CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207071Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA #:	207071
Submission Date:	September 30, 2014
Brand Name:	Finacea Foam
Generic Name:	Azelaic acid (b) (4), 15%
Dosage Form:	Foam
Dosage Strength:	15%
Reviewer:	Chinmay Shukla, Ph.D.
Team Leader:	Doanh Tran, Ph.D.
OCP Division:	Division of Clinical Pharmacology - 3
OND Division:	Division of Dermatology and Dental Products
Sponsor:	Bayer Health Care Pharmaceuticals Inc.
Relevant IND(s):	77516
Submission Type:	New-submission
Indication:	Topical treatment of inflammatory papules and pustules of mild to moderate rosacea in adults

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1. Executive Summary

The applicant of this New Drug Application (NDA) has developed Azelaic acid, 15% Foam formulation for twice daily topical treatment of inflammatory papules and pustules of mild to moderate rosacea in adults. Azelaic acid (Finacea®) Gel, 15% was approved on December 24, 2002 (NDA 21470) for the treatment of inflammatory papules and pustules of mild to moderate rosacea and this product is owned by the same applicant as this NDA. Azelaic acid (Azelex®) Cream, 20% is another product and was approved on September 13, 1995 (NDA 20428) for the treatment of mild-to-moderate inflammatory acne vulgaris (Applicant: Allergan).

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 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

1.1 Recommendation

From a Clinical Pharmacology standpoint, this application is acceptable provided the labeling comments are adequately addressed by the Applicant.

1.2 Post-Marketing Commitments/ Requirements

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

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 C_{max}, AUC_{0-12}, and AUC_{0-36} 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 C_{max}, AUC_{0-12}, and AUC_{0-36}, 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 C_{max}, AUC_{0-12}, and AUC_{0-36}, 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 (C_{max} and AUC_{0-12}) 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).

Dose finding: The applicant did not conduct any new dose finding trials. The dose and dosing regimen for Azelaic acid Foam, 15%, was selected based on the dosing recommendation used in the currently approved Finacea® Gel (NDA 021470), and its known safety and efficacy profile in rosacea. Hence, the proposed dosing regimen (twice daily) and the population (adults with mild to moderate rosacea) for the new Azelaic acid, 15%, Foam formulation is identical to currently approved Finacea® Gel.

Drug interaction assessments and QTc interval prolongation: The applicant has not conducted any new studies with the new Foam formulation and they relied on the information in the currently approved Finacea® Gel NDA. This approach is supported by the results of the maximal use PK trial (1401843) which showed that the systemic exposure of the new Foam was not higher than Finacea® Gel.

Pediatric assessment: The applicant has requested a full waiver of pediatric assessment due to studies being impossible or highly impractical as the number of pediatric subjects with rosacea is extremely small.

Reviewer comments: *The applicant submitted their initial pediatric study plan (iPSP) on 08/05/2014, requesting a full waiver of pediatric assessment. The Agency agreed to the applicant's request for a full waiver on 11/25/2014 (see communication in DARRTS under IND 77516).*

Clinical Pharmacology Briefing: An optional intra-division level briefing was conducted on May 18, 2015 with the following in attendance: CAPT. E. Dennis Bashaw, Lei Zhang, Doanh Tran and Chinmay Shukla.

2. Question Based Review

2.1 Regulatory pathway

2.1.1 What regulatory pathway has the Applicant followed?

The applicant plans to rely on Pharmacology-Toxicology and long term safety information from currently approved Finacea, Gel, 15% (NDA 21470). The applicant of this NDA owns Finacea® Gel, 15%. Hence, this application will follow a 505(b)(1) regulatory pathway.

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry the formulation?

Drug substance and Formulation: Azelaic acid has been found as a naturally-occurring substance in plants, animals and humans and is a constituent of whole grain cereals such as wheat, rye and barley. According to the applicant, azelaic acid can be found in these cereals in amounts ranging from 0.4 to 7 mg per gram and humans are exposed to azelaic acid from both dietary and endogenous sources throughout their lifetime. Endogenously, azelaic acid is formed from potential precursors such as odd-numbered longer-chain dicarboxylic acids [redacted] (b) (4)

Azelaic acid is chemically described with the molecular formula $C_9H_{16}O_4$, and the molecular weight is 188.22 g/mol. The chemical structure of azelaic acid is shown in Figure 1.

Figure 1: Structure of azelaic acid

Formulation: The dosage form is Foam containing 15% [redacted] (b) (4) azelaic acid suspended in an oil-in water (O/W) emulsion. The composition of the to-be-marketed formulation is shown in Table 1 below.

Table 1: Qualitative and quantitative composition of to-be-marketed formulation of Azelaic acid Foam, 15%

100 g foam contains:

Composition	Reference to Standard	Function	Amount [g]
Drug substance			
Azelaic acid [redacted] drug substance	specification	Drug substance	15.00
Excipients			[redacted]
Benzoic acid	USP/NF		
Cetostearyl alcohol	USP/NF		
Dimethyl isosorbide	specification		
Medium-chain triglycerides	USP/NF		
Methylcellulose	USP/NF		
Mono- and di-glycerides	USP/NF		
Polyoxyl 40 stearate	USP/NF		
Polysorbate 80	USP/NF		
Propylene glycol	USP/NF		
Xanthan gum	USP/NF		
Sodium hydroxide [a]	USP/NF		
Purified water	USP/NF		
Total			
[redacted]			

a [redacted]
b
c
d
e

2.2.2 What are the proposed mechanism of action and the therapeutic indications?

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

Therapeutic indication: Topical treatment of inflammatory papules and pustules of mild to moderate rosacea in adult subjects.

2.2.3 What is the proposed route of administration, dosage and dosing frequency?

Proposed route of administration: Topical.

Proposed dosage: Apply a [redacted] of Finacea Foam twice daily (morning and evening) to the entire facial area (cheeks, chin, forehead, and nose).

Proposed dosing frequency: Twice daily.

2.3 General Clinical Pharmacology

2.3.1 What were the clinical trials conducted to support this NDA?

The clinical trials conducted to support this application are shown in Table 2 below.

Table 2: List of all clinical trials to support this NDA

Study ID	Number of Subjects Enrolled	Study Design	Study Objective
Phase I			
1401841	40	db, ra, intra c, vc	Determination of the irritation potential of azelaic acid foam,15% using the 21-day cumulative irritancy test in healthy volunteers
1401842	240	db, ra, intra c, vc	Evaluation of the sensitization potential of azelaic acid foam,15% using a human repeat insult patch testing method (HRIPT) in healthy volunteers
1401843	24	invb, ra, co	Determination of the additional systemic exposure regarding the endogenously occurring substances azelaic acid and its metabolite pimelic acid, resulting from the treatment of patients with azelaic acid foam, 15% in comparison to azelaic acid gel, 15%
Phase II			
1402140	83	mc, db, ra, vc, pg	Comparison of the action of azelaic acid foam, 15% - compared to its vehicle in patients with rosacea
1403120	401	mc, db, ra, vc, pg	Comparison of the efficacy and safety of azelaic acid foam, 15% - compared to its vehicle in patients with rosacea (considered a pivotal study by the sponsor)
Phase III			
1401846	961	mc, db, ra, vc, pg	Comparison of the efficacy and safety of azelaic acid foam, 15% - compared to its vehicle in patients with rosacea (considered a pivotal study by the sponsor)

co: cross over, db: double blind, HRIPT: human repeat insult patch test, intra c: intra-individual comparison, invb: investigator blind, mc: multicenter, pg: parallel groups, ra: randomized, vc: vehicle controlled

2.3.2 How was the dose selected?

The applicant has not conducted any new dose selection trials. The dose and dosing regimen for Azelaic acid Foam, 15%, was selected based on the dosing recommendation used in the currently approved Finacea® Gel (NDA 021470), and its known safety and efficacy profile in rosacea. Hence, the proposed dosing regimen (twice daily) and the population (adults with mild to moderate rosacea) for the new Azelaic acid, 15%, Foam formulation is identical to currently approved Finacea® Gel.

2.3.3 What is the pharmacokinetics (PK) of azelaic acid and pimelic acid (metabolite) under maximal use conditions?

Trial design in brief: The purpose of the maximal use PK trial (1401843) was to assess relative BA of azelaic acid and pimelic acid (metabolite) following twice daily administrations of the new Azelaic acid Foam, 15% formulation compared to Finacea® Gel, 15% in adult subjects with moderate rosacea. This was a randomized crossover trial and the two treatment periods were separated by a 5 to 14 day washout period. 24 subjects with moderate papulopustular rosacea were enrolled and subjects applied approximately 75 mg of azelaic acid (0.5 g foam or 0.5 g gel) per application, twice daily for 6 days with only the morning dose on Day 7. Since azelaic acid is an endogenous substance and can also be absorbed through certain types of diets (especially those rich in

whole grains), each treatment period consisted of a 2 consecutive day baseline assessment of azelaic acid and pimelic acid levels. Post dose serial plasma samples were obtained on Day 7 and trough level samples were obtained on Days 5 and 6 in both the treatment periods. Additional details can be found in Section 4.

