CLINICAL REVIEW

Application Type	NDA Efficacy Supplement
Application Number(s)	207917
Priority or Standard	Standard
Submit Date(s)	Sept 17, 2014
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PDUFA Goal Date	July 17, 2015
Division / Office	DDDP/OND
Reviewer Name(s)	Jane Liedtka
Review Completion Date	May 13, 2015
Established Name	adapalene and benzoyl peroxide Gel, 0.3%/2.5%
(Proposed) Trade Name	Epiduo Forte
Therapeutic Class	retinoid/oxidizing agent
Applicant	Galderma Laboratories LP
Formulation(s)	gel
Dosing Regimen	once per day
Indication(s)	Acne Vulgaris
Intended Population(s)	ages 12 and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The applicant, Galderma Laboratories LP, has submitted a new drug application, NDA 207917 via the 505(b)(2) pathway for a new fixed dose combination product that contains adapalene (0.3%) and benzoyl peroxide (2.5%) in the same gel vehicle and same dosage form as the currently marketed Epiduo gel for use in patients 12 years of age and older with acne vulgaris. NDA 22-320, Epiduo gel (adapalene 0.1%/benzoyl peroxide 2.5 %) was approved for the indication of topical treatment of acne vulgaris in patients 12 years of age and older on Dec 8, 2008. On Feb 1, 2013 efficacy supplement S-004 for NDA 22-320 was approved which expanded the population for Epiduo gel down to 9 years of age and older. NDA 21-753, Differin Gel (adapalene) 0.3% was approved for the topical treatment of acne vulgaris in patients 12 years of age and older on June 19, 2007. The applicant has proposed the trade name Epiduo Forte (EF) for the new product containing adapalene (0.3%) and benzoyl peroxide (2.5%) which has been accepted.

Both active ingredients have been approved individually in various formulations for marketing in the United States. The applicant has demonstrated that EF is safe and effective for the treatment of acne vulgaris in subjects 12 years and older when used once daily for 12 weeks in one single pivotal clinical study. The applicant owns the rights to the data from NDA 21-753 (Differin Gel 0.3%) and NDA 22-320 (Epiduo gel - adapalene 0.1%/benzoyl peroxide 2.5 %) which provide supportive data, including non-clinical data and long-term safety from the clinical experience of the marketed products. The applicant will depend on the literature for safety and efficacy for the benzoyl peroxide (BP) component of the combination therefore they have chosen the 505(b)(2) pathway.

This reviewer recommends that NDA 207917 be approved for the treatment of acne vulgaris in patients in patients 12 years of age and older with acne vulgaris.

1.2 Risk Benefit Assessment

Safety assessments for this application are based on clinical trial results as well as marketing experience for other products with adapalene and benzoyl peroxide. In addition, there is extensive safety experience with each active ingredient marketed as individual formulations or over-the-counter preparations (benzoyl peroxide 2.5% – 10%).

There were no deaths or serious adverse events which were considered related to the proposed product in the development program. The most common adverse events associated with the use of EF are application site irritation and stinging/burning.

No new safety concerns were identified in the clinical trials conducted with EF, and expected adverse events were primarily limited to local irritation adverse reactions. The benefit of this topical product outweighs its risk. This product provides an additional option for the treatment of acne vulgaris in patients 12 years and older.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for REMS or additional risk management steps beyond product labeling.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

Adapalene is a naphthoic acid derivate and retinoid analogue with actions similar to those of retinoids. Benzoyl peroxide is commonly used as an antimicrobial and keratolytic agent in the commercial production of topical drug products, with more than 20 different prescription or over-the-counter drug products currently marketed worldwide.

The drug product, Adapalene 0.3%/Benzoyl Peroxide 2.5 % Gel (EF), is a fixed-dose combination of adapalene 0.3% (w/w) and benzoyl peroxide 2.5% (w/w). EF is a white to very pale yellow opaque gel containing 0.3% w/w (3 mg/g) of adapalene and 2.5% w/w (25 mg/g) of benzoyl peroxide, as the drug substances, dispersed in an aqueous gel dosage form. Adapalene 0.3% / Benzoyl Peroxide 2.5% Gel is packaged in an (b) (4) pump system designed with:

- A white polypropylene (PP) and high density polyethylene (HDPE) bottle
- A white (b) (4) pump/overcap.

Unit filling weights proposed for registration are 15 g, 30 g, 45 g, 60 g and 70 g. (b) (4)

(b) (4) EF is intended for once daily application. The duration of treatment in the pivotal clinical trials was 12 weeks.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are a number of products approved for treatment of acne vulgaris. Pharmacologic categories of approved therapies for acne vulgaris include oral and topical antibiotics (e.g. erythromycin, clindamycin), topical retinoids (e.g. tretinoin, tazarotene) and systemic hormonal therapies (e.g. ethinyl estradiol/norgestimate). The oral formulation of isotretinoin is also available for severe, recalcitrant, nodulo-cystic acne.

2.3 Availability of Proposed Active Ingredient in the United States

Adapalene is widely used in the commercial production of prescription topical drug products. Four different formulations are currently marketed in the USA: Differin® gel 0.1% (NDA# 020380), Differin® cream 0.1% (NDA# 020748), Differin® gel 0.3% (NDA# 021753) and Epiduo® (NDA#022320).

Benzoyl peroxide is widely available, with more than 20 different prescription or over the counter drug products currently marketed worldwide (e.g. Cutacnyl® [benzoyl peroxide] 2.5% gel, Benzac® AC [benzoyl peroxide] gel, marketed by Galderma in US).

2.4 Important Safety Issues with Consideration to Related Drugs

Adapalene, though structurally distinct from retinoic acid is considered a “retinoid” since it acts at retinoic acid receptors. Retinoids are irritants and known teratogens. Use of these products may also make for heightened sun sensitivity because topical retinoids may decrease the number of layers in the stratum corneum.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The development program for the original approval of Epiduo was conducted under IND 67,801. (See clinical review under NDA 22-320 in DARRTS for details of Presubmission Regulatory Activity related to the original approval).

Pre-IND meeting

On May 30, 2012 a Pre-IND meeting (filed under IND (b) (4) in DARRTS) was held with the applicant. The following are some of the important clinical comments and recommendations conveyed at that meeting:

Regarding the maximal use PK study design

- We recommend that the drug products be applied to the entire area of the face, shoulders, upper chest and upper back.
- The amount applied should be sufficient to leave a thin film on the entire area.
- You should record the actual amount applied for each subject.
- Ensure that the target patient population (age, gender, etc.) is properly represented in your maximal use PK study

General Comments

- Provided the maximal use PK study confirms your expectation that the systemic exposure to adapalene from the new fixed-dose combination (adapalene 0.3%/BPO 2.5% gel) is less than or comparable to the systemic exposure resulting from application of the approved Differin (adapalene) 0.3% gel (b) (4)
- The sponsor was advised that a (b) (4) "Clarify how you would use the existing data (regarding photosensitivity, phototoxicity and RIPT dermal safety studies) from other products (specifically Differin Gel .3% and Epiduo gel) to inform labeling for this product, and include your rationale in the IND submission.
- We recommend a three arm trial with the new fixed-dose combination (adapalene 0.3%/BPO 2.5% gel) versus the approved fixed dose combination (adapalene 0.1%/BPO 2.5% gel) versus vehicle, in which you show superiority over the vehicle.
- (b) (4) include your rationale in the NDA submission.

