CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207071Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505 (b)(1)
Application Number(s)	207071
Priority or Standard	Standard
Submit Date(s)	30-SEP-2014
Received Date(s)	30-SEP-2014
PDUFA Goal Date	30-JUL-2014
Division / Office	OND/ODE3/DDDP
Reviewer Name(s)	Gary Chiang MD, MPH
Review Completion Date	15-JUN-2015
Established Name	Azelaic acid, 15%
(Proposed) Trade Name	Finacea
Therapeutic Class	Anti-inflammatory
Applicant	Bayer HealthCare
Formulation(s)	Foam
Dosing Regimen	Topical
Indication(s)	Inflammatory papules and pustules of mild to moderate rosacea
Intended Population(s)	Adults 18 years and older

Template Version: March 6, 2009

Table of Contents

Reference ID: 3780201

Reference ID: 3780201

Table of Tables

Reference ID: 3780201

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Bayer HealthCare submitted an original 505 (b)(1) New Drug Application (NDA) for FINACEA (azelaic acid) Foam, 15% indicated for the topical treatment of inflammatory papules and pustules of mild to moderate (b) (4) rosacea in adults. Benefits of the treatment of rosacea with FINACEA Foam, 15% were demonstrated in two adequate and well-controlled clinical studies. In addition, safety and tolerability was demonstrated in the clinical trials.

From a clinical perspective, it is recommended that FINACEA (azelaic acid) Foam, 15% be approved for the treatment of inflammatory papules and pustules in patients with mild to moderate (b) (4) rosacea.

1.2 Risk Benefit Assessment

Rosacea is a common chronic cutaneous disorder with clinical symptoms including facial redness, dilated blood vessels on facial skin, papules, pustules, and swelling. . The exact cause of rosacea is unknown. Patients frequently require treatment for the inflammatory skin lesions.

The applicant demonstrated that azelaic acid foam, 15% has efficacy in the treatment of papules and pustules in rosacea in two pivotal, randomized, double-blinded, vehicle controlled clinical trials involving a total of 1362 patients. The risk of this product is mostly mild to moderate, non-serious local adverse events, primarily local skin irritation at the application site. The active drug has a well-known history of tolerability and usability in the treatment of rosacea and acne vulgaris. The Risk-Benefit for this drug product is acceptable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

2.1 Product Information

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, (b) (4) . Endogenous plasma concentrations and daily urinary excretion of AzA are highly dependent on dietary intake and endogenous metabolism.

The proposed pharmacological mechanisms of action for azelaic acid includes: inhibition of mitochondria and pigmented cell systems and the inhibitory action on the generation/release of reactive oxygen species in neutrophils.[1] The diverse multiple pharmacological mechanisms of action may account for its clinical effectiveness in multiple pathologically unrelated disorders such as rosacea, acne, melisma, and seborrheic dermatitis, though the precise mechanism in the treatment of rosacea is not known.

2.2 Tables of Currently Available Treatments for Proposed Indications

Most patients with mild to moderate disease can be managed with topical therapies such as metronidazole, azelaic acid, or sulfacetamide-sulfur. Systemic agents are typically used in patients who fail to respond satisfactorily to topical agents or who present with numerous inflammatory lesions. Tetracycline-class antibiotics are first-line systemic agents for papulopustular rosacea; for patients who fail to respond to tetracyclines or who cannot tolerate these drugs, treatment with other oral antibiotics is an option. Laser therapy, intense pulsed light, and photodynamic therapy have also been used in papulopustular rosacea.

Several pro-inflammatory pathways (e.g. elevated levels of cathelicidin) are thought to play important roles in the pathophysiology of rosacea-affected skin, leading to an inflammatory milieu with the expression of several pro-inflammatory cytokines in facial skin.[2] The excessive release of pro-inflammatory mediators such as reactive oxygen species (ROS) into dermal tissue is believed to further contribute to a neutrophil-mediated inflammation, leading to a compromised lymphatic system in the skin as well as a compromised integrity of dermal capillary walls [3], thus contributing to the clinical manifestations of rosacea, including an increased reactivity of the skin to a variety of stimuli.

1 Gollnick H, Layton A. Azelaic acid 15% gel in the treatment of rosacea. Expert Opin Pharmacother. 2008 OCT, 9(15): 2699-706.
2 Gerber, PA, Buhren BA, Steinhoff M, Homey B. Rosacea: The cytokine and chemokine network. J Investig Dermatol Symp Proc. 2011 Dec;1 5(1): 40-7.
3 Jones DA. Rosacea, reactive oxygen species, and azelaic acid. J Clin Aesthet Dermatol. 2009 Jan; 2(1):26-30.

Azelaic acid has been demonstrated to have an inhibitory effect on the release of ROS from neutrophils and in addition exerts scavenging effects on already released ROS.[4] Furthermore, azelaic acid modulates the phosphorylation of p38 mitogen-activated protein (MAP) kinase, an enzyme that is crucial in the activation of the pro-inflammatory signaling cascade of the transcription factor NF-κB, thereby down-regulating this signaling cascade, receptor that suppresses already activated NF-κB, has been shown to be induced under the influence of azelaic acid.[5]

Another anti-inflammatory effect of azelaic acid involves a decrease in the elevated levels of kallikrein-5.[6] Kallikrein-5 processes the intracellular peptide cathelicidin, thus leading to the expression of cathelicidin in keratinocytes. Cathelicidin is thought to have a dual role in immunity because it exerts direct antimicrobial effects, while the molecule at the same time serves as signal for inflammatory reactions. Among observations of cathelicidin function are findings that these peptides can promote leukocyte chemotaxis, angiogenesis, and the expression of extracellular matrix components. [7] Given the clinical features of rosacea that involve a general inflammatory skin reaction, occurring telangiectasias as well as tissue hyperplasia (phymatous rosacea), this pathway is thought to play an important role in the pathogenesis of rosacea, which is further backed by the observation that individuals with rosacea express abnormally high levels of cathelicidin in their facial skin.

4 Akamatsu H, Komura J, Asada Y, Miyachi Y, Niwa Y. Inhibitory effect of azelaic acid on neutrophil functions: a possible cause for its efficacy in treating pathogenetically unrelated diseases. Arch Dermatol Res. 1991; 283(3):162-6.
5 Mastrofancesco A, Ottaviani M, Aspite N, Cardinali G, Izzo E, Graupe K, et al. Azelaic acid modulates the inflammatory response in normal human keratinocytes through PPARgamma activation. Exp Dermatol. 2010 Sep; 19(9):813-20.
6 Coda ad, Hata T, Miller J, Audish D, Kotol P, Two A, et al. Cathelicidin, Kallikrein 5, and serine protease activity is inhibited during treatment of rosacea with azelaic acid 15% gel. J Am Acad Dermatol. 2013 Oct; 69(4):570-7.
7 Yamasaki K, Di Nardo A, Bardan A, Murakami M, Ohtake T, Coda A, et al. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. Nat Med. 2007 Aug; 13(8):975-80.

Table 1: Currently Available Treatments

	Formulation (s)	Conditions of use	Adverse effects
Topical Treatment			
Metronidazole	0.75% gel or cream, 0.75% lotion	Once or Twice daily for 12 weeks	Local irritation, dryness, stinging sensation
Azelaic acid	20% cream 15% gel	Twice daily for 12 weeks	Burning, itching, stinging sensation
Sulfacetamide-sulfur	10%/5% suspension, lotions, cleansers, creams, foams, and cleansing pads	Once or twice daily for 12 weeks	Local irritation, allergic reactions, unfavorable odor
Clindamycin/benzoyl peroxide	1%/5% gel	Once daily for 12 weeks	Local irritation, dryness, stinging sensation
Retinoids	0.1% gel	Once daily for 12 weeks	Local irritation
Oral Treatment			
Tetracyclines	250mg to 1000mg per day	4 to 8 weeks	Antimicrobial resistence, diarrhea, abdominal pain, photosensitivity
Metronidazole	200mg twice daily	4 to 8 weeks	GI distress, disulfram-like reaction with alcohol
Clarithromycin, azithromycin, erythromycin	Multiple	4 to 8 weeks	Antimicrobial resistence, diarrhea, abdominal pain,
Oral Isotretinoin (severe and refractory)	0.5mg to 1.0mg/ day	12 weeks	Dermatitis, teratogenic, iPLEDGE
Laser and intense pulsed light	Addition of photosensitizing agent like aminolevulinic acid		Mixed results and length of results are short lasting

Source: Compiled from current literature and practice guidelines. Not all of these therapies are FDA approved for rosacea.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient in Finacea® Foam is azelaic acid. Azelaic acid is available in the United States as a 20% cream or a 15% gel for the treatment of acne vulgaris and rosacea. There is no generic equivalent available in the US.

2.4 Important Safety Issues With Consideration to Related Drugs

The primary safety concerns identified for azelaic acid is outlined in the FINACEA (azelaic acid) Gel, 15% label with the product approved in 1995. In two vehicle-controlled and one active-controlled US clinical trials, 788 subjects used twice-daily FINACIA (azelaic acid) Gel, 15% for 12 weeks, up to 15 weeks. The most common treatment-related adverse events were: burning/stinging/tingling (29%), pruritus (11%), scaling/dry skin/xerosis (8%), and erythema/irritation (4%).

Table 2: Adverse Events Occurring in ≥ 1% of subjects in the Rosacea Trials for FINACEA (azelaic acid) Gel, 15%

	FINACEA Gel, 15% N=457 (100%)			Vehicle N=331 (100%)		
	Mild n=99 (22%)	Moderate n=61 (13%)	Severe n=27 (6%)	Mild n=46 (14%)	Moderate n=30 (9%)	Severe n=5 (2%)
Burning/stinging/tingling	71 (16%)	42 (9%)	17 (4%)	8 (2%)	6 (2%)	2 (1%)
Pruritus	29 (6%)	18 (4%)	5 (1%)	9 (3%)	6 (2%)	0 (0%)
Scaling/dry skin/xerosis	21 (5%)	10 (2%)	5 (1%)	31 (9%)	14 (4%)	1 (<1%)
Erythema/irritation	6 (1%)	7 (2%)	2 (<1%)	8 (2%)	4 (1%)	2 (1%)
Contact dermatitis	2 (<1%)	3 (1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Edema	3 (1%)	2 (<1%)	0 (0%)	3 (1%)	0 (0%)	0 (0%)
Acne	3 (1%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)

*Subjects may have >1 cutaneous adverse event; thus, the sum of the frequencies of preferred terms may exceed the number of subjects with at least 1 cutaneous adverse event.

In patients using azelaic acid formulations, the following adverse events have been reported: worsening of asthma, vitiligo, depigmentation, small depigmented spots, hypertrichosis, reddening (signs of keratosis pilaris) and exacerbation of recurrent herpes labialis. In post-marketing experiences, iridocyclitis due to accidental exposure of FINACEA to the eyes have been reported.

FINACEA® Gel and its vehicle caused irritant reactions at the application site in human dermal safety studies. FINACEA® Gel caused significantly more irritation than its vehicle in a cumulative irritation study. Some improvement in irritation was demonstrated over the course of the clinical trials, but this improvement might be attributed to subject dropouts. No phototoxicity or photoallergenicity were reported in human dermal safety studies.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

In the development of azelaic acid foam, 15%, the Agency met with Bayer on the following dates:

- 17-JUL-2007, Pre-IND meeting
- 10-JUN-2009, Guidance meeting
- 9-NOV-2011, End-of-Phase 2 meeting
- 9-JUL-2014, Pre-NDA meeting

In all the meetings with the applicant, the Agency advised that a Phase 2 study with "exploratory" objectives would not be considered a pivotal clinical trial for approval. In order for the study to be considered an adequate and well-controlled study, a study needs to have been designed and executed with all the characteristics of a Phase 3 clinical trial (e.g., adequate blinding, appropriate control arm, appropriate endpoints and scales, pre-defined statistical analysis plan, scientifically sound method for handling missing data along with alternative approaches as sensitivity analyses, appropriate controls for multiplicity, sensitivity analyses, etc.). The adequacy of the Phase 2 clinical trial as a substitute for a Phase 3 pivotal clinical trial is a review issue discussed below. In addition to the discussion on the Phase 2 clinical trial, the Agency agreed with the applicant that given the extent of the safety database that exists for azelaic acid gel, 15%, the applicant will not be required to complete a long-term safety study for azelaic acid foam, 15%.

No significant pre-submission issues were found with this application.

2.6 Other Relevant Background Information

Rosacea is a chronic and relapsing inflammatory skin disorder that primarily involves the central face. Common clinical features include facial erythema, telangiectasias, and inflammatory skin lesions. Many patients seek therapy due to concern over the effect of rosacea on physical appearance. As there is no cure for rosacea, treatment is focused on symptom suppression.

Rosacea is divided into four subtypes that are defined by the presence of clinical features.

