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APPLICATION NUMBER:

50-801

MEDICAL REVIEW

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-709
Submission Code	N000
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Stamp Date	December 29, 2003
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Reviewer Name	Jill Lindstrom, MD
Review Completion Date	August 31, 2004
Established Name	Clindamycin Phosphate
(Proposed) Trade Name	undetermined
Therapeutic Class	acne product
Applicant	Connetics
Priority Designation	S
Formulation	foam, aerosol
Dosing Regimen	qd
Indication	topical application in the treatment of acne vulgaris
Intended Population	12 years of age and older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends that Clindamycin Phosphate Foam, 1% be approved for topical administration for the treatment of acne vulgaris in subjects 12 years of age and older.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The standard risk management measures of prescription status, professional labeling and spontaneous adverse event reporting are sufficient risk management activities for this drug product at this time.

1.2.2 Required Phase 4 Commitments

No phase 4 commitments are required.

1.2.3 Other Phase 4 Requests

No phase 4 requests are made.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Clindamycin Phosphate Foam, 1% is a topical antibiotic acne product in an aerosol foam vehicle intended for once daily application for the treatment of acne vulgaris in patients 12 years of age and older. The Sponsor has submitted a 505(b)(2) application with Clindagel as the reference listed drug (RLD). The Sponsor performed a single pivotal phase 3 trial which enrolled 1026 subjects into four arms, with 386 subjects receiving Clindamycin Foam. The phase 2 program consisted of a smaller three-armed efficacy and safety study that enrolled 130 subjects, 53 of whom received Clindamycin Foam. The safety database includes 439 subjects exposed to Clindamycin Foam in phases 2 and 3. Clindamycin Phosphate Foam, 1% is not marketed in any country at this time.

1.3.2 Efficacy

In pivotal trial CLN.C.003, Clindamycin Phosphate Foam, 1% was superior to vehicle and non-inferior to Clindagel® (clindamycin phosphate gel) topical gel, 1% for the treatment of acne vulgaris in subjects 12 years of age and older. The trial was adequate and well-controlled; it was of sound design, sufficiently powered, multi-centered, randomized, vehicle-controlled against both the active and comparator drugs, and double-blind. The trial had four arms: Clindamycin Foam, Vehicle Foam, Clindagel and Vehicle Gel. Co-primary efficacy endpoints included success rate, based on the Investigator's Static Global Assessment dichotomized to success and failure, and percent reduction in lesion counts (total, inflammatory and non-inflammatory), of which the Sponsor needed to win on at least two of the three. The primary endpoint was at week 12, and the analysis group was prespecified in the statistical analysis plan to be the ITT (LOCF) population.

The proportion of subjects who achieved success at week 12 in the Clindamycin Foam group, 31.3%, was significantly greater than the in vehicle group, 18.1%, and non-inferior to the Clindagel group, 27.0 % (FDA analysis). Additionally, the percent reduction in all three lesion counts at week 12 for the Clindamycin Foam group was significantly greater than for the Vehicle Foam group ($p<0.004$), and non-inferior to the Clindagel group.

The Sponsor demonstrated efficacy of Clindamycin Phosphate Foam, 1% for the treatment of acne in subjects 12 years of age and older.

1.3.3 Safety

One thousand one hundred and fifty-six subjects were enrolled in the phase 2 and 3 studies, 439 of whom received Clindamycin Phosphate Foam, 1%. Median duration of exposure was 83 days. The 4-month safety update report was reviewed; it did not contain new safety information.

No deaths occurred during the development program for Clindamycin Foam. No serious adverse events were attributed to study drug use. One serious adverse event, an infected pilonidal cyst and sinus (coded as a dermoid cyst, NOS), was reported in the Clindamycin Phosphate Foam, 1% group, but was not attributed to study drug use. No signal suggestive of antibiotic-associated colitis was identified.

A greater percentage of subjects reported adverse events in the Vehicle Foam group (32%) than in the Clindamycin Foam group (29%), and investigators attributed a greater percentage of adverse events to study drug use in the Vehicle Foam group (15%) than in the Clindamycin Foam group (8%). The only common adverse event (occurring in greater than 1% of subjects) that was reported more frequently in the active than vehicle group was headache, NOS. The majority of adverse events that investigators related to study drug use were application site reactions. The proportions of subjects with application site reactions of all types and specific subtypes were greater in the Vehicle Foam group than the Clindamycin Foam group.

In study CLN.C.004, a standard repeat insult patch test study was performed using Clindamycin Foam and Vehicle Foam to determine their potential to cause cutaneous irritancy or allergenicity. The mean cumulative irritancy scores were similar for Clindamycin Foam and Vehicle Foam; both were greater than the cumulative score for distilled water (negative control) and less than the cumulative score for 0.1% sodium laurel sulfate (positive control). No subjects developed a response indicative of sensitization in the challenge phase.

1.3.4 Dosing Regimen and Administration

Clindamycin Phosphate Foam, 1% is intended to be applied once daily. This is the dosage regimen that was studied in the phase 2 and 3 safety and efficacy trials as well as in the phase 1 bioavailability study. This dosage regimen was selected to correspond with the dosage regimen for the reference listed drug, Clindagel.

1.3.5 Drug-Drug Interactions

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents, and the labeling for Clindagel advises caution in patients receiving both agents. Subjects receiving concomitant treatment with neuromuscular blocking agents were excluded from participation in the clinical studies with Clindamycin Phosphate Foam, 1%. No other drug-drug interactions were identified during the development program.

1.3.6 Special Populations

Both genders, adolescents aged 12 to 16 years, and non-white subjects were adequately represented, as study enrollment in the pivotal trial was reflective of the US population (for gender and race) and disease prevalence (for age).

Subgroup analysis of efficacy results revealed a trend toward lower efficacy among male subjects, adolescents subjects 12 to 16 years of age and black subjects. However, because the study was not powered for these analyses, their significance is not clear.

Subgroup analysis of safety data did not reveal trends based on gender, age or race.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Clindamycin phosphate foam, 1%, is a topical antibiotic acne product in an aerosol foam vehicle for which the Sponsor seeks a proposed indication for topical application in the treatment of acne vulgaris. Clindamycin phosphate, a lincosamide, is a synthetic derivative of lincomycin and belongs to the pharmacologic class of acne products. The foam vehicle is a new dosage form for this drug. The foam is to be applied once daily to the affected area in patients 12 years of age and older. The Sponsor proposed the trade names [redacted] but neither was found to be acceptable. The Sponsor has proposed two additional trade names, [redacted] and Evoclin; consultation with the Division of Drug Medication Errors and Technical Support (DMETS) on the suitability of these tradenames is pending at the time of completion of this review.

2.2 Currently Available Treatment for Indications

Prescription topical treatments indicated for acne vulgaris include clindamycin (gel, solution, lotion, swab), erythromycin (gel, ointment, solution, swab), azeleic acid cream, benzoyl peroxide gel, benzoyl peroxide and erythromycin gel, benzoyl peroxide and clindamycin gel, tretinoin (gel, cream, solution), adapelene (gel and cream) and tazarotene (gel and cream).

2.3 Availability of Proposed Active Ingredient in the United States

Clindamycin phosphate is currently marketed for the treatment of acne vulgaris in various formulations for topical administration, including gel, solution, lotion, and swab. It is also a combined with benzoyl peroxide in a combination product. The concentration of clindamycin phosphate is 1% in all of the topical formulations indicated for the treatment of acne vulgaris. One gel formulation (Clindagel) is applied once daily, and the other gel (Cleocin T) as well as the lotion, solution, swab and combination products are applied twice daily. Clindamycin phosphate is not presently marketed in a foam formulation.

For indications other than the treatment of acne vulgaris, clindamycin phosphate is also marketed as a sterile solution for injection and a cream and ovule/suppository for intravaginal administration. Clindamycin hydrochloride is marketed as an oral capsule, and clindamycin palmitate hydrochloride is marked as an oral solution.

2.4 Important Issues with Pharmacologically Related Products

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin. Pseudomembranous colitis has been reported as an adverse event with topical clindamycin phosphate therapy as well as with systemic therapy. All of the clindamycin phosphate products contain a warning describing the risk of pseudomembranous colitis.

2.5 Presubmission Regulatory Activity

PreIND Meeting: August 16, 2001

- Subjects should have a minimum of 20 comedones (non-inflammatory lesions) and 20 inflammatory lesions at baseline

PreIND Meeting: April 10, 2002

- 505(b)(2) application is an acceptable approval pathway for Clindamycin Phosphate Foam, 1%.
- Clindagel is an acceptable comparator drug product.
- Non-inferiority of Clindamycin Phosphate Foam, 1% versus Clindagel should be based on at least two of the three lesions counts (total, inflammatory, non-inflammatory) and an Investigator's Static Global Assessment score of 0 or 1.
- The Sponsor's proposed non-inferiority margin of 11% "should be acceptable."

Special Protocol Assessment

- The Investigator's Static Global Assessment should be dichotomized for analysis into two categories, "success" for patients with scores of 0 or 1, and "failure" for patients with scores of 2 and greater.
- Demonstration of efficacy rests upon reduction in at least two of the three lesion counts (total, inflammatory, non-inflammatory) and the Investigator's Static Global Assessment.
- Patients need a minimum of 20 inflammatory and 20 non-inflammatory lesions for enrollement.
- Analysis of superiority comparisons should use the intent-to-treat (last observation carried forward) [ITT (LOCF)] population and analyses of non-inferiority should be submitted for both the ITT (LOCF) and per-protocol (PP) populations.
- The Division strongly recommended a non-inferiority margin of 10%.
- The Subject's Global Assessment and the Dermatology Life Quality Index (DLQI) do not have regulatory utility for the indication the Sponsor seeks.

2.6 Other Relevant Background Information

This is a new formulation of clindamycin phosphate (aerosol foam) and is not approved in any country.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The Sponsor describes their product, Clindamycin Phosphate Foam, 1%, as,

"...a non-greasy, non-residue topical product...delivered in VersaFoam™, a quickbreaking, temperature sensitive, foam vehicle platform. Clindamycin Phosphate Foam contains clindamycin phosphate, cetyl alcohol, dehydrated alcohol, polysorbate 60, potassium hydroxide, propylene glycol, purified water, and stearyl alcohol pressurized in [redacted] container with a hydrocarbon

(propane/butane) propellant....The propane/butane propellant propels the product from the container and rapidly evaporates to expand the vehicle into a stable foam structure with temperature-dependent structural integrity. Upon contact of the foam with the skin, body temperature causes the foam structure to collapse, forming a solution."1

The composition of the to-be-marketed formulation is described in Table 1. This formulation was used in all of the clinical trials: phase 1 bioavailability study (CLN.C.001), phase 1 irritation and sensitization study (CLN.C.004), phase 2 efficacy and safety study (CLN.C.002) and phase 3 efficacy and safety pivotal trial (CLN.C.003).

Table 1: Composition of Clindamycin Phosphate Foam, 1%

Component	Function	Concentration w/w[a]%
Aqueous Phase		
Clindamycin phosphate	Active ingredient	—
Potassium hydroxide		
Purified water		
Ethanolic Phase		
Cetyl alcohol		
Dehydrated alcohol		
Polysorbate 60		
Propylene glycol		
Stearyl alcohol		

Source: Sponsor's NDA submission, module 2, volume 1.01, section 2.3, p.3.

The Chemistry review of NDA 21-709 was not available at the time of completion of this review.

3.2 Animal Pharmacology/Toxicology

The Sponsor relied on published literature and prior FDA findings of safety and effectiveness for the reference listed drug Clindagel. Portions of the Sponsor's proposed labeling follow.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenicity of a 1% clindamycin phosphate gel similar to Tradename was evaluated by daily application to mice for two years. The daily doses used in this study were approximately 3 and 15 times higher than the human dose of clindamycin phosphate from 5 milliliters of Tradename, assuming complete absorption and based on a body surface area comparison. No significant increase in tumors was noted in the treated animals

1 Sponsor's NDA submission, module 2, volume 1.01, section 2.3, pp.2-3.

A 1% clindamycin phosphate gel similar to Tradename caused a statistically significant shortening of the median time to tumor onset in a study in hairless mice in which tumors were induced by exposure to simulated sunlight.

Genotoxicity tests performed included a rat micronucleus test and an Ames Salmonella reversion test. Both tests were negative.

Reproduction studies in rats using oral doses of clindamycin hydrochloride and clindamycin palmitate hydrochloride have revealed no evidence of impaired fertility.

Pregnancy: Teratogenic effects - Pregnancy Category B

Reproduction studies have been performed in rats and mice using subcutaneous and oral doses of clindamycin phosphate, clindamycin hydrochloride and clindamycin palmitate hydrochloride. These studies revealed no evidence of fetal harm. The highest dose used in the rat and mouse teratogenicity studies was equivalent to a clindamycin phosphate dose of 432 mg/kg. For a rat, this dose is 84 fold higher, and for a mouse 42 fold higher, than the anticipated human dose of clindamycin phosphate from Tradename based on a mg/m2 comparison. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The Sponsor's NDA submission was the primary source of clinical data used in this review.

