CLINICAL REVIEW

Application Type	NDA
Submission Number	50-819
Submission Code	0000
Letter Date	12-21-07
Stamp Date	12-26-07
PDUFA Goal Date	10-26-08
Reviewer Name	Brenda E. Vaughan, M.D.
Review Completion Date	09-29-08
Established Name	Clindamycin Phosphate/Benzoyl Peroxide
(Proposed) Trade Name	Acanya Gel
Therapeutic Class	Clindamycin (a lincosamide antibiotic) & Benzoyl Peroxide Combination
Applicant	Dow Pharmaceutical Sciences, Inc.
Priority Designation	Standard
Formulation	Topical gel
Dosing Regimen	Once daily
Indication	Acne vulgaris
Intended Population	Patients 12 years or older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, an Approval action is recommended for NDA 50-819 for use of topical combination drug product, Acanya Gel [clindamycin (1%)/benzoyl peroxide (2.5%)] gel, for treatment of acne vulgaris in patients 12 years of age and older. The applicant has established safety and efficacy over vehicle in two 12 week, multi-center, randomized, double-blind, vehicle-controlled, phase 3 clinical trials (DPSI-06-22-2006-012 and DPSI-06-22-2006-017) with use of Acanya Gel in treatment of acne vulgaris and has satisfied the combination drug policy under 21 CFR §300.50.

The 505(b)(2) route of approval for this application is based on published literature; therefore, a clinical bridge is not needed. The applicant's proposed 505(b)(2) route of approval is based on the claim that a clinical bridge to listed product BenzaClin® has been established. However the application is deficient because the NDA application does not include a clinical trial with use of the proposed drug product, Acanya Gel, to any listed drug as per 21 CFR §320.24(b)(4). Instead, the applicant is relying on data from Bioequivalence Study DPS 07-07-2005-001 conducted with listed drug BenzaClin® and [redacted] Although it is scientifically plausible that Acanya Gel and [redacted] are similar (with respect to excipients and excipient levels, [redacted] strength of BPO, propylene glycol and corresponding [redacted] purified water), the applicant did not provide adequate comparative safety and efficacy data to support the sameness of Acanya Gel and [redacted] There is no known precedent for use of a surrogate as the applicant is proposing and it does not appear to this reviewer that current regulations allow for use of a surrogate drug to demonstrate comparative bioavailability under 21 CFR §320.24(b)(4).

1.2 Risk Benefit Assessment

The label includes warnings concerning colitis occurring with use of oral and topical clindamycin and the need for avoidance of ultraviolet light exposure due to a preclinical dermal photocarcinogenicity signal observed with benzoyl peroxide.

1.3 Recommendations for Postmarketing Risk Management Activities

No postmarketing risk management recommendations are needed.

1.4 Recommendations for other Post Marketing Study Commitments

Other topical clindamycin, BPO, and clindamycin/ BPO drug products have been on the market for a number of years; however, it is uncertain whether long term safety data have been assessed in a systematic fashion. Acne vulgaris is considered a chronic disease and the applicant's safety database and literature references did not provide long-term safety data with use of benzoyl peroxide, clindamycin, or clindamycin/BPO topical products containing penetration enhancers such as propylene glycol. A longterm safety study as per ICH-E1A Guideline for Industry: The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Longterm Treatment of Non-Life- Threatening Conditions might be considered.

2 Introduction and Regulatory Background

The sponsor submitted a 505(b)(2) NDA marketing application for use of Acanya Gel for topical treatment of acne vulgaris in subjects twelve years of age and older. Acanya Gel is a combination product, containing 1% clindamycin (1.2% clindamycin phosphate) and 2.5% benzoyl peroxide (BPO). The applicant's proposed intended use is once daily, (b) (4) Throughout the review the combination drug product, 1% clindamycin (1.2% clindamycin phosphate) and 2.5% benzoyl peroxide (BPO), may be referred to as IDP-110 gel, (b) (4) (1/2.5) gel, **(b) (4)**, TRADENAME Gel, or Acanya Gel.

To support approval of Acanya Gel the applicant submitted data from two identical pivotal phase 3 trials (DPSI-06-22-2006-012 and DPSI-06-22-2006-017) and one phase 2 dose-ranging study (DPS-07-12-2005-002) in acne vulgaris subjects comparing the efficacy and safety of Acanya Gel with its active monads (clindamycin and BPO) in gel vehicle and gel vehicle. The phase 3 clinical trials were identical multi-center, randomized, double-blind, active and vehicle-controlled, 4-arm, parallel group comparison studies comparing the efficacy and safety of once daily applications of (b) (4) (1/2.5) gel, (b) (4) vehicle, clindamycin (1%), and benzoyl peroxide (2.5%) gels over 12 weeks in the treatment of moderate to severe acne vulgaris. Studies DPSI-06-22-2006-012 and DPSI-06-22-2006-017 and DPS-07-12-2005-002 are referred to as 012, 017, and 002; respectively, in this review. The applicant also submitted data from a phase 3 bioequivalence clinical trial (DPS 07-07-2005-001) in acne vulgaris subjects to support the 505(b)(2) regulatory route of approval.

As stated above, the applicant is seeking the 505(b)(2) route of NDA approval; however, the application does not contain a clinical trial that directly compares Acanya to an approved listed product to provide clinical information on comparative bioavailability as per 21 CFR 320.24(b)(4). Instead, the applicant submitted data from a phase 3 bioequivalence clinical trial (DPS 07-07-2005-001) in acne vulgaris subjects comparing (b) (4) Gel with the marketed topical combination product BenzaClin (clindamycin 1% - BPO 5%) Gel for 10 weeks. Bioequivalence Study DPS 07-07-2005-001 (b) (4)

According to the applicant, the formulations for Acanya Gel and (b) (4) Gel are similar with respect to excipients and excipient levels except for the following: 1) (b) (4) strength of BPO from (b) (4) 2.5%, 2) the (b) (4) amount of propylene glycol from (b) (4) and 3) the corresponding (b) (4) purified water. The applicant believes that the clinical and nonclinical safety data amassed for (b) (4) Gel fully supports Acanya Gel. In general, the applicant plans to rely on the safety data generated from (b) (4) Gel to support NDA filing for the to-be-marketed Acanya Gel.

(b) (4) Development work starting in 2004 under IND 41,733 was for Acanya Gel containing 1% clindamycin and 2.5% BPO. It should be noted that phase 1 dermal safety studies were conducted with a (b) (4) Gel formulation that is different from the "to-be-marketed" (b) (4) Gel formulation. The Division had no input in study design for the phase 3 bioequivalence clinical trial (DPS 07-07-2005-001) in acne vulgaris subjects comparing (b) (4) Gel with the marketed topical combination product BenzaClin (clindamycin 1% - BPO 5%).

Although the formulations for Acanya Gel and (b) (4) Gel maybe similar with respect to excipients and excipient levels, the applicant did not provide "head to head" data from any clinical trial to support safety and efficacy profile differences or sameness between the two drug products.

2.1 Product Information

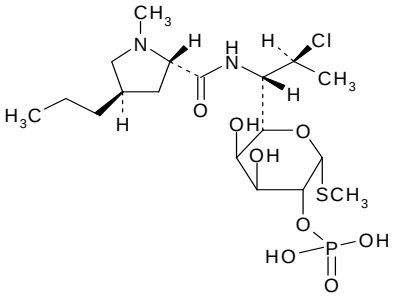
- Description of the product
  Acanya Gel (clindamycin phosphate 1.2% and benzoyl peroxide 2.5%) is a combination product with two active ingredients in a white opaque aqueous gel formulation.
- Established name and proposed trade name
  (b) (4) The applicant's (b) (4) choice, Acanya (b) (4) Gel, is currently under review.

  In a subsequent review (dated 9-26-08), the Proprietary Name Risk Assessment findings indicate that the proposed name, Acanya (b) (4) Gel, does not appear to be vulnerable to name confusion that could lead to medication errors. (b) (4) Conversely, DMEPA does not object to the use of the proprietary name Acanya Gel.
- Chemical class

Clindamycin phosphate is a water-soluble ester of the semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin. Benzoyl peroxide is an antibacterial and keratolytic agent.

The chemical name for clindamycin phosphate is *Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside 2*-(dihydrogen phosphate). The structural formula for clindamycin phosphate is represented below:

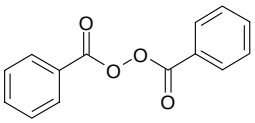
Clindamycin phosphate:



Molecular Formula: $C_{18}H_{34}ClN_2O_8PS$ Molecular Weight: 504.97

The structural formula for benzoyl peroxide is represented below:

Benzoyl peroxide:



Molecular Formula: $C_{14}H_{10}O_4$ Molecular Weight: 242.23

- Pharmacological class
  Lincosamide antibiotic and Benzoyl Peroxide

- Applicant's proposed indications, dosing regimens, age groups
  (b) (4) Gel is indicated for the topical treatment of acne vulgaris in patients 12 years or older. (b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Acne is a common skin disease with onset in adolescence and characterized by papules, pustules, and comedones. Acne vulgaris is multi-factorial in etiology, but is known to develop in the sebaceous follicles with the face as the primary site of involvement face; however, the trunk, buttocks, and extremities can also be affected. Acne vulgaris can present with varying lesion types, sizes and numbers and varying degrees of severity. The prevalence of acne is close to 100% of the population, with individuals differing only in severity of expression. Currently common approved therapies for acne vulgaris include topical (i.e., benzoyl peroxide, antibiotics, retinoids, salicyclic, azelaic acid) and systemic therapy (i.e., antibiotics, isotretinoin, hormonal).

2.3 Availability of Proposed Active Ingredient in the United States

According to the applicant, there are over 70 nonprescription BPO products, 3 prescription BPO/erythromycin combination products, 2 prescription BPO/clindamycin combination products, and 19 prescription clindamycin topical products in the US.

Antibiotic preparations containing erythromycin, tetracycline and clindamycin have become available for the topical treatment of acne vulgaris since the mid 1970s. Topical tetracycline preparations are no longer available in the US.

2.4 Important Safety Issues With Consideration to Related Drugs

The major concern in the use of any clindamycin preparation is the development of diarrhea that may be associated with pseudomembranous colitis. Orally and parenterally administered clindamycin has been associated with severe colitis, which may result in death. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin. Acanya Gel should be discontinued if significant diarrhea occurs.

Labeling for another clindamycin /benzoyl peroxide combination drug product, Duac (clindamycin 1%/benzoyl peroxide) Gel, is being updated to include a post marketing report of anaphylaxis. There is one case report of a 15 year old female in [redacted] requiring emergency room treatment and a second distinct case report involving a 22 year female from [redacted] (b) (6) In the former case, the 15 year old subsequently reported successful use of a benzoyl peroxide product for acne without allergy symptoms. While causality has not been conclusively established and anaphylaxis is rarely reported with clindamycin, the M.O. reviewer concludes that it seems reasonable to assume causality to the clindamycin component of Duac Gel.

Benzoyl peroxide is an oxidizing agent; it may bleach hair and colored fabric. Benzoyl peroxide is not considered to be a carcinogen; however, in one study, using mice known to be highly susceptible to cancer, there was evidence suggestive of benzoyl peroxide as a tumor promoter. The clinical significance of this is unknown.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Advice given to the applicant included:

- **March 7, 2005 Guidance Meeting (b) (4) (1% clindamycin/2.5% benzoyl peroxide) Gel (page 12)**

1. For a 505(b)(2) application, the sponsor should conduct comparisons to the reference listed product(s) to provide clinical information on comparative bioavailability (i.e., 21 CFR

320.24(b)(4)). See guidance meeting minutes from November 12, 2003. With regard to a 505(b)(2), the sponsor should specify the informational pieces that are sought from the reference listed drug product with regard to the Agency's findings of safety and efficacy for that listed drug product.

2. Further, this is a fixed combination product as per 21 CPR 300.50. The sponsor should adequately demonstrate that the combination dyad product is superior to each of the monads in product vehicle and the vehicle alone for each of the primary endpoints. This could be accomplished via two adequate and well-controlled clinical studies that incorporate each of the needed arms…"

- **June 27, 2006 Guidance Meeting (b) (4) (1% clindamycin/2.5% benzoyl peroxide) Gel - 505(b)(2) regulatory route (page 6)**

(Note: The applicant requested an EOP2 meeting; however, meeting advice presented as a Guidance meeting since phase 2 trial was ongoing.)
The sponsor will need to conduct two adequate and well controlled four arm studies: the sponsor's combination product vs. clindamycin in vehicle vs. benzoyl peroxide in vehicle vs. vehicle alone…."

- **September 18, 2006 End-of-Phase 2 Meeting (1% clindamycin/2.5% benzoyl peroxide) Gel**

The information provided in the briefing document appears insufficient for a waiver of phase 2 absorption studies to be granted. The Clindagel data is not sufficient to satisfy the recommended elements of the phase 2 maximal use study which would use a formulation identical to the clinically studied/to-be-marketed formulation. Clindamycin gel product absorption data in place of the combination product would require justification, since there might be differences in absorption due to a vehicle effect. Please submit your rationale to demonstrate why data from the clindamycin only product is sufficient…."

- **February 12, 2007- Submission 0081 (letter date February 9, 2007, stamp date February 12, 2007) Photosafety and Repeat Insult Patch Testing Waiver Requests**

According to the MO reviewer, the formulations for the (b) (4) 1/2.5 and the **(b) (4)** Gels are the same with respect to excipients and excipient levels except for the (b) (4) levels of benzoyl peroxide from (b) (4) 2.5%, the (b) (4) amount of propylene glycol from (b) (4) and the corresponding (b) (4) purified water. A UV/visible spectroscopic study of (b) (4) Gel formulations was conducted to evaluate the absorbance at various wavelengths of the drug products and its components. No significant absorbance for drug products or components was observed above (b) (4) nm. No photosafety concern for either (b) (4) Gel formulation was identified.

- **May 22, 2007- Clinical comments faxed to applicant.**

A waiver of photosafety and further additional insult patch testing was recommended to be granted for (b) (4) 1/ 2.5 Gel, IND 41, 733.

- **November 27, 2007 Pre-NDA Meeting (1% clindamycin/2.5% benzoyl peroxide) Gel**

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at http://www.fda.gov/cder/guidance/index.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf)).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate…"

(page 5) **Additional Clinical Comments:**
"…If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies…."
(b)
(

- **December 26, 2007 NDA 50-819 Application receipt date for (1% clindamycin/2.5% benzoyl peroxide) Gel**

Pursuant to §505(b)(2) of the Federal Food, Drug and Cosmetic Act, and in accordance with Title 21 of the Code of Federal Regulations §314.50, Dow Pharmaceutical Sciences, Inc. (DPSI) herewith submits an original New Drug Application (NDA) for (b) (4) Gel (1.2% clindamycin phosphate, 2.5% benzoyl peroxide), also known as IDP-110 Gel.

(CTD 2, Section 2.2, Introduction) DPSI performed a phase 3 bioequivalence clinical trial in acne vulgaris patients comparing (b) (4) Gel with the marketed topical combination product BenzaClin (clindamycin 1% - BPO 5%) Gel. This study confirmed the safety and efficacy of the (b) (4) Gel formulation and its bioequivalence to the already marketed BenzaClin; (b) (4)
The formulations for Acanya Gel and (b) (4) Gel are similar with respect to excipients and excipient levels except for the (b) (4) strength of BPO from (b) (4) 2.5%, the (b) (4) amount of propylene glycol from (b) (4) and the corresponding (b) (4) purified water. Therefore, DPSI believes that the clinical and nonclinical safety data amassed for

(b) (4) Gel fully supports Acanya Gel. In general, DPSI will rely on the safety data generated from (b) (4) Gel to support this NDA filing for the to-be-marketed Acanya Gel.

- **February 24, 2008**

NDA 50-819 filed.

2.6 Other Relevant Background Information

Acanya gel is not marketed in any country.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Table 1: DSI inspected the following 3 clinical study sites:

Site # (Name, Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
Site 32 Serena Mraz, M.D. Solano Clinical Research 127 Hospital Drive, #202 Vallejo, CA 94589	DPSI-06-22-2006-012	65	Acne Vulgaris
Site 40 Leonard Swinyer, M.D. Dermatology Research Center 3920 South 110 East, Suite 210 Salt Lake City, UT 84124	DPSI-06-22-2006-012	79	Acne Vulgaris
Site 72 Ronald Savin, M.D. The Savin Center, PC 134 Park Street New Haven, CT 06511	DPSI-06-22-2006-017	47	Acne Vulgaris

Study site selection rationale follows:
Selection of the three sites listed above follows:

- Principal Investigator financial disclosure indicates a potential conflict of interest. Dow Pharmaceutical Sciences and a minority shareholder.
-

Overall Assessment of Findings and Recommendations:
The overall assessment of findings and recommendations made by DSI are as follows:

Receipt of the endorsed inspection report for Dr. Mraz is pending. An addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final classification or additional observations of clinical and regulatory significance are discovered after reviewing the EIR(s).

The data generated by the sites of Drs. Mraz, Swinyer, and Savin appear acceptable in support of the respective application

3.2 Compliance with Good Clinical Practices

According to the applicant, studies were conducted in accordance with the ethical principles originating from the Declaration of Helsinki, ICH guidelines, cGCPs and in compliance with local regulatory requirements.

3.3 Financial Disclosures

The Sponsor submitted the following financial disclosure statement for all investigators except for (b) (6)

"I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."

It does not appear that the applicant submitted financial disclosure forms to NDA 50-819 for investigators participating in bioequivalence clinical trial DPS 07-07-2005-00. (b) (4)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

CMC review is pending.

4.2 Clinical Microbiology

The proposed label for Acanya Gel (clindamycin phosphate 1.2% and benzoyl peroxide 2.5%) contains no microbiologic indication. According to the Microbiology consultant, no changes to

the proposed label are recommended and that from a clinical microbiology perspective, the Application is approvable.

According to the Micro consult of concern is (as articulated in this NDA application), topical administration of clindamycin results in increased resistance to various antimicrobials (including the macrolides), and that this effect may have serious implications, including the disruption of gut and respiratory flora with overgrowth of pathogens. Recent studies have suggested that topical administration of BPO alone may be as efficacious as existing topical combinations. Resistance to BPO is currently unknown, and the potential for such resistance appears low. These two factors suggest that additional data would be useful in determining the risks and benefits of topical antimicrobial administration, and that combination products with a reduced concentration of BPO be analyzed for their relative ability to inhibit resistance.

Additional information regarding the ability of the proposed concentration of BPO (2.5%) to inhibit the development of resistance to clindamycin in relevant species including *Propionibacterium acnes* and other skin commensals was requested. This issue is concurrently pending.

4.3 Preclinical Pharmacology/Toxicology

According to the PharmTox reviewer the NDA is approvable from a Pharmacology/Toxicology perspective. (See PharmTox Review).

Key pre-clinical pharm/tox datasets (an Ames test, an in vivo micronucleus assay, a fertility study, and an embryo-fetal development toxicity study in rabbit for clindamycin phosphate or information from the literature, but not referring to any marketed pharmaceutical) are missing from this application if a sufficient clinical bridge is not established. However, it was later determined that this 505(b)(2) application is based on literature and therefore data from a clinical study (clinical bridge) is not needed for approval. However, since bioequivalence clinical trial DPS 07-07-2005-00 is deemed not sufficient and a clinical bridge is not established, the applicant cannot use information contained in the BenzaClin label.

In the absence of a clinical bridge, the application is missing the genotoxicity information for clindamycin (Ames test and in vivo micronucleus assay). The missing genotoxicity is no longer critical and not needed for approval since the applicant conducted and submitted data from an oral and a dermal carcinogenicity study with the drug product (both were negative) and benzoyl peroxide has been shown to be a tumor promoter and tumor progression agent in a number of animal studies.

4.4 Clinical Pharmacology

A direct in vivo bioavailability assessment of Acanya was not submitted in the NDA and the applicant did not provided data to indicate why a direct in vivo bioavailability study under maximal use conditions should not be conducted. At the pre-NDA meeting the applicant was advised that the agency would not commit to the granting of a waiver of in vivo bioavailability

studies. Additionally, the Gel represents a different formulation than Acanya Gel® (clindamycin phosphate 1.2%/benzoyl peroxide 2.5%) proposed for marketing, further reinforcing the need for an in vivo bioavailability study.