Pre-Phase 3 meeting

On Dec 5, 2012 a Pre-Phase 3 meeting (filed under IND 67801 in DARRTS) was held with the applicant. The following are some of the important clinical comments and recommendations conveyed at that meeting:

- You propose a development plan comprised of (1) a 21-day cumulative irritancy study, (2) a Maximal Use Systemic Exposure PK study in subjects aged 12 years and older and (3) a single pivotal active- and vehicle-controlled 3-arm Phase 3 study. We anticipate that the development program you outline could be sufficient for filing if you adequately address the comments that follow.
- (b) (4) relative to a comparator product or in a subgroup of subjects with severe disease would need replication in two studies. The single 3-arm study you propose would not provide adequate information for the proposed subgroup of subjects with severe disease (b) (4) (b) (4)

Meeting discussion

The sponsor stated that they do not plan to claim superiority to the approved Epiduo, and that they do not plan to include "severe" acne in the indication.

- You propose the following co-primary efficacy endpoints which are acceptable:
  - Success Rate, the percentage of subjects with an IGA of clear or almost clear (and therefore at least a 2-grade improvement from Baseline at Week 12 Intent-to-treat [ITT]);
  - Change in Inflammatory Lesion Count from Baseline to Week 12 (ITT);
  - Change in Non-inflammatory Lesion Count from Baseline to Week 12 (ITT);
- We note that your enrollment criteria allow enrollment of subjects with up to four nodules on the face at the baseline visit… To provide sufficient evidence from the proposed single 3-arm pivotal trial to support the approval of your new fixed dose combination product, Adapalene 0.3% / BPO 2.5% Gel, we recommend that the design elements of the trial (such as measurement scale, efficacy endpoints, and population) be the same as (or very similar to) those of the pivotal trials for Epiduo gel. We encourage you to revise your enrollment criteria to reduce the number of nodules permitted at baseline to qualify for enrollment (such as was done in the Epiduo pivotal study 18087 which allowed "no more than one nodule").
- You should reduce number of centers and enroll a reasonable number of subjects in each treatment arm per center (e.g. 12 subjects in each active arm and 4 subjects in vehicle arm per center) to enable a meaningful checking of the consistency of the trial findings across centers. The protocol should pre-specify an algorithm for pooling small centers if actual enrollment does not meet the minimum number of subjects per center.
- The sponsor proposed that trial objectives be tested sequentially and conditionally on success of the previous objective as below:

  1. Demonstrate Adapalene 0.2%/ BPO 2.5% is superior to Vehicle in the combined population of Moderate and Severe patients
  2. Demonstrate Adapalene 0.3%/ BPO 2.5% is superior to Vehicle in Severe patients
  3. Assess the relative efficacy of Adapalene 0.3%/ BPO 2.5% versus Adapalene 0.1%/ BPO 2.5% in severe patients

  The trial efficacy outcome will be considered positive if objectives (1) and (2) are met. The Agency responded that "Provided that you adequately address the suggested revisions to trial design (see answer to question #2), the trial objectives and definition of a positive efficacy outcome appear reasonable. You propose to "assess" the relative efficacy of the new fixed-dose combination versus Epiduo® gel in the subgroup of subjects with severe acne using confidence intervals. (b) (4) you should conduct formal

hypothesis testing instead of using confidence intervals and you would need replication.

Special Protocol Agreement (SPA) letter

A SPA agreement letter was sent to the sponsor on March 11, 2013 which contained the following:

Agreements

1. The general design of your phase 3 study entitled "A Multi-center, Randomized, Double-blind, Parallel-group Vehicle and Active Controlled Study to Compare the Efficacy and Safety of CD0271 0.3%/CD1579 2.5% (EF) Topical Gel Vs Topical Gel Vehicle in Subjects with Acne Vulgaris" is acceptable.
2. The proposed dose regimen is acceptable.
3. The proposed entry criteria of subjects age 12 years and older with facial acne vulgaris of at least moderate severity on the proposed Investigator's Global Assessment (IGA) scale with 20-100 inflammatory lesions and 30-150 non-inflammatory lesions and no more than 2 nodules is acceptable.
4. The proposed safety assessments are acceptable.
5. The proposed co-primary efficacy endpoints of success in IGA, defined as the proportion of subjects with an IGA score of 0 (clear) or 1 (almost clear) at Week 12 and therefore at least 2-grade reduction, and absolute change in inflammatory and non-inflammatory lesion counts from baseline to Week 12 are acceptable.
6. The proposed secondary efficacy endpoints of percent change in inflammatory and noninflammatory lesion counts from baseline to Week 12 are acceptable.
7. The proposed definition of the intent-to-treat (ITT) population as all subjects randomized is acceptable.
8. Your proposal to analyze success in IGA with the Cochran-Mantel-Haenszel (CMH) test is acceptable.
9. Your proposal to analyze absolute change in inflammatory and non-inflammatory lesion counts from baseline to Week 12 with ANCOVA models with terms for the respective baseline lesion count, treatment, and the variables that will be used to stratify the randomization is acceptable.

Additional Comments

1. You stated that the trial efficacy outcome will be considered positive if superiority of the new formulation over vehicle gel is demonstrated in the total population and in the subgroup with severe acne. It should be noted that you expect the treatment effect in the severe population will be similar to the treatment effect in the total population.
2. Generally, once superiority is demonstrated in the total population, subgroup analyses could be used to identify subgroups that would benefit more from

treatment; however, this is not consistent with your expectation. In addition, the Agency reiterates the previous comment that (b) (4) in a subgroup of subject with severe disease would need replication in two studies.

3. You stated that the trial efficacy outcome will be considered positive if superiority of the new formulation over vehicle gel is demonstrated in the total population and in the subgroup with severe acne. You also expect the treatment effect in the severe population will be similar to the treatment effect in the total population. It should be noted that for clinical trials designed for a targeted subgroup, it is expected that the efficacy results for the subgroup is higher than that of the total population. (b) (4) (b) (4) the trial is positive by limiting your criteria to establishing efficacy in the total population. Analysis by severity can be conducted as a subgroup analysis without the requirement of formal hypothesis testing.
4. You proposed to "assess the superiority" of the new formulation versus Epiduo® (adapalene and benzoyl peroxide) Gel, 0.1%/2.5% in the subgroup of subjects with severe acne using confidence intervals. You should provide your regulatory intent of such an assessment.
5. You proposed to stratify the randomization by baseline disease severity (IGA) and country/region, where country/region will have 5 groups (Canada, Russia, and 3 groups for US). The utility of randomly assigning US subjects to 3 groups is not clear. If you expect efficacy to vary across regions of the US, then randomly assigning US subjects to 3 groups could mask regional effects. To investigate potential regional effects, you could define the groups based on geographical location. However, as the Agency is still interested in assessing the center-to-center variability, we still recommend reducing the number of centers to enroll a sufficient number of subjects per center, and stratifying the randomization by center. For randomization stratified by center, the analysis should follow the randomization and be stratified by center as well.
6. You stated that last observation carried forward (LOCF) was chosen as the primary imputation method for missing data because it would allow comparison to historical data obtained on Epiduo® (adapalene and benzoyl peroxide) Gel, 0.1%/2.5% and it would be conservative; however, it should be noted that whether LOCF is conservative would depend on the proportion of missing data in each treatment arm. As your proposed justification does not provide a convincing scientific rationale for LOCF, you are encouraged to select a more scientifically appropriate method (e.g. multiple imputation) as the primary imputation method.