PK of azelaic acid: On Day 7 azelaic acid systemic concentrations were quantifiable in all the subjects. The mean concentration versus time profiles for azelaic acid on Day 7 following administration of the new Foam formulation and Finacea Gel is shown in Figure 2 (baseline uncorrected) and Figure 3 (baseline corrected) and the PK parameters are shown in Table 3.

Figure 2: Mean baseline uncorrected plasma concentration versus time profile for azelaic acid on Day 7

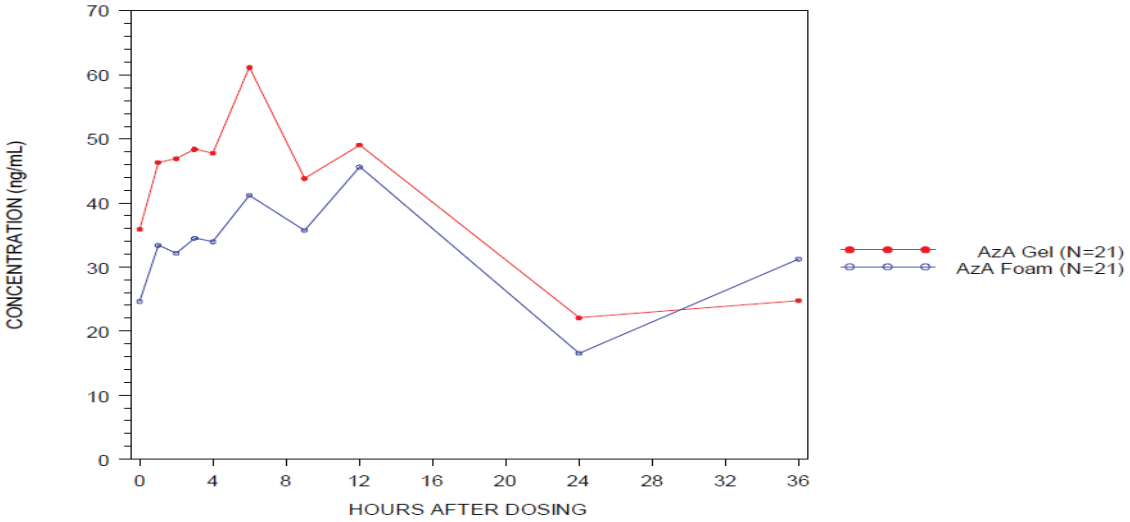


Figure 3: Mean baseline corrected plasma concentration (based on time matched subtraction) versus time profile for azelaic acid on Day 7

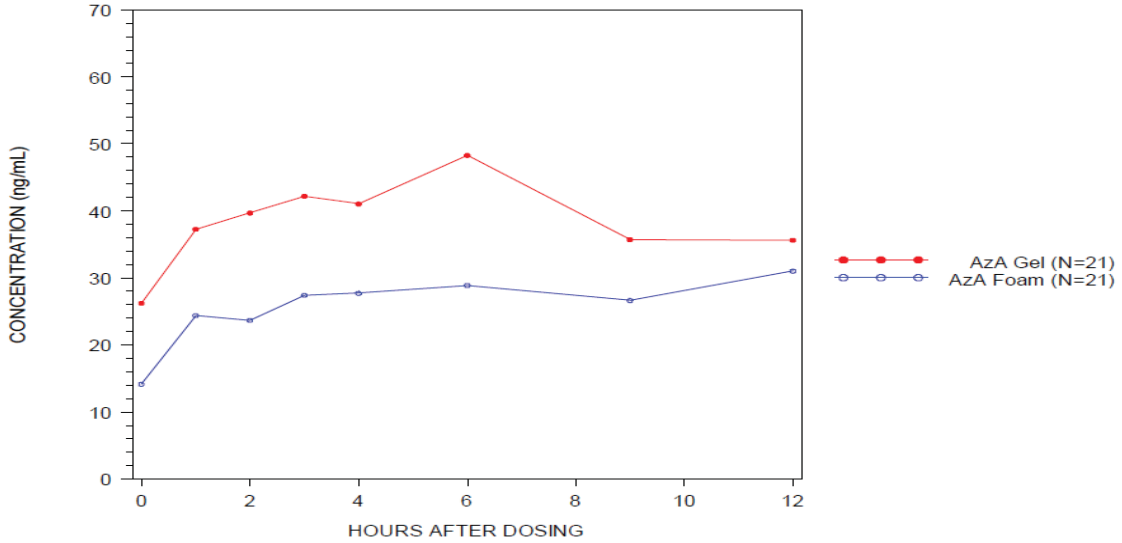


Table 3: PK parameters for azelaic acid (mean ± SD)

PK Parameter	Units	AzA Foam 15%	AzA Gel 15%
AUC(0-12h) Baseline corrected	ng*h/mL	322.8 ± 174.4	475.3 ± 278.6
AUC(0-36h) Baseline corrected	ng*h/mL	852.7 ± 457.0	1126.2 ± 559.0
AUC(0-12h) Baseline uncorrected	ng*h/mL	442.0 ± 177.6	589.1 ± 267.8
AUC(0-36h) Baseline uncorrected	ng*h/mL	1101.7 ± 338.1	1297.0 ± 577.2
Cmax Baseline corrected	ng/mL	40.1 ± 19.1	61.9 ± 40.5
Cmax Baseline uncorrected	ng/mL	51.8 ± 18.5	71.3 ± 40.5
Tmax Baseline corrected	h	7.8 ± 4.7	5.2 ± 3.8
Tmax Baseline uncorrected	h	8.4 ± 4.4	6.3 ± 3.9

PK of pimelic acid: The mean concentration versus time profiles for pimelic acid on Day 7 following administration of the new Foam formulation and Finacea Gel is shown in Figure 4 (baseline uncorrected) and Figure 5 (baseline corrected) and the PK parameters are shown in Table 4.

Figure 4: Mean baseline uncorrected plasma concentration versus time profile for pimelic acid on Day 7

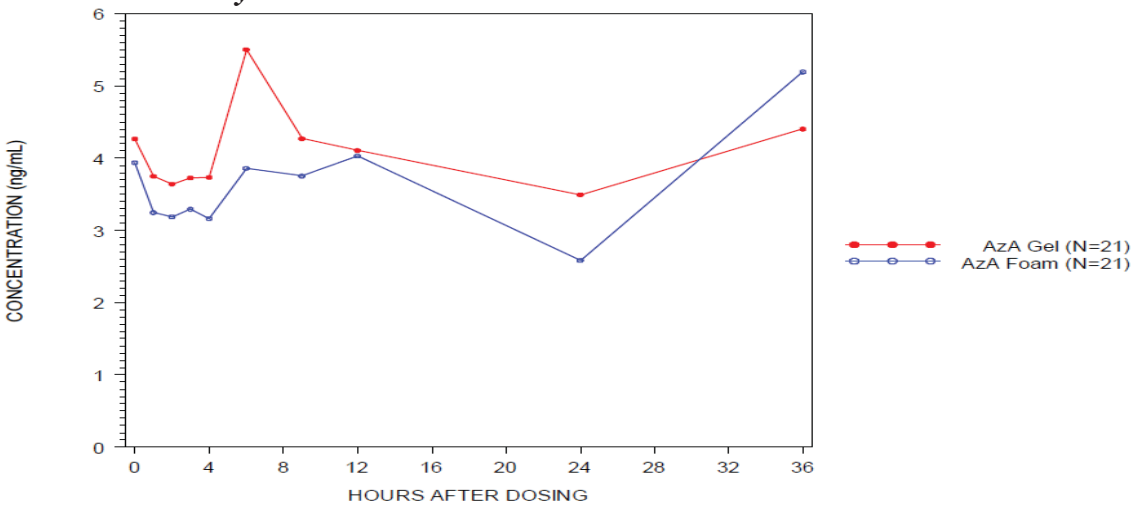


Figure 5: Mean baseline corrected plasma concentration (based on time matched subtraction) versus time profile for pimelic acid on Day 7