Biopham reviewer's conclusion and regulatory recommendation (dated 9/29/08) is that clinical pharmacology information included in this application is not adequate to support the approval of the proposed product, Acanya Gel®. Specifically, the application does not contain adequate in vivo bioavailability information required by 21 CFR §320. The clinical pharmacology review team reminded the applicant of such requirement during the End-of-Phase-2 and pre-NDA meetings.

However according to the reviewer, should the Division determine that there is sufficient safety and efficacy information in the clinical studies database for approval, Biopham still recommends that the vivo bioavailability study be conducted as a Phase IV post marketing commitment. This is in keeping with previous precedent and underscores the need for such information in drug development.

4.4.1 Mechanism of Action

Clindamycin is an antibiotic and BPO is antibacterial agent which has been shown to be effective against *P. acnes* through its oxidizing ability. BPO is assumed to reduce comedones (non-inflammatory lesions) through its keratolytic and desquamative effects.

4.4.2 Pharmacodynamics

As indicated above in Section 4.2, administration of clindamycin results in increased resistance to various antimicrobials (including the macrolides).

4.4.3 Pharmacokinetics

According to the applicant, in 1999 a phase 2 absorption study was conducted to evaluate the absorption properties of clindamycin phosphate gel (Clindagel) versus a comparator product (Cleocin T, 1.2% clindamycin phosphate [1% clindamycin] gel). This was an open label study conducted in 24 patients with acne vulgaris meeting specific inclusion and exclusion criteria. Clindagel was applied topically to the affected and unaffected areas (face, neck, shoulders, chest and back) once a day for 5 consecutive days. A range of 3 to 12 grams of gel was applied to these patients each day. Safety and laboratory endpoints included; adverse event capture, and determinations of plasma and urine levels of clindamycin in these patients. The results of this study showed that the gel was well tolerated in all patients. The 5 day treatment regimen resulted in peak plasma clindamycin concentrations that were less than 5.5 ng/ml. Urine samples collected after multiple treatment applications showed that less than 0.04% of the total dose was excreted in the urine (Cleocin T Package Insert).

The applicant concludes that pharmacokinetic data collected from this trial are consistent with reported values classical pharmacokinetic studies evaluating the half life, Cmax, Tmax, and steady state conditions for the clindamycin formulation in healthy volunteers.

5 Sources of Clinical Data

All clinical trials reviewed to support this application were conducted by or for the applicant. All phase 1 dermal safety studies (except for cumulative irritation potential Study 7002-E1HP-01-04) and Phase 3 Bioequivalence Study DPI-07-07-2005-001 were conducted with (b) (4) gel (a similar drug product). According to the applicant, the formulations for Acanya Gel and (b) (4) Gel are similar with respect to excipients and excipient levels except for the (b) (4) strength of BPO from (b) (4) 2.5%, the (b) (4) amount of propylene glycol from (b) (4) and the corresponding (b) (4) purified water.

5.1 Tables of Clinical Studies

Table 2: Clinical Studies Table

Study #	Phase	Design	Sites	Drug	Control	Review location/section
Phase 3 Studies						
DPI-06-22-2006-012	Phase 3 Efficacy and Safety	12 week, multi-center, randomized, double-blind, vehicle-controlled, 4-arm, parallel group comparison study		IDP-110 ((b) (4) (1/2.5) gel)	A: (b) (4) vehicle, B:clindamycin (1%) C: benzoyl peroxide (2.5%) gels	Section 5.3
DPI-06-22-2006-017	Phase 3 Efficacy and Safety	12 week, multi-center, randomized, double-blind, vehicle-controlled, 4-arm, parallel group comparison study		IDP-110 ((b) (4) (1/2.5) gel)	A: (b) (4) vehicle, B:clindamycin (1%) C: benzoyl peroxide (2.5%) gels	Section 5.3
DPI-07-07-2005-001	Phase 3 BE	10 Week multi-center, randomized, double-blind, vehicle-controlled, 3-arm		(b) (4)	A: Marketed BenzaClin B: vehicle ((b) (4)	Section 7.1.1
Phase 2						
DPI-	Phase 2	12 week		A: IDP-110, qd		Section 7.1.1

07-12-2005-002	dose ranging	multi-center, randomized, double-blind, vehicle-controlled, 6-arm, parallel group comparison		B: IDP-110, bid C: Clindamycin (1%) gel, qd D: BPO (2.5%) gel, qd E: BPO (2.5%) gel, bid F: (b) (4) vehicle gel, qd		
Phase 1						
7002-E1HP-01-04	Phase 1 cumulative irritation potential	3 week single center, evaluator blind, placebo controlled		A: (CP 1%, BPO 5%) B: (CP 1%, BPO3 %, PG 5%) C: (CP 1%, BPO 2.5 %, PG 10%) D: (CP 1%, BPO 2.5 %, PG 5%) E: (CP 1%, BPO 2 %, PG 4%) F: (CP 1%, BPO 1 %, PG 10%) G: (CP 1%, BPO 1 %, PG 2%)	?	Section 7.1.1
CLN-101	Phase 1 dermal irritation and contact sensitization potential in healthy human subjects as a result of repeated applications in 241 healthy subjects	single center, randomized, evaluator-blind, placebo-controlled,		A. 1% Clindamycin/5% BPO B. 5% BPO gel with placebo soln C. 1% clindamycin soln with placebo gel D Benzamycin®, (5% BPO/3% erythromycin E. Benzagel® (5% BPO)	placebo gel with placebo soln	Section 7.1.1
CLN-102	Phase 1 Phototoxicity study In 12 healthy subjects	single center, randomized, double-blind, placebo-controlled,		A. 1% Clindamycin/5% BPO B. 5% BPO/vehicle C. 1% clindamycin /vehicle	vehicle	Section 7.1.1

CLN-103	Phase 1 Photoallergic	single center, randomized, double-blind, placebo-controlled,		A. 1% Clindamycin/5% BPO B. 5% BPO/vehicle C. 1% clindamycin /vehicle	vehicle	Section 7.1.1

5.2 Review Strategy

Phase 1 dermal safety studies and pivotal phase 3 trials were reviewed individually. DPSI-06-22-2006-012 and DPSI-06-22-2006-017 are considered pivotal clinical studies and are reviewed for both efficacy and safety. Phase 3 bioequivalence study, DPI-07-07-2005-001, phase 2 dose ranging study DPI-07-12-2005-002, and phase 1 dermal safety studies are not included in efficacy assessment but are reviewed for safety.

5.3 Discussion of Individual Studies

Both pivotal clinical trials are identical in design and are multi-center, randomized, double-blind, active and vehicle-controlled, 4-arm, parallel group comparison studies comparing efficacy and safety of once daily applications of (b) (4) (1/2.5) gel, (b) (4) vehicle, clindamycin (1%), and benzoyl peroxide (2.5%) gels over 12 weeks in the treatment of moderate to severe acne vulgaris. Studies DPSI-06-22-2006-012 and DPSI-06-22-2006-017 and DPS-07-12-2005-002 are referred to as 012, 017, and 002; respectively, in the review.

Study Objective
Study objective is to evaluate the efficacy and safety, and tolerability of once daily applications of Acanya in comparison with its monads and with its vehicle in subjects with moderate to severe acne.

Inclusion Criteria
Male or female subjects between the ages of 12 and 70 (inclusive), with a score of 3 (moderate) or 4 (severe) on the EGSS assessment at the baseline visit, with facial acne inflammatory lesion (papules, pustules, and nodules) count no less than 17 but no more than 40, non-inflammatory lesion (open and closed comedones) count no less than 20 but no more than 100, and with two or fewer nodules were eligible for study entry. Women of childbearing potential were included provided that the baseline urine pregnancy test was negative and they were willing to practice effective contraception for the duration of the study.

Exclusion Criteria
Of note, the following exclusions criteria were related to safety: 1) female subjects who are pregnant, nursing mothers, planning a pregnancy during the course of the trial, or become pregnant during the study and 2) subjects with a history of regional enteritis, ulcerative colitis, inflammatory bowel disease, pseudomembranous colitis, chronic or recurrent diarrhea, or antibiotic-associated colitis.

Test Materials

Table 3: IDP-110 (1.2% Clindamycin phosphate/2.5% benzoyl peroxide):

Ingredient	%w/w	Quantity per 50 g Jar (g)
Clindamycin Phosphate, USP	1.20[1]	(b) (4)
(b) (4) Benzoyl Peroxide, USP	2.50[2]	
Propylene Glycol, USP	(b) (4)	
Carbomer 980		
Potassium Hydroxide, NF		
Purified Water, USP		

[1] Equivalent to 1% w/w clindamycin
[2] Based on (b) (4) benzoyl peroxide

Once mixed, the drug product is stored at room temperature with a 3 month expiration date from the date of mixing.

Blinding

Each site was to assign a study drug technician who served as the study drug mixer and drug dispenser for the duration of the study. Each subject kit contains four (4) cartons with each carton containing one 50g plastic jar, 10 mL plastic bottle and a mixing paddle.

Randomization

Subjects were randomized to (b) (4) (1/2.5) Gel, once daily, Clindamycin (1%) Gel, once daily, Benzoyl peroxide (2.5%) Gel, once daily, or (b) (4) Gel Vehicle, once daily on a 2:2:2:1 basis. Subjects admitted to the trial were stratified by Evaluator's Global Severity Score and skin phototype (determined by the Fitzpatrick system) and randomized.

Dosing Instructions

Test material was applied to the face once a day for a period of 12 weeks. Test materials use was limited to the face and was applied as a thin coating (a dab the size of a large pea) and gently rubbed in to the skin. Total weekly dosage of test material is anticipated to be approximately 7 g/week or 1 g/day. Hands were to be washed after study drug application. Study drug was stored at room temperature and subjects informed that the test article may bleach hair or colored fabric.

Subject Restrictions During the Study

Subjects should avoid excessive UV exposure by such activities as sun bathing or tanning parlors.

Study Assessments

The determination of efficacy was based on evaluator-blind evaluations of the signs and symptoms of acne vulgaris that included Lesion Counts, Evaluator Global Severity Score (EGSS), and Visual Analog (VAS) scores. Subjects were evaluated at Baseline and at subsequent follow-up visits (Weeks 4, 8, and 12).

Lesion Counts
The lesion count groups are inflammatory, non-inflammatory and total. Facial area lesion counts were recorded from the forehead, left and right cheeks, nose and chin. Facial inflammatory lesions (pustules, papules, and nodules) were counted as follows: pustules and papules were counted and recorded together with nodular lesions counted and recorded separately. Non-inflammatory lesions (open and closed comedones) were counted and recorded together. Lesions counts were collected at each visit and/or upon discontinuation.

Inflammatory lesions are defined as follows:
Papule – a solid, elevated lesion less than .5cm
Pustule – an elevated lesion containing pus less than .5cm
Nodule – palpable solid lesion greater than .5 cm; has depth, not necessarily elevated

Non-inflammatory lesions are defined as follows:
Open comedones (blackhead) – non infected plugged hair follicle with dilated/open orifice; black in color
Closed comedones (whitehead) – non infected plugged hair follicle: small (microscopic) opening at skin surface

Evaluator's Global Severity Score (EGSS)
The Evaluator's Global Severity Score is a static assessment that is independent of the baseline score where the investigator's assessment does not make reference to the baseline value. See Applicant's Table 12.6.2.1 below. The Visual Analogue Scale score was collected in a similar manner. The same investigator should perform each study assessment for each study subject, for consistency in evaluations. The definitions for severity are the same for the EGSS and the VAS assessment.

Table 4 (Applicant's Table 12.6.2.1) Evaluator's Global Severity Score

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost Clear	Rare non-inflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red
2	Mild	Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	Moderate	Non-inflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules, and there may or may not be one small nodulocystic lesion
4	Severe	Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be a few nodulocystic lesions
5	Very Severe	Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules and many nodulocystic lesions

According to the applicant, the Evaluator's Global Severity Scale (EGSS) used is the scale proposed at the Division of Dermatology Advisory Committee (DODAC) and this EGSS is

identical to the scale used for Ziana™ (clindamycin phosphate 1.2% and tretinoin 0.025%) Gel product. At the September 18, 2006 End-of-Phase 2 (EOP-2) Meeting, the Agency reiterated that the EGSS scoring scale should be a 5-grade rather than 6-grade scale.

According to the protocol, the VAS Scale will be compared to the conventional EGSS for validation purposes and as supportive analysis. The applicant was advised at the September 18, 2006 EOP-2 Meeting that the VAS can be measured as an exploratory secondary endpoint but would have little regulatory utility.

Efficacy Measures
Co-Primary Efficacy Variables:

- Absolute change in lesion counts
- Dichotomized in the Evaluator's Global Severity Score at Week 12.

Secondary efficacy included absolute change from baseline to Week 12 in mean non-inflammatory lesion counts. Supportive efficacy variables included mean percent change from baseline to Week 12 in inflammatory lesion counts, mean percent change from baseline to Week 12 in non-inflammatory lesion counts and absolute change from baseline to Week 12 in mean visual analogue scale.

Statistical Methods Planned
Criteria for Evaluation
The intent-to-treat (ITT) population included all subjects enrolled into the study via the Interactive Voice Response (IVR) system that were randomly assigned to treatment and had at least one post-baseline efficacy evaluation. The per-protocol (PP) population included subjects in the ITT that did not meet any of the following criteria: they took any interfering concomitant medications; did not attend the Week 12 visit (except for discontinued subjects due to an AE due to treatment or lack of treatment effect); missed more than one study visit (excluding the Week 12 visit); were not compliant with the dosing regimen (subjects were not permitted to miss more than five consecutive days of dosing and were required to take 80-120% of expected dose); and out of visit window at the 12-week visit. The safety population included all randomized subjects who received the study medication.

Efficacy was evaluated using the Evaluator's Global Severity Score (EGSS) and mean absolute change in inflammatory and non-inflammatory lesion counts. The protocol stated that efficacy would be demonstrated if at Week 12:

- Acanya was superior to each monad and vehicle in EGSS and both lesion counts;
- Acanya was superior to each monad and vehicle in mean absolute change in inflammatory lesions; and
- DP-110 was superior to vehicle in mean absolute change in non-inflammatory lesion counts.

Tests of Superiority for Lesion Count Variables (See Biostat Review)
Tests of superiority for the lesion count change variables were based on either parametric or non-parametric methods consistent with the statistical assumptions required to support the analyses.

Specifically, the tests of superiority were based on an ANOVA with factors of treatment, analysis center, and the interaction between treatment and analysis center and the respective baseline lesion count variable as a covariate or on ranked data submitted to an ANOVA with factors of treatment, analysis center, and the interaction between treatment and analysis center and the respective baseline lesion count variable as a covariate. A test for normality of the absolute or percent change from baseline in inflammatory, and non-inflammatory lesions was based on the Shapiro-Wilk test at a significance level of 0.05 and was applied to the residuals resulting from an ANOVA (unranked). Should a non-parametric analysis be indicated, the absolute or percent changes in lesion count were to be rank transformed prior to submitting them to the ANOVA. The interaction term was to be removed from the model in the event that the p-value for the interaction term is greater than 0.10.

Subset Analyses
Efficacy of Acanya was evaluated by gender, age, race, and baseline disease severity based on the EGSS.

6 INTEGRATED REVIEW of EFFICACY

Statistical superiority of combination drug product Acanya was demonstrated over clindamycin, BPO, and vehicle at predefined study endpoint (Week 12) in two well controlled, multicenter, blinded, randomized, phase 3 clinical trials for treatment of acne vulgaris.

6.1 Indication

The proposed indication is as follows: "(b) (4) Gel is indicated for the topical treatment of acne vulgaris in patients 12 years or older. (b) (4)

6.1.1 Methods

The applicant submitted data from two identical pivotal phase 3 trials, DPSI-06-22-2006-012 (012) and DPSI-06-22-2006-017 (017) in acne vulgaris subjects comparing the efficacy and safety of Acanya Gel with its active monads and its vehicle.

Table 5: Intent-to-Treat (ITT) Population

	Study 012	**Study 017**
No. of Subjects Per Study Arm	399 (IDP – 110)	398 (IDP – 110)
	408 (Clindamycin 1%)	404 (Clindamycin 1%)
	406 (Benzoyl peroxide)	403 (Benzoyl peroxide)
	201 (Vehicle)	194 (Vehicle)
Study Total	**1414**	**1399**

Study 012 was conducted at the following study sites located in the US (study period 10/04/06 to 8/21/07):

Investigators:

(b) (6)

32: Serena Mraz, M.D.

(b) (4)

(b) (6)

(b) (6)

(b) (6)

40: Leonard Swinyer, M.D.

Subjects were enrolled at 33 investigational sites located in the US, one site in Canada, and one Central America (Belize) investigational site (study period 10/05/06 to 8/13/07):

Investigators:

(b) (6)

72: Ronald Savin, M.D.

(b)

(b) (6)

(b) (6)

6.1.2 Demographics

For Study 012, the overall median age was 16.9 years, 54% were female, and 77% were Caucasian. In Study 017, the overall median age was16.6 years, 51% were female, and 77% were Caucasian) are included in the ITT study population. Table #// presents baseline demographic data per clinical trial for the ITT study population.

Table 6 (Statistical Table 21): Baseline Demographics (ITT population)

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Table 21: Baseline Demographics (ITT population)

	Study 012			
	IDP-110 n=399	Clindamycin n=408	BPO n=406	Vehicle n=201
Age (in years)				
Mean (Std)	19.3 (6.5)	19.7 (7.2)	19.4 (7.0)	19.7 (7.1)
Median	17.0	17.2	16.7	16.9
Min, Max	12.2, 46.6	12.1, 49.1	12.0, 53.8	12.2, 44.4
Gender				
Male	184 (46.1%)	193 (47.3%)	167 (41.1%)	107 (53.2%)
Female	215 (53.9%)	215 (52.7%)	239 (58.9%)	94 (46.8%)
Race				
White	308 (77.2%)	311 (76.2%)	295 (72.7%)	155 (77.1%)
Black	65 (16.3%)	70 (17.2%)	82 (20.2%)	34 (16.9%)
Asian	8 (2.0%)	16 (3.9%)	8 (2.0%)	6 (3.0%)
Other	22 (5.5%)	16 (3.9%)	24 (5.9%)	12 (6.0%)

	Study 017			
	IDP-110 n=398	Clindamycin n=404	BPO n=403	Vehicle n=194
Age (in years)				
Mean (Std)	19.1 (7.1)	19.6 (7.4)	18.9 (7.1)	18.9 (6.5)
Median	16.6	17.0	16.3	16.4
Min, Max	12.1, 54.7	12.1, 70.2	12.0, 48.4	12.3, 50.9
Gender				
Male	205 (51.5%)	199 (49.3%)	187 (46.4%)	187 (49.5%)
Female	193 (48.5%)	205 (50.7%)	216 (53.6%)	98 (50.5%)
Race				
White	310 (77.9%)	317 (78.5%)	303 (75.2%)	150 (77.3%)
Black	63 (15.8%)	63 (15.6%)	83 (20.6%)	34 (17.5%)
Asian	9 (2.3%)	11 (2.7%)	10 (2.5%)	5 (2.6%)
Other	21 (5.3%)	19 (4.7%)	15 (3.7%)	6 (3.1%)

Source: Study Report DPSI-06-22-2006-012, pg. 115; Study Report DPSI-06-22-2006-017, pg. 110; and Reviewer analysis.

Baseline Disease Characteristics

In both studies, Baseline EGSS was comparatively balanced between the four arms with majority of subjects having a baseline global score of 3 or moderate. The mean baseline inflammatory and non-inflammatory lesion counts were balanced across treatment arms in both studies.