On March 28, 2013 the sponsor responded to the above SPA letter with a revised protocol that addressed additional comments #5 and #6 above:

- decreased the number of study sites to 35
- agreed to stratify by site and severity
- agreed to multiple imputation methodology as the primary method of handling missing efficacy data

Pediatric Study Plan (PSP)

Under the initial NDA for Epiduo gel, study of acne subjects below the age of 9 was waived. On June 18, 2013 the applicant submitted an initial PSP (iPSP) requesting a waiver for EF so as not to study acne subjects 9-11 years of age. Their rationale for this request included the following:

- In the age group less than 12 years acne "is primarily a noninflammatory disease, and is almost always midline (forehead, nose, sides of nose, and chin)
- "Children in this 9 – 11 year age group rarely, if ever, have acne judged to be severe, when compared to the corresponding acne severity grading in the older population"
- Acne vulgaris in this age group is very amenable to topical treatment with existing products, such as benzoyl peroxide (BPO) in various concentrations and established topical retinoids (tretinoin, adapalene) either alone or in combination with BPO and oral antibiotics in accordance with consensus recommendations
- It is the Sponsor's opinion that the recently approved use of Epiduo gel in children from the age of nine covers the previously unmet medical need in this class of age

In an advice letter dated Sept 13, 2013 regarding the iPSP, the Agency recommended that the sponsor add a 4 week recovery period onto the 13 week minipigs study to assess the reversibility of irritation and/or other dermal reactions. The Agency also advised that the starting age of animals in this study (from the growth curve) should correspond to human pediatric subjects. On Oct 10, 2013 the sponsor submitted a non-clinical response to the Agency addressing these comments. An agreed upon iPSP letter was sent by the Agency on Dec 26, 2013.

Pre-NDA meeting

On June 25, 2014 a Pre-NDA meeting (filed under IND 67801 in DARRTS) was held with the applicant. The following are some of the important clinical comments and recommendations conveyed at that meeting:

- The overall design of the maximal use pharmacokinetic (PK) trial (RD.06.SRE.18229) appears reasonable to support the filing of your NDA
- The (b) (4) appears reasonable. However, final determination will be made during the review of your NDA submission.
- It appears that the Phase 3 study results would support filing.
- We agree that an additional long-term safety study is not needed at this time.
- We agree that additional sensitization, photoallergy and phototoxicity studies are not needed.

- Your proposed format and contents of Module 5 appear reasonable.
- The Agency agrees that separate ISE and ISS narratives are not required in the proposed NDA [Sections 2.7.3 Summary of Clinical Efficacy (SCE) and 2.7.4 Summary of Clinical Safety (SCS) that are sufficiently detailed to also serve as the full narrative portions of the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS)].
- Your proposal to submit study datasets in accordance with the current Study Data Tabulation Model (SDTM) Implementation Guide, version 3.1.2, amendment 1 is acceptable.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Division of Scientific Investigators (DSI) was not consulted to review the conduct of the single safety and efficacy trial (18240). The clinical team, in consultation with the biostatistics reviewer, concluded that there were no irregularities in the data requiring DSI consultation.

3.2 Compliance with Good Clinical Practices

The following statement appeared on page 2 of the Clinical Study Report (CSR) for study # 18240:

> This study was performed in compliance with Good Clinical Practice (GCP) including the archiving of essential study documents. This Clinical Study Report (CSR) complies with the International Conference on Harmonization (ICH) E-3 guidance.

3.3 Financial Disclosures

A single investigator, (b) (6) submitted a disclosable arrangement on form 3455 for the receipt of $52,692.00 in consulting and research fees (including travel costs). (b) (6) enrolled (b) (6) out of 217 subjects (≈5.5%) in trial #18240 at site # (b) (4). The statistical reviewer performed a sensitivity analysis where this site was removed to explore the possible source of an interaction effect. Removal of (b) (6) site still resulted in EF being statistically superior to vehicle gel.

See attached financial disclosure form.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new CMC issues were identified during the review for EF. In the review archived in panorama dated 5/11/15, the CMC reviewer stated “The applicant has provided sufficient information to assure identity, strength, purity, and quality of the drug product. All label/labeling have adequate information as required”. See review by the CMC reviewer for details.

4.2 Clinical Microbiology

Not applicable (See review for original application for Epiduo Gel)

4.3 Preclinical Pharmacology/Toxicology

No new pharmacology-toxicology issues were noted with the new formulation i.e. EF. The pharmacology-toxicology reviewer stated that the application is “Approvable provided the sponsor accepts the recommended changes in the Labeling”. See review by pharmacology-toxicology reviewer dated 5/13/15 for details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

See clinical pharmacology review dated 5/5/2015.

4.4.2 Pharmacodynamics

See clinical pharmacology review dated 5/5/2015.

4.4.3 Pharmacokinetics

The clinical pharmacology program consists of a new maximal use PK trial, #18229, conducted with the new EF formulation. This was a parallel group trial that assessed the relative bioavailability of adapalene following administration of EF or adapalene 0.3% Gel (Differin® Gel), in subjects 12 years and older with severe acne vulgaris. The respective formulations were applied once a day to the face, shoulders, upper chest and upper back. 58 subjects with severe acne were randomized in a 1:1 ratio to the two treatment arms. Subjects were stratified by gender and age groups, i.e. 12 to 17 years

and 18 to 35 years to ensure sufficient numbers of subjects are enrolled in the lower age range (12 to 13 years old). PK was assessed via serial blood sampling on Days 1, 15 and 29.

According to the clinical pharmacology reviewer (See review dated 5/5/2015 in DARRTS)

> …adapalene plasma concentrations were quantifiable at low levels in 50% of subjects treated with adapalene 0.3%/benzoyl peroxide 2.5% Gel (range <0.10 to 0.35 ng/mL) and 33% of subjects treated with adapalene 0.3% Gel (range <0.10 to 0.29 ng/mL). At the end of treatment period (Day 29), adapalene plasma levels were quantifiable in 62% of subjects (range <0.10 to 0.38 ng/mL) and 47% of subjects (range <0.10 to 0.46 ng/mL) treated with adapalene 0.3%/benzoyl peroxide 2.5% Gel and adapalene 0.3% Gel, respectively… adapalene systemic concentrations appears to be at or near steady state following administration of the first dose with little or no accumulation. The mean ± SD Cmax and AUC0-24h of adapalene following administration of the new adapalene 0.3%/benzoyl peroxide 2.5% Gel on Day 29 were quantifiable in 16/26 subjects and were 0.16 ± 0.08 ng/mL and 2.49 ± 1.21 ng.h/mL, respectively…The results of the treatment comparison…showed that the systemic exposure of adapalene following administration of Epiduo Forte Gel are not higher than those produced following administration of Differin, 0.3% Gel.

In addition the clinical pharmacology reviewer stated that

> (b) (4) The reason for not performing a TQT trial is that the systemic exposure of adapalene following administration of this new FDC Gel formulation is comparable to those obtained following administration of Differin® Gel, 0.3% under maximal use conditions and benzoyl peroxide in concentrations ranging from 2.5% to 10% is widely available in prescription and over the counter (OTC) dosage forms. This reviewer (b) (4). No QT interval prolongation signals are reported for Differin Gel, 0.3% or benzoyl peroxide.

