# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**50-802**

# MEDICAL REVIEW

# CLINICAL REVIEW

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| Application Type | 50-802 |
| Submission Number | 0009 |
| Submission Code | AZ |
| Letter Date | May 5, 2006 |
| Stamp Date | May 6, 2006 |
| PDUFA Goal Date | November 8, 2006 |
| Reviewer Name | Brenda Carr, M.D. |
| Review Completion Date | October 12, 2006 |
| Established Name | clindamycin phosphate and tretinoin |
| (Proposed) Trade Name | Ziana™ |
| Therapeutic Class | antibiotic and retinoid |
| Applicant | Dow Pharmaceutical Sciences |
| Priority Designation | S |
| Formulation | gel |
| Dosing Regimen | once daily |
| Indication | acne vulgaris |
| Intended Population | patients 12 years and older |

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# 1 EXECUTIVE SUMMARY

## 1.1 Recommendation on Regulatory Action

This resubmission proposes marketing of a topical gel combination product containing the active ingredients clindamycin phosphate 1.2% (an antibiotic) and tretinoin 0.025% (a retinoid). The product is proposed for the treatment of acne vulgaris in patients 12 years and older and is intended for once daily application. The proposed trade name is Ziana™.

Both clindamycin phosphate and tretinoin are individually marketed in various topical formulations for the treatment of acne vulgaris. It is theorized that each substance primarily targets a different aspect of the acne pathogenic pathway, and some clinicians employ a two-pronged approach to acne treatment by recommending that their patients apply a topical antimicrobial in the morning and a topical retinoid in the evening. The sponsor's combination product would apply these treatment principles, but require only once daily application.

The resubmission included data from one adequate and well-controlled safety and efficacy trial. The sponsor previously submitted safety and efficacy data from two other controlled clinical trials (those data were reviewed when provided in the original submission).

Based on the results from the three controlled clinical trials, the sponsor has adequately demonstrated the efficacy of their combination product in the treatment of acne vulgaris. The sponsor's development program was of appropriate design to demonstrate the contribution of each component to efficacy so as to address the combination policy, 21 CFR 300.50. The results from the three controlled clinical trials adequately demonstrate that each active ingredient, clindamycin phosphate 1.2% and tretinoin 0.025%, contributes to the efficacy of their combination product.

The safety of the sponsor's product was adequately evaluated in the development program, and no new safety concerns were raised.

From a clinical perspective, it is recommended that the application be approved.

## 1.2 Recommendation on Postmarketing Actions

### 1.2.1 Risk Management Activity

There are no recommendations for risk management steps.

### 1.2.2 Required Phase 4 Commitments

There are no recommendations for Phase 4 commitments.

### 1.2.3 Other Phase 4 Requests

There are no Phase 4 requests.

## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

The sponsor conducted three Phase 3 safety and efficacy trials in which their product was evaluated in the treatment of acne vulgaris. The resubmission included data from a two-arm, multi-center, randomized, double-blind, active-controlled study, MP-1501-02. This study evaluated the combination product and clindamycin phosphate, 1.2%.

Safety and efficacy data from two, four-arm, multi-center, randomized, double-blind, active- and vehicle-controlled, parallel Phase 3 trials, 7001-G2HP-06-02 and 7001-G2HP- 7-02 were provided in the original submission. These two studies were of appropriate design for evaluation of a combination product (they were also of identical design). Specifically, these studies evaluated the combination product, clindamycin phosphate, 1.2% (in the sponsor's vehicle), tretinoin, 0.25% (in the sponsor's vehicle) and the vehicle itself. However, in the intent-to-treat analyses for both studies, superiority of the combination product over clindamycin was not demonstrated to a level of statistical significance for the proportion of subjects who were "clear" or "almost clear" on the Evaluator's Global Severity score, a co-primary endpoint. Thus, the contribution of tretinoin to efficacy was not adequately demonstrated in either trial, and the sponsor was advised to conduct an additional clinical study to demonstrate the contribution of tretinoin to the efficacy of the combination product. The data from that new trial, MP-1501-02, were provided in the resubmission.

A total of 2,010 subjects were enrolled in study MP-1501-02: 1,008 in the combination group and 1,002 in the clindamycin group. Total enrollment for the combined studies 7001-G2HP-06-02 and 7001-G2HP- 7-02 was 2,540: 845 received combination product, 426 received clindamycin, 846 received tretinoin, and 423 received vehicle.

### 1.3.2 Efficacy

The efficacy database consisted of subjects who were enrolled in the three safety and efficacy trials. The co-primary efficacy variables were:

(1) mean percent change from baseline at Week 12 in
- inflammatory lesion counts,
- non-inflammatory lesion counts, and
- total lesion counts

(2) the percentage of subjects who were "clear" or "almost clear" at Week 12 as judged by an Evaluator's Global Severity score (or two-grade improvement in study MP-1501-02).

In the primary efficacy analyses for the comparison between the combination product and clindamycin gel and tretinoin gel, superiority was demonstrated if there was statistical significance in:

(1) two of three of the following lesion counts:
- mean percent change from baseline at Week 12 in inflammatory lesion counts,
- mean percent change from baseline at Week 12 in non-inflammatory lesion counts,
- mean percent change from baseline at Week 12 in total lesion counts

(2) the percent of subjects who were "clear" or "almost clear" at Week 12, as judged by an Evaluator's Global Severity Score (or two-grade improvement in study MP-1501-02).

In the primary efficacy analyses for the comparison between the combination product versus vehicle, superiority was demonstrated if there was statistical significance in:

(1) mean percent change from baseline at Week 12 in inflammatory lesion counts, and
(2) mean percent change from baseline at Week 12 in non-inflammatory lesion counts
(3) the percent of subjects who were "clear" or "almost clear" at Week 12, as judged by an Evaluator's Global Severity Score.

Results

In study MP-1501-02, the sponsor's combination product was superior to clindamycin phosphate at efficacy assessment in mean reduction and mean absolute reduction in all lesion counts (inflammatory, non-inflammatory and total) and on the dichotomized global severity scale. These outcomes adequately demonstrate the efficacy of the combination product and the contribution of tretinoin to efficacy.

In study 7001.G2HP-06-02, the combination product was superior to clindamycin, tretinoin and vehicle for all lesion counts. In study 7001.G2HP-0-02 -07, the combination product was superior to clindamycin, tretinoin and vehicle for inflammatory and total lesions (i.e. in two of three lesion counts). The combination was superior to vehicle for non-inflammatory lesions. Superiority of the combination product over tretinoin and vehicle was demonstrated for the proportion of subjects who were "clear" or "almost clear" on the Evaluator's Global Severity (EGS) score at 12 weeks in both four-arm trials. These outcomes provide additional adequate evidence of the efficacy of the combination product and adequately demonstrate the contribution of tretinoin to efficacy.

### 1.3.3 Safety

The safety of the sponsor's product was adequately evaluated in the development program. Specifically,
- Local safety assessments were conducted in all of the efficacy and/or safety studies.
- The sponsor conducted a long-term safety study.
- The sponsor conducted the standard battery of dermal safety studies.

- The sponsor conducted a multiple-dose study in subjects with acne vulgaris to assess the absorption and safety of their product.
- Adverse event data were collected in all of the clinical trials.

In study MP-1501-02, the most frequent adverse events in both treatment groups were in the system organ class of infections and infestations (13.6% of subjects in each treatment group), and nasopharyngitis was the single most frequently reported adverse event in both treatment groups (5.1% of subjects in the combination group and 5.4% of subjects in the clindamycin treatment group). Dry skin and headache were each reported in 2% of the subjects in the combination group. All other adverse events were reported with an incidence below 2%.

In studies 7001.G2HP-06-02 and 7001.G2HP-0-02-07, the largest percentage of adverse events were "respiratory, thoracic and mediastinal disorders." "Skin and subcutaneous disorders" were the second most common category of adverse events for subjects treated with active medication and were more often reported for subjects treated with one of the tretinoin-containing products, consistent with the known irritancy of topical tretinoin. Generally, most adverse events were considered by investigators to be mild in severity and unrelated to study medication.

In the long-term safety study, most adverse events were reported in ≤1% of subjects. Adverse events were most frequently reported in the infections and infestations system organ class (98 events being reported over the year). The most commonly-reported event was upper respiratory tract infection (33 reports; 7%) followed by nasopharyngitis (17 reports; 4%) and sinusitis (13 reports; 3%). There were five reports of gastroenteritis (1%).

No new safety concerns were raised from the sponsor's development program.

### 1.3.4 Dosing Regimen and Administration

Although recommended by the Division, dose-ranging studies were not conducted. Currently marketed topical gel formulations of clindamycin phosphate are dosed either once or twice daily. Currently marketed formulations of tretinoin are dosed once in the evenings. The sponsor based dosing of their product on the dosing of the individually marketed tretinoin and topical clindamycin phosphate products, and elected for once daily dosing.

### 1.3.5 Drug-Drug Interactions

Drug-drug interaction studies were not done.

### 1.3.6 Special Populations

The sponsor's efforts to evaluate gender, age, race and ethnicity effect pertaining to efficacy were adequate. There was no evidence of clinically significant effect of any of these parameters on efficacy.

Subjects 11 years and older were enrolled in the pivotal trials, and the mean age of study subjects was approximately 19 years in all three safety and efficacy studies. The sponsor requested a waiver for patients under the age of 11 years. This is acceptable, since acne vulgaris does not typically occur in the younger age group.

Tretinoin-containing products are classified in Pregnancy Category C. Clindamycin phosphate containing products are classified in Pregnancy Category B. The sponsor appropriately proposes a category C designation for their product and proposes inclusion of approved wording contained in the discussion of teratogenic effects in the Pregnancy portion of the package insert for another tretinoin-containing product (Avita). For obvious reasons, the treatment of acne in pregnancy would differ from that in the non-pregnant patient. Because it contains a retinoid, it is not considered likely that the sponsor's product would be frequently recommended for use during pregnancy.

One pregnancy occurred in study MP-1501-02, and the subject was in the clindamycin phosphate treatment group. The pregnancy ended in miscarriage, and the investigator considered the outcome to be unrelated to study drug.

Five pregnancies occurred in the long-term safety study, an open-label study in which all subjects received treatment with the combination product. The following outcomes were reported: three healthy infants, one elective termination, and one unknown outcome.

Seven subjects became pregnant in studies 7001.G2HP-06-02 and 7001.G2HP-0-02-07, six of whom received tretinoin treatment and one of whom received the combination product. For four subjects, the pregnancy resulted in early discontinuation of treatment. The remaining three subjects had completed the study, their positive pregnancy tests having been discovered at the last study visit. The subject who received treatment with the combination product delivered a male infant who had a neonatal heart murmur. The outcomes of the other pregnancies (all in tretinoin subjects) were: three unknown outcomes, one elective termination, one healthy female. It is not clear to what extent, if any, exposure to study products impacted the pregnancy outcomes.

At this juncture, no data is thought needed for other populations.

# 2 INTRODUCTION AND BACKGROUND

## 2.1 Product Information

This resubmission proposes marketing of a topical gel combination product containing the active ingredients clindamycin phosphate 1.2% (an antibiotic) and tretinoin 0.025% (a retinoid). The proposed indication is for the treatment of acne vulgaris in patients 12 years and older, and the product is intended for once daily application. The proposed trade name is Ziana™ (Clin RA was the original proposed trade name; see comment below).

Because topical antibiotics and topical retinoids are each theorized to primarily target a different aspect of the acne pathogenic pathway, some clinicians employ the two classes of products in the treatment of acne by recommending a topical antibiotic and a topical retinoid for their patients. Typically, the antibiotic is recommended for morning application and the retinoid for the evening. The proposed new product would provide for this dual-action effect in a combination product that would be applied once a day.

***Comment:*** *Clin RA was the trade name proposed both in the original submission (submission date: February 6, 2004) and the resubmission under current review (submission date: May 5, 2006). Well into the review cycle of the resubmission, specifically on August 14, 2006, the sponsor submitted labeling under a new proposed trade name, Ziana™. In some sections of this review, the sponsor's product may still be referred to by the original proposed trade name, Clin RA, e.g. in tables copied from the sponsor's clinical study report which employed Clin RA.*

## 2.2 Currently Available Treatment for Indications

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

## 2.3 Availability of Proposed Active Ingredient in the United States

Both clindamycin phosphate and tretinoin have long been individually marketed in various topical formulations (and concentrations for tretinoin) for the treatment of acne vulgaris. Clindamycin is thought to have an effect primarily against inflammatory lesions through its antimicrobial action against *Propionibacterium acnes.* Other factors may be operative as well. Tretinoin is thought to have an effect primarily against noninflammatory lesions by normalizing follicular keratinization.

There are literature reports of pseudomembranous colitis associated with use of topical clindamycin phosphate, and labeling for topical clindamycin products includes bolded warnings to this effect. The colitis is thought to be a function of the systemic absorption of the clindamycin. It is possible that transdermal absorption of clindamycin could be increased when the clindamycin is used in combination with tretinoin: the tretinoin irritancy could allow for

increased absorption of clindamycin.

Tretinoin is a naturally occurring compound in humans, and in the original submission, the sponsor reported endogenous plasma concentrations to be approximately 1 to 4 ng/mL. Topical retinoids as a class are commonly known to produce some measure of irritancy, particularly in the initial weeks of usage. These effects may include erythema, scaling, itching, and burning. Hypopigmentation may also be seen. Generally, the skin eventually adapts such that the irritancy lessens progressively over time.

## 2.4 Important Issues With Pharmacologically Related Products

Systemic retinoids are teratogens, and the complex regulatory history surrounding this issue is beyond the scope of this document. Topical tretinoin products are categorized in Pregnancy Category C. Per the Pregnancy section of the most recently approved label for a marketed 0.25% gel formulation of tretinoin (Retin A gel; NDA 17-579; date of most recently approved label: June 10, 2002):

"Oral tretinoin has been shown to be teratogenic in rats, mice, hamsters, and subhuman primates...

"Topical tretinoin in animal teratogenicity tests has generated equivocal results. There is evidence for teratogenicity (shortened or kinked tail) of topical tretinoin in Wistar rats at doses greater than 1 mg/kg/day (8 times the maximum human systemic dose adjusted for total body surface area). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day was topically applied. There are other reports in New Zealand White rabbits administered doses of greater than 0.2 mg/kg/day (3.3 times the maximum human systemic dose adjusted for total body surface area) of an increased incidence of domed head and hydrocephaly, typical of retinoid-induced fetal malformations in this species.

"In contrast, several well-controlled animals studies have shown that dermally applied tretinoin may be fetoxic, but not overly teratogenic in rats and rabbits at doses of 1.0 and 0.5 mg/kg/day, respectively (8 times the maximum human systemic does adjusted for total body surface area in both species).

"With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty human cases of temporally associated congenital malformations have been reported during two decades of clinical use of RETIN-A. Although no definite pattern of teratogenicity and no causal association has been established from these cases, five of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known."

## 2.5 Presubmission Regulatory Activity

The submission under current review is a resubmission provided in response to a not-approvable action taken on the original marketing application on December 7, 2004 (submission date February 6, 2004). The stated deficiency in the action letter was:

"The contribution to efficacy of each component of your combination product was not adequately demonstrated. Specifically, the contribution of tretinoin to efficacy was not adequately demonstrated."

The not-approvable letter advised that,

"To address this deficiency, the contribution of tretinoin to the efficacy of this combination product should be documented in an additional clinical study."

***Comment:*** *The reader is referred to the Medical Officer's review of the original submission for regulatory history that preceded the original submission.*

At a "post-NA" meeting held on February 16, 2005, the sponsor proposed to conduct a two-arm study (the combination product versus clindamycin phosphate) to support a resubmission, and the Agency responded by stating,

"A two-armed study that demonstrates the superiority of the Clin-RA product compared to clindamycin in the product vehicle might be acceptable; however, the sponsor should provide a scientific rationale for not including a vehicle arm in the new study. In the proposed two-armed trial, the representation in the severe category and the Inclusion and Exclusion criteria should be the same as in the previously conducted Phase 3 trials."

On February 25, 2005, the sponsor appealed the not-approvable action via the formal dispute resolution process to the Office of Drug Evaluation V; the appeal was denied on March 25, 2005. On September 30, 2005, the sponsor further appealed the matter to the Director of the Office of New Drugs; that appeal was denied on November 3, 2005.

## 2.6 Other Relevant Background Information

The Dermatologic and Ophthalmic Drugs Advisory Committee met on November 4 and 5, 2002 to discuss "development of a proposed draft guidance concerning the development of products for mild to moderate acne vulgaris" (from meeting briefing document).

Discussion points from the meeting that the sponsor has applied in the conduct of the new pivotal trial for the resubmission include:

- In the protocol for the new pivotal trial, the sponsor indicated that the Evaluator's Global Severity Scale was the scale presented by the Agency as a reasonable example of a global severity scale (same scale was used in the sponsor's previous trials).
- The sponsor proposed that success on the Evaluator's Global Severity Scale be measured at efficacy assessment by the percentage of subjects either "clear" or "almost clear" or who had a two-grade improvement from baseline.

***Comment:*** *Discussion at the November 2002 Advisory Committee meeting included that improvement on the Global Severity Scale might still be meaningful, even if a subject did not achieve "clear" or "almost clear."*

# 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

## 3.1 CMC (and Product Microbiology, if Applicable)

While not the basis for the Not Approvable action, the letter also advised that a number of CMC issues be addressed in the resubmission. See the chemistry review.

## 3.2 Animal Pharmacology/Toxicology

There are no pharmacology/toxicology issues pertaining to the resubmission.

# 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

## 4.1 Sources of Clinical Data

The primary source of data for the review of the resubmission are the data from the new Phase 3, pivotal trial, MP-1501-02 and the long-term safety study, MP-1501-01.

The sponsor previously conducted two four-arm, multi-center, randomized, double-blind, active- and vehicle-controlled, parallel Phase 3 trials, 7001-G2HP-06-02 (06) and 7001-G2HP-07-02 (07). The studies were of appropriate design for evaluation of a combination product, and the trials were of identical design. The results from those trials will be presented in brief in this review as they were previously reviewed by the Medical Officer in the original submission.

## 4.2 Tables of Clinical Studies

The sponsor conducted two four-arm, multi-center, randomized, double-blind, active- and vehicle-controlled, parallel Phase 3 trials, 7001-G2HP-06-02 and 7001-G2HP- 07-02:

| **No. Patients** | | **7001.G2HP-06-02** | **7001.G2HP-07-02** | **Total** |
|---|---|---|---|---|
| **(ITT Population)** | Clin-RA | 420 | 425 | 845 |
| | Clindamycin Phosphate | 208 | 218 | 426 |
| | Tretinoin | 417 | 429 | 846 |
| | Vehicle | 207 | 216 | 423 |

**Modified Sponsor Table 3.23 Dermal Safety Study Summaries for Clin-RA Gel**

| Study Information | 7001.G2HP-01-02 21-Day Cumulative Irritation Study | 7001.G2HP-03-02 Repeat Insult Patch Test Study | 7001.G2HP-04-02 Phototoxicity | 7001.G2HP-05-02 Photoallergy |
|---|---|---|---|---|
| Investigaor | Karl Beutner, M.D., Ph.D. | Karl Beutner, M.D., Ph.D. | Karl Beutner, M.D., Ph.D. | Karl Beutner, M.D., Ph.D. |
| No. Entered | 34 | 229 | 27 | 30 |
| No. Evaluable | 34 | 186 | 25 | 28 |
| Age range | 18-55 | 18-55 | 18-53 | 18-41 |
| %Male/%Female | 26/74 | 42/58 | 40/60 | 32/68 |
| Dose | 0.2 mL | 0.2mL | 0.05 mL | 0.2 mL |
| Frequency of Dosing | Nine 48-hour applications over 3 weeks (72-hours on weekends) | Nine 48-hour applications over 3 weeks (72-hours on weekends); one 48-hour challenge application | One 24-hour application | Six 24-hour applications over 3 weeks; one 24-hour challenge application |
| Duration of study | 22 days | 6 weeks | 3 days | 6 weeks |
| Test materials | Clin-RA Gel<br>Clin-RA Gel Vehicle<br>Sodium lauryl sulfate 0.2% | Clin-RA Gel<br>Clin-RA Gel Vehicle<br>Retin A® Gel, 0.025% | Clin-RA Gel<br>Clin-RA Gel Vehicle | Clin-RA Gel<br>Clin-RA Gel Vehicle |

***Comment:*** *The tables of the previous safety and efficacy studies and the dermal safety studies are taken from the Medical Officer's review of the original submission.*

The sponsor also conducted a pharmacokinetic study 7001.G2HP.C-02-02: "Absorption Evaluation of Clindamycin and Tretinoin Following Maximum Topical Exposure to Clin-RA Gel in Subjects with Moderate to Severe Acne Vulgaris."

## 4.3 Review Strategy

The review of efficacy focuses on data from the new Phase 3 trial, MP-1501-02 as data from the other two Phase 3 trials have been previously reviewed.

## 4.4 Data Quality and Integrity

Division of Scientific Investigations inspections were not requested. The applicant's analyses were reviewed, and independent analyses were performed by the biostatistics reviewer.

## 4.5 Compliance with Good Clinical Practices

Per the study reports for the new Phase 3, pivotal trial, MP-1501-02 and the long-term safety study, MP-1501-01, both trials were conducted under standard operating procedures of Medicis Pharmaceutical Corp. which are designed to ensure adherence to Good Clinical Practices and the protection of study subjects, as required by the following directives:

- Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects', Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West, 1996).

- Directive 91/507/EEC: The Rules Governing Medicinal Products in the European Community.
- US 21 Code of Federal Regulations dealing with clinical studies, parts 50 and 56, concerning Informed Subject Consent and Institutional Review Board regulations.

### 4.6 Financial Disclosures

The sponsor disclosed a financial arrangement with one investigator [redacted] an investigator in the long-term safety study, MP-1501-01. [redacted] of the sponsor, and his Financial Disclosure Form indicated a "proprietary or financial interest in the test product such as a patent, trademark, a copyright, or licensing agreement." According to his Financial Disclosure Statement, [redacted] was [redacted] at the time of this study. [redacted] the company was [redacted] He is a [redacted] and the value of this equity position is in excess of $50,000. The sponsor reports that the following steps were taken to minimize the potential for bias: b(6)

*"For the conduct of this trial [redacted] role was that of [redacted] investigator. He was responsible for the supervision of the staff and the overall conduct of the trial. This was primarily a safety study based on the evaluation of the cumulative irritation potential of the product and controls when placed under patches. Thus, the key data here were evaluator results. A number of safeguards were in place to minimize any bias in the conduct of this study. These include the fact that this study was evaluator blinded. In addition, there were multiple evaluators used in the conduct of this trial. During the conduct of the trial, an independent monitor oversaw the conduct of the trial. At the completion of the trial, the data entry and data management were conducted by an independent organization."* b(6)

***Comment:*** *[redacted] was also [redacted] Additionally, he was the investigator for the [redacted] The sponsor appears to have taken reasonable steps to avoid any potential bias from [redacted] involvement in the development program.* b(6)

## 5 CLINICAL PHARMACOLOGY

### 5.1 Pharmacokinetics

**7001.G2HP.C-02-02: "Absorption Evaluation of Clindamycin and Tretinoin Following Maximum Topical Exposure to Clin-RA Gel in Subjects with Moderate to Severe Acne Vulgaris"**

**Note:** This study is briefly described below. A complete review of this study was done by the biopharmaceutics/clinical pharmacology reviewer, and the reader is referred to that review.

**Methodology:** The sponsor conducted a single-center, open-label, multiple dose study in 13 subjects to assess the absorption and safety of Clin-RA Gel in subjects with "severe" acne vulgaris. This study was designed to characterize the absorption of Clin-RA Gel under maximal exposure by daily topical applications for 14 days. Twelve subjects completed the study. Study drug was applied as a four gram dose, which the sponsor estimated to be four times the expected typical upper clinical dose. Plasma levels of clindamycin, tretinoin and the tretinoin metabolites (13-*cis*-retinoic acid and 4-oxo-13-*cis*-retinoic acid) were monitored over the 14 day treatment period, and an absorption curve was defined on the 14th day. A final 24-hour post-dosing blood draw was taken on Day 15.

**Results:** The percentage of subjects with undetectable plasma concentrations for tretinoin (< 1 ng/mL) at $T_{max}$ was 50%, and ranged from 50% to 92% at any given timepoint. The absorption of clindamycin, tretinoin, and key tretinoin metabolites as indicated by the mean $C_{max}$ values ranged from 1.05 to 3.15 ng/mL; mean $T_{max}$ ranged from 3.26 to 6.34 hours; and mean $AUC_{(0-24)}$ ranged from 24.46 to 63.13 ng/mL hour.

**Conclusion:** The sponsor concluded that the result was in agreement with previous studies using combination clindamycin phosphate/tretinoin and clindamycin HCl/tretinoin gel formulations. The sponsor concluded that under conditions of the study, there was no indication of systemic absorption of tretinoin, and the biopharmaceutics/clinical pharmacology reviewer agreed with this conclusion.

### 5.2 Pharmacodynamics

Clindamycin is an antibiotic, and tretinoin is thought to normalize follicular keratinization.

### 5.3 Exposure-Response Relationships

Although recommended by the Division at the pre-IND meeting, the sponsor did not conduct dose-ranging studies. The sponsor elected once daily dosing of their product based on the dosing of individually marketed tretinoin and topical clindamycin phosphate products, specifically Retin-A™ 0.025% Gel and Clindagel™, respectively. While this dosing is consistent with that of marketed formulations of tretinoin, marketed topical gel formulations of clindamycin phosphate are dosed either once or twice daily.

## 6 INTEGRATED REVIEW OF EFFICACY

### 6.1 Indication

The sponsor proposes their product for the treatment of the inflammatory and non-inflammatory lesions associated with acne vulgaris.

### 6.1.1 Methods

The primary source of efficacy data for the review of the resubmission is the data from the new Phase 3, pivotal trial, MP-1501-02.

Additional evidence of efficacy was provided from the two Phase 3 trials, 7001-G2HP-06-02 (06) and 7001-G2HP- 07-02 (07). The data from those two trials were previously reviewed in the Medical Officer's review of the original submission and will be presented here only in brief.

### 6.1.2 General Discussion of Endpoints

For a product intended for the treatment of acne vulgaris, the recommended primary endpoints are lesion counts (inflammatory, non-inflammatory and total) and the evaluator's global assessment. Efficacy is demonstrated by superiority of the product in two of three lesion counts and the proportion of subjects who are "clear" or "almost clear" at efficacy assessment. As the sponsor's product is a combination product (clindamycin and tretinoin), additional considerations apply to the demonstration of its efficacy. Specifically, it is necessary that the contribution of each active ingredient to efficacy be adequately demonstrated.

### 6.1.3 Study Design

**Title:** "A Multicenter, Phase 3, Randomized, Double-Blind, Clinical Trial to Compare the Safety and Efficacy of Clin RA Gel vs Clindamycin Phosphate 1.2% Gel in the Treatment of Acne Vulgaris" (Protocol No. MP-1501-02)

**Study Design:** double-blind, randomized, active-controlled, parallel-group comparison of the safety and efficacy of the combination product with one of its components (clindamycin phosphate 1.2% gel).

***Comment:*** *The conduct of a two-arm trial was acceptable to the Division. The sponsor also conducted two four-armed, multi-center, randomized, double-blind, active- and vehicle-controlled, parallel Phase 3 trials, 7001-G2HP-06-02 (06) and 7001-G2HP- 07-02 (07). These two studies were of appropriate design for evaluation of the sponsor's combination product. Therefore, the development of the sponsor's product has addressed the combination policy (21 CFR 300.50).*

**Methodology:** Subjects were randomized into the study and stratified by Fitzpatrick Skin Type and baseline Evaluator Global Severity Scale (EGSS).

Inclusion Criteria:

1. Were male or female 12 years of age or older;
2. Had given written and verbal informed consent (subjects less than 18 years of age, or less than 19 years of age in Alabama, were to sign an assent for the study and the parent or legal guardian was to sign the informed consent);
3. Had a facial acne inflammatory lesion count (papules and pustules) of no less than 20 but no more than 50;
4. Had a facial acne noninflammatory lesion count (open and closed comedones) of no less than 20 but no more than 100;

5. Had 2 or fewer nodules (defined as an inflammatory lesion greater than or equal to 5 mm in diameter);
6. Had an EGSS of moderate (=3) or severe (=4);
7. If a woman of childbearing potential,
    - Was willing to practice effective contraception for the duration of the study (acceptable methods included hormonal contraception maintained for a period of 3 months prior to the study and persisting through the study period, intrauterine device, condom, diaphragm, or abstinence);
    - Had a negative urine pregnancy test (UPT) at the Baseline visit;
8. Were willing to comply with study instructions and return to the clinic for required visits;
9. Were willing to use an approved cleanser, moisturizer, sunscreen or moisturizer/sunscreen combination product throughout the study.