- Erythematotelangiectatic rosacea: The main features are transient facial erythema (flushing), centrofacial nontransient erythema, telangiectasias, skin sensitivity, edema, and a dry or scaly skin texture.
- Papulopustular rosacea: Patients present with inflammatory papules and pustules on the central face. In addition, persistent erythema telangiectasias, flushing, and other features of erythematotelangiectatic rosacea may occur in patients with papulopustular disease.
- Phymatous rosacea: This is characterized by skin and sebaceous hypertrophy that results in distortion of facial contours. Severe disfigurement may occur.
- Ocular rosacea: Includes a variety of ocular findings may occur in rosacea, including conjunctival hyperemia, anterior blepharitis, keratitis, lid margin telangiectasias, abnormal tearing, cicatrical conjunctivitis, and chalazion or hordeolum (stye) formation.

Features of more than one subtype of rosacea may occur simultaneously.

General treatment includes non-pharmacological intervention for management of cutaneous manifestations of rosacea, regardless of subtype. General avoidance of triggers of flushing, gentle skin care, sun-protection, and use of cosmetic products are recommended for all patients.

3 Ethics and Good Clinical Practices

The Division of Scientific Investigators (DSI) was not consulted to review the conduct of the pivotal trials.

Reviewer's comment: The clinical team, in consultation with the biostatistics review team, concluded that there were no specific concerns about study sites following preliminary review of the data, and no clinical study sites were referred to DSI for inspection.

3.1 Submission Quality and Integrity

Overall, the quality of the application is acceptable.

3.2 Compliance with Good Clinical Practices

The applicant affirmed that the studies were conducted in accordance with the ethical principles originating from the Declaration of Helsinki and the International Conference on Harmonization (ICH) harmonized tripartite guidelines for Good Clinical Practice and the compliance with local and FDA regulatory requirements. The protocol and Informed Consent Forms were reviewed by the Investigations Review Board (IRB) associated with the trial sites or by consulting central IRB. Written informed consents were obtained from subjects at the first (baseline) visit.

3.3 Financial Disclosures

The applicant certified in Form 3454 that they had not entered into any financial arrangements with any of the clinical investigators. It was also affirmed that none of the clinical investigators disclosed any proprietary interest in the product, or significant equity interest in the sponsor company. Certification was made that no investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f).

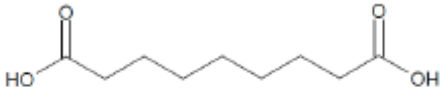
4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC review was conducted by Dr. Hamid Shafiei and the Quality Microbiology review by Dr. Jessica Cole. Azelaic acid belongs to a class of medication called dicarboxylic acids. This

API is used to treat mild to moderate acne both comedonal acne and inflammatory acne. It works by killing the bacteria that infect the skin pores. It is also used as topical gel in the treatment rosacea because of its ability to reduce inflammation. Azelaic acid is a naturally-occurring saturated dicarboxylic acid which is found in wheat, rye, and barely and has been used as an ingredient in number of hair and skin conditioners. Azelaic acid is the active ingredient of number of brand name products such as Azepur 99, Azaclear, Azclear Action, Azelex, White Action Cream, Finevin, Melazepam, Skinoren, and Ezanic. It is also the active ingredient of the drug product, Finacea (azelaic acid) Gel, 15% approved under NDA 21470 on December 24, 2002 for the topical treatment of inflammatory papules and pustules of mild to moderate rosacea. Finacea (azelaic acid) Gel, 15% is currently marketed by the applicant of this NDA application.

Figure 1: Molecular Formula



Azelaic Acid	
Empirical Formula:	$C_9H_{16}O_4$
Molecular Mass:	188.22
CAS Number:	123-99-9

Azelaic acid is a white, odorless crystalline solid. It is poorly soluble in water at 20°C (0.24%) but freely soluble in boiling water and in ethanol. This drug substance is commercially produced by the (b) (4). The full description of manufacturing process, process controls, in-process testing, packaging, and release and stability testing for the azelaic acid manufactured by Bayer Pharma AG as the active ingredient for Finacea (azelaic acid) Foam, 15% is provided in DMF 9289 and DMF (b) (4). Both DMFs have been reviewed and found to be adequate to support this NDA application. The drug substance release specification for azelaic acid includes testing and acceptance criteria for appearance, identity, melting range, clarity of solution, color of solution, assay, related substances, (b) (4), heavy metals, water content, residual solvents (b) (4), particle size, and polymorphism. The proposed API specification is satisfactory. In summary, azelaic acid manufactured by Bayer Pharma AG is considered adequate for use as the active ingredient in the drug product, Finacea (azelaic acid) Foam, 15%.

Finacea (azelaic acid) Foam, 15%, for topical administration is a new hydrophilic foam formulation containing 15% w/w (b) (4) azelaic acid in an oil-in-water emulsion that is filled in an aluminum can with spray valve and cap and pressurized using a propellant for foam delivery.

This drug product is a pressurized oil-in-water emulsion that appears as a white to off-white foam upon actuation. (b) (4) The emulsion contains 15% w/w azelaic acid as the active ingredient and benzoic acid, USP/NF (b) (4) cetostearyl alcohol, USP/NF (b) (4) Dimethyl

isosorbide [redacted], medium-chain triglycerides, USP/NF [redacted] methylcellulose, USP/NF [redacted] mono- and di-glycerides, USP/NF [redacted], polyoxyl 40 stearate, USP/NF [redacted], polysorbate 80, USP/NF [redacted], propylene glycol, USP/NF [redacted], xanthan gum, USP/NF [redacted] sodium hydroxide, USP/NF [redacted], and purified water, USP/NF [redacted] as the excipients. [redacted] The excipients used in the manufacture of Finacea (azelaic acid) Foam, 15% are all compendial with the exception of dimethyl isosorbide. However, dimethyl isosorbide is tested and accepted according to compendial requirements. Therefore, the proposed drug product formulation/composition is satisfactory.

The overall recommendation of CMC is for approval, the applicant has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The overall recommendation is pending an "Acceptable" from the Office of Compliance for the facilities inspections. Labeling discussions are ongoing and labeling will be provided in the finalized review.

4.2 Clinical Microbiology

Clinical Microbiology was not consulted for this NDA. No specific antimicrobial claims are asserted in the application.

4.3 Preclinical Pharmacology/Toxicology

The non-clinical review was conducted by Jianyong Wang, PhD. During the review of this NDA, it was determined that this application is a 505 (b)(1) application. The applicant was able to identify all reference data was owned by Bayer HealthCare Pharmaceuticals Inc. The following section is a brief discussion of the Pharmacology/Toxicology review findings based on the FINACEA (azelaic acid) gel, 15% NDA 21470.

"This NDA is a 505(b)(1) NDA from a Pharmacology/Toxicology perspective because the sponsor owns all the necessary nonclinical data for azelaic acid to support FINACEA Foam, 15%.

Azelaic acid has been shown to have anti-keratinizing, anti-bacterial and anti- inflammatory activities. However, the mechanism(s) by which azelaic acid interferes with the pathogenic events in rosacea are not clear.

Nonclinical safety pharmacology studies did not indicate significant effects of azelaic acid on intermediate metabolism, liver function, renal function, cardiovascular function, smooth muscle or the nervous system, under the study conditions.

Since azelaic acid is a straight chain dicarboxylic acid, it is anticipated that the main process of its elimination is by biotransformation. Systemically absorbed azelaic acid is metabolized by β-oxidation into shorter straight chain dicarboxylic acids (i.e., pimelic and glutaric acids), malonyl-CoA and acetyl-CoA. The results from an in vitro percutaneous absorption study indicate that similar systemic exposure is expected after topical administration of the azelaic acid foam and gel formulations.

Azelaic acid was evaluated for systemic toxicity in rats (27-week study) and monkeys (4-week study) following oral (gavage) administration. No significant systemic toxicity was noted in the two studies except lower body weight gain and thickening of the cuticular ridge of the stomach accompanied by evagination and epithelia overgrowth noted at high dose in the rat study. Dermal toxicity studies were conducted in dogs (26- week study) with 20% azelaic acid cream and in minipigs (13-week study) and mice (13- week study) with 15% azelaic acid pre-foam emulsion. No significant toxicity was noted in the three dermal studies. Only slight dermal irritation was noted in the dog study.

In genetic toxicology studies, azelaic acid was not mutagenic or clastogenic in a battery of in vitro and in vivo genotoxicity tests. There is no concern for its genotoxic potential.

A short-term dermal carcinogenicity study in transgenic mice (Tg.AC assay) was conducted with azelaic acid 15% gel. A statistically significant increase in the incidence of papillomas was noted in males in the vehicle and high dose groups. No effect was noted in females. There was no significant difference in the incidence of papillomas in the vehicle and high dose males, which suggested that the positive finding may be due to the vehicle only. However, considering the positive finding noted in this short-term Tg.AC assay, a 2-year dermal mouse carcinogenicity study is recommended to be conducted as a post-marketing requirement (PMR) with the azelaic acid pre-foam emulsion formulation.

Oral embryofetal developmental studies were conducted with azelaic acid in rats, rabbits, and monkeys. Azelaic acid was administered during the period of organogenesis in all three animal species. Embryotoxicity was observed in rats, rabbits, and monkeys at oral doses that generated maternal toxicity. No teratogenic effects were observed in these studies. An oral peri-and post-natal developmental study was conducted in rats. Embryotoxicity was observed at the high dose that generated maternal toxicity. In addition, slight disturbances in the post-natal development of fetuses were noted in rats at doses that generated maternal toxicity. No effects on sexual maturation of the fetuses were noted in this study.

Azelaic acid is an ocular irritant to the rabbit and monkey eye. It can be presumed that the FINACEA Foam formulation will be an ocular irritant as well. The 15% azelaic acid pre-foam emulsion is a mild irritant to rabbit skin but did not show any dermal irritation in mice. No skin

sensitization potential of azelaic acid was noted. A nonclinical phototoxicity study is not needed for the 15% azelaic acid pre-foam emulsion, since no significant absorption was noted from the UVB/UVA/visible light spectrum.

The multiples of human exposure based on BSA comparison between NOAELs identified in pivotal toxicology studies and the maximum recommended human doses are considered adequate. The proposed clinical use of FINACEA Foam, 15% is supported by nonclinical data."

Reviewer's comment: *The sponsor has agreed to conduct a 2-year dermal mouse carcinogenicity study with the azelaic acid pre-foam emulsion formulation as a PMR. The proposed final report submission is July of 2019. Pharmacology/Toxicology has found that the application is approvable from their perspective. Labeling will be revised based on the review.*

4.4 Clinical Pharmacology

For this NDA, the applicant plans to rely on Pharmacology-Toxicology and long term safety information from currently approved Finacea Gel, 15%. Since the applicant of this NDA owns Finacea® Gel, this application will follow a 505(b)(1) regulatory pathway. The Clinical Pharmacology review was conducted by Dr. Chinmay Shukla.

The clinical program for the new formulation consists of six new clinical trials and this includes:

- Two Phase 1 trials to assess skin irritation and sensitization potential
- A maximal use pharmacokinetic (PK) trial that assessed relative bioavailability (BA) of azelaic acid and pimelic acid (metabolite) following twice daily administration of the new foam formulation versus currently marketed Finacea® Gel in adult subjects with moderate rosacea
- Two Phase 2 efficacy and safety trials
- One Phase 3 trial

The applicant assessed the bioavailability of azelaic acid and pimelic acid (metabolite) following twice daily repeated administration of azelaic acid foam, 15 % versus azelaic acid gel (Finacea Gel), 15 %, under maximal use conditions in a randomized crossover trial in 24 adult subjects with moderate papulopustular rosacea.

On Day 7, azelaic acid systemic concentrations were at steady state. PK parameters Cmax, AUC0-12, and AUC0-36 were calculated and demonstrated that systemic exposure (Cmax and AUC0-12) of azelaic acid following topical application of azelaic acid Foam, 15% were not higher than those observed following application of azelaic acid gel, 15% (Finacea® Gel).

The values of baseline uncorrected PK parameters for azelaic acid (mean ±SD) on Day 7 for azelaic acid foam were 51.8 ± 18.5 ng/mL, 442.0 ± 177.6 ng*hr/mL, and 1101.7 ± 338.1 ng*hr/mL for Cmax, AUC0-12, and AUC0-36, respectively and corresponding baseline

corrected values were 40.1 ± 19.1 ng/mL, 322.8 ± 174.4 ng*hr/mL, and 852.7 ± 457.0 ng*hr/mL for Cmax, AUC0-12, and AUC0-36, respectively.

No dose ranging trials were conducted for this application for the new foam formulation.

The drug-drug interaction potential and QTc assessments were not assessed as the systemic exposure of the foam was not higher than previously observed in the Finacea Gel development program.

The Agency Clinical Pharmacology reviewer, Dr. Shukla states: "From a Clinical Pharmacology standpoint, this application is acceptable provided the labeling comments are adequately addressed by the Applicant."

4.4.1 Mechanism of Action

The mechanism(s) by which azelaic acid interferes with the pathogenic events in rosacea are unknown.

4.4.2 Pharmacodynamics

The pharmacodynamics of azelaic acid foam, 15% is unknown. No drug interaction studies are presented with this NDA.