The final recommendation from the clinical pharmacology reviewer was that “this application is acceptable provided the labeling comments are adequately addressed by the Applicant”.

5 Sources of Clinical Data

5.1 Table of Clinical Trials

Table 1: Table of Clinical Trials Conducted for NDA 209719

Trial#	Population	Type	# of Subjects	Duration
18242	Healthy subjects	Cumulative Irritancy	36	3 weeks
18229	Subjects with severe acne vulgaris	Maximal use PK trial	58	4 weeks
18240	Subjects with moderate to severe acne vulgaris	Phase 3 Safety and Efficacy	503	12

Source: Reviewer's Table

Table 2: List of Clinical Studies Supporting NDA 20917

Adapalene 0.3% Gel				
RD.03.SRE.2644	Dermal Tolerance (Cumulative Irritation and Contact Sensitization)	Healthy subjects	215	Induction: 3 Weeks Rest: 2 Weeks Challenge: Single 48 Hour Application
RD.03.SRE.2645	Dermal Tolerance (Photosensitivity)	Healthy subjects	30	Induction: 3 Weeks Rest: 2 Weeks Challenge: Single 24 Hour Application
1.CG.03.SRE.2646	Dermal Tolerance (Phototoxicity)	Healthy subjects	25	24 Hours
RD.03.SRE.2690	Pharmacokinetics	Subjects with acne vulgaris	16	10 Days
RD.06.SRE.18115	Pharmacokinetics	Subjects with acne vulgaris	51	30 Days
RD.06.SRE.18060	Efficacy/Safety	Subjects with acne vulgaris	214	12 Weeks
RD.06.SRE.18081	Efficacy/Safety	Subjects with acne vulgaris	653	12 Weeks
RD.06.SRE.18082	Long Term Safety	Subjects with acne vulgaris	551	12 Months
Adapalene 0.1%/Benzoyl Peroxide 2.5% Gel				
RD.03.SRE.2681	Dermal Tolerance (Phototoxicity)	Healthy subjects	25	24 Hours
RD.03.SRE.2682	Dermal Tolerance (Photosensitivity)	Healthy subjects	33	Induction: 3 Weeks Rest: 2 Weeks Challenge: Single 24 Hour Application
RD.03.SRE.2683	Dermal Tolerance (Cutaneous Sensitization)	Healthy subjects	251	Induction: 3 Weeks Rest: 2 Weeks Challenge: Single 48 Hour Application
RD.06.SRE.18097	Pharmacokinetics	Subjects with acne vulgaris	24	30 Days
RD.06.SRE.18094	Efficacy/Safety	Subjects with acne vulgaris	517	12 Weeks
RD.06.SRE.18087	Efficacy/Safety	Subjects with acne vulgaris	1668	12 Weeks
RD.06.SRE.18089	Long Term Safety	Subjects with acne vulgaris	452	12 Months

Data Source: Section 5.2, Tabular listing of all clinical studies; Section 2.7.4-1.1, Table 1.

Source: Applicant's Clinical Overview, pg.14

5.2 Review Strategy

Efficacy and safety of EF is derived from the conduct of one safety and efficacy trial (#18240) conducted at sites across the US (25 sites) and Canada (6 sites). Safety information is also derived from one PK study (#18229) and one dermal safety study (#18242).

Efficacy and safety is supported by the entire clinical development program for NDA 22-320 for Epiduo Gel and for Differin Gel 0.3% (see table #2). The trials in these development programs have already been reviewed and will not be discussed in this document.

Safety is also supported by the literature and postmarketing database for each of the monads, adapalene gel 0.3% and benzoyl peroxide 2.5% and for Epiduo Gel.

5.3 Discussion of Individual Studies/Clinical Trials

A detailed description of the protocol for the safety and efficacy trial 18240 is below. This is followed by a brief description of the protocol for the dermal safety trial 18242 which assessed cumulative irritancy potential. See the review by the clinical pharmacology reviewer for a detailed description of trial 18229, the maximal use PK trial.

Clinical Trial #: RD.06.SPR.18240

Title: A Multi-center, Randomized, Double-blind, Parallel-group Vehicle and Active Controlled Study to Compare the Efficacy and Safety of CD0271 0.3% / CD1579 2.5% Topical Gel Versus Topical Gel Vehicle in Subjects with Acne Vulgaris

Objective:

There are 3 sets of efficacy objectives that are specified in a hierarchical order. The 3 objectives will be tested in the order listed below each conditionally depending on the success of the preceding objective. The trial will be considered positive regarding efficacy if objectives (1) and (2) are met.

1. To demonstrate the superiority in efficacy of CD0271 0.3%/CD1579 2.5% Gel versus Topical Gel Vehicle in the treatment of acne vulgaris for up to 12 weeks, in the full population of moderate and severe acne.
2. To demonstrate the superiority in efficacy of CD0271 0.3%/CD1579 2.5% Gel versus Topical Gel Vehicle in the subgroup of subjects with severe acne (Investigator's global Assessment [IGA]=4).
3. To assess the superiority of CD0271 0.3%/CD1579 2.5% versus Epiduo® Gel in the subgroup of subjects with severe acne (IGA=4).

In addition, safety will be assessed during the study; however, it is not part of the hierarchical order defined above.

Table 3 : Principal Investigators

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Source: Reviewer's Table

Institutional Review Board: QUORUM Review IRB,
1501 Fourth Avenue, Suite 800
Seattle WA 98101

Drug Development Phase: 3

Trial Design: multi-center, randomized, double-blind, parallel, vehicle and active-controlled study

Number of Subjects:

As a screen failure rate of approximately 20% is expected, approximately 625 subjects will be screened for a total of 497 subjects who will be randomized/enrolled (in a 3:3:1 ratio for EF, Epiduo Gel, and Topical Gel Vehicle, respectively).

Ages of Subjects for Inclusion: 12 years and older

Inclusion Criteria:

1. Male or female, who is 12 years of age or older at Screening visit.
2. Clinical diagnosis of acne vulgaris with facial involvement.
3. Understand and sign an ICF, or for subjects under the age of 18 years of age (or Age of Majority), an assent form signed by the subject in conjunction with an ICF signed by the parent/legal representative, at screening prior to any investigational procedures being performed.
4. An IGA of Moderate (3) or Severe (4) at Baseline visit.
5. A minimum of 20 but not more than 100 inflammatory lesions (papules and pustules) on the face (including the nose) at Baseline visit.
6. A minimum of 30 but not more than 150 non-inflammatory lesions (open comedones and closed comedones) on the face (including the nose) at Baseline visit.
7. Female of non-childbearing potential (postmenopausal [absence of menstrual bleeding for 1 year prior to Screening, without any other medical reason], hysterectomy or bilateral oophorectomy) or female of childbearing potential with a negative urine pregnancy test (UPT) at Screening and Baseline visits who:
    7.1. Has been strictly abstinent 1 month prior to Baseline and agrees to continue for the duration of the clinical trial and at least 1 month after last study medication application; and/or
    7.2. Agrees to use a highly effective and approved contraceptive method(s) for the duration of the clinical trial and at least 1 month after the last study medication application. A highly effective method of contraception is defined as:
        7.2.a. bilateral tubal ligation
        7.2.b. combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 3 months prior to Baseline
        7.2.c. hormonal intra-uterine device (IUD) inserted at least 1 month prior to Baseline
        7.2.d. vasectomized partner for at least 3 months prior to Baseline.
8. Willing and able to comply with all of the time commitments and procedural requirements of the clinical trial protocol.
9. Apprised of HIPAA, (if in the US), or PIPEDA, (if in Canada), and is willing to share personal information and data, as verified by signing a written authorization at the Screening visit.