Exclusion Criteria:

1. Had participated in a clinical drug or device research study within 30 days of enrollment or were participating in a research study concurrent with this study;
2. Had any dermatological conditions on the face such as acne conglobata, acne fulminans, secondary acne, etc, that could interfere with clinical evaluations;
3. Had any underlying disease or other dermatological condition of the face that required the use of interfering topical or systemic therapy;
4. Had a facial beard or mustache that could interfere with the study assessments;
5. Were female subjects who were pregnant, nursing, planning a pregnancy during the course of the trial, or became pregnant during the study;
6. Had a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis;
7. Were receiving treatment of any type for cancer within the last 6 months;
8. Were unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function;
9. Had a history of hypersensitivity or allergic reactions to any of the study preparations as described in the Investigator's Brochure, including known sensitivities to any dosage form of clindamycin, lincomycin, or tretinoin;
10. Were concomitantly using potentially irritating over-the-counter products that contained ingredients such as benzoyl peroxide, alpha-hydroxy acids, salicylic acid, retinol or glycolic acids;
11. Had not undergone the specified washout periods for the following topical preparations, or required the concurrent use of any of the following topical medications:
    - Antibiotics on the facial area (2 weeks) Other topical anti-acne drugs (2 weeks)
    - Anti-inflammatory agents and corticosteroids on the facial area (4 weeks)
    - Retinoids, including retinol (4 weeks)
12. Had not undergone the specified washout periods for the following systemic medications, or required the concurrent use of any of the following systemic medications:
    - Corticosteroids (including intramuscular injections) (4 weeks)
    - Antibiotics (4 weeks) Other systemic acne treatments (4 weeks)
    - Systemic retinoids (6 months)

Subjects were evaluated at Screening/Baseline and at Weeks 2, 4, 8, and 12. Efficacy assessments were based on blinded evaluator assessments of the signs and symptoms of acne vulgaris. The primary measures of efficacy were:

1. Percent change from Baseline to Week 12 in inflammatory lesion counts
2. Percent change from Baseline to Week 12 in noninflammatory lesion counts
3. Percent change from Baseline to Week 12 in total lesion counts, and

4. The percentage of subjects who were clear or almost clear at Week 12 or had 2 grades of improvement from Baseline to Week 12 in an Evaluator's Global Severity Score (EGSS).

**Evaluator's Global Severity Score (EGSS):**

| Score | Grade | Description |
|---|---|---|
| 0 | Clear | Normal, clear skin with no evidence of acne vulgaris |
| 1 | Almost clear | Rare noninflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red) |
| 2 | Mild | Some noninflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulo-cystic lesions) |
| 3 | Moderate | Noninflammatory 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 nodulo-cystic lesions |
| 5 | Very Severe | Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules and many nodulo-cystic lesions |

***Comment:*** *The assessment of primary efficacy on the global severity scale differs somewhat from that used in the previous Phase 3 studies in that it allowed for two-grade improvement.*

Cutaneous safety and tolerability evaluations (see scales below) and adverse event monitoring were conducted at each visit:

Cutaneous Safety Evaluation

The cutaneous safety evaluation included the assignment of scores by the investigator to the subject's overall condition of facial erythema and scaling as follows:

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

The evaluation of tolerability of the study products included the assignment of scores by the subject to the degree of facial itching, burning, and stinging, as follows:

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

## 6.1.4 Efficacy Findings

A total of 2,010 subjects were included in the safety evaluable and intent-to-treat (ITT) populations: 1,008 in the combination group and 1,002 in the clindamycin group.

**Table 9.4.1**
**Demographics and Baseline Characteristics: ITT Population**

| | Clin RA N = 1008 | Clindamycin N = 1002 |
|---|---|---|
| **Age (years)** | | |
| Mean ± SD | 19.1 ± 7.5 | 19.0 ± 7.0 |
| Median | 16.4 | 16.3 |
| Range | 12.0 - 84.0 | 12.0 - 53.2 |
| **Gender – n (%)** | | |
| Male | 515 (51.1) | 455 (45.4) |
| Female | 493 (48.9) | 547 (54.6) |
| **Race – n (%)** | | |
| White | 765 (75.9) | 758 (75.6) |
| Black | 102 (10.1) | 97 ( 9.7) |
| Hispanic/Latino | 100 ( 9.9) | 103 (10.3) |
| American Indian/Alaskan | 1 ( 0.1) | 5 ( 0.5) |
| Asian/Pacific Islander | 25 ( 2.5) | 28 ( 2.8) |
| Other | 15 ( 1.5) | 11 ( 1.1) |
| **Fitzpatrick Skin Type** | | |
| I | 47 ( 4.7) | 47 ( 4.7) |
| II | 214 (21.2) | 214 (21.4) |
| III | 341 (33.8) | 339 (33.8) |
| IV | 231 (22.9) | 230 (23.0) |
| V | 106 (10.5) | 103 (10.3) |
| VI | 69 ( 6.8) | 69 ( 6.9) |
| **Baseline Global Severity Score** | | |
| 3 | 753 (74.7) | 747 (74.6) |
| 4 | 255 (25.3) | 255 (25.4) |

**Table 10.2.1.1**
**Primary Efficacy Endpoints: ITT Population**

| | Clin RA N = 1008 | Clindamycin N = 1002 | *P* value* |
|---|---|---|---|
| **Dichotomized EGSS** | | | |
| Success† | 381 (37.8) | 318 (31.7) | 0.002 |
| Failure | 627 (62.2) | 684 (68.3) | |
| **Percent Reduction from Baseline to Week 12** | | | |
| **Inflammatory Lesion Count (%)** | | | |
| Mean ± SD | 60.9 ± 35.8 | 54.8 ± 38.0 | <0.001 |
| Range | −215.6 - 100.0 | −146.4 - 100.0 | |
| **Noninflammatory Lesion Count (%)** | | | |
| Mean ± SD | 49.8 ± 37.1 | 41.3 ± 38.6 | <0.001 |
| Range | −157.8 - 100.0 | −184.6 - 100.0 | |
| **Total Lesion Count (%)** | | | |
| Mean ± SD | 54.5 ± 31.6 | 46.9 ± 32.9 | <0.001 |
| Range | −97.4 - 100.0 | −107.4 - 100.0 | |

* *P* values are based on a 2-sided 5% test of the Cochran-Mantel-Haenszel Row Mean Score Statistic, adjusting for investigational center.

† Success was defined as clear or almost clear at Week 12, or at least a 2-grade improvement in EGSS from Baseline to Week 12. If no value was presented at Week 12, then the subject was considered a failure.

*The statistical reviewer's analyses of the co-primary endpoints are presented in Table 1 below.*

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Table 1: Primary Efficacy Results for Study MPI-02 (ITT)

| | Ziana™ Gel ($N = 1008$) | Clindamycin Gel ($N = 1002$) |
|---|---|---|
| **Investigator's Global Assessment** | | |
| Success (%) | 415 (41.2) | 345 (34.4) |
| p-value[1] | - | $< .001$ |
| **Non-inflammatory Lesions** | | |
| Mean (SD) | 49.8 (37.1) | 41.3 (38.6) |
| p-value[2] | - | $< .001$ |
| **Inflammatory Lesions** | | |
| Mean (SD) | 60.9 (35.8) | 54.8 (38.0) |
| p-value[2] | - | $< .001$ |

[1] CMH stratified by center.

[2] ANOVA with terms for treatment and pooled site.

Source: Reviewer's analysis.

*Per the statistical review, the different results (sponsor's and reviewer's) for the global evaluation was attributable to the handling of subjects who did not attend a follow-up visit within a defined window. Specifically, the statistical review states "...prior to database lock the statistical analysis plan was modified such that subjects that did not attend the visit within the protocol defined treatment window were treated as missing. In this case results are provided treating these subjects as missing (define this as the `windowed' analysis). While this strategy is reasonable, it was not pre-specified in the protocol. Thus an analysis is conducted retaining the values recorded despite the fact the subject visit is outside the treatment window (define this as the `as recorded' analysis). Note that the sponsor includes such a strategy in the analysis of the IGA only and not in the analysis of lesion counts. Further, the proposed label reports results based on the `as recorded' analysis." A side-by-side presentation of the different results is provided in Table 6 from the statistical review below:*

## Table 6: IGA Efficacy Results for Ziana™ Gel (ITT)

| | As Recorded† | | Windowed* | |
|---|---|---|---|---|
| | Ziana™ Gel ($N = 1008$) | Clindamycin Gel ($N = 1002$) | Ziana™ Gel ($N = 1008$) | Clindamycin Gel ($N = 1002$) |
| Success (%) | 415 (41.2) | 345 (34.4) | 381 (37.8) | 318 (31.7) |
| p-value | - | $< .001$ | - | 0.0018 |

† Source: Reviewer's Analysis using CMH stratified by pooled site.

* Source: Sponsor's Table 10.3.1.1 using CMH stratified by pooled site.

**Sponsor Table 10.2.2.1 Reduction in Absolute Lesion Counts ITT Population**

| | Clin RA N = 1008 | Clindamycin N = 1002 | *P* value* |
|---|---|---|---|
| **Reduction from Baseline to Week 12** | | | |
| **Inflammatory Lesion Count** | | | |
| Baseline Mean Count± SD | 30.6 ± 8.3 | 30.9 ± 8.7 | |
| Week 12 Mean Count ± SD | 11.9 ± 11.3 | 14.2 ± 13.0 | |
| Mean Count Reduction ± SD | 18.6 ± 12.0 | 16.8 ± 12.7 | <0.001 |
| Range | –69.0 - 48.0 | –52.0 - 49.0 | |
| **Noninflammatory Lesion Count** | | | |
| Baseline Mean Count ± SD | 49.0 ± 20.7 | 48.9 ± 21.1 | |
| Week 12 Mean Count ± SD | 24.9 ± 21.6 | 28.8 ± 22.5 | |
| Mean Count Reduction ± SD | 24.1 ± 20.3 | 20.0 ± 20.3 | <0.001 |
| Range | –71.0 - 93.0 | –94.0 - 81.0 | |
| **Total Lesion Count** | | | |
| Baseline Mean Count ± SD | 79.6 ± 24.1 | 79.8 ± 25.1 | |
| Week 12 Mean Count ± SD | 36.8 ± 28.5 | 43.0 ± 30.2 | |
| Mean Count Reduction ± SD | 42.8 ± 27.3 | 36.8 ± 28.1 | <0.001 |
| Range | –76.0 - 132.0 | –102.0 - 117.0 | |

* Based on a 2-sided 5% test of the Cochran-Mantel-Haenszel Row Mean Score Statistic

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# SUPPORTIVE STUDIES

**Statistical Reviewer's Table 3: Comparison of Lesion Reduction from Baseline to Week 12 (ITT Analysis) Studies 06 and 07***

| Lesion Type Mean (s.d.) | STUDY 06 | | | |
|---|---|---|---|---|
| | Clin-RA (n = 420) | Clindamycin (n = 208) | Tretinoin (n = 417) | Vehicle (n = 207) |
| **Inflammatory** | | | | |
| Mean baseline count | 30.10 (8.64) | 29.30 (8.38) | 29.44 (8.40) | 30.15 (8.43) |
| Mean number reduction | 13.6 (13.0) | 11.4 (12.0) | 10.7 (12.9) | 5.3 (15.6) |
| Mean % reduction | 46.0% (42.2%) | 39.7% (42.6%) | 37.5% (42.3%) | 19.6% (53.0%) |
| p-value (ranked ANOVA)[1] | NA | **0.014** | **< 0.001** | **< 0.001** |
| p-value (ranked ANOVA)[2] | NA | **0.028** | **< 0.001** | **< 0.001** |
| **Non-inflammatory** | | | | |
| Mean baseline count | 50.86 (22.21) | 47.64 (20.77) | 49.53 (21.13) | 49.28 (22.00) |
| Mean number reduction | 19.2 (21.7) | 11.9 (19.4) | 15.6 (20.6) | 6.9 (23.1) |
| Mean % reduction | 37.6% (37.8%) | 24.1% (44.3%) | 31.9% (40.0%) | 13.5% (50.0%) |
| p-value (ranked ANOVA)[1] | NA | **< 0.001** | **0.009** | **< 0.001** |
| p-value (ranked ANOVA)[2] | NA | **< 0.001** | **0.018** | **< 0.001** |
| **Total** | | | | |
| Mean baseline count | 80.96 (25.69) | 76.94 (23.57) | 78.97 (24.20) | 79.43 (24.50) |
| Mean number reduction | 32.8 (28.5) | 23.3 (26.4) | 26.3 (28.0) | 12.2 (32.7) |
| Mean % reduction | 41.4% (33.2%) | 31.3% (33.9%) | 34.7% (34.8%) | 16.5% (42.5%) |
| p-value (ranked ANOVA)[1] | NA | **< 0.001** | **0.001** | **< 0.001** |
| p-value (ranked ANOVA)[2] | NA | **< 0.001** | **0.002** | **< 0.001** |
| **Lesion Type Mean (s.d.)** | **STUDY 07** | | | |
| | Clin-RA (n = 425) | Clindamycin (n = 218) | Tretinoin (n = 429) | Vehicle (n = 216) |
| **Inflammatory** | | | | |
| Mean baseline count | 28.84 (8.15) | 29.44 (8.18) | 29.02 (8.07) | 29.91 (8.50) |
| Mean number reduction | 14.6 (12.6) | 12.2 (14.5) | 11.6 (12.8) | 8.6 (13.6) |
| Mean % reduction | 50.6% (48.8%) | 43.6% (47.4%) | 40.1% (42.5%) | 31.7% (43.9%) |
| p-value (ranked ANOVA)[1] | NA | **0.042** | **< 0.001** | **< 0.001** |
| p-value (ranked ANOVA)[2] | NA | **0.020** | **< 0.001** | **< 0.001** |
| **Non-inflammatory** | | | | |
| Mean baseline count | 46.35 (21.0) | 49.83 (22.39) | 48.11 (21.55) | 48.64 (21.84) |
| Mean number reduction | 15.9 (21.9) | 14.7 (21.7) | 13.8 (27.9) | 7.5 (26.0) |
| Mean % reduction | 35.7% (43.5%) | 30.1% (44.8%) | 29.9% (48.2%) | 18.5% (47.0%) |
| p-value (ranked ANOVA)[1] | NA | **0.328** | **0.333** | **< 0.001** |
| p-value (ranked ANOVA)[2] | NA | **0.088** | **0.110** | **< 0.001** |
| **Total** | | | | |
| Mean baseline count | 75.19 (24.23) | 79.27 (25.52) | 77.14 (24.73) | 78.56 (24.81) |
| Mean number reduction | 30.6 (29.2) | 26.9 (28.6) | 25.5 (34.7) | 16.1 (32.9) |
| Mean % reduction | 41.8% (37.8%) | 35.9% (36.3%) | 34.2% (39.3%) | 23.2% (39.5%) |
| p-value (ranked ANOVA)[1] | NA | **0.082** | **0.021** | **< 0.001** |
| p-value (ranked ANOVA)[2] | NA | **0.018** | **0.002** | **< 0.001** |

[1]p-values listed are the comparisons of mean **absolute** lesion reduction for Clin-RA vs. each of other three treatments.
[2]p-values listed are the comparisons of mean **percent** lesion reduction for Clin-RA vs. each of other three treatments.

***This table is from the statistical review of the original submission**

**Statistical Reviewer's Table 4: EGS Score and Success at Week 12 (ITT Analysis) – Studies 06 and 07***

| Distribution of EGS at wk 12 n (%) | STUDY 06 | | | |
|---|---|---|---|---|
| | Clin-RA (n = 420) | Clindamycin (n = 208) | Tretinoin (n = 417) | Vehicle (n = 207) |
| Clear | 5 (1%) | 2 (1%) | 4 (1%) | 2 (1%) |
| Almost Clear | 83 (20%) | 32 (15%) | 60 (14%) | 16 (8%) |
| Mild | 161 (38%) | 83 (40%) | 154 (37%) | 57 (28%) |
| Moderate | 153 (36%) | 83 (40%) | 180 (43%) | 110 (53%) |
| Severe | 18 (4%) | 7 (3%) | 18 (4%) | 20 (10%) |
| Very Severe | 0 | 1 (< 1%) | 1 (< 1%) | 2 (1%) |
| Percentage of patients with Clear or Almost Clear | 88 (21%) | 34 (16%) | 64 (15%) | 18 (9%) |
| Comparison (p-value)[1] | NA | 0.172 | 0.032 | <0.001 |
| **Distribution of EGS at wk 12 n (%)** | **STUDY 07** | | | |
| | Clin-RA (n = 425) | Clindamycin (n = 218) | Tretinoin (n = 429) | Vehicle (n = 216) |
| Clear | 9 (2%) | 3 (1%) | 3 (1%) | 1 (< 1%) |
| Almost Clear | 88 (21%) | 35 (16%) | 60 (14%) | 16 (7%) |
| Mild | 172 (40%) | 72 (33%) | 151 (35%) | 68 (31%) |
| Moderate | 134 (32%) | 90 (41%) | 184 (43%) | 103 (48%) |
| Severe | 22 (5%) | 17 (8%) | 30 (7%) | 28 (13%) |
| Very Severe | 0 | 0 | 0 | 0 |
| Not Reported | 0 | 1 | 1 | 0 |
| Percentage of patients with Clear or Almost Clear | 97 (23%) | 38 (17%) | 63 (15%) | 17 (8%) |
| Comparison (p-value)[1] | NA | 0.094 | 0.002 | <0.001 |

[1] p-value is the comparison between Clin-RA and each of other three treatments and is based on CMH test adjusting for investigational group.

***This table is from the statistical review of the original submission**

Also, see Section 6.1.6.

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### 6.1.5 Clinical Microbiology

Although the product contains an antibiotic, the proposed indication is not an infectious process, and the sponsor is not seeking an antimicrobial claim.

### 6.1.6 Efficacy Conclusions

In the new study, MP-1501-02, the sponsor's combination product was superior to clindamycin phosphate at efficacy assessment in mean reduction and mean absolute reduction in all lesion counts and on the dichotomized global severity scale. These outcomes adequately demonstrate the efficacy of the combination product and the contribution of tretinoin to efficacy.

The contribution of clindamycin to efficacy (and other evidence of efficacy of the sponsor's product) was adequately demonstrated in the sponsor's previous two Phase 3 safety and efficacy studies:

- 7001.G2HP-06-02: The combination product was superior to clindamycin, tretinoin and vehicle in mean reduction and mean absolute reduction for all lesion counts (inflammatory, non-inflammatory and total).
- 7001.G2HP-07-02: The combination product was superior to clindamycin, tretinoin and vehicle in mean percent reduction and mean absolute reduction in inflammatory lesions, and superior to clindamycin, tretinoin and vehicle in mean percent reduction in total lesions. The combination product was also superior to tretinoin and vehicle in mean absolute reduction of total lesions. The combination product was therefore superior to clindamycin, tretinoin and vehicle in mean percent reduction for two of three lesion counts (inflammatory and total). The combination product was superior to tretinoin in mean percent reduction and mean absolute reduction in inflammatory and total lesion counts, thus demonstrating the contribution of clindamycin to efficacy.
- Superiority of the combination product over tretinoin and vehicle was demonstrated for the proportion of subjects who were "clear" or "almost clear" on the Evaluator's Global Severity (EGS) score at 12 weeks in both trials.

Thus, the sponsor has adequately demonstrated the efficacy of their combination product in the treatment of acne vulgaris. Further, the sponsor has adequately demonstrated that each active ingredient, clindamycin phosphate 1.2% and tretinoin 0.025%, contributes to the efficacy of their combination product.

# 7 INTEGRATED REVIEW OF SAFETY

## 7.1 Methods and Findings

A total of 2,295 subjects received treatment with the sponsor's combination product and are considered in the safety update: 1,853 subjects received the combination product in one of the three Phase 3 safety and efficacy trials, and 442 received treatment with the product in the long-term safety study.

The safety review will focus primarily on the data from the new trial in which the combination product was compared to clindamycin and data from the long-term safety study. The safety data from the previously-conducted Phase 3 trials were reviewed under the original submission and will be summarized in brief in the current review following review of the safety data provided in the resubmission (the reader is referred to the Medical Officer's review of the original submission).

### 7.1.1 Deaths

One subject (34/002) died after Screening in the new pivotal study, but before having received any study medication. The subject was an 18-year-old white male who was killed in an automobile accident. There were no deaths in the long-term safety study.

### 7.1.2 Other Serious Adverse Events

Serious adverse events were reported for five subjects in the new study, two of whom received combination treatment and three of whom received clindamycin treatment:

**Table 11.4.1.1**
**Serious Adverse Events**

| Site/ Subject No. | Adverse Event | Severity | Relation to Treatment | Onset Day | Action Taken/Outcome |
|---|---|---|---|---|---|
| | | | **Clin RA Gel** | | |
| 12/030 | Intentional self-injury | Moderate | Unrelated | 75 | Treatment with Lexapro and Trazadone. Resolved. |
| 45/023 | Depression | Severe | Unrelated | 59 | Treatment with Zoloft/Wellbutrin XL/Prozac. Ongoing at last report. |
| | | | **Clindamycin** | | |
| 13/013 | Abdominoplasty | Severe | Unrelated | 29 | No action taken. Resolved |
| 35/028 | Dermoid cyst | Severe | Unlikely | 45 | Surgical removal of right ovary and fallopian tube. Resolved |
| 53/025 | Tonsillitis | Severe | Unrelated | 92 | Tonsillectomy. Resolved. |

**Subject 12/030:** This subject was a 20-year-old white female who was reported to have a "normal" psychiatric history at screening, per the case report form. The baseline/screening visit was November 8, 2005. The serious adverse event was recorded as a "suicide gesture" on the case report form and occurred on [redacted] The subject cut herself with a straight razor. The event required hospitalization. She completed the study; her last application of study drug was on January 30, 2006. b(6)

**Subject 45/023:** This subject was a 15-year-old white male who was reported to have a "normal" psychiatric history at screening, per the case report form. The baseline/screening visit was October 31, 2005. Depression was recorded on [redacted] as a serious adverse b(6)

event, and the event required hospitalization. Zoloft was begun for treatment of depression on December 29, 2005 and switched to Wellbutrin on January 4, 2006 (discontinued on January 24 due to an allergic reaction). Prozac was started on February 1, 2006. The last application of study drug was January 23, 2006, and the subject completed the study.

***Comment:*** *It is interesting, and perhaps coincidental, that that two serious adverse events that occurred in subjects treated with the sponsor's product, were both psychiatric in nature. Isotretinoin, a systemic retinoid, has been associated with psychiatric events.*

In the long-term safety study, six subjects reported eight serious adverse events:

**Sponsor Table 11-3.1.2**

| Site/ Subject No. | Adverse Event | Severity | Relation to Treatment | Action Taken/Outcome |
|---|---|---|---|---|
| 02-005 | Intractable esophageal reflux | Moderate | Unlikely | Resolved with no residual effects |
| 02-041 | Discomfort due to juvenile bunions | Moderate | Unrelated | Effect still present |
| 03-023 | Pre-eclampsia | Moderate | Unrelated | Resolved with no residual effects |
| | Caesarean section | Moderate | Unrelated | Resolved with no residual effects |
| 03-034 | Cholecystectomy | Moderate | Unrelated | Resolved with no residual effects |
| 05-002 | Dehydration | Severe | Unrelated | Resolved with no residual effects |
| | Vomiting | Severe | Unrelated | Resolved with no residual effects |
| 13-024 | Abdominal pain | Severe | Unlikely | Resolved with no residual effects |

## 7.1.3 Dropouts and Other Significant Adverse Events

See Sections 7.1.3.1 and 7.1.3.2

### 7.1.3.1 Overall profile of dropouts

The overall disposition of dropouts from all Phase 3 safety and efficacy studies is presented in the following table (from sponsor Table 4.1.1.1 of the Integrated Summary of Safety):

**Table 4.1.1.1**
**Subject Disposition, Number (%) of Subjects — Phase 3 Studies**

| | Clin RA N=1853 | Clindamycin N=1428 | Tretinoin N=846 | Clin RA Vehicle N=423 | Overall 4550 |
|---|---|---|---|---|---|
| **Total number of subjects by population (including all subjects) – n(%)** | | | | | |
| Intent-to-Treat (ITT) subjects* | 1853 | 1428 | 846 | 423 | 4550 |
| Per-Protocol subjects | 1337 (72.2) | 1034 (72.4) | 619 (73.2) | 307 (72.6) | 3297 (72.5) |

| | | | | | |
|---|---|---|---|---|---|
| **Number of subjects completing the study** | **1577 (85.1)** | **1197 (83.8)** | **710 (83.9)** | **355 (83.9)** | **3839 (84.4)** |
| **Number of subjects discontinuing the study** | **276 (14.9)** | **231 (16.2)** | **136 (16.1)** | **68 (16.1)** | **711 (15.6)** |
| **Reasons for discontinuation** | | | | | |
| Subject request | 49 ( 2.6) | 48 ( 3.4) | 40 (4.7) | 20 (4.7) | 157 (3.5) |
| Adverse event | 17 ( 0.9) | 4 ( 0.3) | 7 ( 0.8) | 2 ( 0.5) | 30 ( 0.7) |
| Lack of efficacy/worsening of condition | 11 ( 0.6) | 4 ( 0.3) | 12 ( 1.4) | 10 (2.4) | 37 ( 0.8) |
| Lost to follow-up | 147 ( 7.9) | 139 ( 9.7) | 51 ( 6.0) | 26 ( 6.1) | 363 ( 8.0) |
| Protocol violation/noncompliance | 7 ( 0.4) | 5 ( 0.4) | 9 ( 1.1) | 2 ( 0.5) | 23 ( 0.5) |
| Withdrawal of consent | 27 ( 1.5) | 20 ( 1.4) | 0 ( 0.0) | 0 ( 0.0) | 47 ( 1.0) |
| Pregnancy | 1 ( 0.1) | 0 ( 0.0) | 3 ( 0.4) | 0 ( 0.0) | 4 ( 0.1) |
| Inappropriate enrollment | 2 ( 0.1) | 5 ( 0.4) | 8 ( 0.9) | 3 ( 0.7) | 18 ( 0.4) |
| Other | 15 ( 0.8) | 6 ( 0.4) | 6 ( 0.7) | 5 ( 1.2) | 32 ( 0.7) |

The overall disposition of subjects enrolled in the long-term safety study is provided in sponsor Table 4.1.2.1 below:

**Table 4.1.2.1**
**Subject Disposition, Number (%) of Subjects – Long-Term Safety Study**

| | Clin RA N = 442 | | |
|---|---|---|---|
| | **Cohort 1*** **0 – 6 Months** **N = 442** | **Cohort 2†** **0 – 12 Months** **N = 213** | **Total** |
| **Total number of subjects** | | | |
| Enrolled | | | 442 |
| Excluded from Intent-to-Treat | | | 0 |
| Included in Intent-to-Treat | | | 442 |
| Exposed to study drug (started) | 442 | 213‡ | 442 |
| Completed | 352 (79.6) | 195 (91.5) | |
| **Discontinuations** | | | |
| **Total** | **90 (20.4)** | **18 (8.5)** | **108 (24.4)** |
| **Reasons for discontinuation** | | | |
| Acne treatment that required treatment with disallowed therapy | 1 (0.2) | 0 (0.0) | 1 (0.2) |
| Adverse event | 3 (0.7) | 0 (0.0) | 3 (0.7) |
| Subject request | 40 (9.0) | 8 (3.8) | 48 (10.9) |
| Protocol violation | 1(0.2) | 0 (0.0) | 1 (0.2) |
| Lost to follow-up | 44 (10.0) | 7 (3.3) | 51 (11.5) |
| Investigator request§ | 1 (0.2) | 1 (0.5) | 2 (0.5) |
| Not reported | 0 (0.0) | 2 (0.9)‖ | 2 (0.5)‖ |

* **Cohort 1 consisted of all subjects who entered the long-term study and were the population of subjects who were included in the 0- to 6-month analyses.**

† **Cohort 2 consisted of those subjects in Cohort 1 who continued to participate in the study past their 6-month visit and was the population of subjects who were included in the 7- to 12-month analyses.**

‡ **At the request of the sponsor, 139 subjects were discontinued. These subjects, combined with the 90 subjects who discontinued Cohort 1, reduced the enrollment of 442 subjects to 213 for Cohort 2, in accordance with the protocol.**

