CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-470

MEDICAL REVIEW

Clinical Review of NDA 21-470

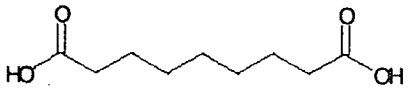
APPLICATION NUMBER:	21-470
SUBMISSION/REVIEW DATES:	
CDER STAMP DATE:	May 15, 2002
FILING DATE:	May 20, 2002
REVIEW COMPLETED:	November 08, 2002
APPLICANT NAME:	Berlex Laboratories
ADDRESS	340 Changebridge Road P.O. Box 1000 Montville, NJ 07045-1000 (973) 487-2000
NAME OF COMPANY OFFICIAL OR CONTACT PERSON	John Hegarty Regulatory Associate Drug Regulatory Affairs 340 Changebridge Road P.O. Box 1000 Montville, NJ 07045-1000 (973) 487-2166
NOMENCLATURE	
TRADENAME	FINACEA™
GENERIC NAME:	azelaic acid
CHEMICAL NAME:	1,7-heptanedicarboxylic acid
CHEMICAL STRUCTURE:	
MOLECULAR FORMULARS:	$C_9 H_{16} O_4$
MOLECULAR WEIGHT:	188.22
DOSAGE FORM:	Cream
ROUTE OF ADMINISTRATION:	Topical
REVIEWERS: EFFICACY:	Brenda Vaughan, M.D., Medical Officer
SAFETY:	Brenda Carr, M.D., Medical Officer
DIVISION:	Dermatologic and Dental Drug Products
DOCUMENTS REVIEWED:	NDA 21-470 (electronic submission) NDA 21-470 BM received 04-19-02 NDA 21-470 NC received 06-03-02 NDA 21-470 SU received 08-01-02 NDA 21-470 NC received 10-09-02 NDA 21-470 BM received 10-29-02

Table of Contents

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Pending agreement by the Sponsor to labeling revisions, from a clinical perspective it is recommended that azelaic acid 15% gel be approved for treatment of the inflammatory papules and pustules in patients with mild to moderate papulopustular facial rosacea.

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

There are no risk management steps being recommended for azelaic acid 15% gel formulation. Nonclinical Phase 4 commitments recommended by Pharm/Tox reviewer follows:

1. The applicant commits to conducting a photoco-carcinogenicity study in male and female mice with the azelaic acid 15% gel.
   Protocol submission: Within 4 months of the date of this letter
   Study Start: Within 6 months of the date of the approval of the protocol
   Final Report Submission: Within 12 months after the study completion.v
2. The applicant commits to conducting an alternative, dermal carcinogenicity study in transgenic mice (Tg.AC assay) with the azelaic acid 15% gel.
   Protocol submission: Within [redacted]months of the date of this letter
   Study Start: Within 6 months of the date of the approval of the protocol
   Final Report Submission: Within 12 months after the study completion.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Azelaic acid (AzA) is a naturally occurring aliphatic dicarboxylic acid, [1,7-heptanedicarboxylic acid, HOOC-$(CH_2)_7$ -COOH], present in animals, humans, and plants. It is a natural constituent in whole grain cereals such as wheat, rye, and barley at concentrations ranging from 0.4 to 7 mg/g. AzA is also endogenously formed from longer chain dicarboxylic acids, metabolism of oleic acid, and -oxidation of C9 monocarboxylic acid. Endogenous plasma concentration and daily urinary excretion of AzA are highly dependent on dietary intake and endogenous metabolism.

FINACEA™(azelaic acid) gel, 15% contains azelaic acid. The marketed azelaic acid is synthesized in the US from a non-plant source (i.e. beef tallow). Currently AzA has been approved in a 20% cream formulation as a topical anti-acne medication (Finevin™ & Azelex®).

Two identical, multicenter, double-blind, randomized, parallel-group studies were conducted in the U.S. to evaluate the efficacy and safety of azelaic acid 15% gel formulation in patients with mild to moderate, stage 2, papulopustular facial rosacea. Results from two Phase 3 clinical trials, Protocol No. A034342 (Clinical Study Report A03125) and Protocol No. 304344 (Clinical Study Report A03126) were submitted by the Sponsor to support efficacy and safety in treatment of papulopustular facial rosacea using FINACEA™(azelaic acid) gel, 15%.

The Sponsor lists two additional Phase 3 studies, Study AE14 (Protocol 90045) and Study AE15 (Protocol 90046), as supportive. These trials were conducted using a 20% cream formulation; therefore, were not used to evaluate efficacy of the 15% gel formulation. A comparative study

report was also submitted as supportive; however, this study was also conducted with a 20% cream formulation of azelaic acid and therefore does not support efficacy of the gel formulation. The Sponsor also conducted a comparative a 15-week comparative study of AzA 15% gel with metronidazole cream under the IND; however, no efficacy data was submitted for review in support of this NDA.

B. Efficacy

Statistical significance was demonstrated in favor of FINACEA™ (azelaic acid) gel, 15% over vehicle in treatment of mild to moderate papulopustular facial rosacea in two identical, multicenter, double-blind, randomized, parallel-group Phase 3 studies. The two primary efficacy endpoints were 1) percent change in inflammatory lesion counts (p-value ≤ 0.0003 & p-value ≤0.0172) and 2) success on Investigator Global Assessment (p-value ≤0.001 & p-value ≤ 0.044).

The Sponsor is asserting a labeling claim for [redacted] Efficacy results although supportive of the primary efficacy endpoint, are not sufficient to support an indication and usage claim for [redacted] since results are not consistent across studies. The Sponsor assessed both decreases from baseline [redacted] and end of study [redacted] ratings. In both studies, statistically significant differences were demonstrated in change in [redacted] (p-value ≤ 0.016 and p-value ≤ 0.006). Although end of study [redacted] ratings was statistically significant (p≤0.002) in Study A03125 this variable was only close to statistical significance (p≤0.079) in Study A03126.

There appears to be some discordance between the effects of active and vehicle on [redacted] in that as an efficacy parameter a statistical difference was noted; however, as a safety parameter no difference was noted between active and vehicle (4% occurrence rate). Overall, baseline disease was mild and no relapse data is available. The submitted data does not support [redacted] as an indication for inclusion in the Indication & Usage Section of the label. [redacted] would be appropriate for inclusion in the clinical trial section of the label.

In the Phase 3 clinical trials, male and female subjects aged 21 to 86 years were enrolled with mild to moderate pustulopapular facial rosacea. A total of 333 patients were exposed to active drug and 331 patients exposed to vehicle in Phase 3. In the Phase 3 efficacy studies, 75% of patients were females and almost all (93%) were of Caucasian origin. As per protocol, the target population was to have moderate stage 2 rosacea with a minimum of ≥8 papules/ pustules, persistent erythema, and telangiectasia; however, at baseline, over half of enrolled patients in both studies were assessed on the Investigator Global Assessment Scale (IGA) as having mild stage 2 rosacea. Additionally at baseline, two patients in the active arm (Study A30126) received scores of minimal stage 2 involvement on the IGA.

Patients were randomized 1:1 (active to vehicle) and topically applied either azelaic acid 15% gel or vehicle, twice daily to the entire facial area (cheeks, chin, forehead, nose). The duration of treatment for each patient was up to 12 weeks. Efficacy, safety, and tolerability were assessed during study visits at Weeks 4, 8, and 12. Patients were instructed that the gel was to be gently rubbed-in (avoiding excessive rubbing). During application, contact with the eyes was to be avoided. Patients were to wait about 30 minutes between application of treatment gel prior to application of cosmetics. No particular special diet was recommended; however, patients were

instructed to avoid any foods and beverages that, in their own experience, might provoke erythema, flushing, and blushing (including spicy food thermally hot drinks including hot coffee and tea, and alcoholic beverages).

As previously mentioned, at baseline in the two pivotal Phase 3 studies over half of the enrolled patients (56% active to 61% vehicle and 56% active to 62% vehicle) did not meet entry criterion of moderate stage 2 rosacea as pre-specified in the protocols (as stated, this could be both Stage 2 and lesser than mild). According to the FDA statistical reviewer, demographics, baseline characteristics, of baseline efficacy measures were similar between the active and placebo groups in both Phase 3 studies. At the request of the FDA clinical review team, the FDA statistician performed a post hoc statistical analysis. Success on the IGA was redefined as improvement over baseline on Investigator Global Assessment. The rationale for modification of the statistical plan was as follows: 1) baseline efficacy characteristics were similar between active and vehicle and 2) the indication for treatment of moderate stage 2 disease could be adjusted in the label. Under this set of circumstances, success at the end of treatment was redefined in patients with a baseline IGA score ≥3 (mild to moderate). For a "success":

- a patient had to achieve an IGA of clear (i.e. score of 0) at the point of measurement if they were mild at baseline (i.e. a score of 2) or
- a patient had to achieve a score of clear or minimal (i.e., 0 or 1) at the end of the study if the baseline score was 3-6 (i.e. "mild to moderate to severe").