Exclusion Criteria:

1. More than 2 acne nodules on the face at Baseline visit.
2. Acne conglobata, acne fulminans, secondary acne (chloracne, drug-induced acne, etc.), nodulo-cystic acne, or acne requiring systemic treatment.
3. Underlying diseases or other dermatologic conditions that require the use of interfering topical or systemic therapy or that might interfere with study assessments such as, but not limited to, atopic dermatitis, perioral dermatitis or rosacea. This includes clinically significant abnormal findings, uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with the interpretation of

the clinical trial results, and/or put the subject at significant risk (according to Investigator's judgment) if he/she participates in the clinical trial.
4. Female who is lactating.
5. Female who is pregnant or intends to conceive a child during the clinical trial or for at least 1 month after the last study medication application.
6. The subject has received, applied or taken the following treatments within the specified timeframe prior to the Baseline visit as defined in Table 3:

Treatment Restrictions

Topical treatments on the subject's face or procedures:	
Acne treatments: - Antibiotics, benzoyl peroxide, azelaic acid, zinc, corticosteroids - Retinoids	 2 weeks 4 weeks
Other topical treatment on treated areas (including laser) including wax epilation	2 weeks
Phototherapy devices for acne (e.g., ClearLight™)	6 weeks
Adhesive cleansing strips (e.g., Pond®, Biore®) Cosmetic procedures (i.e., facials, peeling, comedone extraction)	1 week
Systemic treatments:	
Non steroidal anti-inflammatory drugs	2 weeks
Corticosteroids (except locally acting corticosteroids such as inhaled or intrathecal or dermal application at distance from the face)	1 month
Antibiotics (except penicillin)	1 month
Immunomodulators, biologics	3 months
Oral retinoids	6 months

Note: Prior use of potentially irritating topical products, such as medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices, or lime, is permitted, but their application/use is forbidden during the study. This also includes, but not limited to, alpha hydroxy acid products, antibacterial containing soaps, medicated shaving creams, astringents or preparations with alcohol. Oral vitamin A (up to the recommended daily allowance) and plain penicillin are acceptable prior to and during the study.

Source: Applicant's protocol pg.23

7. The subject is unwilling to refrain from use of prohibited medication during the clinical trial (see Section 5.5.5).
8. Beard or facial hair that might interfere with study assessments.
9. Excessive sun exposure, use of tanning booths or tanning lamps within 1 week prior to baseline and/or an unwillingness to refrain from such exposure/use during the study.
10. Use of hormonal contraceptives, unless the subject is on a stable dose (i.e., at least 3 months of treatment prior to enrollment).
11. Use of hormonal contraceptives solely for the control of acne.
12. Known or suspected allergies or sensitivities to any components of any of the study medication (see Investigator's Brochure/Product label).
13. Current participation in any other clinical trial of a drug or device; or has participated in a drug or device trial within 30 days prior to Baseline.
14. The subject is vulnerable (such as deprived from freedom) as defined in Section 1.61 of the ICH GCP.

Trial Plan:

Subjects will be randomized in a 3:3:1 ratio for EF, Epiduo Gel, and Topical Gel Vehicle, respectively. Randomization will be stratified by investigational site and IGA severities such that 50% of the subjects present an IGA of 3 and 50% present an IGA of 4. Subjects meeting the Inclusion criteria and none of the Exclusion criteria will be randomized at baseline and treated for a period of up to 12 weeks. A Screening period of no more than 2 weeks (14 ± 3 days) will be permitted, at which point the subject is to return for the Baseline Visit. Subjects will then return to the centers for evaluations at Weeks 1, 2, 4, 8, and 12/Early Termination.

Subjects will be instructed to apply moisturizer at least once daily and liberal application should be encouraged. No other topical medication treatment, other than the study medication, moisturizer, and sunscreen will be permitted on the face. Instructions for once daily application to dry skin at night after washing: Apply a thin film on the face. A pea-size amount for each area of the face (e.g., forehead, chin, each cheek), should be used; avoiding the eyes, lips and mucous membranes. Apply a thin film to affected areas on the trunk, if applicable. If a subject experiences persistent dryness or irritation, the Investigator may consider a reduced application frequency as required for the symptomatic relief of skin dryness or irritation. When the once daily treatment regimen must be altered to every other day, (e.g., to treat local irritation) an attempt should be made by the Investigator to return the subject to once daily treatment within two weeks. Treatment compliance will be recorded on the subject dosing calendar.

Throughout the study when possible, the same evaluator will perform the IGA and/or lesion counts for each individual subject. Trained Investigators will assess the subject's acne severity using the IGA scale at each visit.

Table 4: Investigators Global Assessment

0	Clear	Clear skin with no inflammatory or non-inflammatory lesions.
1	Almost Clear	A few scattered comedones and a few small papules.
2	Mild	Easily recognizable; less than half the face is involved. Some comedones and some papules and pustules.
3	Moderate	More than half of the face is involved. Many comedones, papules and pustules. One small nodule may be present.
4	Severe	Entire face is involved. Covered with comedones, numerous papules and pustules. Few nodules may or may not be present.

Source: Applicant's Protocol pg. 34

Each type of lesion will be counted separately and recorded on the appropriate eCRF page. The following are the definitions of lesion types that will be counted:

Inflammatory Lesions

- Papule – a small, red, solid elevation equal to or less than 0.5 cm in diameter.
- Pustule – a small, circumscribed elevation of the skin that contains yellow-white exudate.

Non-inflammatory Lesions

- Open Comedone – a pigmented dilated pilosebaceous orifice (blackhead).
- Closed Comedone – a tiny white papule (whitehead).

Other Lesions

- Nodule – a circumscribed, elevated, solid lesion generally more than 0.5 cm in diameter with palpable depth.

Safety:

The safety parameters are Adverse Events (AEs) and assessment of local tolerability. Physical examination findings and vital signs will also be assessed. The only laboratory safety tests planned for this study are urine pregnancy tests.

Erythema, scaling, dryness, and stinging/burning will be graded at Baseline and each post- Baseline visit as follows (face only):

Erythema: abnormal redness of the skin.

None	0:	No erythema
Mild	1:	Slight pinkness present
Moderate	2:	Definite redness, easily recognized
Severe	3:	Intense redness

Scaling: abnormal shedding of the stratum corneum.

None	0:	No scaling
Mild	1:	Barely perceptible shedding, noticeable only on light scratching or rubbing
Moderate	2:	Obvious but not profuse shedding
Severe	3:	Heavy scale production

Dryness: brittle and/or tight sensation.

None	0:	No dryness
Mild	1:	Slight but definite roughness
Moderate	2:	Moderate roughness
Severe	3:	Marked roughness

Stinging/Burning: prickling pain sensation immediately after (within 5 minutes) of dosing.

None	0:	No stinging/burning
Mild	1:	Slight warm, tingling/stinging sensation; not really bothersome
Moderate	2:	Definite warm, tingling/stinging sensation that is somewhat bothersome
Severe	3:	Hot, tingling/stinging sensation that has caused definite discomfort

Note: Stinging/Burning at the Baseline visit is to be assessed as none (0).