4.2 Tables of Clinical Studies

Table 2: Clinical Studies for Clindamycin Phosphate Foam, 1%

Study Number and Type	Objective	Study Design	Treatment	Number of Subjects	Treatment Duration
Phase 1					
CLN.C.001 bioavailability	Comparative absorption of Clindamycin Phosphate Foam, 1% versus Clindagel	Randomized, open-label	Clindamycin Phosphate Foam, 1%, self-administered 4 gms qAM by topical application to face, neck, upper chest and back	24 subjects with acne vulgaris	5 days
CLN.C.004 Irritation and sensitization	Cumulative irritation and sensitization with clindamycin phosphate foam	Evaluator-blinded patch-site testing	Clindamycin Phosphate Foam, 1%, 0..2mL applied on patches to backs of subjects 3 times weekly for 3 weeks followed by a single 48 hour patch application 2 weeks later	231 healthy subjects	3 weeks followed by 48 hours after a 2 week rest
Phase 2					
CLN.C.002 Safety and Efficacy	Safety and efficacy of Clindamycin Foam in the treatment of acne vulgaris	Multi-center, randomized, investigator-blinded, vehicle-controlled	Clindamycin Phosphate Foam, 1%, once daily, self-administered topical application of a sufficient amount to cover the entire face	130 subjects with acne vulgaris	12 weeks
Phase 3					
CLN.C.003 Safety and Efficacy	Safety and efficacy of Clindamycin Phosphate Foam, 1% versus Vehicle Foam versus Clindagel versus Vehicle Gel	Multi-center, randomized, double-blind, double-dummy, vehicle-controlled	Clindamycin Phosphate Foam, 1%, once daily, self-administered topical application of a sufficient amount to cover the entire face	1026 subject with acne vulgaris	12 weeks

Source: Sponsor's NDA submission module 5, volume 1.03, section 5.2, pp.1-2.

4.3 Review Strategy

The pivotal phase 3 trial, CLN.C.003, was reviewed in detail with regard to both efficacy and safety. The phase 2 trial, CLN.C.002, was also integral to the safety evaluation. All of the studies were reviewed with regard to safety, but the bulk of the drug exposure occurred in phases 2 and 3 (CLN.C.002 and CLN.C.003) and the integrated safety analysis focuses on data from these studies. Drug exposure in the phase 1 cutaneous safety study (CLN.C.004) was minimal; the main contribution of this study was to local irritancy and allergenicity rather than systemic safety or adverse events.

4.4 Data Quality and Integrity

Review of the pivotal trial data by this reviewer and the biostatistics reviewer did not reveal anomalous findings or sites. After consultation with a representative from the Division of Scientific Integrity (DSI), it was decided that no study site investigations were warranted.

4.5 Compliance with Good Clinical Practices

The Sponsor stated that all four studies were conducted in accordance with the ethical principles originating from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP Step 5 dated January 1996) and in compliance with local regulatory requirements. Additionally, the Sponsor affirmed that informed consent was obtained from all patients in each of the four clinical studies prior to any study procedures being performed.

4.6 Financial Disclosures

The Sponsor stated that investigators were required to submit financial disclosure forms. Three investigators received payments of a cumulative monetary value greater than $25,000 which required disclosure. To minimize any potential for bias, none of these three investigators were involved in database management and all remained blinded to the study outcome until study report finalization.

5 CLINICAL PHARMACOLOGY

The Clinical Pharmacology review of NDA 21-709 was not available at the time of completion of this review.

5.1 Pharmacokinetics

In an open label, parallel group study of 24 patients with acne vulgaris (CLN.C.001), 12 patients received Clindamycin Phosphate Foam, 1% once-daily topical administration of approximately 4 grams/day for five days resulting in peak plasma clindamycin concentrations that were less than 3.1 ng/ml. Following multiple applications of Clindamycin Phosphate Foam, 1%, less than 0.024% of the total dose was excreted in the urine. The Sponsor demonstrated that the extent of

systemic clindamycin absorption was lower following the Clindamycin Phosphate Foam administration compared to Clindagel administration. The mean Cmax and mean AUC(0-12) values in plasma on Day 5 were 25% and 9% lower, respectively, following the Clindamycin Phosphate Foam compared to Clindagel, while the amount excreted in urine during the first 12-hours postdose and the estimated renal clearance were 21% and 74% lower, respectively.

5.2 Pharmacodynamics

The Sponsor did not conduct pharmacodynamic studies. A section from the proposed labeling follows.

Microbiology: Although clindamycin phosphate is inactive *in vitro*, rapid *in (vivo)* hydrolysis converts this compound to clindamycin which has antibacterial activity. Clindamycin inhibits bacteria protein synthesis at the ribosomal level by binding to the 50S ribosomal subunit and affecting the process of peptide chain initiation. *In vitro* studies indicated that clindamycin inhibited all tested Propionibacterium acnes cultures at a minimum inhibitory concentration (MIC) of 0.4 µg/ml. Cross-resistance has been demonstrated between clindamycin and erythromycin

5.3 Exposure-Response Relationships

Dose-response was not studied. The Sponsor is pursuing approval via a 505(b)(2) application and selected the dose to correspond with the reference listed drug.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication for Clindamycin Phosphate Foam, 1%, is topical administration for the treatment of acne vulgaris.

6.1.1 Methods

The efficacy evaluation of Clindamycin Phosphate Foam, 1% is based on detailed review of pivotal trial CLN.C.003.

6.1.2 General Discussion of Endpoints

The Division of Dermatologic and Dental Drug Products has historically requested that sponsors use lesion counts (inflammatory, non-inflammatory and total) and an Investigators Global Assessment (IGA) as the co-primary efficacy assessments. Lesion counts are more precise and more objective than the IGA, and they can inform as to the lesion type which is most responsive to treatment, but their correlation with clinical relevance may not be linear, particularly in

subjects with greater numbers of baseline lesions or with small decreases in lesion numbers at endpoint evaluation. The IGA is less precise and less objective than are lesions counts, but it may be more clinically relevant.

Endpoints for evaluation of acne products were the subject of a Dermatologic and Dental Drug Advisory Committee meeting held on November 24 and 25, 2002. The Sponsor's development plan straddled this date and hence their endpoints deviate slightly but acceptably from current thinking. Current Division thinking on endpoints, informed by the Advisory Committee meeting discussion, follows.

The Agency recommends that the Investigator's Global Assessment (IGA) be a static evaluation of qualitative overall acne severity. The global assessment scale should be an ordinal scale with approximately six severity grades (reported only in integers, e.g., 0 to 5). Each grade should be defined by a distinct and clinically relevant morphologic description that minimizes inter-observer variability. The grades on the scale should be sufficiently defined to appropriately and unambiguously represent each severity grade on the scale. For consistency, the same IGA scale should be used throughout the study, including study enrollment, evaluation at endpoint, and for assessment of relapse. The scale should include descriptions of grades of acne more severe than those who will be enrolled to permit classification of subjects who worsen. The IGA scale should allow for dichotomization concerning 'Success' and 'Failure'. In general, the preferred definition of success for the IGA is achieving Grade 0 or 1 (i.e., clear or almost clear) at a pre-specified time point.

The IGA for CLN.C.003, entitled Investigator's Static Global Assessment, utilized a 6-point integer scale (0-5) with morphologic descriptors, shown in Table 3 below. It is consistent with Division thought as described above.

Table 3: Investigator's Static Global Assessment

Score	Definition
Grade 0	Normal, clear skin with no evidence of acne vulgaris
Grade 1	Skin almost clear: rare non-inflammatory lesions present, with rare, non-inflamed papules (papules must be resolving and may be hyper-pigmented, though not pink-red) requiring no further treatment in the investigator's opinion
Grade 2	Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only, no nodulo-cystic lesions)
Grade 3	Non-inflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules, and there may or may not be 1 small nodulo-cystic lesion
Grade 4	Inflammatory lesions are more apparent: many comedones and papules/pustules, there may or may not be a few nodulo-cystic lesions
Grade 5	Highly inflammatory lesions predominate: variable number of comedones, many papules/pustules and nodulo-cystic lesions

Source: Sponsor's NDA submission, module 5, volume 1.07, p.52.

For the acne vulgaris indication, non-inflammatory and inflammatory acne lesion counts are co-primary endpoints along with the IGA. When counting facial acne lesions, all lesions should be counted, including those present on the nose.

The Sponsor's co-primary endpoint, lesion counts, include total lesions in addition to non-inflammatory and inflammatory counts. This represents Division thinking prior to the Advisory committee meeting in Nov, 2002. The Sponsor did not count non-inflammatory lesions on the nose. The Division did not object to this in the Special Protocol Assessment.

6.1.3 Study Design

Pivotal Study: Protocol Number CLN.C.003

Title: A Phase III Multicenter, Randomized, Double-Blind, Double-Dummy, Vehicle-Controlled Study of the Safety and Efficacy of Clincamycin Phosphate Foam, 1%, versus Clindagel® (clindamycin phosphate gel) topical Gel, 1%, for the Treatment of Acne Vulgaris

Investigators

Table 4: Investigators for Study CLN.C.003

Site Number	Center	Patients Enrolled
C01	Alicia Barba, MD; Miami, FL	88
C02	Lawrence Eichenfield, MD; San Diego, CA	81
C03	Toni Funicella, MD; Austin, TX	88
C04	John Humeniuk, MD; Greer, SC	76
C05	Peter Lee, MD; Minneapolis, MN	57
C06	Anne Lucky, MD; Cincinnati, OH	75
C07	Robert Matheson, MD; Portland, OR	16
C08	Ronald Savin, MD; New Haven, CT	84
C09	Alan Shalita, MD; Brooklyn, NY	30
C10	Daniel Stewart, DO; Clinton Township, MI	39
C11	David Whiting, MD; Dallas, TX	76
C12	Steven Kempers, MD; Fridley, MN	25
C13	Christopher Nelson, MD; Pinellas Park, FL	18
C14	Jonathan Dosik, MD; Paramus, NJ	74
C15	Larry Gilderman, DO; Pembroke Pines, FL	30
C16	Jo Lynne Herzog, MD; Birmingham, AL	64
C17	Terry Jones, MD; Bryan, TX	70
C18	Joseph Fowler, Jr., MD; Louisville, KY	35

Source: Sponsor's NDA submission 21-709, vol. 1.07 p.198 and vol. 1.08 pp 724-5.

Objective

The primary objective of this study was to demonstrate the non-inferiority of Clindamycin Phosphate Foam, 1% (Clindamycin Foam) versus Clindagel® (clindamycin phosphate gel) Topical Gel, 1% based on lesion counts (total, inflammatory, and non-inflammatory) and an Investigator's Static Global Assessment. Additional objectives were to demonstrate the superiority of Clindamycin Foam versus Vehicle Foam based on lesions counts (total, inflammatory, and non-inflammatory) and an Investigator's Static Global Assessment, and to evaluate the safety of Clindamycin Foam.

Reviewer comment: The dual objectives of non-inferiority to Clindagel and superiority to vehicle are predicated on the 505(b)(2) approval pathway.

Overall Study Design

This study was conducted as a multicenter, randomized, double-blind, double-dummy, vehicle-controlled trial involving subjects 12 years and older with mild to moderate acne vulgaris. Qualified subjects who met specific enrollment criteria were randomized in a 3:1:3:1 ratio into one of four parallel treatment groups: Clindamycin Foam, Vehicle Foam, Clindagel, and Vehicle Gel. Subjects applied study drug treatment to the face (and neck, chest and back if affected) once daily for 12 weeks, with follow-up at weeks 3, 6, 9 and 12.

Protocol

Inclusion Criteria

- Male or female subjects 12 years of age or older in good general health
- An Investigator's Static Global Assessment score of 2 or greater at Baseline
- Subjects must have both:
    - A minimum of 17 but not more than 40 facial inflammatory lesions (papules plus pustules) including nasal lesions.
    - A minimum of 20 but not more than 150 facial non-inflammatory lesions (open and closed comedones), excluding nasal lesions.
- Pregnant and nursing women may be enrolled at the discretion of the investigator if the benefits of the study medication use outweigh the potential risks.
- The ability and willingness to follow all study procedures, attend all scheduled visits, and successfully complete the study.
- The ability to understand and sign a written informed consent form, which was to be obtained prior to treatment. Subjects under the legal age of consent in the state where the study was conducted were to provide assent and have the written, informed consent of a parent or guardian.

Reviewer comment: The Division recommended a minimum of 20 inflammatory lesions for inclusion in the study, as well as a minimum of 20 non-inflammatory lesions.

Exclusion Criteria

- Any active nodulo-cystic lesions at Baseline.
- History or presence of regional enteritis or inflammatory bowel disease (e.g., ulcerative colitis, pseudomembranous colitis, chronic diarrhea or a history of antibiotic-associated colitis) or similar symptoms.
- Use of topical antibiotics on the face within the past 4 weeks and during the conduct of the study. Use of systemic antibiotics within the past 4 weeks. Use of clindamycin within the past 4 weeks and during the conduct of the study.
- Use of topical steroids on the face or systemic steroids within the past 4 weeks and during the conduct of the study. Use of inhaled, intra-articular or intralesional steroids (other than for facial acne lesions) was acceptable.
- Use of systemic retinoids within the past 3 months.
- Concomitant use of neuromuscular blocking agents. Clindamycin has neuromuscular blocking activities, which may enhance the action of other neuromuscular blocking agents.
- Treatment with estrogens, including oral, implanted and topical contraceptives, or androgens for 12 weeks or less immediately prior to starting study medication. Subjects who had been treated with estrogens, as described above, or androgens for more than 12 consecutive weeks prior to start of study treatment were allowed to enroll as long as they did not expect to change dose, drug, or discontinue use during the study.
- Use of topical anti-acne medications (e.g. benzoyl peroxide, retinoids, azelaic acid, resorcinol, salicylates etc.) within the past 4 weeks and during the conduct of the study. This includes, but is not limited to Phiso Hex BP, Propa P.H., Stri-Dex pads, Sulfoxyl regular/strong.
- Concomitant use of the following types of facial products: abradents, facials, peels containing glycolic or other acid, masks, washes or soaps containing benzoyl peroxide or salicylic acid, non-mild facial cleansers, or moisturizers that contain retinol, salicylic or α- or β-hydroxy acids. Astringents and toners could have been used as long as the subject had been using the same regimen for at least 4 weeks and continued the regimen during the conduct of the study. The use of oil-free sunscreen was allowed as needed.
- Concomitant use of medications that are reported to exacerbate acne, (e.g. mega doses of certain vitamins, such as vitamin D, vitamin B12, haloperidol, halogens such as iodide and bromide, lithium, corticosteroids, hydantoin and phenobarbital) as these could have impacted efficacy assessments. Multivitamins, iron supplements, and folate were acceptable.
- Facial procedure (chemical or laser peel, microdermabrasion, etc.) performed by an esthetician, beautician, physician, nurse, or other practitioner, within the past 2 weeks or during the conduct of the study.
- Concomitant use of tanning booths or sunbathing.
- Known hypersensitivity or previous allergic reaction to any of the active components, lincomycin or excipients of either study medication (see Protocol Section 8.1, Appendix 16.1.1; or refer to Section 9.4.2 of this report).
- Use of any investigational therapy within the past 4 weeks.