Nodule counts, investigator rating of overall improvement, and percent changes in rating of erythema and telangiectasia severity were listed among secondary efficacy variables. No statistically significant improvement of telangiectasia between treatments was found for the ITT-LOCF population. There were no differences in distribution of nodule formation between the active and vehicle.

There is some concern about the large lesion counts in the vehicle groups reported at two sites as compared to other sites for the pivotal studies submitted to the NDA. The Clinical/Stat team recommended inspection by Division of Scientific Investigations (DSI) of the following: Study A03125 (Site 07) and Study A03126 (Site 06). According to Biostat, the effect of removing either of these sites from the studies would not have a meaningful effect on the final efficacy determination.

Safety

The extent of the safety testing was considered adequate to reveal any important safety concerns. Drug-related side effects were limited to cutaneous reactions and were generally mild to moderate in severity. No significant systemic safety concerns were raised. Exposure to the product in the pivotal trials was 12 weeks and was considered adequate relative to the probable marketing use. The appropriate topical safety studies were conducted and revealed that the sponsor's product has the potential to cause irritation, as was borne out in the clinical studies.

The safety database included 1133 subjects who were exposed to the sponsor's product:

- 333 subjects were treated with AzA 15 % gel for the indication of rosacea in the pivotal trials,
- 124 subjects were treated with AzA 15 % gel for the indication of rosacea where the sponsor's product was compared to metronidazole 0.75% gel,

- 383 were treated with AzA 15 % gel in three supportive acne vulgaris trials, and
- 293 subjects were exposed to AzA 15 % gel in the dermal safety studies.

Fifteen additional subjects treated with a AzA 20% cream were included in the safety database for purposes of assessing systemic of exposure to the drug substance.

The pivotal trials were conducted in the U.S., as were the cumulative irritancy and repeat insult patch studies. The acne studies, and the photosensitivity and phototoxicity studies were conducted in Europe.

The 124 subjects who were treated with the sponsor's product in the metronidazole-comparator trial are considered separately in the safety review as their data were submitted in incomplete form as a "draft synopsis" late in the review cycle. However, the synopsis was considered to have contained most of the pertinent safety data, and the AzA 15 % gel data were consistent with that from the pivotal rosacea trials and the acne trials, i.e. the gel was shown to have irritation potential and no systemic safety concerns were raised.

Of the 716 AzA 15% gel-treated subjects in the pivotal rosacea trials and the acne trials, 274 (38%) reported at least one cutaneous adverse event. The most frequently reported cutaneous adverse event for AzA 15% gel subjects was burning/stinging/tingling (148 patients; 21%). Intensity data were recorded for 272 of the 274 AzA 15% gel subjects who reported at least one cutaneous adverse event. Of these, the greatest proportion (24%) of AzA 15% gel subjects had cutaneous adverse events rated by the investigator as mild, while 11% were rated as moderate and 3% were rated as severe.

In the vehicle group, the most frequently reported cutaneous adverse event was scaling/dry skin/xerosis; of 382 subjects, this adverse event was reported in 49 subjects (13%). For vehicle-treated subjects, the intensity levels of cutaneous adverse events were recorded as follows: 15% mild, 8% moderate and 10% severe.

Of the 716 AzA 15% gel-treated subjects, 254 (35%) had at least one cutaneous adverse event considered by the sponsor to have been related to study medication. The maximum relatedness of the cutaneous adverse events to the study medication was assessed as "definite" for 112 (16%), "probable" for 84 (12%), and "possible" for 58 (8%) subjects. "Unlikely" and "no relationship" to study medication were assessed as the maximum relatedness for five (1%) and 14 (2%) subjects, respectively. Systemic adverse events were assessed as related to the study medication for four AzA 15% gel subjects (<1%): pain ("possibly" and "probably" related for one subject each), malaise and headache ("definitely" and "possibly" related, respectively, for one subject each). No systemic adverse events were considered related to study medication in the vehicle group.

Of the 716 AzA 15% gel subjects, 25 (3%) discontinued the study due to cutaneous adverse events. Of these adverse events, burning/stinging/tingling, scaling/dry skin/xerosis, erythema/ irritation; and/or pruritus led to discontinuation most often. Systemic adverse events led to discontinuation for five (1%) AzA 15% gel-treated subjects. Those adverse events were: facial edema, , cerebral thrombosis, pneumonia, malaise, and headache. Of these, the sponsor considered malaise and headache related to study medication ("definitely" and "possibly," respectively).

Of 382 vehicle-treated subjects, six (2%) discontinued the study due to cutaneous adverse events. The highest proportion of vehicle-treated patients discontinued prematurely due to burning/stinging/tingling, scaling/dry skin/xerosis, and/or erythema/irritation. No vehicle-treated subjects discontinued the study due to systemic adverse events.

As discussed, the sponsor submitted a separate "draft synopsis of the clinical study report" for an active-control trial in which their product was compared to Metronidazole 0.75% gel in the treatment of rosacea (A08681). The final study report had not been submitted as the safety review was being concluded.

There was one death in the AzA 15% trials (study A03126). The cause of death was cerebral thrombosis, and the death was not considered to be related to the study medication.

C. Dosing

No clinical dose-finding studies were performed with AzA 15% gel. According to the Sponsor, the incorporation of 20% AzA in the gel base causes a [redacted]. AzA gel study formulation is 15% (SH H 655 BA). A twice-daily treatment regimen was used, consistent with the recommended use of topical AzA 20% cream.

E. Special Populations

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

Most of the subjects in the rosacea and acne trials were Caucasian females. As pertains to rosacea, this is perhaps, at least in part, a function of the population most likely to be affected by this condition. There does not appear to be any reason to consider that there would be significant gender differences in the pharmacology, safety or effectiveness of the AzA 15% gel.

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

Evaluation of Evidence Age (safety)

Nearly 90% of the patients were below age 65; however, according to the Statistical review, it appears that AzA gel is more effective in younger patients although there is evidence that AzA gel is superior to vehicle in patients ≥65. There would not appear to be any significant issues pertaining to use of the product in the geriatric age group.

Evaluation of Evidence for Race or Ethnicity Effects

In regards to efficacy, although the small number of non-Caucasian patients enrolled in the studies is small, there is some evidence that AzA gel may be less effective for non-Caucasian patients than among Caucasian patients. The numbers of subjects in various ethnic and racial groups were too few to permit meaningful conclusions regarding the safety of usage in ethnic/racial subgroups.

Evaluation of Pediatric Program

The Sponsor is requesting a full waiver from the requirement to submit data adequate to assess the safety and efficacy of the drug product for the claimed indication in all relevant pediatric subpopulations (ages 0 to 18 years) in accordance with 21 CFR §314.55(c)(2)(ii) because of the following:

- Rosacea, a chronic inflammatory facial skin disorder, is a common disease affecting approximately 13 million people in the U.S. occurring primarily in middle-aged adults, peaking between the ages of 40 and 50 years.
- Although some case reports exist in the literature, rosacea is rare in children and the Sponsor certifies that it believes that necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed.

The rosacea trials enrolled subjects 18 years and older. This would not appear to significantly impact the safety profile of the drug in the expected marketing population, as the indication sought is not typically seen in subjects younger than 18 years. Such a waiver is appropriate for this product when used for this indication.

Use In Pregnancy

Two subjects in the pivotal trial A03126 became pregnant during the study and completed the trial. Both subjects were randomized to the AzA 15% gel treatment group. While a limited amount of information was provided regarding the pregnancy outcomes, neither infant was reported to have any difficulties: one was reported as "fine" following a "healthy delivery" (gender not provided); the other was reported as a "healthy baby girl" and "born at full term." The data are too limited to draw conclusions about the safety of usage of the sponsor's product during pregnancy.

CLINICAL REVIEW of NDA 21-470
Clinical Review Section

Clinical Review

I. Introduction and Background

Rosacea is a chronic, relatively common disease of unknown origin that primarily affects the central areas of the face characterized initially by recurrent episodes of blushing that becomes persistent dark erythema. Papules, pustules, nodules, vivid red erythema, and telangiectases (the hallmarks of rosacea) follow the episodes of flushing and in severe cases rhinophyma can develop. Rosacea occurs mainly in fair-skinned individuals in the third and fourth decades of life (peaking between the ages of 40 to 50 years). The condition may progress thorough several clinical stages from minor facial flushing to severe disfiguring disease. Although hyperplasia of the sebaceous glands and connective tissue leading to rhinophyma (severe cases) occurs almost exclusively in men, there tends to be a higher incidence of the disease in women. The Sponsor's proposed indication is "topical treatment of inflammatory papules and pustules ——— of rosacea".