An Adverse Event will be recorded if the severity of the signs and symptoms is such that:

- The subject's participation in the study is interrupted at his/her request or at the Investigator's request.

Note: An interruption of study medication greater than 2 weeks (whether no application during this period or temporary change from daily dosing to an alternate day treatment regimen) constitutes as an interruption of study medication and is to be captured as an AE. Interruptions of study medication or changes less than 2 weeks are to be assessed as AEs at the Investigator's discretion.

- The subject permanently discontinues the treatment at his/her request or at the Investigator's request.
- The subject requires concomitant prescription or OTC therapy (other than moisturizers).

Note: Need for increased moisturizer use does NOT constitute an AE.

Any new sign or symptom, which is not included in the scheduled evaluation of tolerability, should be recorded as an Adverse Event, including those of mild intensity.

The AEs of Special Interest for this protocol are pre-defined as follows:

- Suspected sensitization

All safety data will be summarized based on the safety population, by baseline IGA and combined. Local tolerability variables (erythema, scaling, dryness and stinging/burning) will be summarized by severity score and for worst response over time. Adverse events will be tabulated in frequency tables by System Organ Class (SOC) and Preferred Term (PT) based on the MedDRA dictionary.

Table 5: Reasons for Discontinuation

Pregnancy:	**Withdraw the Subject from the clinical trial and follow the procedure described in Section 7.2.4.2.5**
Lack of Efficacy:	Investigator judgment only: based on therapeutic/disease-state expectations. If subject opinion only, mark "subject request" and document it in the comment section of the eCRF Exit Form.
Adverse Event:	Complete an Adverse Event Form.
Subject Request[a]:	Includes consent withdrawal, subject relocation, schedule conflicts. Explain the reason for withdrawal in the comment section of the eCRF Exit Form.
Protocol Violation:	Explain the violation in the comment section of the eCRF Exit Form.
Lost to Follow-up:	Confirmed with two documented phone calls and a certified letter (delivery receipt requested) without answer. Explain in the comment section of the eCRF Exit Form.
Other[a]:	This category is to be used for a subject who discontinues due to a reason other than as specified in the predefined categories above. Explain the reason for discontinuation in the comment section of the eCRF Exit Form.

a If reason for discontinuation is "subject request" or "other", the subject will be questioned to rule out the possibility of an AE (this should be documented in the comment section of the eCRF Exit Form).

Source: Applicant's Protocol, pg.27

Schedule of Assessments

	Scheduled Visits[a]						
Procedures	**Screening Visit**	**Baseline**	**Week 1 (± 3 days)**	**Week 2 (± 3 days)**	**Week 4 (± 7 days)**	**Week 8 (± 7 days)**	**Week 12 / Early Termination Visit (± 7 days)**
Informed Consent, Assent Form, HIPAA, PIPEDA	X						
Photography Consent[b]	X						
Demographics	X						
Medical History	X						
Previous Medications	X						
Vital Signs/Physical Examination	X						X
Inclusion/Exclusion Criteria	X	(X)[a]					
Urine Pregnancy Testing[c]	X	X			X	X	X
Investigator's Global Assessment (face)	X	(X)[a]	X	X	X	X	X
Subject's Assessment of Acne Improvement							X
Lesion Counts (face)	X	(X)[a]	X	X	X	X	X
Local Tolerability Assessment[d]		X	X	X	X	X	X
DLQI / C-DLQI; EQ-5D-3L[e]		X					X
Appreciation Questionnaire							X
Photographs (face)[b]		X	X	X	X	X	X
IRT	X	X			X	X	X
Study Medication Dispensed		X			X	X	
Study Medication Returned					X	X	X
Dosing Calendar Dispensed		X			X	X	
Dosing Calendar Returned & Reviewed			X	X	X	X	X
Concomitant Therapy/Concomitant Procedure[f]	X	X	X	X	X	X	X
Adverse Event[g]	X	(X)[h]	X	X	X	X	X
Exit Form							X

a. If the subject has not received, applied, or taken treatments as noted in Exclusion Criteria #6 the Screening Visit and Baseline Visit will be performed the same day. If the Screening and Baseline visits occur on separate days, inclusion/exclusion criteria, IGA, and Lesion Counts must be reevaluated prior to randomization. Maximum time window allowed between Screening Visit and Baseline Visit is 14 ± 3 days.
b. Selected sites only.
c. Pregnancy testing is mandatory for all females of child-bearing potential at Screening, Baseline, Week 4, Week 8, and Week 12/Early Termination visits. Additional pregnancy testing can be conducted at the discretion of the Investigator during the course of the study.
d. The Investigator must grade and record the severity of the clinical signs (erythema, dryness and scaling); and record the subject's assessment of symptoms (stinging/burning) on the Local Tolerability Assessment Form at each visit from Baseline to Week 12/Early Termination visit.
e. Dermatology Life Quality Index (DLQI), Children's Dermatology Life Quality Index (C-DLQI), and EuroQol (EQ-5D-3L) (see Section 13 Appendices)
f. Medication that continues after Baseline should be recorded on the Concomitant Therapy page of the eCRF. Medical or surgical procedures occurring after Baseline should be recorded on the Procedures page of the eCRF.
g. Events occurring after the Informed Consent Form has been signed should be recorded as Adverse Events in the eCRF.
h. Reevaluate in case of Screening Visit and Baseline Visit on different days.

HIPAA=Health Insurance Portability and Accountability Act of 1996; PIPEDA=Personal Information Protection and Electronic Documents Act

Source: Applicant's Protocol pg.12

Data Analysis:

Co-primary endpoints

- Success Rate, the percentage of subjects with an IGA of clear or almost clear (and therefore at least a 2-grade improvement from Baseline at Week 12 Intent-to-treat [ITT]);
- Change in Inflammatory Lesion Count from Baseline to Week 12 (ITT);
- Change in Non-inflammatory Lesion Count from Baseline to Week 12 (ITT).

Secondary efficacy endpoints

- Percent Changes in Inflammatory and Non-inflammatory Lesion Counts from Baseline to Week 12 (ITT).

The primary hypothesis testing for this trial will be in the form of hierarchical testing of the three treatment groups across and within the 2 severity strata in this clinical trial. The hierarchical test will take place in steps, detailed below. At each step the following co-primary variables will be tested:

(1) IGA Success Rate at Week 12 (ITT),
(2) Change in Inflammatory Lesion Count from Baseline to Week 12 (ITT), and
(3) Change in Non-inflammatory Lesion Count from Baseline to Week 12 (ITT).

It will be required at each step that the test for each variable be significant at a two-tailed alpha level of 0.05. The primary method of imputation for missing data will use multiple imputation techniques. The Last Observation Carried Forward (LOCF) will be used as sensitivity analyses.