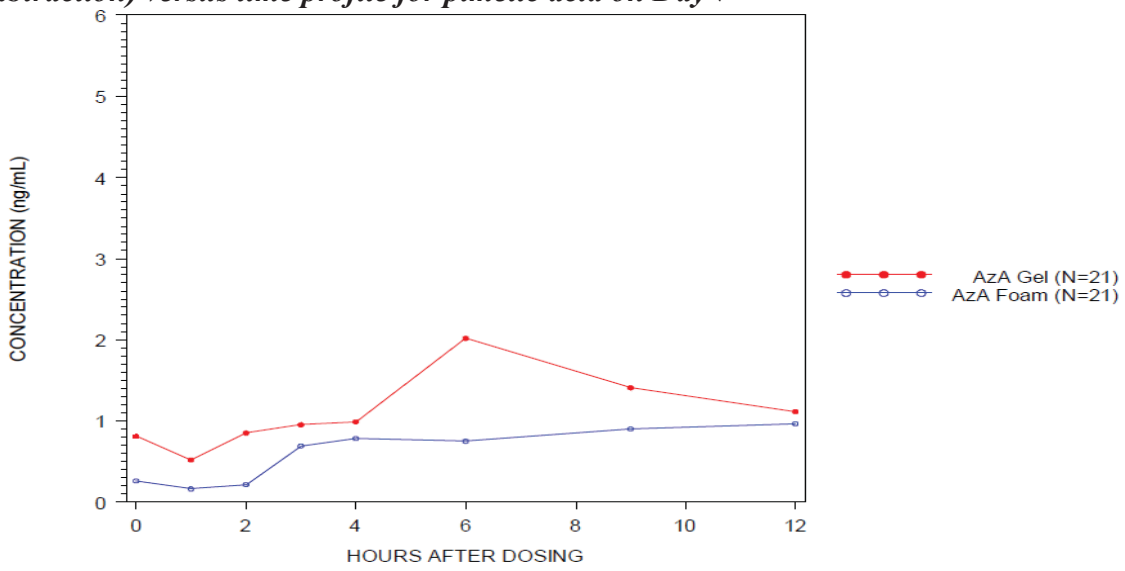


Table 4: PK parameters for pimelic acid (mean ± SD)

PK Parameter	Units	AzA Foam 15%	AzA Gel 15%
AUC(0-12h) Baseline corrected	ng*h/mL	8.4 ± 10.6	15.2 ± 27.7
AUC(0-36h) Baseline corrected	ng*h/mL	27.3 ± 77.8	55.3 ± 67.5
AUC(0-12h) Baseline uncorrected	ng*h/mL	43.4 ± 15.4	51.6 ± 19.2
AUC(0-36h) Baseline uncorrected	ng*h/mL	129.8 ± 39.6	144.6 ± 60.1
Cmax Baseline corrected	ng/mL	2.2 ± 2.4	3.6 ± 3.6
Cmax Baseline uncorrected	ng/mL	5.0 ± 3.0	6.3 ± 4.0
Tmax Baseline corrected	h	8.8 ± 8.6	5.0 ± 5.9
Tmax Baseline uncorrected	h	9.7 ± 7.5	7.7 ± 5.4

Reviewer comments: *The prime purpose of assessing PK of azelaic and pimelic acid is to evaluate the relative BA of the new Foam formulation compared to Finacea® Gel. The results of relative BA assessment are discussed in Section 2.3.4.*

Steady state attainment: Based on the values of trough level concentrations on Days 5, 6 and 7, the systemic drug concentrations of azelaic acid and pimelic acid appear to have reached steady state by Day 5. Details are provided in Section 4.

Baseline trend: Since azelaic acid is an endogenous substance, the applicant evaluated the baseline concentration profiles of azelaic acid and pimelic acid. The results do not indicate any rhythm in the baseline values. Details are provided in Section4.

Method of baseline correction:

- Baseline correction for $AUC_{(0\text{-}12h)}$ was performed by subtracting the individual $AUC_{(0\text{-}12h)}$ pre-treatment value for the respective period while baseline correction for $AUC_{(0\text{-}36h)}$ was performed by subtracting the median individual baseline morning concentration from the measured concentrations for the respective period.
- The baseline-corrected C_{max} was defined for the time interval 0 to 24 h as maximum difference between the concentration observed after treatment (day 7) and the concentration at the corresponding time point during pre-treatment (day -1) from the same period.

Reviewer comments: *The time matched baseline correction method for C_{max} and $AUC_{0\text{-}12h}$ appears reasonable (see Section 4 for details). Furthermore, the method of baseline correction for $AUC_{(0\text{-}36h)}$ using the median individual baseline morning concentration adopted by the applicant, also appears reasonable since there appears to be no rhythm in the baseline.*

2.3.4 What were the results of relative bioavailability (BA) assessment between the two treatments?

The applicant has calculated the 90% confidence interval (CI) on the geometric mean PK parameters and results for azelaic acid are shown below in Table 5 (baseline corrected) and Table 6 (baseline uncorrected); and for pimelic acid are shown in Table 7 (baseline corrected) and Table 8 (baseline uncorrected). The results indicated that systemic exposure of azelaic acid and pimelic acid following administration of the new Foam formulation was not higher than the Gel formulation.

Table 5: 90% confidence interval for azelaic acid (baseline corrected)

Parameter	Treatment A	Treatment B	Ratio	CI	Geometric CV%
AUC0-12 (ng*hr/mL)	318.5	469.9	0.678	0.495 - 0.860	41.2
Cmax (ng/mL)	39.97	61.59	0.649	0.397 - 0.901	50.8

Treatment A: Azelaic Acid Foam, 15%
Treatment B: Azelaic Acid Gel, 15%

Table 6: 90% confidence interval for azelaic acid (baseline uncorrected)

Parameter	Treatment A	Treatment B	Ratio	CI	Geometric CV%
AUC0-12 (ng*hr/mL)	435.6	585.9	0.744	0.608 - 0.879	85.9
AUC0-36h (ng*hr/mL)	1091.7	1276.6	0.855	0.714 - 0.996	116.6
Cmax (ng/mL)	51.18	70.59	0.725	0.500 - 0.950	86.7

Treatment A: Azelaic Acid Foam, 15%
Treatment B: Azelaic Acid Gel, 15%

Table 7: 90% confidence interval for pimelic acid (baseline corrected)

Parameter	Treatment A	Treatment B	Ratio	CI	Geometric CV%
Cmax (ng/mL)	2.34	3.43	0.681	0.190 - 1.172	24.2

Treatment A: Azelaic Acid Foam, 15%
Treatment B: Azelaic Acid Gel, 15%

Reviewer comments: *For pimelic acid, baseline corrected geometric mean AUC values (Table 7) could not be calculated due to several subjects with negative baseline corrected parameters.*

Table 8: 90% confidence interval for pimelic acid (baseline uncorrected)

Parameter	Treatment A	Treatment B	Ratio	CI	Geometric CV%
AUC0-12 (ng*hr/mL)	43.7	51.4	0.849	0.743 - 0.956	136.4
AUC0-36h (ng*hr/mL)	130.8	142.6	0.917	0.767 - 1.067	143.5
Cmax (ng/mL)	5.20	6.17	0.843	0.547 - 1.139	93.5

Treatment A: Azelaic Acid Foam, 15%
Treatment B: Azelaic Acid Gel, 15%

Reviewer comments: *The primary observation of relative BA is based on the 90% confidence interval calculation of azelaic acid baseline corrected mean PK parameters (C_{max} and AUC_{0-12}) shown in Table 5. The results indicate that the systemic exposure of azelaic acid following administration of the Foam formulation were not higher than the Gel.*

The results of this trial indicated that all baseline corrected and uncorrected PK parameters (Cmax, AUC_{0-12h} and AUC_{0-36h}) for both azelaic and pimelic acid had lower mean values for the new Foam formulation compared to Finacea® Gel. The statistical analysis (90% confidence interval) showed that Azelaic acid Foam, 15%, did not result in higher systemic burden of azelaic acid or pimelic acid when compared to Azelaic acid Gel, 15% (Finacea®).

2.3.5 Did the applicant assess drug metabolism?

The applicant has not conducted any new drug metabolism studies. New studies to assess drug metabolism are not needed at this time because azelaic acid is already a marketed product and this applicant owns Azelaic acid Gel, 15% (Finacea®).

2.3.6 What information is submitted to assess or waive TQT trial?

At the time of Pre-NDA meeting, based on the relative BA results (Trial 1401843) between the new Foam and Finacea® Gel, the applicant had requested for a waiver to conduct TQT assessment (see meeting minutes dated 07/16/2014 under IND 77516 in DARRTS). The Agency agreed that the waiver request was reasonable because systemic exposure of the new Foam formulation was not higher than Finacea® Gel under maximal use conditions.