- Current drug or alcohol abuse. (Drug screening was not required.)
- Any other condition which, in the judgment of the investigator, would have put the subject at unacceptable risk for participation in the study.

Withdrawal Criteria

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree, require discontinuation of drug, or both
- Unacceptable toxicitiy
- Subject noncompliance
- Subject request to withdraw

Blinding

Study CLN.C.003 was designed as a randomized, double-blind, double-dummy, vehicle-controlled study. Connetics personnel, investigators and staff, and subjects were blinded to whether subjects received active or vehicle treatments. To maintain the study blind, the active and vehicle foams were packaged and labeled identically, as were the active and vehicle gels. The subject and nurses/coordinators would be aware of which dosage form (foam or gel) the subject received, but would not know whether it was an active or vehicle formulation. The subjects and nurses/coordinators were instructed not to discuss the dosage form with the investigator. The foam treatments (active and vehicle) and gel treatments (active and vehicle) were packaged in identically-appearing subject kits so that the investigator would not know, based on the appearance of the kits, which dosage form the subject received (foam or gel).

Reviewer comment: The terms "double dummy" and "double blind" should be understood in this limited sense.

Study Procedures

Subjects were to be instructed to apply their study drug consistently in the mornings or in the evenings throughout the 12 weeks of the study. Subjects were instructed to apply a sufficient amount of study medication to cover the entire face (including forehead, nose, cheeks and chin). Subjects with neck, upper chest and/or upper back acne, were allowed to apply study medication to these areas as well as to the face, although only facial acne was to be included in the efficacy evaluations. All subjects were to wash their faces with a mild soap, and allow the skin to fully dry before applying study medication. The study medication was to be applied prior to the application of any other skin products that the subject habitually used, such as moisturizers, cosmetics (only powder-based, oil-free formulations were allowed), or sun-protective products. Other than the study medication, no concomitant treatment of acne vulgaris on the face or other body areas was allowed. Table 5 documents the assessments that were to be made throughout the trial.

Table 5: Schedule of Efficacy and Safety Evaluations

Parameter	Visit 1 (Baseline) Week 0 Day 1	Visit 2 Week 3 Day 22±5 d	Visit 3 Week 6 Day 43±5 d	Visit 4 Week 9 Day 64±5 d	Visit 5 or Study Termination Week 12 Day 85±5 d
Efficacy variables					
Lesion count	X	X	X	X	X
Investigator's Static Global Assessment	X	X	X	X	X
Subject's Global Assessment	X	X	X	X	X
Clinical Photography (selected sites)	X		X	X	X
Dermatology Life Quality Index (DLQI or CDLQI)	X				X
Safety Variables					
Signs and symptoms	X	X	X	X	X
Laboratory Assessments (selected sites)	X				X
Adverse experience query	X	X	X	X	X
Urine pregnancy test (all females)	X				X

Source: Sponsor's NDA submission, module 5, volume 1.07, p.50.

Efficacy Endpoints

The primary efficacy endpoints were success rate, defined as the proportion of subjects who have an Investigator's Static Global Assessment score of 0 or 1 at Week 12 (end of treatment), and the percent change in lesions counts (inflammatory, non-inflammatory and total) from Baseline to Week 12 (end of treatment). The primary efficacy variables included Investigator's Static Global Assessment and lesion counts (inflammatory, non-inflammatory and total). These were collected at Baseline and weeks 3, 6, 9 and 12, although the primary efficacy timepoint was week 12. If possible, the same efficacy assessor was to perform all efficacy assessments on the same subject at all visits. Any person responsible for conducting efficacy assessments was required to attend a lesion count training session, as well as to be trained on the definitions for the Investigator's Static Global Assessment.

The Investigator's Static Global Assessment utilized a 6-point integer scale (0-5) with morphologic descriptors, shown in Table 6 below.

Table 6: Investigator's Static Global Assessment Scale

Score	Definition
Grade 0	Normal, clear skin with no evidence of acne vulgaris
Grade 1	Skin almost clear: rare non-inflammatory lesions present, with rare, non-inflamed papules (papules must be resolving and may be hyper-pigmented, though not pink-red) requiring no further treatment in the investigator's opinion
Grade 2	Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only, no nodulo-cystic lesions)
Grade 3	Non-inflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules, and there may or may not be 1 small nodulo-cystic lesion
Grade 4	Inflammatory lesions are more apparent: many comedones and papules/pustules, there may or may not be a few nodulo-cystic lesions
Grade 5	Highly inflammatory lesions predominate: variable number of comedones, many papules/pustules and nodulo-cystic lesions

Source: Sponsor's NDA submission, module 5, volume 1.07, p.52.

The guidelines for counting lesions were as follows:

- The same person was to perform all lesion counts on a given subject as the subject progressed through the study, in order to ensure consistency.
- Only lesions on the face were to be included in these assessments. The face was defined as extending from the hairline to the mandibular line.
- Non-inflammatory lesions (comedones) on the nose were not to be counted.

Secondary/tertiary efficacy assessments include Subject's Global Assessment (SGA) and the Dermatology Life Quality Index (DLQI or CDLQI). The Subject's Global Assessment was obtained at Baseline and weeks 3, 6, 9, and 12, and the Dermatology Life Quality Index at Baseline and week 12.

Secondary Endpoints include:

1. The absolute change in lesion counts (total, inflammatory, non-inflammatory) from Baseline to Week 12.
2. The proportion of subjects who have a Subject's Global Assessment score of 0 or 1 at Week 12.
3. The change in the Subject's Global Assessment from Baseline to Week 12.

The Subject's Global Assessment utilized a five-point scale described in table 7 below.

Table 7: Subject's Global Assessment Scale

Score	Definition
0	My face is basically free of acne, with only an occasional blackhead and/or whitehead
1	My face has several blackheads and/or whiteheads and small pimples, but there are n o tender deep-seated bumps or cycsts
2	My face has several to many blackheads and/or whiteheads and small to medium-sized pimples, and may have one dep-seated bump or cyst
3	My face has many blackheads and/or whiteheads, many medium to large-sized pimples, and perhaps a few deep-seated bumps or cysts
4	My face has blackheads and/or whiteheads, and several to many medium to large-sized pimples and deep-seated bumps or cysts dominate

Source: Sponsor's NDA submission, module 5, vol. 1.08, p.454.

Reviewer comment: The Sponsor was informed that the SGA and the DLQI/CDLQI would not have regulatory utility. These endpoints are not discussed further.

Tertiary endpoints (for which only descriptive analysis was performed) include:

1. The proportion of subjects who have an Investigator's Static Global Assessment score of 0 or 1 at Weeks 3, 6 and 9.
2. The percent (%) change in lesion counts (total, inflammatory, non-inflammatory) from Baseline to Weeks 3, 6 and 9.
3. The absolute change in lesion counts (total, inflammatory, non-inflammatory) from Baseline to Weeks 3, 6 and 9.
4. The proportion of subjects who have a Subject's Global Assessment score of 0 or 1 at Week 3, 6, and 9.
5. The change in the Subject's Global Assessment from Baseline to Weeks 3, 6, and 9.
6. The change in quality of life as measured by the Dermatology Life Quality Index (DLQI) or Children's Dermatology Life Quality Index (CDLQI) from Baseline to Week 12.

Reviewer comment: The tertiary endpoints are not discussed further.

6.1.4 Efficacy Findings

A total of 1026 subjects from 18 investigative sites were enrolled and randomized to receive treatment with Clindamycin Foam, Clindagel, Vehicle Foam or Vehicle Gel.

Table 8: Disposition of Study Subjects, Study CLN.C.003

Disposition	**Clindamycin Foam N (%)**	**Clindagel N (%)**	**Vehicle Foam N (%)**	**Vehicle Gel N (%)**	**Total N (%)**
Randomized	386 (100)	385 (100)	127 (100)	128 (100)	1026 (100)
ITT population	386 (100)	385 (100)	127 (100)	128 (100)	1026 (100)
PP population	336 (87)	336 (87)	110 (87)	108 (84)	890 (87)
Completed study	344 (89)	346 (90)	112 (88)	113 (88)	915 (89)
Discontinued study early	44 (11)	39 (10)	15 (12)	15 (12)	111 (11)
Adverse experience	2 (1)	0 (0)	1 (1)	0 (0)	3 (3)
Non-compliance	3 (1)	2 (1)	0 (0)	3 (2)	8 (7)
Disease progression	0 (0)	0 (0)	1 (0)	0 (0)	1 (1)
Subject request	15 (4)	15 (4)	6 (5)	6 (5)	42 (38)
Other	22 (6)	22 (6)	7 (6)	6 (5)	57 (51)

Source: Sponsor's NDA submission, module 5, volume 1.07, pp.87, 90.

Of the 1026 randomized subjects, 136 were excluded from the Per-Protocol population. These subjects were distributed by treatment groups as follows: 51 subjects in the Clindamycin Foam group, 51 subjects in the Clindagel group, and 17 subjects the Vehicle Foam group and 21 subjects in the Vehicle Gel group. Reasons for exclusion included missing greater than 16 total study doses (101 subjects), failure to meet entry criteria without obtaining an exemption to participate (11 subjects), failure to undergo efficacy evaluations at the baseline and week 12 visits (10 subjects), unblinding of treatment modality (foam or gel; 8 subjects), use of prohibited medications (7 subjects), use of the wrong study treatment (1 subject) and incorrect dosing (1 subject). Three subjects who missed greater than 16 total study doses also had a second reason for exclusion (one subject also failed to meet entry criteria and two subjects also used prohibited medications). One subject (No. 03-0462; Clindagel) was dispensed and used study drug from the wrong study kit (No. 03-0460; Clindagel) between Weeks 3 and 6.

Patient demographics are outlined in Table 9.

Table 9: Demographic Characteristics of Study Subjects, ITT Population, Study CLN.C.003

Demographic Parameter	Clindamycin Foam N (%)	Clindagel N (%)	Vehicle Foam N (%)	Vehicle Gel N (%)	p-value
Age					
Mean (std)	19.1 (6.4)	18.7 (6.1)	18.8 (6.3)	18.9 (7.3)	0.5811
Median	17.0	17.0	16.0	16.0	
Age Category					
12-16 years	189 (49)	192 (50)	67 (53)	68 (53)	0.7969
17-65 years	197 (51)	193 (50)	60 (47)	60 (47)	
Gender					
Male	180 (47)	175 (45)	59 (46)	62 (48)	0.9483
Female	206 (53)	210 (55)	68 (54)	66 (52)	
Race					
Asian	4 (1)	5 (1)	1 (1)	3 (2)	0.9703
Caucasian	252 (65)	242 (63)	84 (66)	79 (62)	
Black	68 (18)	69 (18)	25 (20)	22 (17)	
Hispanic	56 (15)	65 (17)	16 (13)	22 (17)	
Other	6 (2)	4 (1)	1 (1)	2 (2)	

Source: Sponsor's NDA submission, module 5, volume 1.07, p.92.

Reviewer comment: Age, race and gender appear to be comparably distributed across the study arms. There is adequate enrollment of adolescents aged 12 to 16 years. Racial enrollment approximates that of the US population.

Baseline disease severity is outlined in Table 10.

Table 10: Disease Characteristics at Baseline, ITT Population, Study CLN.C.003

	Clindamycin Foam	Clindagel	Vehicle Foam	Vehicle Gel	p-value
Number of Subjects	386	385	127	128	
Total Lesions					
mean (std)	71.6 (28.1)	73.9 (29.2)	72.1 (31.0)	72.2 (27.6)	0.5479
median	64.0	66.0	63.0	63.5	
Inflammatory Lesions					
mean (std)	25.9 (7.0)	26.0 (7.5)	25.2 (6.9)	26.4 (7.7)	0.6315
median	24.0	24.0	23.0	24.5	
Non-inflammatory Lesions					
mean (std)	45.7 (25.6)	47.9 (27.0)	46.9 (28.8)	45.8 (24.7)	0.7245
median	38.5	41.0	37.0	37.5	
Investigator's Static Global Assessment Score N (%)					
2	137 (35)	141 (37)	51 (40)	56 (44)	0.3502
3	210 (54)	216 (56)	65 (51)	58 (45)	
4	39 (10)	28 (7)	11 (9)	14 (11)	

Source: Sponsor's NDA submission, module 5, volume 1.07, p.93.

Reviewer comments: Acne severity at Baseline, as measured by lesions counts (total, inflammatory and non-inflammatory) and Investigator's Static Global Assessment Score, is similar across all four study arms.

Efficacy Endpoint Outcomes

Success Rate

Table 11: Investigator's Static Global Assessment: Subjects with Success at Week 12, Sponsor's Analysis

	Clindamycin Foam	**Clindagel**	**Vehicle Foam**	**Vehicle Gel**
Number of Subjects	386	385	127	128
ITT, LOCF				
Success[a]	120 (31%)	105 (27%)	23 (18%)	26 (20%)
Confidence Limit[b]		-2.60%, 10.23%		
p-Value[c]			0.0025	
p-Value[d]				0.1118
PP, LOCF				
Success[a]	117 (35%)	99 (29%)	23 (21%)	23 (21%)
Confidence Limit[b]		-1.69%, 12.41%		
p-Value[c]			0.0030	

Source: Sponsor's NDA submission module 5, volume 1.07, p.100.
[a]Success is defined as the proportion of subjects who have an Investigator's Static Global Assessment score of 0 or 1 at Week 12 (or end of treatment).
[b]Two sided 95% confidence interval for the difference in success rate between Clindamycin Foam and Clindagel.
[c]p-value is derived from Cochran-Mantel_Haenszel test (α=0.05) stratified by site and compares Clindamycin Foam against Vehicle Foam.
[d]p-value is derived from Cochran-Mantel_Haenszel test (α=0.05) stratified by site and compares Clindagel against Vehicle Gel.

