ADSL.XPT \\cdsesub1\evsprod\anda207955\0000\m5\datasets\tret-05\analysis\adsl.xpt However, for all subjects excluded from ITT, the values for ITTEXRSN are missing.

Identification of the PP Population/ Reasons for Exclusion Format: SAS .xpt file	X	Per-Protocol population flag variable PPROTFL is found in data set ADSL.XPT. Variable PPEXRSN for reasons of exclusion, is also found in ADSL.XPT \\cdsesub1\evsprod\anda207955\0000\m5\datasets\tret-05\analysis\adsl.xpt However, for some subjects excluded from PP, the values for PPEXRSN are missing.
Raw Data (NO – LOCF) Format: SAS .xpt file	X	The raw data is provided in data set ADEF.XPT \\cdsesub1\evsprod\anda207955\0000\m5\datasets\tret-05\analysis\adef.xpt
LOCF Data Format: SAS .xpt file	X	The sponsor does not provide a separate file for LOCF data but the LOCF indicator-type variable, DTYPE, is provided in the data set ADEF.XPT \\cdsesub1\evsprod\anda207955\0000\m5\datasets\tret-05\analysis\adef.xpt
Subject's measurements/visits/dates Format: SAS .xpt file	X	Information about the dates of subjects visits is provided in the file VS.XPT \\cdsesub1\evsprod\anda207955\0000\m5\datasets\tret-05\listings\vs.xpt but this file does not include any measurement variables. Subjects' measurements at baseline are given through the variables INFILL, NONINFILL and NODULCSL in data set ADSL.XPT \\cdsesub1\evsprod\anda207955\0000\m5\datasets\tret-05\analysis\adsl.xpt All subjects' measurements for all visits are given in the data file: \\cdsesub1\evsprod\anda207955\0000\m5\datasets\tret-05\listings\qs.xpt
Data to evaluate treatment & rating compliance (Nasal Only) Format: SAS .xpt file		

Sponsor Statistical Analyses & Summary	X	Sponsor's statistical analyses and summary are presented in the study report file REPORT-BODY.PDF \\cdsesub1\evsprod\anda207955\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\tret-05\report-body.pdf
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Comments to the statistical reviewer:

The sponsor does not include separate data sets for the modified Intend-to-Treat (mITT) and the Per-Protocol (PP) populations. The sponsor does not include a separate data set for the LOCF information. This information can be extracted and combined by the statistical reviewer from the available data sets and the flag variables included in these data sets.

Subjects' measurements per visit, per subject are provided only for Visit 1 (baseline). For visit 5, the variable AVAL in data set ADEF.XPT gives the percent change in inflammatory and non-inflammatory counts from baseline to Visit 5. Although both the actual counts for Visits 2-5 and the IGA scores, are not given in any analysis data file, this information is provided in the data listing file <\\cdsesub1\evsprod\anda207955\0000\m5\datasets\tret-05\listings\qs.xpt>. In this file, the variable QSORRES summarizes these measurements vertically so the statistical reviewer will have to use SAS to extract the information per subject, per visit or per measurement type.

The sponsor used an ANCOVA model to construct a 90% confidence interval of the Test/Reference ratio of the mean percent change from baseline to week 12 (Visit 5) in the inflammatory and non-inflammatory lesion counts, in order to establish equivalence.

For Inflammatory lesion counts the derived 90% confidence interval for the Test/Reference ratio of the means was [0.82, 1.02] and for Non-Inflammatory lesion counts, the derived 90% confidence interval for the Test/Reference ratio of the means was [0.97, 1.20]. Therefore the Reference product passes the equivalence test for both endpoints according to the sponsor's analysis.

A non-parametric rank based ANCOVA was also considered to deal with highly skewed data. Additionally, both the Test and the Reference products are tested for superiority over Placebo.