4.4.3 Pharmacokinetics

The applicant assessed relative BA of azelaic acid and pimelic acid (metabolite) following twice daily repeated administration of Azelaic acid Foam, 15 % versus Azelaic acid Gel (Finacea® Gel), 15 %, under maximal use conditions in a randomized crossover trial (1401843) in 24 adult subjects with moderate papulopustular rosacea. The two treatment periods were separated by a 5 to 14 day washout period. Since azelaic acid is an endogenous substance and can also be absorbed from certain types of diets, each treatment period consisted of a 2-consecutive-day baseline assessment of azelaic acid and pimelic acid systemic concentrations. The baseline assessment was followed by drug application twice a day for 7 days. Plasma sampling for PK assessment was done on days -2, -1, 1, 5, 6 and 7 in both the periods, with serial sampling on Day -1 (baseline) and Day 7 (post dose). Assessment of rosacea was conducted at screening and at days 1 and 7 in both the periods. On Day 7, azelaic acid systemic concentrations were at steady state and were quantifiable in all the subjects following application of both new Foam and Gel formulations. PK parameters Cmax, AUC0-12, and AUC0-36 were calculated with and without baseline adjustment. The values of baseline uncorrected PK parameters for azelaic acid (mean ± SD) on Day 7 for Azelaic acid Foam were 51.8 ± 18.5 ng/mL, 442.0 ± 177.6 ng*hr/mL, and 1101.7 ± 338.1 ng*hr/mL for Cmax, AUC0-12, and AUC0-36, respectively and corresponding baseline corrected values were 40.1 ± 19.1 ng/mL, 322.8 ± 174.4 ng*hr/mL, and 852.7 ± 457.0 ng*hr/mL for Cmax, AUC0-12, and AUC0-36, respectively. The PK of azelaic

acid following administration of Azelaic acid Gel and the PK of pimelic acid are described under Section 2.3.3.

Baseline corrected relative BA assessment at steady state demonstrated that systemic exposure (Cmax and AUC0-12) of azelaic acid following topical application of Azelaic acid Foam, 15% were not higher than those observed following application of Azelaic acid Gel, 15% (Finacea® Gel).

5 Sources of Clinical Data

The applicant submitted an exploratory Phase 2 dose-ranging clinical trial, a Phase 2b randomized, placebo-controlled clinical trial, and a Phase 3 randomized, placebo-controlled clinical trial as evidence of safety of efficacy in the treatment of subjects with papulopustular rosacea. The Phase 2b clinical trial was identical to the Phase 3 clinical trial and will be considered a pivotal safety and efficacy trial. In this section, a brief review of the Phase 3 clinical protocol will be presented.

5.1 Tables of Studies/Clinical Trials

Table 3: Clinical Development Plan for Azelaic Acid Foam, 15%

	Number of subjects	Study Design
Phase 2		
1402140	83	A 12-Week exploratory, multicenter, double-blind, vehicle-controlled study to investigate the safety and efficacy of topical azelaic acid 15% foam twice daily in patients with papulopustular rosacea
1403120	401	Randomized, double-blind, vehicle-controlled, multicenter, parallel-group study to investigate safety and efficacy of Azelaic Acid (AzA) Foam, 15% topically applied twice daily (BID) in subjects with papulopustular rosacea
Phase 3		
1401846	961	A randomized, double-blind, vehicle-controlled, multicenter, parallel-group clinical trial to assess the safety and efficacy of Azelaic Acid Foam, 15% topically applied twice daily for 12 weeks in patients with papulopustular rosacea

5.2 Review Strategy

The protocol described in this section is the pivotal Phase 3 clinical trial 1401846. The Phase 2b clinical trial is of similar design and randomized 400 subjects in 20 U.S. centers. The two clinical trials were sufficiently similar in design and statistical analysis, and the phase 2 trial as deemed adequate as a replication of study results.

Reviewer's comment: *The conclusion that the Phase 2b clinical trial was sufficient to be evaluated as a pivotal trial was based on discussion between the sponsor and the Agency. The Agency specified that any pivotal trials would need to be a well-controlled study. The study needs to have been designed and executed with all the characteristics of a Phase 3 clinical trial (e.g., adequate blinding, appropriate control arm, appropriate endpoints and scales, pre-defined statistical analysis plan, scientifically sound method for handling missing data along with alternative approaches as sensitivity analyses, appropriate controls for multiplicity, sensitivity analyses, etc.). And in the end, the adequacy of the Phase 2 clinical trial as a substitute for a Phase 3 pivotal clinical trial will be a review issue. If there are in consistencies between the studies, the evidence for efficacy and safety would be compromised.*

5.3 Discussion of Individual Studies/Clinical Trials

Title: A randomized, double-blind, vehicle-controlled, multicenter, parallel-group clinical trial to assess the safety and efficacy of azelaic acid foam, 15% topically applied twice daily for 12 weeks in patients with papulopustular rosacea

Objectives:

- To determine the efficacy of azelaic acid (AzA) foam, 15% compared to vehicle topically applied twice daily in papulopustular rosacea evaluated by therapeutic success rate according to IGA and nominal change in inflammatory lesion count from baseline to end of treatment.

Secondary objectives of this study are:

- To determine the efficacy of AzA foam, 15% compared to vehicle topically applied twice daily in papulopustular rosacea evaluated by therapeutic response rate according to IGA and percentage change in inflammatory lesion count from baseline to end of treatment
- To assess the safety and tolerability of topical AzA foam, 15% and vehicle applied non-occlusive at a daily dose of 1 g foam for a total of 12 weeks including evaluation of local cutaneous AEs
- To assess the effect of AzA foam, 15% and vehicle on erythema, telangiectasia and facial skin color
- To assess self-reported outcome parameters via the subject's global assessments on treatment response and tolerability as well as subject's opinion on cosmetic acceptability and opinion on practicability of product use in facial areas next to the hair line

- To assess the effect of AzA Foam, 15% and vehicle on parameters of quality of life in papulopustular rosacea evaluated using the RosaQoL, the DLQI and the EQ-5D-5L
- To assess long-term effects of the treatment and recurrence of the disease after end of treatment in a 4-week follow-up phase

Route of administration: Topical, 75 mg azelaic acid (0.5 g) foam per application, twice daily for 12 weeks

According to the protocol, for a single application; approximately 0.5 g foam of the investigational product, the size of a (b) (4), will be administered topically in a non-occlusive fashion. Because each application of 0. 5g AzA Foam, 15% contains 75 mg AzA, this result in a total daily dose of 150 mg AzA (twice daily dose regimen). Given that the total skin surface area of an average adult is 1.5 to 2.0 square meter and the proportion of the face is approximately 5%, the area to be treated with AzA Foam, 15% or vehicle is 750 to 1000 square centimeter, i.e. per dosage, 75 mg AzA will be applied to 750 to 1000 square centimeter skin corresponding to an application of 0.075 to 0.1 mg AzA (0.5 to 0.67 mg foam) per square centimeter skin.

Reviewer's comment: *The Dosage and Administration portion of the label specifies the use of* (b) (4) *amount applied twice daily. Generally, labeling should be consistent with the terms applied to measure the application of the product. The use of this term is not adequate to determine a 0.5 gram dosage per application.* (b) (4) *does not exist in any precedent labeling for topically applied products.*

Inclusion criteria:

- Diagnosis of papulopustular rosacea (IGA score of moderate or severe) presenting a minimum of 12 and no more than 50 inflammatory lesions (papules and/or pustules) and persistent erythema with or without telangiectasia
- Free of any clinically significant disease, which could interfere with the study
- Male or female subject aged ≥ 18 years
- Willingness of subject to follow all study procedures
- Signed written informed consent before any study-related activities are carried out

Exclusion criteria:

- Subjects who are known to be non-responders to azelaic acid
- Presence of dermatoses that might interfere with rosacea diagnosis and/or evaluation such as acne, atopic dermatitis, facial psoriasis, seborrheic dermatitis, perioral dermatitis, and various telangiectatic states basically not related to rosacea
- Ocular rosacea; phymatous rosacea; subjects with plaque-type rosacea lesions, papulopustular rosacea that requires systemic treatment
- Topical use of any prescription or non-prescription medication to treat rosacea (retinoids, pimecrolimus, corticosteroids, erythromycin, metronidazole, tacrolimus, permethrin,

azelaic acid, clindamycin, benzoyl peroxide, sulfacetamide-sulfur) within 6 weeks prior to randomization and throughout the study

- Systemic use of any prescription or non-prescription medication to treat rosacea
  - Retinoids within 6 months prior to randomization and throughout the study
  - Tetracycline (e.g., doxycycline, minocycline) within 2 months prior to randomization and throughout the study
  - Corticosteroids, erythromycin, azithromycin, and/or metronidazole within 4 weeks prior to randomization and throughout the study
- Facial laser surgery for telangiectasia (or other conditions) within 6 weeks prior to randomization
- Use of any treatment for rosacea other than the investigational products during the study
- Expected use or change of dose in the past 90 days of beta blockers, vasodilators, vasoconstrictors, non-steroidal anti-inflammatory drugs (NSAIDs), hormonal treatment, and/or drugs causing acneiform eruptions (e.g. isoniazide)
- Known hypersensitivity to any ingredients of the investigational product formulation
- Alcohol or drug abuse (history and/or current abuse)
- Incapability of giving fully informed consent
- Participation in another clinical research in parallel or within the last 4 weeks before randomization in this study
- The subject planned to be enrolled is an employee of the Sponsor, the CRO or the investigator or is directly associated with the investigator or the trial
- Any condition or therapy that in the investigator's opinion may pose a risk to the subject or that could interfere with any evaluation in the study
- Previous assignment to treatment during this study

Study Design:
This is a randomized, double-blind, vehicle-controlled, multicenter phase 3 study carried out in two parallel groups of subjects with papulopustular rosacea. Subjects will receive twice daily (morning and evening) AzA foam, 15% or twice daily (morning and evening) vehicle for a total of 12 weeks for the purpose of determining safety and efficacy.

Nine hundred sixty-one male or female subjects (approximately 480 subjects per treatment group) aged 18 years or older were included in this study. There will be approximately 40 centers participating in the study, thus approximately 24 subjects per site will be included. The study duration for each subject, including screening visit, baseline visit, treatment duration including the end-of-treatment visit, and end-of-study visit will be up to 17 weeks.

Prohibited and Concomitant Medications:

During the study, use of any treatment for rosacea other than the investigational products is prohibited. Use of particular medication is prohibited prior to and during the study, i.e., until the end-of-study visit:

- Topical use of any prescription or non-prescription medication to treat rosacea (retinoids, pimecrolimus, corticosteroids, erythromycin, metronidazole, tacrolimus, permethrin, AzA, clindamycin, benzoyl peroxide, sulfacetamide-sulfur) within 6 weeks prior to randomization and throughout the study
- Systemic use of any prescription or non-prescription medication to treat rosacea

- Retinoids within 6 months prior to randomization and throughout the study
- Tetracycline (e.g., doxycycline, minocycline) within 2 months prior to randomization and throughout the study
- Corticosteroids, erythromycin, azithromycine, and/or metronidazole within 4 weeks prior to randomization and throughout the study

In case beta blockers, vasodilators, vasoconstrictors, hormonal treatment, and/or drugs causing acneiform eruptions (e.g., isoniazide) have to be used, the subject should be stable on that medication and no change or initiation of treatment should be expected for at least 90 days prior to randomization and throughout the study.

The use of oral contraceptives, if used with a stable dose during the past 90 days, is allowed during the study.

If treatment with oral antibiotics is required during the study, for example in case of an infection, it should be attempted, if possible, to select an antibiotic not affecting rosacea. Oral antibiotics that also affect rosacea include tetracycline, erythromycin, doxycycline, minocycline, azithromycin and ampicillin. These agents may be used for the treatment of a concurrent disease (e.g. an infection) for a maximum of 10 days. If for medical reasons a course of oral antibiotic treatment for > 10 days is required, patients must be discontinued from further participation in the study.

Subject and Study Withdrawal:

Subjects must be withdrawn from the study for the following reasons:

- At their own request or at the request of their legally acceptable representative
- If, in the investigator's opinion, continuation of the study would be harmful to the subject's well-being
- In case of the occurrence of an exclusion criterion after the baseline visit which is clinically relevant and affects the subject's safety or may interfere with the study outcome, if discontinuation is considered necessary by the investigator and/or the sponsor
- In case of the occurrence of a disease requiring treatment which may interfere with the proper evaluation of the subject
- In case of the occurrence of a suspected unexpected serious adverse reaction (SUSAR)
- In case of unblinding / code-breaking; regardless if it happened accidentally or on purpose for whatever reason

- In case of the occurrence of an AE, if discontinuation of the investigational product is desired (or considered necessary) by the investigator and/or the subject and/or the sponsor
- In case of an allergic reaction to the investigational product
- At any time during the study and without giving reasons, a subject may decline to participate any further. The subject will not suffer any disadvantage as a result.
- At the specific request of the sponsor

Subjects may be withdrawn from the study for the following reasons:

- In case of non-compliance with the study protocol requirements (incl. frequency of application of study medication) at the discretion of the investigator; reasons for this decision have to be fully documented in the CRF

Efficacy:

The primary variable for assessment of efficacy is the Investigators Global Assessment (IGA) and the inflammatory lesion counts at 12 weeks. For the primary analysis, the IGA will be dichotomized into success (IGA score clear and minimal) and failure (IGA scores mild, moderate, and severe).