Table 12: Investigator's Static Global Assessment: Subjects with Success at Week 12, ITT, LOCF, FDA Analysis

	Clindamycin Foam	**Clindagel**	**Vehicle Foam**	**Vehicle Gel**
Number of Subjects	386	385	127	128
Success[a]	31.1%	27.3%	18.1%	20.3%
Confidence Limit[b]		-2.3, 9.8		
p-Value[c]			0.0025	
p-Value[d]				0.1118

Source: Dr. Steven Thomson, Biostatistician, FDA.
[a]Success is defined as the proportion of subjects who have an Investigator's Static Global Assessment score of 0 or 1 at Week 12 (or end of treatment).
[b]Clindamycin Foam versus Clindagel – non-inferiority bounds at Week 12 (or end of treatment).
[c]p-value compares Clindamycin Foam against Vehicle Foam.
[d]p-value compares Clindagel against Vehicle Gel.

Reviewer comment: By both the Sponsor's analysis and the FDA biostatistician's analysis, Clindamycin Foam is superior to vehicle and non-inferior to Clindagel as assessed by success rate (ISGA dichotomized to success and failure).

Table 13: Percent Reduction in Lesions counts from Baseline to Week 12, ITT (LOCF), Sponsor's Analysis

	Clindamycin Foam	Clindagel	Vehicle Foam	Vehicle Gel
Number of Subjects	386	385	127	128
Total Lesions				
n[a]	385	384	127	128
Mean (std)	42.8 (27.5)	35.7 (31.6)	30.5 (29.6)	27.6 (34.4)
Confidence limit[b]		3.03%, 11.20%		
p-value[c]			<0.0001 <0.0001	
Inflammatory Lesions				
n[a]	385	384	127	128
Mean (std)	49.0 (37.1)	45.0 (37.6)	34.7 (37.5)	36.6 (40.5)
Confidence limit[d]		-0.97%, 9.17%		
p-value[c]			0.0001 <0.0001	
Non-inflammatory Lesions				
n[a]	386	384	127	128
Mean (std)	38.3 (31.7)	30.2 (28.8)	27.1 (38.4)	20.8 (45.8)
Confidence limit[e]		3.25%, 13.03%		
p-value[c]			0.0018 0.0038	

Source: Sponsor's NDA submission, module 5, volume 1.07, p.103.
[a]Due to subjects who had missed Baseline lesion evaluations, there is an inconsistency in the n for individual treatment groups for lesions counts (total, inflammatory, and non-inflammatory).
[b]Two-sided 95% confidence interval for the difference in mean percent reduction between Clindamycin Foam and Clindagel for total lesions.
[c]P-values are derived from a parametric ANOVA model (top) and a rank-transformed model (bottom) (α=0.05) with terms for treatment and site and compare Clindamycin Foam against Vehicle Foam.
[d]Two-sided 95% confidence interval for the difference in mean percent reduction between Clindamycin Foam and Clindagel for inflammatory lesions.
[e]Two-sided 95% confidence interval for the difference in mean percent reduction between Clindamycin Foam and Clindagel for non-inflammatory lesions.

Table 14: Percent Reduction in Lesions counts from Baseline to Week 12, PP Population, Sponsor's Analysis

	Clindamycin Foam	Clindagel	Vehicle Foam	Vehicle Gel
Number of Subjects	336	336	110	108
Total Lesions				
Mean (std)	46.0 (26.2)	38.7 (31.6)	33.6 (30.0)	28.2 (35.5)
Confidence limit[a]		3.13%, 11.76%		
p-value[b]			<0.0001 0.0002	
Inflammatory Lesions				
Mean (std)	53.0 (35.6)	48.9 (37.1)	39.5 (36.5)	38.5 (39.8)
Confidence limit[c]		-0.75%, 9.78%		
p-value[b]			0.0002 <0.0001	
Non-inflammatory Lesions				
Mean (std)	41.2 (31.2)	32.8 (39.3)	29.1 (39.9)	20.3 (48.1)
Confidence limit[d]		3.10%, 13.68%		
p-value[b]			0.0026 0.0057	

Source: Sponsor's NDA submission, module 5, volume 1.07, p.107.
[a]Two-sided 95% confidence interval for the difference in mean percent reduction between Clindamycin Foam and Clindagel for total lesions.
[b]P-values are derived from a parametric ANOVA model (top) and a rank-transformed model (bottom) (α=0.05) with terms for treatment and site and compare Clindamycin Foam against Vehicle Foam.
[c]Two-sided 95% confidence interval for the difference in mean percent reduction between Clindamycin Foam and Clindagel for inflammatory lesions.
[d]Two-sided 95% confidence interval for the difference in mean percent reduction between Clindamycin Foam and Clindagel for non-inflammatory lesions.

Table 15: Percent Reduction in Lesions counts from Baseline to Week 12, ITT (LOCF), FDA Analysis

	Clindamycin Foam	Clindagel	Vehicle Foam	Vehicle Gel
Number of Subjects	386	385	127	128
Total Lesions				
Mean (std)	42.8 (27.5)	35.7 (31.6)	30.6 (29.6)	27.7 (34.3)
Confidence limit[a]		3.3%, 11.7%		
p-value[b]			<0.0001	
Inflammatory Lesions				
Mean (std)	49.2 (36.8)	45.2 (37.6)	35.0 (37.3)	37.0 (40.2)
Confidence limit[a]		-0.6%, 9.7%		
p-value[b]			<0.0001	
Non-inflammatory Lesions				
Mean (std)	38.3 (31.7)	30.2 (38.8)	27.1 (38.4)	20.8 (45.8)
Confidence limit[a]		3.1%, 13.5%		
p-value[b]			0.0014	

Source: Source: Dr. Steven Thomson, Biostatistician, FDA.
[a]Two-sided 95% confidence interval for the difference in mean percent reduction between Clindamycin Foam and Clindagel for respective lesions.
[b]P-values compare Clindamycin Foam against Vehicle Foam, superiority test from ANOVA contrast.

Reviewer comment: In both the ITT (LOCF) and the PP populations, and by both the Sponsor's and the FDA biostatistician's analyses, Clindamycin Foam was superior to Vehicle Foam in percent reduction of all three lesions counts (total, inflammatory and non-inflammatory). Similarly, in both the ITT (LOCF) and PP populations, Clindamycin Foam was non-inferior to Clindagel in percent reduction of all three lesions counts (total, inflammatory and non-inflammatory), regardless of whether a 10% bound (Division preference) or 11% bound (Sponsor's preference) is used.

Subgroup analysis of efficacy results revealed a trend toward lower efficacy among men, adolescents 12 to 16 years of age and blacks (see Table 15, below). Success rate at 12 weeks in the Clindamycin Foam group was higher among females (38%) than males (23%), and males failed to beat Vehicle Foam for this endpoint but the study was not powered for this analysis. Similarly, success rate at 12 weeks in the Clindamycin Foam group was higher among subjects 17 – 65 years (41%) than subjects 12 – 16 years (21%), and subjects 12 – 16 years failed to beat Vehicle Foam for this endpoint but the study was not powered for this analysis.

In blacks, Vehicle Gel beat Clindamycin Foam for success rate and percent reduction in total and inflammatory lesion counts.

Table 16: Investigator's Static Global Assessment: subgroup analyses for success at 12 weeks, ITT population

	Clindamycin Foam	Clindagel	Vehicle Foam	Vehicle Gel
Males				
Number of subjects	180	175	59	62
Success	42 (23%)	44 (25%)	8 (14%)	12 (19%)
Confidence limit[a]		-10.73%, 7.11%		
P-value[b]			0.2488	
Females				
Number of subjects	206	210	68	66
Success	78 (38%)	61 (29%)	15 (22%)	14 (21%)
Confidence limit[a]		-0.22%, 17.85%		
P-value[b]			0.0042	
Age 12 – 16 Years				
Number of subjects	189	192	67	68
Success	40 (21%)	45 (23%)	7 (10%)	12 (18%)
Confidence limit[a]		-10.63%, 6.08%		
P-value[b]			0.0594	
Age 17 – 65 Years				
Number of subjects	197	193	60	60
Success	80 (41%)	60 (31%)	16 (27%)	14 (23%)
Confidence limit[a]		0.05%, 18.99%		
P-value[b]			0.0240	
Black Race				
Number of subjects	68	69	25	22
Success	18 (26%)	15 (22$)	3 (12%)	8 (36%)

[a]Two-sided 95% confidence interval for the difference in success rate between Clindamycin Foam and Clindagel.
[b]P-value is derived from cochran-Mantel-Haenszel test (α=0.05) stratified by site and compares Clindamycin Foam against Vehicle Foam.
Source: Sponsor's NDA submission, module 5, vol. 1.07, pp.289-95.

Reviewer comment: Because the study was not powered for the subgroup analysis, the significance and clinical relevance of the trends is not clear.

6.1.5 Clinical Microbiology

The Sponsor did not perform any clinical microbiology studies. The following is taken from the Clinical Pharmacology, Microbiology section of the reference listed drug for this application (Clindagel):

> Although clindamycin phosphate is inactive in vitro, rapid in vitro hydrolysis converts this compound to clindamycin which has antibacterial activity. Clindamycin inhibits bacteria protein synthesis at the ribosomal level by binding to the 50S ribosomal subunit and affecting the process of peptide chain initiation. In vitro studies indicated that clindamycin inhibited all tested *Propionibacterium acnes* cultures at a minimum inhibitory concentration (MIC) of 0.4 µg/ml. Cross-resistance has been demonstrated between clindamycin and erythromycin.

6.1.6 Efficacy Conclusions

Clindamycin Phosphate Foam, 1% is superior to Vehicle Foam and non-inferior to Clindagel in the treatment of acne vulgaris in subjects 12 years of age and older, as assessed by success rate (ISGA dichotomized to success and failure) and percent reduction in lesions counts (total, inflammatory and non-inflammatory). The conclusions are robust.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety review of Clindamycin Phosphate Foam, 1% will focus on adverse events, systemic safety (laboratory evaluation), and local safety (local signs and symptoms of facial acne in Phase 2 and Phase 3 studies, and cutaneous irritancy and allergenicity in Phase 1 repeat insult patch test study). Adverse events in the comparator arm, Clindagel, have not been included unless necessary for comparison.

7.1.1 Deaths

No subjects died in any of the four clinical studies (CLN.C.001, CLN.C.002, CLN.C.003, CLN.C.004).

7.1.2 Other Serious Adverse Events

Table 17 describes the incidence of serious adverse events (SAE) in pivotal trial CLN.C.003, excluding the comparator arm. None of the serious adverse events were considered by the investigators to be related to study drug use.

Table 17: Incidence of SAEs Classified by MedDRA System Organ Class and Preferred Term, Safety Population

	Clindamycin Foam	**Vehicle Foam**
Number of Subjects	439	154
Subjects with a SAE	1 (0%)	1 (1%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS		
Dermoid cyst NOS	**1 (0%)**	0 (0%)
PSYCHIATRIC DISORDERS		
Bipolar disorder NEC	0 (0%)	**1 (1%)**

Source: Sponsor's NDA submission, module 2, volume 1.01, section 2.7.4, p.41.

No SAEs occurred in studies CLN.C.001, CLN.C.002 or CLN.C.004.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Table 18: Reason for Study Drug Discontinuation, CLN.C.002 and CLN.C.003 (ITT Population)

	Clindamycin Foam	**Clindagel**	**Vehicle Foam**	**Vehicle Gel**
Number of Subjects	439	435	154	128
Subjects who Completed Study	391 (39%)	392 (90%)	134 (87%)	113 (88%)
Subjects who Discontinued	48 (11%)	43 (10%)	20 (13%)	14 (12%)
Reasons for Discontinuation				
Adverse Event	2 (0%)	1 (0%)	2 (1%)	0 (0%)
Subject Non-compliance	3 (1%)	4 (1%)	0 (0%)	3 (2%)
Disease Progression	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Subject Request to Withdraw	17 (4%)	16 (4%)	9 (6%)	6(5%)
Subject Died	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other Reason	26 (6%)	22 (5%)	8 (5%)	6 (5%)

Source: Sponsor's NDA submission, module 2, vol 1.01, p.42.

7.1.3.2 Adverse events associated with dropouts

Five subjects discontinued study drug due to AEs: 2/439 in the Clindamycin Foam group (contact dermatitis of the eyes, 1 subject, and moderate facial itching, 1 subject), 1/435 in the Clindagel group (severe application site dryness), 2/154 in the Vehicle Foam group (moderate application site burning, 1 subject, uncontrolled bipolar disorder, 1 subject), 0/128 in the Vehicle

Gel group. For the subject in the Vehicle Foam group with uncontrolled bipolar disorder, the investigator assessed this AE as probably not related to study drug, as the subject had abruptly discontinued medication for the bipolar disorder. However, in the remaining four subjects, the AEs that resulted in discontinuation may have been related to study drug use. In the subjects in the Clindamycin Foam group, the onset of the AE that resulted in study drug discontinuation occurred at 3 weeks (contact dermatitis of the eyes) and 6 weeks (facial itching).

7.1.3.3 Other significant adverse events

None identified.

7.1.4 Other Search Strategies

Table 19 describes the incidence of severe AEs in the safety population. None of the severe adverse events were considered by the investigators to be related to study drug use.