Table 7 (Statistical Table 22): Baseline Disease Severity that follows:

Table 22: Baseline Disease Severity

	Study 012			
	IDP-110 n=399	Clindamycin n=408	BPO n=406	Vehicle n=201
EGSS				
3	328 (82.2%)	332 (81.4%)	341 (84.1%)	163 (81.1%)
4	71 (17.8%)	76 (18.6%)	65 (16.0%)	38 (18.9%)
Inflammatory lesion count				
Mean (Std)	26.8 (6.9)	26.8 (6.8)	26.3 (6.7)	26.9 (6.9)
Median	26	26	25	26
Min, Max	17, 42	17, 48	17, 42	16, 41
Non-inflammatory lesion count				
Mean (Std)	48.4 (21.7)	45.8 (20.3)	48.9 (21.3)	44.0 (20.2)
Median	43	41	44	37
Min, Max	20, 100	20, 100	20, 100	20, 100

	Study 017			
	IDP-110 n=398	Clindamycin n=404	BPO n=403	Vehicle n=194
EGSS				
3	315 (79.1%)	321 (79.5%)	326 (80.9%)	156 (80.4%)
4	83 (20.9%)	83 (20.5%)	77 (19.1%)	38 (19.6%)
Inflammatory lesion count				
Mean (Std)	26.0 (7.0)	25.7 (6.8)	25.3 (6.8)	25.3 (6.4)
Median	24.5	24	23	24
Min, Max	17, 41	17, 41	17, 42	17, 40
Non-inflammatory lesion count				
Mean (Std)	46.5 (21.1)	44.9 (20.1)	44.7 (20.8)	44.1 (18.2)
Median	40	39	39	40
Min, Max	20, 100	20, 100	20, 100	20, 94

Source: Study Report DPSI-06-22-2006-012, pg. 134; Study Report DPSI-06-22-2006-017, pg. 130; and Reviewer analysis.

6.1.3 Patient Disposition

Study 012

In Study 012, a total of 1414 subjects were included in the ITT population, 79 subjects were excluded from the safety population, and 281 subjects were excluded from the PP population. A total of 1220 subjects completed the study. One hundred ninety-four (194) subjects prematurely discontinued from the study due to the following: adverse event (10 subjects); subject request (57 subjects); protocol violation (9 subjects); lost to follow-up (98 subjects); pregnancy (1 subject); lack of efficacy (8 subjects); and other (11 subjects). Of the 79 subjects excluded from the safety population, 67 had no documented use of study medication and 12 had no post-Baseline evaluations.

Out of 202 additional subjects excluded from PP, 17 violated inclusion/exclusion requirements, 96 missed the final Week 12 evaluation, 8 used a prohibited medication, 18 were non-dosing compliant, 1 missed more than one interim visit, and 62 had an off-schedule final Week 12 evaluation.

Out of 1414 subjects enrolled in Study 012 at 32 investigative sites, 399 were randomized to Acanya, 408 to clindamycin (1%) gel, 406 to benzoyl peroxide (2.5%) gel, and 201 to the Acanya vehicle. In these same treatment groups, respectively, 357 (89.5%), 353 (86.5%), 343 (84.5%), and 167 (83.1%) subjects completed the study.

Study 017

A total of 1399 subjects were enrolled in the Study 017 and included in the ITT population, 57 subjects were excluded from the safety population and 186 subjects were excluded from the PP population. A total of 1272 subjects completed the study. One hundred twenty-seven (127) subjects prematurely discontinued from the study due to: adverse event (11 subjects); subject request (44 subjects); protocol violation (3 subjects); lost to follow-up (59 subjects); pregnancy (3 subjects); lack of efficacy (4 subjects); and other (3 subjects). Of the 57 subjects excluded from the safety population, 50 had no documented use of study medication and 7 had no post-Baseline evaluations. These subjects also were excluded from the PP population. Of the 129 additional subjects excluded from PP, 1 violated inclusion/exclusion requirements, 54 missed the final Week 12 evaluation, 14 used a prohibited medication, 15 were non-dosing compliant, and 45 had an off-schedule final Week 12 evaluation.

Of 1399 subjects enrolled in the study, 398 were randomized to Acanya, 404 to clindamycin (1%) gel, 403 to benzoyl peroxide (2.5%) gel, and 194 to the Acanya vehicle. In these same treatment groups, respectively, 367 (92.2%), 371 (91.8%), 368 (91.3%), and 166 (85.6%) subjects completed the study.

Summary table for both pivotal phase 3 studies follows:

Table 8 Enrollment Summary for Phase 3 Studies 012 and 017 (IND 41733 Doc 109)

	Study 012	**Study 017**	**Total**
Total Enrolled	1414	1399	2813
Total Completed	1220	1272	2492
Early Termination	194	127	321

6.1.4 Analysis of Primary Endpoint(s)

The applicant and the agency agreed on endpoints and study design with exception of EGSS grading scale. As previously mentioned, the Agency recommended a 5-grade scale; however, the applicant assessed EGSS on a six-point scale. For topical acne therapy, subjects categorized as Grade 5 (i.e., with many nodulocystic lesions) would have been excluded from study participation as only subjects with two or fewer nodules were eligible for study entry. Minutes from the EOP2 meeting indicates that "success" would be demonstrated if:

"1. The sponsor's combination product is superior to vehicle in inflammatory and non-inflammatory lesion counts and the global severity score, and
2. The sponsor's combination product demonstrates superiority to both monads in global severity score and inflammatory lesion counts. Non-inflammatory lesion counts will be assessed for each of the arms, however, the dyad will not have to demonstrate superiority over the monads for this endpoint."

The statistical reviewer's analysis of primary efficacy data (EGSS and lesion counts) follows on the next page in Table 9 (Statistical Table 5):

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Table 9 (Statistical Table 5): Primary Efficacy Results - Number (%) of Successes on EGSS at

Week 12 (ITT)

Table 5: Primary Efficacy Results - Number (%) of Successes on EGSS at Week 12 (ITT)

	Study 012			
	IDP-110 n=399	Clindamycin n=408	BPO n=406	Vehicle n=201
Number of successes (%)	131 (32.8%)	100 (24.5%)	96 (23.6%)	38 (18.9%)
p-value†	NA	0.002	0.001	<0.0001

	Study 017			
	IDP-110 n=398	Clindamycin n=404	BPO n=403	Vehicle n=194
Number of successes (%)	147 (36.9%)	114 (28.2%)	114 (28.3%)	27 (13.9%)
p-value†	NA	0.009	0.009	<0.0001

† P-values were calculated using logistic regression with treatment, analysis center, dichotomized skin type, and baseline severity as factors.

Missing values were imputed using LOCF

Source: Study Report DPSI-06-22-2006-012, pg. 67; Study Report DPSI-06-22-2006-017, pg. 65; and reviewer analysis.

Subjects' global severity score was dichotomized to "success" if the global severity at Week 12 was at least 2 grades less than baseline. According to the statistical reviewer's results, approximately 33% of the IDP- 110 arm subjects had a two grade improvement from baseline at Week 12 in Study 012. Also at Week 12 in Study 012, the success rate in both monad arms was approximately 24% and success rate in the vehicle study arm was approximately 19%. Success rates were approximately 37% in the Acanya arm, 28% in both monads, and 14% in the vehicle arm in Study 017. Based on the EGSS score, the differences in the success rates of Acanya compared to each monad and vehicle were statistically significant with p-values less than 0.01 in both studies.

Lesion Counts

Table 10 (Statistical Table 6) presents the statistical reviewer's results of the mean absolute change from baseline in mean absolute change from baseline in inflammatory and non-inflammatory lesion count at Week 12.

The mean absolute change in inflammatory lesion count was approximately 15 in the Acanya arm, 12 and 13 in the clindamycin and BPO arms, and 9 in the vehicle arm in Study 012. In Study 017, the mean absolute change was approximately 14 in the Acanya arm, 11 in both monad arms, and 6 in the vehicle arm. The differences in mean absolute change from baseline at

Week 12 of Acanya compared to each monads and vehicle were statistically significant with p-values less than 0.012 in both studies.

The mean absolute change in non-inflammatory lesion count was approximately 22 in the Acanya arm, 18 and 21 in the clindamycin and BPO arms, and 13 in the vehicle arm in Study 012. In Study 017, the mean absolute change was approximately 19 in the Acanya arm, 15 in both monad arms, and 8 in the vehicle arm. The differences in mean absolute change from baseline at Week 12 of Acanya compared to clindamycin and vehicle were statistically significant with p-values less than 0.007 in both studies. The difference of Acanya compared to BPO was not statistically significant with a p-value of 0.134 in Study 012. It should be noted that statistical significance in non-inflammatory lesion count of Acanya compared to each monad was not required to establish efficacy of Acanya.

Table 10 (Statistical Table 6): Primary Efficacy Results - Mean Absolute Change in Lesion Counts at Week 12 (ITT)

Table 6: Primary Efficacy Results - Mean Absolute Change in Lesion Counts at Week 12 (ITT)

	Study 012			
	IDP-110 n=399	Clindamycin n=408	BPO n=406	Vehicle n=201
Inflammatory lesions				
Mean absolute change (sd)	14.8 (10.8)	12.2 (11.6)	13.0 (10.4)	9.0 (11.9)
p-value†	NA	<0.001	0.012	<0.001
Non-inflammatory lesions				
Mean absolute change (sd)	22.1 (21.2)	17.9 (19.9)	20.6 (22.0)	13.2 (20.4)
p-value†	NA	0.005	0.134	<0.001

	Study 017			
	IDP-110 n=398	Clindamycin n=404	BPO n=403	Vehicle n=194
Inflammatory lesions				
Mean absolute change (sd)	13.7 (10.5)	11.3 (11.7)	11.2 (10.6)	5.7 (12.6)
p-value†	NA	0.003	0.001	<0.001
Non-inflammatory lesions				
Mean absolute change (sd)	19.0 (19.9)	14.9 (18.8)	15.2 (19.0)	8.3 (19.8)
p-value†	NA	0.007	0.016	<0.001

† P-values were calculated using ANCOVA with the baseline inflammatory count as covariate and treatment, analysis center, dichotomized skin type, and baseline severity as factors. Each arm was tested against IDP-110.

Missing values were imputed using LOCF.

Source: Reviewer analysis.

Analysis of Secondary Endpoints(s)

The protocol defined analyses of percent change in the inflammatory and non-inflammatory lesion count as supportive. The sponsor also proposed to analyze the absolute change from baseline to Week 12 using a visual analogue scale (VAS), completed by evaluators. The statistical review does not include analysis of the VAS as the applicant was informed that VAS would have limited regulatory utility. The differences in lesion count percent change were all statistically significant in both lesion types with p-values less than 0.037 in both studies. (See Statistical Review for details).

6.1.5 Other Endpoints

Efficacy Results over Time
Subjects were treated for 12 weeks. EGSS and lesion counts were evaluated at baseline, Weeks 4, 8, and 12. Based on analysis of success rates based on EGSS scores and mean absolute change in inflammatory and non-inflammatory lesion count over time, efficacy of Acanya increased over time (See Statistical review, page 21, Figures 1 and 2).

6.1.6 Subpopulations

Baseline demographic variables were generally balanced across treatment arms in pivotal Studies 012 and 017, average ages of subjects were 19.5 and 19.1 years, respectively. Ages ranged from 12.0 to 53.8 years in Study 012 and from 12.0 to 70.2 years in Study 017. The majority of subjects were Caucasian in both studies.

Gender

The female study population experienced a better response in the dichotomized global severity score in the Acanya Gel and clindamycin gel treatment groups but was essentially comparable to the male population in the BPO gel and vehicle gel groups.

Age

EGSS success rates were presented by age groups. The 25%, 50%, and 75% quantile of age was approximately 15.2, 16.9, and 21.1, respectively. Age groups were formed based on these quantiles. The success rate was relatively consistent across age groups studied.

Race (Ethnicity)

According to the agency's statistical reviewer the success rate of the Acanya arm was higher in Caucasians than other arms in both studies. Success rate was highest in the Clindamycin arm in `Other' subgroup in both studies. In Asians, the success rate was highest in the BPO arm. Asian and 'Other' subjects were only a small proportion of the sample and therefore inference from these subgroups has limited meaning.

According to the applicant's assessment, the absolute change in inflammatory and non-inflammatory lesions was similar for the Hispanic and White populations. The dichotomized global success rate in the Hispanic and White populations was nearly the same (38%) for the Acanya Gel treatment group. For the ITT population, there was approximately an 11% difference in the dichotomized global success rate between the White/Hispanic groups and the Black group in favor of the White/Hispanic group. There is a smaller difference observed between the racial subgroups treated with the vehicle.

Efficacy Conclusion

Statistical superiority of combination drug product Acanya gel has been demonstrated over its monads, clindamycin and BPO, and its vehicle in two well-controlled, phase 3, multi-center, randomized, double-blind, vehicle-controlled, 12 week clinical studies (012 and 017). Efficacy was evaluated using the Evaluator's Global Severity Score (EGSS) and mean absolute change in inflammatory and non-inflammatory lesion counts at Week 12 as agreed upon. All co-primary endpoints required to establish efficacy were statistically significant in both studies with p-values less than 0.012.

7 Review of Safety

Safety Summary

Bioequivalence Study DPS 07-07-2005-001 is being reviewed mainly to support safety. As previously stated, in support of an in vivo comparative bioavailability study to bridge Acanya gel to listed drug BenzaClin®, the applicant submitted Bioequivalence Study DPS-07-07-2005-001 (001) to the NDA. Study 001 is conducted with a similar but different formulation from Acanya gel (i.e., the same with respect to excipients and excipient levels except for the levels of benzoyl peroxide from 2.5%, the amount of propylene glycol from and the corresponding purified water).

Bioequivalence Study Protocol Number: DPS-07-07-2005-001
Title: "A Phase III Multi-Center, Randomized, Evaluator-Blind, Vehicle Controlled, Three-Arm Clinical Trial to Evaluate the Bioequivalence of Gel to BenzaClin® Gel, and Superiority to Gel Vehicle, in the Treatment of Acne Vulgaris"

Study Design:
A phase 3 multi-center, randomized, evaluator-blind, active controlled and vehicle-controlled, parallel comparison involving subjects with mild to severe acne vulgaris bioequivalence study with clinical endpoints.

Objectives

- To establish the bioequivalence of (b) (4) Gel, and BenzaClin® Gel in the treatment of acne vulgaris
- To establish superiority of the two active formulations over the vehicle

Inclusion Criteria
Male or female subjects 12 years of age or older with facial acne needed the following for study entry: 1) a score of 2 (mild), 3 (moderate) or 4 (severe) on the Evaluator's Global Severity assessment at the baseline visit were enrolled, 2) facial acne inflammatory lesion (papules, pustules, and nodules) count no less than 17 but no more than 40; non-inflammatory lesion (open and closed comedones) count no less than 20 but no more than 100 (comedones on the nose are included in this count); and with two or fewer nodules (defined as an inflammatory lesion greater than or equal to 5 mm in diameter). Women of childbearing potential were included provided they willing to practice effective contraception for the duration of the study and had a negative urine pregnancy test at the baseline visit.

Of note, in pivotal phase 3 studies, moderate severity (Grade 3) was needed for study participation; however, subjects were allowed entry with less severe disease (i.e., a score of 2).

Exclusion Criteria
Exclusion criteria pertaining to safety included the following: 1) female subjects who are pregnant, nursing mothers, planning a pregnancy during the course of the trial, or become pregnant during the study and 2) subjects with a history of regional enteritis, ulcerative colitis, inflammatory bowel disease, pseudomembranous colitis, chronic or recurrent diarrhea, or antibiotic-associated colitis.

Randomization and Blinding
Subjects were randomized to (b) (4) Gel, BenzaClin® Gel, and (b) (4) Gel Vehicle on a 2:2:1 basis. Due to the difference in compounding of the test materials, each site designated an unblinded technician or other designated staff person (who did not perform any subject assessments) to prepare and dispense the test material.

Selection of Doses in the Study
Subject, treatment duration, and dosage selections were based on the currently approved BenzaClin® label.

Treatment Compliance
The unblinded pharmacist or designated dispenser questioned the subject on history of medication use since the last visit and assessment of the amount of returned study medication relative to the application area.

Test Materials
Reference listed drug (RLD)
Each gram of BenzaClin Topical Gel contains, as dispensed, 10 mg (1%) clindamycin as phosphate and 50 mg (5%) benzoyl peroxide in a base of carbomer, sodium hydroxide, dioctyl sodium sulfosuccinate, and purified water.

(b) (4)

Formulation that is subject of this NDA is presented below for comparison; however, this formulation was not included in the study design of the bioequivalence study.

Table 13 IDP 110 gel -NDA 50-819 (1.2% Clindamycin phosphate/2.5% benzoyl peroxide):

Ingredient	%w/w	Quantity per 50 g Jar (g)
Clindamycin Phosphate, USP	1.20[1]	(b) (4)
(b) (4) Benzoyl Peroxide, USP	2.50[2]	
Propylene Glycol, USP	(b) (4)	
Carbomer 980		
Potassium Hydroxide, NF		
Purified Water, USP		

[1] Equivalent to 1% w/w clindamycin
[2] Based on (b) (4) benzoyl peroxide

Efficacy Variables
Lesion counts and Evaluator's Global Severity Score were assessed and collected at Baseline, Week 3, Week 6 and Week 10 (or upon discontinuation).

At each visit the evaluator counted the total number of inflammatory lesions on the subject's forehead, right cheek, left cheek, chin and nose. Nodules were counted separately but were included in the total inflammatory lesion count. At baseline, nodules were counted to determine eligibility and were included in the statistical analysis of inflammatory lesion counts. All inflammatory lesions were counted at once rather than counting papules and pustules separately. The evaluator also counted the total number of non-inflammatory lesions on the subject's forehead, right cheek, left cheek, chin and nose. All non-inflammatory lesions were counted at once, except for the nose, which was counted separately.

In the pivotal phase 3 studies, all non-inflammatory lesions were counted at once and non-inflammatory lesions on the nose were not counted separately.

Inflammatory lesions are defined as follows:
Papule – a small, solid elevation less than 5 mm in diameter. Most of the lesion is above the surface of the skin.
Pustule – a small, circumscribed elevation less than 5 mm in diameter that contains yellow-white exudate.
Nodule – an inflammatory lesion greater than or equal to 5 mm in diameter (not included in the count of total inflammatory lesions).

Non-inflammatory lesions are defined as follows:
Open comedones (black head) - a lesion in which the follicle opening is widely dilated with the contents protruding out onto the surface of the skin, with compacted melanin cells giving the plug a black appearance.
Closed comedones (white head) - a lesion in which the follicle opening is closed, but the sebaceous gland is enlarged by the pressure of the sebum build up, which in turn causes the skin around the follicle to thin and become elevated with a white appearance.

Table 14 The Evaluator's Global Severity Scale

Table 9.5.1.2.1.-1: Evaluator's Global Severity Score

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost clear	Rare, non-inflammatory lesions present with rare, non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
2	Mild	Some non-inflammatory lesions are present with few inflammatory lesions (papules/pustules only; no nodulo-cystic lesions)
3	Moderate	Non-inflammatory lesions predominate with multiple inflammatory lesions evident: several to many comedones and papules/pustules, and there may or may not be one small nodulo-cystic lesion
4	Severe	Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be a few nodule-cystic lesions
5	Very Severe	Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules and many nodulo-cystic lesions

The EGSS scoring scales are identical in all 3 phase 3 studies.

Efficacy Measures

Primary efficacy:

- Absolute change from baseline to Week 10 in mean inflammatory lesion counts;
- Absolute change from baseline to Week 10 in mean non-inflammatory lesion counts;

Secondary efficacy*:*

- Mean percent change from baseline to Week 10 in inflammatory lesion counts;
- Mean percent change from baseline to Week 10 in non-inflammatory lesion counts;
- Percent of subjects who achieved a two-point reduction at Week 10 in the Evaluator's Global Severity Score from baseline.

The Evaluator's Global Severity Score was recorded for each subject and was dichotomized into "success" and "failure" with a subject considered a success if the Global Severity Score at the Week 10 was at least two grades less than baseline.

Primary efficacy variables are different from those recommended by the Division for the acne vulgaris indication. This reviewer is uncertain whether there was agreement as to study design

and efficacy endpoints or whether this study was submitted to the Agency under IND 41,733 for review.

Primary and secondary bioequivalence analyses were conducted on the per-protocol (PP) population.
Primary and secondary superiority analyses were conducted on the intent-to-treat (ITT) population.

Bioequivalence
Statistical bioequivalence of (b) (4) Gel (Test) and BenzaClin® Gel (Reference) were based on percent change from baseline to Week 10 in inflammatory and non-inflammatory lesions and were established if the 90% confidence interval for the Test/Reference Product group ratio in the inflammatory and non-inflammatory lesion count percent change was within the interval 0.80 to 1.25 in the PP population.

Statistical methods Planned
Criteria for Evaluation
Primary Bioequivalence Analyses
Tests for demonstrating the statistical bioequivalence of (b) (4) Gel (Test) and BenzaClin® Gel (Reference) were based on absolute change from baseline to Week 10 in inflammatory and non-inflammatory lesions and were established if the 90% confidence interval for the Test/Reference Product group ratio in the inflammatory and noninflammatory lesion count absolute change was within the interval 0.80 to 1.25 in the PP population.