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

- Established Name: Azelaic acid
- Proposed Trade Name: FINACEA™
- Sponsor's Proposed Indication: Treatment of inflammatory papules and pustules ——— of rosacea
- Proposed Dose/Regimen: A thin layer of FINACEA™ should be applied twice daily, in the morning and evening, to the entire affected areas and gently massaged into the shin.
- Age Group ≥ 18 years

B. State of Armamentarium for Indication(s)

The only approved topical drugs listed in the electronic PDR for the rosacea indication all contain metronidazole, a member of the imidazole class of antibacterial agents classified therapuetically as an antiprotozole and antibacterial agent. The listed approved drugs are as follows:

MetroCream (Galderma)
MetroGel (Galderma)
MetroLotion (Galderma)
Noritate Cream (Dermik)

C. Important Milestones in Product Development

Regulatory Background

Pre-IND/End of Phase 2 Meeting held September 27, 2000
Pre-NDA Meeting held August 30, 2001

Pertinent regulatory history pertaining to the development of the NDA

AzA gel 15% is a [redacted]

The rosacea indication is being studied under IND 61,324. Currently, topical AzA is approved in the US and Europe as a 20% cream.

No clinical dose-finding studies were performed with AzA 15% gel. According to the Sponsor, the incorporation of 20% AzA in the gel base causes a [redacted] therefore, a lower AzA content was selected for the AzA 15% gel (SH H 655 BA). A twice-daily treatment regimen was used based on the recommended use of topical AzA 20% cream for the acne vulgaris indication.

D. Other Relevant Information

Finacea (azelaic acid gel [redacted] contains azelaic acid (AzA), a naturally occurring, straight-chained, saturated 9 carbon dicarboxylic acid (HOOC-$(CH_2)_7$-COOH). AzA has been categorized and approved as a topical anti-acne medication (Finevin™ & Azelex®). In acne, AzA has been characterized as an antikeratinizing and antibacterial agent. The mechanism of action of AzA 15% gel in pathogenic events of rosacea is unknown; however, thought to include an anti-inflammatory effect.

E. Important Issues with Pharmacologically Related Agents

Azelaic acid is a naturally occurring saturated dicarboxylic acid. AzA is currently marketed in the US in a topical cream formulation under Allergan's approved NDA 20-428. Berlex and Allergan co-market the drug product under NDA 20-428 using the tradenames, Finevin™ (AzA cream, 20%) and Azelex® (AzA cream, 20%), respectively. Berlex's parent company, Schering AG, Berlin, Germany, manufactures the drug substance that is used in both the approved cream formulation and the gel formulation that is the subject of this NDA. [redacted] drug substance is used for both formulations.

Since 1988, AzA 20% cream (oil-in-water emulsion) has been authorized for marketing in over 86 countries worldwide and marketed in 79 countries for the indications acne vulgaris and melasma under the tradenames: Skinoren ®, Azelan ®, Azalea ®, Cutacelan® and in the US as Azelex ®. AzA cream, 20% is approved in the US as Azelex® and Finevin™ under NDA 20-428, which is held by Allergan Inc, Irvine, CA. Berlex Laboratories is an approved distributor of Finevin™ (azelaic acid) cream, 20% under NDA 20-428.

According to the current Azelex® label, there have been isolated reports of hypopigmentation after use of azeleic acid, and the label advises that patients with dark complexions be monitored for early signs of hypopigmentation, since use of the product has not been well-studied in these patients. The following information is provided in the "Adverse Reactions" section of the Azelex package insert:

"During U.S. clinical trials with AZELEX®, adverse reactions were generally mild and transient in nature. The most common adverse reactions occurring in approximately 1-5% of patients were pruritus, burning, stinging and tingling. Other adverse reactions such as erythema, dryness, rash, peeling, irritation, dermatitis, and contact dermatitis were reported in less than 1% of subjects. There is the potential for experiencing allergic reactions with use of AZELEX®.

In patients using azelaic acid formulations, the following additional adverse experiences have been reported rarely: worsening of asthma, vitiligo depigmentation, small depigmented spots, hypertrichosis, reddening (signs of keratosis pilaris), and exacerbation of recurrent herpes labialis ."

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

A. Chemistry

The CMC review has not been completed.

B. Animal Pharmacology and Toxicology

According to the Pharm/Tox review, the application is approvable from a pharmacology-toxicology perspective provided that the recommended changes in the label outlined in the review are incorporated into the final label for Finacea gel.

In the skin and other organs, 5α-reductase converts testosterone to dihydrotestosterone. Because AzA inhibits 5α-reductase in vitro, the possibility of anti-androgenic effects on male offspring was investigated as part of the reproduction toxicology program. According to the sponsor, AzA had no effect on the development of genitalia, including anogenital distance, in offspring of rat dams orally administered 2500 mg/kg/day of AzA during the entire reproductive period or during late gestation and lactation.

The sponsor reported that local tolerance and ocular tolerance studies of AzA were conducted primarily with the 20% cream formulation; however, two studies were conducted with the 15% gel. Single or repeated applications of AzA 15% gel or the placebo gel formulation to the intact skin of albino rabbits produced slight incompatibility reactions. AzA was not a contact sensitizer in a maximization test conducted in guinea pigs. Primary, ocular tolerance studies in rabbits revealed moderate to severe ocular irritation with a preservative-free formulation of AzA 20% cream. This irritation was judged to be mainly due to AzA itself because the vehicle alone caused only slight irritation. Based on the results of these studies, patients should be advised to avoid contact with the eyes during application of topical preparations containing AzA.

Reviewer's comment: The pharmacology/toxicology reviewer's conclusions included that 1) "... the general toxicology studies conducted for azelaic acid appear to be adequate. No additional general toxicology studies are recommended for Finacea (azelaic acid 15%) gel at this time (p.13 of review) " 2) The design of the peri-and post-natal developmental study in rats...covers the critical period of concern (period of sexual maturation). No effects were noted on the development (or sexual maturation)of the male or female fetus in this study. In addition, pharmacokinetic studies have demonstrated that after oral administration of azelaic acid, very little (<0.1%) or no azelaic acid crosses the placenta in rabbits and rats, respectively. It would be anticipated that after topical administration of the 15% azelaic acid gel, the fetus would probably not be exposed to azelaic acid, which provides an additional measure of comfort for not being concerned about the possible inhibition of 5 -reductase in the fetus during developmen (p.19)."

C. Microbiology

No anti-microbial claims are being made as a mechanism of action for rosacea indication. According to the submission, AzA 15% gel is a non-sterile, topical drug product which contains benzoic acid (~~~) as a preservative. Additionally, the Sponsor asserts that study results confirms that the drug meets the United States Pharmacopeia (USP) requirement for preservative effectiveness over extended periods and when subjected to microbial challenge.

D. Statistics

According to the Statistical Review, from a statistical point of view, both in terms of lesion counts and the investigator's global assessment, there were statistically significant differences in favor of AzA over its vehicle.

E. Biopharmaceutics

See Biopharm review for details of the PK studies.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

AzA, an aliphatic dicarboxylic acid [1,7-heptanedicarboxylic acid, HOOC-$(CH_2)_7$ -COOH], is naturally occurring and found in wheat, rye, and barley at concentrations ranging from 0.4 to 7 mg/g. Dietary intake of AzA from just 1 ounce of cereal is estimated to be 11 to 196 mg. AzA was the first dicarboxylic acid proposed as an alternative energy substrate in parenteral nutrition. Studies have been conducted accordingly using a 10-g dose as an intravenous infusion over 90 minutes with no major safety issues.

AzA is also endogenously formed from longer chain dicarboxylic acids, metabolism of oleic acid, and -oxidation of C9 monocarboxylic acid. Endogenous plasma concentration and daily urinary excretion of AzA are highly dependent on dietary intake and endogenous metabolism. Pharmacokinetic studies in humans demonstrate a low systemic burden of AzA after topical application of AzA 20% cream, and that plasma concentration and daily urinary excretion of AzA are in the range of values observed in subjects on a normal diet.

Among the PK studies submitted, the systemic absorption of AzA 15% gel was assessed in a 12-week, randomized, double-blind, multicenter study comparing the efficacy and safety of AzA 15% gel with its vehicle in patients with moderate, papulopustular facial rosacea . Plasma AzA concentrations (predose and 1, 2, and 4 hours postdose) were monitored in 27 rosacea patients from 1 study center who had received treatment for at least 8 weeks.

According to the Sponsor, although plasma AzA concentrations in rosacea patients treated with AzA 15% gel were consistently higher compared with the vehicle group, these values were all within the range observed in volunteers (52 ng/mL) and acne patients (83.8 ng/mL) on a regular diet, and in volunteers (136 ng/mL) and acne patients (89.6 ng/mL) treated with AzA 20% cream. According to the Sponsor, this indicates that topical treatment with AzA 15% gel did not increase the normal systemic burden of AzA beyond that derived from dietary and endogenous sources.