The number of inflammatory lesions, i.e., the number of facial papules and the number of facial pustules, will be counted at screening (documentation in the subject file (source data) to be sure in-/exclusion criteria are fulfilled), at visit 1 (baseline) as well as at visits 2 to 5 (documentation also in the CRF). For the primary analysis, the nominal change in inflammatory lesion count will be calculated.

Table 4: Investigators Global Assessment

clear	no papules and/or pustules; no erythema
minimal	rare papules and/or pustules; faint, up to but not including mild erythema
mild	few papules and/or pustules; mild erythema
moderate	pronounced number of papules and/or pustules[1]; moderate erythema
severe	numerous papules and/or pustules, occasionally with confluent areas of inflamed lesions; moderate to severe erythema

Secondary variables:

Efficacy of AzA Foam, 15% and vehicle in papulopustular rosacea will be additionally investigated using percent change in inflammatory lesion count and therapeutic response.

Reference ID: 3780201

For therapeutic response, the IGA will be dichotomized into responder (IGA scores clear, minimal, and mild) and non-responder.

For change in erythema rating, changes for a subject are grouped into 'improved', 'no change' or 'worsened' for a post-baseline visit as compared to baseline.

Table 5: Score for rating of erythema

clear or almost clear	no visible erythema or minimal 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

Erythema will be assessed at visit 1 (baseline) and visits 2 to 5.

Table 6: Score for rating telangiectasias

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% to 30% of the facial area
severe	many fine vessels and/or large vessels discernible, involves more than 30% of the facial area

Telangiectasia's will be assessed at visit 1 (baseline), and visits 2 to 5.

For change in telangiectasia rating, changes for a subject are grouped into 'improved', 'no change' or 'worsened' for a post-baseline visit as compared to baseline.

AzA has been shown to inhibit tyrosinase and is effective in treatment of hyperpigmentary disorders. No change on the color of facial skin unaffected by hyperpigmentary disorders is expected.

Table 7: Score for rating facial skin color

normal skin color compared to skin outside the treatment area
barely visible skin-lightening compared to skin outside the treatment area
mild skin-lightening compared to skin outside the treatment area
moderate skin-lightening compared to skin outside the treatment area
severe skin-lightening compared to skin outside the treatment area

Facial skin color will be assessed at visit 1 (baseline), and visits 2 to 5.

Photography will be documented at visit 1 (baseline), visit 2, visit 3, visit 4 (end-of-treatment), and visit 5.

Safety:

Adverse events will be recorded. Safety laboratories include a pregnancy test in females of child bearing potential. Other variables including a Rosacea quality of life questionnaire (RosaQoL), Dermatology Life Quality Index (DLQI), and EuroQoL Group Questionnaire.

6 Review of Efficacy

Efficacy Summary

The primary and secondary efficacy for azelaic acid foam, 15% was established by one Phase 3 clinical trial and one Phase 2 clinical trial. The design of the Phase 2 proved that the primary efficacy endpoint was adequately prespecified in the protocol; however, the secondary endpoints, including multiplicity adjustments, were not adequately prespecified. The combined pivotal Phase 2 and Phase 3 clinical trials demonstrating the efficacy and safety of the azelaic acid foam, 15% sufficiently provided data for the co-primary endpoints of IGA treatment success (clear or minimal) at Week 12 and absolute change in inflammatory lesions at Week 12.

Table 8: Efficacy Results at Week 12

	Study 120		Study 846	
	Azelaic Acid N=198	Vehicle N=203	Azelaic Acid N=483	Vehicle N=478
Primary Endpoints				
IGA clear or minimal	86 (43.4%)	66 (32.5%)	155 (32.1%)	112 (23.4%)
	p=0.017		p=0.001	
Change in inflammatory lesions	-13.0 (0.6)	-9.7 (0.6)	-13.0 (0.4)	-10.2 (0.4)
	p < 0.001		p < 0.001	
Secondary Endpoint				
Grouped erythema rating				
Improved	123 (62.1%)	108 (53.2%)	297 (61.5%)	245 (51.3%)
No change	68 (34.3%)	91 (44.8%)	178 (36.9%)	221 (46.2%)
Worsened	7 (3.5%)	4 (2.0%)	8 (1.7%)	12 (2.5%)
	p=0.138		p=0.001	

Source: Agency Biostatistical Review by Dr. Kathleen Fritsch Ph.D.

The studies enrolled subjects age 18 and older with a diagnosis of papulopustular rosacea with an IGA score of moderate to severe, 12-50 inflammatory lesions, and persistent erythema with or without telangiectasia. Subjects applied treatment twice daily for 12 weeks.

Reviewer's comment: *The total effect on rosacea is a 10% reduction to clear or minimal on IGA and an average reduction of 3 inflammatory lesions.*

6.1 Indication

Azelaic acid foam, 15% is for the topical treatment of inflammatory papules and pustules of mild to moderate (b) (4) rosacea in subjects 18 years and older.

6.1.1 Methods

The applicant provided one pivotal Phase 3 clinical trial and one pivotal Phase 2 clinical trial with prespecified co-primary efficacy endpoints of IGA treatment success (clear or minimal) at Week 12 and absolute change in inflammatory lesions at Week 12. The protocol for Phase 3 Study 846 was submitted as a Special Protocol Assessment. The Agency provided agreement regarding the overall design and primary endpoints, but the Agency did not provide agreements regarding the secondary endpoints. Study 846 defined three secondary endpoints: (1) percent change in inflammatory lesions from baseline to Week 12, (2) response rate (clear, minimal, or mild on the IGA) at Week 12, and (3) grouped change in erythema rating (improved, no change, or worsened) at Week 12. The Phase 2 study (Study 120) defined percent change in inflammatory lesions and clear, minimal, or mild on the IGA as key secondary endpoints and

Reference ID: 3780201

grouped change in erythema rating as an 'other' secondary endpoint, one of a number of 'other' secondary endpoints. The secondary endpoints of IGA clear, minimal, and mild and percent reduction in inflammatory lesions were closely related to the primary efficacy endpoints.

Table 9: Clinical Studies Overview

Study Numbers	140	120	846
Study Design	Phase 2, Randomized, double-blind, vehicle-controlled	Phase 2, Randomized, double-blind, vehicle-controlled	Phase 3, Randomized, double-blind, vehicle-controlled
Treatment arms and Sample Size	Azelaic acid – 41 Vehicle - 42	Azelaic acid – 198 Vehicle - 203	Azelaic acid – 483 Vehicle - 478
Inclusion criteria	≥18 years 10-50 inflam. lesions	≥18 years 12-50 inflam. lesions IGA mod. or severe	≥18 years 12-50 inflam. lesions IGA mod. or severe
Treatment regimen	Twice daily for 12 weeks	Twice daily for 12 weeks	Twice daily for 12 weeks
Co-primary endpoints	-IGA clear or minimal -Abs. reduction in inflam. lesions -Grouped change in erythema	-IGA clear or minimal -Abs. reduction in inflam. lesions	-IGA clear or minimal -Abs. reduction in inflam. lesions
Study location	US	US	US
Study dates	Jan. 2008-June 2008	Dec. 2009 – Aug. 2010	Sep. 2012 – Jan. 2014

Source: Agency Biostatistical Review by Dr. Kathleen Fritsch Ph.D.

Note that clinical study 140 was not used in the primary analysis as this was an exploratory Phase 2 trial.

6.1.2 Demographics

The demographic of the pivotal (Phase 2 and Phase 3) clinical trials are well balanced in terms of characteristics of the subjects. The mean age was 50 and a majority of the subjects were female (73%) and White (95.7%).

Table 10: Summary of Demographic and Baseline Characteristics (Pivotal Trials)

	Primary Analysis (N=1362)
Age (years)	
n	50.6 (12.6)
Mean (SD)	50
Median	19, 92
Min, Max	
Age group (years) [n(%)]	

< 65	1163 (85.4)
≥ 65	199 (14.6)
Gender [n(%)]	
Males	362 (26.6)
Female	1000 (73.4)
Race [n(%)]	
White	1304 (95.7)
Black	11 (0.8)
Asian	19 (1.4)
American Indian or Alaska Native	3 (0.2)
Native Hawaiian or Other Pacific Islander	1 (0.1)
Multiple	7 (0.5)
White, Black	2
White, Asian	3
White American Indian or Alaska Native	2
Other	--
Not Reported	17 (1.2)
Race group [n(%)]	
White	1304 (95.7)
Non-White *	41 (3.0)
Not Reported	17 (1.2)
Ethnicity [n(%)]	
Hispanic or Latino	307 (22.5)
Not Hispanic or Latino	1036 (76.1)
No Reported	19 (1.4)
Height (inches)	
n	**1362**
Mean (SD)	65.8 (3.7)
Median	65
Min, Max	49, 77
Weight (pounds)	
n	**1360**
Mean (SD)	185.7 (47.5)
Median	180
Min, Max	91, 398
BMI (kg/m^2)	
n	**1360**
Mean (SD)	30.1 (7.1)
Median	29
Min, Max	16, 61
Previous duration of rosacea (years)	
n	**1306**
Mean (SD)	10.9 (10.1)
Median	8
Min, Max	<1, 63
Investigators Global Assessment [n(%)]	
Clear	0
Minimal	0
Mild	0
Moderate	1195 (87.7)
Severe	167 (12.3)

Lesion count	
n	**1362**
Mean (SD)	21.3 (9.0)
Median	18
Min, Max	12, 50
Lesion count group [n(%)]	
≤ 14	350 (25.7)
<14	1012 (74.3)
Erythema rating [n(%)]	
Clear or almost clear	0
Mild	113 (8.3)
Moderate	1065 (78.2)
Severe	184 (13.5)

*Non-White includes every category (including multiple races)

As in the treatment indication, the demographics showed that a majority of the subjects had moderate to severe (87%, 12%, respectively) rosacea as assessed by the IGA and the average median duration of rosacea was 8 years.

6.1.3 Subject Disposition

The majority of subjects completed 12 weeks of treatment: 539 (79.1%) subjects in the azelaic acid foam, 15% treatment group and 525 (77.1%) subjects in the vehicle group. The mean duration of double-blind treatment was 80.1 days in the azelaic acid foam, 15% treatment group and 79.2 days in the vehicle group. Double-blind treatment in the azelaic acid foam, 15% treatment group ranged from 1 day to 154 days and in the vehicle group from 1 day to 157 days. The mean duration in the study was 107.7 days in the azelaic acid foam, 15% group and 106.6 days in the vehicle group and ranged from 1 to 256 days in the azelaic acid foam, 15% treatment group and from 1 to 204 days in the vehicle group. There were no notable differences between the 2 groups in number of completed weeks of treatment, duration of double-blind treatment, or duration in the study. Over the course of treatment, subjects assigned to the azelaic acid foam, 15% treatment group received a mean of 104.3g (1.3g/day) of study drug and subjects assigned to the vehicle foam group received a mean of 122.6g (1.5g/day) of vehicle.

Mean treatment compliance was 96.9% for the azelaic acid foam, 15% group and 96.5% for the vehicle group. Mean missed doses were 3.5 for the azelaic acid foam, 15% group and 3.7 for the vehicle group.

Study 120 randomized 198 subjects to azelaic acid and 203 to vehicle. Study 846 randomized 483 subjects to azelaic acid and 478 to vehicle. The clinical study report for Study 846 states that 484 subjects were randomized to azelaic acid and 477 subjects were randomized to vehicle, because Subject 20-020 was misclassified in the original database due to an investigator reporting error (The investigator reported that Kit 516 (azelaic acid) was dispensed when Kit 615 (vehicle) was actually the randomized and dispensed kit number.). The applicant corrected the database used in the ISS and ISE reports and proposed labeling. Results presented in this review use the corrected treatment assignment for Subject 20-020.

Reference ID: 3780201

Similar proportions of azelaic acid and vehicle subjects discontinued treatment prior to the end of the treatment period in Study 120 (approximately 10-11%); however a larger percentage of vehicle subjects than azelaic acid subjects discontinued treatment in Study 846 (17% vs. 13%). Subjects were to be followed for 4 weeks after the end of the treatment period. Thus, subjects could complete the treatment period, but discontinue before the end of the study. In Study 120, all subjects who discontinued treatment also discontinued the study; however, some subjects in Study 846 discontinued treatment but completed follow-up. The most common reasons for discontinuing treatment or follow-up were lost to follow-up and withdrawal by subject.