Table 19: Incidence of Severe AEs Classified by MedDRA System Organ Class and Preferred Term, Safety Population

	Clindamycin Foam	**Vehicle Foam**
Number of Subjects	439	154
Subjects with a severe AE	**4 (1%)**	**2 (1%)**
CONGENITAL, FAMILIAL AND GENETIC DISORDERS		
Dermoid cyst NOS	**1 (0.2%)**	0 (0%)
GASTROINTESTINAL DISORDERS		
Food poisoning NOS	0 (0%)	**1 (1%)**
Nausea	0 (0%)	**1 (1%)**
Vomiting NOS	0 (0%)	**1 (1%)**
INFECTIONS AND INFESTATIONS		
Influenza	**1 (0.2%)**	0 (0%)
Sinusitis NOS	0 (0%)	**1 (1%)**
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Post procedural pain	**1 (0.2%)**	0 (0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Tendon rupture	**1 (0.2%)**	0 (0%)
NERVOUS SYSTEM DISORDERS		
Dizziness	0 (0%)	**1 (1%)**
Headache NOS	**1 (0.2%)**	0 (0%)
Syncope	0 (0%)	**1 (1%)**
PSYCHIATRIC DISORDERS		
Bipolar disorder NEC	0 (0%)	**1 (1%)**

Source: Sponsor's NDA submission, module 2, volume 1.01, section 2.7.4, pp.38-40, and reviewer's calculations (for those AEs occurring in less than 1% of subjects).

Local Safety

In the pivotal trial, Study CLN.C.003, investigators actively assessed for what the Sponsor termed the signs (scaling, dryness, erythema, oiliness) and symptoms (burning, itching) of acne. These signs and symptoms were assessed at baseline and weeks 3, 6, 9, and 12 (or end of study for subjects who terminated early) according to the scales below (tables 20 and 21).

Table 20: Scale for Evaluation of Signs: Scaling, Dryness, Erythema, Oiliness

Scale	Numeric Value	Category Descriptor
None	0	Normal
Trace	1	Mild and localized
Mild	2	Mild and diffuse
Moderate	3	Moderate and diffuse
Marked	4	Moderate and dense
Severe	5	Prominent and dense

Source: Sponsor's NDA submission, module 5, volume 1.08, p.34.

Table 21: Scale for Evaluation of Symptoms: Burning, Itching

Scale	Numeric Value	Category Descriptor
None	0	Normal, no discomfort
Trace	1	An awareness, but no discomfort and no intervention required
Mild	2	A noticeable discomfort that causes intermittent awareness
Moderate	3	A noticeable discomfort that causes continuous awareness
Marked	4	A definite discomfort that causes continuous awareness and interferes occasionally with normal daily activities
Severe	5	A definite continuous discomfort that interferes with normal daily activities

Source: Sponsor's NDA submission, module 5, volume 1.08, p.34.

Table 22 summarizes the change in score for the six signs/symptoms from baseline to week 12 for the ITT population.

Table22: Change from Baseline for Acne Signs/Symptoms, Study CLN.C.003, ITT Population

		Clindamycin Foam	Vehicle Foam
Scaling			
Baseline	n	386	127
	mean (std)	0.2 (0.5)	0.2 (0.4)
Change at Week 12	n	348	114
	mean (std)	-0.1 (0.5)	0.0 (0.6)
Dryness			
Baseline	n	386	127
	mean (std)	0.2 (0.6)	0.2 (0.5)
Change at Week 12	n	348	114
	mean (std)	-0.1 (0.6)	0.1 (0.6)
Erythema			
Baseline	n	386	127
	mean (std)	0.7 (1.0)	0.7 (0.9)
Change at Week 12	n	348	114
	mean (std)	-0.3 (0.8)	-0.3 (0.6)
Oiliness			
Baseline	n	386	127
	mean (std)	1.4 (1.3)	1.2 (1.2)
Change at Week 12	n	348	114
	mean (std)	-0.6 (1.0)	-0.4 (1.1)
Burning			
Baseline	n	386	127
	mean (std)	0.1 (0.4)	0.1 (0.3)
Change at Week 12	n	348	114
	mean (std)	0.0 (0.5)	0.1 (0.5)
Itching			
Baseline	n	386	127
	mean (std)	0.3 (0.7)	0.2 (0.5)
Change at Week 12	n	348	114
	mean (std)	-0.2 (0.7)	-0.2 (0.8)

Source: Compiled from Sponsor's NDA submission, module 5, vol. 1.07, pp.389-394.

Baseline mean scores were identical (scaling, dryness, erythema, burning) or very similar (oiliness, itching) between the Clindamycin Foam and Vehicle Foam groups. For all six parameters, in both the active and vehicle groups, the mean change at week 12 was less than one. Additionally, the difference in the mean change at week 12 between the active and vehicle groups was 0.2 or less for each parameter.

Local Safety – Cutaneous Irritancy and Allergenicity

The results of the repeat-insult patch test study to evaluate cutaneous irritancy and allergenicity are presented in section 7.1.12, Special Safety Studies

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In all of the clinical studies (CLN.C.001, CLN.C.002, CLN.C.003, CLN.C.004), investigators were to instruct subjects to report any physical changes or new symptoms noticed during the study, and investigators were to record AEs at each visit following the baseline visit. In studies CLN.C.002 and CLN.C.003, investigators also actively assessed scaling, dryness, erythema, oiliness, burning, and itching; these results are discussed in section 7.1.4, Other Search Strategies.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The Sponsor's categorization of AEs and use of preferred terms appears reasonable.

7.1.5.3 Incidence of common adverse events

Table 23 summarizes the adverse events that occurred in >1% of subjects in the safety population.

Table 23: Summary of AEs Occuring in >1% of Subjects, Safety Population

	Clindamycin Foam	**Vehicle Foam**
Number of subjects	439	154
Subjects with an AE	128 (29%)	**50 (32%)**
Nasopharyngitis	15 (3%)	**8 (5%)**
Application site burning	27 (6%)	**14 (9%)**
Upper respiratory tract infection NOS	9 (2%)	3 (2%)
Headache NOS	**12 (3%)**	1 (1%)
Sinusitis NOS	11 (3%)	**6 (4%)**
Application site dryness	4 (1%)	**5 (3%)**
Application site pruritus	5 (1%)	**5 (3%)**
Application site reaction NOS	3 (1%)	**4 (3%)**

Source: Sponsor's NDA submission, module 2, volume 1.01, section 2.7.4, p.30.

The proportion of subjects who reported an adverse event was slightly higher among subjects treated with Vehicle Foam. More subjects treated with Vehicle Foam reported application site burning, dryness, pruritus, and reactions NOS than did subjects treated with Clindamycin Foam; all of the application site reactions were attributed as related to study drug by the investigators, and are discussed below.

Table 24 lists adverse events that investigators ascribed as related to study drug use.

Table 24: Summary of AEs Related to Study Drug, Safety Population

	Clindamycin Foam	Vehicle Foam	p-value[a]
Number of Subjects	439	154	
Subjects w/a treatment-related AE	33 (8%)	**23 (15%)**	0.0068
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	31 (7%)	**22 (14%)**	0.0069
Application site burning	27 (6%)	**14 (9%)**	0.2159
Application site desquamation	1 (0.2%)	**1 (1%)**	
Application site dryness	4 (1%)	**5 (3%)**	
Application site irritation	0 (0%)	**1 (1%)**	
Application site pruritus	5 (1%)	**5 (3%)**	
Application site reaction NOS	3 (1%)	**4 (3%)**	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0%)	**1 (1%)**	
Sunburn	0 (0%)	**1 (1%)**	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**2 (0.5%)**	0 (0%)	
Dermatitis allergic	**1 (0.2%)**	0 (0%)	
Dermatitis contact	**1 (0.2%)**	0 (0%)	

Source: Sponsor's NDA submission module 2, volume 1.01, section 2.7.4, pp.36-37, and reviewer's calculations (for AEs occurring in >1% of subjects).
[a]p-values are based on comparing Clindamycin Foam versus Vehicle Foam using the chi-square test (α=0.10) and are calculated when the incidence is $\geq$5% in any treatment group.

A significantly greater proportion of subjects treated with Vehicle Foam compared to Clindamycin Foam experienced AEs that the investigator related to study drug use. The majority of these AEs were application site reactions. The proportion of subjects with treatment-related application site reactions of all types combined was significantly greater among subjects treated with Vehicle Foam than Clindamycin Foam. The proportion of subjects with the specific subtypes of application site reactions, such as burning, desquamation, dryness, irritation, pruritus, or reaction NOS, was greater in each case among subjects treated with Vehicle Foam

than those treated with Clindamycin Foam, however the differences were not statistically significant for the reaction subtypes.

Reviewer comment: The anti-inflammatory action of the active ingredient may have contributed to the lower rate of application site reactions in the Clindamycin Foam group, although the magnitude of this effect is considered to be small.

Allergic dermatitis was reported as an AE in one subject in the Clindamycin Foam group; this AE was not reported in the Vehicle Foam group. The case report form describes "contact dermatitis of the eyes" without further elaboration. The severity of the AE was rated as mild, the frequency as continuous, and the relationship to study drug as probable. There is no clinical description. The AE was reported at the first follow-up visit, visit 2, at study week 3. The subject was terminated from study enrollment at that visit. Patch testing was not reported to have been done.

Reviewer comment: Although the distribution of the dermatitis is not specified, periocular distribution is presumed from the diagnosis of "contact dermatitis of the eyes." Allergic contact dermatitis in this distribution is common because the thin eyelid epidermis allows ready penetration of allergens, transferred from the fingers, which may not have been able to penetrate the thicker glabrous skin. However, were study drug the etiologic agent of this subject's presumed allergic contact dermatitis, one would expect to see involvement at all areas of application (the subject had acne on face, neck and back), in addition to the lids (exposed not by direct application but transfer from the fingertips). The timing of the eruption is consistent with an allergen related to study involvement, possibilities of which include study drug (either active or vehicle components) or an allergen encountered in the clinic setting (e.g. ink from carbonless forms).

7.1.5.4 Common adverse event tables

Table 25: Summary of AEs Occuring in >1% of Subjects, Safety Population

	Clindamycin Foam	**Vehicle Foam**
Number of subjects	439	154
Subjects with an AE	128 (29%)	**50 (32%)**
Nasopharyngitis	15 (3%)	**8 (5%)**
Application site burning	27 (6%)	**14 (9%)**
Upper respiratory tract infection NOS	9 (2%)	3 (2%)
Headache NOS	**12 (3%)**	1 (1%)
Sinusitis NOS	11 (3%)	**6 (4%)**
Application site pruritus	5 (1%)	**5 (3%)**
Application site reaction NOS	3 (1%)	**4 (3%)**

Source: Sponsor's NDA submission, module 2, volume 1.01, section 2.7.4, p.30.

7.1.5.5 Identifying common and drug-related adverse events

There is insufficient evidence to conclude that headache, NOS, is a drug-related adverse event.

Although application site reactions occurred more frequently among the Vehicle Foam group than the Clindamycin Foam group, the inclusion of known potential cutaneous irritants and allergens in the drug product make the occurrence of these AEs probable in the postmarketing period. However, the incidence is expected to be low.

7.1.5.6 Additional analyses and explorations

No additional analyses are indicated.

7.1.6 Less Common Adverse Events

Pseudomembranous colitis has been reported following administration of oral and topical clindamycin. The incidence of AEs which may be markers for pseudomembranous colitis are detailed in the table below.

Table 26

Preferred Term	Clindamycin Foam N=439	Clindagel N=435	Vehicle Foam N=154	Vehicle Gel N=128
Abdominal pain NOS	0 (0%)	3 (1%)	0 (0%)	0 (0%)
Abdominal pain upper	1 (0.2%)	2 (0.5%)	0 (0%)	0 (0%)
Diarrhoea NOS	0 (0%)	1 (0.2%)	0 (0%)	0 (0%)
Gastroenteritis NOS	1 (0.2%)	1 (0.2%)	1 (1%)	0 (0%)

Source: Sponsor's NDA submission module 2, vol. 1.01, section 2.7.4, pp.22-23.

There does not appear to be a signal for pseudomembranous colitis. However, this rare AE may yet occur with wider use of Clindamycin Foam in the postmarketing phase.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Complete blood count (CBC) and chemistry panel tests (AST, ALT, alkaline phosphatase, total bilirubin, calcium, bicarbonate, chloride, creatinine, glucose, potassium, sodium) were assayed in the phase 1 open-label bioavailability study (CLN.C.001) and the phase 3 pivotal trial (CLN.C.003).

Table 27: Number of Subjects Exposed to Study Drug with Laboratory Assessments

	CLN.C.001	CLN.C.003
Baseline	12	98
Follow-up*	12	92

*Follow-up for CLN.C.001 was 6 days and for CLN.C.003 was 12 weeks

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Pivotal trial CLN.C.003 was the only study that was vehicle-controlled for which laboratory assessments were obtained. Additionally, the short duration (6 days) of study CLN.C.001 makes pooling with the pivotal trial impractical.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Table 28: Summary of Hematology Results

	Clindamycin Foam		**Vehicle Foam**	
	Baseline	Week 12/End of Treatment	Baseline	Week 12/End of Treatment
WBC ($x10^3$/uL)				
N	98	92	31	30
Mean (std)	7.796 (1.884)	7.898 (2.355)	7.643 (1.976)	7.758 (2.102)
RBC Total Count ($x10^6$/uL)				
N	98	92	31	30
Mean (std)	4.82 (0.49)	4.78 (0.47)	4.91 (0.32)	4.84 (0.37)
Hemoglobin (g/dL)				
N	98	92	31	30
Mean (std)	14.16 (1.32)	14.09 (1.30)	13.98 (1.20)	13.78 (1.18)
Hematocrit (%)				
N	98	92	31	30
Mean (std)	42.0 (3.9)	41.5 (3.6)	41.7 (2.8)	40.8 (3.1)
Platelet Count ($x10^3$/uL)				
N	98	92	31	30
Mean (std)	292.7 (68.3)	284.7 (68.2)	284.8 (52.0)	285.1 (55.1)

Source: Sponsor's NDA submission module 5, vol. 1.07, pp.166-8.