2.3.7 What is the summary of safety?

According to the applicant, overall there was low incidence of drug-related treatment-emergent adverse events TEAEs. TEAEs were higher in the Foam group compared to vehicle (31.9% vs. 24.5%), however TEAEs leading to withdrawal of the study drug were low (1.8%). There were no deaths reported in subjects on the active treatment and no severe adverse events (SAEs) reported to be related to the drug. The applicant also claims that majority of adverse events (AEs) were mild to moderate in intensity and were mostly local cutaneous events and were mild in intensity and these included application site discoloration, dryness, erythema, pain, pruritus, and seborrhea. The applicant has further claimed that the local events were similar between the treatment groups.

Reviewer comments: *For additional details, see Clinical review for overall analysis of safety data.*

2.3.8 What is the summary of efficacy?

Azelaic acid Foam, 15% was evaluated for the treatment of papulopustular rosacea in two pivotal, multicenter, randomized, double-blind, vehicle-controlled, 12-week clinical trials involving a total of 1362 (active: 681; vehicle: 681) subjects aged 19 to 92 years (mean age = 50.6 years). Overall, 95.7% of subjects were Caucasian and 73.4% of subjects were female. Enrolled subjects had papulopustular rosacea with a mean lesion count of 21.3 (range 12 to 50) inflammatory papules and pustules.

Active drug or its vehicle were to be applied twice daily for 12 weeks. The primary efficacy endpoints included both (1) nominal change in inflammatory lesion count from baseline as well as (2) success defined as a score of "clear" or "minimal" with at least 2-step reduction from baseline on a 5-point scale Investigator's Global Assessment (IGA). The results indicated that azelaic acid Foam was superior to its vehicle in the treatment of rosacea in reducing the number of inflammatory papules and pustules and demonstrating success according to IGA at the end of treatment (Table 9).

Table 9: Success rate according to IGA and nominal change in inflammatory lesion count from baseline

	Study 1		Study 2		Overall	
	Finacea Foam,15% N=483	**Vehicle** N=478	**Finacea Foam,15%** N=198	**Vehicle** N=203	**Finacea Foam,15%** N=681	**Vehicle** N=681
IGA success rate	32.1%	23.4%	43.4%	32.5%	35.4%	26.1%
Mean nominal change in inflammatory lesion count from baseline	-13.2	-10.3	-13.3	-9.5	-13.3	-10.1

Reviewer comments: *For additional details see Clinical and Biostatics reviews.*

2.4 Intrinsic Factors

What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.4.1 Effect of age and gender

The applicant has not evaluated the effect of age and gender on the PK of azelaic acid.

2.4.2 Pediatric subjects

The applicant has requested a full waiver of pediatric assessment due to studies being impossible or highly impractical as the number of pediatric subjects with rosacea is extremely small.

Reviewer comments: *The applicant submitted their initial pediatric study plan (iPSP) on 08/05/2014, requesting a full waiver of pediatric assessment. The Agency agreed to the applicant's request for a full waiver on 11/25/2014 (see communication in DARRTS under IND 77516).*

2.4.3 Renal and hepatic impairment

The effect of renal and hepatic impairment on PK of azelaic acid following administration of the new Foam formulation was not evaluated by the applicant.

2.4.4 What pregnancy and lactation use information is there in the application?

The applicant has not conducted any trials in pregnant and lactating women.

2.5 Extrinsic Factors

2.5.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure or response?

The influence of extrinsic factors on dose-exposure and/or response was not evaluated in vivo.

2.5.2 Drug interactions

The applicant has not conducted any new drug interaction studies with this NDA. The drug interaction information will be obtained from Finacea® Gel, 15 % label.

2.6 General Biopharmaceutics

2.6.1 Based on biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

The concept of BCS classification does not apply to topically applied products.

2.6.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The to-be-marketed formulation was used in the maximal use PK trial and the Phase 2 and Phase 3 trials and there was no manufacturing site change. Hence relative bioavailability assessment to bridge between clinical and to-be-marketed formulation is not needed.

2.6.3 What data support or do not support a waiver of in vivo BE data?

The to-be-marketed formulation was used in the maximal use PK trial and the Phase 2 and Phase 3 trials.

2.6.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Effect of food on the BA is not evaluated for topical formulations.

2.7 Analytical Section

2.7.1 How are the active moieties identified, and measured in the clinical trials?

The active moieties were identified and measured using high performance liquid chromatography and tandem mass spectrometry (LC-MS/MS).

2.7.2 Which metabolites have been selected for analysis and why?

The parent compound azelaic acid and major metabolite pimelic acid, were selected for analysis.

2.7.3 For all moieties measured, is free, bound, or total measured?

Total concentration was measured.

2.7.4 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

The range of standard curve was:

- For azelaic acid: 1 ng/mL to 500 ng/mL
- For pimelic acid: 0.5 ng/mL to 250 ng/mL

This range was adequate as none of the plasma concentrations for azelaic acid and pimelic acid clinical trials exceeded the upper limit of the concentration range.

2.7.5 What are the accuracy and precision at LLOQ?

Inter-Batch Results

Analyte	Exp. conc. [ng/mL]	Mean calc. conc. [ng/mL]	CV [%]	Mean acc. [%]	Number of samples
Azelaic acid	1.00	0.990	14.48	98.8	18
Pimelic acid	0.500	0.469	9.26	93.8	18

Intra-Batch Results

Analyte	Exp. conc. [ng/mL]	Mean calc. conc. [ng/mL]	CV [%]	Mean acc. [%]	Number of samples
Azelaic acid	1.00	1.03	9.84	103.0	6
Pimelic acid	0.500	0.526	7.30	105.0	6

2.7.6 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler, etc.)?

Parameter	*Azelaic acid*	*Pimelic acid*
Freeze/Thaw cycle stability	3 cycles at - 20ºC	3 cycles at - 20ºC
Room temperature stability	4 hours	4 hours
Auto-sampler stability	29 hours	29 hours
Long term stability	12 months at - 25 ºC	12 months at - 25 ºC

Reviewer comments: *The duration of long term PK sample stability was adequate to cover the duration of PK sample storage for the maximal use PK trial.*

2.7.7 What are the results of incurred sample reanalysis (ISR)?

Seventy samples (approximately 6.4% of the total samples, at least two samples per subject) were selected for incurred sample reanalysis. The results showed that 82.9% samples met the ISR requirements for both azelaic and pimelic acid.

3. Detailed Labeling Recommendations

The following changes are recommended in Sponsor's proposed labeling. The **bold and underlined** text indicates insertion recommended by the reviewer and the ~~strikethrough~~ text indicates recommended deletion.

8.3 Nursing Mothers

It is not known if azelaic acid is ~~secreted~~ **excreted** in~~to~~ human milk *in vivo*. (b) (4) [redacted]

(b) (4) [redacted] No well-controlled studies of topically administered azelaic acid in nursing women are available. **A decision whether to discontinue nursing or to discontinue the drug should take into account the importance of the drug to the mother.**

Reviewer comments: *The deletions in this section were proposed due to* (b) (4) [redacted]

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(b) (4) [redacted]

(b) (4)

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

12.2 Pharmacodynamics

~~Efficacy of Finacea Foam is being driven by a local~~ (b) (4) ~~of action of azelaic acid.~~ **The pharmacodynamics of Finacea Foam in the treatment of rosacea is unknown.**

12.3 Pharmacokinetics

(b) (4)

Pharmacokinetics (PK) of azelaic acid and its metabolite pimelic acid was assessed in 21 adult subjects with moderate papulopustular rosacea with a minimum of 15 and no more than 50 inflammatory lesions (papules and/or pustules). Endogenous plasma concentrations of azelaic acid and (b) (4) pimelic acid **were measured over various time points over 2 days prior to treatment initiation. The endogenous plasma concentrations varied** (b) (4) -widely across subjects **and the** (b) (4) **m**ean ± SD values of **endogenous azelaic acid plasma concentrations ranged between 4.5± 2.4 ng/mL and 14.6 ± 5.6 ng/mL and pimelic acid plasma concentrations ranged between 2.2 ± 1.1 ng/mL and 3.7 ± 3.1 ng/mL.** (b) (4)

Following topical dermal applications of **a mean dose of 0.94 g** (b) (4) of Finacea Foam (**141** (b) (4) mg azelaic acid) twice daily for 7 consecutive days**, systemic concentrations of azelaic acid were at steady state by Day 5. On Day 7 the mean ± SD maximum azelaic acid and pimelic acid plasma concentrations (C_{max}) were 51.8 ± 18.5 ng/mL and 5.0 ± 3.0 ng/mL, respectively; and the mean ± SD systemic exposure of azelaic acid and pimelic acid within a dosing interval (AUC_{0-12h}) were 442.0 ± 177.6 ng.h/mL and 43.4 ± 15.4 ng.h/mL, respectively.** (b) (4)

Reviewer comments: (b) (4) [redacted]

(b) (4) [redacted]

(b) (4) **A**zelaic acid (b) (4) is **mainly** excreted unchanged in the urine**, but undergoes some** (b) (4) ß-oxidation (b) (4) to shorter chain dicarboxylic acids. (b) (4) [redacted]

(b) (4) [redacted]

4. Individual study report

Study number: 1401843

Title: Investigator-blinded, randomized, cross-over, multiple dose, phase 1 study on safety and PK of topically applied Azelaic acid Foam, 15% compared to Azelaic acid Gel, 15% in subjects with papulopustular rosacea.