According to the sponsor, measurement of the urinary excretion of AzA in acne patients treated twice daily for eight weeks with either AzA 20% cream or AzA 15% gel showed no specific

differences between the cream and gel formulation. Also, the plasma AzA concentrations measured in rosacea patients treated with AzA 15% gel were well within the range observed in acne patients during long-term treatment with AzA 20% cream. The sponsor considers this to suggest that the results of clinical chemistry determined in two studies with AzA 20% cream over 5 months and 12 months, respectively, may also apply to AzA 15% gel.
In neither of the two studies were any AzA-related effects of pathological significance found on enzymes, lipids, carbohydrates, electrolytes and other clinical chemistry parameters or on blood counts and the urine analysis. Deviations from normal values in single cases were attributable to concurrent diseases, nutrition, and to other treatment-unrelated factors expected during such long therapy duration.

B. Pharmacodynamics
The Sponsor conducted five Phase 1 safety studies. All Phase 1 safety studies listed below with the exception of Study AQ63 (Scarification Test Study conducted in Germany) were conducted with the to-be-marketed formulation. These studies are listed below:

- ✔ Study A04832: "A 21-Day, Vehicle-Controlled, Observer-Blind Study To Evaluate The Local Tolerability Of Azelaic Acid, 15% Gel In Healthy Volunteers, Using A Cumulative Irritant Patch Test Design" conducted in the U.S between April 30, 2001 and June 4, 2001.
- ✔ Study A04766: "A Randomized, Vehicle-Controlled, Observer-Blind Study to Evaluate the Sensitizing Potential of Topically Applied Azelaic Acid, 15% Gel in 200 Healthy Volunteers, using a Human Repeat Insult Patch Test".
- ✔ Study AZ01: "A 5 Days Randomized Controlled Double Blind Safety Study In Twelve Healthy Volunteers On The Phototoxi Potential Of Azelaic Acid Hydrogel SH H 655 BA And Its Vehicle After A Single Topical Occlusive Treatment", conducted in Germany.
- ✔ Study AZ00: "A 33 Days Randomized, Controlled, Double-Blin, Intra-Individual Safety Study In Twenty-Four Healthy Volunteers On The Photosensitizing Potential Of 15% Azelaic Acid Hydrogel Sh H 655 BA And Its Vehicle In A Maximization Test Design (Repeated Insult Patch/Photopatch Test) With 7 Topical Occlusive Treatments" conducted in Germany.
- ✔ Study AQ63: Scarification Test Study conducted in Germany.

IV. Description of Clinical Data and Sources

A. Overall Data
This efficacy review is based primarily on data submitted by the Sponsor. The safety data reviewed were from clinical trials conducted by the sponsor in the U.S. and Europe: two rosacea pivotal trials (A03125 and A03126), four dermal safety studies (A04766, A04832, AZ00, and AZ01), and four supportive acne trials (AQ87, AQ86, AU36, and A03160; conducted in Europe). Additionally, on October 9, 2002, the reviewer received a "draft synopsis" of the study report for trial A08681, in which the sponsor's product was compared to Metronidazole 0.75% cream in the treatment of rosacea.

B. Tables Listing the Clinical Trials
Efficacy review is based on the two Phase 3 studies that follows:

According to the submission the following changes were in response to 08 May 2001 FDA letter. Enrollment was completed 30 Mar 2001. On 08 May 2001, the FDA offered some clinical and statistical comments. According to the Sponsor, selected comments and the actions taken in the analysis to address them are as follows:

- FDA suggested that the washout periods should be a minimum of 4 weeks for all pre-study topical and systemic rosacea medications and medications that might affect rosacea, rather than the 2 week minimum for topical and 4 week minimum for systemic medications used in this study. In response, separate analyses were conducted on a subset of the ITT population (the modified intent-to-treat [MITT] population) who met the FDA recommended washout periods. These analyses included inflammatory lesion counts and investigator global assessments.
- FDA suggested that the percent change in lesion count from baseline could be added as an additional endpoint. Percent change in lesion count was included as an additional secondary endpoint.
- FDA proposed additional analyses using the investigator's global assessment at the termination visit. FDA suggested computing a static dichotomous endpoint (success or failure) based on the investigator's global assessment score at the last visit.
  The recommended analyses were performed, defining success in 2 ways: (1) a rating of ***clear*** and (2) a rating of ***clear, minimal, or mild***. Patients who prematurely withdrew from the study because of lack of efficacy were coded as failures regardless of their end of treatment assessment. For both definitions of success, the frequency and percent of patients who were a success were summarized and compared across treatment groups using a CMH general association test controlling for study center. The homogeneity of the treatment effect across centers was assessed using the Breslow-Day test at the 15% significance level.

Reviewer's comments:

At the Pre IND/End of Phase 2 meeting held between the Sponsor and the Division on 09/27/00, in addition to other recommendations, the Division provided the Sponsor with recommendations for primary efficacy endpoints for rosacea and suggested washout periods prior to initiation of the Phase 3 studies. The Division did not recommend separate analyses be conducted on a subset of the ITT population (the modified intent-to-treat [MITT] population) who met the washout periods recommended by the Division. Washout periods are to avoid possible drug-drug interactions and to avoid carry-over effect.

Study Results Sponsor's Protocol No. 304342 (Clinical Study Report A03125)

(Note: Clinical Study Report is referred to as Study in the body of the review).

A total of 428 patients screened for entry into the study, 329 patients (164 to AzA 15% gel and 165 to vehicle) were randomized and received study medication with 99 screen failures. Of the 329 patients who received study medication, 283 (86%) completed the study, and 46 (14%) patients discontinued the study prematurely.

List of investigators

Site Number	Name of Principal Investigator	Number Enrolled
01	Charles Birbara, MD	40
02	Terry Jones, MD	24
03	Leslie Capin, MD	30
04	Boni Elewski, MD	20

Report No. (Protocol No.)	Investigator(s) (Country) Publication	Start Date (mm/yy) Duration of Treatment Completion Status	Study Design Study Phase	Dose Treatment	Number of Subjects Who Received Treatment[a]	Age Range in Years (Mean) Sex Race	1) Location of Report 2) Location of Publication 3) Location of CRF Tabulations 4) Location of CRFs
2. ROSACEA							
2.1 Controlled Clinical Studies With Case Report Forms Available							
2.1.1 Controlled Clinical Studies With the Gel Formulation							
A03125 (304342)	Birbara C Capin L Elewski B Heffernan M Jones T Kaminester L Lawlor K Lee-Rugh S Ling M Proffitt J Stewart D Thiboutot D Weiss J All study sites were located in the US.	01/01 12 weeks Completed	Double-blind, randomized, vehicle-controlled, parallel-group, multicenter Phase 3	15% AzA gel Vehicle gel	164 165	21-84 (48.0) 24-77 (49.2) 85 Males 244 Females 314 Caucasians 2 Blacks 11 Hispanics 1 Asian 1 Other	1) a03125.pdf 2) NA 3) define.pdf 4) 044.pdf
A03126 (304344)	Purcell S T Gold M Hebert A Herzog J Katz I Kempers S Maloney M Matheson R Nigra T Parker D Rafal E Rist T Stone K Tschen E All study sites were located in the US.	02/01 12 weeks Completed	Double-blind, randomized, vehicle-controlled, parallel-group, multicenter Phase 3	15% AzA gel Vehicle gel	169 168	24-85 (47.6) 23-78 (47.0) 94 Males 241 Females 300 Caucasians 4 Blacks 29 Hispanics 2 Others	1) a03126.pdf 2) NA 3) define.pdf 4) 182.pdf

APPEARS THIS WAY
ON ORIGINAL

In addition to the pivotal trials, information and data from the following studies were reviewed for the safety review:

Trial (where conducted) Indication	**Study Design or Type Phase**	**Treatment: # of subjects Start Date;Duration**	**Age range in years (mean) Gender Race**
AQ86 (Portugal, Germany, Greece) Acne	Double-blind, randomized, vehicle-controlled, parallel-group, multicenter Phase 3	Aza 15% gel: 78 Vehicle gel: 51 3 months	13-43 (21.0) 14-45 (21.3) 54 males; 75 females 126 Caucasians; 1 Black; 1 Hispanic; 1 Asian
AQ87 (Germany, Norway, Austria) Acne	Double-blind, randomized, vehicle-controlled, parallel-group, multicenter Phase 3	Aza 15% gel: 176 BPO 5%*: 175 4 months	13-45 (21.0) 11-42 (20.9) 135 males; 216 females 340 Caucasians; 1 Hispanic; 6 Asian; 4 Others
AO3160 (Germany, the Netherlands, Greece) Acne	Open-label, randomized, active-controlled, parallel-group, multicenter Phase 3	Aza 15% gel: 114 Clindamycin 1% gel: 115 4 months	14-50 (22.1) 13-38 (20.1) 102 males; 127 females 224 Caucasians; 2 Blacks; 1 Hispanic; 2 Asians
A04832 (U.S.)	21-Day Cumulative Irritant Patch Test Phase I	Aza 15% gel: 37 SLS 0.1%: 37 Vehicle: 37	19-75 (44.7) 8 males; 29 females 33 Caucasians; 1 Black; 3 Hispanics
AO4766 (U.S.)	Repeat Insult Patch Test Induction Phase 1	Aza 15% gel: 220 SLS 0.1%: 220 Vehicle: 220	18-75 years 55 males; females 187 Caucasians; 1 Black; 22 Hispanics; 7 Asians; 3 Others
AZ00 (Germany)	Photosensitization Potential Study Phase 1	Aza 15% gel: 24 Vehicle: 24	18-60 (36.1) 3 males; 21 females 24 Caucasians
AZ01 (Germany)	Photoxicity Potential Study Phase 1	Aza 15% gel: 12 Vehicle: 12	26-62 (45.0) 1 male; 11 females 12 Caucasians
AU36 (Germany) Acne	Double-blind, randomized, controlled, parallel-group, single-center Phase 2	Aza 15% gel: 15 Aza 20% cream: 15 01/98; 8 weeks	16-32 (23.6) 16-43 (24.7) 12 males; 18 females 30 Caucasians
AE14 (Norway, Germany, Hungary) Rosacea	Double-blind, randomized, vehicle-controlled, parallel-group, multicenter Phase 3	Aza 20% cream: 76 Vehicle: 39 10/90; 3 months	27-80 (48.4) 24-73 (50.6) 56 males; 59 females Race information not available

AE15 (United Kingdom) Rosacea	Double-blind, randomized, vehicle-controlled, intraindividual comparison, single center Phase 3	Aza 20% cream: 35 Vehicle: 35	24-82 (53.7) 16 males; 19 Females 35 Caucasians

C. Postmarketing Experience

AzA 15% gel is approved in Australia and the Czech Republic for treatment of acne vulgaris, and in Switzerland for the treatment of mild to moderate acne vulgaris. However, according to the Sponsor, it has not yet been launched anywhere due to business reasons. Review of Marketing Authorization Applications (MAAs) for treatment of acne vulgaris are currently ongoing in Austria, Hungary, and Poland. No MAAs have been withdrawn. No MAAs have been submitted for indications regarding the treatment of rosacea.

D. Literature Review

The literature submitted was not reviewed in depth since the articles did not appear to relate to efficacy data with use of the gel formulation.

V. Clinical Review Methods

A. How the Review Was Conducted

Dr. Brenda Vaughan reviewed the efficacy related materials and Dr. Brenda Carr reviewed the safety for this NDA. Frequent consultations and clinical group meetings were conducted around the review of this NDA. Additionally discussions were held with other disciplines involved in the review of this NDA (Chemistry/CMC, Pharmacology-Toxicology, Biopharmaceutics, Biometrics). The two separate parts of the NDA review were combined into this one review.

Two Phase 3 clinical trials, Clinical Study Report A03125 (Protocol 304342) and Study A03126 (Protocol 304344), were considered pivotal in support of efficacy and safety with use of azelaic acid (AzA) 15% gel formulation in treatment of rosacea. The Sponsor submitted two additional Phase 3 studies, Study AE14 (Protocol 90045) and Study AE15 (Protocol 90046), as supportive in which a 20% cream formulation of AzA was used. These clinical trials do not support efficacy of the 15% formulation. Additionally, the Sponsor submitted a study report as supportive and this study also was conducted with a 20% cream formulation of azelaic acid.

The Integrated Summary of Safety includes a review of safety data from the two rosacea studies conducted in the U.S. (the pivotal trials, A03125 and A03126) and four supportive acne studies conducted in Europe (AQ87, AQ86, A03160, and AU36). All were phase 3 trials except for study AU36 which was an exploratory phase 2 study in which the onset of action of AzA 15% gel and AzA 20% cream were compared. The formulation used in all of studies was the to-be-marketed AzA 15% gel (formulation code SH H 655 BA). Vehicle served as the control in the rosacea pivotal studies and in one acne study (AQ86), while AzA 20% cream, benzoyl peroxide 5% and clindamycin 1% gel were the comparators in the remaining three acne studies (AU36, AQ87, and A03160, respectively).

The safety data from each rosacea pivotal trial were reviewed separately and with the same emphasis. Subjects treated with AzA 20% cream (AU36) were included in the safety database for purposes of assessing systemic exposure to the drug substance. The safety review does not consider the benzoyl peroxide 5% and clindamycin 1% gel data from the acne trials.

On October 9, 2002, the reviewer was provided a "draft synopsis" of the clinical study report for trial A08681, "A 15-week, randomized, double-blind multicenter study comparing the clinical efficacy and safety of Azelic Acid 15% gel (SH H 655 BA) with Metronidazole 0.75% gel in patients with papulo-pustular facial rosacea." The safety data provided in the draft synopsis were reviewed; the efficacy data were not. The data from the draft synopsis are discussed separately since they were incomplete.

Four phase 1 dermal safety studies (A04766, A04832, AZ00, and AZ01) were conducted with the to-be-marketed formulation. These data were reviewed separately and with the same emphasis.

Three additional studies did not employ the to-be-marketed formulation: two phase 3 studies (AE14 and AE15) studied a AzA 20% cream formulation, and a phase 1 scarification study (AQ63) studied two other AzA 15% gel formulations (SH H 655 A and SH H 655 B). Studies AE14, AE15, and AQ63 are briefly commented upon in the safety review.

The sponsor submitted a Periodic Safety Update Report on July 30, 2002. The safety update is discussed separately in the Integrated Summary of Safety.

B. Overview of Materials Consulted in Review

Materials reviewed included an official electronic document, Reviewer's Aid on CD-ROM, and paper copies (requested by the clinical review team) designated as Volumes 1 of 1 and 1-30.

The Medical Officer's review of IND 61,324, N-020 (submission date October 10, 2001) was reviewed. Submission N-020 contained the protocol for the phase 3 trial, "A 15-week, randomized, double-blind multicenter study comparing the clinical efficacy and safety of Azelic Acid 15% gel (SH H 655 BA) with Metronidazole 0.75% gel in patients with papulo-pustular facial rosacea." The safety review was otherwise based on data and information either orginally contained in the NDA or received in response to requests for additional information.

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

DSI audits have been requested; however, results are unknown at the time of this review.

Randomly-selected case report forms from the pivotal rosacea studies were reviewed. Case report forms were not available from the acne trials. All available case report forms for serious adverse events were reviewed.

Protocol/Site Identification:

There is some concern about the large lesion counts in the vehicle groups reported in these sites as compared to other sites for the pivotal studies submitted to the NDA, the following protocols/sites have been recommended for inspection.

Indication	Study#/Protocol #	Site (Name and Address)	# of Patients Enrolled
Moderate Papulo/Pustular Rosacea	Study: A03126 Protocol: 304344	6 Dr. Steven Kempers	18

Moderate Papulo/Pustular Rosacea	Study: A03125 Protocol: 304342	7	Dr. Kean Lawlor, MD	40

D. Were Trials Conducted in Accordance with Accepted Ethical Standards
According to the Sponsor. The studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization (ICH)-GCP guidelines.

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

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions
In two identical, multicenter, double-blind, randomized, parallel-group Phase 3 studies conducted with FINACEA™ (azelaic acid) gel, 15%, statistical significance over vehicle was demonstrated for two primary efficacy endpoints. The primary efficacy endpoints were percent change in inflammatory lesion counts (p-value = 0.0003 & p-value = 0.0172) and success on the Investigator Global Assessment (p-value = 0.001 & p-value = 0.044).

The Sponsor is asserting a labeling claim for [redacted] efficacy variable). Efficacy results although supportive of the primary efficacy endpoint, are not sufficient to support an indication and usage claim for treatment of [redacted] since results are not consistent across studies. The Sponsor assessed both decreases from baseline in [redacted] and end of study [redacted] ratings. In both studies, statistically significant differences were demonstrated in change in [redacted] (p-value ≤ 0.016 and p-value ≤ 0.006). Although end of study [redacted] ratings was statistically significant (p≤0.002) in Study A03125 this variable was only close to statistical significance (p≤0.079) in Study A03126.

There appears to be some discordance between the effects of active and vehicle on [redacted] in that as an efficacy parameter a statistical difference was noted; however, as a safety parameter no difference was noted between active and vehicle (4% occurrence rate). Overall, baseline disease was mild and no relapse data is available. The submitted data does not support [redacted] as an indication for inclusion in the Indication & Usage Section of the label. [redacted] would be appropriate for inclusion in the clinical trial section of the label.