Table 29: Summary of Chemistry Test Results

	Clindamycin Foam		Vehicle Foam	
	Baseline	Week 12/End of Treatment	Baseline	Week 12/End of Treatment
Bilirubin Total (mg/dL)				
N	95	89	29	30
Mean (std)	0.52 (0.30)	0.55 (0.38)	0.55 (0.42)	0.44 (0.23)
Alkaline Phosphatase (U/L)				
N	98	92	31	31
Mean (std)	120.0 (83.9)	117.3(75.8)	126.5 (91.6)	117.7 (77.2)
ALT (SGPT) (U/L)				
N	98	92	31	31
Mean (std)	19.3 (12.6)	19.9 (14.1)	16.7 (8.0)	19.4 (11.5)
AST (SGOT) (U/L)				
N	98	89	30	30
Mean (std)	21.9 (10.4)	21.6 (9.9)	19,8 (3.9)2	20.8 (6.2)
Calcium (mg/dL)				
N	98	92	31	31
Mean (std)	9.86 (0.33)	9.80 (0.34)	9.96 (0.39)	9.93 (0.43)
Bicarbonate (mEq/L)				
N	98	92	31	31
Mean (std)	23.84 (1.86)	24.05 (1.66)	23.57 (2.75)	24.43 (1.99)
Chloride (mEq/L)				
N	98	92	31	31
Mean (std)	106.6 (2.1)	107.7 (2.0)	106.7 (2.8)	107.0 (1.6)
Creatinine (mg/dL)				
N	98	92	31	31
Mean (std)	0.76 (0.14)	0.75 (0.14)	0.74 (0.15)	0.73 (0.13)
Glucose (mg/dL)				
N	98	92	31	31
Mean (std)	89.4 (12.3)	92.7 (17.5)	88.5 (12.2)	90.5 (12.6)
Sodium (mEq/L)				
N	98	92	31	31
Mean (std)	142.2 (2.0)	142.2 (2.0)	142.1 (2.1)	141.7 (1.5)
Potassium (mEq/L)				
N	98	92	31	31
Mean (std)	4.25 (0.34)	4.26 (0.36)	4.29 (0.32)	4.34 (0.31)

Source: Sponsor's NDA submission module 5, vol. 1.07, pp.169-172.

Reviewer's comment: There were no clinically significant differences in mean values across study groups or time (baseline and end of study) for either hematology or chemistry parameters.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Individual subject data was reviewed for abnormal clinical laboratory parameters as follows for hematology: white blood count < 3 or > 14 x 103/uL, hemoglobin < 10.5 g/dL for females and any abnormality for males, platelet count < 100 x 103/uL or > 500 x 103/uL. Chemistry tests were reviewed for the following abnormal clinical parameters: total bilirubin > 2.5 x the upper limit of normal (ULN), alkaline phosphatase > 2.5 x ULN, ALT (SGPT) > 2.5 x ULN, AST (SGOT) > 2.5 x ULN, creatinine > 1.5 x ULN and glucose < 50 or > 140 mg/dL.

Table 30

Treatment Group Subject No.	Laboratory Parameter (units)	Baseline Results	Week 12 (End of Treatment) Results
	Hematology		
C03-0042	White Blood Count ($x10^3$/uL)	13.46	16.14
C08-0130	White Blood Count ($x10^3$/uL)	12.14	15.55
C08-0481	Platelet Count ($x10^3$/uL)	525	452
	Chemistry		
C03-0008	ALT/SGPT (U/L)	103	108
C03-0008	AST/SGOT (U/L)	91[a]	87[a]
C08-0599	Glucose (mg/dL)	146	88
C11-0092	AST/SGOT (U/L)	18	102
C11-0092	AST/SGOT (U/L)	-	14[a]
C11-0350	Glucose (mg/dL)	77	142

[a]Repeat test

Source: Sponsor's NDA submission module 5, vol. 1.07, pp.173-4.

Two subjects (C03-0042 and C08-0130, Clindamycin Foam) had elevated WBC at end of treatment without identifiable cause; the investigators did not consider the elevations clinically significant and did not report them as AEs. One subject had elevated platelet count at baseline which returned to normal at week 12 (end of treatment).

One subject (C03-0008, Clindamycin Foam) had elevated ALT (SGPT) and AST (SGOT) at Baseline and repeat testing, which remained elevated at Week 12 (end of treatment). One subject (C11-0092, Clindamycin Foam) had a normal AST value at Baseline and elevated value at Week 12 (end of treatment), which resolved upon repeat testing 3 weeks later (14 U/L); this subject also had an elevated ALT (54U/L), which the investigator attributed to an intercurrent illness and reported as an AE not related to study drug. One subject (C08-0599, Clindamycin Foam) had glucose value > 140 mg/dL at Baseline (based on random samples) and no significant medical history, but glucose value was within the normal range at Week 12 (end of treatment). Subject No. 011-0350 (Clindamycin Foam) had a normal glucose value at Baseline, which increased to 142 mg/dL (a random sample) at Week 12. This subject had a medical history of hypoglycemia and the Week 12 elevated glucose reading was not considered significant by the investigator.

No subjects in the Vehicle Foam group had hematologic or chemistry abnormalities exceeding the above parameters.

Reviewer comment: No signal for neutropenia or hepatotoxicity is identified.

Urine pregnancy tests were obtained for women of childbearing potential. Two subjects in the Clindamycin Foam group and two in the Vehicle Foam group had positive pregnancy tests. In the Clindamycin Foam group, subjects C11-0635 and C16-0822 had positive pregnancy tests at week 12 (end of treatment). In the Vehicle Foam group, subject C05-0736 was confirmed pregnant at week 6 and completed the study, and subject C08-0595 was confirmed pregnant at baseline and withdrawn at the investigator's discretion. As subjects were allowed to be pregnant during the study, no follow up of the pregnant subjects was done.

Reviewer comment: Clindamycin phosphate drug products garner a pregnancy category rating of B. Women of childbearing potential were not required to use contraception to participate in the pivotal trial, and pregnant subjects were allowed to be enrolled and continue in the study at the investigator's discretion.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

There were no marked outliers.

Subject C08-0595, Vehicle Foam group, withdrew from the study following a positive pregnancy test.

7.1.7.4 Additional analyses and explorations

No additional analyses or explorations were done.

7.1.7.5 Special assessments

No special assessments were performed.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were assessed at baseline in studies CLN.C.001 (phase 1 bioavailability), CLN.C.002 (phase 2 efficacy and safety study) and CLN.C.003 (phase 3 pivotal trial), thirty minutes prior to drug dosing in CLN.C.001, and at each follow-up visit in CLN.C.003. Vital sign testing was not performed in study CLN.C.004 (cutaneous irritancy and allergenicity study).

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Vital signs data from pivotal trial CLN.C.003 will be analyzed below. Vital signs were either not obtained, obtained only at baseline or obtained for short duration in the remaining studies and will not be considered further.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Table 31

	Clindamycin Foam		Vehicle Foam	
	Baseline	Week 12/End of Treatment	Baseline	Week 12/End of Treatment
Systolic Blood Pressure				
N	383	354	126	118
Mean (std)	114.2 (11.8)	112.6 (11.2)	114.5 (13.2)	114.1 (11.1)
Diastolic Blood Pressure				
N	383	354	126	118
Mean (std)	71.0 (9.2)	70.5 (9.8)	71.0 (9.0)	70.2 (9.5)
Pulse				
N	383	354	126	118
Mean (std)	72.3 (9.4)	72.9 (9.3)	73.1 (10.5)	72.8 (9.1)

Source: Sponsor's NDA submission module 5, volume 1.07, pp.178-179.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Using systolic BP >140, diastolic BP >90, and HR >100, vital signs data were analyzed for outliers. In the Clindamycin Foam group, five subjects were noted to have vital signs outside these parameters at either baseline or week 12, and in the Vehicle Foam group, eight subjects were noted to have vital signs outside these parameters at those timepoints.

Table 32

	Clindamycin Foam					
Treatment Group Subject No.	Baseline			Week 12 (end of treatment)		
	Systolic BP	Diastolic BP	Heart rate	Systolic BP	Diastolic BP	Heart rate
C02-0766	**143**	73	69	138	79	80
C04-0063	**152**	88	62	**150**	88	72
C16-1090	138	74	72	**150**	90	80
C17-0908	128	**100**	72	140	**100**	86
C17-0956	126	84	78	**142**	84	60
	Vehicle Foam					
C02-0281	140	70	84	**142**	74	80
C06-0538	134	**92**	14	132	88	80
C07-0167	**147**	73	75	136	78	65
C08-0136	127	78	**108**	127	76	96
C14-0892	**152**	63	72	**147**	58	78
C14-1058	135	73	68	135	72	**109**
C16-1102	136	98	80	130	**92**	76
C17-0981	130	**100**	70	128	**100**	68

Source: Sponsor's NDA submission module 5, vol. 1.21, pp.4577-4673

Reviewer comment: Despite a few outliers in both the active and vehicle groups, there is no trend toward abnormalities of vital signs over time. No safety signal for elevations of heart rate, systolic or diastolic blood pressure is identified.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

There were no marked outliers for vital signs or dropouts for vital sign abnormalities.

7.1.8.4 Additional analyses and explorations

None performed.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECGs were not performed during any of the studies of Clindamycin Foam. Clindamycin Phosphate Foam, 1% is topically applied. Other topical clindamycin products are not known to produce cardiac effects. Systemic absorption of Clindamycin Foam is less than that for

Clindagel. For these reasons, the Agency did not request the Sponsor to perform ECG testing during their development program.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable because ECGs were not performed.

7.1.9.3 Standard analyses and explorations of ECG data

Not applicable because ECGs were not performed.

7.1.9.4 Additional analyses and explorations

Not applicable because ECGs were not performed

7.1.10 Immunogenicity

Not applicable, as drug is not a therapeutic protein. Assessment for allergenicity (type IV delayed hypersensitivity) is discussed in section 7.1.12, Special Safety Studies.

7.1.11 Human Carcinogenicity

No tumors were reported in any of the studies. However, all of the studies were of short duration (12 weeks or less).

7.1.12 Special Safety Studies

Local Safety – Cutaneous Irritancy and Allergenicity

A standard repeat insult patch test study was performed using Clindamycin Foam and Vehicle Foam to determine their potential to cause cutaneous irritancy or allergenicity.

Study CLN.C.004: A Cumulative Irritation and Skin Sensitization Study of Clindamycin Phosphate Foam, 1%.

Study Design

Two hundred and forty subjects enrolled in this single-center, randomized, controlled, evaluator-blinded, intra-subject study consisting of induction, rest and challenge phases. Test articles included Clindamycin Foam, Vehicle Foam, 0.1% sodium lauryl sulfate (SLS) (positive control), and distilled water (negative control). After screening and enrollment, 0.2mL of each test article was applied under separate occlusive patches onto the subject's back in the sequence dictated by the randomization schedule. During the induction phase (days 1-22), the subjects returned at 48/72 hour intervals (M, W, F) for 8 subsequent visits, at which time the patches were removed and the application sites assessed for signs of irritation or inflammation. At all but the final

induction phase visit, occlusive patches with additional test article were applied to the same sites after assessment was completed. After the rest phase (days 23-35), during which no applications were made, test articles were applied under occlusive patches on naïve sites on the subjects' backs (challenge phase). The patches were removed and the sites assessed 48 hours later, and again at 72 hours, and at 96 hours if inflammation was present at the 72-hour assessment. Any subject showing a reaction suggestive of delayed contact sensitization was to be rechallenged two weeks following the completion of the first challenge evaluation. Sensitization was suspected during the challenge phase for reactions that demonstrated erythema and either edema, papules and/or vesiculation.

Results

By the reviewer's calculation, two hundred and sixteen subjects completed the induction phase. For the Clindamycin Phosphate Foam, 1%, 85 subjects had maximum scores of 0 or 1 (no or minimal response), 96 had maximal scores of 2 (definite erythema, no edema), 4 had maximal scores of 3 (definite erythema, definite edema), and 31 had maximum scores of 2D (erythema with epidermal damage). For the Vehicle Foam, 90 subjects had maximum scores of 0 or 1 (no or minimal response), 95 had maximum scores of 2 (definite erythema, no edema), 3 had maximal scores of 3 (definite erythema, definite edema), and 28 had maximum scores of 2D (erythema with epidermal damage). For the 0.1% SLS (positive control), 5 subjects had maximum scores of 0 or 1 (no or minimal response), 44 had maximum scores of 2 (definite erythema, no edema), 2 had maximal scores of 3 (definite erythema, definite edema), and 163 had maximum scores of 2D (erythema with epidermal damage), and 2 had maximum scores of 3D (definite erythema, definite edema, epidermal damage). For the distilled water (negative control), 162 subjects had maximum scores of 0 or 1 (no or minimal response), 54 had maximum scores of 2 (definite erythema, no edema), and 0 had maximal scores of 3 (definite erythema, definite edema) or 2D (erythema with epidermal damage). These results are summarized in the table below.

Table 33

	No reaction	**Minimal reaction**	**Definite erythema; no edema**	**Definite erythema; definite edema**	**Definite erythema; damage to epidermis**	**Definite erythema and edema; damage to epidermis**
Clindamycin Foam n=216	24	61	96	4	31	0
Vehicle Foam n=216	26	64	95	3	28	0
SLS (positive control) n=216	1	4	44	2	163	2
Distilled water (negative control) n=216	162	54	0	0	0	0

Source: Reviewer's calculations

The statistical analysis of cumulative irritancy is summarized in Table 34.