§ **Investigator request (at 0 to 6 months): Subject intrauterine pregnancy (IUP) with high risk factor. Investigator request (at 0 to 12 months): Pregnancy.**

‖ **Subjects 12-4 and 12-22 completed 6 months (Cohort 1) and started Cohort 2, but had incomplete data. Their status at 12 months was unknown and is considered not reported.**

7.1.3.2 Adverse events associated with dropouts

Seven subjects in the combination group and four subjects in the clindamycin group discontinued the new study because of adverse events. None of the adverse events resulting in subject discontinuation were serious or severe. Of the two subjects in the combination group who experienced rash, one case was considered possibly related to study drug, and the other was considered unlikely related to study drug. The report of rash in the clindamycin group was considered unrelated to study drug. Other adverse events resulting in study discontinuation in the combination group were: hypersensitivity, erythema, and dry skin (all in the same subject and considered treatment related); acne; nasopharyngitis; and a skin nodule:

**From Sponsor Table 11.3.2.1: Adverse Events Leading to Subject Discontinuation in the Clin RA Group**

| Site/ Subject No. | Adverse Event | Severity | Relation to Treatment | Onset Day | Action Taken/Outcome |
|---|---|---|---|---|---|
| | | | Clin RA Gel | | |
| 14/035 | Rash (hands) | Mild | Unlikely | 12 | Discontinued study treatment. Ongoing at last report. |
| | Rash (knees) | Moderate | Unlikely | 13 | Discontinued study treatment. Ongoing at last report. |
| 23/016 | Hypersensitivity | Moderate | Related | 43 | Discontinued study treatment. Received Adult Acnomel. Ongoing at discontinuation |
| 26/058 | Erythema | Mild | Related | 5 | Discontinued study treatment. AE resolved with no residual effects. |
| | Dry skin | Mild | Related | 5 | Discontinued study treatment. AE resolved with no residual effects. |
| | Skin exfoliation | Mild | Related | 5 | Discontinued study treatment. AE resolved with no residual effects. |
| 27/024 | Rash | Mild | Possible | 64 | Discontinued study treatment. AE resolved with no residual effects. |
| 32/049 | Acne | Moderate | Unlikely | 18 | Discontinued study treatment. AE resolved with no residual effects. |
| 44/005 | Nasopharyngitis | Mild | Unrelated | 28 | Discontinued study treatment. AE resolved with no residual effects. |
| 49/057 | Skin nodule | Moderate | Unlikely | 54 | Discontinued study treatment. AE ongoing at last report. |

Adverse events resulting in study discontinuation in the clindamycin treatment group in the new study were: skin tightness and dry skin (in the same subject), herpes zoster, dysfunctional uterine bleeding, and rash:

**From Sponsor Table 11.3.2.1: Adverse Events Leading to Subject Discontinuation in the Clindamycin Group**

**Clindamycin Phosphate Gel**

| Site/ Subject No. | Adverse Event | Severity | Relation to Treatment | Onset Day | Action Taken/Outcome |
|---|---|---|---|---|---|
| 23/055 | Skin tightness | Moderate | Probable | 6 | Discontinued study treatment. Subject lost to follow-up. |
| | Dry skin | Moderate | Probable | 6 | Discontinued study treatment. Subject lost to follow-up. |
| 32/008 | Herpes zoster | Moderate | Unrelated | 13 | Discontinued study treatment. AE reported resolved after treatment with unspecified information. Subject lost to follow-up. |
| 32/064 | Dysfunctional uterine bleeding | Moderate | Unrelated | 21 | Discontinued study treatment. AE resolved with no residual effects. |
| 39/106 | Rash | Moderate | Unrelated | 15 | Discontinued study treatment. AE treated with Zantac, Zyrtec, Prednisone, and Clarinex. AE resolved with no residual effects. |

Three subjects (0.7%) discontinued the long-term safety study because of an adverse event:

- Subject 06-031 was a 26-year old white female who consented to the study on February 24, 2004. She experienced worsening of seasonal allergies on May 1, 2004 and an acne flare on June 9, 2004, both of moderate severity and unrelated to study medication. She discontinued the study July 15, 2004 due to increased dryness of face, which was considered by the investigator to be of mild severity and of possible relationship to study medication. However, it is noted that the subject reported she had begun Accutane on June 9, 2004.
- Subject 06-034 was a 15-year old white male who consented to the study on February 12, 2004. He discontinued the study March 23, 2004 due to Crohn's Disease, which was considered by the investigator to be of mild severity and unrelated to study medication.
- Subject 13-004 was a 26-year old white female who consented to the study on February 12, 2004. She experienced three episodes of irritant dermatitis (on February 17, 2004, February 19, 2004, and March 16, 2004) all of mild severity and considered related to the study medication. She discontinued the study April 13, 2004. The adverse event resolved without sequelae within 48 hours after discontinuing the study.

### 7.1.3.3 Other significant adverse events

One pregnancy occurred in the new safety and efficacy trial. Five subjects became pregnant in the long-term safety study. The pregnancies are discussed in Section 7.1.14.

## 7.1.4 Other Search Strategies

The dermal safety studies were reviewed in the original submission and are discussed in brief in Section 7.1.12 of this review. No other search strategies were employed.

## 7.1.5 Common Adverse Events

In the new safety and efficacy study, 270 subjects (26.8%) in the combination group experienced 409 adverse events, and 236 subjects (23.6%) in the clindamycin group experienced 387 adverse events. The most frequently reported adverse events in both treatment groups were in the system organ class of infections and infestations (13.6% of subjects in each treatment group), and nasopharyngitis was the single most frequently reported adverse event in both treatment groups (5.1% of subjects in the combination group; 5.4% of subjects in the clindamycin group). Dry skin and headache were each reported in 2% of the subjects in the combination group. All other adverse events were reported with an incidence < 2%.

**Table 11.3.1.2**
**Summary of Adverse Event Incidence - No. (%) of Subjects**
**(At Least 1% of Subjects in Either Treatment Group)**
**Safety Evaluable Population**

| | Clin RA N = 1008 | Clindamycin N = 1002 |
|---|---|---|
| **At least one treatment emergent event** | **270 (26.8)** | **236 (23.6)** |
| **Infections and infestations** | **137 (13.6)** | **136 (13.6)** |
| Nasopharyngitis | 51 (5.1) | 54 (5.4) |
| Upper respiratory tract infection | 12 (1.2) | 17 (1.7) |
| Sinusitis | 12 (1.2) | 14 (1.4) |
| Pharyngitis streptococcal | 9 (0.9) | 12 (1.2) |
| Gastroenteritis viral | 9 (0.9) | 11 (1.1) |
| Influenza | 11 (1.1) | 7 (0.7) |
| **Respiratory, thoracic, and mediastinal disorders** | **41 (4.1)** | **38 (3.8)** |
| Pharyngolaryngeal pain | 19 (1.9) | 16 (1.6) |
| Cough | 12 (1.2) | 15 (1.5) |
| **Skin and subcutaneous tissue disorders** | **44 (4.4)** | **27 (2.7)** |
| Dry skin | 20 (2.0) | 7 (0.7) |
| **Gastrointestinal disorders** | **29 (2.9)** | **33 (3.3)** |
| Nausea | 11 (1.1) | 7 (0.7) |
| **Nervous system disorders** | **23 (2.3)** | **17 (1.7)** |
| Headache | 20 (2.0) | 12 (1.2) |

Note: All percentages are rounded. Subjects are counted only once within each row of the table.

Cutaneous safety and tolerability data from the new safety and efficacy study are presented below:

**Table 11.2.1**
**Cutaneous Safety and Tolerability**
**Number (%) of Subjects***

| | | Clin RA (N=1008) | Clindamycin (N=1002) |
|---|---|---|---|
| **Baseline** | | **N = 1008** | **N = 1002** |
| | Scaling | 158 (15.7) | 154 (15.4) |
| | Erythema | 409 (40.6) | 383 (38.2) |
| | Itching | 138 (13.7) | 141 (14.1) |
| | Burning | 32 (3.2) | 27 (2.7) |
| | Stinging | 24 (2.4) | 25 (2.5) |
| **Week 2** | | **N = 942** | **N = 925** |
| | Scaling | 251 (26.6) | 132 (14.2) |
| | Erythema | 391 (41.5) | 322 (34.8) |
| | Itching | 104 (11.0) | 74 (8.0) |
| | Burning | 79 (8.4) | 16 (1.7) |
| | Stinging | 40 (4.2) | 15 (1.6) |
| **Week4** | | **N = 922** | **N = 902** |
| | Scaling | 245 (26.6) | 122 (13.5) |
| | Erythema | 338 (36.7) | 295 (32.7) |
| | Itching | 87 (9.4) | 60 (6.7) |
| | Burning | 51 (5.5) | 8 (0.9) |
| | Stinging | 36 (3.9) | 12 (1.3) |
| **Week 8** | | **N = 857** | **N = 852** |
| | Scaling | 210 (24.5) | 113 (13.3) |
| | Erythema | 289 (33.7) | 247 (29.0) |
| | Itching | 70 (8.2) | 50 (5.9) |
| | Burning | 30 (3.5) | 14 (1.6) |
| | Stinging | 19 (2.2) | 9 (1.1) |
| **Week 12** | | **N = 887** | **N = 862** |
| | Scaling | 182 (20.5) | 97 (11.3) |
| | Erythema | 256 (28.9) | 250 (29.0) |
| | Itching | 47 (5.3) | 39 (4.5) |
| | Burning | 35 (3.9) | 6 (0.7) |
| | Stinging | 14 (1.6) | 6 (0.7) |

* Subjects are included who had safety or tolerability effects graded from 1 (mild) to 3 (severe).

***Comment:*** *Scaling progressively increased over the course of treatment in the combination group until Week 12 and was consistently higher throughout treatment in this group compared to the clindamycin group. By Week 12, scaling appeared to be trending downward in the combination group. This pattern is consistent with a tretinoin effect, and the Week 12 results suggest acclimation to the product. Erythema generally remained comparable between treatment groups over the course of treatment.*

*While a progressive increase in itching was not observed, this symptom was higher during treatment in the combination group compared to the clindamycin group until Week 12, when itching was comparable between treatment groups. Burning and stinging were consistently higher throughout treatment in the combination group compared to the clindamycin group. Burning and stinging peaked by Week 2 and generally progressively decreased through Week 12. These effects would also be consistent with tretinoin.*

In the long-term safety study, most adverse events were reported in ≤1% of subjects. Adverse events were most frequently reported in the infections and infestations system organ class (98 events being reported over the year). The most commonly-reported event was upper respiratory tract infection (33 reports; 7%) followed by nasopharyngitis (17 reports; 4%) and sinusitis (13 reports; 3%). There were five reports of gastroenteritis (1%).

Also, over the year-long course of the long-term safety, 18 subjects (4%) reported adverse events in the gastrointestinal disorders system organ class. There was one report of each of the following adverse events in the gastrointestinal disorders system organ class (<1%): abdominal pain, abdominal pain lower, dyspepsia and stomach discomfort. There were two reports of diarrhea over the course of the study. The most commonly reported adverse event in the gastrointestinal disorders system organ class was "gastoesophageal reflux disease" (5 reports; 1%).

**Table 11-2.2.1: Summary of Adverse Events by System Organ Class (in =5% of Subjects): Long-Term Safety Study**

| System Organ Class | 1st Quarter N=442 n (%) | 2nd Quarter N=386 n (%) | 3rd Quarter N=214 n (%) | 4th Quarter N=203 n (%) |
|---|---|---|---|---|
| **Infections and Infestations** | 51 (12%) | 34 (9%) | 29(14%) | 21 (10%) |
| Upper respiratory tract infection | 10 (2%) | 8 (2%) | 10 (5%) | 11 (5%) |
| **Skin and subcutaneous disorders** | 17 (4%) | 18 (5%) | 13 (6%) | 4 (2%) |
| Acne | 10 (2%) | 11 (3%) | 10 (5%) | 4 (2%) |
| **Injury, poisoning and procedural** | 22 (5%) | 15 (4%) | 3 (1%) | 2 (1%) |

## Adverse Events in the Supportive Studies

The largest percentage of adverse events were in the respiratory, thoracic and mediastinal disorders system organ class. Skin and subcutaneous disorders were the second most common category of adverse events for subjects treated with active medication and were more often reported for subjects treated with one of the tretinoin-containing products, consistent with the known irritancy of topical tretinoin. Generally, most adverse events were considered by investigators to be mild in severity and unrelated to study medication.

### 7.1.5.1 Eliciting adverse events data in the development program

At each visit, beginning with the dosing visit, the Investigator asked the subject about adverse events using an open question, e.g. "have you noticed any change in your health since the last visit?" Any adverse event, whether or not it was related to the study products, was to be reported on the Adverse Event form along with the date of onset, the severity, and the outcome.

### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The categorization and preferred terms of adverse events was appropriate.

7.1.5.3 Incidence of common adverse events

See Section 7.1.5.

7.1.5.4 Common adverse event tables

See Section 7.1.5.

7.1.5.5 Identifying common and drug-related adverse events

In the new safety and efficacy study, treatment-related adverse events were reported in 4.2% of subjects in the combination group and 1.7% of subjects in the clindamycin group. Skin and subcutaneous tissue disorders were generally the most common and were more commonly reported in the combination group (3.4%) compared to the clindamycin group (1.4%). Dry skin was the most frequently reported treatment-related adverse event in both treatment groups (2.3% in the combination group and 0.6% in the clindamycin group). No other treatment-related adverse events were observed in more than 1% of subjects in either treatment group.

**Table 11.3.1.3**
**Number (%) of Subjects with Treatment-Related, Treatment-Emergent Adverse Events During the Treatment Phase by System Organ Class and Preferred Term (At Least 2 Subjects in Either Treatment Group)**

| | Clin RA N = 1008 | Clindamycin N = 1002 |
|---|---|---|
| **At Least One Treatment-Related, Treatment-Emergent Adverse Event** | **42 (4.2)** | **17 (1.7)** |
| **Skin and subcutaneous tissue disorders** | **34 (3.4)** | **14 (1.4)** |
| Dry skin | 23 (2.3) | 6 (0.6) |
| Rash scaly | 7 (0.7) | 1 (0.1) |
| Skin burning sensation | 4 (0.4) | 1 (0.1) |
| Erythema | 4 (0.4) | 0 |
| Pruritus | 3 (0.3) | 1 (0.1) |
| Skin exfoliation | 3 (0.3) | 0 |
| Rash | 2 (0.2) | 0 |
| Skin tightness | 0 | 2 (0.2) |
| **General disorders and administration site conditions** | **7 (0.7)** | **0** |
| Application site reaction | 3 (0.3) | 0 |
| Pain | 2 (0.2) | 0 |

NOS = not otherwise specified

Note: All percentages are rounded. Subjects are counted only once in each row of the table. Events that have a relation of possible, probable, or definite are counted as treatment-related events.

***Comment:*** *These events are not concerning and their more frequent occurrence in the combination group is consistent with the tretinoin content.*

7.1.5.6 Additional analyses and explorations

No additional analyses or explorations were conducted.

## 7.1.6 Less Common Adverse Events

In the new safety and efficacy study, adverse events in the gastrointestinal system organ class were reported more often in the clindamycin group (33 events; 3.3%) than in the combination group (29 events; 2.9%). Nausea was the only adverse event in this system organ class in either treatment group that was reported at an incidence of $\geq 1\%$: there 11 reports in the combination group (1.1%) There were seven reports of nausea in the clindamycin group (0.7%). Diarrhea was reported with the same frequency in both treatment groups (two reports in each group; 0.2%). There was one report of abdominal pain, and it occurred in the clindamycin group. "Abdominal pain, upper" was reported by three subjects (0.3%) in the combination group and six subjects (0.6%) in the clindamycin group.

***Comment:*** *These data are presented because of the risk of colitis with topical clindamycin.*

## 7.1.12 Special Safety Studies

The dermal safety studies were reviewed in the Medical Officer's review of the original submission and are presented in brief in this review:

**7001-G2HP-01-02: A Single Center, Evaluator-Blind Evaluation of the Cumulative Irritation Potential of Clin-RA Gel, Vehicle Gel and Control Following Repeated Topical Application to Healthy Subjects.**

Under conditions of the study, the sponsor's product was shown to be moderately irritating.

**7001-G2HP-03-02: A Single Center, Evaluator-blind Determination of the Cumulative Irritation and Contact Sensitization Potential of Clin-RA Gel, Clin-RA Gel Vehicle, and Retin A Gel 0.025% Control Following Repeated Topical Applications to Healthy Subjects**

The results suggested that the sponsor's product has low potential for causing contact sensitization reactions.

**7001-G2HP-04-02: A Single Center, Evaluator-blind Assessment of the Phototoxicity Potential of Clin-RA Gel and Vehicle Following Topical Application to the Skin of Healthy Subjects.**

Under the conditions of the study, the sponsor's product had a very low potential for causing phototoxic reactions.

**7001-G2HP-05-02: A Single Center, Evaluator-Blind Determination of the Photoallergy Potential of Clin-RA Gel and Vehicle Gel Following Repeated Topical Application to Healthy Subjects**

Under the conditions of the study, the sponsor's product had a very low potential for causing photoallergic reactions.

## 7.1.14 Human Reproduction and Pregnancy Data

One pregnancy occurred in the new pivotal trial: A 16-year-old female (Subject 15/086) began treatment with clindamycin phosphate gel on October 18, 2005. She had begun using a NUVA ring for contraception during the study. On January 12, 2006 (the day of her final study visit), she tested positive for pregnancy. Her last use of study product was on January 11, 2006, and she completed the study on January 12, 2006 (Day 87). The subject called the site on February 28, 2006 (135 days after starting drug and 48 days after completing treatment) to report that she had had a miscarriage. The investigator considered the miscarriage to be unrelated to study drug.

Five pregnancies occurred in the long-term safety study:

- Subject 02-047 was a 28-year old Hispanic/Latino female who consented to the study on February 25, 2004. On August 11, 2004, she informed the study site that she was pregnant and stopped her study medication. Her last visit date was July 14, 2004. She did not return for follow-up visits nor return phone calls or acknowledge multiple attempts to contact her. The subject was considered lost to follow-up.
- Subject 03-003 was a 35-year old white female who consented to the study on January 26, 2004. The subject became aware of her pregnancy on September 16, 2004 and stopped her study medication October 6, 2004. Her final visit date was October 7, 2005. The report of the birth of her healthy infant was received on May 17, 2005.
- Subject 03-023 was a 21-year old white female who consented to the study on February 6, 2004. Her last study visit was April 30, 2004. On [redacted], she experienced pre-eclampsia and the baby was therefore delivered, one month early by Caesarian section. The baby was reported to be "normal." b(6)
- Subject 03-036 was a 30-year old white female who consented to the study on February 20, 2004. The subject became aware of her pregnancy on May 11, 2004, informing the study site on May 18, 2004, at which time study medication was discontinued. Her final study visit was on May 20, 2004. She delivered a healthy infant on [redacted] b(6)
- Subject 07-031 was a 21-year old Hispanic/Latino female who consented to the study on February 26, 2004. The subject became aware of her pregnancy on August 8, 2004, informing the study site on August 12, 2004, which was the date of her last visit. She underwent elective termination of the pregnancy for personal reasons on [redacted] b(6)

## 7.1.16 Overdose Experience

No overdose experience was reported.

### 7.1.17 Postmarketing Experience

The product is not marketed.

## 7.2 Adequacy of Patient Exposure and Safety Assessments

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

The primary population used to evaluate safety was the intent-to-treat population.

#### 7.2.1.1 Study type and design/patient enumeration

See Section 4.2.

#### 7.2.1.2 Demographics

The table below provides overall demographic information for the three safety and efficacy studies.

**Table 4.2.1.1**
**Demographic and Subject Characteristics, Intent-to-Treat Subjects – Phase 3 Studies**

| Variable | Clin RA N=1853 | Clindamycin N=1428 | Tretinoin N=846 | Clin RA Vehicle N=423 | Overall N=4550 | *P* Value |
|---|---|---|---|---|---|---|
| **Age (years)** | | | | | | |
| N | 1853 | 1428 | 845 | 423 | 4549 | 0.845* |
| Mean (SD) | 19.19 (±7.4) | 19.77 (±7.2) | 19.68 (± 7.7) | 19.35 (±7.7) | 19.3 (± 7.4) | |
| Median | 16.5 | 16.4 | 16.6 | 16.5 | 16.5 | |
| Range | 11.6 – 84.0 | 11.7 – 53.2 | 12.0 – 55.0 | 11.6 – 52.8 | 11.6 – 84.0 | |
| **Race – n (%)** | | | | | | |
| White | 1381 (74.5) | 1058 (74.1) | 577 (68.2) | 286 (67.6) | 3302 (72.6) | 0.150† |
| Black | 207 (11.2) | 154 (10.8) | 125 (14.8) | 69 (16.3) | 555 (12.2) | |
| Asian/Pacific Islander | 37 (2.0) | 38 (2.7) | 17 (2.0) | 10 (2.4) | 102 (2.2) | |
| Hispanic/Latino | 202 (10.9) | 154 (10.8) | 111 (13.1) | 50 (11.8) | 517 (11.4) | |
| American/Alaskan Native | 7 (0.4) | 8 (0.6) | 6 (0.7) | 2 (0.5) | 23 (0.5) | |
| Other | 19 (1.0) | 16 (1.1) | 10 (1.2) | 6 (1.4) | 51 (1.1) | |
| **Gender – n (%)** | | | | | | |
| Male | 927 (50.0) | 679 (47.6) | 408 (48.2) | 203 (48.0) | 2217 (48.7) | 0.635† |
| Female | 926 (50.0) | 749 (52.5) | 438 (51.8) | 220 (52.0) | 2333 (51.3) | |

SD = Standard deviation
Note: Subjects enrolled in Phase 3 studies 7001-G2HP-06-02 and 7001-G2HP-02 received treatment with Clin RA, clindamycin phosphate 1.2%, tretinoin 0.025%, or Clin RA Gel vehicle. Subjects enrolled in Phase 3 study MP-1501-02 received treatment with Clin RA Gel or clindamycin phosphate 1.2%.
* Values for treatment comparisons are from a 2-way analysis of variance with factors of treatment and investigational group.
† *P* values for treatment comparisons are from a Cochran-Mantel-Haenszel test of row mean scores, stratified by investigational group.

#### 7.2.1.3 Extent of exposure (dose/duration)

The extent of exposure to study products is presented from the new pivotal study. Mean amounts and number of applications was similar between treatment groups.

**Table 11.1.1**
**Study Drug Exposure: ITT Population**

| | Clin RA N = 1008 | Clindamycin N = 1002 |
|---|---|---|
| **Total amount of product used (g)*** | | |
| N | 929 | 912 |
| Mean ± SD | 29.27 ± 17.18 | 30.10 ± 17.15 |
| Range | 0.50 - 112.05 | 0.60 - 92.50 |
| **Total no. of applications†** | | |
| N | 945 | 924 |
| Mean ± SD | 79.39 ± 14.86 | 79.61 ± 14.21 |
| Range | 2 - 125 | 4 - 133 |
| **Average amount used per application (g/app)*** | | |
| N | 929 | 912 |
| Mean ± SD | 0.368 ± 0.218 | 0.377 ± 0.205 |
| Range | 0.040 - 2.300 | 0.050 - 1.176 |

* Subjects who did not return their tubes were excluded from the N's for the total amount of product used and the average amount of product used.

† Subjects who did not record the number of applications were excluded from the N for total number of applications.

## 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary sources of data were used to evaluate safety.

### 7.2.2.2 Postmarketing experience

The product is not marketed.

### 7.2.2.3 Literature

The resubmission included summaries of papers published in the medical literature since submission of the original marketing application (the full references of the summarized papers were also provided). The sponsor limited the references to those "that were considered as most descriptive of the information available on clindamycin and tretinoin pharmacology, and studies of safety and efficacy."

## 7.2.3 Adequacy of Overall Clinical Experience

An adequate number of subjects were exposed to the drug to characterize its safety in the short-term (12 weeks) and long-term (up to one year). Doses and durations of exposure were adequate to assess the safety of the product for its intended use. The designs of the studies were adequate to answer safety questions. Topical safety was adequately assessed in the development program in the Phase 3 studies (including the long-term safety study) and the Phase 1 dermal safety studies.

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

The adequacy of the assessment of safety has been previously discussed. See Section 7.2.3. Given the long history of marketing of the active ingredients, their safety has been well established. There are no recommendations for further study.

### 7.2.8 Assessment of Quality and Completeness of Data

See Section 7.2.3.

### 7.2.9 Additional Submissions, Including Safety Update

The Safety Update consisted of data from the sponsor's development program and a review of the literature. Specifically, the sponsor provided the safety data from the new study, the previously-conducted Phase 3 studies, the long-term safety study and an integrated summary of safety data. However, the focus of the integrated safety data was on the comparison of the combination product to clindamycin, since the data from the tretinoin and vehicle arms were unchanged from the original submission. The safety update did not raise any new safety concerns.

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

Treatment-related adverse events were reported in 4.2% of subjects in the combination group and 1.7% of subjects in the clindamycin group in the new study. Skin and subcutaneous tissue disorders were generally the most common and were more commonly reported in the combination group (3.4%) compared to the clindamycin group (1.4%). Dry skin was the most frequently reported treatment-related adverse event in both treatment groups (2.3% in the combination group and 0.6% in the clindamycin group). No other treatment-related adverse events were observed in more than 1% of subjects in either treatment group.

Scaling progressively increased over the course of treatment in the combination group until Week 12 and was consistently higher throughout treatment in this group compared to the clindamycin group. By Week 12, scaling appeared to be trending downward in the combination group. This pattern is consistent with a tretinoin effect, and the Week 12 results suggest acclimation to the product. Erythema generally remained comparable between treatment groups over the course of treatment.

While a progressive increase in itching was not observed, this symptom occurred at a higher incidence during treatment in the combination group compared to the clindamycin group until Week 12, when itching was comparable between treatment groups. Burning and stinging were consistently higher throughout treatment in the combination group compared to the clindamycin group. Burning and stinging peaked by Week 2 and generally progressively decreased through Week 12. These effects would also be consistent with tretinoin.

Safety considerations pertaining to the sponsor's product would be on the local and systemic levels. Local safety issues would include the potential for the sponsor's tretinoin-containing product to cause irritancy. Systemic safety issues would pertain to the potential for systemic exposure to either of the actives from use of the compound and the consequences from such exposures. The sponsor's development program was adequate in design to assess these local and systemic safety issues. Specifically,

- Local safety assessments were conducted in all of the efficacy and/or safety studies.
- The sponsor conducted a long-term safety study.
- The sponsor conducted the standard battery of dermal safety studies.
- The sponsor conducted a multiple-dose study in subjects with acne vulgaris to assess the absorption and safety of their product.
- Adverse event data were collected in all of the clinical trials.

One of the most important potential safety issues relates to the extent of systemic exposure to clindamycin from the combination product and the risks from such exposure, the most significant probably being pseudomembranous colitis. In the new safety and efficacy study, gastrointestinal adverse events were reported more often in the clindamycin group (33 events; 3.3%) than in the combination group (29 events; 2.9%). Over the year-long course of the long-term safety study, 18 subjects (4%) reported adverse events in the gastrointestinal disorders system organ class. The only events for which more than one report was received were: gastoesophageal reflux disease (five reports; 1%), toothache (three reports; 1%), diarrhea (two reports; < 1%), and vomiting (two reports; < 1%). In the previous safety and efficacy studies, gastrointestinal disorders were reported at similar rates across treatment groups, and no individual event was reported at > 1% in any treatment group. Based on review of the available data, there does not appear to be a substantial risk for this complication. Consistent with package inserts for marketed clindamycin products (including topical formulations), inclusion of a warning regarding this risk should adequately advise of it.

No new safety concerns were raised in the sponsor's development program.

## 7.4 General Methodology

### 7.4.1 Pooling data Across Studies to Estimate and Compare Incidence

The pooling of adverse event data from the three safety and efficacy trials was accomplished by combining of the numerator events and the denominators (reflecting the number of subjects in a particular treatment group).

#### 7.4.1.1 Pooled data vs. individual study data

The safety review was focused on data from the new (two-arm) pivotal trial and the long-term safety study. Data from the tretinoin and vehicle arms were provided in the original submission (and the information pertaining to these two arms is unchanged from the original submission).

#### 7.4.1.2 Combining data

See Sections 7.4.1 and 7.4.1.1.

### 7.4.2 Explorations for Predictive Factors

These explorations were not done.

#### 7.4.2.1 Explorations for dose dependency for adverse findings

Onset and resolution of cutaneous adverse events were consistent with the once daily topical application of a tretinoin-containing product, the usual dosing frequency.