B. General Approach to Review of the Efficacy of the Drug
Data from two Phase 3 clinical trials conducted in the US were submitted for review. Male and female patients aged 21 to 86 years were enrolled in the studies with a total of 333 patients

exposed to active drug and 331 patients exposed to vehicle. In these Phase 3 studies, 75% of patients were females and almost all (93%) were of Caucasian origin. Patients with moderate stage 2 rosacea with a minimum of ≥8 papules/ pustules, and persistent erythema and telangiectasia were slated as the target population.

At baseline in both Phase 3 studies, over half of enrolled patients at baseline had an Investigator Global Assessment (IGA) score of mild stage 2 rosacea. According to the entry criteria, patients were to have moderate stage 2 rosacea. The Sponsor was queried as to why patients with a score less than 4 on the IGA at baseline were not considered protocol violations. The Sponsor indicated that the eligibility criteria did not name a definite score point on the IGA scale. Nonetheless, the IGA scores at baseline should have reflected entry criteria (stage 2 disease of moderate severity). However, according to the FDA Statistician, baseline characteristics were comparable for the active and vehicle treatment arms in both Phase 3 studies.

At the Pre-NDA meeting, the Division recommended statistical analysis based on the intent-to-treat (ITT) population with Last-Observation-Carried-Forward (ITT-LOCF). In the NDA submission, the Sponsor refers to the ITT-LOCF recommended by the Division as the R-LOCF (revised method-LOCF) population. The primary efficacy endpoints recommended by the Division were:

- change in inflammatory lesions from baseline at the end of study and
- the proportion of patients in the active group vs. the vehicle group who achieve a static global assessment score of 0 (clear) and 1 (minimal) at the end of study as described in the Investigator's Global Assessment Score.

The Division recommends that the static Investigator Global Assessment at the end of treatment be dichotomized (success/failure). At entry in the two pivotal Phase 3 studies, over half of the enrolled patients (56% active to 61% vehicle and 56% active to 62% vehicle) did not meet entry criterion of moderate stage 2 rosacea as pre-specified in the protocols. According to the FDA statistical review, baseline characteristics were similar between the active and placebo groups in both Phase 3 studies. As suggested by the clinical review team, statistical analysis was modified by the FDA statistician to include improvement over baseline for success on Investigator Global Assessment. The statistical plan was modified because of the following: 1) demographics, baseline characteristics, of baseline efficacy measures were similar between active and vehicle and 2) the indication for treatment of moderate stage 2 disease could be adjusted in the label to treatment of mild stage 2 disease. Under this set of circumstances, the clinical review team deemed it appropriate to modify the definition of "success" at the end of treatment. To be considered a "success" at the end of treatment patients with a baseline IGA score ≥3 (mild to moderate) had to:

- achieve an IGA of clear (i.e. score of 0) at the point of measurement if they were mild at baseline (i.e. a score of 2) or
- achieve a score of clear or minimal (i.e., 0 or 1) at the end of the study if the baseline score was 3-6 (i.e. "mild to moderate" to "severe").

C. Detailed Review of Trials by Indication
Indication #1 Treatment of Moderate Papulopustular Facial Rosacea
Sponsor's Protocol No. 304342 (Report A03125)
Title: "A 12-Week, Randomized, Double-Blind Multicenter Study Comparing

The Clinical Efficacy And Safety Of Azelaic Acid 15% Gel (SH H 655 BA) With Its Vehicle in Patients With Moderate, Papulopustular Facial Rosacea"
(Study Dates: January 17, 2001 to July 6, 2001)
Protocol
Objective/Rationale
The objectives of this study were to evaluate the efficacy and safety of AzA 15% gel compared to its vehicle (gel base) in male and female patients with moderate, papulopustular, rosacea (stage 2 rosacea) during a 12-week treatment period.
Overall Design
This was a Phase 3, multicenter, double-blind, randomized, parallel-group study to evaluate the efficacy and safety of azelaic acid 15% gel in patients with moderate, papulopustular facial rosacea. Following eligibility evaluation, patients enrolled in the study applied either azelaic acid 15% gel or vehicle topically, twice daily to the entire facial area. The duration of treatment for each patient was up to 12 weeks. Efficacy, safety, and tolerability were assessed during study visits at Weeks 4, 8, and 12.

The target population was patients with stage 2 rosacea. Patients with very mild rosacea (stage 1) and severe forms of rosacea (stage 3) were to be excluded. Stages of rosacea were characterized as follows:

Stage 1- fluctuating erythema with no or only very few papules and/ or pustules
Stage 2- persistent erythema, telangiectasia and papules/ pustules
Stage 3- large inflamed nodules, furunculoid infiltrations, tissue hyperplasia (rhinophyma and other phymas)

Population, procedures
Inclusion criteria
Patients were eligible for inclusion in the study if they met all of the following criteria:

- Moderate, papulopustular facial rosacea (stage 2 rosacea) with:
  - ✔ A minimum of 8 (≥8) and a maximum of 50 (≤50) inflamed papules and/or pustules,
  - ✔ Persistent erythema and telangiectasia
- Male and female patients
- Age ≥18 years
- Ability and willingness to accept and comply with the administration of the investigational drugs over 12 weeks and to comply with the required medical examinations
- Signed informed consent

Reviewer's comments:

- *According to the Sponsor's Investigator's Global Assessment (IGA) scoring scale, moderate, papulopustular facial rosacea (stage 2 rosacea) is a score of 4. Moderate stage 2 rosacea is described as pronounced number of papules and/or pustules; moderate erythema; mild to moderate telangiectasia.*
- *The Sponsor was advised that it might be difficult to demonstrate statistical superiority with less than 10 lesions present at entry.*

Exclusion criteria
Patients who met any of the following criteria were not to be included in the study:

- Mild rosacea (stage 1 rosacea) characterized by transient erythema and/or the absence of papules/ pustules
- Severe rosacea (stage 3 rosacea) characterized by accompanying rhinophyma or other phymas, rosacea conglobata, and rosacea fulminans
- Rosacea with marked ocular manifestations
- Steroid rosacea
- Presence of dermatoses that might interfere with rosacea diagnosis and/or evaluation such as acne, facial psoriasis, seborrhoic dermatitis, perioral dermatitis, and various telangiectatic states basically not related to rosacea
- Treatment with oral isotretinoin (Accutane, Roche Dermatologics) during the 6 months prior to study entry
- Treatment of the face with topical retinoids (tretinoin, isotretinoin) during the 2 weeks prior to study entry
- Treatment with oral antibiotics - tetracyclines, erythromycin, metronidazole Œ during the 4 weeks prior to study entry
- Treatment with topical antibiotics - tetracyclines, erythromycin, metronidazole - during the 2 weeks prior to study entry
- Treatment with systemic corticosteroids during the 4 weeks prior to study entry
- Treatment of the face with topical corticosteroids during the 2 weeks prior to study entry
- Treatment of the face with topical imidazole antimycotics during the 2 weeks prior to study entry
- Use of a sauna during the 2 weeks prior to study entry and during the study
- Facial laser surgery for telangiectasia (or other conditions) during the 6 weeks prior to study entry
- Concurrent use of any treatment (other than study medication) that affects rosacea:
  - ✔ Systemic and/or topical antibiotics
  - ✔ Systemic and/or topical corticoids
  - ✔ Systemic and/or topical retinoids
  - ✔ Topical imidazole antimycotics
  - ✔ Chronic treatment with nonsteroidal anti-inflammatory drugs (NSAIDs)
  - ✔ Drugs causing acneiform eruptions (eg, tuberculostatics [isoniazid], anabolic hormones)
- History of hypersensitivity to propylene glycol or to any other ingredient of the trial drug

Study Plan

This was a 12-week study consisting of the following visits screening, baseline, and treatment phase at weeks 4, 8, and 12.

Screening

During pretreatment screening, the basic eligibility of each patient was established. If a patient did not require washout then the screening and baseline visits coincided, and both screening and baseline activities were completed in 1 visit.

Baseline visit (Day 0)
At baseline, the general patient data were recorded and documented on the CRF. Investigator's global assessment of clinical appearance (severity) of stage 2 rosacea on a static score from 0 to 6, baseline intensity (severity) of erythema and telangiectasia, baseline number of facial papules and pustules, and any untoward cutaneous signs or symptoms were recorded.

Standardized facial photographs were taken of all consenting patients at Study Center No.13. Photographs were for demonstration purposes only.

Randomization
Eligible patients were randomly assigned 1 to 1 to active or vehicle treatments groups. The randomization list was prepared by means of a random number generator program.

Blinding
The study medication was blinded in accordance with the randomization list that was generated and stored at Berlex Laboratories. The study medication was packaged at Berlex Laboratories.