Reference ID: 3780201

Table 11: Disposition of Subjects in Clinical Trials 120 and 846

	Study 120		Study 846	
	Azelaic Acid	Vehicle	Azelaic Acid	Vehicle
Subjects randomized and dispensed medication (ITT)	198	203	483	478
Completed treatment	177 (89%)	183 (90%)	419 (87%)	399 (83%)
Discontinued treatment	21 (11%)	20 (10%)	64 (13%)	79 (17%)
Completed treatment and follow-up	175 (88%)	178 (88%)	402 (83%)	381 (80%)
Completed treatment but discontinued follow-up	2 (1%)	5 (2%)	17 (4%)	18 (4%)
Death	--	--	--	1 (<1%)
Lost to follow-up	1 (<1%)	3 (1%)	7 (1%)	7 (1%)
Other	--	--	2 (<1%)	3 (<1%)
Protocol violation	1 (<1%)	--	2 (<1%)	1 (<1%)
Withdrawal by subject	--	1 (<1%)	5 (1%)	3 (<1%)
Lack of efficacy	--	1 (<1%)	--	--
Discontinued treatment but completed follow-up	--	--	7 (1%)	13 (3%)
Adverse event	--	--	2 (<1%)	5 (1%)
Other	--	--	1 (<1%)	--
Protocol Violation	--	--	3 (<1%)	3 (<1%)
Withdrawal by subject	--	--	1 (<1%)	5 (1%)
Discontinued treatment and follow-up[a]	21 (11%)	20 (10%)	57 (12%)	66 (14%)
Adverse event	4 (2%)	1 (<1%)	4 (<1%)	7 (1%)
Lost to follow-up	8 (4%)	10 (5%)	28 (6%)	23 (5%)
Other	2 (1%)	1 (<1%)	1 (<1%)	3 (<1%)
Protocol violation	2 (1%)	2 (1%)	1 (<1%)	2 (<1%)
Withdrawal by subject	5 (3%)	6 (3%)	23 (5%)	31 (6%)

a Reason for discontinuing treatment.
Source: Agency Biostatistical Analysis and ise-iss Applicant submission

6.1.4 Analysis of Primary Endpoint(s)

Studies 120 and 846 were randomized double-blind, vehicle-controlled studies evaluating the safety and efficacy of azelaic acid foam 15% in the treatment of rosacea. Study 120 was designed as a Phase 2 study and Study 846 was designed as a Phase 3 study. The studies enrolled subjects age 18 and older with a diagnosis of papulopustular rosacea with an IGA score of moderate to severe, 12-50 inflammatory lesions, and persistent erythema with or without telangiectasia. Subjects were randomized in a 1:1 ratio to either azelaic acid foam or vehicle foam. Subjects applied treatment twice daily for 12 weeks. Subjects were evaluated at

screening, baseline, and Days 28, 56, 84 (end of treatment), and 112 (post-treatment follow-up). The primary efficacy timepoint was Week 12 (Day 84/end of treatment).

Although Study 120 was designed as a Phase 2 study, statistical methods for the primary efficacy endpoints were prespecified. However, the analysis methods for the secondary endpoints were not clearly prespecified and no multiplicity adjustments were prespecified for the secondary endpoints in the protocol. Study 846 was designed as a Phase 3 study and had adequate prespecification of analysis methods for the primary and secondary endpoints.

Both studies had co-primary endpoints of success on the IGA (clear or minimal) at Week 12 and absolute change in inflammatory lesions at Week 12. Both endpoints needed to demonstrate statistical significance. The studies both used an IGA scale with categories clear, minimal, mild, moderate, and severe; however the morphological descriptors used in each of the studies differed slightly as follows:

Table 12: Investigator's Global Assessment (IGA)

	Study 120	Study 846
Clear	Virtually no rosacea, ie. no papules and/or pustules; no erythema	No papules and/or pustules; no erythema
Minimal	Rare papules and/or pustules; residual to mild erythema	Rare papules and/or pustules; faint, up to but no including mild erythema
Mild	Few papules and/or pustules; mild erythema	Few papules and/or pustules; mild erythema
Moderate	Pronounced number of papules and/or pustules; moderate erythema	Pronounced number of papules and/or pustules; moderate erythema
Severe	Numerous papules and/or pustules, occasionally with confluent areas of inflamed lesions; moderate to severe erythema	Numerous papules and/or pustules, occasionally with confluent area of inflamed lesions; moderate to severe erythema

Source: Agency Biostatistical Review by Dr. Kathleen Fritsch Ph.D.

Azelaic acid foam was superior to vehicle foam on both IGA success rate and change in inflammatory lesions at Week 12 in both Studies 120 and 846 ($p<0.017$, two-sided).

The treatment effects were consistent across the two studies for the two primary endpoints, with approximately 10% more subjects achieving IGA success on the azelaic arm versus the vehicle arm and a reduction of approximately 3 additional inflammatory lesions on the azelaic acid arm versus the vehicle arm in both studies. The vehicle IGA success rate was higher in Study 120 than in Study 846 (33% vs. 23%).

Table 13: IGA Success Rate (clear or minimal) at Week 12 (120 and 846)

Study 120		Study 846	
Azelaic Acid N=198	Vehicle N=203	Azelaic Acid N=483	Vehicle N=478
86 (43.4%)	66 (32.5%)	155 (32.1%)	112 (23.4%)
p=0.017		p=0.001	

Source: Agency Biostatistical Review by Dr. Kathleen Fritsch Ph.D.

Table 14: Change in Inflammatory Lesions from Baseline to Week 12 (120)

	Nominal value		Change from baseline	
	Azelaic Acid N=198	Vehicle N=203	Azelaic Acid N=198	Vehicle N=203
Baseline [mean (SD)]	21.6 (9.9)	20.4 (8.8)		
End of treatment				
[mean (SD)]	8.2 (8.9)	10.8 (10.3)	-13.3 (10.4)	-9.5 (9.7)
[adjusted mean (SE)]	8.0 (0.6)	11.3 (0.6)	-13.0 (0.6)	-9.7 (0.6)
			$p < 0.001$	

Source: Agency Biostatistical Review by Dr. Kathleen Fritsch Ph.D.

Table 15: Change in Inflammatory Lesions from Baseline to Week 12 (846)

	Nominal value		Change from baseline	
	Azelaic Acid N=483	Vehicle N=478	Azelaic Acid N=483	Vehicle N=478
Baseline [mean (SD)]	21.7 (9.1)	21.2 (8.7)		
End of treatment				
[mean (SD)]	8.5 (8.9)	10.8 (11.3)	-13.2 (9.5)	-10.3 (9.8)
[adjusted mean (SE)]	8.5 (0.4)	11.2 (0.4)	-13.0 (0.4)	-10.2 (0.4)
			<0.001	

Source: Agency Biostatistical Review by Dr. Kathleen Fritsch Ph.D.

6.1.5 Analysis of Secondary Endpoints(s)

The studies differed in their designation of secondary endpoints. Study 120 defined two secondary endpoints. The first secondary endpoint was defined as 'response rate' where a response was defined as achieving clear, minimal, or mild on the IGA at Week 12. The other secondary endpoint was percent change in inflammatory lesions from baseline to Week 12. Study 120 was designed as Phase 2 study and did not include methods for adjusting multiplicity across secondary endpoints. All secondary endpoints were to be analyzed at the nominal 0.05 two-sided significance level.

Protocol 120 also defined a number of other secondary efficacy endpoints. The other secondary endpoints included assessments of erythema and telangiectasia. Erythema was assessed on a 4-point scale (clear or almost clear, mild, moderate, severe). Telangiectasia was also assessed on a 4-point scale (no, mild, moderate, severe). Mean erythema and telangiectasia scores were to be analyzed at each visit. The scores were also to be categorized into improved, unchanged, or worsened relative to baseline for analysis at each visit. The protocol also defined additional analyses on the IGA scores (mean nominal scores and change from baseline), and additional analyses based on the subject's global assessment of treatment response, subject's opinion on local tolerability, rating of facial skin color, and quality of life.

Study 846 defined three secondary endpoints. The three secondary endpoints were to be analyzed in sequential order (1) percent change in inflammatory lesions from baseline to Week 12, (2) response rate (clear, minimal, or mild) at Week 12, and (3) grouped change in erythema rating (improved, no change, or worsened) at Week 12.

Table 16: Secondary Efficacy Endpoints at Week 12 in Trials 120 and 846

	Study 120		Study 846	
	Azelaic acid N=198	Vehicle N=203	Azelaic acid N=483	Vehicle N=478
Percent reduction in lesions				
[mean (SD)]	-62.4% (35.7%)	-47.7% (41.3%)	-61.6% (33.5%)	-50.8% (40.0%)
[adjusted mean (SE)]	-63.4% (2.7%)	-47.9% (2.7%)	-60.7% (1.7%)	-49.5% (1.7%)
	p<0.001		p<0.001	
IGA clear, minimal, mild	137 (69.2%)	117 (57.6%)	320 (66.3%)	260 (54.4%)
	p=0.012		p<0.001	
Grouped erythema rating				
Improved	123 (62.1%)	108 (53.2%)	297 (61.5%)	245 (51.3%)
No change	68 (34.3%)	91 (44.8%)	178 (36.9%)	221 (46.2%)
Worsened	7 (3.5%)	4 (2.0%)	8 (1.7%)	12 (2.5%)
	p=0.138[a]		p=0.001[a]	

a P-value from the CMH test stratified on pooled centers using table scores. Note that in the ISE, the applicant presented one-sided p-values (0.069 for Study 120 and <0.001 for Study 846) rather than two-sided p-values.
Source: Agency Biostatistical Review by Dr. Kathleen Fritsch Ph.D.

The treatment effect for the percent reduction in inflammatory lesions was about 15% in Study 120 and 11% in Study 846, and the results are consistent with the primary efficacy endpoint of absolute reduction in lesions. The secondary endpoint of response rate (IGA clear, minimal, or mild) differs from the primary endpoints of treatment success (IGA clear or minimal) due to the inclusion of subjects with scores of mild at the end of treatment. In Study 120, similar proportions of azelaic acid and vehicle subjects had an IGA score of mild at the end of treatment (25.8% for azelaic acid and 25.1% for vehicle) leading to very similar treatment effects when 'mild' is included in the response definition or not (about 11%). In Study 846, slightly more azelaic acid and vehicle subjects had an IGA score of mild at the end of treatment (34.2% vs 31.0%), leading to a slightly larger treatment effect when 'mild' is included in the response

definition versus when it is not included (about 12% vs. 9%). Note that because the majority of subjects (≥ 87%) had an IGA score of moderate at baseline, improving 1 grade to a score of mild may not represent much of a clinically meaningful change.

Although the proportion of subjects who improved their erythema rating was greater on the azelaic acid arm than the vehicle arm in both studies, the results were not even nominally significant in Study 120 under either of the applicant's analysis methods (CMH or Wilcoxon). Note also that the proportion of subjects whose erythema worsened was greater on the azelaic acid arm than the vehicle arm in Study 120. As the grouped change in erythema endpoint allows for the category of improved for only a 1-point improvement on the erythema rating scale, such changes may not be clinically important.

(b) (4)

6.1.6 Other Endpoints

No other endpoints were evaluated in the pivotal clinical trials.

6.1.7 Subpopulations

There were too few subjects who reported a race other than white for meaningful subgroup analysis by age group or race. Treatment effects across age group, gender, and ethnicity were generally consistent in favor of azelaic acid. All subjects were enrolled in the United States.

Table 17: IGA Treatment Success Rates by Subgroup

	Study 120		Study 846	
	Azelaic acid N=198	Vehicle N=203	Azelaic acid N=483	Vehicle N=478
Age (years)				
< 65	76/180 (42%)	60/187 (32%)	119/407 (29%)	90/389 (23%)
≥ 65	10/18 (56%)	6/16 (38%)	36/76 (47%)	22/89 (25%)
Gender				
Male	13/43 (30%)	17/60 (28%)	38/129 (29%)	29/130 (22%)
Female	73/155 (47%)	49/143 (34%)	117/354 (33%)	83/348 (24%)
Race				
White	83/190 (44%)	63/196 (32%)	150/463 (32%)	105/455 (23%)
Not white	3/8 (38%)	3/7 (43%)	5/20 (25%)	7/23 (30%)
Ethnicity				
Hispanic or Latino	22/58 (38%)	14/53 (26%)	35/98 (36%)	26/98 (27%)
Not Hispanic or Latino/Not reported	64/140 (46%)	52/150 (35%)	120/385 (31%)	86/380 (23%)

Source: Biostatistical Review by Dr. Kathleen Fritsch, Ph.D.

Table 18: Mean Change in Inflammatory Lesions by Subgroup

	Study 120		Study 846	
Mean [N]	Azelaic acid N=198	Vehicle N=203	Azelaic acid N=483	Vehicle N=478
Age (years)				
< 65	-13.6 [180]	-9.5 [187]	-13.2 [407]	-10.1 [389]
≥ 65	-10.8 [18]	-9.4 [16]	-13.2 [76]	-11.2 [89]
Gender				
Male	-15.3 [43]	-9.2 [60]	-13.0 [129]	-9.8 [130]
Female	-12.8 [155]	-9.7 [143]	-13.3 [354]	-10.5 [348]
Race				
White	-13.3 [190]	-9.6 [196]	-13.4 [463]	-10.4 [455]
Not white	-13.3 [8]	-8.7 [7]	-9.8 [20]	-9.7 [23]
Ethnicity				
Hispanic or Latino	-12.4 [58]	-7.1 [53]	-11.5 [98]	-10.1 [98]
Not Hispanic or Latino/Not reported	-13.7 [140]	-10.4 [150]	-13.7 [385]	-10.4 [380]

Table presents Mean change and [subgroup sample size]
Source: Biostatistical Review by Dr. Kathleen Fritsch, Ph.D.