#### 7.4.2.2 Explorations for time dependency for adverse findings

Time to onset and resolution of cutaneous adverse events were consistent with once daily topical application of a tretinoin-containing product.

#### 7.4.2.3 Explorations for drug-demographic interactions

These explorations were not done.

#### 7.4.2.4 Explorations for drug-disease interactions

These explorations were not done.

#### 7.4.2.5 Explorations for drug-drug interactions

These explorations were not done.

### 7.4.3 Causality Determination

The nature of the cutaneous adverse events, their time to onset and resolution were consistent with known effects of topical tretinoin products.

# 8 ADDITIONAL CLINICAL ISSUES

## 8.1 Dosing Regimen and Administration

Dose-ranging studies were not conducted. Currently marketed formulations of tretinoin are dosed once in the evening. Currently marketed topical gel formulations of clindamycin phosphate are dosed either once or twice daily. Rather than conduct dose-ranging studies, the sponsor based their dosing regimen on those for the individually marketed tretinoin and topical clindamycin phosphate products, electing once daily dosing.

### 8.2 Drug-Drug Interactions

These studies were not conducted.

### 8.3 Special Populations

The sponsor's efforts to evaluate the effects of age, gender or skin type/race and ethnicity on efficacy were adequate. There was no evidence of clinically significant effect of any of these parameters on efficacy. Evaluation of these parameters on safety was not found in the resubmission.

### 8.4 Pediatrics

The sponsor requested a waiver for patients under the age of 11 years. This is reasonable because acne vulgaris does not generally affect patients in this younger age group.

### 8.5 Advisory Committee Meeting

See Section 2.6

### 8.6 Literature Review

See Section 7.2.2.3

### 8.7 Postmarketing Risk Management Plan

There are no recommendations for a post-marketing risk management plan.

## 9 OVERALL ASSESSMENT

### 9.1 Conclusions

This resubmission proposes marketing of a topical gel combination product containing the active ingredients clindamycin phosphate 1.2% (an antibiotic) and tretinoin 0.025% (a retinoid). The product is proposed for the treatment of acne vulgaris in patients 12 years and older and is intended for once daily application. The proposed trade name is Ziana™.

The resubmission included data from one adequate and well-controlled safety and efficacy trial. The sponsor previously submitted safety and efficacy data from two other well-controlled clinical trials (those data were reviewed when provided in the original submission).

Based on the results from the three controlled clinical trials, the sponsor has adequately demonstrated the efficacy of their combination product in the treatment of acne vulgaris. The sponsor's development program was of appropriate design to demonstrate the contribution of

each component to efficacy so as to address the combination policy, as put forth in 21 CFR 300.50. The sponsor has adequately demonstrated that each active ingredient, clindamycin phosphate 1.2% and tretinoin 0.025%, contributes to the efficacy of their combination product.

The sponsor's development program permitted adequate evaluation of the safety of their product. Specifically,

- Local safety assessments were conducted in all of the efficacy and/or safety studies.
- The sponsor conducted a long-term safety study.
- The sponsor conducted the standard battery of dermal safety studies.
- The sponsor conducted a multiple-dose study in subjects with acne vulgaris to assess the absorption and safety of their product.
- Adverse event data were collected in all of the clinical trials.

No new safety concerns were raised in the sponsor's development program.

## 9.2 Recommendation on Regulatory Action

From a clinical perspective, it is recommended that the application be approved.

## 9.3 Recommendation on Postmarketing Actions

### 9.3.1 Risk Management Activity

There are no recommendations for risk management steps.

### 9.3.2 Required Phase 4 Commitments

There are no recommendations for Phase 4 commitments.

### 9.3.3 Other Phase 4 Requests

There are no Phase 4 requests.

## 9.4 Labeling Review

The labeling review is ongoing.

## 9.5 Comments to Applicant

There are no comments for the applicant.

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/s/

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Brenda Carr
10/12/2006 12:57:55 PM
MEDICAL OFFICER

Markham Luke
10/13/2006 01:39:51 PM
MEDICAL OFFICER
See also Biostat review regarding previous approvability issue and satisfactory Complete Response.

Susan Walker
10/31/2006 09:05:06 AM
DIRECTOR

**NDA 50-802: Medical Officer's Memo to File**

A Not Approvable action was recommended for NDA 50-802. The deficiency may be summarized as follows:

The contribution to efficacy of each component of the sponsor's combination product was not adequately demonstrated. Specifically, the contribution of tretinoin to efficacy was not adequately demonstrated.

To address this deficiency, it is recommended that the sponsor conduct an additional four-armed clinical study. The recommended study arms are: the sponsor's product, clindamycin, tretinoin gel (both in the sponsor's vehicle) and the sponsor's vehicle. The estimated treatment effect from the previously conducted Phase 3 trials can be used to help in calculating the samples size for the recommended additional study.

Brenda Carr, M.D.
Medical Officer/Dermatology

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/s/

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Brenda Carr
12/7/04 10:50:18 AM
MEDICAL OFFICER

Markham Luke
12/7/04 12:41:46 PM
MEDICAL OFFICER
Addendum to Clinical Review

Jonathan Wilkin
12/7/04 02:26:02 PM
MEDICAL OFFICER
agree with recommendation as current policy, and would be willling to reconsider with Biostat the need for more than only two treatment arms, complete product and clindamycin-only.

# CLINICAL REVIEW of NDA 21-739

| | |
|---|---|
| Application Type: | 21-739 |
| Submission Number: | 000 |
| Submission Code: | |
| Letter Date: | February 6, 2004 |
| Stamp Date: | February 9, 2004 |
| PDUFA Goal Date: | December 9, 2004 |
| Reviewer Name: | Brenda Carr, M.D. |
| Review Completion Date: | October 28, 2004 |
| Established Name: | clindamycin phosphate and tretinoin |
| (Proposed) Trade Name: | Clin-RA |
| Therapeutic Class: | antibiotic and retinoid |
| Applicant: | Dow Pharmaceutical Sciences |
| Priority Designation: | S |
| Formulation: | gel |
| Dosing Regimen: | once daily |
| Indication: | acne vulgaris |
| Intended Population: | patients 12 years and older |

# Table of Contents

## Executive Summary

I. Recommendations

A. Recommendation on Approvability

The sponsor has submitted a marketing application for a topical gel combination product containing clindamycin phosphate 1.2% and tretinoin 0.025%. The product is proposed for treatment of acne vulgaris in patients 12 years and older, and the product is intended for once daily application. The proposed trade name is Clin-RA.

Both clindamycin phosphate and tretinoin are individually marketed in various formulations for the treatment of acne vulgaris. Each product targets a different aspect of the acne pathogenic pathway, and clinicians commonly employ a two-pronged approach to acne treatment by recommending that their patients apply a topical antimicrobial in the morning and tretinoin in the evening. The sponsor's product would provide for a dual-action product with once daily application.

From a clinical perspective, a Not Approvable action is recommended for this application, as the contribution of each component to efficacy was not adequately demonstrated.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

There are no recommendations for Phase 4 studies or risk management steps.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The sponsor conducted two identical, four-armed, multi-center, randomized, double-blind, active- and vehicle-controlled, parallel Phase 3 trials, 7001-G2HP-06-02 (06) and 7001-G2HP-07-02 (07). The studies were of appropriate design for evaluation of a combination product.

Study 06 enrolled a total of 1252 subjects: 420 received Clin-RA Gel, 208 received clindamycin, 417 received tretinoin, and 207 received Clin-RA vehicle. Study 07 enrolled 1288 subjects: 425 received Clin-RA Gel, 218 received clindamycin, 429 received tretinoin, and 216 received Clin-RA vehicle. Total enrollment for the combined studies was 2540: 845 received Clin-RA Gel, 426 received clindamycin, 846 received tretinoin, and 423 received Clin-RA vehicle. The efficacy database consisted of subjects who were enrolled in these two trials.

In development of the product, the Division advised that the sponsor conduct a Phase 2 trial to estimate the treatment effect of Clin-RA Gel and each of its components and that these estimates be used for calculating the sample size for Phase 3 trials. It was also recommended that the studies be powered for the Evaluator's Global Severity score. The sponsor elected not to follow this advice.

B. Efficacy

The co-primary efficacy variables were:
(1) mean percent change from baseline at Week 12 in
- inflammatory lesion counts,
- non-inflammatory lesion counts, and
- total lesion counts

(2) the percent of subjects who cleared or almost cleared at Week 12 as judged by an Evaluator's Global Severity score.

In the primary efficacy analyses for the comparison between Clin-RA Gel and clindamycin gel and tretinoin gel superiority was demonstrated if there was statistical significance in:

(1) two of three of the following lesion counts:
- mean percent change from baseline at Week 12 in inflammatory lesion counts,
- mean percent change from baseline at Week 12 in non-inflammatory lesion counts,
- mean percent change from baseline at Week 12 in total lesion counts

(2) the percent of subjects who were "clear" or "almost clear" at Week 12, as judged by an Evaluator's Global Severity Score.

In the primary efficacy analyses for the comparison for the comparison between Clin-RA Gel versus vehicle, superiority was demonstrated if there was statistical significance in:
(1) mean percent change from baseline at Week 12 in inflammatory lesion counts, and
(2) mean percent change from baseline at Week 12 in non-inflammatory lesion counts
(3) the percent of subjects who were "clear" or "almost clear" at Week 12, as judged by an Evaluator's Global Severity Score.

Results

Superiority of Clin-RA over clindamycin, tretinoin and vehicle was demonstrated for all lesion counts (inflammatory, non-inflammatory and total) in study 7001.G2HP-06-02.

Superiority of Clin-RA over clindamycin, tretinoin and vehicle was demonstrated for inflammatory and total lesions in study 7001.G2HP-0-02 (07). Superiority of Clin-RA over vehicle was demonstrated for non-inflammatory lesions. However, superiority of Clin-RA over clindamycin and tretinoin was not demonstrated for non-inflammatory lesions in study 07, although Clin-RA trended towards superiority over clindamycin in mean percent change of non-inflammatory lesions ($p=0.88$). Thus, superiority of Clin-RA over clindamycin, tretinoin and vehicle was demonstrated in two of three lesion counts (inflammatory and total).

Superiority of Clin-RA over tretinoin and vehicle was demonstrated for the proportion of subjects who were "clear" or "almost clear" on the Evaluator's Global Severity (EGS) score at 12 weeks in both pivotal trials. However, superiority of Clin-RA over clindamycin was not demonstrated for the proportion of subjects who were "clear" or "almost clear" on the EGS in the intent-to-treat analysis to a level of statistical significance in either pivotal trial.

C. Safety

No new safety concerns identified. The largest percentage of adverse events were "respiratory, thoracic and mediastinal disorders." "Skin and subcutaneous disorders" were the second most common category of adverse events for subjects treated with active medication and were more often reported for subjects treated with one of the tretinoin-containing products, consistent with the known irritancy of topical tretinoin. Generally, most adverse events were considered by investigators to be mild in severity and unrelated to study medication.

D. Dosing

Dose-ranging studies were not conducted. Currently marketed topical gel formulations of clindamycin phosphate are dosed either once or twice daily. Currently marketed formulations of tretinoin are dosed once in the evenings. The sponsor based dosing of their product on the dosing of the individually marketed tretinoin and topical clindamycin phosphate products, and elected for once daily dosing. At the pre-IND meeting, the Division recommended that the sponsor conduct dose-ranging studies, since it could not be assumed that the safety and efficacy profiles of the combination used once daily would be the same as the profiles for the products individually used once daily.

E. Special Populations

The sponsor's efforts to evaluate gender effect pertaining to efficacy were adequate. There was no evidence of clinically significant gender effect on efficacy. The sponsor's efforts to evaluate the effects of age, race and ethnicity pertaining to efficacy were adequate. There was no evidence of clinically significant effect for any of these parameters on efficacy.

Subjects 11 years and older were enrolled in the pivotal trials, and the mean age of study subjects was approximately 19 years. The sponsor requested a waiver for patients under the age of 11 years. This is acceptable, since acne vulgaris does not typically occur in the younger age group.

Tretinoin-containing products are classified in Pregnancy Category C. Clindamycin phosphate-containing products are classified in Pregnancy Category B. The sponsor appropriately proposes a category C designation for their product and proposes inclusion of approved wording contained in the discussion of teratogenic effects in the Pregnancy portion of the package insert for another tretinoin-containing product (Avita). For obvious reasons, the treatment of acne in pregnancy would differ from that in the non-pregnant patient. Because it contains a retinoid, it is not likely that the sponsor's product would be frequently recommended for use during pregnancy. Seven subjects became pregnant during the pivotal trials, six of whom received tretinoin treatment and one of whom received Clin-RA Gel treatment. For four subjects, the pregnancy resulted in early discontinuation of treatment. The remaining three subjects had completed the study, with their positive pregnancy tests having been discovered at the last study visit. The pregnancy outcomes were variable, and it is not clear to what extent, if any, exposure to study products impacted the outcomes.

At this juncture, no data is thought needed for other populations.

**Clinical Review**

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

The sponsor has submitted a marketing application for a topical gel combination product containing clindamycin phosphate 1.2% (an antibiotic) and tretinoin 0.025% (a retinoid). The proposed indication is treatment of acne vulgaris, and the product is intended for once daily application. The product is proposed for use in patients 12 years and older. The proposed trade name is Clin-RA.

B. State of Armamentarium for Indication

There are a number of products approved for treatment of acne vulgaris. These treatments include both topical and systemic products. Categories of treatment include antibiotics, retinoids and hormonal therapies. Both clindamycin phosphate and tretinoin are individually marketed in various formulations for the treatment of acne vulgaris. Clindamycin is thought to have an effect primarily against inflammatory lesions through its antimicrobial action against *Propionibacterium acnes*. Other factors may be operative as well. Tretinoin is thought to have an effect primarily against noninflammatory lesions: it "normalizes the keratinization of the follicular infundibulum" (Section 8.1, "Clinical Data Summary and Results Analysis").

Because each product targets a different aspect of the acne pathogenic pathway, clinicians commonly employ a two-pronged approach to acne treatment by recommending a topical antimicrobial and a topical retinoid for their patients. Typically, the antimicrobial is recommended for application in the morning and the retinoid for application in the evening. The applications are separated as such because of a potential for mutual inactivation if applied simultaneously. The proposed new product would provide for a dual-action combination product that is applied once a day.

It is the sponsor's belief that their product "represents a rational combination therapy based on the distinctively different mechanisms of action of the two active drugs, clindamycin and tretinoin" (Section 8.1). This would appear to be a sound scientific rationale for marketing. It is unclear how efficacy of the combination product would compare to that of the same components applied separately, and establishing such would require head-to-head trials. The most obvious and/or significant apparent benefit would appear to pertain to patient convenience.

C. Important Milestones in Product Development

Pre-IND Meeting: September 24, 2001

Advice given to the sponsor included:

- The sponsor was encouraged to conduct a Phase 2 study to determine the contribution of each active ingredient to the drug effect, and to determine point estimates for the Phase 3

trials.

- The suggested lesion counts were 20-50 inflammatory lesions, 20-100 non-inflammatory lesions and $\leq 2$ nodules.
- The sponsor was encouraged to conduct a Phase 2 trial to estimate the treatment effect of Clin-RA Gel and each of its components and to use the estimates for calculating the sample size for Phase 3 trials.
- It was recommended that the sponsor conduct mean change and mean percent change analyses in Phase 3.

End-of-Phase 2 Meeting: December 16, 2002

In the briefing package, the sponsor proposed that, in addition to lesion counts, efficacy be based on an Evaluator's Global Severity Score of "clear" or "almost clear," or a two-grade improvement from baseline. The sponsor was advised that while two-grade improvement data could be submitted as supportive, the Division would measure efficacy by the proportion of subjects who are "clear" or "almost clear" at efficacy evaluation. Additionally, the sponsor was advised that the representativeness in the "severe" category would be important to the meaningfulness of the two-grade improvement data. Pertaining to lesion counts, the sponsor was requested to present the change and mean percent change in lesion counts from baseline to week 12.

The statistical reviewer offered the following advice regarding the sponsor's proposed enrollment strategy: "Adequacy of the sample size depends on having reliable estimates for the various treatment arms in the trial. For the sample size determination the sponsor used...information from (Product X) to get estimates for differences in percent change from baseline for the combination and tretinoin and clindamycin for inflammatory, non-inflammatory and total lesions. However, the sample size calculation was not powered for the co-primary endpoint, the dichotomized Evaluator's Global Evaluation (EGE). It is recommended that the sponsor power their Phase 3 trials for this co-primary endpoint along with allowance for drop-out to ensure that Phase 3 trials are not under-powered."

Pre-NDA Meeting: October 1, 2003

Advice given to the sponsor included:

- The sponsor would need to demonstrate the safety of long-term use of their product; the sponsor was referred to ICH-E1A Guideline for Industry.
- If the NDA does not contain a Clinical Microbiology section, the wording below would likely be considered acceptable for the Microbiology section of the label: [redacted] b(4)
- Pertaining to the several secondary endpoints, the statistical reviewer advised that, "if efficacy results for these endpoints are intended for labeling, then these endpoints need to be clinically relevant and multiplicity adjustment would be needed.

*Comments: 1) The sponsor elected not to conduct a Phase 2 study for determination of the contribution of each active ingredient to efficacy and for determination of point estimates. 2)The long-term safety study is underway (protocol MP-1501-0). An interim report was included in the Safety Update, received August 23, 2004, and is discussed below in Section VII, "Integrated Review of Safety." 2) The sponsor did not include a Microbiology section, as an antibacterial claim is not being pursued. The sponsor proposes using the wording discussed above for the Microbiology section of the Clin-RA label. This wording is based on the wording for the Microbiology section of the Benzaclin label (approved December 21, 2000). Benzaclin is a combination product of benzoyl peroxide and clindamycin phosphate and is the most recently approved topical clindamycin-containing product. The wording discussed for the Microbiology section of the Clin-RA label is largely identical to that in Benzaclin's, having been modified to delete the reference to benzoyl peroxide.*

D. Other Relevant Information

The Dermatologic and Ophthalmic Drugs Advisory Committee met on November 4 and 5, 2002 for purposes of discussing "development of a proposed draft guidance concerning the development of products for mild to moderate acne vulgaris" (from meeting briefing document). Discussion points from the meeting that the sponsor has applied in the marketing application include:

- In the protocols for the pivotal trials, the sponsor indicated that the Evaluator's Global Severity Scale was the scale presented by the Agency as a reasonable example of a global severity scale.
- In the briefing package for the End-of-Phase 2 meeting, the sponsor proposed that a "win" on the Evaluator's Global Severity Scale be considered either "clear" or "almost clear" or a two-grade improvement from baseline.

*Comment: Discussion at the November 2002 Advisory Committee meeting included that improvement on the Global Severity Scale might/could still be meaningful, even if a subject did not achieve "clear" or "almost clear."*

E. Important Issues with Pharmacologically Related Agents

There are literature reports of pseudomembranous colitis associated with use of topical clindamycin phosphate, and labeling for topical clindamycin products includes bolded warnings to this effect. The colitis is thought to be a function of the systemic absorption of the clindamycin. It is possible that transdermal absorption of clindamycin could be increased when the clindamycin is used in combination with tretinoin: the tretinoin irritancy could allow for increased absorption of clindamycin.

Tretinoin is a naturally occurring compound in humans, and the sponsor reports endogenous plasma concentrations to be approximately 1 to 4 ng/mL. Topical retinoids as a class are commonly known to produce some measure of irritancy, particularly in the initial weeks of usage. These effects may include erythema, scaling, itching, and burning. Hypopigmentation may also be seen. Generally, the skin eventually adapts such that the irritancy is progressively

minimized over time. Use may also make for heightened sun sensitivity because topical retinoids may decrease the number of layers in the stratum corneum.

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Formula #781-62 of Clin-RA Gel was used in the clinical development of the product. Specifically, this formulation was used in the two pivotal studies, the four dermal safety studies, and the absorption study. The quantitative composition of Clin-RA Gel and reference articles are listed in the following table:

**Formula Composition of Clin-RA Gel and Reference Articles (Sponsor Table 8.2 from the Clinical Data Summary and Results Analysis)**

| Component | Clin-RA Gel Formula # 781-62 | Clindamycin Phosphate 1.2% Gel | Tretinoin 0.025% Gel | Vehicle |
|---|---|---|---|---|
| Clindamycin Phosphate, USP | 1.20[a] | 1.20[a] | NA | NA |
| Tretinoin, USP | 0.025 | NA | 0.025 | NA |
| Butylated Hydroxytoluene, NF | | | | |
| Citric Acid, (Anhydrous), USP | | | | |
| Edetate Disodium, (Dihydrate), USP | | | | |
| Methylparaben, NF | | | | |
| Propylparaben, NF | | | | |
| Polysorbate 80, NF | | | | |
| Glycerin, USP | | | | |
| Tromethamine (25%)*, USP | | | | |
| Carbopol 981 NF (a.k.a. Carbomer Homopolymer) | | | | |
| Purified Water*, USP | | | | |

b(4)

[a]1.2% Clindamycin Phosphate is equivalent to 1.0% Clindamycin

[redacted] was added to Clindamycin phosphate 1.2% Gel and Clin-RA Gel vehicle to match the color to the tretinoin-containing study materials.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The sponsor believes the transdermal absorption of tretinoin and clindamycin to be well characterized (Section 3.7.1 of the NDA) stating:

- "Transdermal absorption studies from topically applied tretinoin formulations have repeatedly yielded little to no systemic availability and no association with systemic toxicity.
- Transdermal absorption studies from topically applied formulations containing clindamycin have suggested that the extent of percutaneous absorption varies depending on the vehicle and clindamycin form (ester or salt). Absorption of clindamycin from

clindamycin HCl preparations has been reported to result in higher plasma levels than with Clindamycin phosphate."

The sponsor submitted a literature review (with the references) in support of the marketing application. According to the sponsor, the references indicate the extent of systemic availability of both clindamycin and tretinoin after topical application to be low, 1-7% and 1-5%, respectively (Section 3.7.1).

**7001.G2HP.C-02-02: "Absorption Evaluation of Clindamycin and Tretinoin Following Maximum Topical Exposure to Clin-RA Gel in Subjects with Moderate to Severe Acne Vulgaris"**

**Note:** This study is briefly described below. A complete review of this study was done by the biopharmaceutics/clinical pharmacology reviewer, and the reader is referred to that review.

**Methodology:** The sponsor conducted a single-center, open-label, multiple dose study to assess the absorption and safety of Clin-RA Gel in subjects with acne vulgaris. This study was designed to characterize the absorption of Clin-RA Gel under maximal exposure by daily topical applications for 14 days. Thirteen subjects with "severe" acne vulgaris involving an area of approximately 1000 to 2500 $cm^2$ (facial area, chest and back) were to apply Clin-RA Gel daily for 14 days. Twelve subjects completed the study. Study drug was applied to the face, neck, back and chest as a four gram dose, which the sponsor estimated to be four times the expected typical upper clinical dose.

Plasma levels of clindamycin, tretinoin and the tretinoin metabolites (13-*cis*-retinoic acid and 4-oxo-13-*cis*-retinoic acid) were monitored over the 14 day treatment period, and an absorption curve was defined on the $14^{th}$ day. A final 24-hour post-dosing blood draw was taken on Day 15.

**Results:** The percentage of subjects with undetectable plasma concentrations for tretinoin (< 1 ng/mL) at $T_{max}$ was 50%, and ranged from 50% to 92% at any given timepoint. The absorption of clindamycin, tretinoin, and key tretinoin metabolites as indicated by the mean $C_{max}$ values ranged from 1.05 to 3.15 ng/mL; mean $T_{max}$ ranged from 3.26 to 6.34 hours; and mean $AUC_{(0-24)}$ ranged from 24.46 to 63.13 ng/mL hour.

**Conclusion:** The sponsor concluded that the result was in agreement with previous studies using combination clindamycin phosphate/tretinoin and clindamycin HCl/tretinoin gel formulations. The sponsor concluded that under conditions of the study, there was no indication of systemic absorption of tretinoin, and 50% or more of the subjects had undetectable levels (< 1 ng/mL) at any given timepoint.

B. Pharmacodynamics

Clindamycin is an antimicrobial, and tretinoin is thought to normalize follicular keratinization.

IV. Description of Clinical Data and Sources

A. Overall Data

The sponsor conducted seven clinical studies in support of the marketing application: two pivotal Phase 3 trials, four dermal safety studies, and one pharmacokinetic study. The data reviewed were from the sponsor's clinical development program. IND 65,531, the sponsor's IND, was also reviewed.

Note: The remainder of this page is intentionally left blank.

## B. Tables Listing the Clinical Trials

**Modified SponsorTable 3.24 Phase 3 Study Summaries for Clin-RA Gel Pivotal Studies**

**Protocol Numbers** 7001.G2HP-06-02 and 7001.G2HP-07-02

**Study Titles** A Multi-Center, Phase 3, Randomized, Double-Blind, 4-Arm Clinical Trial to Compare the Safety and Efficacy of Clin-RA Gel vs. Clindamycin Phosphate 1.2% Gel vs. Tretinoin 0.025% Gel vs. Clin-RA Gel Vehicle in the Treatment of Acne Vulgaris

**Indication** Acne Vulgaris

**Investigators**

| | | | |
|---|---|---|---|
| Elizabeth Arthur, M.D. | Harry Sharata, M.D. | James Aton, M.D. | Lewis Kaminester, M.D. |
| Michael Gold, M.D. | Badalamenti Silos, M.D. | Susan Barker, M.D. | David Kaplan, M.D. |
| Scott Dinehart, M.D. | Stacy Smith, M.D. | Debra Breneman, M.D. | Robert Loss, M.D. |
| Charles Fixler, M.D. | Daniel Stewart, M.D. | Alicia Bucko, M.D. | Keith Loven, M.D. |
| Javier Flores, M.D | Joseph Story, M.D. | Sharon Camden, M.D. | Robert Martin, M.D. |
| George Neumaier, M.D. | Dow Stough, M.D. | Michelle Chambers, M.D. | Stephen Miller, M.D. |
| Jon Hanifin, M.D. | Leonard Swinyer, M.D. | Nancy Egan, M.D. | Eric Olson, M.D. |
| Michael Heffernan, M.D. | Naji Tawfik, M.D. | Lawrence Eichenfield, M.D. | Marina Peredo, M.D. |
| Steven Kempers, M.D. | Yardy Tse, M.D. | Alan Fleischer, Jr., M.D. | Phoebe Rich, M.D. |
| David McDaniel, M.D. | Zoe Draelos, M.D. | Joseph Fowler, M.D. | James Robinson, M.D. |
| Alan Menter, M.D. | Hector Wiltz, M.D. | Daniel Groisser, M.D. | Jeffrey Sobell, M.D. |
| Christopher Nelson, M.D. | Joel Schlessinger, M.D. | Adelaide Hebert, M.D. | Jennifer Vesper, M.D. |
| David Pariser, M.D. | Richard Childers, M.D. | Daniel Hogan, M.D. | Jonathan Weiss, M.D. |
| Robert Schwartz, M.D. | Norman Kanof, M.D. | Robert Ilowite, M.D. | Patricia Westmoreland,M.D. |
| | | Michael Jarratt, M.D. | Paul Yamauchi, M.D. |
| | | Terry Jones, M.D. | |

**Study Design** Multi center, double-blind, randomized, parallel, vehicle-controlled

| **No. Patients** | | **7001.G2HP-06-02** | **7001.G2HP-07-02** | **Total** |
|---|---|---|---|---|
| **(ITT Population)** | Clin-RA | 420 | 425 | 845 |
| | Clindamycin Phosphate | 208 | 218 | 426 |
| | Tretinoin | 417 | 429 | 846 |
| | Vehicle | 207 | 216 | 423 |

**Age Range (mean)** 11-59 (18.98)

**Male/Female** 1247 (49%)/1293 (51%)

**Treatment Frequency** QD for 12 weeks

**Test Materials** Clin-RA Gel (Formula # 781-62)
Clin-RA Gel Vehicle
Clindamycin 1.2% Gel
Tretinoin 0.025% Gel (Retin-A)

**Modified Sponsor Table 3.23 Dermal Safety Study Summaries for Clin-RA Gel**

| Study Information | 7001.G2HP-01-02 21-Day Cumulative Irritation Study | 7001.G2HP-03-02 Repeat Insult Patch Test Study | 7001.G2HP-04-02 Phototoxicity | 7001.G2HP-05-02 Photoallergy |
|---|---|---|---|---|
| **Investigaor** | Karl Beutner, M.D., Ph.D. | Karl Beutner, M.D., Ph.D. | Karl Beutner, M.D., Ph.D. | Karl Beutner, M.D., Ph.D. |
| **No. Entered** | 34 | 229 | 27 | 30 |
| **No. Evaluable** | 34 | 186 | 25 | 28 |
| **Age range** | 18-55 | 18-55 | 18-53 | 18-41 |
| **%Male/%Female** | 26/74 | 42/58 | 40/60 | 32/68 |
| **Dose** | 0.2 mL | 0.2mL | 0.05 mL | 0.2 mL |
| **Frequency of Dosing** | Nine 48-hour applications over 3 weeks (72-hours on weekends) | Nine 48-hour applications over 3 weeks (72-hours on weekends); one 48-hour challenge application | One 24-hour application | Six 24-hour applications over 3 weeks; one 24-hour challenge application |
| **Duration of study** | 22 days | 6 weeks | 3 days | 6 weeks |
| **Test materials** | Clin-RA Gel<br>Clin-RA Gel Vehicle<br>Sodium lauryl sulfate 0.2% | Clin-RA Gel<br>Clin-RA Gel Vehicle<br>Retin A® Gel, 0.025% | Clin-RA Gel<br>Clin-RA Gel Vehicle | Clin-RA Gel<br>Clin-RA Gel Vehicle |

**Note:** The Clin-RA gel formulation used in the dermal safety studies was the same as that used in the phase 3 trials, i.e. Formula 781-62)

The seventh study conducted by the sponsor in support was a pharmacokinetic study 7001.G2HP.C-02-02: "Absorption Evaluation of Clindamycin and Tretinoin Following Maximum Topical Exposure to Clin-RA Gel in Subjects with Moderate to Severe Acne Vulgaris" (See Section III A).