Bioanalytical facility: (b) (4)

Trial objectives:

- Assessment of PK of Azelaic Acid after repeated dermal application of Azelaic Acid Foam, 15% and Azelaic Acid Gel, 15% in subjects with papulopustular rosacea
- Assessment of safety of Azelaic Acid Foam, 15% after repeated dermal application in subjects with papulopustular rosacea
- Comparison of pharmacokinetics of Azelaic Acid Foam, 15% and Azelaic Acid Gel, 15% after repeated dermal application in subjects with papulopustular rosacea

Trial design: This was a randomized cross-over trial to assess relative BA of azelaic acid and pimelic acid (metabolite) following twice daily administrations of the new Azelaic acid Foam, 15% formulation compared to Azelaic acid Gel, 15% (Finacea® Gel) in adult subjects with moderate rosacea. Moderate disease was defined as a minimum 15 and no more than 50 inflammatory lesions (papules and/or pustules) and persistent erythema with or without telangiectasia.

Reviewer comments: *Crossover design was considered at the time of protocol review and was reasonable because the 7 day treatment per period was unlikely to have any impact (i.e. improvement) on disease severity, which would impact the maximal use conditions.*

24 adult subjects with moderate papulopustular rosacea were enrolled and 21 subjects completed the trial. The reasons for discontinuation from the trial are shown below:

- Subject 2008 – Prematurely discontinued due to fever.
- Subject 2028 – Prematurely discontinued from before the 2nd period due to the inclusion criteria of disease severity not met. The inclusion criterion was moderate disease and this subject had moderate disease at the initiation of the 1st period. However, at the time of the initiation of the 2nd period, this subject had severe disease resulting in the subject being discontinued. This subject completed the 1st period.
- Subject 2033 – Prematurely discontinued due to rash on the forearm.

Since azelaic acid is an endogenous substance and can also be absorbed through certain types of diets (especially those rich in whole grains), 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 for 7 days,

where subjects were to apply 75 mg of azelaic acid (0.5 g Foam or 0.5 g Gel) per application, twice daily for 6 days and on day 7, drug was applied only once in the morning. The two treatment periods were separated by a 5 to 14 day washout period. The average amount of formulation used per dose is shown in Table 10 below.

Table 10: Amount of study drug used per treatment

		AzA Gel 15% (N=24)	AzA Foam 15% (N=24)
Number of application	n	24	23
	Nmiss	0	1
	Mean	12.8	13.0
	SD	1.0	0.0
	Min	8	13
	Median	13.0	13.0
	Max	13	13
Average study drug used per dose (gram)	n	24	23
	Nmiss	0	1
	Mean	0.9166	0.9372
	SD	0.3863	0.7046
	Min	0.454	0.224
	Median	0.8102	0.7725
	Max	1.657	3.305
Total study drug used (gram)	n	24	23
	Nmiss	0	1
	Mean	11.5851	12.1835
	SD	4.6721	9.1600
	Min	5.897	2.913
	Median	10.5329	10.0429
	Max	21.546	42.970

Reviewer comments: *The daily dose (BID) (mean ± SD) of Foam formulation used in the Phase 2 trial (1403120) and Phase 3 trial (1201846) were 1.3 ± 0.53 g (Median = 1.2 g) and 1.3 ± 0.73 g (Median = 1.1 g), respectively. The data presented in Table 10 suggests that the mean dose used in the maximal use PK trial was within the upper range of that used in the Phase 2 and Phase 3 trials.*

Plasma sampling for PK assessment was done on days -2, -1, 1, 5, 6 and 7 in both the periods. Specifically, blood samples were collected at Days -2 (morning baseline), -1 (morning baseline, and 1, 2, 3, 4, 6, 9, and 12 hours after morning baseline sample); on Day 1 (before the morning dose and 12 hours after the morning dose); before the morning dose on Days 5 and 6. On Day 7 plasma samples were obtained before the morning dose and at 1, 2, 3, 4, 6, 9, 12, 24, and 36 hours after dosing. Assessment of rosacea was conducted at screening and at days 1 and 7 in both the periods. PK parameters like C_{max}, AUC_{0-12}, and AUC_{0-36} were calculated with and without baseline adjustment.

Demographics of the population: Summary of demographic characters is shown in Table 11.

Reviewer comments: *The population studied appears to represent American population.*

Table 11: Summary of demographic data

		(N=24)
Age (years)		
	n	24
	Mean	37.6
	SD	13.7
	Median	40.5
	Min	18
	Max	61
Age group		
18-29	n (%)	8 (33.3%)
30-39	n (%)	3 (12.5%)
40-49	n (%)	7 (29.2%)
50-65	n (%)	6 (25.0%)
>65	n (%)	0 (0.0%)
Sex		
Female	n (%)	14 (58.3%)
Male	n (%)	10 (41.7%)
Race		
White	n (%)	12 (50.0%)
Black or African American	n (%)	8 (33.3%)
Asian	n (%)	1 (4.2%)
American Indian or Alaska Native	n (%)	1 (4.2%)

Disease severity: Summary of disease severity is shown in Table 12.

Table 12: Summary of disease severity at each visit

	AzA Foam, 15%	AzA Gel, 15%	Overall
Screening			
Number of subjects	-	-	24
1-clear	-	-	0 (0.0%)
2-minimal	-	-	0 (0.0%)
3-mild	-	-	0 (0.0%)
4-moderate	-	-	22 (91.7%)
5-severe	-	-	2 (8.3%)
Last visit of study (12)			
Number of subjects	-	-	22
1-clear	-	-	0 (0.0%)
2-minimal	-	-	0 (0.0%)
3-mild	-	-	1 (4.5%)
4-moderate	-	-	21 (95.5%)
5-severe	-	-	0 (0.0%)
First visit of treatment phase (3 or 9)			
Number of subjects	24	24	-
1-clear	0 (0.0%)	0 (0.0%)	-
2-minimal	0 (0.0%)	0 (0.0%)	-

	AzA Foam, 15%	AzA Gel, 15%	Overall
3-mild	0 (0.0%)	0 (0.0%)	-
4-moderate	24 (100.0%)	23 (95.8%)	-
5-severe	0 (0.0%)	1 (4.2%)	-
Last visit of treatment phase (6 or 12)			
Number of subjects	23	23	-
1-clear	0 (0.0%)	0 (0.0%)	-
2-minimal	0 (0.0%)	0 (0.0%)	-
3-mild	3 (13.0%)	3 (13.0%)	-
4-moderate	20 (87.0%)	20 (87.0%)	-
5-severe	0 (0.0%)	0 (0.0%)	-

Reviewer comments: *From the data presented in Table 12, most of the subjects had moderate disease at the time of initiation of both the treatment periods (Visit 3 and Visit9), which confirms that maximal use conditions with respect to disease severity for the crossover study design.*

PK results: The mean concentration versus time profiles for azelaic acid and pimelic acid and a summary of PK parameters are provided under Section 2.3.3 and will not be repeated here.

Individual subject baseline corrected concentration versus time profiles for azelaic acid shown in Figures 6 (Foam) and 7 (Gel) below. And corresponding individual subject baseline corrected concentration versus time profiles for pimelic acid is shown in Figures 8 (Foam) and 9 (Gel) below.