AZA gel, 15% and its vehicle were not identical in appearance in that the vehicle was translucent and active was opaque. According to the briefing package submitted by the Sponsor at the PreIND/End-of-Phase2 meeting held on 09/27/00, this difference in appearance is caused by the incorporation of the active drug substance into the vehicle; therefore, to ensure blinding during patient selection and during study treatment:

1. The tube openings were sealed with a metal membrane. Even after removal of the tube screw cap it is not possible to get access to the study medication without destroying that metal membrane.
2. The study medication was not be dispensed by the investigator, but was to be dispensed by study nurses (practice /clinic nurses) *not involved with the selection and the assessment* of the patients. The study nurse was to dispense two carton boxes (each containing one tube) per patient at baseline and at the control visits after 4 and 8 weeks
3. At the control visits after Week 4, 8 and 12, patients were to return empty, partially used, and unused tubes to the study nurse *before* being examined by the investigator. The medication has to be returned in the carton boxes (empty carton boxes were to be given to the patients to ensure that return boxes were available).
4. Patients participating in the pharmacokinetic analysis were required to apply their gel in isolation at the study site following the predose blood draw.

Identity of Investigational Products
FINACEA™ (azelaic acid) gel, 15%
The topical preparation, SH H 655 BA, is an aqueous gel formulation containing 15% AzA as the active compound. The control treatment, SH H 655 PBA, (vehicle/gel base), did not contain the active compound.
The study medications (AzA 15% gel and the vehicle gel) were supplied in 30g tubes.
The compositions of the gels are as follows:

SH H 655 BA (Batch No. 03002)	**Vehicle gel** (Batch No. 03001)
15% Azelaic acid	--

Polyacrylic acid	Polyacrylic acid
Propylene glycol	Propylene glycol
Lecithin	Lecithin
Medium-chain length triglycerides	Medium-chain length triglycerides
Polysorbate 80	Polysorbate 80
EDTA- [redacted]	EDTA- [redacted]
Benzoic acid	Benzoic acid
NaOH [redacted]	NaOH [redacted]
Purified water	Purified water

Treatments Administered

Application frequency follows:

- The trial preparations were applied to the face *twice daily* - in the morning and in the evening - over the entire individual treatment period of 12 weeks

Mode of application was as follows:

- Before application the skin should be cleansed and patted dry with a soft towel.
- Very mild soaps or mild soapless cleansing lotion were to be considered for cleansing. Normal soaps and alcoholic cleansers must strictly be avoided. In view of the individual susceptibility, it is recommended that the patients continue their established, well-tolerated cleansing habits in order to avoid irritation.
- The gel was to be applied to the entire facial area (cheeks, chin, forehead, nose). Approximately 0.5g = approximately 1 inch of gel shall be used per application for the entire facial area.
- The gel should be gently rubbed-in; excessive rubbing-in must be avoided. During application, contact with the eyes should be avoided. In case of accidental exposure, the eyes should be rinsed with plenty of water.

Concomitant therapy

Concomitant medications that were considered to be necessary for a patient's welfare and would not interfere with the patient's evaluability or response to the study treatment were allowed at the discretion of the investigator. Patients were to avoid all topical medications that might cause local irritation, including soaps, alcoholic cleansers, tinctures, astringents, abrasives, and peeling agents. In accordance with the exclusion criteria, the following restrictions applied to concomitant medication during the entire 12-week study period:

- Agents were permitted for the treatment of a concurrent disease (e.g., an infection) for a maximum of 10 days. Oral antibiotics that can affect rosacea include tetracycline, erythromycin, doxycycline, minocycline, and ampicillin. If for medical reasons a course of oral antibiotic treatment for more than 10 days was required, patients were discontinued from further participation in the study.
- No concurrent administration of medications that may cause acneiform eruptions 2 such as tuberculostatics (isoniazid), anabolic hormones, and glucocorticoids

There were no general objections to the use of cosmetics. Patients were asked to observe the following:

- Only nonmedicated cosmetics could be used.
- Cosmetics could not contain comedogenic substances or substances causing acneiform eruptions.

- Cosmetics could not be irritating.
- Patients were to have an interval of about 30 minutes between application of treatment gel and application of cosmetics.

Diet
No particular rosacea diet was recommended. However, patients were instructed to avoid any foods and beverages that, in their own experience, might provoke erythema, flushing, and blushing (including spicy food and alcoholic beverages). Patients were instructed to avoid thermally hot drinks, including hot coffee and tea.

Treatment phase (Weeks 4, 8, and 12)
During the treatment phase, patients returned for examination after 4, 8, and 12 weeks, with an assessment window of +/-7 days for Weeks 4 and 8, and +14/-5 for Week 12/last available visit. Lesion counting was performed under constant lighting, and all make-up was removed prior to counting. To provide consistency, each patient was assessed by the same investigator over the entire treatment period, when possible.

At each of these visits, the following activities were completed:
- Numbers of facial lesions (papules, pustules, and nodules) were recorded.
- Investigator's global assessment of rosacea severity on a static score from 0 to 6 was recorded.
- Severity of erythema was recorded.
- Severity of telangiectasia was recorded.
- Adverse events were recorded.
- Concomitant medications were recorded.
- All unused and partially used tubes of study medication dispensed at the previous visit were collected.
- Study medication (Weeks 4 and 8) was dispensed.
- Blood samples were drawn at predose and 1, 2, and 4 hours post dose (i.e., post-gel application) for pharmacokinetic analysis (consenting patients at Study A03126 Center No. 10 only who completed at least 4 weeks of therapy).

Week 12 or Final Visit
In addition to the regular treatment phase assessments (inflammatory lesion count, global assessment of rosacea, severity of erythema and of telangiectasia, AEs, and concomitant medications), the following were also done at Week 12/Final Visit:
- Investigators and patients each rated the overall improvement.
- Patients offered their opinion about both the cosmetic acceptance and local tolerability of the study treatment.
- A urine hormonal pregnancy test (HCG test, EPT®-test) was performed in female patients of childbearing potential, and the patient was informed of the results.
- Standardized photographs (for demonstration purposes only) were taken of consenting patients at Study Center No. 13.

Reviewer's comments:

No agreement between the Sponsor and the Division regarding the regulatory utility of rating of overall improvement by investigators and patients or patient assessment of cosmetic acceptance and local tolerability of the study treatment.

Efficacy Measurements
Each patient's initial condition and course of rosacea was assessed by the following: 1) counting inflammatory lesions, 2) the investigator's global assessment of rosacea, 3) rating erythema and telangiectasia severity and 4) investigator's rating of overall improvement at the end of therapy. Patients were also asked to assess their overall improvement, as well as both the cosmetic acceptance and the tolerability of the study medication.

Counting of facial inflammatory papules and pustules
The number of facial inflammatory papules and pustules is to be recorded at baseline and then after 4 weeks, 8 weeks, and after 12 weeks of therapy.

The following scales were used in the efficacy assessments:
Investigator's Global Assessment
The investigator's global assessment was performed at baseline and after 4, 8, and 12 weeks of treatment. The global assessment was expressed in accordance with a static 7-point score from 0 to 6 describing the clinical status (severity) of stage 2 rosacea in each patient. The static score was used only for the description of papulopustular rosacea, not for rosacea in general.

According to the protocol, a score of 6 = severe did not implicate a stage 3 rosacea with nodules and rhinophyma, but rather a severe form of stage 2, papulopustular rosacea:

stage 1 rosacea	stage 2: papulo-pustular rosacea							stage 3 rosacea
flushing, blushing	score:	0	1	2	3	4	5	6	nodular,

Numerical Score

Definition	Description	
0	Clear	No papules and/or pustules; no or residual erythema; no or mild to moderate telangiectasia
1	Minimal	Rare papules and/or pustules; residual to mild erythema; mild to moderate telangiectasia
2	Mild	Few papules and/or pustules; mild erythema; mild to moderate telangiectasia
3	Mild to moderate	Distinct number of papules and/or pustules; mild to moderate erythema; mild to moderate telangiectasia
4	Moderate	Pronounced number of papules and/or pustules; moderate erythema; mild to moderate telangiectasia
5	Moderate to severe	Many papules and/or pustules, occasionally with large inflamed lesions; moderate erythema; moderate degree of telangiectasia
6	Severe	Numerous papules and/or pustules, occasionally with confluent areas of inflamed lesions; moderate or severe erythema; moderate or severe telangiectasia

Reviewer's comments:
At baseline, a numerical score of 4 on the IGA would have been consistent with moderate stage 2 severity.

Erythema
The intensity (severity) of erythema is to be rated as follows:

no:	either no visible erythema or minimal residual erythema
mild:	slight erythema either centrofacial or generalized to whole face
moderate:	pronounced erythema either centrofacial or generalized to whole face
severe:	severe erythema / red to purple hue, either centrofacial or generalized to whole face

Telangiectasia
The severity of telangiectasia is to be rated as follows:

no:	no telangiectasia
mild:	only few fine vessels discernible, involves 10% or less of the facial area
moderate:	multiple fine vessels and/or few large vessels discernible, involves 10% - 30% of the facial area
severe:	many fine vessels and/or large vessels discernible, involves more than 30% of the facial area

Rating of overall improvement
At the end of study medication, both the investigators and the patients shall rate their subjective impression of overall improvement. The rating shall reflect the achieved overall improvement based on the comparison of the rosacea condition at the end of study medication with the condition at baseline.