The analysis of bioequivalence involved only the active study drugs and was computed from estimates derived from an analysis of covariance (COVANOVA) with factors of product, stratifying baseline variables, and covariate baseline inflammatory and non-inflammatory lesion count, respectively. The ratio statistics for the 90% confidence interval was computed by the methods of Fieller's Theorem based on least squares estimates from the COVANOVA.

Secondary Bioequivalence Analyses
Secondary tests for demonstrating the statistical bioequivalence of (b) (4) Gel (Test) and BenzaClin® Gel (Reference) were based on percent change from baseline to Week 10 in inflammatory and non-inflammatory lesions and were established if the 90% confidence interval for the Test/Reference Product group ratio in the inflammatory and non-inflammatory lesion count percent change was within the interval 0.80 to 1.25 in the PP population.

The analysis of bioequivalence involved only the active study drugs and was computed from estimates derived from a COVANOVA with factors of product, stratifying baseline variables, and covariate baseline inflammatory and non-inflammatory lesion count, respectively. The ratio statistics for the 90% confidence interval were computed by the methods of Fieller's Theorem based on least squares estimates from the COVANOVA.

An additional secondary analysis of bioequivalence for the dichotomized Evaluator's Global Severity Score at Week 10 was established if the 90% confidence interval of the difference in success rates was contained within the interval –0.20 to +0.20 in the PP population. The 90% confidence interval was calculated using Wald's method with Yates' continuity correction. The analysis of bioequivalence involved only the active product groups. A last observation carried forward (LOCF) was used to estimate any missing data. Additionally, failure was imputed for the dichotomized Evaluator's Global Severity Score for subjects discontinued due to lack of treatment effect.

Superiority Efficacy Analyses
For tests of superiority, ITT subjects and all three study drugs were included in the COVANOVA analysis. Pairwise contrasts between the vehicle and each active study drug for absolute change from baseline to Week 10 for inflammatory and noninflammatory lesions were performed to provide comparisons between Test Product and Vehicle groups, as well as the Reference Product and Vehicle groups. A LOCF was used to estimate any missing lesion count data. The COVANOVA included factors of product, stratifying baseline variables, and baseline inflammatory or non-inflammatory lesion count, respectively.

Secondary Superiority Efficacy Analyses
Additional secondary superiority analyses were conducted for percent change from baseline in lesion counts. These tests for superiority were done for the ITT subjects and all three study drugs were included in the COVANOVA analysis. Pairwise contrasts between the vehicle and each active study drug for percent change from baseline to Week 10 for inflammatory and non-inflammatory lesions were performed to provide comparisons between Test Product and Vehicle groups, as well as the Reference Product and Vehicle groups. A LOCF was used to estimate any missing lesion count data. The COVANOVA included factors of product, stratifying baseline variables, and baseline inflammatory or non-inflammatory lesion count, respectively.

Also, pairwise comparisons were conducted between the vehicle and each active study drug using the Fisher's Exact test for the proportion of dichotomized Global Severity Scores as a secondary superiority analysis for the ITT subjects. An LOCF was used to estimate any missing data. Additionally, failure was imputed for the dichotomized Evaluator's Global Severity Score for subjects discontinued due to lack of treatment effect.

Descriptive Statistics
Descriptive statistics were presented for the following parameters by treatment group for both the ITT and PP populations:
- Inflammatory lesion counts at Baseline and Weeks 3, 6 and 10;
- Non-inflammatory lesion counts at Baseline and Weeks 3, 6 and 10;
- Frequency and percent distributions of the Evaluator's Global Severity Score at Baseline and Weeks 3, 6 and 10;
- Frequency and percent distributions of the dichotomized Evaluator's Global Severity Score at Baseline and Weeks 3, 6 and 10;

• Mean absolute and percent change from baseline in inflammatory lesion counts at Weeks 3, 6 and 10;
• Mean absolute and percent change from baseline in non-inflammatory lesion counts at Weeks 3, 6 and 10.

Study Results
Study Dates: September 1, 2005 to August 25, 2006
The first subject signed informed consent and was enrolled into the study on September 1, 2005 and the final subject visit occurred on August 25, 2006.

Investigators
Site: Investigator
(b) (6)

(b) (4)

Number of subjects (planned and analyzed):
A total of 1236 subjects were enrolled in the study and randomized with a ratio of 2:2:1 as follows:

- 498 Subjects randomized to (b) (4) Gel, twice daily application.
- 494 Subjects randomized to BenzaClin® Gel, twice daily application.
- 244 Subjects randomized to (b) (4) Gel Vehicle, twice daily application

(b) (4)

Two analysis populations were defined in the FDA medical reviewer's report:

Intent-to-treat population (ITT) – All subjects randomized to treatment and treated, with at least one post-baseline visit.
Per-protocol population (PP) – All subjects in the ITT population who completed the study and were evaluable for the analyses based on the protocol and FDA medical and statistical reviewer's best judgment.

According to the best judgment of the FDA medical and statistical reviewers, the determination of clinical equivalence of the two active treatments was to be assessed using the FDA's Per Protocol population (FPP), while the superiority comparison of the two active treatments to placebo was to be assessed using the FDA's Intent-to-treat population (FITT).

Statistical Analysis Results

1236 patients were enrolled. The FITT population included 1182 patients. The FPP population included 875 patients.

Table 15: number of subjects in each population per treatment arm

The following table shows the number of patients in each population per treatment arm[&]

	Test	Reference	Placebo	Total
Enrollment	**498**	**494**	**244**	**1236**
Did not receive medication	*1*	*4*		*5*
No post-dose evaluation	*16*	*18*	*11*	*45*
Sponsor's ITT population (ITT)	*481*	*472*	*233*	*1186*
Missed more than one visit	*1*	*2*		*3*
Failed inclusion criteria	*1*			*1*
Missed week 10 visit	*23*	*18*	*9*	*50*
Non-dosing compliant	*1*	*2*	*4*	*7*
Off-schedule week 10 visit	*63*	*57*	*35*	*155*
Took prohibited medicine	*2*	*5*	*1*	*8*
Total exclusion from sponsor's PP population	*108*	*106*	*60*	*274*
Sponsor's PP population (PP)	*390*	*388*	*184*	*962*
Exclusion from the FITT and FPP populations				
No baseline evaluation*[1]	3	1		4
FDA's ITT population (FITT)	**478**	**471**	**233**	**1182**
Exclusion from the FPP population				
Birth control or hormonal therapy started/switched less than three months before the study*[2]	2		1	3
Baseline lesion counts out of inclusion criteria	2	5		7
Missing week 10 visit	2	4	2	8
Out of the visit window (day 70±4) at week 10 visit	13	25	6	44
Prohibited concomitant medication use	8	9	6	23
Inclusion in the FPP population				
Discontinued due to lack of treatment effect**		+1	+1	+2
Total exclusion from FDA's PP population	138	149	74	361
FDA's PP population	**360**	**345**	**170**	**875**

&: Patient(s) may have multiple reasons to be excluded from the FITT and FPP populations.
*1: Four patients: 102-80 (test), 104-154 (reference), 104-161 (test), and 111-65 (test).
*2: Three patients: 103-36 (test), 103-114 (test), and 106-52 (placebo).
**: Two patients: 103-54 (placebo) and 104-88 (reference).

Four hundred fifty-five (455) subjects randomized to the (b) (4) treatment group completed the study and 43 subjects prematurely discontinued due to the following reasons: adverse reaction (3 subjects), subject request (15 subjects), lost to follow-up (23 subjects), pregnancy (1 subject) and other (1 subject).

Demographic Characteristics

The table below shows the age, gender, and race distribution for the FITT population.
The age, gender, and race of patients were comparably distributed among the three treatment groups for the FITT and FPP populations with/without centers 104 and 105.

Table 16: Age, gender, and race distribution for the FITT population

	Test	Reference	Placebo	Total
Age (years)				
Mean (standard deviation)	19.2 (6.15)	18.9 (6.12)	19.7 (6.63)	19.2 (6.24)
Median (range)	17.1 (12.1-46.0)	16.8 (12.0-48.4)	17.2 (12.1-48.2)	17.1 (12.0-48.4)
Gender				
Male	226	206	118	550
Female	252	265	115	632
Race*				
White	353	344	169	866
Black/African American	45	49	19	113
American Indian/Alaskan Native	5	3	4	12
Asian	23	29	13	65
Native Hawaiian/Pacific Island	5	6	5	16
Other	46	40	23	109

*: Patient 105-145 (test) missed race record in the data set.

An analysis for homogeneity of the inflammatory and non-inflammatory lesion counts for the FITT and FPP populations with/without centers 104 and 105 at the baseline visit was performed. There were no statistically significant differences among treatment arms for these populations at the baseline visit.

Four hundred fifty (450) subjects randomized to the BenzaClin® treatment group completed the study and 44 subjects prematurely discontinued due to the following reasons: adverse reaction (6 subjects), subject request (15 subjects), lost to follow-up (15 subjects), pregnancy (1 subject), and other (7 subjects). Two hundred twenty-two subjects randomized to the (b) (4) Vehicle treatment group completed the study and 22 subjects prematurely discontinued due to the following reasons: adverse reaction (2 subjects), subject request (8 subjects), and lost to follow-up (12 subjects).

The following adjustments to the submitted datasets were made in accordance with recommendations of the FDA medical reviewers and our (medical and statistical reviewers) best judgment.[1]

Exclusion from the FDA's Intent-to-treat (FITT) and Per-Protocol (FPP) populations
1) Four patients, 102-80 (test), 104-154 (reference), 104-161 (test), and 111-65 (test), did not have baseline evaluations.

Exclusion from the FDA's Per-Protocol (FPP) population
1) Three patients, 103-36 (test), 103-114 (test), and 106-52 (placebo), started or switched birth control or hormonal therapy, etc. less than three months before the study.
2) Seven patients (2:5:0 for test:reference:placebo) had baseline lesion counts out of inclusion criteria - [17,40] for papules/pustules total and [20,100] for open/closed comedones[2].
3) Eight patients (2:4:2 for test:reference:placebo) did not have a week 10 visit (early discontinuation).
4) Forty-four patients (13:25:6 for test:reference:placebo) were out of visit window (day 70±4) at the week 10 visit.

5) Twenty-three patients (8:9:6 for test:reference:placebo) used prohibited concomitant medication prior to and/or during the study.

Primary endpoint:
Percent change from baseline of inflammatory and non-inflammatory lesion counts at week 10

Table 17 (Applicant's Table 1.1) : Efficacy analysis for the percent change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at week 10 for the FITT population.

Table 1.1: Efficacy analysis for the percent change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at week 10 for the FITT population.

	Test vs. placebo			Ref. vs. placebo		
Variable	Test Drug LS Mean	Placebo LS Mean	p-value	Ref. Drug LS Mean	Placebo LS Mean	p-value
Inflammatory						
Raw	59.88	33.19	<0.0001	61.17	33.13	<0.0001
Rank	n/a	n/a	<0.0001	n/a	n/a	<0.0001
Non-inflammatory						
Raw	53.53	30.30	<0.0001	51.76	29.41	<0.0001
Rank	n/a	n/a	<0.0001	n/a	n/a	<0.0001

According to the FDA statistical reviewer, the test and reference treatments were statistically significantly better than placebo for the percent change from baseline in inflammatory and non-inflammatory lesion counts at week 10 in the FITT study population.

Table 1.2: Equivalence Analysis for the percent change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at week 10 for the FPP populations

Table 1.2: Equivalence Analysis for the percent change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at week 10 for the FPP populations

Raw				Rank	
Test LS mean	Ref. LS mean	90% Confidence Interval (%)	Pass/Fail	90% Confidence Interval (%)	Pass/Fail
Inflammatory					
61.08	61.49	92.8, 106.3	Pass	97.5, 105.6	Pass
Non-inflammatory					
54.54	52.83	96.4, 110.6	Pass	97.5, 108.0	Pass

According to the FDA statistical reviewer, the equivalence test was passed for the percent change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at week 10 for the FPP populations

Secondary efficacy endpoints:
Change from baseline of inflammatory and non-inflammatory lesion counts at week 10

Table 18 (Applicant's Table 2.1): Efficacy analysis for the change from baseline of inflammatory and noninflammatory lesion counts (raw and rank values) at week 10 for the FITT population

Table 2.1: Efficacy analysis for the change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at week 10 for the FITT population

	Test vs. placebo			Ref. vs. placebo		
Variable	Test Drug LS Mean	Placebo LS Mean	p-value	Ref. Drug LS Mean	Placebo LS Mean	p-value
Inflammatory						
Raw	15.45	8.66	<0.0001	15.62	8.52	<0.0001
Rank	n/a	n/a	<0.0001	n/a	n/a	<0.0001
Non-inflammatory						
Raw	23.71	14.12	<0.0001	23.21	13.61	<0.0001
Rank	n/a	n/a	<0.0001	n/a	n/a	<0.0001

Test and reference treatments were statistically better than placebo for the percent change from baseline in inflammatory and non-inflammatory lesion counts at week 10 in the FITT study population

Table 19 (Applicant's Table 2.2): Equivalence Analysis for the change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at week 10 for the FPP populations

Table 2.2: Equivalence Analysis for the change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at week 10 for the FPP populations

Raw				Rank	
Test LS mean	Ref. LS mean	90% Confidence Interval (%)	Pass/Fail	90% Confidence Interval (%)	Pass/Fail
Inflammatory					
15.55	15.81	91.2, 106.2	Pass	94.9, 106.8	Pass
Non-inflammatory					
24.20	23.39	94.4, 113.5	Pass	94.7, 112.5	Pass

The equivalence test was passed for the change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at Week 10 for the FPP population.

Additional analysis for the population without sites 104 and 105 were performed. Without centers 104 and 105:
1) Test and reference treatments were statistically better than placebo for the percent change from baseline in inflammatory and noninflammatory lesion counts at week 10 in the FITT study population and
2) The equivalence test was passed for the change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at Week 10 for the FPP population.

Applicant's Efficacy Conclusion
According to the applicant's analyses, at the study endpoint (Week 10), (b) (4) (b) (4) Gel and BenzaClin® Gel demonstrated statistical superiority over (b) (4) Vehicle Gel ($p<0.001$) for all primary and secondary variables.

The bioequivalence analysis of the co-primary endpoints, absolute change from Baseline in inflammatory and non-inflammatory lesions at Week 10, demonstrated bioequivalence as did the bioequivalence analyses of the co-secondary endpoints, percent change from Baseline in inflammatory and non-inflammatory lesions and dichotomized global severity.

Comparisons of active treatments to [redacted] Vehicle Gel confirmed superiority of each active treatment over [redacted] Vehicle Gel ($p<0.001$). Collectively and individually, the body of evidence supports the bio-equivalence of [redacted] Gel to BenzaClin® Gel.

The following comments on the applicant's statistical analysis were included in the statistical review:
"As described in the FDA medical review's report, the sponsor analyzed the percent change and change from baseline of inflammatory and non-inflammatory lesion counts at week 10 for their ITT and PP populations using the methods of Fieller's Theorem based on least squares estimates from the analysis of covariance with factors of treatment, stratifying baseline variables of skin tone (Fitzpatrick skin typing test) and baseline Evaluator's Global Severity Score and corresponding baseline lesion count. The sponsor's statistical analysis shows: 1) Test and reference treatments were statistically significantly better than placebo for the percent change and change from baseline of inflammatory and non-inflammatory lesion counts at week 10 for their ITT population. 2) The 90% Confidence Interval (CI) for the test/reference ratio of mean percent reduction from baseline for inflammatory lesion count to be (0.91, 1.07) and that of non-inflammatory lesion count to be (0.93, 1.11) at Week 10, within the bioequivalence limits of [0.80, 1.25]. There was no detail provided as to how the sponsor obtained the 90% confidence interval using the ANCOVA model.

According to the best judgment of the FDA medical and statistical reviewers, our statistical analysis was carried out for the inflammatory and non-inflammatory lesion counts using our traditional ANOVA model. An analysis for homogeneity of the stratifying baseline variables of skin tone and Evaluator's Global Severity Score was performed. There were no statistically significantly differences between treatment arms.

(b) (4) statistical review supports the applicant's findings that test and reference treatments were statistically better than placebo for the percent change from baseline in inflammatory and non-inflammatory lesion counts at week 10 in the FITT study population and equivalence test was passed for the change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at Week 10 for the FPP population.

Reviewer Conclusion:
Study 001 included: 1) milder disease severity (23 % of subjects had mild disease or Grade 2 at entry vs. Baseline Grade 3 entry criterion required for pivotal phase 3 studies and 2) primary efficacy variables are not those recommended by the Division for similar drug products for the acne vulgaris indication. The (b) (4) statistical review supports bioequivalence; none-the-less, data from this study does not suffice as a clinical bridge to Acanya gel.

Although (b) (4) statistical review supports the applicant's findings, it is uncertain whether statistical findings alone are sufficient **(b) (4)** The applicant is attempting to establish an indirect clinical bridge for Acanya to BenzaClin with use of data from Study DPS 07-07-2005-001 (001) conducted with BenzaClin and (b) (4) and is relying on safety data generated from (b) (4) Lack of a direct comparison does not allow for a product to product bridge and may not be sufficient for 505(b)(2) route of approval for NDA 50-819.

Should the applicant's two drug products be deemed so similar that they are interchangeable and the clinical bridge is established with use of **(b) (4)**

Safety Results (Study DPS 07-07-2005-001)

Table 20 (Applicant's Table 14.3.1): Extent of Exposure

Table 14.3.1: Extent of Exposure

	Intent-to-Treat Subjects			Per-Protocol Subjects		
	(b) (4) (N=481)	BenzaClin (N=472)	(b) (4) Vehicle (N=233)	(b) (4) (N=390)	BenzaClin (N=388)	(b) (4) Vehicle (N=184)
Duration of Treatment (Days)						
N	471	467	230	390	388	184
Mean	69.4	69.7	69.5	70.4	70.3	70.1
Median	9.2	9.8	9.8	5.7	7.1	6.5
Range	2.0-95.0	2.0-92.0	7.0-92.0	2.0-76.0	2.0-76.0	7.0-76.0
Number of Applications						
N	470	466	230	390	388	184
Mean	135.1	135.8	136.1	136.5	136.5	137.0
Median	17.3	18.4	16.8	11.4	13.7	10.9
Range	5.0-188.0	3.0-182.0	41.0-181.0	5.0-150.0	3.0-150.0	41.0-150.0
Weight of Study Medication Used (grams)						
N	450	450	223	375	375	178
Mean	51.2	57.1	56.0	52.0	57.9	57.4
Median	27.2	28.7	26.7	27.4	28.4	27.0
Range	0.8-191.0	0.8-185.3	6.4-149.5	0.8-191.0	0.8-185.3	6.9-149.5
Compliant*						
Yes	460 (98%)	454 (97%)	225 (98%)	383 (98%)	384 (99%)	184 (100%)
No	11 (2%)	12 (3%)	5 (2%)	7 (2%)	4 (1%)	0 (0%)
Unknown	10	6	3	0	0	0

* Subjects were not compliant with the dosing regimen if they applied less than 80% or more than 120% of the expected applications and/or missed more than ten (10) consecutive applications of study drug.

SOURCE: KJG\DOW\07_07_2005_001\ANALYSIS\I_EXP (Sep 20, 2006 16:58)

Table 21 (Applicant's Table 14.3.3.1): Adverse Event Characteristics (Safety Subjects)

Table 14.3.3.1: Adverse Event Characteristics
(Safety Subjects)

	(b) (4) (N=497)	BenzaClin (N=490)	(b) (4) Vehicle (N=244)
Number of Events Reported	204	204	101
Number of Subjects Reporting One or More Events[a]	148 (30%)	156 (32%)	79 (32%)
Serious[b]			
Yes	0 (0%)	6 (3%)	1 (1%)
No	204 (100%)	198 (97%)	100 (99%)
Severity of Events[b]			
Mild	111 (54%)	122 (62%)	54 (54%)
Moderate	84 (41%)	72 (36%)	38 (38%)
Severe	9 (4%)	4 (2%)	8 (8%)
Not Reported[c]	0	6	1
Relationship to Study Medication[b]			
Definitely Unrelated	123 (60%)	145 (71%)	69 (68%)
Unlikely	57 (28%)	44 (22%)	25 (25%)
Possible	4 (2%)	3 (1%)	3 (3%)
Probable	7 (3%)	5 (2%)	1 (1%)
Definitely Related	13 (6%)	7 (3%)	3 (3%)

[a] Percentages based on number of subjects.
[b] Percentages based on number of events reported.
[c] Severity was not reported on Serious Adverse Events.