C. Postmarketing Experience

The sponsor asserts that Clin-RA Gel is not marketed outside of the United States. Clindamycin and tretinoin have been marketed individually for acne vulgaris in various formulations and, pertaining to tretinoin, various concentrations for years.

D. Literature Review

The sponsor submitted the application under Section 505(b)(2) of the Act. Per Section, 3.6.2, the application relied on nonclinical pharmacology and toxicology data available from the literature (using Medline and Toxline databases) for clindamycin and tretinoin. The sponsor also included clinical references.

V. Clinical Review Methods

A. How the Review was Conducted

The pivotal trials and the dermal safety studies were reviewed individually. The dermal safety studies were not considered in the determination of efficacy.

B. Overview of Materials Consulted in Review

The materials and information reviewed were those included in the sponsor's application, those submitted by the sponsor in response to Information Requests, and those submitted in the Safety Update. Additionally, the sponsor's IND (#65,531) was reviewed.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Division of Scientific Integrity audits were not conducted for any study sites. The medical reviewer independently reviewed aspects of the sponsor's data. The statistical reviewer conducted independent analyses of the sponsor's data.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trials appear to have been conducted in accordance with accepted ethical standards.

E. Evaluation of Financial Disclosure

Disclosure of financial interests and arrangements were submitted for [redacted] Ph.D. who was stated to be [redacted] stockholder of the sponsor. [redacted] was involved in [redacted] studies submitted in the application. [redacted] Per the Financial Disclosure statement, steps taken to minimize potential for bias in the dermal safety studies included the blinding of evaluators and the use of multiple evaluators. [redacted] did not apply test articles or draw blood samples in the pharmacokinetic study. b(6)

[redacted] was involved in the design of the protocol for the Phase 3 studies and served as medical monitor for the Phase 3 studies. As medical monitor, his responsibilities included addressing "safety questions that arose during the study and any questions sites might have had regarding eligibility, adverse events, concurrent medications and exclusionary medications." [redacted] was said not to have conducted any safety or efficacy evaluations. There were independent study monitors and independent contractors [redacted] b(4)

*Comment: The sponsor appears to have taken reasonable steps to avoid any potential bias from [redacted] involvement in the development program.*

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Superiority of Clin-RA over clindamycin, tretinoin and vehicle was demonstrated for all lesion counts (inflammatory, non-inflammatory and total) in study 7001.G2HP-06-02

Superiority of Clin-RA over clindamycin, tretinoin and vehicle was demonstrated for

inflammatory lesions in study 7001.G2HP-0-02 (07). Superiority of Clin-RA over vehicle was demonstrated for non-inflammatory lesions. However, superiority of Clin-RA over clindamycin and tretinoin was not demonstrated for non-inflammatory lesions in study 07 when either mean reduction or mean percent reduction were considered; however, Clin-RA trended towards superiority over clindamycin in mean percent change of non-inflammatory lesions (p=0.88). In regard to total lesions, superiority of Clin-RA over clindamycin, tretinoin and vehicle was demonstrated in study 07 when mean percent change was considered. Superiority of Clin-RA over tretinoin and vehicle was also demonstrated in study 07 when mean reduction was considered; however, Clin-RA trended towards superiority over clindamycin in mean reduction of total lesions (p=0.82). Thus, superiority of Clin-RA over clindamycin, tretinoin and vehicle was demonstrated in mean percent change for two of three lesion counts (inflammatory and total).

Superiority of Clin-RA over tretinoin and vehicle was demonstrated for the proportion of subjects who were "clear" or "almost clear" on the Evaluator's Global Severity (EGS) score at 12 weeks in both pivotal trials. However, superiority of Clin-RA over clindamycin was not demonstrated for the proportion of subjects who were "clear" or "almost clear" on the EGS in the intent-to-treat analysis to a level of statistical significance in either pivotal trial.

B. General Approach to Review of the Efficacy of the Drug

The sponsor conducted two identical, four-armed, multi-center, randomized, double-blind, active- and vehicle-controlled, parallel Phase 3 trials, 7001-G2HP-06-02 and 7001-G2HP-07-02. The studies were of appropriate design to evaluate a combination product. The efficacy database consisted of subjects who were enrolled in these two trials.

**Intent-to-Treat Population for the Phase 3 Trials**

| | **7001.G2HP-*06*-02** | **7001.G2HP-*07*-02** | **Combined** |
|---|---|---|---|
| **No. Subjects Enrolled per Treatment Group** | 420 Clin-RA Gel | 425 Clin-RA Gel | 845 Clin-RA Gel |
| | 208 Clindamycin Gel | 218 Clindamycin Gel | 426 Clindamycin Gel |
| | 417 Tretinoin Gel | 429 Tretinoin Gel | 846 Tretinoin Gel |
| | 207 Clin-RA Vehicle | 216 Clin-RA Vehicle | 423 Clin-RA Vehicle |
| **Total** | 1252 | 1288 | 2540 |

**7001-G2HP-06-02: A Multi-Center, Phase 3, Randomized, Double-Blind, 4-Arm Clinical Trial to Compare the Safety and Efficacy of Clin-RA Gel vs. Clindamycin Phosphate 1.2% Gel vs. Tretinoin 0.025% Gel vs. Vehicle in the Treatment of Acne Vulgaris"** (Study Period: February 11, 2003 to October 21, 2003)

**Sponsor Table 14.1.1: Summary of Subject Enrollment and Evaluability by Investigator**

| Site | Investigator | Enrolled | Clin-RA ITT | Clin-RA PP | Clindamycin ITT | Clindamycin PP | Tretinoin ITT | Tretinoin PP | Vehicle ITT | Vehicle PP |
|---|---|---|---|---|---|---|---|---|---|---|
| 600 | Elizabeth Arthur | 97 | 33 | 26 | 16 | 14 | 32 | 26 | 16 | 14 |
| 601 | Micheal Gold | 47 | 16 | 13 | 7 | 4 | 16 | 11 | 8 | 7 |
| 602 | Scott Dinehart | 92 | 31 | 19 | 16 | 6 | 30 | 20 | 15 | 8 |
| 603 | Charles Fixler | 45 | 16 | 11 | 7 | 5 | 14 | 8 | 8 | 6 |
| 604 | Javier Flores | 66 | 22 | 20 | 11 | 10 | 22 | 21 | 11 | 10 |
| 606 | George Neumaier | 59 | 19 | 18 | 10 | 10 | 20 | 17 | 10 | 9 |
| 607 | Jon Hanifin | 26 | 9 | 7 | 5 | 3 | 8 | 5 | 4 | 1 |
| 609 | James Milbauer | 29 | 10 | 8 | 5 | 4 | 9 | 8 | 5 | 3 |
| 610 | Steven Kempers | 45 | 15 | 13 | 8 | 6 | 14 | 11 | 8 | 7 |
| 611 | David McDaniel | 33 | 10 | 5 | 6 | 4 | 12 | 7 | 5 | 2 |
| 612 | Alan Menter | 36 | 12 | 9 | 6 | 4 | 12 | 8 | 6 | 2 |
| 613 | Christopher Nelson | 35 | 11 | 4 | 6 | 4 | 12 | 5 | 6 | 3 |
| 614 | David M. Pariser | 26 | 9 | 4 | 4 | 3 | 9 | 6 | 4 | 3 |
| 616 | Henry Sharata | 31 | 10 | 9 | 5 | 3 | 11 | 9 | 5 | 5 |
| 617 | Stephanie Silos-Badalamenti | 2 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 618 | Stacy Smith | 54 | 18 | 14 | 9 | 5 | 18 | 16 | 9 | 9 |
| 619 | Daniel M. Stewart | 22 | 8 | 6 | 3 | 3 | 7 | 6 | 4 | 2 |
| 620 | Joseph Story | 39 | 12 | 6 | 7 | 5 | 14 | 5 | 6 | 4 |
| 621 | Dow B. Stough | 62 | 22 | 19 | 10 | 10 | 20 | 17 | 10 | 10 |
| 622 | Leonard Swinyer | 66 | 22 | 19 | 11 | 10 | 22 | 18 | 11 | 11 |
| 623 | Naji Tawfik | 46 | 15 | 11 | 8 | 5 | 16 | 9 | 7 | 6 |
| 624 | Helen Mary Torok | 55 | 18 | 16 | 9 | 9 | 19 | 15 | 9 | 8 |
| 625 | Yardy Tse | 10 | 3 | 2 | 2 | 1 | 4 | 4 | 1 | 0 |
| 626 | Zoe Draelos | 39 | 14 | 12 | 6 | 2 | 12 | 11 | 7 | 6 |
| 627 | Hector Wiltz | 78 | 26 | 22 | 13 | 11 | 26 | 22 | 13 | 12 |
| 628 | Joel Schlessinger | 29 | 10 | 1 | 4 | 3 | 10 | 5 | 5 | 3 |
| 629 | Richard Childers | 38 | 12 | 8 | 7 | 5 | 12 | 10 | 7 | 5 |
| 630 | Norman Kanof | 45 | 15 | 14 | 7 | 6 | 16 | 13 | 7 | 7 |

**7001-G2HP-07-02: A Multi-Center, Phase 3, Randomized, Double-Blind, 4-Arm Clinical Trial to Compare the Safety and Efficacy of Clin-RA Gel vs. Clindamycin Phosphate 1.2% Gel vs. Tretinoin 0.025% Gel vs. Vehicle in the Treatment of Acne Vulgaris"** (Study Period: February 11, 2003 to October 21, 2003)

**Sponsor Table 14.1.1: Summary of Subject Enrollment and Evaluability by Investigator**

| Site | Investigator | Enrolled | Clin-RA ITT | Clin-RA PP | Clindamycin ITT | Clindamycin PP | Tretinoin ITT | Tretinoin PP | Vehicle ITT | Vehicle PP |
|---|---|---|---|---|---|---|---|---|---|---|
| 700 | Michelle Chambers | 55 | 19 | 10 | 9 | 4 | 18 | 11 | 9 | 2 |
| 701 | Terry Jones | 47 | 16 | 11 | 8 | 8 | 16 | 15 | 7 | 7 |
| 702 | David Kaplan | 29 | 10 | 6 | 5 | 4 | 9 | 5 | 5 | 4 |
| 703 | James Aton | 52 | 17 | 10 | 8 | 3 | 18 | 13 | 9 | 3 |
| 704 | Susan Barker | 27 | 8 | 8 | 5 | 4 | 9 | 7 | 5 | 3 |
| 705 | Debra Brenerman | 51 | 16 | 8 | 9 | 4 | 18 | 9 | 8 | 4 |
| 706 | Alicia Bucko | 78 | 26 | 19 | 13 | 11 | 26 | 18 | 13 | 11 |
| 707 | Sharon Camden | 13 | 4 | 1 | 3 | 0 | 4 | 1 | 2 | 0 |
| 708 | Lawrence Eichenfield | 39 | 14 | 12 | 7 | 3 | 12 | 10 | 6 | 3 |
| 709 | Alan Fleischer | 58 | 19 | 11 | 10 | 9 | 20 | 15 | 9 | 7 |
| 710 | Jonathan Weiss | 21 | 7 | 6 | 3 | 2 | 7 | 6 | 4 | 4 |
| 711 | Adelaide Hebert | 39 | 13 | 11 | 6 | 5 | 14 | 7 | 6 | 5 |
| 712 | Steven Proper | 54 | 18 | 16 | 9 | 8 | 18 | 13 | 9 | 8 |
| 713 | Robert Ilowite | 7 | 2 | 1 | 1 | 1 | 3 | 2 | 1 | 0 |
| 714 | Michael Jarratt | 48 | 16 | 11 | 8 | 7 | 16 | 12 | 8 | 6 |
| 715 | Lewis Kaminester | 24 | 8 | 5 | 4 | 2 | 8 | 5 | 4 | 3 |
| 716 | Robert W. Loss | 40 | 13 | 10 | 7 | 6 | 13 | 10 | 7 | 5 |
| 717 | Keith Loven | 27 | 9 | 6 | 5 | 3 | 8 | 7 | 5 | 2 |
| 718 | Robert Martin | 14 | 5 | 3 | 2 | 2 | 4 | 3 | 3 | 1 |
| 719 | Daniel Groisser | 46 | 15 | 10 | 8 | 5 | 15 | 10 | 8 | 4 |
| 720 | James Robinson | 9 | 3 | 3 | 2 | 2 | 3 | 2 | 1 | 0 |
| 721 | Phoebe Rich | 29 | 9 | 6 | 5 | 5 | 10 | 7 | 5 | 3 |
| 722 | Patricia Westmoreland | 44 | 14 | 10 | 8 | 7 | 14 | 13 | 8 | 6 |
| 723 | Paul Yamauchi | 48 | 16 | 14 | 8 | 8 | 16 | 15 | 8 | 7 |
| 724 | Nancy Egan | 32 | 10 | 9 | 5 | 5 | 11 | 10 | 6 | 6 |
| 725 | Joseph Fowler | 60 | 20 | 8 | 10 | 5 | 20 | 17 | 10 | 8 |
| 726 | Stephen Miller | 33 | 10 | 6 | 6 | 3 | 11 | 7 | 6 | 5 |
| 727 | Daniel Hogan | 90 | 30 | 25 | 15 | 14 | 30 | 22 | 15 | 9 |
| 728 | Jeffrey Sobell | 6 | 2 | 2 | 1 | 0 | 2 | 0 | 1 | 0 |
| 729 | Eric Olson | 24 | 8 | 3 | 4 | 3 | 8 | 5 | 4 | 2 |
| 730 | Marina Peredo | 72 | 24 | 18 | 12 | 11 | 24 | 18 | 12 | 9 |
| 731 | Jennifer Vesper | 72 | 24 | 14 | 12 | 7 | 24 | 11 | 12 | 7 |

C. Detailed Review of Trials

Subjects were randomized to Clin-RA Gel, Tretinoin 0.025% Gel, Clindamycin phosphate 1.2% Gel and Clin-RA Gel vehicle on a 2:2:1:1 basis. In Section 9.2 of the study reports, the sponsor indicates that subject selection, treatment duration, and dosages were based on the currently approved labeling for products containing clindamycin phosphate 1.2% (Clindagel™) and tretinoin 0.025% (Retin-A® 0.025% Gel).

Subjects applied the study material for 12 weeks, once a day at bedtime, after cleansing with a sponsor-approved cleanser and warm water. After the face had dried completely, the subjects squeezed no more than half an inch of medication (or pea size) onto the tip of one finger. The dose was then dotted onto six areas on the face (chin, left cheek, right cheek, nose, left forehead, right forehead) and gently rubbed into the skin. Subjects were instructed to continue using the

same approved facial cleanser and moisturizer. An approved sunscreen was applied according to the directions on the bottle. Facial makeup may have been applied according to the subject's normal daily routine (except for study visits).

Inclusion Criteria

1. Male or female 12 years of age or older;
2. Written and verbal informed consent was obtained. Subjects less than 18 years of age signed an assent for the study and the parent(s) or legal guardian(s) signed the informed consent;
3. Subjects with facial acne inflammatory lesion (papules and pustules) count no less than 20 but no more than 50;
4. Subjects with facial acne non-inflammatory lesion (open and closed comedones) count no less than 20 but no more than 100;
5. Subjects with two or fewer nodules (defined as an inflammatory lesion greater than equal to 5 mm in diameter);
6. Women of childbearing potential were willing to practice effective contraception duration of the study. (Effective contraception was defined as stabilized on oral contraceptive for at least 3 months, IUD, condom with spermicidal, diaphragm with spermicidal, implant, injection or abstinence.) Females on birth control pills had taken the same type pill for at least three months prior to entering the study and have not changed type during the study. Those who had used birth control pills in the past had discontinued usage at least three months prior to the start of the study. Any female subject who was premenses at the start of the study and reached childbearing potential during the study had a pregnancy test performed at the next visit;
7. Women of childbearing potential had a negative urine pregnancy test at the baseline visit;
8. Subjects were willing to comply with study instructions and return to the clinic for required visits. Subjects under 18 years of age were accompanied by the parent or legal guardian at the time of assent/consent signing.
9. Subjects were willing to use an approved moisturizer, sunscreen, or moisturizer/sunscreen combination product throughout the study.

Exclusion Criteria

1. Participation in a clinical drug or device research study within 30 days of enrollment or participation in research study concurrent with this study;
2. Any dermatological conditions on the face that could interfere with clinical evaluations such as acne conglobata, acne fulminans, secondary acne, etc.;
3. Any underlying disease(s) or some other dermatological condition of the face that required the use of interfering topical or systemic therapy;
4. Subjects with a facial beard or mustache that could interfere with the study assessments;
5. Female subjects who were pregnant, nursing mothers, planning a pregnancy during the course of the trial, or became pregnant during the study;
6. History of regional enteritis, ulcerative colitis or antibiotic-associated colitis;
7. Treatment of any type for cancer within the last 6 months;
8. Subjects who were unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function;
9. History of hypersensitivity or allergic reactions to any of the study preparations as described in the Investigator's Brochure, including known sensitivities to any dosage form of clindamycin, lincomycin or tretinoin;
10. Concomitant use of potentially irritating over-the-counter products that contained ingredients such as benzoyl peroxide, alpha-hydroxy acid, salicylic acid, retinol or glycolic acids;
11. Subjects who had not undergone the specified washout period(s) for the following **topical** preparations or subjects who required the concurrent use of any of the following **topical** medications:
    - Topical astringents and abrasives 1 week
    - Antibiotics on the facial area 2 weeks

- Non-approved moisturizers or sunscreens 2 weeks
- Other topical anti-acne drugs 2 weeks
- Anti-inflammatories and corticosteroids on the facial area 4 weeks
- Retinoids, including retinol 4 weeks

12. Subjects who had not undergone the specified washout period(s) for the following **systemic** medications or subjects who required the concurrent use of any of the following **systemic** medications:
    - Corticosteroids (including 4 weeks intramuscular injections)
    - Antibiotics 4 weeks
    - Other systemic acne treatments 4 weeks
    - Systemic retinoids 6 months

**Lesion Counts**

Each lesion type (inflammatory and non-inflammatory) was counted and recorded. Inflammatory lesion counts were taken from the facial area (forehead, left and right cheeks, chin above the jaw line, and nose). Non-inflammatory lesion counts were taken from the facial area (forehead, left and right cheeks, nose and chin above the jaw line). Counting of lesions on the nose was to be performed separately from the other areas of the face, but included in the total non-inflammatory lesion count. The number of nodules/cysts was assessed for subject inclusion/exclusion criteria only and was not included in the inflammatory group count or the statistical analyses.

Inflammatory lesions were defined as follows:

- **Papule** – a small, solid elevation less than 5 mm in diameter. Most of the lesion was above the surface of the skin.
- **Pustule** – a small, circumscribed elevation less than 5 mm in diameter that contained yellowwhite exudates
- **Nodule** – an inflammatory lesion greater than or equal to 5 mm in diameter (counted separately; not included in the count of inflammatory lesions).

Non-inflammatory lesions were defined as follows:

- **Open comedones** - a lesion in which the follicular opening was 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** – a lesion in which the follicular opening was closed, but the sebaceous gland was enlarged by the pressure of the sebum build up, which in turn caused the skin around the follicle to thin and become elevated with a white appearance.

## Evaluator's Global Severity Score

The sponsor used the Evaluator's Global Severity Scale that was proposed by the Agency as being reasonable at the Advisory Committee meeting of November 4, and 5, 2002.

**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: several to many comedones and papules/pustules only, 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. |

Evaluations were performed at Baseline, Week 2, Week 4, Week 8 and Week 12 (or upon discontinuation), and mean percent change from baseline for inflammatory, non-inflammatory, and total lesion counts was recorded. The Evaluator's Global Severity Scale was used to describe the severity grade and subsequent score.

## Efficacy Measures

The co-primary efficacy variables were:

(1) mean percent change from baseline at Week 12 in
- inflammatory lesion counts,
- non-inflammatory lesion counts, and
- total lesion counts

(2) the percent of subjects who who were "clear" or "almost clear" at Week 12 as judged by an Evaluator's Global Severity score.

Secondary measurements of efficacy were the mean percent change from Baseline at Weeks 2, 4, and 8 in inflammatory lesions, the mean percent change from Baseline at Weeks 2, 4, and 8 in non-inflammatory lesions, the mean percent change from Baseline at Weeks 2, 4, and 8 in total lesions, the percent of subjects who were clear or almost clear at Weeks 2, 4, and 8, as judged by the Evaluator's Global Severity Score.

## Statistical and Analytical Plans

### Populations

An intent-to-treat (ITT) analysis was conducted on all subjects receiving the study drug for

safety and for tests of superiority (primary analysis).

*Comment: This review will only consider the ITT population.*

Criteria for Success

The primary efficacy analyses were conducted on the ITT population.

In the primary efficacy analyses for the comparison between Clin-RA Gel and clindamycin gel and tretinoin gel superiority was demonstrated if there was statistical significance in:

(1) two of three of the following lesion counts:
- mean percent change from baseline at Week 12 in inflammatory lesion counts,
- mean percent change from baseline at Week 12 in non-inflammatory lesion counts,
- mean percent change from baseline at Week 12 in total lesion counts

(2) the percent of subjects who were "clear" or "almost clear" at Week 12, as judged by an Evaluator's Global Severity Score.

In the primary efficacy analyses for the comparison for the comparison between Clin-RA Gel versus vehicle, superiority was demonstrated if there was statistical significance in:
(1) mean percent change from baseline at Week 12 in inflammatory lesion counts
(2) mean percent change from baseline at Week 12 in non-inflammatory lesion counts
(3) the percent of subjects who were "clear" or "almost clear" at Week 12, as judged by an Evaluator's Global Severity Score.

Subset Analyses

The consistency of the treatment effect on the primary analyses was investigated for the different genders, races, and ages. For the subgroup analysis of race, all races that were not Caucasian were combined if necessary. For the subgroup analysis of age, all subjects age 16 and under were combined and all subjects over 16 years of age were combined.

The sponsor also performed a supplemental, supportive set of analyses to characterize the treatment effect for the subset of subjects who had a baseline Evaluator's Global Severity Score of severe. The proportion of these subjects who showed at least a two-grade reduction in the Evaluator's Global Severity Score at Week 12 was tabulated.

**Disposition**

Summary tables for subject completion/discontinuation status in the pivotal trials are presented below:

Sponsor Table 10.1.2: Summary of Subject Completion/Discontinuation Status (study 06)

| | Clin-RA | Clindamycin | Tretinoin | Vehicle | Total |
|---|---|---|---|---|---|
| Subjects Enrolled | 420 | 208 | 417 | 207 | 1252 |
| Completion/Discontinuation per Investigator | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Study Completion | 366 | 176 | 363 | 182 | 1087 |
| Study Discontinuation | | | | | |
| Lack of Efficacy/Worsening of Condition | 6 | 2 | 2 | 3 | 13 |
| Adverse Event Treatment Related | 3 | 0 | 3 | 0 | 6 |
| Adverse Event Non-Treatment Related | 3 | 1 | 1 | 1 | 6 |
| Subject Request | 5 | 9 | 19 | 6 | 39 |
| Protocol Violation | 2 | 2 | 3 | 1 | 8 |
| Lost to Follow-up | 26 | 13 | 18 | 11 | 68 |
| Pregnancy | 1 | 0 | 1 | 0 | 2 |
| Inappropriate Enrollment (inclusion/exclusion) | 1 | 4 | 6 | 1 | 12 |
| Other | 7 | 1 | 1 | 2 | 11 |

Sponsor Table 10.1.2: Summary of Subject Completion/Discontinuation Status (study 07)

| | Clin-RA | Clindamycin | Tretinoin | Vehicle | Total |
|---|---|---|---|---|---|
| Subjects Enrolled | 425 | 218 | 429 | 216 | 1288 |
| Completion/Discontinuation per Investigator | | | | | |
| Study Completion | 352 | 183 | 347 | 173 | 1055 |
| Study Discontinuation | | | | | |
| Lack of Efficacy/Worsening of Condition | 5 | 2 | 10 | 7 | 24 |
| Adverse Event | 5 | 1 | 3 | 1 | 10 |
| Subject Request | 27 | 11 | 21 | 14 | 73 |
| Protocol Violation | 3 | 0 | 6 | 1 | 10 |
| Lost to Follow-up | 29 | 18 | 33 | 15 | 95 |
| Pregnancy | 0 | 0 | 2 | 0 | 2 |
| Inappropriate Enrollment (inclusion/exclusion) | 1 | 1 | 2 | 2 | 6 |
| Other | 3 | 2 | 5 | 3 | 13 |

## Demographics

Demographic characteristics for the intent-to-treat (ITT) population are presented in the following table:

**From Sponsor ISE Table 8.6 Demographic Characteristics Combined Studies (ITT*Population)**

| **Population** | **Clin-RA Gel N=845** | **Clindamycin Phosphate 1.2% gel N=426** | **Tretinoin 0.025% gel N=846** | **Clin-RA Gel Vehicle N=423** |
|---|---|---|---|---|
| **Mean Age in Years (min-max)** | 19 (11-59) | 19 (11-52) | 19 (11-55) | 19 (11-52) |
| **Race** | | | | |
| **White** | 616 (73%) | 300 (70%) | 577 (68%) | 286 (68%) |
| **Black** | 105 (12%) | 57 (13%) | 125 (15%) | 69 (16%) |
| **Asian/Pacific Islander** | 12 (1%) | 10 (2%) | 17 (2%) | 10 (2%) |
| **Hispanic/Latino** | 102 (12%) | 51 (12%) | 111 (13%) | 50 (12%) |
| **American/ Alaskan Native** | 6 (1%) | 3 (1%) | 6 (1%) | 2 (<1%) |
| **Other** | 4 (<1%) | 5 (1%) | 10 (1%) | 6 (1%) |
| **Gender** | | | | |
| **Male** | 412 (49%) | 224 (53%) | 408 (48%) | 203 (48%) |
| **Female** | 433 (51%) | 202 (47%) | 438 (52%) | 220 (52%) |