Table 34: Mean Cumulative Irritancy Indices

Test Article	Mean (±SD)
Clindamycin Foam	0.93 (± 0.68)
Vehicle Foam	0.89 (± 0.68)
0.1% SLS	1.64 (± 0.61)
Distilled Water	0.07 (± 0.15)

Source: Sponsor's NDA submission, module 5, vol. , section 5.3.5.4, p.38.

Reviewer comment: Clindamycin Foam and Vehicle Foam are more irritating than distilled water but less irritating that sodium laurel sulfate. The irritation scores for the Clindamycin Foam and the Vehicle Foam are essentially identical, suggesting that one or more excipients rather than the active ingredient are responsible for the irritation seen. Dehydrated alcohol and propylene glycol are both recognized causes of irritant dermatitis. Occlusion has likely amplified the irritant reaction, as more erythema and edema were seen with provactive irritant patch testing than in the pivotal trial.

Two hundred and twelve subjects completed the challenge phase of the study. A reaction of 3, definite erythema and definite edema, was considered suggestive of sensitization reaction. No subject had a reaction of 3 during the challenge phase, and no subject underwent repeat challenge testing. Additionally, no subject had a reaction of 2 at the 72 hour challenge phase evaluation. The table below summarizes the challenge responses by test article.

Table 35: Summary of Challenge Phase Responses

Response/Score	**Time post-challenge patch application**	
	48 hr (n=212)	**72 hr (n=212)**
Clindamycin Foam		
0/no reaction	139 (66%)	164 (77%)
1/minimal reaction	60 (28%)	48 (23%)
2/definite erythema, no edema	13 (6%)	0
Vehicle Foam		
0/no reaction	138 (65%)	173 (82%)
1/minimal reaction	64 (30%)	39 (18%)
2/definite erythema, no edema	10 (5%)	0
0.1% SLS		
0/no reaction	148 (70%)	179 (84%)
1/minimal reaction	60 (28%)	33 (16%)
2/definite erythema, no edema	4 (2%)	0
Distilled Water		
0/no reaction	207 (98%)	210 (99%)
1/minimal reaction	5 (2%)	2 (1%)
2/definite erythema, no edema	0	0

Source: Sponsor's NDA submission, module 5, volume 1.27, p.40.

Reviewer comment: Clindamycin phosphate, the active ingredient, as well as five of the vehicle ingredients (cetyl alcohol, ethanol, Polysorbate 60, propylene glycol, and stearyl alcohol), have been reported as sensitizers. The frequency of reported allergic contact dermatitis from these ingredients is rare. Wider use of the Sponsor's product in the post-marketing phase may result in infrequent occurrence of true allergic contact dermatitis from these components. Water and potassium hydroxide are not considered potential sensitizers.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No instances of drug abuse were reported in either study CLN.C.002 or CLN.C.003. Topical clindamycin phosphate does not have a known abuse potential, does not produce withdrawal phenomenon, and does not belong to a class of compounds associated with these effects.

7.1.14 Human Reproduction and Pregnancy Data

Urine pregnancy tests were obtained for women of childbearing potential. Two subjects in the Clindamycin Foam group and two in the Vehicle Foam group had positive pregnancy tests. In the Clindamycin Foam group, subjects C11-0635 and C16-0822 had positive pregnancy tests at week 12 (end of treatment). In the Vehicle Foam group, subject C05-0736 was confirmed pregnant at week 6 and completed the study, and subject C08-0595 was confirmed pregnant at baseline and withdrawn at the investigator's discretion. As subjects were allowed to be pregnant during the study, no follow up of the pregnant subjects was done.

Reviewer comment: Clindamycin phosphate drug products garner a pregnancy category rating of B. Women of childbearing potential were not required to use contraception to participate in the pivotal trial, and pregnant subjects were allowed to be enrolled and continue in the study at the investigator's discretion.

7.1.15 Assessment of Effect on Growth

Not applicable because of short study duration.

7.1.16 Overdose Experience

No instances of overdose were reported in the phase 2 or phase 3 trials. Clindamycin Phosphate Foam, 1% is applied topically but may be absorbed in sufficient amounts to produce systemic effects. .

7.1.17 Postmarketing Experience

The Sponsor's drug product is not marketed in any country at the time of the writing of this review.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Four clinical studies were conducted with Clindamycin Phosphate Foam, 1%. The studies are grouped according to phase, with phases 2 and 3 considered together (table 37).

Table 36: Phase 1 Studies

Study Number	**CLN.C.001**	**CLN.C.004**
Design	Randomized, open-label	Intra-individual, evaluator-blinded, randomized, vehicle-controlled
Objective	Bioavailability	Irritation and sensitization/repeat insult patch test
Formulation(s)	Clindamycin Phosphate Foam, 1% Clindagel	Clindamycin Phosphate Foam, 1% Vehicle Foam Sodium lauryl sulfate (positive control) Distilled water (negative control)
Enrollment	24 subjects with acne vulgaris	231 healthy subjects
Dose	4 gms qAM applied topically to face, neck, upper chest and upper back	0.2mL applied under occlusive patches on the backs of subjects three times per week for three weeks, followed by a single 48 hour application 2 weeks later
Duration	5 days	3 weeks, followed by 48 hours after a 2 week rest
Measurement timepoints	Baseline (d1) and days 2-6; on day 6, 1hr, 2hr, 4hr, 8hr and 12hr after study drug application	Baseline and days 1, 3, 5, 8, 10, 12, 15, 17, 19 and 33.
Measurements related to safety	Serum chemistries, hematology, AEs	Irritation, sensitization, AE

Table 37: Phase 2 and 3 Studies

Study Number	**CLN.C.002**	**CLN.C.003**
Design	Multi-center, randomized, investigator-blinded, vehicle-controlled	Multi-center, randomized, double-blind, double-dummy, vehicle-controlled
Objective	Efficacy and safety	Efficacy and safety
Formulations (N enrolled)	Clindamycin Foam, 1% (53) Vehicle Foam (50) Clindagel (27)	Clindamycin Foam, 1% (386) Vehicle Foam (385) Clindagel (127) Vehicle Gel (128)
Enrollment	130 subjects with acne vulgaris	1026 subjects with acne vulgaris
Dose	Topical application once daily of a sufficient amount to cover the entire face	Topical application once daily of a sufficient amount to cover the entire face
Duration	12 weeks	12 weeks
Measurement timepoints	Baseline, weeks 3, 6, 9 and 12	Baseline, weeks 3, 6, 9 and 12.
Measurements related to safety	Signs and symptoms of facial acne, AEs	Signs and symptoms of facial acne, AEs, serum chemistries and hematology

7.2.1.2 Demographics

Table 38

	Clindamycin Foam	Clindagel	Vehicle Foam	Vehicle Gel	US population[2]
Total Number of Subjects	439	435	154	128	
Age					
Mean (std)	19.0 (6.4)	18.6 (6.3)	18.7 (6.6)	18.9 (7.3)	
Median	16.0	16.0	16.0	16.0	
Min, max	12, 48	12, 50	12, 46	12, 55	
Sex					
Male	210 (48%)	200 (46%)	77 (50%)	62 (48%)	
Female	229 (52%)	235 (54%)	77 (50%)	66 (52%)	
Race					
Caucasian	291 (66%)	281 (65%)	105 (68%)	79 (62%)	75.1%
Black	77 (18%)	74 (17%)	28 (18%)	22 (17%)	12.3%
Hispanic	61 (14%)	70 (16%)	19 (12%)	22 (17%)	12.5%*
Other	10 (2%)	10 (2%)	2 (1%)	5 (4%)	

Source: Sponsor's NDA submission module 2, volume 1.01, section 2.7.4, p.6.
* In the Census 2000, race was evaluated separately from ethnicity; "Hispanic or Latino" was a category for ethnicity but not for race. In the phase 2 & 3 studies, "Hispanic" was a category for race.

[2] Overview of Race and Hispanic Origin, U.S. Census Bureau Census 2000 Brief, March 2001; p.3.

Reviewer comment: The treatment groups are similar with regard to age, sex and race. The age distribution reflects that of the disease. Both genders are well-represented. The racial enrollment reflects that of the US population.

7.2.1.3 Extent of exposure (dose/duration)

Table 39 documents the extent of exposure for the phase 2 and phase 3 studies.

Table 39: Phases 2 and 3 Study Drug Exposure, ITT population

	Clindamycin Foam	**Clindagel**	**Vehicle Foam**	**Vehicle Gel**
Number of Subjects	439	435	154	128
Days on Study Drug				
n	408	408	146	121
Mean (SD)	82.64 (10.88)	82.68 (9.44)	80.97 (12.57)	81.42 (12.52)
Median	83.00	83.00	83.00	83.00
Study Drug Usage (g)[a]				
n	425	420	149	125
Mean (SD)	98.13 (61.60)	89.93 (52.75)	103.72 (66.40)	84.07 (45.81)
Median	84.00	79.70	86.30	78.50

[a]Study drug usage is define as total container weight dispensed minus total container weight returned.
Source: Sponsor's NDA submission, 1.2, volume 1.01, section 2.7.4, p.5.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No studies other than the four submitted to the NDA were used in the review of safety.

7.2.2.2 Postmarketing experience

There has been no postmarketing experience with the Sponsor's drug product, as Clindamycin Phosphate Foam, 1% is not approved in any country at the time of writing of this review.

7.2.2.3 Literature

The Sponsor submitted literature regarding treatment options for acne vulgaris, systemic absorption from topical application of clindamycin hydrochloride and clindamycin phosphate, case reports of allergic contact dermatitis to topical clindamycin, and case reports of

psuedomembranous colitis as a complication of topical treatment with clindamycin phosphate. The literature review is acceptable.

7.2.3 Adequacy of Overall Clinical Experience

Four hundred thirty-nine subjects were exposed to Clindamycin Phosphate Foam, 1% for a mean of 82 days in the phase 2 and 3 trials. The median age of subjects was 16.0 years, so the pediatric age group older than 12 years was adequately represented. The racial makeup of the trials roughly approximates the racial mix of the US population.

The dose, once daily application, was determined by that of the reference listed drug, Clindagel. The duration of the pivotal trial, 12 weeks, was similarly determined and is standard for acne trials. The Sponsor is relying on the Agency's findings of safety for Clindagel to meet the requirements of ICH-E1A, clinical safety of drugs intended for long-term treatment of non-life threatening conditions.

The design of the pivotal study, with both comparator and vehicle arms, is acceptable to assess safety and efficacy.

The exclusion of subjects with a history or presence of regional enteritis or inflammatory bowel disease (e.g., ulcerative colitis, pseudomembranous colitis, chronic diarrhea or a history of antibiotic-associated colitis) or similar symptoms, is acceptable, as use of topical clindamycin preparations are contraindicated in this population.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

For this 505(b)(2) application, the Sponsor did not perform animal or *in vitro* testing, but relied on the Agency's finding for the reference listed product. The Pharmacotoxicology reviewer found the available animal and *in vitro* testing to be adequate.

7.2.5 Adequacy of Routine Clinical Testing

In pivotal study CLN.C.003, CBC and chemistry panel tests (including LFTs) were obtained at baseline and at week 12. As neutropenia, eosinophilia and liver function test abnormalities have been reported with the use of systemic clindamycin, and systemic absorption occurs following topical administration, the laboratory tests were appropriate. The package insert for Cleocin HCL (clindamycin hydrochloride) capsules recommends, "[d]uring prolonged therapy, periodic liver and kidney function tests and blood counts should be performed." Because systemic exposure following topical administration is much less than with oral or parenteral administration, greater frequency of testing was not warranted.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

For this 505(b)(2) application, the Sponsor did not perform metabolic, clearance or interaction workup, but relied on the Agency's finding for the reference listed product.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The Sponsor has conducted an adequate repeat insult patch test study to assess for cutaneous irritancy and allergenicity, as is standard for topical medications.

The Sponsor actively solicited for complaints of scaling, dryness, erythema, burning, and itching, which may be indicative of irritation from the vehicle.

The Sponsor did not actively solicit for signs and symptoms of psuedomembranous colitis. However, this potential AE is rare with topical clindamycin phosphate.

7.2.8 Assessment of Quality and Completeness of Data

Deficiencies in the quality or completeness of the safety data were not identified.

7.2.9 Additional Submissions, Including Safety Update

A four-month safety update report was submitted on April 30, 2004 (CDER stamp date). The Sponsor reported no new safety information in that report. The Sponsor denied conducting any additional clinical or non-clinical studies with Clindamycin Phosphate Foam, 1%, other than those reported in the NDA.

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

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Adverse event data from the phase 2 and phase 3 studies (CLN.C.002 and CLN.C.003) were pooled together. Both studies were of 12 weeks duration, and both included active, comparator and vehicle foam arms; CLN.C.003 also included a vehicle gel arm.

7.4.1.2 Combining data

The pooled studies were simply combined without weighting.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Not applicable, as only one dose (Clindamycin Phosphate Foam, 1%) was evaluated for this 505(b)(2) application.

7.4.2.2 Explorations for time dependency for adverse findings

For the two subjects in the Clindamycin Foam group who withdrew from study due to AEs, the timings of the AEs were consistent with a relation to study drug use.

Other analyses for time-dependency were not performed. Both studies were of short duration (12 weeks).

7.4.2.3 Explorations for drug-demographic interactions

Adverse event profiles did not appear to vary with age, gender or race.

7.4.2.4 Explorations for drug-disease interactions

Both co-primary efficacy assessments, the ISGA scale and lesion counts, allowed for capture of disease exacerbation during therapy. Few subjects worsened during the course of the pivotal trial.

7.4.2.5 Explorations for drug-drug interactions

No drug-drug interactions were identified. Subjects on neuromuscular blocking agents (with which clindamycin may interact) were excluded from enrollment.