SOURCE: KJG\DOW\07_07_2005_001\ANALYSIS\I_AE01_T1 (Sep 20, 2006 17:22)

Table 22 (Applicant's Table 14.3.3.2): Summary of Adverse Events (Safety Subjects)
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Table 14.3.3.2: Summary of Adverse Events
(Safety Subjects)
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Adverse Event[a]	(b) (4) (N=497)	BenzaClin (N=490)	(b) (4) Vehicle (N=244)
Eye disorders	1 (0.2%)	2 (0.4%)	2 (0.8%)
Conjunctivitis	0 (0.0%)	1 (0.2%)	0 (0.0%)
Eye inflammation	0 (0.0%)	1 (0.2%)	0 (0.0%)
Eye irritation	1 (0.2%)	0 (0.0%)	0 (0.0%)
Eye pruritus	0 (0.0%)	0 (0.0%)	1 (0.4%)
Photophobia	0 (0.0%)	0 (0.0%)	1 (0.4%)
Gastrointestinal disorders	10 (2.0%)	11 (2.2%)	3 (1.2%)
Abdominal pain	1 (0.2%)	0 (0.0%)	0 (0.0%)
Abdominal pain lower	1 (0.2%)	0 (0.0%)	0 (0.0%)
Abdominal pain upper	1 (0.2%)	1 (0.2%)	0 (0.0%)
Aphthous stomatitis	1 (0.2%)	0 (0.0%)	0 (0.0%)
Dental discomfort	0 (0.0%)	0 (0.0%)	1 (0.4%)
Diarrhoea	4 (0.8%)	2 (0.4%)	0 (0.0%)
Food poisoning	0 (0.0%)	1 (0.2%)	0 (0.0%)
Gastroenteritis eosinophilic	0 (0.0%)	1 (0.2%)	0 (0.0%)
Gastrointestinal disorder	0 (0.0%)	1 (0.2%)	0 (0.0%)
Gingival oedema	0 (0.0%)	1 (0.2%)	0 (0.0%)
Haematochezia	1 (0.2%)	0 (0.0%)	0 (0.0%)
Inguinal hernia	0 (0.0%)	0 (0.0%)	1 (0.4%)
Nausea	1 (0.2%)	1 (0.2%)	0 (0.0%)
Stomach discomfort	0 (0.0%)	1 (0.2%)	0 (0.0%)
Toothache	0 (0.0%)	2 (0.4%)	1 (0.4%)
Vomiting	0 (0.0%)	1 (0.2%)	0 (0.0%)

[a] Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the MedDRA system organ class or preferred term. At each level of summarization (system organ class or preferred term), subjects are only counted once. Percentages of subjects in each treatment group are also given.

Of note, there is a 0.8% incidence of diarrhea in (b) (4) vs. 0.4% in BenzaClin study arm. No reports of diarrhea in the vehicle study arm.

Table 23 (Applicant's Table 14.3.3.2): Summary of Adverse Events (Safety Subjects)
(Page 2 of 7)

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Table 14.3.3.2: Summary of Adverse Events
(Safety Subjects)
(Page 2 of 7)

Adverse Event[a]	(b) (4) (N=497)	BenzaClin (N=490)	(b) (4) Vehicle (N=244)
General disorders and administration site conditions	18 (3.6%)	16 (3.3%)	6 (2.5%)
Accidental death	0 (0.0%)	1 (0.2%)	0 (0.0%)
Application site dermatitis	1 (0.2%)	0 (0.0%)	1 (0.4%)
Application site dryness	4 (0.8%)	4 (0.8%)	2 (0.8%)
Application site eczema	0 (0.0%)	1 (0.2%)	0 (0.0%)
Application site erythema	2 (0.4%)	1 (0.2%)	1 (0.4%)
Application site excoriation	0 (0.0%)	1 (0.2%)	0 (0.0%)
Application site exfoliation	1 (0.2%)	0 (0.0%)	0 (0.0%)
Application site irritation	8 (1.6%)	3 (0.6%)	1 (0.4%)
Application site oedema	1 (0.2%)	0 (0.0%)	0 (0.0%)
Application site pruritus	1 (0.2%)	1 (0.2%)	1 (0.4%)
Application site swelling	1 (0.2%)	2 (0.4%)	0 (0.0%)
Influenza like illness	1 (0.2%)	3 (0.6%)	0 (0.0%)
Pyrexia	2 (0.4%)	0 (0.0%)	1 (0.4%)
Immune system disorders	3 (0.6%)	3 (0.6%)	1 (0.4%)
Drug hypersensitivity	0 (0.0%)	1 (0.2%)	0 (0.0%)
Hypersensitivity	2 (0.4%)	1 (0.2%)	0 (0.0%)
Seasonal allergy	1 (0.2%)	1 (0.2%)	1 (0.4%)
Infections and infestations	93 (18.7%)	91 (18.6%)	45 (18.4%)
Bronchitis	3 (0.6%)	1 (0.2%)	0 (0.0%)
Bronchitis acute	0 (0.0%)	0 (0.0%)	1 (0.4%)
Conjunctivitis infective	0 (0.0%)	2 (0.4%)	0 (0.0%)
Ear infection	3 (0.6%)	0 (0.0%)	3 (1.2%)
Folliculitis	1 (0.2%)	0 (0.0%)	0 (0.0%)

[a] Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the MedDRA system organ class or preferred term. At each level of summarization (system organ class or preferred term), subjects are only counted once. Percentages of subjects in each treatment group are also given.

SOURCE: KJG\DOW\07_07_2005_001\ANALYSIS\I_AE01_T2 (Oct 18, 2006, 08:19)

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Table 14.3.3.2: Summary of Adverse Events
(Safety Subjects)
(Page 3 of 7)

Adverse Event[a]	(b) (4) (N=497)	BenzaClin (N=490)	(b) (4) Vehicle (N=244)
Infections and infestations (Continued)			
Fungal infection	1 (0.2%)	0 (0.0%)	0 (0.0%)
Furuncle	0 (0.0%)	0 (0.0%)	1 (0.4%)
Gastroenteritis	4 (0.8%)	1 (0.2%)	0 (0.0%)
Gastroenteritis viral	4 (0.8%)	5 (1.0%)	2 (0.8%)
Herpes simplex	1 (0.2%)	0 (0.0%)	0 (0.0%)
Hordeolum	1 (0.2%)	0 (0.0%)	1 (0.4%)
Influenza	2 (0.4%)	6 (1.2%)	1 (0.4%)
Lower respiratory tract infection	1 (0.2%)	0 (0.0%)	1 (0.4%)
Nasopharyngitis	33 (6.6%)	27 (5.5%)	15 (6.1%)
Oral candidiasis	0 (0.0%)	0 (0.0%)	1 (0.4%)
Otitis externa	1 (0.2%)	0 (0.0%)	0 (0.0%)
Otitis media	0 (0.0%)	1 (0.2%)	1 (0.4%)
Paronychia	0 (0.0%)	1 (0.2%)	0 (0.0%)
Peritonsillar abscess	0 (0.0%)	1 (0.2%)	0 (0.0%)
Pharyngitis streptococcal	4 (0.8%)	1 (0.2%)	0 (0.0%)
Pneumonia	1 (0.2%)	0 (0.0%)	1 (0.4%)
Respiratory tract infection	0 (0.0%)	1 (0.2%)	0 (0.0%)
Sinusitis	0 (0.0%)	3 (0.6%)	1 (0.4%)
Skin infection	1 (0.2%)	0 (0.0%)	0 (0.0%)
Subcutaneous abscess	1 (0.2%)	0 (0.0%)	0 (0.0%)
Tinea infection	0 (0.0%)	1 (0.2%)	0 (0.0%)
Tonsillitis	1 (0.2%)	0 (0.0%)	0 (0.0%)

[a] Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the MedDRA system organ class or preferred term. At each level of summarization (system organ class or preferred term), subjects are only counted once. Percentages of subjects in each treatment group are also given.

SOURCE: KJG\DOW\07_07_2005_001\ANALYSIS\I_AE01_T2 (Oct 18, 2006 08:19)

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Table 14.3.3.2: Summary of Adverse Events
(Safety Subjects)
(Page 4 of 7)

Adverse Event[a]	(b) (4) (N=497)	BenzaClin (N=490)	(b) (4) Vehicle (N=244)
Infections and infestations (Continued)			
Tooth infection	1 (0.2%)	0 (0.0%)	0 (0.0%)
Upper respiratory tract infection	38 (7.6%)	38 (7.8%)	20 (8.2%)
Urinary tract infection	4 (0.8%)	2 (0.4%)	0 (0.0%)
Vaginitis bacterial	0 (0.0%)	1 (0.2%)	1 (0.4%)
Varicella	0 (0.0%)	1 (0.2%)	0 (0.0%)
Vulvovaginal mycotic infection	1 (0.2%)	1 (0.2%)	0 (0.0%)
Injury, poisoning and procedural complications	13 (2.6%)	12 (2.4%)	11 (4.5%)
Concussion	0 (0.0%)	2 (0.4%)	0 (0.0%)
Contusion	0 (0.0%)	1 (0.2%)	0 (0.0%)
Foot fracture	0 (0.0%)	0 (0.0%)	2 (0.8%)
Hand fracture	0 (0.0%)	0 (0.0%)	1 (0.4%)
Joint injury	0 (0.0%)	0 (0.0%)	1 (0.4%)
Joint sprain	3 (0.6%)	0 (0.0%)	3 (1.2%)
Ligament injury	0 (0.0%)	1 (0.2%)	0 (0.0%)
Limb injury	1 (0.2%)	2 (0.4%)	1 (0.4%)
Lower limb fracture	0 (0.0%)	0 (0.0%)	1 (0.4%)
Neck injury	0 (0.0%)	1 (0.2%)	0 (0.0%)
Post-traumatic pain	0 (0.0%)	1 (0.2%)	0 (0.0%)
Procedural pain	1 (0.2%)	1 (0.2%)	2 (0.8%)
Road traffic accident	2 (0.4%)	2 (0.4%)	0 (0.0%)
Skin laceration	1 (0.2%)	3 (0.6%)	1 (0.4%)
Sunburn	5 (1.0%)	0 (0.0%)	1 (0.4%)

[a] Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the MedDRA system organ class or preferred term. At each level of summarization (system organ class or preferred term), subjects are only counted once. Percentages of subjects in each treatment group are also given.

SOURCE: KJG\DOW\07_07_2005_001\ANALYSIS\I_AE01_T2 (Oct 18, 2006 08:19)

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Table 14.3.3.2: Summary of Adverse Events
(Safety Subjects)
(Page 5 of 7)

Adverse Event[a]	(b) (4) (N=497)	BenzaClin (N=490)	(b) (4) Vehicle (N=244)
Metabolism and nutrition disorders	1 (0.2%)	1 (0.2%)	0 (0.0%)
Diabetes mellitus non-insulin-dependent	1 (0.2%)	0 (0.0%)	0 (0.0%)
Fluid retention	0 (0.0%)	1 (0.2%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	7 (1.4%)	3 (0.6%)	2 (0.8%)
Arthralgia	2 (0.4%)	0 (0.0%)	0 (0.0%)
Back pain	2 (0.4%)	1 (0.2%)	1 (0.4%)
Costochondritis	0 (0.0%)	1 (0.2%)	0 (0.0%)
Myalgia	3 (0.6%)	0 (0.0%)	0 (0.0%)
Neck pain	0 (0.0%)	1 (0.2%)	1 (0.4%)
Nervous system disorders	11 (2.2%)	13 (2.7%)	6 (2.5%)
Headache	8 (1.6%)	10 (2.0%)	3 (1.2%)
Loss of consciousness	0 (0.0%)	0 (0.0%)	1 (0.4%)
Migraine	1 (0.2%)	0 (0.0%)	0 (0.0%)
Multiple sclerosis	0 (0.0%)	1 (0.2%)	0 (0.0%)
Sinus headache	1 (0.2%)	0 (0.0%)	1 (0.4%)
Syncope	0 (0.0%)	1 (0.2%)	1 (0.4%)
Tension headache	1 (0.2%)	1 (0.2%)	0 (0.0%)
Psychiatric disorders	4 (0.8%)	2 (0.4%)	0 (0.0%)
Attention deficit/hyperactivity disorder	1 (0.2%)	0 (0.0%)	0 (0.0%)
Depression	0 (0.0%)	2 (0.4%)	0 (0.0%)
Insomnia	2 (0.4%)	0 (0.0%)	0 (0.0%)
Stress	1 (0.2%)	0 (0.0%)	0 (0.0%)
Suicidal ideation	0 (0.0%)	1 (0.2%)	0 (0.0%)

[a] Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the MedDRA system organ class or preferred term. At each level of summarization (system organ class or preferred term), subjects are only counted once. Percentages of subjects in each treatment group are also given.

SOURCE: KJG\DOW\07_07_2005_001\ANALYSIS\I_AE01_T2 (Oct 18, 2006 08:19)

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Table 14.3.3.2: Summary of Adverse Events
(Safety Subjects)
(Page 6 of 7)

Adverse Event[a]	(b) (4) (N=497)	BenzaClin (N=490)	(b) (4) Vehicle (N=244)
Reproductive system and breast disorders	1 (0.2%)	2 (0.4%)	3 (1.2%)
Dysmenorrhoea	1 (0.2%)	1 (0.2%)	3 (1.2%)
Metrorrhagia	0 (0.0%)	1 (0.2%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	9 (1.8%)	13 (2.7%)	5 (2.0%)
Asthma	0 (0.0%)	2 (0.4%)	0 (0.0%)
Cough	3 (0.6%)	3 (0.6%)	2 (0.8%)
Dyspnoea exacerbated	0 (0.0%)	1 (0.2%)	0 (0.0%)
Nasal congestion	0 (0.0%)	2 (0.4%)	1 (0.4%)
Pharyngolaryngeal pain	4 (0.8%)	8 (1.6%)	2 (0.8%)
Pulmonary congestion	0 (0.0%)	1 (0.2%)	0 (0.0%)
Rhinorrhoea	0 (0.0%)	0 (0.0%)	1 (0.4%)
Sinus congestion	2 (0.4%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	5 (1.0%)	7 (1.4%)	3 (1.2%)
Acne	1 (0.2%)	0 (0.0%)	0 (0.0%)
Dermatitis atopic	0 (0.0%)	0 (0.0%)	1 (0.4%)
Dermatitis contact	0 (0.0%)	1 (0.2%)	0 (0.0%)
Dyshidrosis	0 (0.0%)	0 (0.0%)	1 (0.4%)
Eczema	0 (0.0%)	1 (0.2%)	0 (0.0%)
Hair growth abnormal	0 (0.0%)	1 (0.2%)	0 (0.0%)
Ingrowing nail	0 (0.0%)	1 (0.2%)	0 (0.0%)
Pityriasis rosea	1 (0.2%)	0 (0.0%)	0 (0.0%)
Rash	2 (0.4%)	0 (0.0%)	1 (0.4%)
Scar	0 (0.0%)	1 (0.2%)	0 (0.0%)
Urticaria	1 (0.2%)	2 (0.4%)	0 (0.0%)

[a] Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the MedDRA system organ class or preferred term. At each level of summarization (system organ class or preferred term), subjects are only counted once. Percentages of subjects in each treatment group are also given.

SOURCE: KJG\DOW\07 07 2005 001\ANALYSIS\I AE01 T2 (Oct 18, 2006 08:19)

Urticaria noted in both active study arms.

Table 14.3.3.2: Summary of Adverse Events
(Safety Subjects)
(Page 7 of 7)

Adverse Event[a]	(b) (4) (N=497)	BenzaClin (N=490)	(b) (4) Vehicle (N=244)
Surgical and medical procedures	3 (0.6%)	7 (1.4%)	1 (0.4%)
Breast cosmetic surgery	0 (0.0%)	0 (0.0%)	1 (0.4%)
Nail operation	1 (0.2%)	0 (0.0%)	0 (0.0%)
Tooth extraction	1 (0.2%)	5 (1.0%)	0 (0.0%)
Tooth repair	1 (0.2%)	1 (0.2%)	0 (0.0%)
Wisdom teeth removal	0 (0.0%)	1 (0.2%)	0 (0.0%)
Vascular disorders	1 (0.2%)	0 (0.0%)	0 (0.0%)
Hypertension	1 (0.2%)	0 (0.0%)	0 (0.0%)

[a] Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that map to the MedDRA system organ class or preferred term. At each level of summarization (system organ class or preferred term), subjects are only counted once. Percentages of subjects in each treatment group are also given.

SOURCE: KJG\DOW\07_07_2005_001\ANALYSIS\I_AE01_T2 (Oct 18, 2006 08:19)

7.1 Methods

Safety Monitoring
Safety assessments were conducted throughout the study at the following time points: Baseline (Visit 2, Day 0), Weeks 4, 8, and 12. For BE study 001, AEs and cutaneous safety evaluations were assessed at Baseline and at Weeks 3, 6 and 10 for each treatment group.

Safety measurements included:

- Cutaneous Safety Evaluations
- Tolerability Evaluations (subject reported evaluations of skin sensations)
- Adverse Events (AEs)

Vital signs were not collected during the study.

Cutaneous Safety Evaluation
(To be assessed at the time of the study visit.)
Scaling:
0 – None No scaling
1 – Mild Barely perceptible, fine scales present to limited areas of the face
2 – Moderate Fine scale generalized to all areas of the face
3 – Severe Scaling and peeling of skin over all areas of the face

Erythema:
0 – None No evidence of erythema present
1 – Mild Slight pink coloration
2 – Moderate Definite redness
3 – Severe Marked erythema, bright red to dusky dark red in color

Tolerability Evaluation
(To be reviewed with the Subject at the study visit as Average over the period since the previous visit.)

Itching:
0 – None No itching
1- Mild Slight itching, not really bothersome
2 – Moderate Definite itching that is somewhat bothersome
3 – Severe Intense itching that may interrupt daily activities and/or sleep

Burning:
0 – None No burning
1 – Mild Slight burning sensation; not really bothersome
2 – Moderate Definite warm, burning sensation that is somewhat bothersome
3 – Severe Hot burning sensation that causes definite discomfort and may interrupt daily activities and/or sleep

Stinging:

0 – None No stinging
1 – Mild Slight stinging sensation, not really bothersome
2 – Moderate Definite stinging sensation that is somewhat bothersome
3 – Severe Stinging sensation that causes definite discomfort and may interrupt daily activities and/or sleep

Clinical Laboratory Evaluation
Pregnancy testing of female subjects of childbearing potential was the only laboratory measurement performed during the study.

7.1.1 Clinical Studies Used to Evaluate Safety

The following clinical studies were reviewed for safety: phase 3 trials (DPSI-06-22-2006-012 and DPSI-06-22-2006-017), phase 2 dose-ranging study (DPS-07-12-2005-002), phase 3 bioequivalence clinical trial (DPS 07-07-2005-001), Phase 1 cumulative irritation potential Study 7002-E1HP-01-04 , Phase 1 dermal irritation and contact sensitization potential CLN-101, phase 1 Phototoxicity Study CLN-102, phase 1 photoallergic CLN-103.

7.1.2 Adequacy of Data

All adverse events occurring during the study will be recorded and classified on the basis of MedDRA terminology for the interim analyses intent-to-treat population.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Incidence rates were pooled for phase 3 trials (DPSI-06-22-2006-012 and DPSI-06-22-2006-017) and phase 2 dose-ranging study (DPS-07-12-2005-002. These studies were identical in duration and study drug formulation used.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall, an adequate number of subjects were exposed to the drug to satisfy recommendations in the ICH guidance on numbers needed to assess safety. However, extent and duration of exposure is inadequate in that acne is a chronic disease and the study duration was only 12 weeks in duration; however, in clinical practice patients are usually switched to a different regimen if treatment is unsatisfactory or stopped or decreased if clearance is achieved.

A total of 4803 subjects were evaluated in the clinical safety program. Of these, 314 were healthy subjects and 4489 were subjects with acne. The safety studies that included healthy subjects were the phase 1 studies (CLN-101, CLN-102, CLN-103, in which subjects were exposed to a combination 1% clindamycin/5% BPO), and 7002-E1HP-01-04 (in which subjects were exposed to a combination of 1% clindamycin and concentrations of BPO from 1% to 5%).