- Investigator overall ratings: 1 = *complete remission, 2 = marked improvement 3 = moderate improvement, 4 =no improvement, 5 = deterioration*
- Patient overall ratings: *1 = excellent improvement, 2 = good improvement, 3 = moderate improvement, 4 = no improvement, 5 = worse.*

The investigator's global assessment scores at baseline and study termination were used to classify patients as responders or nonresponders.

Responders were defined by the Sponsor as:
a) Patients who achieved a ***clear*** or ***minimal*** final global assessment *and* whose global assessment score decreased by at least 1 unit from baseline to the end of treatment, *and* who did not prematurely discontinue study medication due to lack of efficacy.
OR
b) Patients who achieved a clinically favorable ***mild*** final global assessment *and* whose global assessment score decreased by at least 2 units at the end of treatment compared to baseline, *and* who did not prematurely discontinue study medication due to lack of efficacy.

The nonresponder group included all patients who did not fulfill the criteria defined for the responders. In particular, patients who prematurely discontinued study medication due to lack of efficacy were considered to be nonresponders.

Primary efficacy variables
The 2 primary efficacy endpoints originally defined in the protocol and the analysis plan for statistical evaluation were:

- Change in inflammatory lesion count from baseline to Week 12

- Investigator's global assessment of rosacea dichotomized in terms of responders and nonresponders

Reviewer's comment:
At the PreNDA meeting on August 30, 2001, the Division recommended that in addition to the analyses proposed by the Sponsor, the Sponsor should provide in the NDA an analysis based on the ITT-LOCF population for the following primary efficacy endpoints:

- *change in inflammatory lesions from baseline at the end of study and*
- *the proportion of patients in the active group vs. the vehicle group who achieve a static global assessment score of 0 (clear) and 1 (minimial) at the end of study as described in the Investigator's Global Assessment Score.*

It was also noted at the PreNDA meeting that the Sponsor's proposed numerous secondary efficacy endpoints and that there were no agreements with the Division regarding the secondary efficacy endpoints.

Secondary efficacy variables
The secondary efficacy variables defined in the protocol or the statistical analysis plan were as follows:

- Total lesion count (sum of papules, pustules, and nodules)
- Nodule count
- Percent change in inflammatory lesion count (sum of papules and pustules) from baseline to Week 12 or last available visit. Percent change was calculated as the baseline value subtracted from the Week 12/last visit value, divided by baseline value, and multiplied by 100.
- Change in rating of erythema
- Change in the rating of telangiectasia
- Sponsor's Alternative Evaluation of Investigator's global assessment of rosacea follows: The number of units of change from baseline to the end of treatment were also analyzed by the Sponsor:
  - Investigator's global assessment of rosacea dichotomized into success or failure, where success was defined as a rating of ***clear*** at the end of treatment. Patients who prematurely withdrew from the study because of a lack of efficacy were coded as failures.
  - Investigator's global assessment of rosacea dichotomized into success or failure, where success was defined as a rating of ***clea***r, ***minima***l, or ***mild*** at the end of treatment. Patients who prematurely withdrew from the study because of a lack of efficacy were coded as failures.

Reviewer's comment: *There were no agreements made regarding the secondary efficacy endpoints listed above. Presence of nodules (stage 3) was an exclusion criterion. It is unclear why nodule count was considered an efficacy variable by the Sponsor since patients developing nodules while enrolled in the study demonstrates disease progression.*

Other Efficacy Variables

- Rating of overall improvement at the end of study medication by both the investigators and the patients.
- Cosmetic acceptance of the topical preparation at the end of the study..

Treatment compliance
At each post baseline visit, patients were required to return all unused, partially used, or empty containers to the investigators before receiving new study medication. For drug accountability, the number of tubes dispensed and returned at the study visits was documented on the CRF. All study medication tubes were weighed prior to the study medication being shipped to the clinical sites, and again after the tubes were returned to Berlex Clinical Studies Department.

Statistical Considerations
Statistical methods (See Statistical Review)
Efficacy and safety data will be analyzed. Summary tables (descriptive statistics and/or frequency tables) will be provided for all background and baseline variables, efficacy variables and safety variables. Statistical tests will be two-tailed at the 0.05 level of significance. The *second primary variable* – the dichotomized investigator's global assessment (a binary criterion) – will be analyzed by a Mantel-Haenszel test controlling for centers.

Interim analysis
No statistical interim analysis will be performed.

Safety Measures (Safety is being reviewed separately by Brenda Carr.)
Safety is to be assessed at each control visit. Safety assessment includes recording of adverse events (AE) and serious adverse events (SAE).

Protocol amendments
There are 4 protocol amendments listed.
Amendment 1 (Date: December 21, 2000) addressed the FDA request to add pregnancy screening for all female patients of childbearing potential. This screening was performed at the baseline visit, and the patient's last visit.
Amendment 2 (Date: January 24, 2001) added standardized facial photographs. Study Site No. 13 had standardized photographs taken at baseline and the last visit of all consenting patients. Photographs were for demonstration purposes only. No efficacy or safety analyses were performed.
Amendment 3 (Date: April 4, 2001)
To add monitoring of plasma concentrations of azelaic acid (AzA) and its main metabolite pimelic acid at steady state with the objective to determine the effect of twice daily application of Finevin Gel on endogenous plasma AzA and pimelic acid concentrations.
Amendment 4 (Date: April 30, 2001) Statistical Analysis of Pharmacokinetic Data
Plasma concentrations of azelaic acid (AzA) and its metabolite, pimelic acid, will be measured at steady state for approximately 30 patients at a particular study site. Blood samples will be drawn at the following time-points: pre-dose (time 0), 1 hour post dose, 2 hours post-dose, and 4-hours post-dose. The plasma concentration time curve will be displayed for each patient. Summary descriptive statistics (median, mean, standard deviation) of the concentration levels at each sampling time by treatment group will be provided. A 95% 2-sided confidence interval for the mean treatment difference in concentration levels will be estimated by time-point and for both concentrations.

05	Michael Heffernan, MD	19
06	Lewis Kaminester, MD	26
07	Kean Lawlor, MD	40
08	Sooji Lee-Rugh, MD	17
09	Mark Ling, MD	18
10	John Proffitt, MD	40
11	Daniel Stewart, DO	25
13	Diane Thiboutot, MD	20
15	Jonathan Weiss, MD	10

Demographics, Evaluability

Demographics and Baseline Characteristics (ITT Population) for Report A03125 follows:

Text Table 5: Demographic and Baseline Characteristics (ITT Population)

	AzA 15% gel (N=164)	Vehicle (N=165)	p-value[a]
Mean age (years [range])	48.0 (21-84)	49.2 (24-77)	0.3801
Sex (n [%])			0.6147
Male	40 (24%)	45 (27%)	
Female	124 (76%)	120 (73%)	
Race (n [%])			0.2872
Caucasian	159 (97%)	155 (94%)	
Black	0 (0%)	2 (1%)	
Hispanic	4 (2%)	7 (4%)	
Asian	1 (1%)	0 (0%)	
Other			
Pacific islander	0 (0%)	1 (1%)	
Mean height (cm)	167.8	167.9	0.9405
Mean weight (kg)	81.7	81.1	0.7916
Body mass index	29.1	28.8	0.7316
Mean previous duration of rosacea (months)	100.2	88.5	0.3076
0-6 months	8 (5%)	7 (4%)	
>6 months-2 years	26 (16%)	38 (23%)	
>2 years-5 years	50 (30%)	54 (33%)	
> 5 years	80 (49%)	66 (40%)	

AzA = azelaic acid; ITT = intent to treat; N = total number of patients; n = number of patients.
[a]Continuous variables: t-test for independent groups; Categorical variables: Fisher's exact test; Ordinal variables: Wilcoxon rank-sum test.
Reference: Section 14.1, Table 3.

Reviewer's comment:

According to the FDA Statistician, within each study there were no statistically significant differences between the active and vehicle treatment groups in demographics, baseline characteristics, of baseline efficacy measures.

Baseline Investigator Global Assessment (n [%])

Clear	0/164 (0%)	0/165 (0%)
Minimal	0/164 (0%)	0/165 (0%)
Mild	25/164 (15%)	33/165 (20%)
Mild to Moderate	67/164 (41%)	68/165 (41%)
Moderate	57/164 (35%)	53/165 (32%)
Moderate to Severe	14/164 (9%)	8/165 (5%)
Severe	1/164 (1%)	3/165 (2%)

Reviewer's comment:

The entry criteria was moderate, papulopustular facial rosacea (stage 2); therefore, all patients should have had an IGA score of 4 (moderate) or higher at baseline.