* intent-to- treat

## Baseline Disease Characteristics

Baseline disease characteristics for the ITT population are presented in the following tables:

| Sponsor ISE Table 8.7 Baseline Lesion counts (ITT) Mean (minimum-maximum) | | | | |
|---|---|---|---|---|
| **Population** | **Clin-RA gel** | **Clindamycin Phosphate 1.2% gel** | **Tretinoin 0.025% gel** | **Clin-RA Gel Vehicle** |
| ***Study 1 (7001.G2HP-06-02)*** | | | | |
| Inflammatory | 30.1 (19-54) | 29.3 (17-63) | 29.4 (5-54) | 30.2 (20-54) |
| Non-inflammatory | 50.9 (20-141) | 47.6 (15-99) | 49.5 (13-117) | 49.3 (20-100) |
| Total | 81.0 (41-195) | 76.9 (38-147) | 79.0 (21-155) | 79.4 (40-142) |
| ***Study 2 (7001.G2HP-07-02)*** | | | | |
| Inflammatory | 28.8 (4-50) | 29.4 (19-58) | 29.0 (13-52) | 29.9 (20-53) |
| Non-inflammatory | 46.4 (14-113) | 49.8 (15-100) | 48.1 (11-126) | 48.6 (9-110) |
| Total | 75.2 (24-159) | 79.3 (41-146) | 77 (27-156) | 78.6 (29-145) |
| ***Combined Studies*** | | | | |
| Inflammatory | 29.5 (4-54) | 29.4 (17-63) | 29.2 (5-54) | 30.0 (20-54) |
| Non-inflammatory | 48.6 (14-141) | 48.8 (15-100) | 48.8 (11-126) | 49.9 (9-110) |
| Total | 78.1 (24-195) | 78.1 (38-147) | 78.0 (21-156) | 79.0 (29-145) |

| Sponsor ISE Table 8.7 Baseline Evaluator's Global Severity Score (ITT) Number (%) of Subjects | | | | |
|---|---|---|---|---|
| **Population** | **Clin-RA gel** | **Clindamycin Phosphate 1.2% gel** | **Tretinoin 0.025% gel** | **Clin-RA Gel Vehicle** |
| ***Study 1 (7001.G2HP-06-02)*** | | | | |
| 2-Mild | 68 (16%) | 34 (16%) | 52 (13%) | 30 (14%) |
| 3-Moderate | 304 (72%) | 148 (71%) | 325 (78%) | 153 (74%) |
| 4-Severe | 48 (11%) | 26 (13%) | 39 (9%) | 24 (12%) |
| 5-Very Severe | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| ***Study 2 (7001.G2HP-07-02)*** | | | | |
| 2-Mild | 50 (12%) | 18 (8%) | 39 (9%) | 16 (7%) |
| 3-Moderate | 301 (71%) | 153 (71%) | 310 (72%) | 161 (75%) |
| 4-Severe | 71 (17%) | 45 (21%) | 79 (18%) | 38 (18%) |
| 5-Very Severe | 1 (<1%) | 1 (<1%) | 0 (0%) | 1 (<1%) |
| ***Combined Studies*** | | | | |
| 2-Mild | 118 (14%) | 52 (12%) | 91 (11%) | 46 (11%) |
| 3-Moderate | 605 (72%) | 301 (71%) | 635 (75%) | 314 (74%) |
| 4-Severe | 119 (14%) | 71 (17%) | 118 (14%) | 62 (15%) |
| 5-Very Severe | 1 (<1%) | 1 (<1%) | 0 (0%) | 1 (<1%) |

## RESULTS

The statistical reviewer's analyses of the primary efficacy data (i.e. lesion counts and Evaluator's Global Severity) are presented in the following tables:

**Statistical Reviewer's Table 3: Comparison of Lesion Reduction from Baseline to Week 12 (ITT Analysis) Studies 06 and 07**

| Lesion Type Mean (s.d.) | STUDY 06 | | | |
|---|---|---|---|---|
| | Clin-RA (n = 420) | Clindamycin (n = 208) | Tretinoin (n = 417) | Vehicle (n = 207) |
| **Inflammatory** | | | | |
| Mean baseline count | 30.10 (8.64) | 29.30 (8.38) | 29.44 (8.40) | 30.15 (8.43) |
| Mean number reduction | 13.6 (13.0) | 11.4 (12.0) | 10.7 (12.9) | 5.3 (15.6) |
| Mean % reduction | 46.0% (42.2%) | 39.7% (42.6%) | 37.5% (42.3%) | 19.6% (53.0%) |
| p-value (ranked ANOVA)[1] | NA | **0.014** | **< 0.001** | **< 0.001** |
| p-value (ranked ANOVA)[2] | NA | **0.028** | **< 0.001** | **< 0.001** |
| **Non-inflammatory** | | | | |
| Mean baseline count | 50.86 (22.21) | 47.64 (20.77) | 49.53 (21.13) | 49.28 (22.00) |
| Mean number reduction | 19.2 (21.7) | 11.9 (19.4) | 15.6 (20.6) | 6.9 (23.1) |
| Mean % reduction | 37.6% (37.8%) | 24.1% (44.3%) | 31.9% (40.0%) | 13.5% (50.0%) |
| p-value (ranked ANOVA)[1] | NA | **< 0.001** | **0.009** | **< 0.001** |
| p-value (ranked ANOVA)[2] | NA | **< 0.001** | **0.018** | **< 0.001** |
| **Total** | | | | |
| Mean baseline count | 80.96 (25.69) | 76.94 (23.57) | 78.97 (24.20) | 79.43 (24.50) |
| Mean number reduction | 32.8 (28.5) | 23.3 (26.4) | 26.3 (28.0) | 12.2 (32.7) |
| Mean % reduction | 41.4% (33.2%) | 31.3% (33.9%) | 34.7% (34.8%) | 16.5% (42.5%) |
| p-value (ranked ANOVA)[1] | NA | **< 0.001** | **0.001** | **< 0.001** |
| p-value (ranked ANOVA)[2] | NA | **< 0.001** | **0.002** | **< 0.001** |
| **Lesion Type Mean (s.d.)** | **STUDY 07** | | | |
| | Clin-RA (n = 425) | Clindamycin (n = 218) | Tretinoin (n = 429) | Vehicle (n = 216) |
| **Inflammatory** | | | | |
| Mean baseline count | 28.84 (8.15) | 29.44 (8.18) | 29.02 (8.07) | 29.91 (8.50) |
| Mean number reduction | 14.6 (12.6) | 12.2 (14.5) | 11.6 (12.8) | 8.6 (13.6) |
| Mean % reduction | 50.6% (48.8%) | 43.6% (47.4%) | 40.1% (42.5%) | 31.7% (43.9%) |
| p-value (ranked ANOVA)[1] | NA | **0.042** | **< 0.001** | **< 0.001** |
| p-value (ranked ANOVA)[2] | NA | **0.020** | **< 0.001** | **< 0.001** |
| **Non-inflammatory** | | | | |
| Mean baseline count | 46.35 (21.0) | 49.83 (22.39) | 48.11 (21.55) | 48.64 (21.84) |
| Mean number reduction | 15.9 (21.9) | 14.7 (21.7) | 13.8 (27.9) | 7.5 (26.0) |
| Mean % reduction | 35.7% (43.5%) | 30.1% (44.8%) | 29.9% (48.2%) | 18.5% (47.0%) |
| p-value (ranked ANOVA)[1] | NA | **0.328** | **0.333** | **< 0.001** |
| p-value (ranked ANOVA)[2] | NA | **0.088** | **0.110** | **< 0.001** |
| **Total** | | | | |
| Mean baseline count | 75.19 (24.23) | 79.27 (25.52) | 77.14 (24.73) | 78.56 (24.81) |
| Mean number reduction | 30.6 (29.2) | 26.9 (28.6) | 25.5 (34.7) | 16.1 (32.9) |
| Mean % reduction | 41.8% (37.8%) | 35.9% (36.3%) | 34.2% (39.3%) | 23.2% (39.5%) |
| p-value (ranked ANOVA)[1] | NA | **0.082** | **0.021** | **< 0.001** |
| p-value (ranked ANOVA)[2] | NA | **0.018** | **0.002** | **< 0.001** |

[1]p-values listed are the comparisons of mean **absolute** lesion reduction for Clin-RA vs. each of other three treatments.
[2]p-values listed are the comparisons of mean **percent** lesion reduction for Clin-RA vs. each of other three treatments.

**Statistical Reviewer's Table 4: EGS Score and Success at Week 12 (ITT Analysis) – Studies 06 and 07**

| Distribution of EGS at wk 12 n (%) | STUDY 06 | | | |
|---|---|---|---|---|
| | Clin-RA (n = 420) | Clindamycin (n = 208) | Tretinoin (n = 417) | Vehicle (n = 207) |
| Clear | 5 (1%) | 2 (1%) | 4 (1%) | 2 (1%) |
| Almost Clear | 83 (20%) | 32 (15%) | 60 (14%) | 16 (8%) |
| Mild | 161 (38%) | 83 (40%) | 154 (37%) | 57 (28%) |
| Moderate | 153 (36%) | 83 (40%) | 180 (43%) | 110 (53%) |
| Severe | 18 (4%) | 7 (3%) | 18 (4%) | 20 (10%) |
| Very Severe | 0 | 1 (< 1%) | 1 (< 1%) | 2 (1%) |
| Percentage of patients with Clear or Almost Clear | 88 (21%) | 34 (16%) | 64 (15%) | 18 (9%) |
| Comparison (p-value)[1] | NA | 0.172 | 0.032 | <0.001 |
| **Distribution of EGS at wk 12 n (%)** | **STUDY 07** | | | |
| | Clin-RA (n = 425) | Clindamycin (n = 218) | Tretinoin (n = 429) | Vehicle (n = 216) |
| Clear | 9 (2%) | 3 (1%) | 3 (1%) | 1 (< 1%) |
| Almost Clear | 88 (21%) | 35 (16%) | 60 (14%) | 16 (7%) |
| Mild | 172 (40%) | 72 (33%) | 151 (35%) | 68 (31%) |
| Moderate | 134 (32%) | 90 (41%) | 184 (43%) | 103 (48%) |
| Severe | 22 (5%) | 17 (8%) | 30 (7%) | 28 (13%) |
| Very Severe | 0 | 0 | 0 | 0 |
| Not Reported | 0 | 1 | 1 | 0 |
| Percentage of patients with Clear or Almost Clear | 97 (23%) | 38 (17%) | 63 (15%) | 17 (8%) |
| Comparison (p-value)[1] | NA | 0.094 | 0.002 | <0.001 |

[1] p-value is the comparison between Clin-RA and each of other three treatments and is based on CMH test adjusting for investigational group.

## Two-Grade Improvement

The sponsor conducted a supplemental set of analyses of the dichotomized Evaluator's Global Severity Score to characterize the treatment effect for the proportion of subjects who showed at least a two-grade reduction or were rated "clear"or "almost clear" in Evaluator's Global Severity Score at Week 12. The statistical reviewer's analyses of the two-grade reduction data for the Clin-RA versus clindamycin comparison are included in the following table:

**Statistical Reviewer's Table 5: Treatment Success and Modified Success Rates in the EGS Score at Week 12**

| Analysis | Variable | Study 06 | | | Study 07 | | |
|---|---|---|---|---|---|---|---|
| ITT | Treatment | Clin-RA (n = 420) | Clindamycin (n = 208) | p-value[3] | Clin-RA (n = 425) | Clindamycin (n = 218) | p-value[3] |
| | Treatment Success[1] rate | 88 (21%) | 34 (16%) | 0.172 | 97 (23%) | 38 (17%) | 0.094 |
| | Modified Success[2] rate | 101 (24%) | 38 (18%) | 0.100 | 118 (28%) | 44 (20%) | 0.030 |
| PP | Treatment | Clin-RA (n = 317) | Clindamycin (n = 155) | p-value[3] | Clin-RA (n = 293) | Clindamycin (n = 161) | p-value[3] |
| | Treatment uccess[1] rate | 79 (25%) | 25 (16%) | 0.037 | 81 (28%) | 34 (21%) | 0.130 |
| | Modified Success[2] rate | 90 (28%) | 28 (18%) | 0.020 | 100 (34%) | 40 (25%) | 0.031 |

[1] Treatment success is the Division's recommended co-primary efficacy endpoint, defined as clear or almost clear in the EGS score at week 12.
[2] Modified success is defined as clear or almost clear or at least a 2-grade improvement from baseline in the EGS score at week 12.
[3] p-value is based on CMH test adjusting for investigational group.

**Subgroup Analyses**

The sponsor conducted subgroup analyses for gender, race and age.

Gender

A statistically significant difference in response between genders was demonstrated for percent change from baseline in all three lesion counts, with females responding better than males. Similarly, females had higher success rates on the dichotomized Evaluator's Global Severity scores at Week 12. These results were generally true across all treatment groups.

Race

Subjects were sub-grouped as Caucasian and non-Caucasian. There was a significant difference in the percent change in inflammatory lesions for race for all treatment groups, but no treatment by race interaction was noted. This difference favored non-Caucasians. A consistent difference was not seen for race with regard to non-inflammatory lesion counts. There was a significant difference in total lesion response by race. A significant difference in treatment response between races was demonstrated for the dichotomized Evaluator's Global Severity scores in favor of the non-Caucasians.

Age

Subjects were sub-grouped into those 16 years or younger or older than 16. A statistically significant difference in response between age groups was demonstrated in all analyses for percent change from baseline in all three lesion counts in favor of the older sub-group. Similarly, the older sub-group had higher success rates on the dichotomized Evaluator's Global Severity scores at Week 12. These results were generally true across all treatment groups.

*Comment: There appears to be no clinically significant treatment effect by sub-group.*

D. Efficacy Conclusions

The studies were designed appropriately for the sponsor's combination product, i.e. the four-armed studies were designed to demonstrate the contribution of each component to efficacy.

Lesion Counts

Superiority of Clin-RA over clindamycin, tretinoin and vehicle was demonstrated for all lesion counts (inflammatory, non-inflammatory and total) in study 7001.G2HP-06-02 (06) when both mean change and mean percent change were considered. Note: The sponsor's pre-specified primary analysis was "mean percent change."

Superiority of Clin-RA over clindamycin, tretinoin and vehicle was demonstrated for inflammatory lesions in study 7001.G2HP-0-02 (07). Superiority of Clin-RA over clindamycin and tretinoin was not demonstrated for non-inflammatory lesions in study 07 when either mean

reduction or mean percent reduction were considered; however, Clin-RA trended towards superiority over clindamycin in mean percent change of non-inflammatory lesions (p=0.88). In regard to total lesions, superiority of Clin-RA over clindamycin, tretinoin and vehicle was demonstrated in study 07 when mean percent reduction was considered. Superiority of Clin-RA over tretinoin and vehicle was also demonstrated in study 07 when mean reduction was considered; however, Clin-RA trended towards superiority over clindamycin in mean reduction of total lesions (p=0.82).

Clin-RA appeared to be more effective against inflammatory lesions than non-inflammatory lesions in both studies. This could reflect an "enhancement" of clindamycin effect with a contributory effect of tretinoin. Tretinoin may have allowed for increased clindaymycin absorption, permitting better access into the follicles and *P. acnes*. In both studies, while the treatment effects of clindamycin and tretinoin against inflammatory lesions were similar, this effect was slightly higher for clindamycin. This would not be unexpected since clindamycin is most active against inflammatory lesions. When compared to each other, the effects of clindamycin and tretinoin against non-inflammatory lesions were not consistent across the pivotal trials. Pertaining to total lesion counts, the effects of clindamycin and tretinoin were similar. This is probably driven by the inflammatory lesions.

Evaluator's Global Severity

Superiority of Clin-RA over tretinoin and vehicle was demonstrated for the proportion of subjects who were "clear" or "almost clear" on the Evaluator's Global Severity (EGS) score at 12 weeks in both pivotal trials. The results were largely driven by those who were "almost clear" as few subjects attained the "clear" state, and the results were similar across treatment groups and across both trials. The proportion of subjects who achieved the "almost clear" state was similar for the clindamycin and tretinoin groups in both pivotal trials and consistent across studies. This is consistent with the lesion count data where the clindamycin and tretinoin were similar on inflammatory lesions, and inflammatory lesions have more impact on the global assessment.

However, superiority of Clin-RA over clindamycin was not demonstrated for the proportion of subjects who were "clear" or "almost clear" on the EGS in the intent-to-treat analysis to a level of statistical significance in either pivotal trial, although treatment effects for clindamycin and tretinoin were similar, as discussed above. Thus, the contribution of tretinoin to efficacy was not adequately demonstrated. This is likely attributable to marked difference in the powering of the monad arms, with half as many subjects being enrolled in the clindaymcin group. The lack of demonstration of superiority of Clin-RA over clindamycin on the EGS in the primary analyses appears to be a function of the sponsor's having underpowered the clindamycin arm.

The risk of this outcome was one that the sponsor was seemingly willing to accept in not heeding the Division's advice regarding the powering of studies. The Division was very specific in its advice to the sponsor in the development of this product. The advice offered included:

- "The Sponsor is encouraged to do a phase 2 study to determine the contribution of each active ingredient to the drug effect, and to determine point estimates for the phase 3 trials" (Pre-IND meeting, September 24, 2001).

- "The sponsor is encouraged to conduct a Phase 2 trial to estimate the treatment effect of Clin-RA Gel as well as each of its components and then to use such estimates for calculating the samples size fro Phase 3 trials" (Pre-IND meeting).
- "Adequacy of the sample size depends on having reliable estimates for the various treatment arms in the trial. For the sample size determination the sponsor used...information from (Product X) to get estimates for differences in percent change from baseline for the combination and tretinoin and clindamycin for inflammatory, non-inflammatory and total lesions. However, the sample size calculation was not powered for the co-primary endpoint, the dichotomized Evaluator's Global Evaluation (EGE). It is recommended that the sponsor power their Phase 3 trials for this co-primary endpoint along with allowance for drop-out to ensure that Phase 3 trials are not under-powered" (End-of-Phase 2 Meeting, December 16, 2002). Note: This comment was in response to the sponsor's request for the Division's concurrence on their proposal of "a treatment ratio of 2:2:1:1 for Clin-RA Gel:Tretinoin 0.025%:Clindamycin phosphate 1.2%: Clin-RA Gel vehicle, respectively, based on the power calculations of our statistical consultant."
- "It is noted that the sponsor indicated that as no previous studies using the Evaluator Global Evaluation (EGE) from which to base power calculations, that it is their risk to proceed with current power calculation based only on percent change from baseline for inflammatory, noninflammatory and total lesions." (Statistical reviewer's comment regarding the phase 3 protocols, provided to the sponsor on March 27, 2003).

It is noted that even when the sponsor's proposed modified EGS was considered (i.e. "clear" or "almost clear" or a 2-grade improvement for subjects who were in the severe category at enrollment), statistical significance was demonstrated only in one study, 7001.G2HP-07-02.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

No new safety concerns identified. The largest percentage of adverse events were "respiratory, thoracic and mediastinal disorders." "Skin and subcutaneous disorders" were the second most common category of adverse events for subjects treated with active medication and were more often reported for subjects treated with one of the tretinoin-containing products. Most adverse events were considered by investigators to be mild in severity and unrelated to study medication.

B. Description of Patient Exposure

As was done with efficacy, the safety review will consider the intent-to-treat population, defined as all subjects who applied any of the study products (see "Demographics" table in the discussion of efficacy). There were no statistically significant differences in baseline or demographic characteristics among the four treatment groups for average age, for race or gender. A majority of subjects were white (>70%), 12-16% were black, 1-3% were Asian/Pacific Islander, 12-14% were Hispanic/Latino, 0-1% were American/Alaskan Native and 0-2% were Other. There were similar numbers of male (48% to 54%) and female (46% to 52%) patients enrolled in each of the four groups.

The specified duration of treatment in the Phase 3 studies was 12 weeks or 84 days. The numbers of subjects who completed the 12-week treatment course in each treatment group are as follows: 718 (85%) in the Clin-RA Gel group, 359 (84%) in the clindamycin group, 710 (84%) in the tretinoin group 355 (84%), and in the vehicle group.

Adverse events were coded according to World Health Organization Adverse Reaction Terminology and tabulated separately by body system and individual preferred terms in decreasing frequency. All reported adverse events were summarized by the number of patients reporting adverse events, body system, severity, seriousness, and relationship to study medication.

C. Methods and Specific Findings of Safety Review

Safety evaluations were conducted at each study visit (Baseline and Weeks 2, 4, 8, and 12). Safety was evaluated by the Cutaneous Safety Evaluation (erythema and scaling), the Tolerability Evaluation (itching, burning, and stinging), and by the incidence of adverse events reported. Laboratory data were not collected in the pivotal trials.

**Cutaneous Safety Evaluation**

Cutaneous safety was assessed by the degree of scaling and erythema. The following scales were employed in the assessment of those signs:

**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 |

Scaling and erythema were essentially limited to the Clin-RA and tretinoin treatment groups. Mean scaling and erythema scores tended to peak around Week 2 for Clin-RA treated subjects with progressive decrease to baseline by Week 12 (end-of-treatment). For tretinoin-treated subjects these mean scores tended to show peaks around Week 2 or Week 4, with progressive decrease to Week 12.

Summary graphs of the mean scaling and erythema scores are found in the Appendix.

*Comment: The initial increase in scaling and erythema and their subsequent progressive decrease towards baseline are consistent with the irritancy commonly experienced in the initial weeks of tretinoin use. Typically, the skin eventually adapts with the development of tolerance. That these effects were not paralleled in the vehicle arm suggests that the vehicle may not be a*

*significant contributor to irritancy.*

**Tolerability Evaluation**

Tolerability was assessed by the degree of itching, burning, and stinging. The following scales were employed in the assessment of those symptoms:

**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 |

Similar to the Cutaneous Safety Evaluation, increases in the mean scores for itching, burning and stinging were more seen with Clin-RA and tretinoin-treated subjects and had peaked by the Week 2 or 4 assessment. Mean tolerability for all parameters was generally in the mild cateogory.

Summary graphs of the mean itching, burning and stinging scores are found in the Appendix.

*Comment: These patterns are again consistent with tretinoin effects.*

**ADVERSE EVENTS**

A total of 643 subjects reported 950 non-serious adverse events. The percentage of subjects reporting at least one adverse event was similar across all treatment groups: Clin-RA Gel 27%, clindamycin, 24%, tretinoin 27%, and vehicle 22%.

**Modified Sponsor ISS Table 8.65 Summary of Adverse Events (Intent-to-Treat Subjects)**

| | Clin-RA (n=845) n % | Clindamycin (n=426) n % | Tretinoin (n=846) n % | Vehicle (n=423) n % |
|---|---|---|---|---|
| **# of events reported** | 358 | 147 | 323 | 138 |
| **# of subjects reporting one or more events** | 225 (27%) | 102 (24%) | 225 (27%) | 91 (22%) |
| **Severity of event** | | | | |
| **Mild** | 212 (59%) | 93 (63%) | 209 (65%) | 100 (72%) |
| **Moderate** | 127 (36%) | 49 (33%) | 96 (30%) | 37 (27%) |
| **Severe** | 18 (5%) | 5 (3%) | 16 (5%) | 1 (1%) |
| **Serious** | | | | |
| **Yes** | 7 (2%) | 3 (2%) | 4 (1%) | 2 (1%) |
| **No** | 351 (98%) | 144 (98%) | 319 (99%) | 136 (99%) |
| **Relationship to study drug** | | | | |
| **Unrelated** | 265 (74%) | 124 (84%) | 227 (70%) | 94 (68%) |
| **Unlikely** | 42 (12%) | 17 (12%) | 49 (15%) | 36 (26%) |
| **Possible** | 20 (6%) | 4 (3%) | 23 (7%) | 7 (5%) |
| **Probable** | 22 (6%) | 1 (1%) | 16 (5%) | 9 (1%) |
| **Related** | 9 (3%) | 1 (%) | 7 (2%) | 0 (0%) |

A table of all adverse events that occurred at > 1% frequency is found in the Appendix.

The largest percentage of adverse events were "respiratory, thoracic and mediastinal disorders." By treatment group, these events were reported in the following percentages: 10% tretinoin, 9% Clin-RA Gel, 9% vehicle, and 8% clindamycin.

"Skin and subcutaneous disorders" were the second most common category of adverse events for subjects treated with active medication and were more often reported for subjects treated with one of the tretinoin-containing products. By treatment group, these events were reported in the following percentages: 8% tretinoin, 7% Clin-RA Gel, 4% vehicle, and 4% Clindamycin. The most commonly reported reactions in this category were "application site dryness" (reported in 2% of Clin-RA-treated subjects, 2% of tretinoin-treated subjects, and ≤ 1% of clindamycin and vehicle-treated subjects) and "sunburn" (2% of tretinoin-treated subjects and ≤ 1% of subjects in all other treatment groups).

"Gastrointestinal disorders" were reported at a similar percentage across treatment groups: 3% in all three active treatment groups and 4% in the vehicle group. No individual event was reported at > 1% in any treatment group. Three events were reported at the 1% level in certain treatment groups:

- "Abdominal pain upper" was reported in 1% of clindamycin-treated subjects and 1% of vehicle-treated subjects.
- "Gastroenteritis viral" was reported in 1% of Clin-RA-treated subjects.
- "Oral pain" was reported in 1% of clindamycin-treated subjects.

All other individually reported gastrointestinal events occurred in < 1% of subjects in each treatment group. One of the gastrointestinal disorders was considered to be related to study medication: one clindamycin-treated subject was reported to have experienced "bloody diarrhea

(colitis)" of moderate severity. That subject is discussed below:

- The subject was a 12-year old female who was randomized to clindamycin treatment on May 29, 2003 and applied her last dose on June 3, 2003. The mother reported that the subject awoke with mild abdominal pain during the early morning hours of June 5, 2003 and experienced three loose stools with bright red blood. No fever or chills were reported. The subject returned to sleep and awoke asymptomatic later that morning. The subject was evaluated at the study site on June 9, 2003, and her examination was normal, including a rectal examination negative for blood. The child remained asymptomatic and was terminated from the study. The event lasted one day and did not require treatment. The investigator evaluated this event as being related to study medication.

*Comment: The "bloody diarrhea" appears not to have been documented, and the nature of this event is unclear. The clinical course was not typical of pseudomembranous colitis. Stool assay for Clostridium difficile toxins might have been helpful.*

There were nine reports coded as "gastroenteritis viral" in the pivotal trials, all of which were reported from study 7001-G2HP-07-02, but from different study sites. All of these events were reported as "stomach virus," and all were considered by the investigators as being either unrelated or unlikely related to study medication. All of the events resolved and none required discontinuation from the study. Seven of these events were reported in subjects who were treated with clindamycin-containing products (five Clin-RA and two clindamycin).

*Comment: The clustering of these events primarily to the Clin-RA and clindamycin arms raises the possibility of a drug effect. Further, that most of these events were in the Clin-RA arm raises the possibility that this was because more clindamycin got absorbed because of tretinoin effects, e.g. irritancy. However, it is noted that there were no reports of similar events in 7001-G2HP-06-02.*

**Non-Serious Adverse Reactions That Resulted in Discontinuation of Study Medication**

Of the 643 subjects reporting non-serious adverse events, 20 terminated early from the study. Seven of these 20 subjects experienced adverse events that were evaluated by the investigators as being unrelated to the study medication. The remaining 13 subjects who terminated early from the study had adverse events that were evaluated by the investigators as being related, probably related, or possibly related to study medication. Of these 13 subjects, 10 (8 Clin-RA-treated subjects and 2 tretinoin-treated subjects) terminated early due to cutaneous reactions at the treatment site, e.g. burning, itching, dryness, erythema, hypopigmentation, 2 due to sunburn (both tretinoin-treated), and 1 clindamycin-treated subject experienced colitis (discussed above).

*Comment: Use of tretinoin may be associated with heightened sun sensitivity. This may be due the decreased number of layers of the stratum corneum with tretinoin use.*

Subjects who Became Pregnant

The Inclusion Criteria required a negative pregnancy test at baseline and that women of

childbearing potential practice effective contraception for the duration of the study (see Inclusion Criteria). Urine pregnancy testing was repeated at the last study visit (Week 12).

Seven subjects became pregnant during the pivotal trials, six of whom received tretinoin treatment and one of whom received Clin-RA Gel treatment. For four subjects, the pregnancy resulted in early discontinuation of treatment. The remaining three subjects had completed the study, with their positive pregnancy tests having been discovered at the last study visit. In response to an Information Request, the sponsor submitted the available information pertaining to the outcomes of the pregnancies.

| Subject(site)/age | Treatment Group | Date of Randomization | Date Pregnancy Discovered | Outcome |
|---|---|---|---|---|
| 494(603)/19 yrs | Tretinoin | 04/04/03 | "sometime in June" | Unknown (lost to follow-up) |
| 1071(616)/24 yrs | Tretinoin | 05/28/03 | 08/20/03 | Miscarriage or [redacted] |
| 1171(618)/33 yrs | Clin-RA | 05/19/03 | 06/05/03; confirmed at study site 06/06/03 | 3345 gm male delivere [redacted] 49.5 cm, Apgar 02 and 09 at 1 and 5 minutes, respectively; neonatal heart murmur |
| 1869(700)/22 yrs | Tretinoin | 04/14/03 | 07.14/03 | Voluntary abortion [redacted] |
| 2227(701)/23 yrs | Tretinoin | 06/18/03 | 08/14/03; confirmed at study site 08/18/03 | Unknown (lost to follow-up) |
| 2423(709)/19 yrs | Tretinoin | 06/13/03 | 09/09/03 | "healthy" female 7lbs., 14 oz.;21-3/4 inches |
| 2458(705)/32 yrs | Tretinoin | 06/26/03 | Stopped dosing 08/27/03 because of pregnancy; confirmed at study site 09/11/03 | Unknown (lost to follow-up) |

*Comment: Tretinoin-containing products are classified in Pregnancy Category C. Clindamycin phosphate-containing products are classified in Pregnancy Category B. The sponsor appropriately proposes a category C designation for their product and proposes inclusion of approved wording contained in the discussion of teratogenic effects in the Pregnancy portion of the package insert for another tretinoin-containing product (Avita). For obvious reasons, the treatment of acne in the pregnant female would differ from that in the non-pregnant female. Because it contains a retinoid, it is not likely that the sponsor's product would be frequently recommended for use during pregnancy.*

**Deaths, Other Serious Adverse Events, and Other Significant Adverse Events**

There were no deaths in the development program.