Clinical Trial #: 18242

Title: Evaluation of the Cutaneous Cumulative Irritancy Potential of CD0271 0.3% /CD1579 2.5 % Gel and Corresponding Vehicle Following Repeated Applications to the Skin of Healthy Subjects

Objective: To determine the cutaneous cumulative irritancy potential of repeated applications of CD0271 0.3% / CD1579 2.5 % Topical Gel and corresponding vehicle following repeated applications to the skin of healthy subjects

Principal Investigator(s): Jonathan Dosik, MD
TKL Research, Inc.
1 Palmer Terrace
Carlstadt NJ 07071

Institutional Review Board: IntegReview Ethical Review Board
3001 S. Lamar Blvd., Suite 210

Austin, TX 78704

Drug Development Phase: one

Study Design: Single-center, randomized, vehicle, negative and positive-controlled, evaluator blinded, intra-individual design clinical trial

Number of Subjects: 60 screened to randomize 35 to obtain 30 evaluable subjects

Ages of Subjects for Inclusion: 18 to 65 years

Key Inclusion Criteria:

- In the opinion of the Investigator, in good general health
- Skin phototype of I to IV (Wolff and Fitzpatrick 2007)
- Female of childbearing potential with a negative urine pregnancy test (UPT) at screening and Baseline

  Female of childbearing potential who agrees to use a double-barrier contraception method throughout the study and until at least one month after the last study drug application. Double-barrier contraception is defined as the use of condom and a highly effective and approved method of contraception such as:
  - Bilateral tubal ligation
  - Combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 1 month prior to baseline visit
  - Hormonal intra-uterine device (IUD) inserted at least 1 month prior to baseline visit
  - Vasectomized partner for at least 3 months prior to baseline visit

Key Exclusion Criteria:

- Disease or therapy leading to immunosuppression
- Known or suspected allergies or sensitivities to any of the components of the study drugs (see Investigator's Brochure/Product label).
- The subject has received, applied, or taken any treatments outlined in Table 2 within the specified washout period.

Study Plan: Single-center, randomized, vehicle, negative and positive-controlled, evaluator blinded, intra-individual design clinical trial enrolling healthy male and female subjects. 6 study drugs will be used in the study including CD0271 0.3% / CD1579 2.5% Topical Gel, corresponding

vehicle, comparators, white petrolatum as a negative control, and 0.1% sodium lauryl sulfate (SLS) as a positive control.

Study drugs will be applied under semi-occlusive patches to designated skin sites on the subject's back daily for three consecutive weeks. Patches will remain in place for 24 hours. The treatment period duration is 22 days. A Skin Reaction Assessment [6 point scale] will be performed at least 30 minutes after patch removal for each designated skin site on days 2-22.

Data Analysis:

The skin reaction scores will be summarized by descriptive statistics. Mean Cumulative Irritancy Index (MCII) will be calculated and summarized by study drug. The worst score over time for each subject will also be summarized by study drug.

Incidence of Adverse Events by treatment will be tabulated when applicable. Adverse event that would not be reported on a specific zone will be summarized under each treatment. Moreover, additional summaries considering the subject as a whole will be performed.

Safety:

- Skin Reaction Assessment - a 6-point skin reaction scale ranging from 0 = No response to 4 = Bullous (large blister), spreading, or other severe reaction).
- Adverse Events
- Vital signs/physical examination

6 Review of Efficacy

The review of efficacy below is for trial 18240.

Efficacy Summary

The efficacy of EF was demonstrated in Trial 18240, a multi-center, randomized, double-blind, parallel-group vehicle and active controlled trial in which 503 subjects aged 12 and older were randomized to three arms: EF (217 subjects), Epiduo (217 subjects) and vehicle (69 subjects) for the treatment of acne vulgaris.

The demographics for trial 18240 revealed a slight majority of female subjects (≈52%), a majority of Caucasian subjects (≈75-79%), and a mean age of 18.5 - 20.1 years. Enrolled subjects had a baseline severity of moderate (49.9%) or severe (50.1%) with inflammatory lesions counts ranging from a mean of 36 - 39 and non-inflammatory lesions counts ranging from 59 – 61. With regard to disposition, ≈91% of the EF

subjects completed the trial versus≈ 98% of the Epiduo subjects and≈ 98 of vehicle subjects.

EF was statistically superior to vehicle for all of the co-primary endpoints at week 12 in the ITT population. The success rate for subjects treated with EF was 33.7% (clear or almost clear) at the end of the 12 week treatment period vs 27.3% for Epiduo and 11% for vehicle. The change in inflammatory lesion counts for subjects treated with EF was -27.8 at the end of the 12 week treatment period vs 26.5% for Epiduo and -13.2 for vehicle. The change in non-inflammatory lesion counts for subjects treated with Epiduo Forte was -40.5 at the end of the 12 week treatment period vs 40.0% for Epiduo and -19.7 for vehicle. EF was statistically superior to vehicle for both of the secondary efficacy endpoints at week 12 in the ITT population.

6.1 Indication

EF is a fixed-dose combination of 0.3% adapalene and 2.5% benzoyl peroxide, developed for the topical treatment of acne vulgaris in patients 12 years of age and older.

6.1.1 Methods

The efficacy of EF is demonstrated in Trial 18240, a multi-center, randomized, double-blind, parallel-group vehicle and active controlled trial, which is reviewed in detail in this document. The efficacy of EF is supported by previous trials for Epiduo and Differin 0.3% gel. (See Table 2 for complete list of supporting trials). The supportive historical trials will not be reviewed in this document. See Section 5 for details of the protocol for trial 18240.

6.1.2 Demographics

Trial 18240 randomized 503 subjects to three arms: EF (217 subjects), Epiduo (217 subjects) and vehicle (69 subjects). Of the randomized subjects, 252 (50.1%) had a baseline severity score of 4 (severe) and 251 (49.9%) had a baseline severity score of 3 (moderate). The lesions counts were also well balanced across the study arms with inflammatory lesions counts ranging from a mean of 36.4 - 39.2 and non-inflammatory lesions counts ranging from 58.9 – 60.7.

Demographic characteristics of the subjects in trial 18240 were similar across groups. There was a slight predominance of female subjects (52.1% for EF, 52.5% for Epiduo and 52.2% for vehicle).The mean age ranged from 18.5 - 20.1 years across the arms. The majority of subjects in all three arms were white (75.4%-78.8%). African American subjects were represented as 16.1% of subjects in the EF arm, 17.1% of subjects in the Epiduo arm and 18.8% of subjects in the vehicle arm. The majority of subjects were skin phototypes II – IV.

Table 6: Demographic Characteristics in Trial 18240 (ITT)

Variable	CD0271 0.3%/ CD1579 2.5% Gel (N=217)	CD0271 0.1%/ CD1579 2.5% Gel (N=217)	Vehicle Gel (N=69)	Total (N=503)	P-value
Gender					
Male	104 (47.9%)	103 (47.5%)	33 (47.8%)	240 (47.7%)	
Female	113 (52.1%)	114 (52.5%)	36 (52.2%)	263 (52.3%)	0.988
Total	217(100.0%)	217(100.0%)	69(100.0%)	503(100.0%)	
Age (Year)					
N	217	217	69	503	
Mean	20.1	19.4	18.5	19.6	
SD	7.59	6.75	5.72	7.01	0.245
Median	17.0	17.0	16.0	17.0	
Q1 , Q3	15 , 23	15 , 22	15 , 21	15 , 22	
Minimum, Maximum	12 , 57	12 , 49	12 , 36	12 , 57	
12-17	111 (51.2%)	119 (54.8%)	43 (62.3%)	273 (54.3%)	
18-64	106 (48.8%)	98 (45.2%)	26 (37.7%)	230 (45.7%)	0.265
65 and above	0	0	0	0	
Total	217(100.0%)	217(100.0%)	69(100.0%)	503(100.0%)	
Race					
White	171 (78.8%)	166 (76.5%)	52 (75.4%)	389 (77.3%)	
Black Or African American	35 (16.1%)	37 (17.1%)	13 (18.8%)	85 (16.9%)	
Asian	5 (2.3%)	3 (1.4%)	2 (2.9%)	10 (2.0%)	
American Indian Or Alaska Native	0	0	0	0	0.644
Native Hawaiian Or Other Pacific Islander	0	1 (0.5%)	1 (1.4%)	2 (0.4%)	
Other	6 (2.8%)	10 (4.6%)	1 (1.4%)	17 (3.4%)	
Total	217(100.0%)	217(100.0%)	69(100.0%)	503(100.0%)	
Ethnicity					
Hispanic or Latino	59 (27.2%)	56 (25.8%)	14 (20.3%)	129 (25.6%)	
Not Hispanic or Latino	158 (72.8%)	161 (74.2%)	55 (79.7%)	374 (74.4%)	0.520
Total	217(100.0%)	217(100.0%)	69(100.0%)	503(100.0%)	