In phase 3 Study DPS-07-07-2005-001, acne subjects were exposed to (b) (4) Gel. A phase 2 study (DPS-07-12-2005-002) and 2 phase 3 studies (DPSI-06-22-2006-012 and DPSI-06-22-2006-017) exposed subject with acne to Acanya Gel.

The total weight of study medication used during Study 012 averaged 64.3 grams in the Acanya treatment group, 60.9 grams in the clindamycin (1%) gel treatment group, 62.1 grams in the benzoyl peroxide (2.5%) gel treatment group, and 62.9 grams in the Acanya vehicle treatment group.

The total weight of study medication used during the Study 017 averaged 58.5 grams in the Acanya treatment group, 57.8 grams in the clindamycin (1%) gel treatment group, 63.7 grams in the benzoyl peroxide (2.5%) gel treatment group, and 53.3 grams in the Acanya vehicle treatment group.

7.2.2 Explorations for Dose Response

Study medication was applied for 84 days (12 weeks) by most subjects in all four arms. The median treatment duration was 84 days for all treatment study arms in both studies. In Study 012, the mean treatment duration was 82.9 (range 9 - 116 days) in the Acanya arm, 82.2 (2 - 119 days) and 81.8 (4 - 135 days) in the clindamycin and BPO arms, and 80.8 (9 - 120 days) in the vehicle arm. The mean treatment duration was similar across treatment arms in Study 017: 82.8 (range 1 - 102 days) in the Acanya arm, 84.0 (6 - 109 days) and 82.9 (1 - 115 days) in the clindamycin and BPO arms, and 81.4 (11 - 99 days) in the vehicle arm.

Table 24 (Applicant's Table 14.3.0): Extent of Exposure - Applications of Study Medication and Dosing Compliance (DPSI-07-12-2005-002, DPSI-06-22-2006-012 and DPSI-06-22-2006-017 Combined) (Mod. 5, ISS, pg. 21)

Integrated Summary of Safety IDP-110 Gel

Table 14.3.0: Extent of Exposure - Applications of Study Medication and Dosing Compliance
(DPSI-07-12-2005-002, DPSI-06-22-2006-012 and DPSI-06-22-2006-017 Combined)
(Page 1 of 3)

Intent-to-Treat Subjects	IDP-110	Clindamycin Gel, 1%	Benzoyl Peroxide Gel, 2.5%	IDP-110 Vehicle Gel
Number of Subjects	872	894	887	434
Number of Applications				
N	831	828	822	400
Mean	81.2	81.6	81.3	79.7
STD	11.6	9.8	11.1	14.6
Range	1.0-114.0	6.0-116.0	4.0-135.0	0.0-117.0
Compliant*				
Yes	810 (97.5%)	811 (97.9%)	794 (96.6%)	381 (95.3%)
No	21 (2.5%)	17 (2.1%)	28 (3.4%)	19 (4.8%)
Unknown	41	66	65	34

* A subject was considered compliant with the dosing regimen if the subject applied at least 80% but no more than 120% of expected applications and did not miss more than five consecutive applications.

SOURCE: KGLYNN\DOW\IDP110_ISS\ANALYSIS\I_EXP (Oct 8, 2007 14:30)

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed.

7.2.4 Routine Clinical Testing

Urine Pregnancy Test for all females of childbearing potential was the only routine clinical testing performed. The testing kits were supplied by the Sponsor. Urine pregnancy tests with a minimum sensitivity of 25mIU -HCG/mL of urine was performed within 72 hours prior to the start of study medication at Visit 2 and at Visits 3, 4, and 5 (end of study).

7.2.5 Metabolic, Clearance, and Interaction Workup

According to the label, Acanya Gel should not be used in combination with erythromycin-containing products due to its clindamycin component. *In vitro* studies have shown antagonism between these two antimicrobials. The clinical significance of this *in vitro* antagonism is not known.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There is a risk of colitis associated with oral and topical use of clindamycin phosphate; however, these cases are rare in association with topical clindamycin use. Other effects that have been reported in association with topical formulations of clindamycin include abdominal pain, gastrointestinal disturbances, contact dermatitis, irritation, oily skin, and gram-negative folliculitis.

Side effects reported with the use of benzoyl peroxide include contact dermatitis, skin dryness, scaling, erythema and edema. The most frequently reported adverse reactions to the combination products of clindamycin and benzoyl peroxide are dry skin, pruritus, peeling, erythema and sunburn.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths observed in either of the two phase 3 studies or the phase 2 study. One death occurred in the BenzaClin study arm in Bioequivalence Study DPS 07-07-2005-001 due to a pedestrian auto accident.

7.3.2 Nonfatal Serious Adverse Events

There were 15 subjects with a total of 15 SAEs, all of which were evaluated by the investigators as being unrelated to study medication. Three of these SAEs resulted in early discontinuation of treatment and early termination of the subjects. In Bioequivalence Study DPS 07-07-2005-001 (001), 4 subjects had SAEs resulting in hospitalization. Of the remaining 3 SAEs in Study 001, depression was considered treatment related. Other SAEs included: severe headache, exacerbation of signs and symptoms of multiple sclerosis, and asthma (Benzaclin). One subject in the (b) (4) vehicle treatment study arm was kept in the hospital overnight for observation after elective breast reduction surgery.

The following four serious adverse events were reported during the study 012: uterine leiomyoma was reported in the Acanya treatment group, one (possible congestive heart failure) was reported in the clindamycin (1%) gel treatment group, and two others (gun shot wound and breast cancer) were reported in the benzoyl peroxide (2.5%) gel treatment group. In Study 017, six serious adverse events were reported during the study, two within each active treatment group. Depression and oppositional defiant disorder were reported in the Acanya treatment group, within the clindamycin (1%) gel treatment group one report each of appendicitis and cellulitis; and small intestinal obstruction and gallstones were reported within the benzoyl peroxide (2.5%) gel treatment group.

There were two subjects who had SAEs reported during the course of the Study DPS-07-12-2005-002. A 16-year-old male assigned to treatment with (1/2.5) Gel diagnosed with attention deficit hyperactivity disorder (ADHD) and a 16-year-old male assigned to treatment with Clindamycin (1%) Gel QD, was involved in a snow boarding accident.

Table 25 (Applicant's Table 14.3.1.2.8.1): Summary of Serious Adverse Events by System Organ Class and Preferred Term (DPSI-07-12-2005-002, DPSI-06-22-2006-012 and DPSI-06-22-2006-017 Combined) (Safety Subjects)

Table 14.3.1.2.8.1: Summary of Serious Adverse Events by System Organ Class and Preferred Term
(DPSI-07-12-2005-002, DPSI-06-22-2006-012 and DPSI-06-22-2006-017 Combined)
(Safety Subjects)
(Page 1 of 2)

	IDP-110 (N=851)	Clindamycin Gel, 1% (N=852)	Benzoyl Peroxide Gel, 2.5% (N=840)	IDP-110 Vehicle Gel (N=413)
Number of Subjects Who Reported at Least One Serious Adverse Event	4 (0.5%)	4 (0.5%)	3 (0.4%)	0 (0.0%)
Adverse Event[a]				
Infections and infestations	0 (0.0%)	2 (0.2%)	0 (0.0%)	0 (0.0%)
Appendicitis	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Cellulitis	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Injury, poisoning and procedural complications	0 (0.0%)	1 (0.1%)	1 (0.1%)	0 (0.0%)
Concussion	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Rib fracture	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Skull fractured base	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Gun shot wound	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Investigations	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Investigation	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Nervous system disorders	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Convulsion	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Psychiatric disorders	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Abnormal behaviour	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Depression	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oppositional defiant disorder	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Uterine leiomyoma	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[a] Counts reflect numbers of subjects reporting one or more adverse events classified to MedDRA (Version 9.1) system organ classes and preferred terms. At each level of summarization (system organ class or preferred term) subjects are only counted once.

SOURCE: KGLYNN\DOW\IDP110_ISS\ANALYSIS\S_AESER1 (Oct 17, 2007 08:57)

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Table 26 (Applicant's Table 14.3.1.2.8.1): Summary of Serious Adverse Events by System Organ Class and Preferred Term (DPSI-07-12-2005-002, DPSI-06-22-2006-012 and DPSI-06-22-2006-017 Combined) (Safety Subjects) Continued

Table 14.3.1.2.8.1: Summary of Serious Adverse Events by System Organ Class and Preferred Term
(DPSI-07-12-2005-002, DPSI-06-22-2006-012 and DPSI-06-22-2006-017 Combined)
(Safety Subjects)
(Page 2 of 2)

	IDP-110 (N=851)	Clindamycin Gel, 1% (N=852)	Benzoyl Peroxide Gel, 2.5% (N=840)	IDP-110 Vehicle Gel (N=413)
Adverse Event[a]				
Gastrointestinal disorders	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Small intestinal obstruction	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Surgical and medical procedures	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Cholecystectomy	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)

[a] Counts reflect numbers of subjects reporting one or more adverse events classified to MedDRA (Version 9.1) system organ classes and preferred terms. At each level of summarization (system organ class or preferred term) subjects are only counted once.

SOURCE: KGLYNN\DOW\IDP110_ISS\ANALYSIS\S_AESER1 (Oct 17, 2007 08:57)

7.3.3 Dropouts and/or Discontinuations

Table 27 (Statistical Table 4): Number (%) of Subjects Who Discontinue the Study: Classified by the Reason for Discontinuation (ITT)

Table 4: Number (%) of Subjects Who Discontinue the Study: Classified by the Reason for Discontinuation (ITT)

	Study 012			
	IDP-110 n=399	Clindamycin n=408	BPO n=406	Vehicle n=201
Subjects who discontinued	**42 (10.5%)**	**55 (13.5%)**	**63 (15.5%)**	**34 (16.9%)**
Reason				
Adverse event	1 (<1%)	3 (1%)	6 (1.5%)	0 (0%)
Subject request	13 (3.3%)	16 (3.9%)	16 (3.9%)	12 (6.0%)
Protocol violation	5 (1.3%)	0 (0%)	2 (<1%)	2 (1.0%)
Lost to follow-up	20 (5.0%)	29 (7.1%)	33 (8.1%)	16 (8.0%)
Pregnancy	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Lack of efficacy	1 (<1%)	2 (<1%)	4 (1%)	1 (<1%)
Other	2 (1.0%)	7 (1.7%)	2 (<1%)	3 (1.5%)

	Study 017			
	IDP-110 n=398	Clindamycin n=404	BPO n=403	Vehicle n=194
Subjects who discontinued	**31 (7.8%)**	**33 (8.2%)**	**35 (8.7%)**	**28 (14.3%)**
Reason				
Adverse event	6 (1.5%)	1 (<1%)	2 (<1%)	2 (1.0%)
Subject request	6 (1.5%)	11 (2.7%)	15 (3.7%)	12 (6.2%)
Protocol violation	2 (1.0%)	0 (0%)	0 (0%)	1 (1.0%)
Lost to follow-up	12 (3.0%)	20 (5.0%)	16 (4.0%)	11 (5.7%)
Pregnancy	2 (1.0%)	0 (0%)	0 (0%)	1 (1%)
Lack of efficacy	2 (1.0%)	1 (<1%)	0 (0%)	1 (1.0%)
Other	1 (<1%)	0 (0%)	1 (<1%)	1 (1.0%)

Source: Study Report DPSI-06-22-2006-012, pg. 115; Study Report DPSI-06-22-2006-017, pg. 115 and Reviewer analysis.

7.3.4 Significant Adverse Events

Other Significant Adverse Events
In study 012, eight subjects discontinued the study medication due to non-serious, treatment-related adverse events; 11 other subjects experienced treatment-related adverse events for which medication was not discontinued. Six subjects discontinued the study medication due to non-

serious, treatment-related adverse events; 5 other subjects experienced treatment-related adverse events for which medication was not discontinued.

7.4 Supportive Safety Results

Table 28 (Applicant's Table 14.3.1.2.1): Summary of Adverse Events that Resulted in Discontinuation of Study Medication (Safety Subjects) DPSI-06-22-2006-017

Table 14.3.1.2.1: Summary of Adverse Events that Resulted in Discontinuation of Study Medication (Safety Subjects)

	IDP-110 (N=387)	Clindamycin Gel, 1% (N=385)	Benzoyl Peroxide Gel, 2.5% (N=385)	IDP-110 Vehicle Gel (N=185)
Number of Subjects Who Discontinued Use of Study Mediation Due to Adverse Events	7 (1.8%)	1 (0.3%)	2 (0.5%)	3 (1.6%)
Adverse Event*				
Injury, poisoning and procedural complications	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Sunburn	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	3 (0.8%)	0 (0.0%)	1 (0.3%)	2 (1.1%)
Dermatitis contact	1 (0.3%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Acne	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Rash pruritic	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Gastrointestinal disorders	2 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Diarrhoea	2 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Abdominal pain	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Abdominal pain upper	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions	1 (0.3%)	0 (0.0%)	1 (0.3%)	1 (0.5%)
Inflammation	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Application site irritation	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.5%)
Application site pruritus	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Vascular disorders	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypertension	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

* Counts reflect numbers of subjects reporting one or more adverse events classified to MedDRA (Version 9.1) system organ classes and preferred terms. At each level of summarization (system organ class or preferred term) subjects are only counted once.

SOURCE: KGLYNN\DOW\06 22 2006 017\ANALYSIS\S AE02 (Oct 8, 2007 11:36)

Of note, there were 2 cases of diarrhea leading to study drug discontinuation in the Acanya study arm (Study 017); however, there were no reports of diarrhea leading to study drug discontinuation in Study 012.

Table 29 (Applicant's Table 14.3.1.2.1): Summary of Adverse Events that Resulted in Discontinuation of Study Medication (Safety Subjects) DPSI-06-22-2006-012

Table 14.3.1.2.1: Summary of Adverse Events that Resulted in Discontinuation of Study Medication
(Safety Subjects)

	IDP-110 (N=386)	Clindamycin Gel, 1% (N=385)	Benzoyl Peroxide Gel, 2.5% (N=376)	IDP-110 Vehicle Gel (N=188)
Number of Subjects Who Discontinued Use of Study Mediation Due to Adverse Events	1 (0.3%)	4 (1.0%)	4 (1.1%)	0 (0.0%)
Adverse Event[a]				
Skin and subcutaneous tissue disorders	0 (0.0%)	3 (0.8%)	2 (0.5%)	0 (0.0%)
Acne	0 (0.0%)	2 (0.5%)	0 (0.0%)	0 (0.0%)
Rash	0 (0.0%)	1 (0.3%)	1 (0.3%)	0 (0.0%)
Dry skin	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Erythema	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Pruritus generalised	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Urticaria localised	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Pregnancy, puerperium and perinatal conditions	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Pregnancy	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Application site irritation	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Application site pain	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Infections and infestations	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Pharyngitis streptococcal	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Injury, poisoning and procedural complications	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Gun shot wound	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)

[a] Counts reflect numbers of subjects reporting one or more adverse events classified to MedDRA (Version 9.1) system organ classes and preferred terms. At each level of summarization (system organ class or preferred term) subjects are only counted once.

SOURCE: KGLYNN\DOW\06_22_2006_012\ANALYSIS\S_AE02 (Oct 8, 2007 10:55)

7.4.1 Common Adverse Events

In Studies 012 and 017, a total of 339 (25.4%) and 301 (22.3%) subjects, respectively reported at least one adverse event. The highest proportion of subjects reporting AEs was in the BPO study arm (28.5%), followed by Acanya (27.5%), vehicle (26.6%) and clindamycin (19.7%). The proportion of subjects who experienced at least one AE was highest in Acanya arm (24.8%), followed by clindamycin (22.3%), vehicle (21.6%) and BPO (20.5%) in Study 017. See Table 30 below for AE rates by system organ classes (SOC) that experienced by at least 1% of the subjects per treatment arm.

Table 30 (Statistical Table 14): AEs by System Organ Class in at Least 1% of Subjects per Treatment Arm

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Table 14: AEs by System Organ Class in at Least 1% of Subjects per Treatment Arm

	Study 012			
SOC	IDP-110 n=386	Clindamycin n=385	BPO n=376	Vehicle n=188
Infections and infestations	56 (15.0%)	41 (10.6%)	62 (16.5%)	29 (15.4%)
Nervous system disorders	12 (3.1%)	11 (2.9%)	10 (2.7%)	5 (2.7%)
Respiratory, thoracic and mediastinal disorders	8 (2.1%)	8 (2.1%)	12 (3.2%)	3 (1.6%)
Gastroinetestinal disorders	6 (1.6%)	8 (2.1%)	5 (1.3%)	7 (3.7%)
Injury, poisoning and procedural complications	12 (3.1%)	7 (1.8%)	11 (2.9%)	6 (3.2%)
Psychiatric disorders	5 (1.3%)	4 (1.0%)	3 (0.8%)	0 (0.0%)
Skin and subcutaneous tissue disorders	3 (0.8%)	3 (0.8%)	9 (2.4%)	3 (1.6%)
General disorders and administration site conditions	2 (0.5%)	3 (0.8%)	5 (1.3%)	2 (1.1%)
Musculoskeleta and connective tissue disorders	4 (1.0%)	2 (0.5%)	4 (1.1%)	2 (1.1%)

	Study 017			
SOC	IDP-110 n=387	Clindamycin n=385	BPO n=385	Vehicle n=185
Infections and infestations	54 (14.0%)	52 (13.5%)	54 (14.0%)	18 (9.7%)
Respiratory, thoracic and mediastinal disorders	17 (4.4%)	14 (3.6%)	5 (1.3%)	10 (5.4%)
Gastroinetestinal disorders	6 (1.6%)	7 (1.8%)	7 (1.8%)	1 (0.5%)
Injury, poisoning and procedural complications	5 (1.3%)	7 (1.8%)	5 (1.3%)	4 (2.2%)
Nervous system disorders	16 (4.1%)	5 (1.3%)	6 (1.6%)	4 (2.2%)
General disorders and administration site conditions	2 (0.5%)	4 (1.0%)	3 (0.8%)	3 (1.6%)
Skin and subcutaneous tissue disorders	4 (1.0%)	2 (0.5%)	5 (1.3%)	4 (2.2%)
Surgical and medical procedures	1 (0.3%)	0 (0.0%)	4 (1.0%)	0 (0.0%)

Source: Study Report DPSI-06-22-2006-012, pg. 301-308; and Study Report DPSI-06-22-2006-017, pg. 300-306.

The most common AEs in the infections and infestations class were nasopharyngitis and upper respiratory tract infection in both studies.

The greatest number of AEs for all groups were related to Infections and Infestations (mainly upper respiratory tract infections and nasopharygitis) where (b) (4) Gel had 93/204 (18.7%) compared to 91/204 (18.6%) for BenzaClin and 45/101 (18.4%) for the vehicle. AEs related to General Disorders and Administration Site Conditions were 18 (3.6%), 16 (3.3%), and 6 (2.5%) for (b) (4) Gel, BenzaClin and vehicle, respectively.