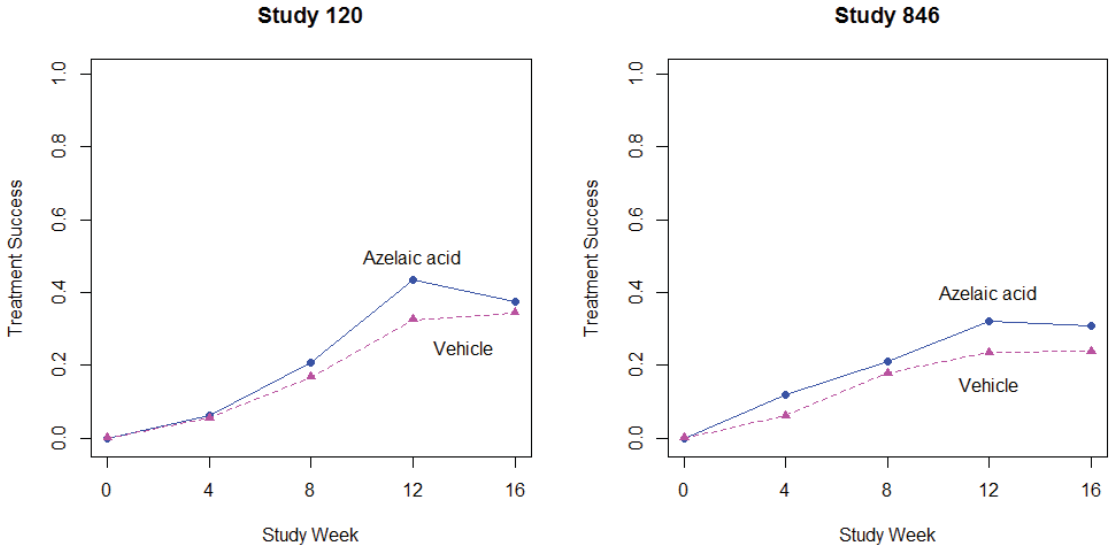
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Special dosing analysis was not done. The azelaic acid moiety is well known and marketed as an acne product.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Treatment success rates increased over time through Week 12 (end of treatment) with treatment success rates higher on the azelaic acid arm than the vehicle arm, though the differences between the two arms were small. The difference between the two arms was greatest at the end of the treatment period (Week12). Treatment success on the azelaic acid arm decreased slightly after treatment ended between Weeks 12 and 16. Although the treatment success rates on both the azelaic acid arm and the vehicle arm were higher in Study 120 than 846, the treatment effects were similar in the two studies.

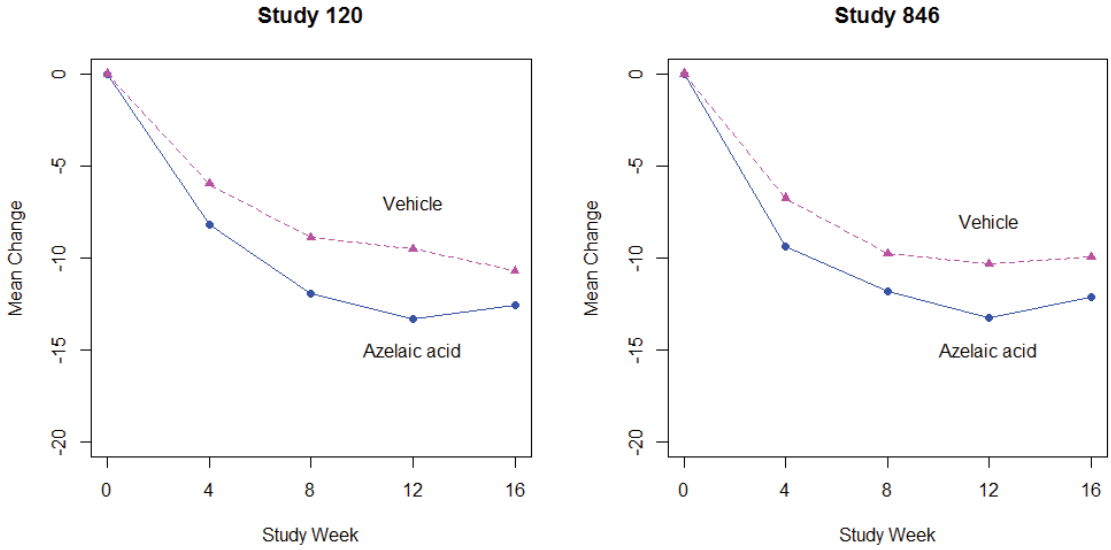
Figure 2: Treatment Success Rates over Time



Source: Biostatistical Review by Dr. Kathleen Fritsch, Ph.D.

The mean change in inflammatory lesions decreased over time through Week 12 (end of treatment) with greater decreases on the azelaic acid arm than the vehicle arm. The difference between the two arms was greatest at the end of the treatment period (Week12). The results were similar in the two studies.

Figure 3: Mean Change in Inflammatory Lesion Counts over Time



Source: Biostatistical Review by Dr. Kathleen Fritsch, Ph.D.

6.1.10 Additional Efficacy Issues/Analyses

Both studies defined the full analysis set population (FAS) as the primary efficacy analysis population. The FAS is defined as all subjects randomized and dispensed study medication. The per protocol population was defined as subjects who did not discontinue prematurely or had any major protocol deviations.

The primary method of handling missing data in the efficacy analyses was last observation carried forward (LOCF). Sensitivity analyses for IGA success include treating subjects with missing IGA observations as failures, and treating subjects with missing IGA observations as successes. Sensitivity analyses for change in lesion counts include imputing the median value within each treatment group among subjects with complete data, and conducting a repeated measures analysis on the lesion counts with factors for treatment, study week, and treatment-by-study week interaction using the unstructured covariance model.

Study 120, with 401 subjects, was conducted at 20 centers in the US. The five smallest centers (fewer than 10 subjects) were pooled into an analysis center leading to 16 analysis centers. Study 846, with 961 subjects, was conducted at 48 centers in the US. The 10 smallest centers (fewer than 10 subjects) were pooled into an analysis center leading to 39 analysis centers. The response rates and mean changes in lesion counts across centers were variable, but because each center had only a small proportion of the overall sample size, no center is overly influential on the overall results.

Reference ID: 3780201

Reviewer's comment: *The evidence that has been provided that azelaic acid foam, 15% is efficacious in the treatment of* (b) (4) *rosacea in adults 18 years and older appears to be sufficient for approval. The reviewer is aware that a single pivotal Phase 3 clinical trial was conducted and that the smaller pivotal Phase 2 clinical trial was deemed adequate to provide safety and efficacy information in the approval process. The Agency was aware that the applicant intended to use the smaller Phase 2 study as a pivotal trial early on and provided appropriate recommendations to ensure that the study would be adequately powered with appropriate endpoints. The active ingredient, azelaic acid, is well known clinically for the use in rosacea and has a long safety track record from two marketed products. In addition to the long safety history, the FINACEA FOAM product appears to have less irritation effects due to the formulation as shown in the topical safety studies. In conclusion, given the marketing history, the clinical experience, and the safety experience of azelaic acid for the treatment of rosacea, this reviewer recommends for the approval of the FINACEA FOAM product.*

Labeling will provide adequate treatment information for this drug product. (b) (4)

7 Review of Safety

Safety Summary

Azelaic acid foam, 15% was generally well tolerated. In the pooled analysis of Phase 2 and Phase 3 clinical trials, a total of 11 serious TEAEs (including one case of death) were reported: 4 SAEs in subjects treated with azelaic acid foam, 15% and 7 SAEs in subjects treated with vehicle. The death occurred in a subject randomized to vehicle. The SAEs (presented as PTs) included cases of cardiac failure congestive, hepatotoxicity, cellulitis and deep vein thrombosis in subjects included in the azelaic acid foam, 15% group as well as gastroenteritis viral, hemorrhage, accidental death, post-concussion syndrome, intervertebral disc degeneration, thyroid cancer and bipolar disorder in subjects included in the vehicle group. None of the SAEs were assessed by the investigator and by company assessment as related to study drug.

Reviewer's comment: *The safe use of azelaic acid for the treatment of rosacea is demonstrated by the clinical trials and its long time marketing history as a gel and a cream. Relatively few safety issues exist with this topical treatment, and labeling is adequate to convey these risks.*

7.1 Methods

A total of 746 subjects with papulopustular rosacea were treated with azelaic acid foam, 15% in Phase 1, Phase 2, and Phase 3 development program for this product. Two hundred eighty (280) healthy subjects were exposed to azelaic acid pre-foam emulsion, 15% in Phase 1 clinical trials.

A total of 3 clinical trials will be pooled for evaluation of safety in azelaic acid foam, 15%. These clinical trials enrolled papulopustular rosacea subjects and had identical treatment applications and endpoints.

In addition, a large, post marketing safety database exists for azelaic acid in the United States from NDA 021470 (FINACEA® Gel, 15%) approved 24-DEC-2002 as well as NDA 020428 (AZELEX® Cream, 20%) approved 13-SEP-1995.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This review will focus on the pooled safety analyses of the single pivotal Phase 2 clinical trial (1403120) and the pivotal Phase 3 clinical trial (1401846). The two trials were of similar design and duration of treatment, as well as were conducted in subjects with papulopustular rosacea. Compared to the two pivotal studies, the definition of baseline disease severity was slightly different in the eligibility criteria and no follow-up period was considered in the design of the Phase 2 trial (1402140). The inclusion of study 1402140 to the pooled safety analysis did not provide any additional safety information.

Table 19: Clinical Trials Pooled for the Safety Population

	Number of subjects	azelaic acid foam, 15%	Vehicle	Total
Phase 2				
1402140	83	41	42	83
Phase 2b				
1403120 [a]	401	198	203	401
Phase 3				
1401846 [a]	961	483	723	961

[a] Pivotal trials pooled for safety population analysis

7.1.2 Categorization of Adverse Events

The safety profile is based on Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOCs) and preferred terms (PTs, MedDRA Version 16.1). The safety data are presented as treatment-emergent adverse events (TEAEs). A TEAE is defined as an adverse event (AE) that emerges after start of treatment until end of study, having been absent pre-treatment, or worsens relative to the pre-treatment state.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The safety database in this review comprises of 681 subjects randomized to azelaic acid foam, 15% in the two pivotal clinical trials (1403120 and 1401846). All subjects in the pivotal clinical trials were treated with azelaic acid foam, 15% twice daily for 12 weeks.

7.2 Adequacy of Safety Assessments

The assessments of safety for this topical drug are adequate. There are no specific safety concerns for this product.

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

The overall exposure to azelaic acid foam, 15% in the pivotal clinical trials (N= 1362) is summarized in the table below. The results of the studies indicated that the majority of the subjects were exposed to the planned dose of study drug. When necessary, AEs were managed with dose reductions. Therefore, the safety data evaluated and presented in this submission together with the safety profile presented for FINACEA® Gel in NDA 021470 is representative of that expected to be seen in subjects treated with azelaic acid foam, 15%.

Table 20: Summary of Exposure to Study Drug (Full Analysis Set)

	Safety Pool Overall (N=1362)
	n (%)
Number of completed weeks of treatment	
0	43 (3.2)
1	8 (0.6)
2	3 (0.2)
3	8 (0.6)
4	33 (2.4)
5	10 (0.7)
6	9 (0.7)
7	11 (0.8)
8	19 (1.4)
9	10 (0.7)
10	9 (0.7)
11	133 (9.8)
12 or more	1064 (78.1)
Missing	2 (0.1)
Duration of Treatment (days) [a]	
n	1360
Mean (SD)	79.7 (20.3)
Median	85.0

Min, Max	1, 157
Duration of study (days) [b]	
n	1362
Mean	107.1 (27.4)
Median	113
Min, Max	1, 256
Average Daily Study Drug Used (gm) [c]	
n	1236
Mean	1.4 (0.71)
Median	1.3
Min, Max	0, 8
Total Study Drug Used (gm)	
n	1238
Mean	113 (58.56)
Median	103.5
Min, Max	0, 389

a Duration of treatment= last day of dosing – first day of dosing +1
b Duration in study = last day on study – date of randomization+1
c Average daily study drug used = total study drug used/duration of treatment
Source: ISS/ISE

Reviewer's comment: *Sufficient exposure to the study drug product was attained during the two clinical trials. Over 78% of the subjects completed 12 or more weeks of study drug exposure. The mean amount of drug (1.4 grams/day) used is indicative of adequate exposure.*

Table 21: Subject Disposition and Analysis Population (All Subjects)

	Primary Analysis
Subjects Screened	**1642**
Subjects discontinued prior to randomization [n(%)] **Primary reason not randomized**	280 (17.1)
Adverse event	0
Death	0
Withdrawal by subject	3 (0.2)
Lost to follow-up	0
Screen failure	272 (16.6)
Other	5 (0.3)
Unknown	0
Subjects randomized and study drug dispensed	1362 (100.0)
Fall analysis set [a], FAS [n(%)]	1178 (86.5)
Prematurely discontinued treatment phase [n(%)] **Primary reason for discontinuing treatment phase**	**184 (13.5)**
Adverse event	23 (1.7)
Death	0
Withdrawal by subject	71 (5.2)
Lost to follow-up	69 (5.1)
Protocol deviation	13 (1.0)

Other	8 (0.6)
Unknown	0
Complete follow up [n(%)]	1156 (84.9)
Prematurely discontinued from follow up [n(%)] **Primary reason for discontinuation from follow-up**	**131 (9.6)**
Adverse event	7 (0.5)
Death	1 (0.1) [b]
Withdrawal by subject	57 (4.2)
Lost to follow-up	41 (3.0)
Protocol deviation	12 (0.9)
Other	13 (1.0)
Unknown	0

[a] FAS-full analysis set: all subjects who are randomized and received study medications.
[b] One death occurred in a subjected randomized to vehicle. This was an 83 years old man who experienced fatal head trauma after falling. Investigators deemed this AE as not related to drug.