7.4.3 Causality Determination

Application site reactions such as burning, dryness, pruritus, and application site reaction NOS were common in both the active and vehicle foam groups. The known potential of vehicle ingredients for irritancy, as well as active and vehicle foam cumulative irritancy scores greater than the score for the negative control (distilled water) in the cutaneous safety study (CLN.C.004), support the causality of vehicle in application site reactions.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosing regimen for Clindamycin Phosphate Foam, 1% is once daily application to the skin. This is the dosing regimen that was used in the phase 2 and phase 3 clinical studies, and it is the dosing regimen for Clindagel, the reference listed drug for this application..

8.2 Drug-Drug Interactions

No drug-drug interactions were noted in subjects treated with either Clindamycin Phosphate Foam, 1% or Clindagel or their vehicles in either study CLN.C.002 or study CLN.C.003.

The PRECAUTIONS, Drug Interactions section from the label of the reference listed drug (Clindagel) states the following:

> Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.

8.3 Special Populations

Clindamycin Phosphate Foam, 1% has not been studied in children younger than 12 years of age, or in adults over 65 years of age. Acne vulgaris is not prevalent in either of these populations.

Other topical clindamycin phosphate drug products have a pregnancy category rating of B. Women of childbearing potential were not required to use contraception to participate in the pivotal trial, and pregnant subjects were allowed to be enrolled and continue in the study at the investigator's discretion. Two subjects in the Clindamycin Foam group had positive pregnancy tests at week 12 (end of treatment). No follow-up of these pregnancies was performed. Clindamycin Phosphate Foam, 1% should be used during pregnancy only if clearly needed.

It is not known whether clindamycin is excreted in human milk following use of Clindamycin Phosphate Foam, 1%. However, orally and parenterally administered clindamycin has been reported to appear in breast milk3. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatrics

Clindamycin Phosphate Foam, 1% is a new dosage form, so a pediatric assessment is required per the Pediatric Research Equity Act (PREA). The Sponsor requested a waiver for pediatric

3 Professional labeling for Clindagel

studies for the topical treatment of acne vulgaris in children less than twelve years of age. The waiver was granted because acne vulgaris is not prevalent in the population younger than twelve years of age, and it would have been impractical to recruit sufficient numbers of subjects from this demographic. The pivotal study CLN.C.003 included sufficient numbers of adolescent subjects to make a determination of safety and efficacy for pediatric subjects 12 years of age and older. The Sponsor appears to have complied with the requirements of PREA.

8.5 Advisory Committee Meeting

Not applicable, as no Advisory Committee was convened in response to this application.

8.6 Literature Review

As discussed in section 7.2.2.3, the literature reports a case of psuedomembranous colitis following topical application of clindamycin.

8.7 Postmarketing Risk Management Plan

The Sponsor has submitted proposed labeling. Routine risk minimization measures such as professional labeling, prescription status, and spontaneous adverse event reporting, comprise an adequate risk management plan for this drug at this time.

8.8 Other Relevant Materials

The Sponsor submitted two tradenames, [redacted]. Consultation with DMETS revealed the potential for prescribing and dispensing errors with both names, and neither name was accepted. The Sponsor has submitted two additional tradenames, [redacted] and Evoclin; DMETS consultation regarding these names is pending at the time of completion of this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

Clindamycin Phosphate Foam, 1% is a topical antibiotic acne product in an aerosol foam vehicle intended for once daily application for the treatment of acne vulgaris in patients 12 years of age and older.

In NDA 21-709, the Sponsor demonstrated in a single phase 3 trial that Clindamycin Phosphate Foam, 1% was superior to vehicle and non-inferior to Clindagel® (clindamycin phosphate gel) topical gel, 1% for the treatment of acne vulgaris in the above population. The pivotal trial was adequate and well-controlled. Co-primary efficacy endpoints included Investigator's Static Global Assessment, dichotomized to success and failure, and percent reduction in lesion counts (total, inflammatory and non-inflammatory), assessed at week 12 in the ITT (LOCF) population.

The proportion of subjects who achieved success at week 12 in the Clindamycin Foam group was significantly greater than the in vehicle group and non-inferior to the Clindagel group. Additionally, the percent reduction in all three lesion counts for the Clindamycin Foam group was significantly greater than for the Vehicle Foam group and non-inferior to the Clindagel group. The conclusions are robust.

No deaths occurred during the development program for Clindamycin Foam, and no serious adverse events were attributed to study drug use. The most frequent adverse events related to study drug use were application site burning and application site pruritus; both occurred more frequently in the Vehicle Foam group than in the Clindamycin Foam group. No signal suggestive of antibiotic-associated colitis was identified.

9.2 Recommendation on Regulatory Action

This reviewer recommends approval of Clindamycin Phosphate Foam, 1% for topical application in the treatment of acne vulgaris in patients 12 years of age and older.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Prescription status, professional labeling and spontaneous adverse event reporting are sufficient risk management activities for this drug product at this time.

9.3.2 Required Phase 4 Commitments

No phase 4 commitments are required.

9.3.3 Other Phase 4 Requests

No phase 4 requests are made.

9.4 Labeling Review

The proposed labeling, which should parallel that for the reference listed product, was generally acceptable. Deletions were suggested to make the Description section non-promotional, and changes were made to the table in the Adverse Reactions section to make it more informative.

9.5 Comments to Applicant

This reviewer has no comments for the Sponsor.

6 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Medical Review 1

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

/s/

Jill Lindstrom
9/1/04 12:06:31 PM
MEDICAL OFFICER

Markham Luke
9/1/04 01:38:33 PM
MEDICAL OFFICER
Concur with Dr. Lindstrom's recommendation for Approval. Labeling for discussion with Sponsor should include information about subgroup analyses for special populations.

Jonathan Wilkin
9/19/04 05:34:50 PM
MEDICAL OFFICER
Agree with primary reviewer's assessment and recommendation. labeling alrea includes statements about special populations. The word "platform" in the description does not add any value
and may be deleted.

45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the NDA application: **YES** **NO**

CLINICAL:

1. On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin? Yes

2. Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin? Yes

3. On its face, is the clinical section of the NDA legible so that substantive review can begin? Yes

4. If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product (i.e., appropriately designed dose- ranging studies)? Dose ranging studies were not required, as the sponsor submitted a 505(b)(2) application. The reference-listed drug is Clindagel, which is applied once daily. The sponsor conducted a phase 2 safety and efficacy study to obtain preliminary efficacy data for power calculations for use in designing their phase 3 study.

   Study Number:CLN.C 002
   Study Title: A Phase II Multicenter, Randomized Investigator-Blinded Study to Evaluate the Safety and Efficacy of Clindamycin Phosphate Foam, 1% Versus Vehicle Foam and Clindagel™ (clindamycin phosphate gel) Topical Gel, 1% in Subjects with Acne Vulgaris

   Sample Size: 130 Arms: three: clindamycin foam, 1%; vehicle foam; Clindagel 1%
   NDA Volume: Module 5, Vol 1.03 Pages: 5.3.5.1.1

5. On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application?

   Application Type: 505(b)(2) Reference drug: Clindagel™ (clindamycin phosphate gel) Topical Gel, 1%

   Identification of pivotal trial:

   Pivotal Study #1: Protocol Number: CLN.C.003
   Page Location in NDA:
   Protocol: module 5, volume 1.08 Study Report: module 5 volume 1.07 (5.3.5.1.2)

Is this an adequate multi-centered trial?

Site Number	Center	Patients Enrolled
C01	Alicia Barba, MD; Miami, FL	88
C02	Lawrence Eichenfield, MD; San Diego, CA	81
C03	Toni Funicella, MD; Austin, TX	88
C04	John Humeniuk, MD; Greer, SC	76
C05	Peter Lee, MD; Minneapolis, MN	57
C06	Anne Lucky, MD; Cincinnati, OH	75
C07	Robert Matheson, MD; Portland, OR	16
C08	Ronald Savin, MD; New Haven, CT	84
C09	Alan Shalita, MD; Brooklyn, NY	30
C10	Daniel Stewart, DO; Clinton Township, MI	39
C11	David Whiting, MD; Dallas, TX	76
C12	Steven Kempers, MD; Fridley, MN	25
C13	Christopher Nelson, MD; Pinellas Park, FL	18
C14	Jonathan Dosik, MD; Paramus, NJ	74
C15	Larry Gilderman, DO; Pembroke Pines, FL	30
C16	Jo Lynne Herzog, MD; Birmingham, AL	64
C17	Terry Jones, MD; Bryan, TX	70
C18	Joseph Fowler, Jr., MD; Louisville, KY	35

Source: Sponsor's NDA submission 21-709, vol. 1.07 p.198 and vol. 1.08 pp 724-5.

Study Title: A Phase III Multicenter, Randomized, Double-Blind, Double-Dummy, Vehicle-Controlled Study of the Safety and Efficacy of Clindamycin Phosphate Foam, 1%, versus Clindagel® (clindamycin phosphate gel) Topical Gel, 1%, for the Treatment of Acne Vulgaris.

Study design:

Randomized: Yes
Double Blind: Yes
Placebo controlled: Yes
Multicentered: Yes

Indication: mild to moderate acne vulgaris

Study arms (dosage, duration, treatment length for each arm):

1. clindamycin foam, 1%, applied qd for 12 weeks
2. vehicle foam, applied qd for 12 weeks
3. Clindagel, 1%, applied qd for 12 weeks
4. Vehicle gel, applied qd for 12 weeks

Efficacy endpoints (Primary and secondary):

Primary

1. The percent (%) change in lesions counts (total, inflammatory, non-inflammatory) from Baseline to Week 12 (end of treatment)
2. The proportion of subjects who have an Investigator's Static Global Assessment score of 0 or 1 at Week 12 (end of treatment)

Secondary

1. The proportion of subjects who have an Investigator's Static Global Assessment score of 0 or 1 at Weeks 3, 6 and 9.
2. The change from Baseline to Weeks 3, 6, 9 and 12 in the individual scores of severity of the signs (scaling, dryness, erythema, oiliness) and symptoms (burning, itching) of facial acne vulgaris.
3. The absolute change in lesion counts (total, inflammatory, non-inflammatory) from Baseline to Weeks 3, 6, 9 and 12.
4. The percent (%) change in lesion counts (total, inflammatory, non-inflammatory) from Baseline to Weeks 3, 6, and 9.
5. The proportion of subjects who have a Subject's Global Assessment score of 0 or 1 at Weeks 3, 6, 9 and 12.
6. The change in the Subject's Global Assessment from Baseline to Weeks 3, 6, 9 and 12.
7. The change in the Dermatology Life Quality Index (DLQI) or Children's Dermatology Life Quality Index (CDLQI) from Baseline to Week 12.

How measured:

The primary efficacy assessments, lesion counts and the Investigator's Static Global Assessment, were to be conducted by the investigator or a designee at Baseline and Weeks 3, 6, 9 and 12.

The guidelines for counting lesions were as follows:

1. The same person was to perform all lesion counts on a given subject as the subject progressed through the study, in order to ensure consistency.
2. Only lesions on the face were to be included in these assessments. The face was defined as extending from the hairline to the mandibular line.
3. Non-inflammatory lesions (comedones) on the nose were not to be counted.

The Investigator's Static Global Assessment scale is presented in the table below:

Score	Definition
Grade 0	Normal, clear skin with no evidence of acne vulgaris
Grade 1	Skin almost clear: rare non-inflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyper-pigmented, though not pink-red) requiring no further treatment in the Investigator's opinion
Grade 2	Some non-inflammatory lesions are present, with few inflammatory lesion (papules/pustules only, no nodulo-cystic lesions)
Grade 3	Non-inflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules, and there may or may not be 1 small nodulo-cystic lesion
Grade 4	Inflammatory lesions are more apparent: many comedones and papules/pustules, there may or may not be a few nodulo-cystic lesions
Grade 5	Highly inflammatory lesions predominate: variable number of comedones, many papules/pustules and nodulo-cystic lesions

6. Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?

Proposed indication from sponsor's draft labeling: "...topical application in the treatment of acne vulgaris"

As designed, could endpoints in pivotal trial #1 support labeling? yes

7. Are all data sets for pivotal efficacy studies complete for all indications requested? Yes, per Biostatistics Reviewer

8. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?

   PreIND Mtg: Yes
   IND number/s: 64,577
   PreIND Mtg Dates: August 16, 2001; April 10, 2002
   EP2 Meeting Date: None
   Agency response to Phase 3 protocols: SPA July 29, 2002
   PreNDA meeting date: None

   Do endpoints as described by sponsor in pivotal Study 1 conform to previous agency commitments? Yes
   Are the pivotal trials multi-centered? Yes
   Are there adequate numbers of patients enrolled? Yes

9. Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Yes. Has the applicant submitted line listings in the format agreed to previously by the Division? No prior agreement with the Division.

10. Has the application submitted a rationale for assuming the applicability of foreign data (disease specific microbiologic specific) in the submission to the US population? The pivotal study was conducted in the US.

11. Has the applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division? The Division did not request additional case record forms.

12. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division? Yes

13. Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? Yes.

14. Has the applicant submitted draft labeling consistent with 21CFR 201.56 and 21CFR 201.57, current divisional policies, and the design of the development package? Yes

15. Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor? Yes

16. Has the applicant complied with the requirements of the Pediatric Rule?
    a) Is this an indication that would be applicable to the pediatric population? Yes

b) What pediatric ages are included in the protocol? 12 to 17 years, inclusive
c) Does the sponsor request pediatric labeling? Yes. What age groups? 12 to 17 years, inclusive

17. Financial disclosure of investigator

Does the NDA contain the appropriate form to comply with the filing requirement for Financial Disclosure for Investigators? Yes

18. From a clinical perspective, is this NDA fileable? Yes

_____
Reviewing Medical Officer

_____
Medical Team Leader

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

/s/

Jill Lindstrom
3/23/04 02:10:22 PM
MEDICAL OFFICER

Markham Luke
3/23/04 03:19:43 PM
MEDICAL OFFICER
We need to see if the 11% non-inferiority margin that the Sponsor proposed without agreement by Agency (?) factors into the demonstration of efficacy for this product.