Per review of the study reports, 11 subjects experienced 16 serious adverse events, all of which were evaluated by the investigators as being unrelated to study medication. Two of these subjects were discontinued from treatment and terminated from the study because of their serious adverse events: one subject displayed behavioral changes that required admission to a psychiatric unit; the other subject had a history of esophageal dysmotility and hiatal hernia and experienced worsening of esophageal pain. The remaining nine subjects remained in the study, and these subjects experienced assorted events: orthopedic injuries (four), behavior disorder (two), cholelithiasis/cholecystectomy (two), and headache (one).

**Dermal Safety Studies**

The sponsor conducted four dermal safety studies in healthy volunteers to evaluate the safety of Clin RA Gel. All of the dermal safety studies were conducted with the formulation evaluated in the pivotal trials. Karl R. Beutner, M.D., Ph.D. was the investigator for all four dermal safety studies.

**7001-G2HP-01-02: A Single Center, Evaluator-Blind Evaluation of the Cumulative Irritation Potential of Clin-RA Gel, Vehicle Gel and Control Following Repeated Topical Application to Healthy Subjects.**

**Investigational Test Article:** Clin-RA Gel

**Control Test Articles:** Clin-RA Gel Vehicle Gel and 0.2% sodium lauryl sulfate

**Treatment duration:** 3 weeks

**Design:** Single center, evaluator-blind, phase 1 study

**Methodology:** Clin-RA Gel, 0.2% Sodium lauryl sulfate, and vehicle gel were applied under separate occlusive patches on the backs of subjects 3 times per week for 3 weeks. Each application was observed 48 hours (72 hours on weekends) later for signs of irritation or inflammation.

**Criteria for Evaluation:** Skin reactions were evaluated using the following scale:
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

Other signs of skin reaction such as dryness, cracking, peeling, etc. were noted, if applicable.

**Results:** Thirty-four subjects were enrolled in the study. All completed the study, and all were considered evaluable.

The test material cumulative irritation index was calculated as follows:

34 evaluable subjects x 9 gradings x 4 (highest possible score per grading) = 1224

- Clin-RA Gel : 646.5/1224
- Vehicle: 103/1224
- 0.2% Sodium Lauryl Sulfate (Positive Control): 196/1224

Supplemental analyses were performed to determine differences between test articles. For

these analyses, the 21-Day Cumulative Irritation Score was obtained by summing the Irritation Scores for Visit 3 through Visit 11. Therefore, a maximum total score of 36 for each patch was possible. Results are shown in Sponsor Table 1 below:

Table 1: Between Patch Analysis
21-Day Cumulative Irritation Scores

| Parameter | Vehicle | Control | Clin-RA Gel | p-value |
|---|---|---|---|---|
| 21-Day Cumulative Irritation Score | | | | |
| N (%): | 34 (100%) | 34 (100%) | 34 (100%) | |
| Mean: | 3.15 | 5.76 | 19.01 | <0.01 |
| Std. Dev.: | 5.2 | 8.3 | 7.2 | |
| Median: | 1.75 | 1.5 | 21 | <0.01 |
| Min.-Max.: | 0 – 24 | 0 – 29 | 3 – 28.5 | |

No serious adverse events were reported during the study.

*Comment: Under conditions of the study, Clin-RA was shown to be moderately irritating, and the vehicle does not appear to be contributing significantly to the irritancy. Vehicle was less irritating than the positive control. The demonstration of irritancy is not surprising given that the sponsor's product contains tretinoin, and tretinoin products typically cause some degree of irritation. No comment can be made regarding the individual contribution of each active to the irritancy of the compound since the monads were not tested. However, it is likely that tretinoin is the major contributor to irritancy, given what is known about the effects of both topical tretinoin and topical clindamycin.*

**7001-G2HP-03-02: A Single Center, Evaluator-blind Determination of the Cumulative Irritation and Contact Sensitization Potential of Clin-RA Gel, Clin-RA Gel Vehicle, and Retin A Gel 0.025% Control Following Repeated Topical Applications to Healthy Subjects**

**Investigational Test Article:** Clin-RA Gel (1.2% Clindamycin phosphate, 0.025% Tretinoin)

**Control Test Article:** Clin-RA Gel Vehicle, Retin A Gel (0.025% Tretinoin)

**Treatment Duration (study period):** 6 weeks

**Design:** Single-center, evaluator-blind, phase 1 study

**Methodology:** The study phases were:

- **Induction:** Clin-RA Gel, Clin-RA Gel Vehicle, and Retin A Gel (0.025% Tretinoin) were applied under separate occlusive patches on the backs of subjects 3 times per week for 3 weeks. Each application was observed 48 hours (72 hours on weekends) later for signs of irritation or inflammation.
- **Rest Period:** A rest period of 2 weeks followed the induction/irritation phase; no patches were applied during this period.
- **Challenge:** After the rest period, patches for Clin-RA Gel and Clin-RA Gel Vehicle only were applied to different sites on the back for 48 hours. Sites were evaluated at 48 hours and 72 hours post-patching to assess for sensitization.

Sites were also evaluated at 96 hours post-patching, if needed.

There was also an optional re-challenge phase to confirm suspected positive sensitization reactions.

**Safety Evaluation:** Assessment of skin irritation was according to the same scale used in the cumulative irritancy testing (see above) from 0 (no sign of irritation) to 4 (erythema with edema and blistering).

The criteria for a contact sensitization reaction were:
1) The patch site reached a Grade 3 or 4 reaction,
2) The reaction persisted at least 24 hours after the removal of the occluded patch, and
3) The reaction was reproducible upon re-challenge.

**Results:** Two hundred twenty nine subjects were enrolled and treated with test articles. Two-hundred fifteen subjects completed the study and were considered evaluable for the evaluation of sensitization potential.

Fourteen subjects terminated the study early and were not included in the population for determining sensitization:

- three discontinued due to noncompliance by missing two or more of the scheduled visits.
- five subjects withdrew consent.
- two discontinued due to scheduling conflicts.
- four subjects discontinued due to adverse events, two of which were probably related to the test articles, one that was possibly related and one that was unrelated to the test articles.

Contact Sensitization

The highest observed score during the challenge phase for the Clin-RA Gel vehicle was one observation of a score of 1 (Slight Erythema) at 48 hours post-patching, which resolved by 72 hours. The highest observed score during the challenge phase (one subject) for the Clin-RA Gel was a 3 (Erythema with marked edema) 72 hours post-patching that persisted at 96 hours post-patching. (This subject was re-challenged and is further discussed below). Most reactions recorded during the challenge phase were 0 (no sign of irritation) with 26 observations of 0.5 (barely perceptible erythema), 5 observations of 1 (slight erythema) and 1 observation of 2 (noticeable erythema with slight infiltration).

Two subjects were re-challenged. One subject had re-challenge scores of 0 and 1 at 48 and 72 hours after patching, respectively, suggesting that the challenge score of 3 may not have reflected contact sensitization. A second subject was re-challenged due to a delayed observation after patching during the challenge phase, and neither the challenge or re-challenge scores were consistent with contact sensitization.

*Comment: The results suggest that Clin-RA Gel has low potential for causing contact sensitization reactions.*

Cumulative Irritancy

As with the cumulative irritancy study, Clin-RA was shown to have the potential to cause moderate irritancy, while the vehicle was not significantly irritating.

*Comment: The results of the cumulative irritancy portion of this study were similar to and, therefore, supportive of those from 7001-G2HP-01-02 (the cumulative irritation study). The results will not be further discussed.*

**7001-G2HP-04-02: A Single Center, Evaluator-blind Assessment of the Phototoxicity Potential of Clin-RA Gel and Vehicle Following Topical Application to the Skin of Healthy Subjects.**

**Investigational Test Articles:** Clin-RA Gel

**Control Test Article:** Clin-RA Gel Vehicle

**Treatment Duration:** (study period) 48 hours

**Methodology:** A subject's minimal erythema dose (MED) was determined before randomization into the study. On Day 1, three pairs of test sites were identified on the subject's back. Two sites had Clin-RA Gel applied, two sites had vehicle gel applied, and two sites had no product applied (control sites). After the test articles dried, one of each paired site was covered, and the uncovered sites were treated with 10 times the MED equivalent with UVA radiation, followed by 0.5 times the MED of full spectrum solar simulator UVA/UVB radiation. Evaluations of skin reactions were made 5-15 minutes, 24 and 48 hours after irradiation. Evaluations were scored by the same scale as was used in the cumulative irritancy study (see above).

**Number of Subjects:** Twenty-seven healthy subjects were enrolled, and 25 subjects were considered evaluable. Subjects with Skin Types II, III and IV volunteered for the study.

**Results:** No reactions greater than 1 (slight erythema) were noted at any test site. At the irradiated sites, no reactions greater than barely perceptible erythema were noted at the readings performed 5-15 minutes after irradiation. At the 24 and 48 hour readings, slight erythema was noted at the untreated, vehicle-treated, and Clin-RA treated sites for one subject. There was no erythema reported at irradiated sites of 18 of the 25 evaluable subjects. The frequency of these reactions was comparable at the treated (Clin-RA or vehicle) and the untreated, irradiated control sites.

Based on the test site erythema scores the investigator concluded that under the conditions of this study the Clin-RA Gel and Clin-RA Gel Vehicle have a very low potential for causing phototoxic reactions.

*Comment: The reviewer agrees with the investigator's conclusion.*

**8.14.2.4 7001-G2HP-05-02: A Single Center, Evaluator-Blind Determination of the Photoallergy Potential of Clin-RA Gel and Vehicle Gel Following Repeated Topical Application to Healthy Subjects**

**Investigational Test Article:** Clin-RA Gel (1.2% clindamycin phosphate, 0.025% tretinoin)

**Control Test Article:** Clin-RA Gel Vehicle

**Treatment Duration (study period):** 6 weeks

**Design:** Single center, evaluator blind, phase 1 study

**Methodology:** Subjects with Skin types I-IV were eligible to be enrolled into the study. There were three phases to this study:

- **Induction:** Three pairs of test sites were identified on the subject's back. Two pairs were treated with Clin-RA Gel, two pairs were treated with vehicle and two sites were untreated, control sites. Occlusive patches were applied for 24 hours. After patch removal, one site of each pair was exposed to ultraviolet (UV) light (10 times the MED equivalent time of UVA plus 0.5 times the MED equivalent time of UVA and UVB). Skin reactions were evaluated on visits 2, 3 and 4 of the first test week and visits 1, 2, 3 and 4 of each subsequent test week.
- **Rest Period:** 2 week rest period
- **Challenge:** Duplicate patches of each test article and vehicle were applied to previously untreated test sites. The challenge patches were removed after 24 hours. One of each pair of test sites and an untreated, UV unexposed test site were exposed to UV radiation (10 times the MED equivalent time of UVA plus 0.5 times the MED equivalent time of UVA and UVB). Sites were evaluated 5-15 minutes, 24 hours and 48 hours after UV exposure.

**Number of Subjects:** 30 healthy subjects enrolled with 28 completing the study.

**Safety Evaluation:** Assessment of skin irritation was on scale of 0 (no sign of irritation) to 4 (erythema with edema and blistering). Other signs of skin reaction such as dryness, cracking and peeling were noted as comments. Photocontact allergy potential was evaluated by the assessment of the application sites during the challenge phase of the study and, as needed, a re-challenge phase.

The criteria for a photocontact allergy reaction were:
1) The patch site reached a Grade 3 or 4 reaction,
2) The reaction was persistent after the removal of the occluded patch,
3) The reaction was reproducible upon re-challenge.

**Results:** Of the 30 subjects enrolled, 28 completed the study (one subject discontinued because of an intercurrent illness, and one was excluded because of use of an exclusionary medication).

Induction Phase

The highest reaction noted for the vehicle and control was Grade 2 (noticeable erythema with slight infiltration): twice with vehicle and once at an unpatched, control site. There were 33 Grade 2 reactions seen with Clin-RA Gel. There were six reports of Grade 3 reactions (erythema with marked edema) and seven reports of Grade 4 reactions (erythema with edema and blistering) with Clin-RA Gel. Reactions at the Clin-RA Gel sites were noted at comparable rates at irradiated and non-irradiated sites. The investigator theorized that the reaction noted during induction could have been attributable to irritation from application of the retinoid under occlusion.

Challenge Phase

No reaction greater than Grade 1 (slight erythema) was recorded at any test site. Grade 0 (no irritation) was the most common score during the challenge phase, and was recorded for 130 Clin-RA sites, 135 vehicle sites and 140 unpatched, control sites. Grade 0.5 reactions (barely perceptible erythema) were recorded at 24, 21, and 17 readings for Clin-RA, vehicle, and unpatched, respectively. Grade 1 reactions (slight erythema) were recorded for 14 Clin-RA sites, 12 vehicle sites and 11 unpatched sites.

The investigator concluded that under the conditions of this study, the Clin-RA Gel and Clin-RA Gel Vehicle have a very low potential for causing photoallergic reactions.

*Comment: The reviewer agrees with the investigator's conclusion. However, there were only 28 evaluable subjects, and it is generally recommended that enrollment be sufficient to allow for at least 50 evaluable subjects for this type of study.*

**Safety Update**

The Safety Update was submitted on August 20, 2004 and consisted of (1) information regarding the outcomes of the pregnancies that occurred in the pivotal trials and (2) an interim report for the ongoing, long-term safety study, MP-1501-01. Only the long-term safety study will be discussed here as the pregnancy outcome information was discussed above.

**MP-1501-01: A Multi-center, Open-label, Long-term Safety Trial of Clin RA Gel in the Treatment of Acne Vulgaris**

**Date of First Enrollment:** January 23, 2004

**Analysis Date of Interim Study Report:** August 4, 2004

**Objectives:** The primary objective of the study is to assess the long-term safety of Clin-RA as a monotherapy or with other concomitant acne medications over a six- month or one-year period. The secondary objective of the study is to assess patterns of use of the new combination formulation by following the circumstances for treatment discontinuation and re-initiation of therapy.

**Methodology:** This is a multi-center (13 sites), open-label study involving subjects with mild, moderate, or severe acne vulgaris. The number of subjects enrolled is 442. Subjects apply study drug once daily. The duration of treatment will be one year for the first 200 subjects completing six months of the study and choosing to continue participation. The study duration for the remaining subjects will be six months. Subjects will be evaluated at Screen/Baseline and at monthly intervals.

*Comment: Enrollment is sufficient to address subject numbers at the six-month and one-year time points, per ICH E1A.*

Safety will be evaluated by the Cutaneous Safety Evaluation scores (erythema and scaling), the Tolerability Evaluation (itching, burning, and stinging) and by the incidence of adverse events reported. The scales for safety assessment are the same as those used in the pivotal trials. Safety will be evaluated at monthly intervals. While this is a safety study, efficacy will be assessed based on the signs and symptoms of acne vulgaris.

**Main Criteria for Inclusion:**

- Male or female subjects 12 years of age or older
- Mild, moderate or severe acne as assessed by the Evaluator's Global Severity Score (same scale as was used in the pivotal trials)

*Comment: Lesion counts are not being done in this study.*

**Main Criteria for Exclusion:**

- Any dermatological conditions on the face that could interfere with clinical evaluations such as acne conglobata, acne fulminans, secondary acne, etc.;
- History of regional enteritis, ulcerative colitis or antibiotic-associated colitis;
- Use of the following at screening/baseline:
  - topical antibiotics on the facial area (azelic acid, erythromycin)
  - anti-inflammatories and corticosteroids on the face
  - topical retinoids, including retinol, on the face

*Comment: Section 5.3.2 of the protocol indicates that topical antibiotics, anti-inflammatories corticosteroids and topical retinoids are also prohibited from use on the face during the study. However, astringents and abrasives, over-the-counter acne medications, oral antibiotics, oral contraceptives and systemic retinoids are all allowed. Therefore, little could be concluded regarding the efficacy of Clin-RA from this study, since the use of concomitant acne therapies is permitted during the study. Also, use of certain topicals could potentially impact the safety findings by increasing irritancy when used in combination with the sponsor's product, which is itself potentially irritating.*

**Safety Results:** From study start through April 30, 2004, 91 subjects have reported 120 adverse events. The reported events were generally mild. Fifty-three percent of all adverse events reported were classified as unrelated to study drug. There have been no reports of severe incidents of Cutaneous Safety or Tolerability evaluations. There have been no deaths, serious

adverse events or other significant adverse events reported. Two pregnancies have been reported. Both subjects have been discontinued from the study and will be followed through delivery.

**Conclusion:** Based on the data available to date, no new safety concerns have been raised regarding long-term use of Clin-RA..

D. Adequacy of Safety Testing

Pertaining to the pivotal trials, the numbers of subjects and nature and frequency of safety assessments were adequate to detect adverse events which might occur in the short-term. Given the chronic nature of the indication, the safety of long-term use of the sponsor's product is needed. The sponsor has undertaken a long-term safety study, planned for a year's duration, and proposed enrollment is so as to fulfill the spirit of the ICH E1A guideline. It is noted that the long-term safety of each of the actives individually is well-established, since each of these products has been marketed for years.

Safety considerations pertaining to the sponsor's product would be on the local and systemic levels. Local safety issues would include the potential for the sponsor's tretinoin-containing product to cause irritancy. Systemic safety issues would pertain to the potential for systemic exposure to either of the actives from use of the compound and the consequences from such exposures. The sponsor's development program was adequate in design to assess these local and systemic safety issues. Specifically,

- Local safety assessments were conducted throughout the pivotal studies.
- The sponsor conducted the standard battery of dermal safety studies.
- The sponsor conducted a multiple-dose study to assess the absorption and safety of Clin-RA Gel in subjects with acne vulgaris.
- A long-term safety study is ongoing.
- Adverse event data was (or is being) collected in all of the clinical trials.

E. Summary of Critical Safety Findings and Limitations of Data

No new safety concerns identified. Most adverse events were considered by investigators to be mild in severity and unrelated to study medication. The tretinoin-containing products, i.e. the Clin-RA Gel and the tretinoin comparator, were shown to be somewhat irritating, consistent with tretinoin effect. Most local effects tended to peak around the second week of treatment for the Clin-RA group, and trended towards progressive decrease towards, to or below baseline by the end of treatment (Week 12).

While sunburn reactions were reported in all treatment groups, they were reported at highest frequency in tretinoin-treated subjects. Heightened sensitivity to ultraviolet light is reported with use of tretinoin and may be a function of the decrease in the number of layers of the stratum corneum. Avoidance of ultraviolet light and regular use of sunscreen would probably be advisable for users of Clin-RA, given the tretinoin content.

One of the most important potential safety issues relates to the extent of systemic exposure to

clindamycin from Clin-RA and the risks from such exposure, the most significant probably being pseudomembranous colitis. Gastrointestinal disorders were reported at a similar rates across treatment groups, and no individual event was reported at > 1% in any treatment group. The single report of "bloody diarrhea," evaluated as related to Clin-RA treatment, was not documented, and certain aspects of the subject's clinical course were not consistent with pseudomembranous colitis. Based on review of the available data, there does not appear to be a substantial risk for this complication. Inclusion of a warning advising of this risk in the package insert should adequately advise of this risk.

VIII. Dosing, Regimen, and Administration Issues

Dose-ranging studies were not conducted. Currently marketed formulations of tretinoin are dosed once in the evenings. Currently marketed topical gel formulations of clindamycin phosphate are dosed either once or twice daily. Rather than conduct dose-ranging studies, the sponsor based their dosing regimen on those for the individually marketed tretinoin and topical clindamycin phosphate products, electing once daily dosing. At the pre-IND meeting, the Division recommended that the sponsor conduct dose-ranging studies, since it could not be assumed that the safety and efficacy profiles of the combination used once daily would be the same as the profiles for the products individually used once daily.

*Comment: While there is no topical antibiotic/retinoid combination marketed in the U. S., clinicians commonly employ the principles of this combination treatment approach in the treatment of acne by recommending a topical antibiotic for application in the morning and topical retinoid for application in the evening.*

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The sponsor's efforts to evaluate gender effect on efficacy were adequate. There was no clinically significant evidence of gender effect on efficacy. No evaluation of gender effect on safety was found.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The sponsor's efforts to evaluate the effects of age, race and ethnicity on efficacy were adequate. There was no evidence of effect of any of these parameters on efficacy. No evaluation of these parameters on safety was found.

C. Evaluation of Pediatric Program

The sponsor requested a waiver for patients under the age of 11 years. This is reasonable because acne vulgaris does not generally affect patients in this younger age group.

D. Comments on Data Available or Needed in Other Populations

At this juncture, no data is thought needed for other populations.

X. Conclusions and Recommendations

A. Conclusions

For a product intended for the treatment of acne vulgaris, the recommended primary endpoints are lesion counts (inflammatory, non-inflammatory and total) and the evaluator's global assessment. Efficacy is demonstrated by superiority of the product in two of three lesion counts and the proportion of subjects who are "clear" or "almost clear" at efficacy assessment. As Clin-RA is a combination product (clindamycin and tretinoin), additional considerations apply to the demonstration of its efficacy. Specifically, it is necessary that the contribution of each active component to efficacy be demonstrated.

Superiority of Clin-RA over clindamycin, tretinoin and vehicle was demonstrated for all lesion counts (inflammatory, non-inflammatory and total) in study 7001.G2HP-06-02 (06) when both mean reduction and mean percent reduction were considered.

Superiority of Clin-RA over clindamycin, tretinoin and vehicle was demonstrated for inflammatory and total lesions in study 7001.G2HP-0-02 (07). Superiority of Clin-RA over vehicle was demonstrated for non-inflammatory lesions. However, superiority of Clin-RA over clindamycin and tretinoin was not demonstrated for non-inflammatory lesions in study 07, although Clin-RA trended towards superiority over clindamycin in mean percent change of non-inflammatory lesions ($p=0.88$). Thus, superiority of Clin-RA over clindamycin, tretinoin and vehicle was demonstrated in two of three lesion counts (inflammatory and total).

Superiority of Clin-RA over tretinoin and vehicle was demonstrated for the proportion of subjects who were "clear" or "almost clear" on the Evaluator's Global Severity (EGS) score at efficacy assessment in both pivotal trials. However, in the intent-to-treat analysis superiority of Clin-RA over clindamycin was not demonstrated for the proportion of subjects who were "clear" or "almost clear" on the EGS score to a level of statistical significance in either pivotal trial.

While some measure of efficacy was shown, the contribution of each component to efficacy of Clin-RA was not demonstrated. The lack of a consistent and unequivocal demonstration of superiority of Clin-RA over clindamycin in the primary analyses appears to be a function of the sponsor's having underpowered the clindamycin arm. In development of the product, the Division advised that the sponsor conduct a Phase 2 trial to estimate the treatment effect of Clin-RA Gel and each of its components and to use the estimates for calculating the sample size for Phase 3 trials and that the studies be powered for the EGS. The risk of this outcome was one that the sponsor was seemingly willing to accept in choosing not to follow the Division's advice regarding the powering of studies.

If the sponsor's product addressed some unmet medical need in the marketplace, this might have been a factor to consider in coming to a decision regarding a recommendation for an action on

the application. However, there are numerous products already marketed for treatment of acne vulgaris, including clindamycin and tretinoin products, and it is not clear that the sponsor's product would offer a clinically significant or particulary unique advantage over already available products. The primary advantage that the sponsor's product would appear to offer is patient convenience. That being the case, in the opinion of the reviewer, demonstration of efficacy should be convincing and unequivocal.

There were no new safety concerns raised from data available from use of Clin-RA. Clin-RA was shown to be moderately irritating. The demonstration of irritancy is not surprising given the tretinoin content, and tretinoin-containing products typically cause some degree of irritation. No comment can be made regarding the individual contribution of each active to the irritancy of the compound since the monads were not tested. However, it is likely that tretinoin is the major contributor to irritancy, given what is known about the effects of both topical tretinoin and topical clindamycin.

B. Recommendations

A Not Approvable action is recommended for this application.

XI. Appendix

A. Table of Adverse Events

A table of adverse events that occurred at $\geq$ 1% frequency is on the following pages

**Adverse Events Occurring at ≥ 1% Incidence by Body System (Intent-to-Treat Subjects)**

| | Clin-RA (N=845) | Clindamycin (N=426) | Tretinoin (N=846) | Vehicle (N=423) | |
|---|---|---|---|---|---|
| **System Organ Class+** | **n** | **n** | **n** | **%n** | **%** |
| Ear and labyrinth disorders | 9 (1%) | 5 (1%) | 7 (1%) | 1 (<1%) | |
| Ear infection | 5 (1%) | 2(<1%) | 2(<1%) | 0 (0%) | |
| Gastrointestinal disorders | 28 (3%) | 12 (3%) | 28 (3%) | 15 (4%) | |
| Abdominal pain upper | 3 (<1%) | 4 (1%) | 1 (<1%) | 4 (1%) | |
| Gastroenteritis viral | 5 (1%) | 2 (<1%) | 1 (<1%) | 1(<1%) | |
| Oral pain | 2(<1%) | 3 (1%) | 2(<1%) | 1 (<1%) | |
| General disorders and administration site conditions | 8 (1%) | 1 (<1%) | 0 (0%) | 4 (1%) | |
| Pyrexia | 4 (<1%) | 1 (<1%) | 0 (0%) | 3 (1%) | |
| Immune system disorders | 12 (1%) | 7 (2%) | 8 (1%) | 3 (1%) | |
| Hypersensitivity | 5 (1%) | 6 (1%) | 3 (<1%) | 0 (0%) | |
| Seasonal allergy | 7 (1%) | 2(<1%) | 4 (<1%) | 2(<1%) | |
| Infections and infestations | 13 (2%) | 5 (1%) | 7 (1%) | 4 (1%) | |
| Streptococcal infection | 9 (1%) | 1 (<1%) | 4 (<1%) | 1 (<1%) | |
| Musculoskeletal and connective tissue disorders | 22 (3%) | 11 (3%) | 23 (3%) | 11 (3%) | |
| Fracture | 4 (<1%) | 3 (1%) | 1 (<1%) | 3 (1%) | |
| Joint sprain | 2(<1%) | 3 (1%) | 4 (<1%) | 1 (<1%) | |
| Myalgia | 6 (1%) | 2(<1%) | 8 (1%) | 3 (1%) | |
| Nervous system disorders | 25 (3%) | 15 (4%) | 15 (2%) | 17 (4%) | |
| Headache | 19 (2%) | 12 (3%) | 12 (1%) | 11 (3%) | |
| Pregnancy, puerperium and perinatal conditions | 1 (<1%) | 0 (0%) | 5 (1%) | 0 (0%) | |
| Pregnancy | 1 (<1%) | 0 (0%) | 5 (1%) | 0 (0%) | |
| Psychiatric disorders | 7 (1%) | 5 (1%) | 3 (<1%) | 4 (1%) | |
| Depression | 5 (1%) | 2(<1%) | 1 (<1%) | 1 (<1%) | |
| Reproductive system and breast disorders | 6 (1%) | 2(<1%) | 3 (<1%) | 1 (<1%) | |
| Dysmenorrhoea | 5 (1%) | 2(<1%) | 3 (<1%) | 1 (<1%) | |
| Respiratory, thoracic and mediastinal disorders | 76 (9%) | 36 (8%) | 87 (10%) | 38 (9%) | |
| Cough | 7 (1%) | 5 (1%) | 9 (1%) | 2(<1%) | |
| Influenza | 6 (1%) | 2(<1%) | 1 (<1%) | 3 (1%) | |
| Nasal congestion | 3 (<1%) | 0 (0%) | 5 (1%) | 0 (0%) | |
| Nasopharyngitis | 13 (2%) | 10 (2%) | 16 (2%) | 5 (1%) | |
| Pharyngitis | 4 (<1%) | 1 (<1%) | 0 (0%) | 1 (<1%) | |
| Pharyngolaryngeal pain | 10 (1%) | 2(<1%) | 5 (1%) | 7 (2%) | |
| Rhinitis | 5 (1%) | 2(<1%) | 3 (<1%) | 0 (0%) | |
| Sinus congestion | 2(<1%) | 2(<1%) | 1 (<1%) | 4 (1%) | |
| Sinusitis | 7 (1%) | 3 (1%) | 15 (2%) | 4 (1%) | |

| | | | | |
|---|---|---|---|---|
| Upper respiratory tract infection | 21 (2%) | 8 (2%) | 24 (3%) | 11 (3%) |
| Skin and subcutaneous tissue disorders | 62 (7%) | 19 (4%) | 67 (8%) | 17 (4%) |
| Application site burning | 6 (1%) | 0 (0%) | 6 (1%) | 1 (<1%) |
| Application site dryness | 16 (2%) | 2(<1%) | 18 (2%) | 5 (1%) |
| Herpes simplex | 1 (<1%) | 1 (<1%) | 4 (<1%) | 5 (1%) |
| Oily skin | 5 (1%) | 0 (0%) | 3 (<1%) | 0 (0%) |
| Sunburn | 11 (1%) | 6 (1%) | 21 (2%) | 2(<1%) |
| Wisdom teeth removal | 1 (<1%) | 3 (1%) | 2(<1%) | 0 (0%) |

+ Counts reflect numbers of subjects reporting one or more adverse events that map to the MedDRA system organ class (Version 6.1). At each level of summarization (system organ class or event) subjects are only counted once under the greatest reported severity.