Figure 6: Individual subject PK profile for azelaic acid (corrected) on day 7
Treatment: Azelaic Acid Foam, 15%

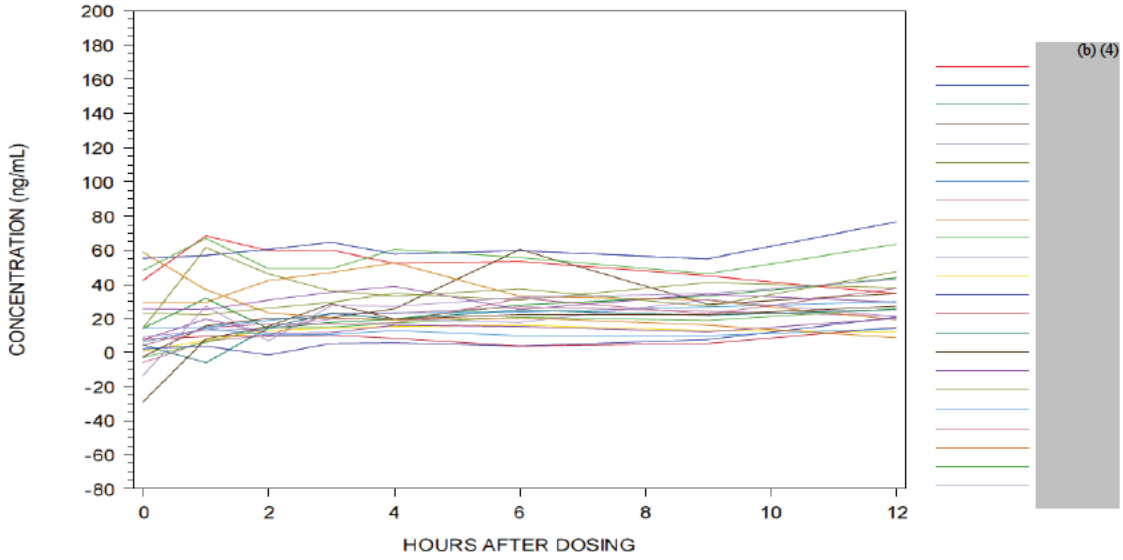


Figure 7: Individual subject PK profile for azelaic acid (corrected) on day 7
Treatment: Azelaic Acid Gel, 15%

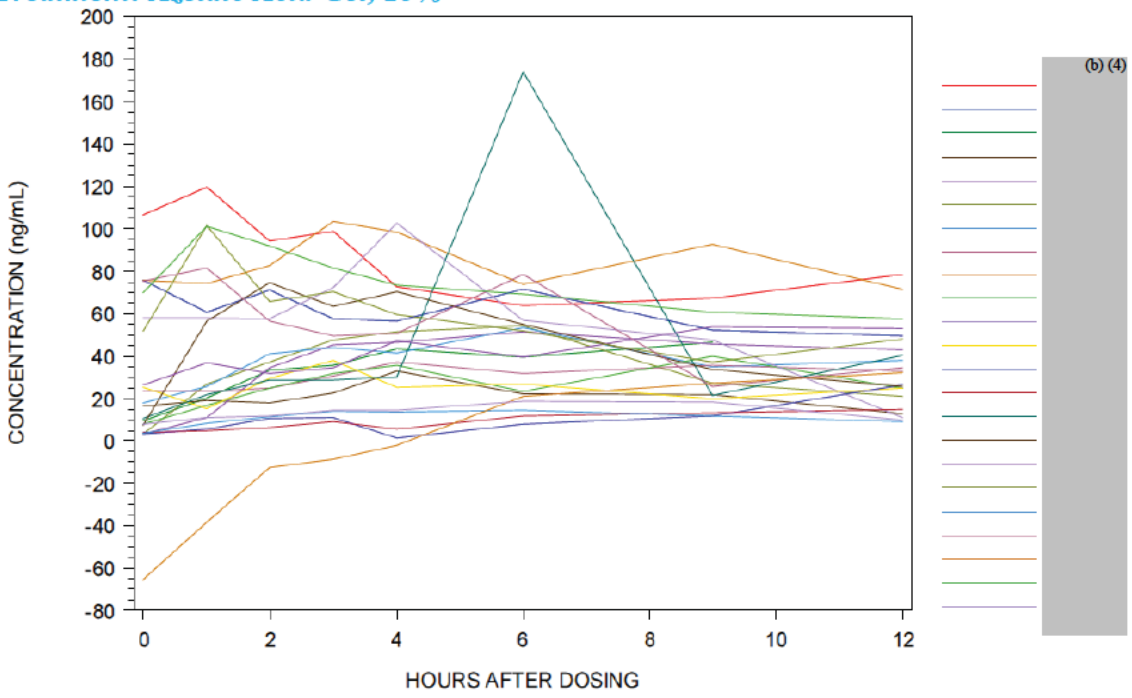


Figure 8: Individual subject PK profile for pimelic acid (corrected) on day 7
Treatment: Azelaic Acid Foam, 15%

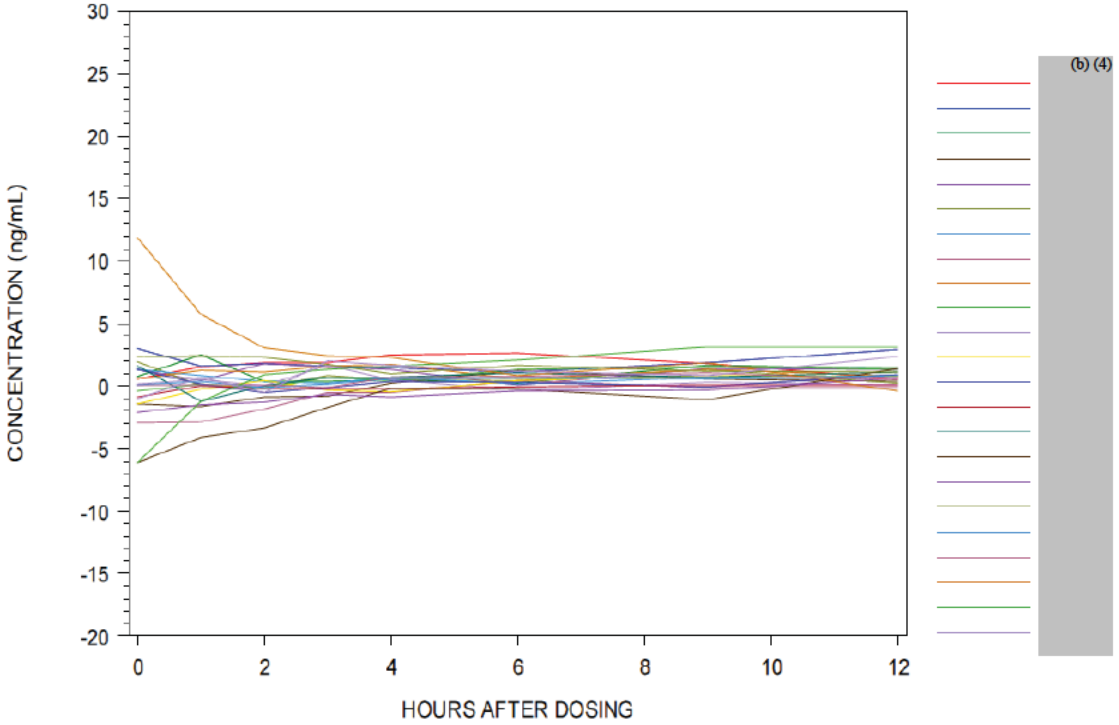
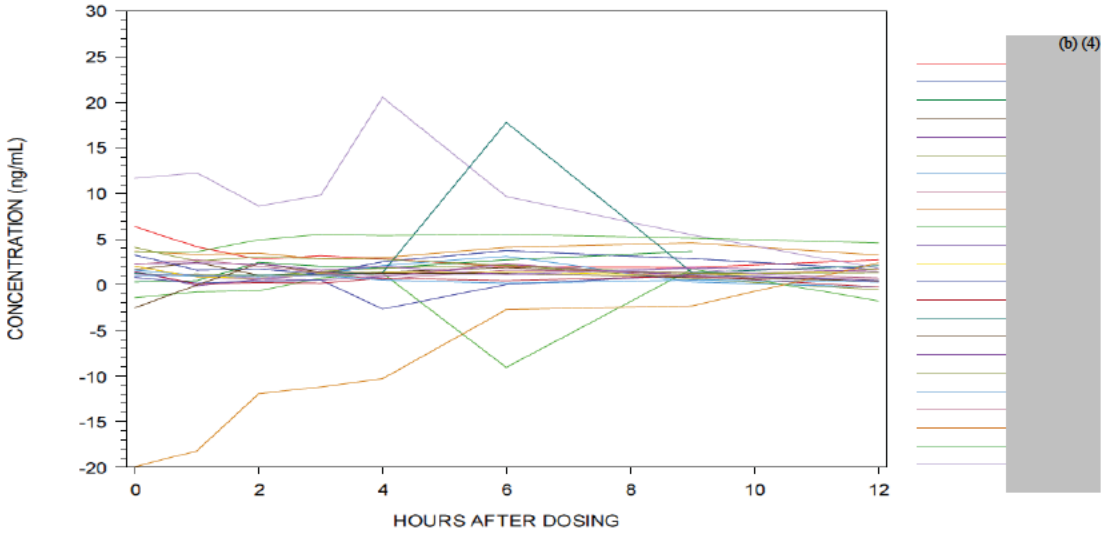


Figure 9: Individual subject PK profile for pimelic acid (corrected) on day 7
Treatment: Azelaic Acid Gel, 15%



Azelaic acid Individual subject PK parameters estimated using baseline corrected systemic concentrations following administration of the Foam formulation is shown in Table 13 and following administration of the Gel is shown in Table 14. For pimelic acid, the individual subject PK parameters using baseline corrected concentrations following administration of the Foam formulation is shown in Table 15 and for the Gel formulation is shown in Table 16.