The primary safety analysis consisting of the pivotal studies screened 1642 subjects, of which 1362 were randomized to treatment; 681 were randomized to azelaic acid foam, 15% and 681 were randomized to vehicle. A total of 1178 (86.5%) subjects completed the treatment phase. A small proportion of the subjects discontinued treatment and/or follow-up including refusal to participate in the follow-up period. The most reported reason for discontinuation from the treatment phase was withdrawal by subject 71 (5.2%). The most reported reason for discontinuing from follow-up was withdrawal by the subject (57 [4.2%] subjects). A very small proportion of the subjects (23 [1.7%]) withdrew from the treatment phase of the study because of an AE.

Section 6.1.2 provided detailed demographics and characteristics of the study population. In addition to the described demographics, information on prior and concomitant medications was reported. Overall, 133 (9.8%) subjects had reported prior medication use; 72 (10.6%) subjects in the azelaic acid foam, 15% treatment group and 61 (9.0%) subjects in the vehicle treatment group. The most frequently reported prior medications were metronidazole (19 [2.8%] subjects in the azelaic acid foam, 15% group and 14 [2.1%] subjects in the vehicle group) and doxycycline (7 [1.0%] subjects in the azelaic acid foam, 15% group and 9 [1.3%] subjects in the vehicle group). There were no notable differences between treatment groups in prior medications.

A total of 1024 (75.2%) of subjects took at least one concomitant medication. The most common concomitant medication by PT class were acetylsalicylic acid, paracetamol, lisinopril and multivitamin.

7.2.2 Explorations for Dose Response

The proposed indication for azelaic acid foam, 15% is the same as it is for the currently approved 15% gel formulation (FINACEA® (azelaic acid) Gel, 15%). In the United States, the respective new drug application (NDA) 021470 for FINACEA® (azelaic acid) Gel, 15% was approved on

December 24, 2002. The dose-response relationship for this topical product in the treatment of rosacea has been previously explored and was not repeated for this application.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was conducted during the development program of the drug product.

7.2.4 Routine Clinical Testing

Clinical laboratory evaluations were performed in particular phase 1 studies (study 1401841, study 1401842 and study 1401843) presented in this SCS. In study 1401841, clinical laboratory evaluations were performed before exposure to the study drugs and at the end of study, while in study 1401842, clinical laboratory evaluations were performed only before exposure to the study drugs. In study 1401843, clinical laboratory evaluations were performed at Day -2 and Day -1 before the beginning of each treatment period, immediately before application of the study drug and at the end of each treatment period. All laboratory evaluations were performed with respect to reference ranges defined for every parameter for each individual study.

There were no clinically relevant laboratory abnormalities for hematology, biochemistry and urinalysis reported in the studies described above. The results from clinical laboratory evaluations after exposure with azelaic acid foam, 15% are consistent with those previously described for other azelaic acid-containing topical formulations (i.e., FINACEA® Gel NDA 021470). Based on data from the phase 1 pharmacokinetic study (study 1401843) indicating that treatment with azelaic acid foam, 15% does not result in a higher systemic exposure compared to azelaic acid gel, 15% (Section 4.4), no difference between azelaic acid foam, 15% and FINACEA® (azelaic acid) Gel, 15% in risk for triggering clinically relevant laboratory abnormalities is expected.

7.2.5 Metabolic, Clearance, and Interaction Workup

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

A detailed discussion of adverse events in post-marketing of FINACEA (azelaic acid) gel, 15% is presented in Section 8. No other evaluations for potential adverse events are conducted during this development plan.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in any subjects included in the azelaic acid foam, 15% treatment group. One death occurred in a subjected randomized to vehicle. This was an 83 years old man who experienced fatal head trauma after falling. Investigators deemed this AE as not related to "drug".

7.3.2 Nonfatal Serious Adverse Events

All TEAEs in the pivotal Phase 2 and Phase 3 clinical trial was combined for analysis. The azelaic acid foam, 15% was well tolerated and the TEAEs were comparable to vehicle in the pooled safety analysis.

Table 22: Treatment Emergent Adverse Events Occurring in ≥ 1% of Subjects in pivotal Phase 2 and Phase 3 clinical trials

	All Adverse Events			
	Azelaic acid foam, 15% (N=681)		Vehicle (N=681)	
System Organ Class Preferred Term	Number of events	Number (%) of subjects	Number of events	Number (%) of subjects
Any AE	358	217 (31.9)	252	167 (24.5)
Infections and Infestations				
Any event	90	81 (11.9)	70	63 (9.3)
Nasopharyngitis	28	26 (3.8)	25	24 (3.5)
Upper respiratory tract infection	12	12 (1.8)	10	9 (1.3)
General disorder and administrative site conditions				
Any event	86	57 (8.4)	56	38 (5.6)
Application site pain	42	32 (4.7)	10	9 (1.3)
Application site pruritus	13	13 (19)	2	2 (0.3)
Nervous system disorder				
Any event	50	34 (5.0)	21	18 (2.6)
Headache	46	30 (4.4)	16	13 (1.9)
Injury, poisoning, and procedural complications				
Any event	24	21 (3.1)	13	11 (1.6)
Skin and subcutaneous tissue disorder				
Any event	22	18 (2.6)	25	13 (1.9)
Respiratory, thoracic, and mediastinal disorder				
Any event	17	13 (1.9)	15	14 (2.1)
Gastrointestinal disorders				

Any event	13	11 (1.6)	8	6 (0.9)
Musculoskeletal and connective tissue disorders				
Any event	10	10 (1.5)	17	14 (2.1)
Neoplasm benign, malignant, and unspecified (incl. cyst and polyps)				
Any event	9	7 (1.0)	6	5 (0.7)

In the azelaic acid foam, 15% group, the most frequent (≥ 1% of subjects) observed TEAEs by PT (SOC) included application site pain (general disorders and administrative site conditions; 4.7% of subjects), headache (nervous system disorders; 4.4% of subjects), nasopharyngitis (infections and infestations; 3.8% of subjects), application site pruritus (general disorders and administrative site conditions; 1.9% of subjects), and upper respiratory tract infection (infections and infestations; 1.8% of subjects). The most frequently (≥ 1% of subjects) observed drug-related TEAEs by PT (SOC) included application site pain (general disorders and administrative site conditions; 4.7% of subjects) and application site pruritus (general disorders and administrative site conditions; 1.9% of subjects).

The most frequently (≥ 1% of subjects) observed TEAEs by PT (SOC) observed with vehicle included nasopharyngitis (infections and infestations; 3.5% of subjects), headache (nervous system disorders; 1.9% of subjects), application site pain (general disorders and administrative site conditions; 1.3% of subjects) and upper respiratory tract infection (infections and infestations; 1.3% of subjects).

At least one drug-related TEAE occurred in 8.5% and 4.6% of subjects in the azelaic acid foam, 15% group and vehicle group, respectively. In both treatment groups, most of the reported drug-related TEAEs were administrative site conditions, and the most common drug-related TEAE was administrative site pain in both groups (azelaic acid foam, 15% group, 4.7%; vehicle group, 1.3%).

7.3.3 Dropouts and/or Discontinuations

Discontinuations and dropouts were uncommon in the pooled safety analysis of the pivotal Phase 2 and Phase 3 clinical trials. The majority of the withdrawals due to an AE were caused by application site AEs.

Table 23: Summary of Adverse Events Leading to Study Drug Withdrawal

	All Adverse Events			
	Azelaic acid foam, 15% (N=681)		Vehicle (N=681)	
Number of events	**All**	**Drug Related**	**All**	**Drug Related**
AEs reported	359	88	256	46
TEAEs reported	358	88	252	46
SAEs reported	4	0	7	0

AEs leading to study drug withdrawal	17	13	20	12
AEs leading to death	0	0	0	0
Prevalence of TEAEs				
Baseline-Week4	174	79	86	29
Week5-Week8	150	36	120	29
Week9-Weke12	139	30	87	21
Week13-Week16	93	23	62	10

The incidence of AEs leading to discontinuation of study drug was generally low. For azelaic acid foam, 15%, drug-related AEs (presented as PTs) causing discontinuation of study drug in the safety analysis included application site pain, application site erythema, application site reaction, application site dryness, application site papules, application site urticaria, application site dermatitis, application site erosion, application site hypersensitivity, application site scab, headache, urticaria and rosacea.

Of note, in the vehicle group, TEAEs observed in the SOC immune system disorders included application site hypersensitivity in 1 (0.1%) subject. The application site hypersensitivity occurred on the face. The subject was exposed to the study drug for 62 days at the time the TEAE was recorded. The event was considered related to study drug by the investigator.

7.3.4 Significant Adverse Events

A total of 11 serious TEAEs which occurred in 11 subjects were reported in pooled studies. Four (4) SAEs were observed in subjects treated with azelaic acid foam, 15% and 7 SAEs occurred in subjects treated with vehicle.

The SAEs (presented as PTs) included cases of cardiac failure congestive, hepatotoxicity, cellulitis and deep vein thrombosis in subjects included in the azelaic acid foam, 15% group as well as gastroenteritis viral, hemorrhage, accidental death, post-concussion syndrome, intervertebral disc degeneration, thyroid cancer and bipolar disorder in subjects included in the vehicle group. None of the SAEs was assessed as related to study drug by either the investigator or this reviewer.

7.3.5 Submission Specific Primary Safety Concerns

As for all topical products, the primary safety concerns are application site specific safety events. For azelaic acid, there is significant experience of the active ingredient for the treatment of rosacea. Azelaic acid exists as a 15% gel and as a 20% cream, with enough post-marketing experience to assist in the evaluation of long-term safety for this foam product. The AEs for application site safety issues are discussed in common AE section. The post-marketing safety concerns are discussed in Section 8.

Reference ID: 3780201

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common adverse events were local cutaneous reactions that are commonly seen in topical products. The events show in the table below includes combined MedDRA preferred terms to describe the adverse events more fully. FINACEA Foam appears to be well tolerated in the pivotal trials.

Table 24: Incidence of Adverse Drug Reactions Reported in ≥ 0.1% of Subjects Treated with Finacea Foam and Corresponding Values in Subjects Treated with Vehicle

System/Organ Class Preferred Term	Finacea Foam, 15% (N=681) n (%)	Vehicle (N=681) n (%)
Local Cutaneous Adverse Events		
Application site pain*	42 (6.2%)	10 (1.5%)
Application site pruritus	17 (2.5%)	2 (0.3%)
Application site dryness	5 (0.7%)	5 (0.7%)
Application site erythema	5 (0.7%)	6 (0.9%)
Application site reaction	3 (0.4%)	0 (0.0%)
Application site exfoliation	2 (0.3%)	1 (0.1%)
Local Swelling	1 (0.1%)	1 (0.1%)
Dermatitis contact	3 (0.4%)	2 (0.3%)
Urticaria	2 (0.3%)	0 (0.0%)

*Similar terms were combined.
Source: IR request to the sponsor during the review and the ISS

Reviewer's comment: *The site specific adverse events were less than those reported for the gel product. Labeling will include all local adverse events that are ≥ 0.5%. Some events were equal to or less than the vehicle events.*

7.4.2 Laboratory Findings

Standard laboratory studies were not done with these clinical trials.

7.4.3 Vital Signs

Vital signs (systolic and diastolic blood pressure, heart rate) were assessed in particular phase 1 studies (study 1401841, study 1401842, and study 1401843). Measurements were done before exposure to the study drugs, after 5, 6 and 7 days of exposure to the study drugs (study 1401843 only) and at the end of the study.

There were no AE reports related to changes in vital signs (blood pressure and heart rate).

7.4.4 Electrocardiograms (ECGs)

No ECGs were completed with these clinical trials.

7.4.5 Special Safety Studies/Clinical Trials

Dermal safety studies were conduct with the final to-be-marketed FINACEA foam, 15% product. The cumulative irritant patch test and the sensitizing potential testing will be discussed in this section.

Study 1401841:

TITLE: A randomized, double-blind, vehicle-controlled phase 1 dermal safety study using a 21 day cumulative irritant patch test design to evaluate the local tolerability of Azelaic Acid 15% Pre-Foam formulation in healthy volunteers.

This was a 21-day cumulative irritation study. The test fields were located on the upper arms and marked on the skin. On days of dosing test chambers containing the test substances were applied to the test fields for approximately 24 hours. One test field was occluded with a test chamber, containing no test product but distilled water (negative control), and 1 test chamber contained 200 µL of SLS 0.05% solution (positive control). The study preparations were applied daily. Clinical assessments took place on each dosing day after removal of the test chambers and before renewal of treatment. The local tolerability was assessed visually by using a numeric 8-point scale (scores ranging from 0 to 7) together with a scoring system for effects on superficial skin layers (scores ranging from A to H).