B. Summary Graphs of Cutaneous Safety and Tolerability Evaluations

Figure 14.3.1.2: Summary of Scaling Means at Baseline and Weeks 2, 4, 8 and 12
(Intent-to-Treat Subjects)

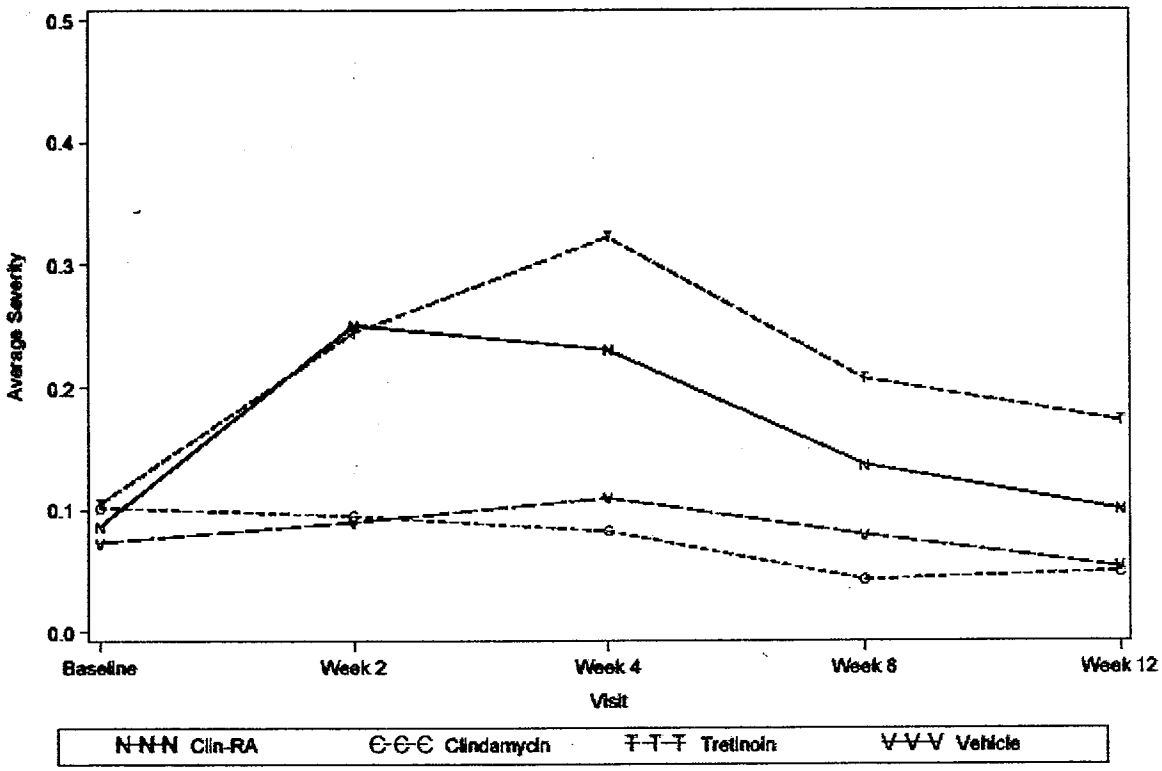


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Figure 14.3.1.1: Summary of Erythema Means at Baseline and Weeks 2, 4, 8 and 12
(Intent-to-Treat Subjects)

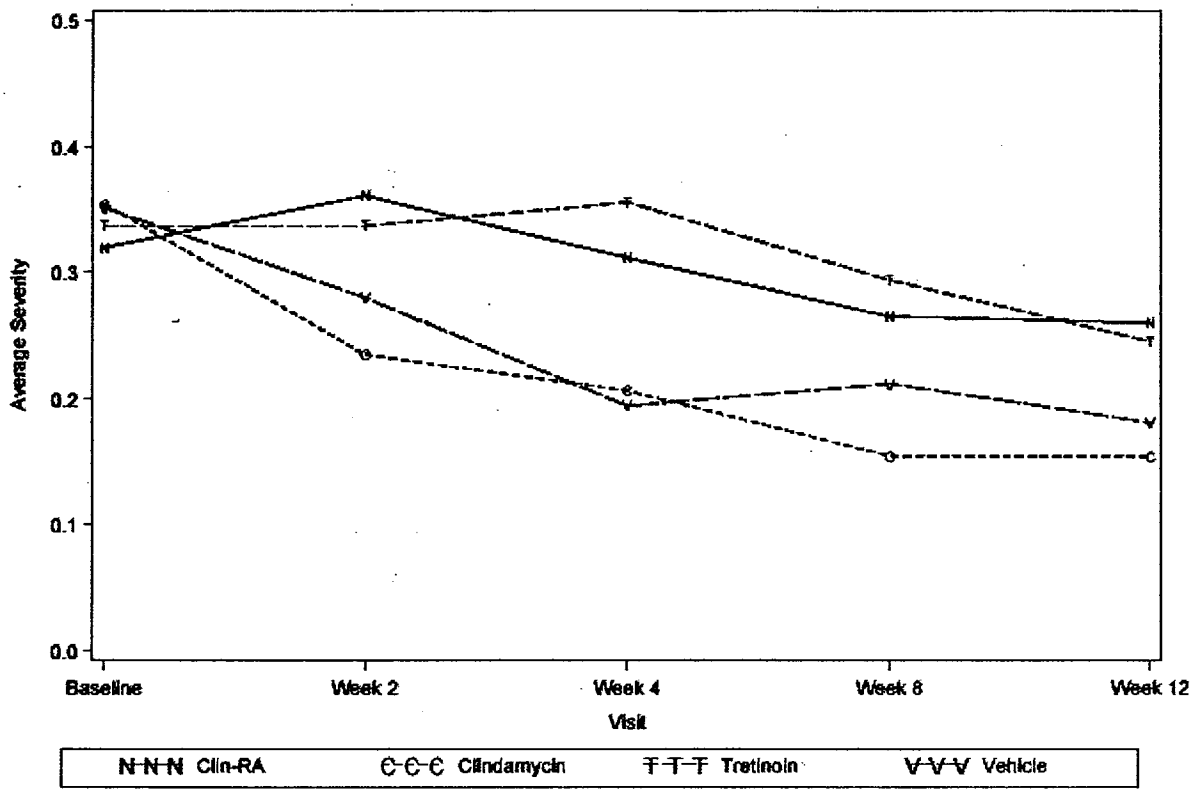


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Figure 14.3.1.4: Summary of Burning Means at Baseline and Weeks 2, 4, 8 and 12
(Intent-to-Treat Subjects)

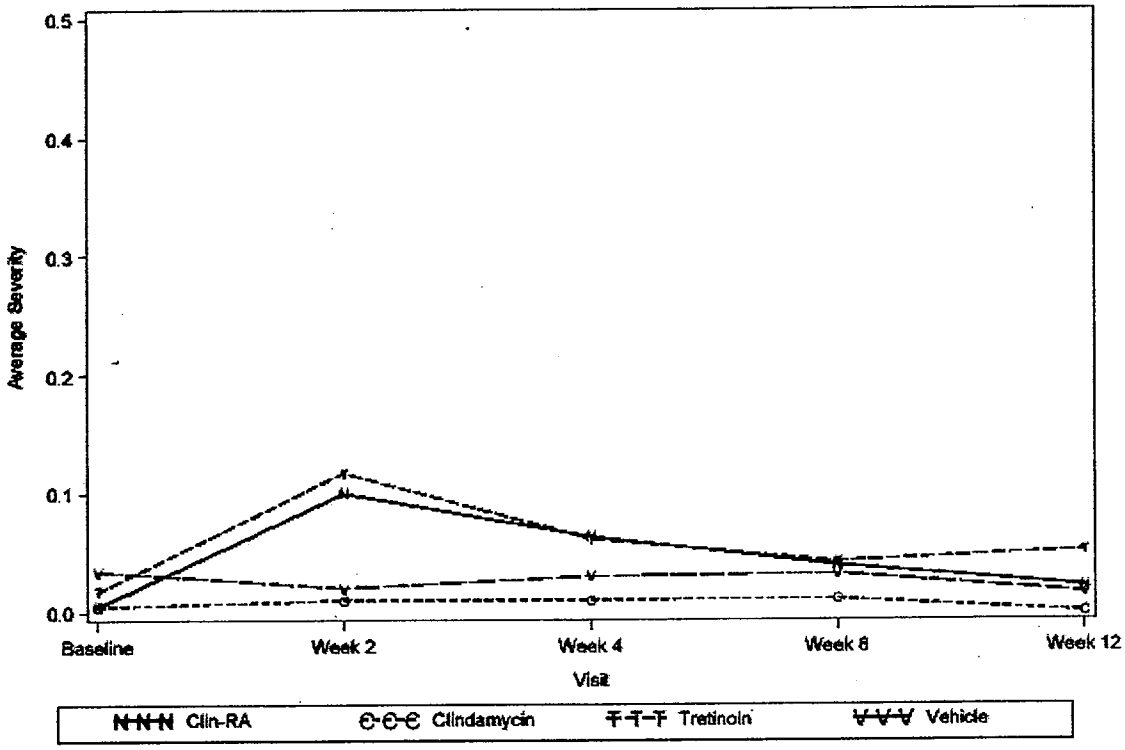


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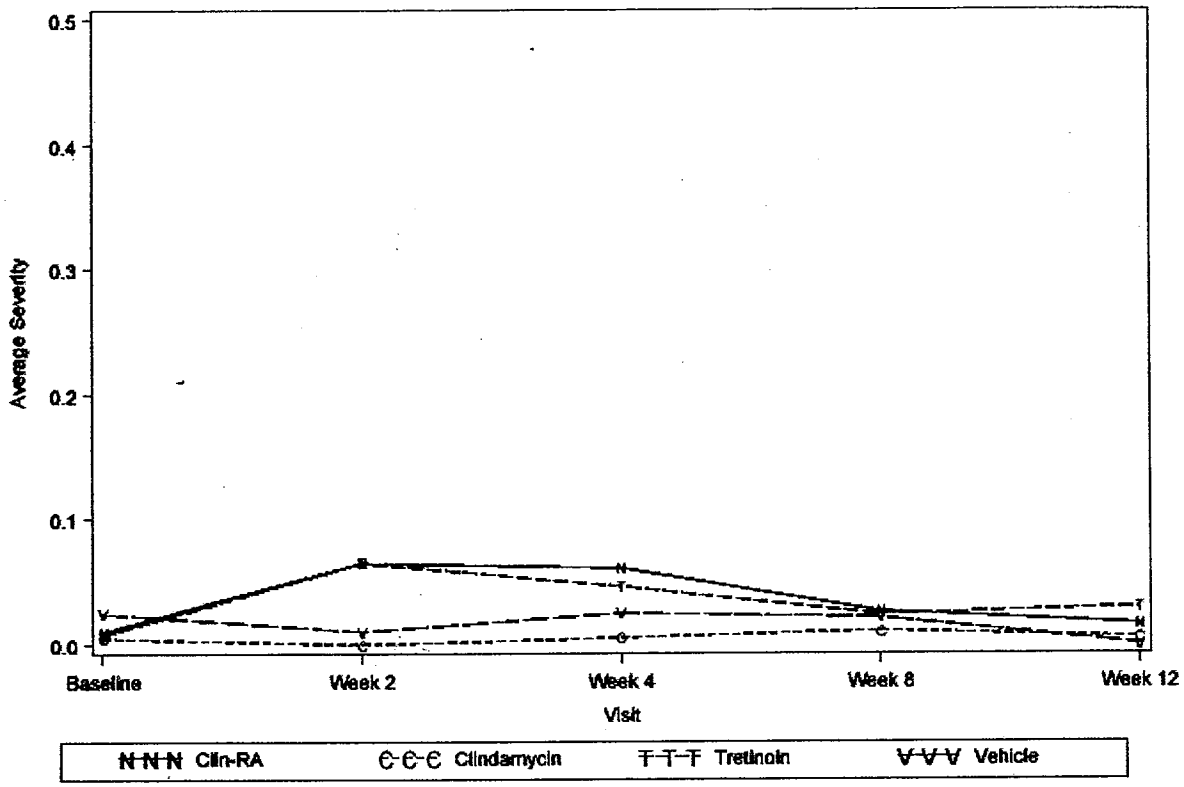
Figure 14.3.1.5: Summary of Stinging Means at Baseline and Weeks 2, 4, 8 and 12
(Intent-to-Treat Subjects)

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/s/

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Brenda Carr
11/1/04 07:38:50 AM
MEDICAL OFFICER

Markham Luke
11/1/04 11:10:01 AM
MEDICAL OFFICER
Concur with Dr. Carr's recommendation.

Jonathan Wilkin
12/7/04 02:16:04 PM
MEDICAL OFFICER
see MOR memo to file dated 12/7/04

## 45 DAY MEETING CHECKLIST

**FILEABILITY of NDA 21-739:**

**On initial overview of the application: YES**

**Drug:** ClinRA Gel (clindamycin phosphate 1% and tretinoin 0.025%)

**Indication:** acne vulgaris

**CLINICAL:**

1. **On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?** yes (Note: fully electronic submission)

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

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

4. **If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product (i.e., appropriately designed dose- ranging studies)?** Dose-ranging studies not conducted

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

   **Application Type:** 505(b)(2)

   **Identification of pivotal trials:**

   **Pivotal Study #1:** "A Multi-Center, Phase 3, Randomized, Double-Blind, 4-Arm Clinical Trial to Compare the Safety and Efficacy of Clin-RA Gel vs. Clindamycin Phosphate 1.2% Gel vs. Tretinoin 0.025% Gel vs. Vehicle in the Treatment of Acne Vulgaris"

   **Protocol Number:** 7001-G2HP-06-02

   **Study Period:** February 11, 2003 to October 21, 2003

**Is this an adequate multi-centered trial?** yes

Table 14.1.1: Summary of Subject Enrollment and Evaluability by Investigator

| Site | Investigator | Enrolled | Clin-RA ITT | Clin-RA PP | Clindamycin ITT | Clindamycin PP | Tretinoin ITT | Tretinoin PP | Vehicle ITT | Vehicle PP |
|---|---|---|---|---|---|---|---|---|---|---|
| 600 | Elizabeth Arthur | 97 | 33 | 26 | 16 | 14 | 32 | 26 | 16 | 14 |
| 601 | Micheal Gold | 47 | 16 | 13 | 7 | 4 | 16 | 11 | 8 | 7 |
| 602 | Scott Dinehart | 92 | 31 | 19 | 16 | 6 | 30 | 20 | 15 | 8 |
| 603 | Charles Fixler | 45 | 16 | 11 | 7 | 5 | 14 | 8 | 8 | 6 |
| 604 | Javier Flores | 66 | 22 | 20 | 11 | 10 | 22 | 21 | 11 | 10 |
| 606 | George Neumaier | 59 | 19 | 18 | 10 | 10 | 20 | 17 | 10 | 9 |
| 607 | Jon Hanifin | 26 | 9 | 7 | 5 | 3 | 8 | 5 | 4 | 1 |
| 609 | James Milbauer | 29 | 10 | 8 | 5 | 4 | 9 | 8 | 5 | 3 |
| 610 | Steven Kempers | 45 | 15 | 13 | 8 | 6 | 14 | 11 | 8 | 7 |
| 611 | David McDaniel | 33 | 10 | 5 | 6 | 4 | 12 | 7 | 5 | 2 |
| 612 | Alan Menter | 36 | 12 | 9 | 6 | 4 | 12 | 8 | 6 | 2 |
| 613 | Christopher Nelson | 35 | 11 | 4 | 6 | 4 | 12 | 5 | 6 | 3 |
| 614 | David M. Pariser | 26 | 9 | 4 | 4 | 3 | 9 | 6 | 4 | 3 |
| 616 | Henry Sharata | 31 | 10 | 9 | 5 | 3 | 11 | 9 | 5 | 5 |
| 617 | Stephanie Silos-Badalamenti | 2 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 618 | Stacy Smith | 54 | 18 | 14 | 9 | 5 | 18 | 16 | 9 | 9 |
| 619 | Daniel M. Stewart | 22 | 8 | 6 | 3 | 3 | 7 | 6 | 4 | 2 |
| 620 | Joseph Story | 39 | 12 | 6 | 7 | 5 | 14 | 5 | 6 | 4 |
| 621 | Dow B. Stough | 62 | 22 | 19 | 10 | 10 | 20 | 17 | 10 | 10 |
| 622 | Leonard Swinyer | 66 | 22 | 19 | 11 | 10 | 22 | 18 | 11 | 11 |
| 623 | Naji Tawfik | 46 | 15 | 11 | 8 | 5 | 16 | 9 | 7 | 6 |
| 624 | Helen Mary Torok | 55 | 18 | 16 | 9 | 9 | 19 | 15 | 9 | 8 |
| 625 | Yardy Tse | 10 | 3 | 2 | 2 | 1 | 4 | 4 | 1 | 0 |
| 626 | Zoe Draelos | 39 | 14 | 12 | 6 | 2 | 12 | 11 | 7 | 6 |
| 627 | Hector Wiltz | 78 | 26 | 22 | 13 | 11 | 26 | 22 | 13 | 12 |
| 628 | Joel Schlessinger | 29 | 10 | 1 | 4 | 3 | 10 | 5 | 5 | 3 |
| 629 | Richard Childers | 38 | 12 | 8 | 7 | 5 | 12 | 10 | 7 | 5 |
| 630 | Norman Kanof | 45 | 15 | 14 | 7 | 6 | 16 | 13 | 7 | 7 |

**Study design:** Randomized, Double Blind, Active-Controlled and Vehicle-Controlled, Parallel-Group, Multi-centered

**Indication:** acne vulgaris

**Study arms (dosage, duration, treatment length for each arm):** four study arms:
Clin-RA Gel (clindamycin phosphate 1.2% and tretinoin 0.025%), Clindamycin phosphate 1.2% Gel, Tretinoin 0.025% Gel, and Clin-RA Gel Vehicle duration of treatment was 12 weeks

Topical application of study materials was made to the face once daily prior to bedtime for a period of 12 weeks. Subject selection, selection of treatment duration, and dosages were based on the currently-approved labeling for products containing clindamycin phosphate 1.2% (Clindagel TM) and tretinoin 0.025% (Retin-A® 0.025% Gel).

**Efficacy endpoints (Primary and secondary):**

Primary measurements of efficacy for the comparison between Clin-RA Gel and Clindamycin Gel and Tretinoin, were:

**1)** two out of three of the following lesion counts:
- mean percent change from baseline at Week 12 in inflammatory lesion counts
- mean percent change from baseline at Week 12 in non-inflammatory lesion counts
- mean percent change from baseline at Week 12 in total lesion counts

**2)** percent of subjects who were clear or almost clear at Week 12, as judged by an Evaluator's Global Severity Score.

Primary measurements of efficacy for Clin-RA Gel versus Vehicle were:
- mean percent change from baseline at Week 12 in inflammatory lesion counts,
- mean percent change from baseline at Week 12 in non-inflammatory lesion counts, and
- the percent of subjects who were clear or almost clear at Week 12, as judged by an Evaluator's Global Severity Score.

Secondary measurements of efficacy were:
- mean percent change from Baseline at Weeks 2, 4, and 8 in inflammatory lesions,
- mean percent change from Baseline at Weeks 2, 4, and 8 in non-inflammatory lesions,
- mean percent change from Baseline at Weeks 2, 4, and 8 in total lesions,
- percent of subjects who were clear or almost clear at Weeks 2, 4, and 8, as judged by the Evaluator's Global Severity Score.

**********

**Pivotal Study #2:** "A Multi-Center, Phase 3, Randomized, Double-Blind, 4-Arm Clinical Trial to Compare the Safety and Efficacy of Clin-RA Gel vs. Clindamycin Phosphate 1.2% Gel vs. Tretinoin 0.025% Gel vs. Vehicle in the Treatment of Acne Vulgaris"

**Protocol Number:** 7001-G2HP-07-02

**Study Period:** February 11, 2003 to October 21, 2003

**Has the sponsor stated that this protocol is identical in design to Study #1?** Yes (Section 8.4.2 of ISE)

**Is this an adequate multi-centered trial?** yes

Table 14.1.1: Summary of Subject Enrollment and Evaluability by Investigator

| Site | Investigator | Enrolled | Clin- RA ITT | Clin- RA PP | Clindamycin ITT | Clindamycin PP | Tretinoin ITT | Tretinoin PP | Vehicle ITT | Vehicle PP |
|---|---|---|---|---|---|---|---|---|---|---|
| 700 | Michelle Chambers | 55 | 19 | 10 | 9 | 4 | 18 | 11 | 9 | 2 |
| 701 | Terry Jones | 47 | 16 | 11 | 8 | 8 | 16 | 15 | 7 | 7 |
| 702 | David Kaplan | 29 | 10 | 6 | 5 | 4 | 9 | 5 | 5 | 4 |
| 703 | James Aton | 52 | 17 | 10 | 8 | 3 | 18 | 13 | 9 | 3 |
| 704 | Susan Barker | 27 | 8 | 8 | 5 | 4 | 9 | 7 | 5 | 3 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 705 | Debra Breneman | 51 | 16 | 8 | 9 | 4 | 18 | 9 | 8 | 4 |
| 706 | Alicia Bucko | 78 | 26 | 19 | 13 | 11 | 26 | 18 | 13 | 11 |
| 707 | Sharon Camden | 13 | 4 | 1 | 3 | 0 | 4 | 1 | 2 | 0 |
| 708 | Lawrence Eichenfield | 39 | 14 | 12 | 7 | 3 | 12 | 10 | 6 | 3 |
| 709 | Alan Fleischer | 58 | 19 | 11 | 10 | 9 | 20 | 15 | 9 | 7 |
| 710 | Jonathan Weiss | 21 | 7 | 6 | 3 | 2 | 7 | 6 | 4 | 4 |
| 711 | Adelaide Hebert | 39 | 13 | 11 | 6 | 5 | 14 | 7 | 6 | 5 |
| 712 | Steven Proper | 54 | 18 | 16 | 9 | 8 | 18 | 13 | 9 | 8 |
| 713 | Robert Ilowite | 7 | 2 | 1 | 1 | 1 | 3 | 2 | 1 | 0 |
| 714 | Michael Jarratt | 48 | 16 | 11 | 8 | 7 | 16 | 12 | 8 | 6 |
| 715 | Lewis Kaminester | 24 | 8 | 5 | 4 | 2 | 8 | 5 | 4 | 3 |
| 716 | Robert W. Loss | 40 | 13 | 10 | 7 | 6 | 13 | 10 | 7 | 5 |
| 717 | Keith Loven | 27 | 9 | 6 | 5 | 3 | 8 | 7 | 5 | 2 |
| 718 | Robert Martin | 14 | 5 | 3 | 2 | 2 | 4 | 3 | 3 | 1 |
| 719 | Daniel Groisser | 46 | 15 | 10 | 8 | 5 | 15 | 10 | 8 | 4 |
| 720 | James Robinson | 9 | 3 | 3 | 2 | 2 | 3 | 2 | 1 | 0 |
| 721 | Phoebe Rich | 29 | 9 | 6 | 5 | 5 | 10 | 7 | 5 | 3 |
| 722 | Patricia Westmoreland | 44 | 14 | 10 | 8 | 7 | 14 | 13 | 8 | 6 |
| 723 | Paul Yamauchi | 48 | 16 | 14 | 8 | 8 | 16 | 15 | 8 | 7 |
| 724 | Nancy Egan | 32 | 10 | 9 | 5 | 5 | 11 | 10 | 6 | 6 |
| 725 | Joseph Fowler | 60 | 20 | 8 | 10 | 5 | 20 | 17 | 10 | 8 |
| 726 | Stephen Miller | 33 | 10 | 6 | 6 | 3 | 11 | 7 | 6 | 5 |
| 727 | Daniel Hogan | 90 | 30 | 25 | 15 | 14 | 30 | 22 | 15 | 9 |
| 728 | Jeffrey Sobell | 6 | 2 | 2 | 1 | 0 | 2 | 0 | 1 | 0 |
| 729 | Eric Olson | 24 | 8 | 3 | 4 | 3 | 8 | 5 | 4 | 2 |
| 730 | Marina Peredo | 72 | 24 | 18 | 12 | 11 | 24 | 18 | 12 | 9 |
| 731 | Jennifer Vesper | 72 | 24 | 14 | 12 | 7 | 24 | 11 | 12 | 7 |

**Study Title:** "A Multi-Center, Phase 3, Randomized, Double-Blind, 4-Arm Clinical Trial to Compare the Safety and Efficacy of Clin-RA Gel vs. Clindamycin Phosphate 1.2% Gel vs. Tretinoin 0.025% Gel vs. Vehicle in the Treatment of Acne Vulgaris"

**Study design:** same as trial #1

**Indication:** acne vulgaris

**Study arms (dosage, duration, treatment length for each arm):** same as trial #1

**Efficacy endpoints (Primary and secondary):** same

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

   **Proposed indication from sponsor's draft labeling:** topical treatment of acne vulgaris

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

   **As designed, could endpoints in pivotal trial #2 support labeling?** yes

7. **Are all data sets for pivotal efficacy studies complete for all indications (indications) requested?** see stats filing checklist

8. **Do all pivotal efficacy studies appear to be adequate and well-controlled**

**within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?** yes

**IND number/s:** 65,531
**PreIND Mtg Date:** September 24, 2001
**EP2 Meeting Date:** December 16, 2002
**Agency response to Phase 3 protocols:**
**PreNDA meeting date:** October 1, 2003

**Do endpoints as described by sponsor in pivotal Study 1 conform to previous agency commitments?** yes

**Do endpoints as described by sponsor in pivotal Study 2 conform to previous agency commitments?** yes

**Are the pivotal trials multi-centered?** yes

**Are there adequate numbers of patients enrolled?** yes

9. **Has the applicant submitted line listings in a format to allow reasonable review of the patient data?** yes **Has the applicant submitted line listings in the format agreed to previously by the Division?** yes

10. **Has the application submitted a rationale for assuming the applicability of foreign data (disease specific microbiologic specific) in the submission to the US population?** NA

11. **Has the applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division?** it appears so

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

13. **Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?** yes; literature reports (Section 6)

14. **Has the applicant submitted draft -labeling consistent with 21CFR 201.56 and 21CFR 201.57, current divisional policies, and the design of the development package?** yes **Has applicant included a Word copy of draft-labeling?** not found

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

16. **Has the applicant complied with the requirements of PREA?** yes
    a) **Is this an indication that would be applicable to the pediatric population?** potentially
    b) **What pediatric ages are included in the protocol(s)?** 12 years or older
    c) **Does the sponsor request pediatric labeling?** yes **If yes, what age groups?** down to 12 years of age (draft labeling)

The sponosr requests a waiver for pediatric subjects under 11 years of age (Mar, 26, 004 fax)

17. **Financial disclosure of investigator**

    a) **Does the NDA contain the appropriate form to comply with the filing requirement for Financial Disclosure for Investigators?** yes

18. **From a clinical perspective, is this NDA fileable? If "no", please state below why it is not.** yes

**If certain claims are not fileable please state which claims they are and why they are not fileable.**

Brenda Carr, M.D.
Reviewing Medical Officer

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Medical Team Leader

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

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/s/
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Brenda Carr
4/1/04 02:17:47 PM
MEDICAL OFFICER

Markham Luke
4/1/04 02:54:32 PM
MEDICAL OFFICER
Concur with fileable decisiion.