The sponsor provided a summary of local signs and symptoms with use of Acanya (b) (4) Gel and vehicle gel -combined results from 2 studies (DPSI-06-22-2006-012 and DPSI-06-22-2006-017)

Table 31 (Applicant's Seq. 19 Amendment 9/15/08)Local Signs and Symptoms with Use of Acanya (b) (4) Gel and Vehicle Gel -
Combined Results from 2 Studies (DPSI-06-22-2006-012 and DPSI-06-22-2006-017)

Local signs and symptoms with use of ACANYA (b) (4) Gel and vehicle gel Combined results from 2 studies						
ACANYA (b) (4) Gel (n= 773)						
	Before Treatment (Baseline)			End of Treatment (Week 12)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	22%	4%	0%	15%	2%	0%
Scaling	8%	<1%	0%	8%	1%	0%
Itching	10%	2%	0%	6%	<1%	0%
Burning	3%	<1%	0%	2%	<1%	0%
Stinging	2%	<1%	0%	1%	<1%	0%
Vehicle Gel (n=373)						
	Before Treatment (Baseline)			End of Treatment (Week 12)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	19%	4%	0%	17%	3%	<1%
Scaling	8%	1%	0%	12%	2%	0%
Itching	11%	1%	0%	5%	<1%	0%
Burning	2%	<1%	0%	2%	0%	0%
Stinging	2%	<1%	0%	<1%	0%	0%

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DPS-07-12-2005-002 Table 14.3.5 Summary of Cutaneous Safety and Tolerability at Each Evaluation (Safety Subjects)

Overall, the twice daily Acanya Gel, and the twice daily BPO (2.5%) gel treatments caused more scaling, erythema, burning, and stinging over the 12 weeks of treatment. At Week 4, itching was more prevalent in the Acanya Gel b.i.d. and the BPO (2.5%) gel q.d. treatment groups; subjects treated with Acanya Gel vehicle q.d. had the highest mean itching at Week 8, with the vehicle showing the highest itching scores. After that time, the incidence for all groups declined to baseline levels. The detailed results of the cutaneous and safety tolerability evaluations are in: DPS-07-12-2005-002 Listing 16.2.7.1.2 Cutaneous Safety and Tolerability Evaluations

Figure 2.7.4.2.5.1.2.2.1 Cutaneous and Safety Tolerability at Each Evaluation: Scaling

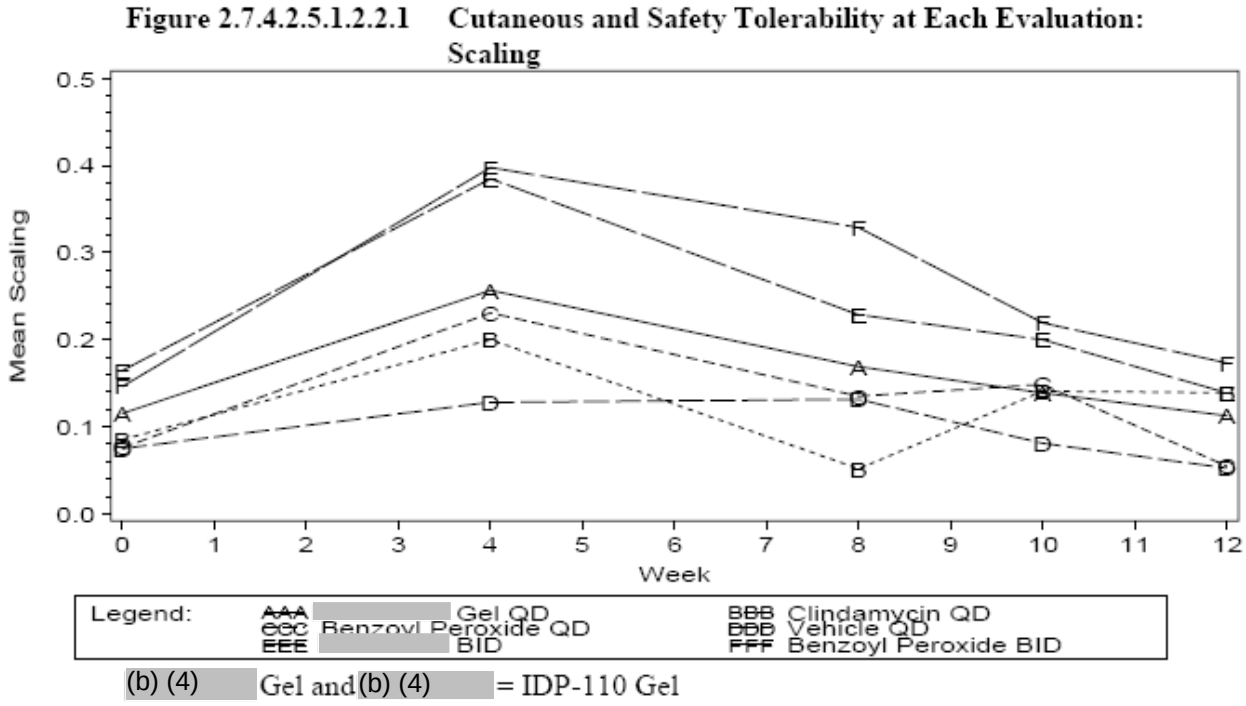


Figure 2.7.4.2.5.1.2.2.2 Cutaneous and Safety Tolerability at Each Evaluation: Erythema

Figure 2.7.4.2.5.1.2.2.2 Cutaneous and Safety Tolerability at Each Evaluation: Erythema

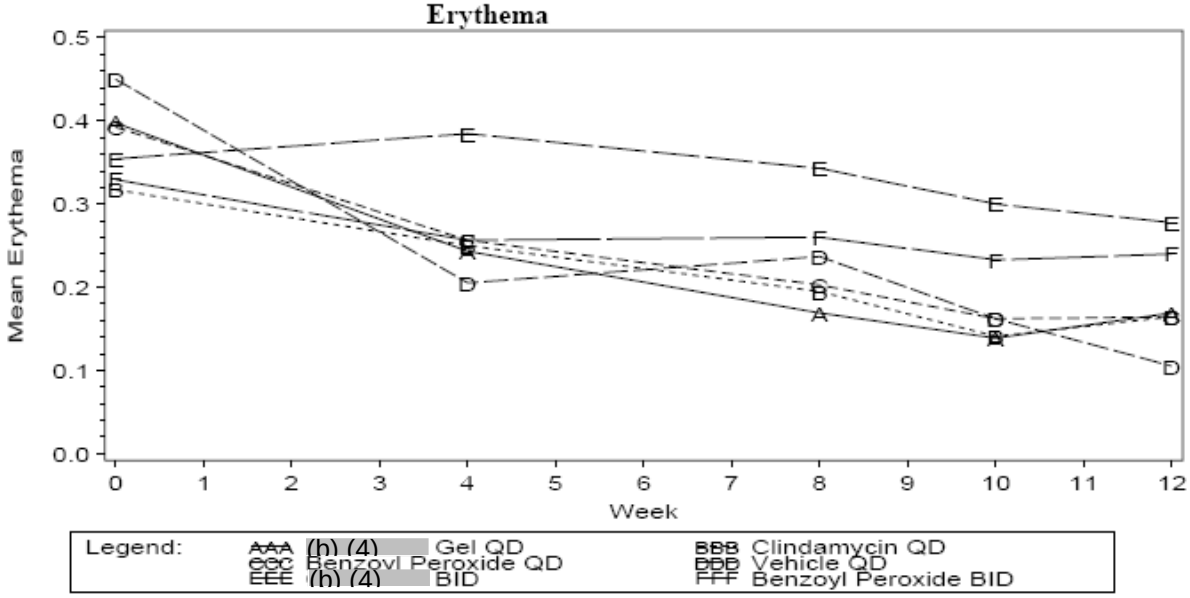


Figure 2.7.4.2.5.1.2.2.3 Cutaneous and Safety Tolerability at Each Evaluation: Itching

Figure 2.7.4.2.5.1.2.2.3 Cutaneous and Safety Tolerability at Each Evaluation: Itching

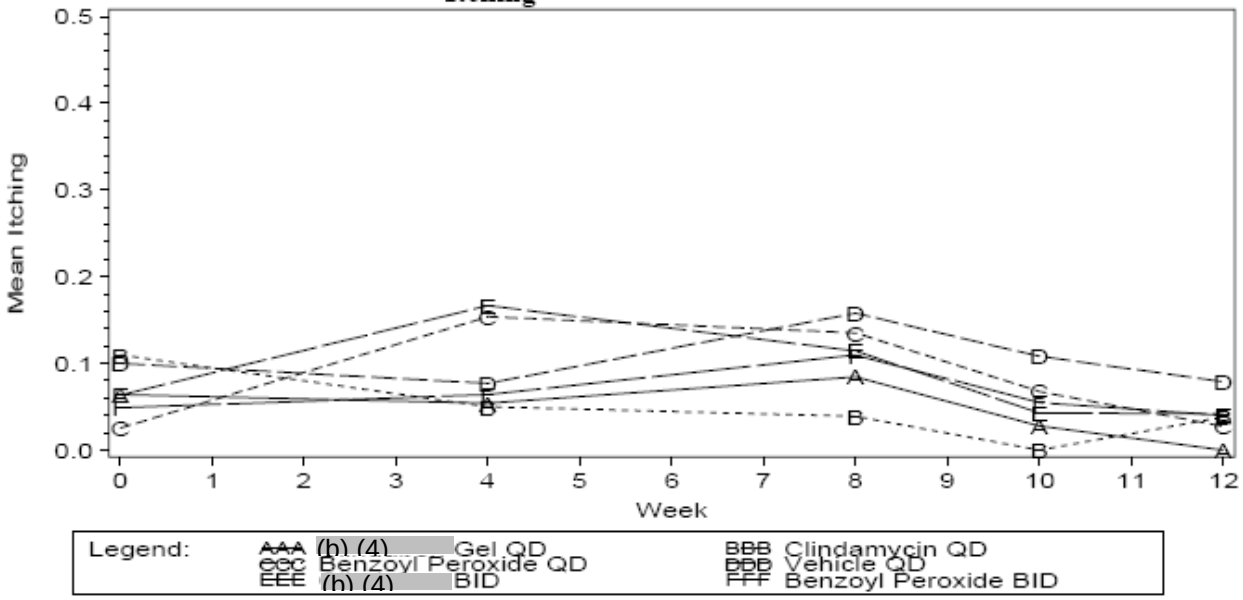


Figure 2.7.4.2.5.1.2.2.4 Cutaneous and Safety Tolerability at Each Evaluation: Burning

Figure 2.7.4.2.5.1.2.2.4 Cutaneous and Safety Tolerability at Each Evaluation: Burning

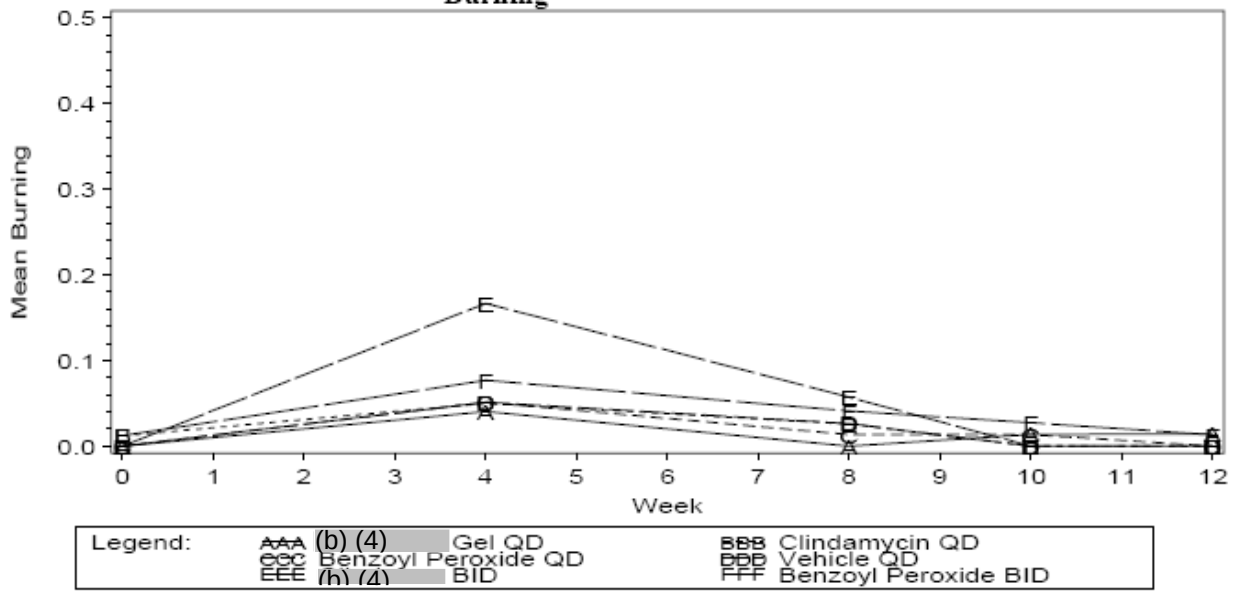
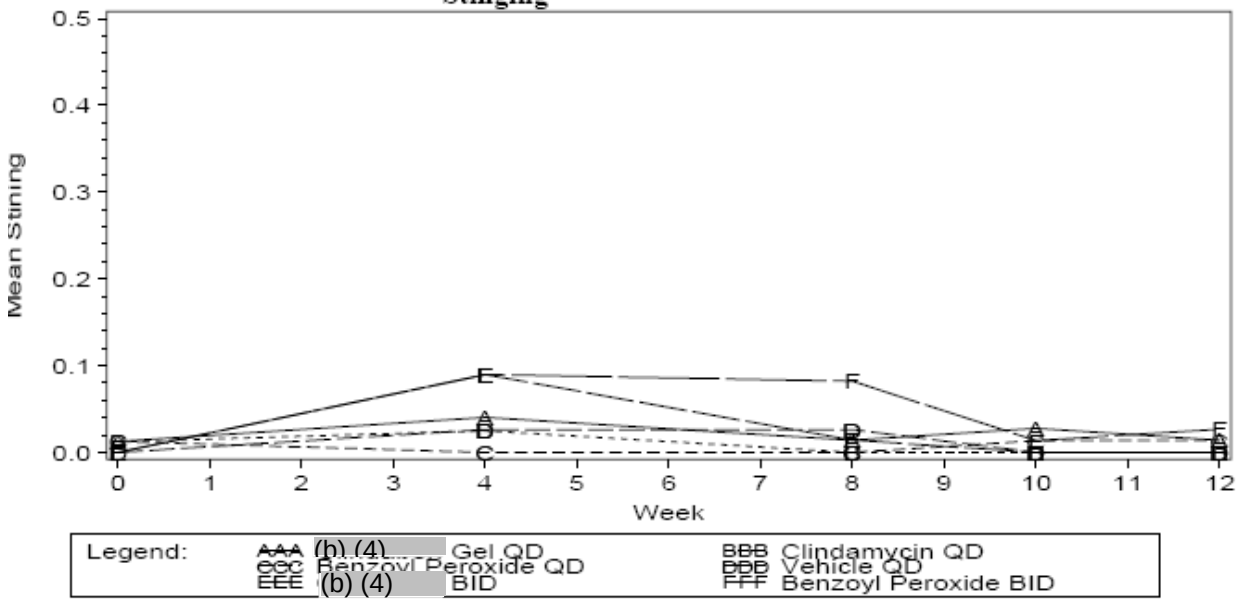


Figure 2.7.4.2.5.1.2.2.5 Cutaneous and Safety Tolerability at Each Evaluation: Stinging

Figure 2.7.4.2.5.1.2.2.5 Cutaneous and Safety Tolerability at Each Evaluation: Stinging



Cutaneous Safety Conclusion

In regard to cutaneous safety and tolerability, no substantive differences were observed between Acanya gel, its vehicle gel, clindamycin gel, and BPO gel in scaling, erythema, itching, burning,

and stinging. At the end of Study 012 and Study 017, the percentage of subjects with mild to moderate scaling ranged from 8% (Acanya) to 14% (Acanya vehicle) and from 8.1% (clindamycin [1%] gel) to 14.5% (Acanya vehicle), respectively. The percentage of subjects across all treatment groups who had mild to moderate erythema, itching, burning, and stinging were similar between the two phase 3 pivotal studies. At Week 12 for Studies 012 and 017, mild to moderate erythema, itching, burning, and stinging were approximately 15%, 6%, 2%, and 1% and 18%, 5%, 2%, and 1%, respectively.

7.4.2 Laboratory Findings

Pregnancy testing was the only laboratory testing performed during the study period.

7.4.3 Vital Signs

Vital signs were not monitored.

7.4.4 Electrocardiograms (ECGs)

ECGs were not obtained.

7.4.5 Special Safety Studies

Dermal Safety Studies

Waivers Granted

The applicant submitted data from four dermal safety studies 1) Study Protocols CLN-102 (A Single Center, Placebo-Controlled Phototoxicity Study Of 1% Clindamcin/5% Benzoyl Peroxide Gel In Health Volunteers"), 2) CLN-103 ("(A Single Center, Placebo-Controlled Photoallergy Study Of 1% Clindamcin/5% Benzoyl Peroxide Gel In Health Volunteers"), 3) Phase 1 Study 7002-E1HP-01-04: 21-Day Cumulative Irritation, and 4) Protocol No. CLN-101 "A Single-Center, Placebo Controlled, Contact Irritation/ Sensitization Study In Health Volunteers (A Human Repeat Insult Patch Test)". All dermal safety studies (except the cumulative irritation potential study) were conducted with (b) (4) Gel. The applicant submitted a formal request (S#081) and was granted a waiver to conduct photosafety and repeat insult patch test studies for (b) (4) Gel (1/2.5%).

The following statement is from Memorandum to File for IND 41,733 (dated March 12, 2007, Serial # 081):

> "The sponsor has submitted a formal waiver request for the requirement to conduct the photosafety and repeat insult patch test studies for (b) (4) Gel (1/2.5%). UV/Visible spectra data **(b) (4)** are submitted as the rationale for the waiver. The formulations for the (b) (4) 1/2.5 and the (b) (4) Gels are the same with respect to excipients and excipient levels except for the (b) (4) levels of benzoyl peroxide from (b) (4) 2.5%, the

(b) (4) amount of propylene glycol from (b) (4) and the corresponding (b) (4) purified water."

The following formulation was used in conduct of the dermal safety studies:

Components/Composition of Drug Product After Admixture:

		%w/w
Active Constituents:	clindamycin phosphate, USP	(b) (4)
	(b) (4) benzoyl peroxide, USP	
Inactive Constituents:	(b) (4)	

This (b) (4) *formulation is different from the "to-be-marketed"* (b) (4) *formulation.*

(b) (4)

Phase 1 Study 7002-E1HP-01-04: 21-Day Cumulative Irritation
A Single Center, Evaluator-Blind Determination of the Cumulative Irritation Potential of (b) (4) Gel Formulations and Control Following Repeated Topical Application to Healthy Subjects.

Study Period: June 10, 2004 - July 14, 2004
Design: Single-center, evaluator-blind

Study Population: Healthy male or female subjects 18 years of age or older

Primary objective: To estimate the cumulative irritation to the test materials on the intent-to-treat (ITT) population.

Treatment Duration: 3 weeks under occlusion

Study Procedures
(b) (4) Gel formulations and sodium lauryl sulfate (0.1 mL) were applied under separate occlusive patches on the backs of subjects three times a week for three weeks. Each application was observed 48 hours (72 hours on weekends) later for signs of irritation or inflammation.

(b) (4) Gel Formulations and Control Tested

Table 33 (Applicant's Table 2.7.4.1.1.4.1) (b) (4) Gel Formulations

Table 2.7.4.1.1.4.1 Gel Formulations

Designation	A	B	C	D	E	F	G
Clindamycin phosphate (CP)	1%	1%	1%	1%	1%	1%	1%
BPO	5%	3%	2.5%	2.5%	2%	1%	1%
Propylene glycol (PG)	10%	6%	10%	5%	4%	10%	2%
Control Test Article	Sodium Lauryl Sulfate, 0.3%						

Criteria for Evaluation:
The following grading system was used:
0 = No sign of irritation
0.5 = Barely perceptible erythema
1 = Slight erythema
2 = Noticeable erythema with slight infiltration
3 = Erythema with marked edema
4 = Erythema with edema and blistering

For each test article the irritation scores from all subjects was added across evaluation days to calculate a cumulative irritation score. A Grade 4 score was carried forward. If a subject discontinued early, the last observed evaluation scores for all test articles was carried forward.

The cumulative irritation scores were tested pair-wise for test article differences using Fisher's protected least significant differences with the two-way analysis of variance (ANOVA), including main effects of subject and test article without interaction.

Study Results
Thirty-five healthy subjects were enrolled and 33 subjects completed the study. Of randomized to receive the test articles. Thirty-three (33) subjects completed the study. Of the subjects who did not complete, one subject had the drug applied but had no evaluations since this subject did not return to the site after the first study visit. The other subject that did not complete the study was discontinued due to non-compliance with study visits.

There were 35 evaluable subjects that received 9 gradings with a highest possible score of 4 per grading, the maximum cumulative irritation score was 1260 (35 subjects x 9 evaluations x Grade 4= 1260). The total scores for each treatment group ate found in Table 1.