Forty subjects completed the study. Safety variables included AEs, vital signs, and laboratory variables. It was concluded from this study that 15% azelaic acid formulation showed higher cumulative irritation than the vehicle pre-foam formulation, which showed an irritation potential comparable to the negative irritant control of distilled water.

Study 1401842:

TITLE: A randomized, double-blind, vehicle controlled phase 1 dermal safety study to evaluate the sensitizing potential of topically applied azelaic acid 15% pre-foam formulation in healthy subjects using a Human Repeated Insult Patch Test Design

The primary objective of this study was to determine the dermal sensitization potential of azelaic acid 15% pre-foam formulation after repeated topical application under controlled patch conditions in healthy subjects compared to its vehicle. In addition, the safety of azelaic acid 15% pre-foam formulation and its vehicle was to be assessed after topical, occlusive application to

Reference ID: 3780201

circumscribed test areas by evaluation of adverse events and laboratory evaluations reported during the study.

The study completed 228 subjects completed the induction phase and 211 subjects completed the challenge phase of the study. Under the conditions used in this study, with occlusive application of investigational products on three days per week for three weeks (induction phase), a single application after a rest period of at least 14 days (challenge phase) and a re-challenge as soon as challenge reactions had resolved (if applicable), azelaic acid 15% pre-foam formulation showed no sensitizing potential. However, in 3 subjects a possible sensitization reaction in the challenge phase could not be finally confirmed or rejected in the re-challenge phase. A probable sensitization to the vehicle pre-foam formulation was observed in one subject. No sensitization was observed for the negative control (distilled water).

During the study, 84 TEAEs were reported. Fifty-three (53) TEAEs were considered to be related to the investigational product. No clinical relevant safety laboratory parameters were observed.

Application of azelaic acid 15% pre-foam formulation was considered safe and did not show a sensitizing potential under the conditions of this study; this was confirmed by visual assessment. Although the study results do not finally exclude sensitization by the vehicle pre-foam formulation, a sensitizing potential of the vehicle alone (while the same formulation, plus the active substance azelaic acid, did not lead to this reaction while being applied in parallel and in the same subject based on the intra-individual comparison design of the study) is considered to be highly unlikely when one takes into account the composition of the vehicle, the preclinical results and the study conditions.

Reviewers comment: *The dermal safety study provided above is acceptable. The topical product azelaic acid foam, 15% is a mild irritant and a non-sensitizer. Hypersensitivity is considered a known safety concern for azelaic acid foam, 15% based on the post-marketing surveillance data received for other topical azelaic acid containing formulations and the well-known risk of propylene glycol and cetostearyl alcohol which are contained as excipients in azelaic acid foam, 15%.* (b) (4)

7.4.6 Immunogenicity

Immunogenicity was no assessed for this topical rosacea product.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Specific dosing dependency for adverse events was not evaluated in the clinical trials during the development program. Rosacea is considered a chronic condition and reuse of the product for this disease is highly likely to maintain control. Given the long history of use in a post-marketing setting, long-term use adverse event are not expected.

7.5.2 Time Dependency for Adverse Events

There does not appear to be any specific timed adverse events associated with the use of the drug product.

7.5.3 Drug-Demographic Interactions

No effects of age, sex, race, or ethnicity were found with the investigational product based on the safety data analysis. There were no significant signals in the safety results based on intrinsic factors investigated.

Of the total number of subjects in clinical studies of FINACEA Foam, 18.8% were 65 and over, while 7.2% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

7.5.4 Drug-Disease Interactions

Extrinsic triggers that may be associated with the initiation or aggravation of rosacea including ultraviolet radiation, heat (rarely noxious cold), spicy food, alcohol, stress, and microbial infestation on the face or in the gut (bacterial overgrowth). Therefore, patients should be advised to avoid triggers to help manage rosacea

7.5.5 Drug-Drug Interactions

There is no drug-drug interaction studies provided in this application. No interaction potential is expected for this topical product.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No carcinogenicity is expected for this topical product.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies of topically administered azelaic acid in pregnant women. Therefore, azelaic acid foam, 15% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known if azelaic acid is secreted into human milk in vivo. However, an in vitro equilibrium dialysis experiment demonstrated that passage of drug into maternal milk may occur. Since azelaic acid is not concentrated in milk and the amount reaching the systemic circulation after topical application of azelaic acid is considered not to be clinically relevant, a meaningful change from baseline azelaic acid levels in the milk is not expected.

However, caution should be exercised when azelaic acid foam, 15% is administered to a nursing woman. No well-controlled studies of topically administered azelaic acid in nursing women are available.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and efficacy of FINACEA Foam in children below the age of 18 years have not been established.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no overdose or drug abuse potential for this drug product. Rebound and withdrawal is not applicable. Rosacea is considered a chronic disease and reuse and re-application of this product is likely to occur.

7.7 Additional Submissions / Safety Issues

No additional safety issues are found in this application.

8 Postmarket Experience

A large safety database exists for azelaic acid and spans twenty years of marketing history. Specifically in the US, this database is inclusive of NDA 021470 (FINACEA® (azelaic acid) Gel, 15% approved 24 DEC 2002) as well as NDA 020428 (AZELEX® (azelaic acid) Cream, 20% approved 13 SEP 1995). Worldwide, Bayer currently markets 106 azelaic acid-containing

formulations in over 80 countries and under different trademarks for both acne and rosacea: 70 cream formulations and 36 gel formulations. In 2013, approximately (b) (4) units of azelaic acid formulations were sold, with an estimated 3.02 million person-months (approximately 251,710 person-years) of exposure in 2013 (based on the current Periodic Safety Update Report (PSUR) covering the period 03 Jan 2013 – 02 Jan 2014). Based on unit sales figure as reported in sequential azelaic acid PSURs/PBRERs since launch of azelaic acid in 1990 to 2014, the combined exposure to azelaic acid in these approved formulations exceeds an estimated 3.8 million person-years (Section 6). A favorable risk benefit ratio for the azelaic acid containing formulations can be confirmed from the PSURs over the last 12 years.

Focus is also placed on selected topics of special interest/relevance to this azelaic acid foam, 15% submission inclusive of: 1) skin irritation (included in the "warnings and precautions" section of the US Package Insert for FINACEA (azelaic acid) Gel, 15%), 2) hypersensitivity (b) (4) 3) overdose (general systemic safety concern) and 4) significant cardiac disorders (for the purposes of providing data supporting a lack of cardiotoxicity associated with topical azelaic acid).

Skin Irritation
From the first launch of an azelaic acid containing formulation in 1990 up to the cut-off date of this review (31 JUL 2014): a) thirty-eight (38) cases reporting skin irritation were received for FINACEA® (azelaic acid) Gel, 15% and b) fourteen (14) cases were received for azelaic acid cream, 20%. The search criterion in the Bayer Safety Database was MedDRA version 17.0 PT 'skin irritation'.

Of the 38 cases cumulatively received for FINACEA® (azelaic acid) Gel, 15% four (4) cases were received after the end date of the reporting period (02 JAN 2014) of the most recent PBRER/PSUR (PBRER/PSUR Azelaic Acid 02/2014 Version 21.0) and no case was received for azelaic acid cream, 20%. Three of these 4 cases consist of consumer reports from Brazil and one of these cases is a medically confirmed case report from the US (2014-045507). None of these cases indicates any new relevant safety information beyond the already well-known and adequately labeled potential occurrence of skin irritation, usually during the first few weeks of treatment, for FINACEA (azelaic acid) Gel, 15%.

Hypersensitivity
Thirty-one (31) cases reporting hypersensitivity were cumulatively received from the first launch up to the cut-off date of this review (31 JUL 2014) for FINACEA® (azelaic acid) Gel, 15%. The search criteria in the Bayer Safety Database were MedDRA version 17.0 PTs 'hypersensitivity' and 'drug hypersensitivity.

Three of these cases were received after the end date of the reporting period (02 JAN 2014) of the most recent PBRER/PSUR. Two (2) of these cases were non-serious consumer reports from the US (2014-067702) and Brazil (2014-089652) reporting allergic reaction and allergy, respectively. The third case report was a serious medically confirmed case report from Brazil (2014-080758) reporting allergic reaction to AZELAN and wheals around the mouth.

For the azelaic acid cream formulation, fourteen (14) cases of hypersensitivity were cumulatively received. None of these 14 cases was received after the end date of the reporting period (02 JAN 2014) of the most recent PBRER/PSUR.

Additionally, one (1) serious, medically confirmed case reporting anaphylactic reaction, angioedema, face edema, swallowing difficult and edema of anterior neck assessed as related by both the reporter and the company (US-SHR-02-002047) and one (1) non-serious, medically confirmed case reporting eczema on face and neck and suspected type IV allergy (94/310270/1) are contained in the Bayer Safety Database up to the cut-off date of this review (31 JUL 2014) for azelaic acid cream, 20%.

Moreover, in MedDRA SOC skin and subcutaneous tissue disorders under the PT 'dermatitis allergic", there are cumulatively three (3) cases for FINACEA® (azelaic acid) Gel, 15% and six (6) cases for azelaic acid cream, 20% and under the PT 'dermatitis contact', there are cumulatively six (6) cases for FINACEA® (azelaic acid) Gel, 15% and eight (8) cases for azelaic acid cream, 20% contained in the Bayer Safety Database up to the cut-off date of this review (31 JUL 2014) indicating drug hypersensitivity reactions supposably being immunologically mediated. Other reported events for FINACEA® (azelaic acid) Gel, 15% as well as for azelaic acid cream, 20% (e.g. eczema, rash, urticaria) might also point to potentially underlying drug hypersensitivity reactions of both allergic and non-allergic nature.

Hypersensitivity is considered a known safety concern for azelaic acid foam, 15% based on the post-marketing surveillance data received for other topical azelaic acid containing formulations and the well-known risk of propylene glycol and cetostearyl alcohol which are contained as excipients in azelaic acid foam, 15% for causing hypersensitivity when applied topically to the skin of human beings. (b) (4)

Cardiac Disorders

There are 11 cases of cardiac disorders in Bayer´s safety database from the first launch of an azelaic acid containing formulation in 1990 up to the cut-off date of this review (31 JUL 2014) for FINACEA® (azelaic acid) Gel, 15% and five (5) cases for azelaic acid cream, 20%.

No case of cardiac disorders for either formulation was received after the end date of the reporting period (02 JAN 2014) of the most recent PBRER/PSUR.

There is extensive and long-lasting clinical experience with FINACEA® (azelaic acid) Gel, 15% worldwide and since its approval in 2002 in the US. Compared to the estimated cumulative exposure to topical azelaic acid-containing formulations of more than 3.8 million person-years since the first launch of a topical formulation containing azelaic acid marketed by Bayer, the number of adverse reactions pointing to any type of cardiac disorder is very low and does not

indicate any specific pattern or accumulation. Therefore, cardiac disorders are currently not classified as a safety concern.

Additionally, the following adverse reactions and topics are being closely monitored in PSURs/PBRERs for Bayer's topical azelaic acid: worsening of asthma, skin cancer, hypertrichosis, oral herpes infections and photosensitivity reactions.

Reviewer's comment: *Adequate post-marketing safety database is presented for the cream and gel formulations of azelaic acid which dates back to 1995.*

9 Appendices

i. Label

9.1 Literature Review/References

1. Akamatsu H, Komura J, Asada Y, Miyachi Y, Niwa Y. Inhibitory effect of azelaic acid on neutrophil functions: a possible cause for its efficacy in treating pathogenetically unrelated diseases. Arch Dermatol Res. 1991; 283(3):162-6.
2. Gerber, PA, Buhren BA, Steinhoff M, Homey B. Rosacea: The cytokine and chemokine network. J Investig Dermatol Symp Proc. 2011 Dec;1 5(1): 40-7.
3. Gollnick H, Layton A. Azelaic acid 15% gel in the treatment of rosacea. Expert Opin Pharmacother. 2008 OCT, 9(15): 2699-706.
4. Jones DA. Rosacea, reactive oxygen species, and azelaic acid. J Clin Aesthet Dermatol. 2009 Jan; 2(1):26-30.
5. Mastrofancesco A, Ottaviani M, Aspite N, Cardinali G, Izzo E, Graupe K, et al. Azelaic acid modulates the inflammatory response in normal human keratinocytes through PPARgamma activation. Exp Dermatol. 2010 Sep; 19(9):813-20.
6. Coda ad, Hata T, Miller J, Audish D, Kotol P, Two A, et al. Cathelicidin, Kallikrein 5, and serine protease activity is inhibited during treatment of rosacea with azelaic acid 15% gel. J Am Acad Dermatol. 2013 Oct; 69(4):570-7.
7. Yamasaki K, Di Nardo A, Bardan A, Murakami M, Ohtake T, Coda A, et al. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. Nat Med. 2007 Aug; 13(8):975-80.

9.2 Labeling Recommendations

Specific labeling recommendations are provided to the edit of the applicant provided draft labeling. The final labeling will be contained in the approval letter.

9.3 Advisory Committee Meeting

No advisory committee was convened for this drug product. No novel or complex regulatory issues arose during the development program or the Agency review.

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

GARY T CHIANG
06/16/2015

DAVID L KETTL
06/17/2015