Table 13: Individual subject PK parameters (baseline corrected) for azelaic acid
Treatment: Azelaic Acid Foam, 15%

Subject ID	Cmax (ng/mL)	Tmax (hr)	AUC (0-12) (ng*hr/mL)	AUC (0-36) (ng*hr/mL)	Baseline (ng/mL)	Equil (ng/mL)
2003	68.38	1.0	607.6	1460.6	.	.
2004	76.60	12.0	723.7	1530.6	.	.
2015	60.40	6.0	380.9	1174.3	.	.
2017	38.65	4.0	371.0	897.7	.	.
2019	41.15	9.0	398.0	1053.0	.	.
2020	29.80	12.0	281.5	768.2	.	.
2021	26.70	6.0	242.0	318.0	.	.
2023	52.40	4.0	415.0	993.7	.	.
2025	25.70	12.0	205.7	960.8	.	.
2031	31.20	9.0	248.9	906.1	.	.
2036	20.50	12.0	79.8	536.5	.	.
2040	14.90	12.0	91.7	456.6	.	.
2041	25.30	12.0	228.2	812.0	.	.
3005	28.74	3.0	228.8	-368.3	.	.
3011	19.71	12.0	175.0	361.7	.	.
3013	61.27	1.0	444.8	1311.4	.	.

Subject ID	Cmax (ng/mL)	Tmax (hr)	AUC (0-12) (ng*hr/mL)	AUC (0-36) (ng*hr/mL)	Baseline (ng/mL)	Equil (ng/mL)
3015	14.14	12.0	132.1	477.8	.	.
3017	37.41	12.0	278.3	854.0	.	.
3019	58.91	0.0	250.1	866.4	.	.
3020	66.80	1.0	651.8	1575.8	.	.
3023	42.90	12.0	343.2	959.1	.	.
N	21.00	21.0	21.0	21.0	0.00	0.00
Mean	40.07	7.8	322.8	852.7	.	.
SD	19.05	4.7	174.4	457.0	.	.
CV	47.54	59.9	54.0	53.6	.	.
Min	14.14	0.0	79.8	-368.3	.	.
Median	37.41	9.0	278.3	897.7	.	.
Max	76.60	12.0	723.7	1575.8	.	.
GeoM	35.70	6.3	278.5	.	.	.
GeoSD	1.66	2.5	1.8	.	.	.
GeoCV	47.51	83.3	51.6	.	.	.
Lower	21.53	2.5	155.7	.	.	.
Upper	59.20	15.5	498.0	.	.	.

Table 14: Individual subject PK parameters (baseline corrected) for azelaic acid
Treatment: Azelaic Acid Gel, 15%

Subject ID	Cmax (ng/mL)	Tmax (hr)	AUC (0-12) (ng*hr/mL)	AUC (0-36) (ng*hr/mL)	Baseline (ng/mL)	Equil (ng/mL)
2003	119.72	1.0	953.0	1818.3	.	.
2004	75.74	0.0	722.0	1464.8	.	.
2015	32.91	4.0	256.8	745.1	.	.
2017	51.60	6.0	492.3	970.9	.	.
2019	54.02	6.0	438.0	893.4	.	.
2020	53.54	6.0	476.9	955.1	.	.
2021	37.29	4.0	382.5	1129.3	.	.
2023	103.27	3.0	1015.1	2366.8	.	.
2025	40.00	9.0	345.9	1032.5	.	.
2031	37.78	3.0	296.8	752.1	.	.
2036	26.54	12.0	125.0	671.1	.	.
2040	14.80	12.0	121.7	506.1	.	.
2041	174.10	6.0	690.3	2160.9	.	.

Subject ID	Cmax (ng/mL)	Tmax (hr)	AUC (0-12) (ng*hr/mL)	AUC (0-36) (ng*hr/mL)	Baseline (ng/mL)	Equil (ng/mL)
3005	74.57	2.0	579.4	797.4	.	.
3011	53.80	9.0	526.9	1209.9	.	.
3013	101.69	1.0	665.6	1600.7	.	.
3015	14.57	6.0	141.3	358.8	.	.
3017	81.56	1.0	625.6	1179.6	.	.
3019	32.18	12.0	86.4	656.4	.	.
3020	100.97	1.0	859.9	1858.1	.	.
3023	18.67	6.0	178.8	521.9	.	.
N	21.00	21.0	21.0	21.0	0.00	0.00
Mean	61.87	5.2	475.3	1126.2	.	.
SD	40.47	3.8	278.6	559.0	.	.
CV	65.42	72.9	58.6	49.6	.	.
Min	14.57	0.0	86.4	358.8	.	.
Median	53.54	6.0	476.9	970.9	.	.
Max	174.10	12.0	1015.1	2366.8	.	.
GeoM	50.21	4.1	383.5	1002.0	.	.
GeoSD	1.98	2.4	2.1	1.7	.	.
GeoCV	58.83	77.8	62.9	47.3	.	.
Lower	25.31	1.7	184.4	606.8	.	.
Upper	99.63	9.8	797.7	1654.6	.	.

Table 15: Individual subject PK parameters (baseline corrected) for pimelic acid
Treatment: Azelaic Acid Foam, 15%

Subject ID	Cmax (ng/mL)	Tmax (hr)	AUC (0-12) (ng*hr/mL)	AUC (0-36) (ng*hr/mL)	Baseline (ng/mL)	Equil (ng/mL)
2003	2.62	6.0	22.2	46.2	.	.
2004	2.98	0.0	21.6	38.4	.	.
2015	1.29	6.0	1.9	31.6	.	.
2017	1.83	2.0	13.0	62.3	.	.
2019	1.97	0.0	8.0	50.0	.	.
2020	1.35	0.0	7.1	68.3	.	.
2021	0.43	6.0	-6.9	-132.5	.	.
2023	1.74	4.0	13.7	26.0	.	.
2025	1.53	9.0	11.1	52.4	.	.
2031	1.91	24.0	3.3	56.6	.	.
2036	1.67	24.0	2.9	51.8	.	.
2040	0.16	24.0	-0.8	30.9	.	.
2041	1.61	0.0	7.8	77.4	.	.
3005	1.42	12.0	-14.3	-211.9	.	.
3011	0.65	12.0	-6.8	-83.9	.	.
3013	2.42	1.0	18.7	74.7	.	.

Subject ID	Cmax (ng/mL)	Tmax (hr)	AUC (0-12) (ng*hr/mL)	AUC (0-36) (ng*hr/mL)	Baseline (ng/mL)	Equil (ng/mL)
3015	1.42	24.0	6.0	25.4	.	.
3017	1.05	9.0	7.1	39.2	.	.
3019	11.88	0.0	28.0	131.5	.	.
3020	3.15	9.0	19.7	88.7	.	.
3023	2.39	12.0	13.4	49.6	.	.
N	21.00	21.0	21.0	21.0	0.00	0.00
Mean	2.17	8.8	8.4	27.3	.	.
SD	2.35	8.6	10.6	77.8	.	.
CV	108.70	98.7	125.6	285.4	.	.
Min	0.16	0.0	-14.3	-211.9	.	.
Median	1.67	6.0	7.8	49.6	.	.
Max	11.88	24.0	28.0	131.5	.	.
GeoM	1.57	8.5	.	.	.	.
GeoSD	2.29	2.5	.	.	.	.
GeoCV	72.83	83.4	.	.	.	.
Lower	0.69	3.4	.	.	.	.
Upper	3.60	21.0	.	.	.	.

Table 16: Individual subject PK parameters (baseline corrected) for pimelic acid
Treatment: Azelaic Acid Gel, 15%

Subject ID	Cmax (ng/mL)	Tmax (hr)	AUC (0-12) (ng*hr/mL)	AUC (0-36) (ng*hr/mL)	Baseline (ng/mL)	Equil (ng/mL)
2003	6.37	0.0	32.2	23.2	.	.
2004	3.71	6.0	30.1	76.0	.	.
2015	2.44	1.0	16.2	63.0	.	.
2017	2.23	6.0	14.3	53.5	.	.
2019	3.87	24.0	13.4	91.3	.	.
2020	3.12	6.0	15.0	40.1	.	.
2021	2.02	0.0	13.7	46.0	.	.
2023	4.58	9.0	44.9	123.9	.	.
2025	1.77	9.0	-19.4	4.2	.	.
2031	2.04	0.0	15.1	42.3	.	.
2036	1.07	9.0	1.4	42.2	.	.
2040	1.42	0.0	5.9	36.8	.	.
2041	17.79	6.0	57.5	268.8	.	.
3005	2.28	2.0	10.6	-72.2	.	.
3011	2.36	1.0	21.1	56.7	.	.
3013	4.11	0.0	25.8	88.7	.	.