Table 24 (Applicant's Table 1) Ratio of Total Score to Total Score Possible

Table 1
Ratio of Total Score to Total Score Possible

Treatment		Total Score/Maximum Possible Score
(b) (4)	Gel (5% BPO, 1% CP, 10% PG)	358.0/1260
	Gel (3% BPO, 1% CP, 6% PG)	281.5/1260
	Gel (2.5% BPO, 1% CP, 10% PG)	275.0/1260
	Gel (2.5% BPO, 1% CP, 5% PG)	240.0/1260
	Gel (2% BPO, 1% CP, 4% PG)	259.5/1260
	Gel (1% BPO, 1% CP, 10% PG)	258.0/1260
	Gel (1% BPO, 1% CP, 2% PG)	234.0/1260
Sodium Lauryl Sulfate, 0.3%		152.5/1260

All 35 subjects have been included in the computation of the Maximum Possible Score for each treatment.

SOURCE: jmorway\DOW\7002E1HP\21DAY_1\I_RATIO (Jul 30, 2004 15:31)

The cumulative irritation scores were tested pair-wise for test article differences using Fisher's protected least significant differences with the two-way analysis of variance (ANOV A), including main effects of subject and test article without interaction. The results of this analysis are shown in Table 2. (b) (4) Gel Formulation A (5% Benzoyl peroxide, 10% Propylene glycol, 1 % Clindamycin phosphate) was statistically significantly more irritating than all other (b) (4) Gel formulations. When the Benzoyl peroxide concentration was reduced to 3% or 2.5% (with 6% and 5% Propylene glycol, respectively), mean irritation scores were reduced by 21.4% and 32.9%, respectively.

Conclusion:

This reviewer concurs with the applicant's assessment that cumulative irritation scores increased in a dose response manner with increasing BPO concentration. There were two pairs of formulations with the same concentration of BPO (1% and 2.5%) but different concentrations of propylene glycol. Formulations with increased propylene glycol concentration resulted in numerically higher cumulative irritation scores.

Protocol No. CLN-101
"A Single-Center, Placebo Controlled, Contact Irritation/ Sensitization Study In Health Volunteers (A Human Repeat Insult Patch Test"

Study Period: May 5, 1993 through 11 July 1993. A confirmatory rechallenge was conducted on selected subjects from July 26, 1993 through July 30, 1993.

Study Design
This was a randomized, double-blind, placebo-controlled, Phase I investigation using 241 healthy male or female volunteers ages 18 to 65 years of age to evaluate the contact irritation/sensitization potential of clindamycin/benzoyl peroxide gel combination, gel containing the individual components, and the gel vehicle. Two marketed treatments were included for comparison.

Of note, Acanya (1% clindamycin phosphate solution/2.5% benzoyl peroxide gel combination) is not included in the panel. The applicant received a waiver from conduct of an additional sensitization study because (b) (4) *1/2.5 and* (b) (4) *Gels formulations are the same with respect to excipients and excipient levels except for the* (b) (4) *levels of benzoyl peroxide from* (b) (4) *2.5%, the* (b) (4) *amount of propylene glycol from* (b) (4) *and the corresponding* (b) (4) *purified water. (See below- Waivers Granted)*

Test Materials
The Sponsor supplied the following formulations (b) (4)

- 1 % clindamycin phosphate solution/5% benzoyl peroxide gel combination;
- 5% benzoyl peroxide gel with placebo solution;
- 1 % clindamycin phosphate solution with placebo gel;
- placebo gel with placebo solution.
- Benzamycin® (5% benzoyl peroxidej3% erythromycin)
- Benzagel® (5% benzoyl peroxide)

(b) (4)

Study Procedures
The study consisted of a two week screening period followed by 10 exposures with the test solutions under semi-occluded patches over a 6-week period as follows:

- Screening Phase -2 week Screening/Recruitment Phase

- Induction Phase -- 9 applications during 3 weeks
- Rest Period - absence of application for 14 days
- Challenge Phase - 1 additional application duiring the week following g the Rest Phase .

Patches were applied to the upper back and dermal irritation/sensitization was evaluated every 48 hours (72 hours over the weekend).

Grading of Response

Grade	Interpretation
Negative (0)	No Reaction
Plus/Minus (±)	Minimal Reaction (faint erythema)
One Plus (+)	Definite Erythema
Two Plus (+ +)	Erythema with Edema
Three Plus (+ + +)	Erythema, Edema and Vesiculation

Data Interpretation Guidelines
Skin responses of 2 + or greater at 96 hours of the Challenge Phase were considered to be suggestive of the induction of delayed contact hypersensitivity. In addition, 2+ responses that increased in severity or maintained 2 + severity from the 48th hour to the 96th hour challenge gradings were presumptive evidence of contact allergy, all other responses at 96 hours were considered indicative of primary irritation.

Persistent (i.e., 96 hours or longer) skin responses with papules and/or edema that occurred during the first week of induction were generally considered to indicate pre-existing delayed contact hypersensitivity. Persistent reactions of this type that developed later in the induction period indicated induction of contact hypersensitivity.

Study Results
Two hundred forty-one subjects were enrolled in this clinical trial and 209 subjects completed the study.

Dermal Evaluations
Product A (1 % clidamycin/5% benzoyl peroxide)
Scattered minimal (±) to mild (+) skin reactions were noted during the induction period with stronger reactions more prevalent during the later inductions possibly suggestive of the induction of sensitization.

In the Challenge Phase, 21 subject presented responses which increased in severity and/or maintained a 2+ severity from the 48th hour to the 96th hour gradings which are suggestive of contact allergy. Other responses which decreased in severity may be indicative of primary irritation.

b. Product B (1% clidamycin/vehicle)

There were transient. and scattered minimal to mild reactions with three subjects developing transient + + reactions during the latter half of the induction period. Reactions during the Challenge Phase were also scattered but neither persisted nor increased in seventy beyond a + + from the 48th hour to the 96th hour challenge readings except in subject number 45.

c. Product C (5% benzoyl peroxide/vehicle)
There were many minimal (±) to mild (+) reactions noted during the induction period with stronger skin reactions (+ + to + + +) more prevalent in the second half suggestive of possible sensitization.

In the Challenge Phase, 26 subjects presented responses which increased in seventy and/or maintained seventy from the 48th hour to the 96th hour gradings which may be suggestive of contact allergy. Other responses which decreased in severity may be indicative of primary irritation.

d. Product D (vehicle/vehicle)
There were transient and scattered minimal (±) to mild (+) reactions with two subjects (number 85 and 114) developing a + + reaction during the induction period. Responses during the Challenge Phase were also scattered, but were 1 + or less at 96 hours which are more suggestive of irritation type of responses.

Summary and Conclusions
This Repeat Insult Patch Test was completed by 209 subjects. Thirty-three subjects were considered reactors based on persistent or accelerating reactions at 96 hours of the challenge. Out of this number seven subjects had apparent allergic reactions to all four BPO products. Some apparent allergic reactions may have been irritant reactions as was later shown when previous reactors did not respond in a confirmatory rechallenge.

For Product A (1 % clidamycin/5% benzoyl peroxide), some apparent allergic reactions may have been irritant reactions as was demonstrated by the confirmatory rechallenge. The sensitization potential of this product must be considered when extrapolating from results of this study to large number of users.

Product B (1% clidamycin/vehicle) the sensitization potential of this product appears minimal.
Product C (5% benzoyl peroxide/vehicle) the sensitization potential of the product must be considered when extrapolating from results of this study to large number of users.

Product D (vehicle/vehicle) the sensitization potential of this product is minimal

Protocol No. CLN-103 "A Single Center, Placebo-Controlled Photoallergy Study Of 1% Clindamycin/5% Benzoyl Peroxide Gel In Healthy Volunteers"

Study Dates
Photoallergy Study CLN-103 was conducted from 18 October 1993 through 13 January 1994.

Objectives

The primary objective was to determine in a placebo controlled trial if the combination of 1 % clindamycin phosphate and 5% benzoyl peroxide or its individual components would produce photoallergic ski reactions using a controlled patch test procedure.

The secondary objective was to assess the irritation sensitization potential of 1% Clindamycin 5% benzoyl peroxide applied twice daily to the antecubital fossa during the challenge week.

Study Design

This was a randomized, double-blind, placebo-controlled, phase I investigation using 28 normal volunteers to evaluate the photo allergic potential of clindamycin/benzoyl peroxide gel combination, gel containing the individual components, and the gel vehicle.

Material Application and Treatment Sequence Assignment

The study consisted of four phases over approximately seven weeks: screening phase (including minimal erythema dose (MED) determination), induction phase, rest phase, and a challenge phase. The sponsor supplied all test materials to the investigator in coded containers (A, B, C, and D). All four test materials were applied in duplicate to the mid-lower back of each subject based on a predetermined computer generated randomization schedule. The treatment sequence for each subject was documented on a case report form and maintained throughout the trial. In addition, a jar of 1 % clidamycin/5% benzoyl peroxide was dispensed to each subject for twice daily open applications to the antecubital fossa during the Challenge Phase.

The study consisted of the following stages:

- Screening/Admission Phase with MED Determination
  Prior to drug application, the minimal erythema dose was determined for each subject in a non-tanned, non-sun-exposed area on the back below the belt-lie. The MED was individually determined by administering five tied exposures of full spectrum UV (UV A/UV) light. The exposure sites were 1 cm wide. The site with the smallest perceptible erythema (faint redness with distinct edges) was selected as the MED for that individual.
- Induction Phase - One application twice weekly during the first three weeks on Mondays and Thursdays, followed by photoexposure approximately 24 hours after each application. Response appraisals were performed approximately 24 hours or 72 hours post-exposure.
- Rest Phase - Absence of application for two weeks.
- Challenge Phase One additional application during the week following the rest phase, followed by photoexposure approximately 24 hours later.

Response appraisal was done immediately before and following exposure and every day during that week (Wednesday, Thursday and Friday). In addition, twice daily applications of 1 % clindamycin/5% benzoyl peroxide gel was applied to the antecubital fossa from Monday to Sunday. A follow-up evaluation was conducted on the Monday following the last application.

Light Source

A (b) (4) watt (b) (4) solar simulator ((b) (4) with a continuous emission spectrum in the ultraviolet and visible wavelengths ((b) (4) nanometers) was used for

this study. For UVA exposures, a (b) (4) (UV absorbing filter) was interposed. Total irradiance of the solar simulator and uniformity of the beam was measured using an (b) (4). The light source was calibrated on 30 September 1993 by (b) (4).

Grading of Responses
Each test site was evaluated by the designated evaluator according to the schedule specified above. The test site on the antecubital fossa was evaluated daily during the periods of application and approximately 12-24 hours after the last application. All results were recorded in the case report form using the following scale:
Negative (0)
Plus-Minus (±)
One Plus (+)
Two Plus (++)
Three Plus (+ + +)
No reaction
Minimal reaction (faint erythema)
Definite erythema
Erythema with edema
Erythema, edema and vesiculation

Special Notations

Hr	Hyperpigmentation
V	Vesiculation
Pv	Papulo-vesicular response
D or d	Damage to epiderms: D = oozing, crusting and/or superficial erosions, d-drying/scaling
E	Edema

NOTE: Although there is no specific notation for reactions that spread beyond the border, al such reactions were clearly documented in the case report form. Unsolicited subjective comments offered by the subjects were also recorded in the case report form during the study.

The evaluation for photocontact allergy was based on the 72 hour post-irradiation reading during the challenge phase.

Study results
Study dates from November 29, 1993 - January 13, 1994

Subject Selection
Twenty-eight healthy Caucasian adults (4 males and 24 females, age 20-69 years) Fitzpatrick skin types I, II, and III were randomized. All subjects satisfied the inclusion/exclusion characteristics required by the protocol except for subject number 2 who was over the age limit of the protocol. Twenty-seven subjects completed the study. Twenty-six of these subjects are considered evaluable since subject number 2 was over the age limit of the protocol.

Dropped Subjects
Subject number 27 ((b) (6)) voluntarily withdrew from the study on 17 December 1993 (Day 19) due to a family emergency.

Protocol Deviations
Deviations included isolated doses of a non-steroidal anti-inflammatory drug and/or antihistamine containing medication to treat symptoms of a concomitant illness. In addition two subjects (numbers 10 and 20) missed an induction visit during the induction phase, which both subjects made up at the end of the induction period. Subject number 2 was discovered to be 69 years of age during the study, but was allowed to complete the investigation.

During the challenge phase, it was necessary to relocate the open patch application from the antecubital fossa to the lateral surface of the upper arm on subjects no. 2, 8, 9, 13 and 20 due to skin reactions and reported discomfort.

Follow-up Evaluations
Follow-up evaluations after the Challenge Phase were conducted on subjects number 2, 3, 8, 21, and 23 to monitor skin responses at the end of the study.

Adverse Events
Twenty-four subjects reported a total of 91 adverse events during the trial. These adverse events included concomitant illnesses (i.e. headache, cold symptoms, sore throat, backache) and/or dermatological symptoms such as itching and burning.

Product A- 1 % clindamycin/5% benzoyl peroxide
During the first half of the induction period, skin responses tended to be stronger on the irradiated sites than on the non-irradiated sites. Similar intense skin reactions were noted on the irradiated test sites and the non-irradiated sites towards the latter half of the induction phase. Weaker and less frequent reactions were noted with the vehicle particularly on the non-irradiated sites. The irradiated untreated control sites exhibited inflammatory reaction during the induction period, but not nearly as intense or recurring as the treated counterparts.

In the challenge phase nearly equivalent responses were noted on both irradiated and non-irradiated sites. The vehicle and the irradiated untreated control sites remained essentially non-reactive.

Applicant's Conclusion
In view of the skin response pattern and intensity of responses, one subject appeared to present a reaction to the 1% clindamycin/5% BPO that is suggestive of photoallergy. The individual components; however, did not show any evidence of photoallergy. This reviewer concurs with the applicant's assessment.

Protocol Number CLN-102 "A Single Center, Placebo-Controlled Phototoxicity Study Of 1% Clindamcin/5% Benzoyl Peroxide Gel In Health Volunteers"

Objective
The purpose of this study was to determine in a placebo controlled trial if the combination of 1% clindamycin phosphate and 5% benzoyl peroxide or its individual components would produce photo toxic skin reactions using a controlled patch test procedure.

Study Design
This was a randomized, double blind, placebo-controlled, Phase I investigation evaluating the phototoxic potential of clindamycin/benzoyl peroxide gel combination, gels containing the individual components, and the gel vehicle.

Study summary
Twenty-nine subjects were screened to participate in the study: 17 were excluded, and 12 subjects (eight females, four males; 18-61 years of age) were enrolled in the study. Eleven of these subjects completed the evaluation.

Each subject participated in the study for five days. The screening visit consisted of a skin evaluation, a written informed consent, medical history, and an eligibility checklist. A urine pregnancy test was performed on al females of child-bearing potential.

Day 1
Eligibility of each subject was confirmed and a pregnancy test was repeated on females. A subject number was assigned, and semi-occlusive treatment patches were applied to the night and left side of the mid-lower back of each subject, according to a randomization code.

Day 2
Patches on the left side of the back were removed and evaluated. Each site including one untreated control site was irradiated with 18 J / cm^2 of UVA within ten minutes after removing the patches. The patches on the right side were then removed and all sites were evaluated immediately and, at 24 hours (Day 3), 48 hours (Day 4), and 72 hours (Day 5), post irradiation. Three subjects (1, 6, and 11) reported adverse events during the study which included headache (n=2) and itching and burning on all test sites (n=1). All adverse events resolved, but two subjects (6 and 11) required medication.

Conclusion
In view of the distribution and pattern of skin responses observed in this study, the investigator concluded that the phototoxic potential of the 1% clindamycin/5% benzoyl peroxide gel or its individual components is minimal. This reviewer concurs with the applicant's assessment.

Safety Update
The 120-day safety update consisted of a summary of pregnancy outcomes for clinical studies for studies DPS-07-07-2005-001, DPS-07-12-2005-002, DPS-06-22-2006-012, and DPS-06-22-2006-017 (See Section 7.6.2 for pregnancy outcomes). A safety update was submitted under IND 41,733 (Supporting Doc #109).

7.4.6 Immunogenicity

Clindamycin and benzoyl peroxide are not therapeutic proteins; therefore, are not expected to elicit an immune response.

7.5 Other Safety Explorations

According to the applicant (Mod.2, Section 2.7.4.5) safety in special groups and situations assessment evaluations were not considered relevant for the topical Acanya Gel trials and were not included in the study designs.

7.5.1 Drug-Drug Interactions

The following drug-drug interactions with erythromycin, concomitant topical medication, and neuromuscular blocking agents are listed in the proposed label:

- Acanya Gel should not be used in combination with erythromycin-containing products due to its clindamycin component. *In vitro* studies have shown antagonism between these two antimicrobials. The clinical significance of this *in vitro* antagonism is not known.
- Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents.
- Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, Acanya Gel should be used with caution in patients receiving such agents.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Controlled clinical studies were 12 weeks in duration or shorter; therefore, assessment of the carcinogenic effects with long term use of Acanya Gel is not feasible based on data submitted in this application.

7.6.2 Human Reproduction and Pregnancy Data

Acanya Gel is labeled Pregnancy Category C. A total of 10 pregnancies were reported that resulted in early discontinuation of treatment and early termination of the subjects. Two pregnancies were reported in Study 001 and 5 pregnancies were reported in the Phase 3 pivotal studies. One female in Study 012 and four females became pregnant during Study 017. They were assigned as follows: BPO gel, (n=2), Acanya Gel (n=2), clindamycin gel, (n=1), (b) (4) Gel (n=1), and (b) (4) Gel vehicle (1) treatment groups.

Pregnancy outcomes were provided by the applicant for 7 of the 9 in the 120 day safety report. Outcomes are available for all subjects except Subject #081(b) (6)) assigned to the (b) (4) Gel

study arm who was reported as no information received and 2 subjects from Study DPS-07-12-2005-002 (both loss to follow-up.

Protocol No. DPS-07-07-2005-001 Site #104, Subject #0106 (b) (6)
Protocol No. DPS-07-07-2005-001 Site #108, Subject #081 (b)
Protocol No. DPS-06-22-2006-012 Site #34, Subject #032 (b)
Protocol No. DPS-06-22-2006-017 Site #58, Subject #005 (b)
Protocol No. DPS-06-22-2006-017 Site #64, Subject #020 (b) (6)
Protocol No. DPS-06-22-2006-017 Site #67, Subject #054 (b) (6)
Protocol No. DPS-06-22-2006-017 Site #74, Subject #061 (b) (6)

Except for Subject #061 (b) (6)) who experienced hyperemesis gravidarum during pregnancy, pregnancies were essentially uneventful resulting deliveries without complications in those reporting.

7.6.3 Pediatrics and Effect on Growth

(b) (4)
The rationale provided by the application pertains only to pediatric patents 12 years and older.

The applicant performed subgroup analysis of inflammatory and non-inflammatory lesions and dichotomized global severity scores by age in the ITT population. This categorization of ages placed approximately half of the subjects in each group for the entire group of phase 3 subjects. According to the applicant's assessment, for the parameter inflammatory lesion absolute change there were no differences in the response in either age group. The dichotomized EGSS was higher at week 12 in the older subjects (37.9% versus 31.9%). The younger subjects experienced a higher reduction of non-inflammatory lesion counts in the Acanya Gel treatment group than did the older subjects (22.6 versus 18.6).

Effect on growth was not assessed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose, drug abuse potential, withdrawal and rebound were not addressed in the application and are not expected to occur with this topical medication. Of concern is the potential for development of antimicrobial resistance.

7.7 Additional Submissions

8 Postmarketing Experience

Acanya gel has not been marketed.

9 Appendices

9.1 Literature Review/References

The applicant's literature search was adequate and provided references on the topic of antibiotic resistance in the topical treatment of acne vulgaris.

9.2 Labeling Recommendations

Labeling recommendations in included the following:

- Inclusion of description of the pivotal clinical trials and efficacy results.
- Inclusion of the Evaluator's Global Severity Scoring (EGSS) scale used in the clinical trials.
- TRADENAME Gel should be applied to the affected areas on the face once daily.
- Deletion of the table below and requested that sponsor provide a table describing clinical study results from the two pivotal trials of the following: TRADENAME Gel vs. Vehicle gel - comparison at 12 weeks of (1) skin irritation (sum of itching ,burning and stinging), (2) erythema and (3) scaling.

(b) (4)

9.3 Advisory Committee Meeting

An advisory meeting was not held for this drug product.

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

/s/

Brenda Vaughan
10/6/2008 04:30:51 PM
MEDICAL OFFICER

Markham Luke
10/15/2008 09:24:30 AM
MEDICAL OFFICER
Cuncur with Approval recommendation. Labeling to be discussed and agreed upon with the sponsor.