Subject ID	Cmax (ng/mL)	Tmax (hr)	AUC (0-12) (ng*hr/mL)	AUC (0-36) (ng*hr/mL)	Baseline (ng/mL)	Equil (ng/mL)
3015	0.99	0.0	6.4	27.5	.	.
3017	2.74	1.0	17.6	29.9	.	.
3019	2.35	12.0	-76.9	-52.1	.	.
3020	5.53	3.0	60.0	120.1	.	.
3023	1.72	9.0	13.7	52.4	.	.
N	21.00	21.0	21.0	21.0	0.00	0.00
Mean	3.55	5.0	15.2	55.3	.	.
SD	3.56	5.9	27.7	67.5	.	.
CV	100.20	118.5	183.0	122.0	.	.
Min	0.99	0.0	-76.9	-72.2	.	.
Median	2.36	3.0	15.0	46.0	.	.
Max	17.79	24.0	60.0	268.8	.	.
GeoM	2.76	4.8	.	.	.	.
GeoSD	1.91	2.7	.	.	.	.
GeoCV	56.09	97.0	.	.	.	.
Lower	1.44	1.8	.	.	.	.
Upper	5.29	12.7	.	.	.	.

Steady state attainment: Table 17 and Table 18 below provide information on mean ± SD trough concentrations of azelaic acid and pimelic acid, respectively. The data suggests that steady state was attained by Day 5 for both azelaic and pimelic acid.

Table 17: Pretreatment and trough concentrations (mean ± SD) of azelaic acid (ng/mL)

Treatment	Day 1 (0 h)	Day 5 (0 h)	Day 6 (0 h)	Day 7 (0 h)
Foam	4.52 ± 2.43	24.16 ± 24.26	25.44 ± 19.83	24.64 ± 21.23
Gel	5.16 ± 6.53	32.31 ± 28.06	30.21 ± 26.87	35.92 ± 32.71

Table 18: Pretreatment and trough concentrations (mean ± SD) of pimelic acid (ng/mL)

Treatment	Day 1 (0 h)	Day 5 (0 h)	Day 6 (0 h)	Day 7 (0 h)
Foam	2.33 ± 1.07	4.08 ± 2.62	3.28 ± 1.78	4.27 ± 2.43
Gel	2.20 ± 1.08	3.13 ± 1.93	3.15 ± 1.50	3.94 ± 3.37

Baseline trend: Since azelaic acid is an endogenous substance, the applicant evaluated the baseline concentration profiles of azelaic acid (Figure 10) and pimelic acid (Figure 11) (data in Table 19 and Table 20, respectively).

Figure 10: Baseline concentration versus time profile for azelaic acid on Day -1

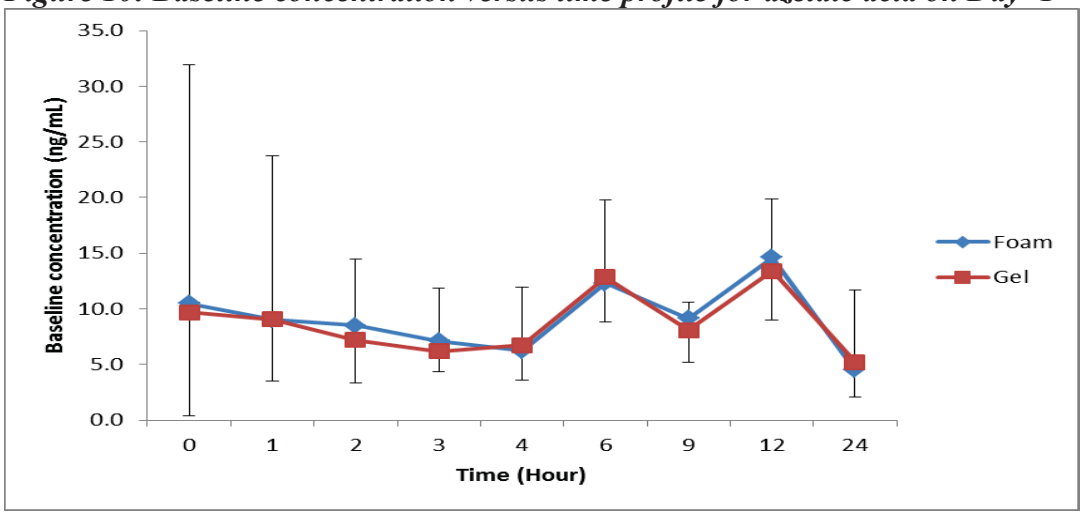


Figure 11: Baseline concentration versus time profile for pimelic acid on Day -1

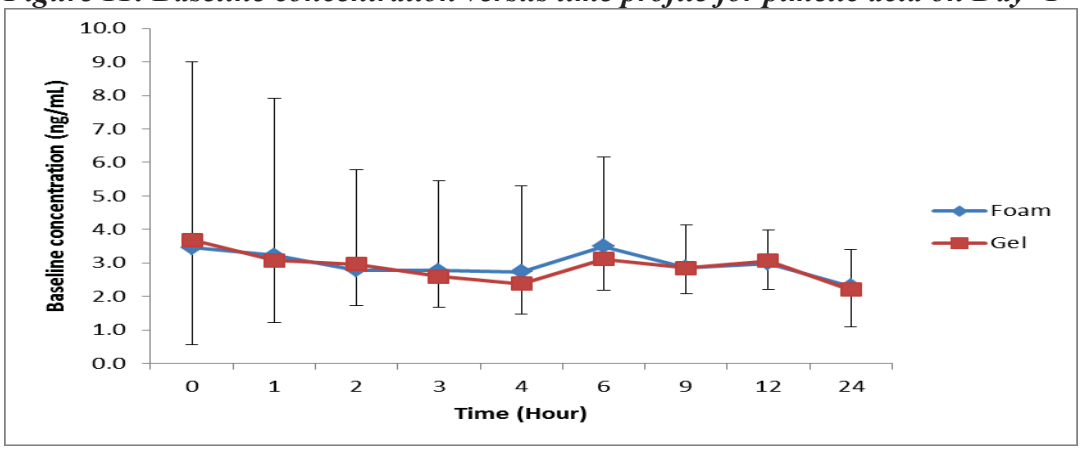


Table 19: Baseline concentrations (ng/mL) for azelaic acid

		Day -2 (0 hour)	Day -1 (0 hour)	Day -1 (1 hour)	Day -1 (2 hour)	Day -1 (3 hour)	Day -1 (4 hour)	Day -1 (6 hour)	Day -1 (9 hour)	Day -1 (12 hour)	Day 1 (0 hour)
Foam	Mean	7.9	10.5	9.0	8.5	7.1	6.2	12.3	9.1	14.6	4.5
	SD	9.0	10.1	5.5	5.2	2.7	2.6	3.5	4.0	5.6	2.4
Gel	Mean	5.3	9.7	9.1	7.2	6.2	6.7	12.9	8.1	13.4	5.2
	SD	3.4	22.2	14.7	7.3	5.7	5.3	6.9	2.5	6.4	6.5

Table 20: Baseline concentrations (ng/mL) for pimelic acid Foam

		Day -2 (0 hour)	Day -1 (0 hour)	Day -1 (1 hour)	Day -1 (2 hour)	Day -1 (3 hour)	Day -1 (4 hour)	Day -1 (6 hour)	Day -1 (9 hour)	Day -1 (12 hour)	Day 1 (0 hour)
Foam	Mean	2.5	3.5	3.2	2.8	2.8	2.7	3.5	2.9	3.0	2.3
	SD	1.4	5.6	4.7	3.0	2.7	2.6	2.7	1.3	1.0	1.1
Gel	Mean	3.0	3.7	3.1	3.0	2.6	2.4	3.1	2.9	3.1	2.2
	SD	2.1	3.1	1.9	1.2	0.9	0.9	0.9	0.8	0.9	1.1

Method of baseline correction: See Section 2.3.3 for details.

Treatment comparisons: See Section 2.3.4 for details.

PK observations: The results of this trial indicated that all baseline corrected and uncorrected PK parameters (Cmax, $AUC_{0\text{-}12h}$) for both azelaic and pimelic acid had lower mean values for the new Azelaic acid Foam, 15% formulation compared to Azelaic acid Gel, 15%. Inferential statistical analysis (90% confidence interval calculation using the geometric mean PK parameters) showed that the systemic exposure of baseline corrected azelaic acid following application of Azelaic acid Foam, 15%, was not higher compared to Azelaic acid Gel, 15% (Finacea®) following 7 days BID topical administration in adult subjects with rosacea.

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/s/

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05/21/2015

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