P-values for nominal categorical variables were based on the CMH general association statistic, controlling for Baseline IGA.
P-values for ordinal categorical variables except Baseline IGA were based on the CMH row mean difference statistic, RIDIT transformed score, controlling for Baseline IGA.
P-values for continuous variables were based on two-way ANOVA model with terms for treatment and Baseline IGA.
Data source: Table 14.1.3.1

Source: Applicant's Clinical Study Report, 18240 pg.44

6.1.3 Subject Disposition

The majority of subjects in trial 18240 completed the trial, 90.8% in the EF arm, 89.5% in the Epiduo arm and 89.4% in the vehicle arm. The reasons for discontinuations are displayed in the table below:

Table 7: Primary Reason for Early Termination (ITT)

Population	Epiduo Forte	Epiduo	Vehicle Gel	Total
Primary Reason for Early Termination, ITT	**20 (9.2%)**	**25 (11.5%)**	**8 (11.6%)**	**53 (10.5%)**
Lack of Efficacy	0	0	1 (1.4%)	1 (0.2%)
Adverse Event	1 (0.5%)	1 (0.5%)	0	2 (0.4%)
Subject's Request	6 (2.8%)	13 (6.0%)	2 (2.9%)	21 (4.2%)
Protocol Violation	1 (0.5%)	2 (0.9%)	0	3 (0.6%)
Lost to Follow-up	12 (5.5%)	8 (3.7%)	4 (5.8%)	24 (4.8%)
Other	0	1 (0.5%)	0	1 (0.2%)
Pregnancy	0	0	1 (1.4%)	1 (0.2%)

Note: Percentages were based on the number of subjects in the ITT population in each treatment group.
Note: Subject 8259-007 was entered in IRT as IGA=4 incorrectly, and was included in the correct group of IGA=3 for all statistical analyses.
Note: Subject 8133-011 was dispensed a wrong kit number at week 8 by error, and was included in ITT and Safety populations under the originally randomized treatment group, but was excluded from the Per Protocol Population for all statistical analyses.
a) The Intent-to-Treat (ITT) Population was defined as all subjects who were randomized.
b) The Per-Protocol (PP) Population was defined as the ITT subjects who had no major protocol deviations.
c) The Safety Population was defined as the ITT Population who applied the study medication at least once. In practice, only the subjects who returned their medication unopened were excluded from the safety population.
Data source: Table 14.1.1.1

Source: Applicant's Clinical Study Report, 18240 pg 41

The majority of the discontinuations were due to lost to follow-up and subject's request. In general the discontinuations were balanced across groups and only 2 were due to adverse events (see Section 7.3.3 for details).

6.1.4 Analysis of Primary Endpoint(s)

The Primary Efficacy Endpoints for trial 18240 were

- Success in IGA, defined as the proportion of subjects with an IGA score of 0 (clear) or 1 (almost clear) at Week 12 (at least 2-grade reduction) and
- Absolute change in inflammatory lesion counts from baseline to Week 12
- Absolute change in non-inflammatory lesion counts from baseline to Week 12

The results for the Primary Efficacy Endpoints are presented in the table below from the statistical reviewer's midcycle review:

Table 8: Results for the Co-Primary Efficacy Endpoints at Week 12 (ITT)

Endpoints	EPIDUO FORTE Gel (N=217)	EPIDUO Gel (N=217)	Vehicle Gel (N=69)	P-value(1)
Co-Primary:				
IGA (clear or almost clear): n (%)	73.2 (33.7%)	59.2 (27.3%)	7.6 (11.0%)	<0.001(2)
Absolute Change in:				
Inflammatory Lesions: Mean	27.8	26.5	13.2	<0.001(3)
Non-Inflammatory Lesions: Mean	40.5	40.0	19.7	<0.001(3)

(1) EPIDUO FORTE vs. Vehicle
(2) P-value from a CMH test stratified by baseline IGA and analysis center using MI methodology (Schafer 1997).
(3) P-value from an ANCOVA model with terms for treatment, analysis center, baseline IGA severity, and baseline lesion counts.
*The values displayed are the averages over the 5 imputed datasets (MI).
ITT: Intent-to-Treat
Source: Statistical Reviewer's Midcycle Review

EF was statistically superior to vehicle for all of the co-primary endpoints at week 12 in the ITT population. Epiduo was also statistically superior to vehicle for all of the co-primary endpoints at week 12 in the ITT population. The table to be placed in Section 14, Clinical Studies is still under negotiation with the Applicant at the time of this review. The results for the co-primary efficacy endpoints stratified by baseline severity were also assessed and are presented below.

Per Protocol (PP) analyses were also performed for the co-primary efficacy endpoints at week 12 for trial 18240. Results for success rate, changes in inflammatory and non-inflammatory lesion counts in the overall population (combined severity strata) were also statistically significant for the EF arm vs the vehicle arm.

Table 9: Results for the Co-Primary Efficacy Endpoints at Week 12 by Baseline Disease Severity (ITT)

Endpoints	Epiduo Forte (N=217)	Epiduo (N=217)	Vehicle (N=69)	P-value[1]
IGA (clear or almost clear): n (%)				
Overall	33.7%	27.3%	11.0%	<0.001
IGA=3 (moderate)[2]	35.5%	34.5%	10.3%	
IGA=4 (severe)[3]	31.9%	20.5%	11.8%	0.029
Absolute Change in Inflammatory Lesions				
Overall	27.8	26.5	13.2	<0.001
IGA=3 (moderate)[2]	18.8	22.4	12.1	
IGA=4 (severe)[3]	37.2	30.2	14.3	<0.001
Absolute Change in Non-Inflammatory Lesions				
Overall	40.5	40.0	19.7	<0.001
IGA=3 (moderate)[2]	34.8	35.9	21.5	
IGA=4 (severe)[3]	46.3	43.9	17.8	<0.001

(1) EPIDUO FORTE vs. Vehicle
(2) Moderate Sample Sizes = (N_{EF}, N_E, N_V) = (111,105, 35)
(3) Severe Sample Sizes = (N_{EF}, N_E, N_V) = (106,112, 34)
*The values displayed are the averages over the 5 imputed datasets (MI).

Source: Reviewer's Table (modified from the statistical reviewer's table in mid-cycle review)

The severe subgroup for trial 18240 had a larger decrease in the number of inflammatory and non-inflammatory lesions. This is not unexpected since these subjects had a larger number of lesions at baseline. For the IGA success component of the co-primary endpoint, the severe subgroup had a smaller percentage of success vs the moderate subgroup (31.9% vs 35.5% respectively).

Success on all 3 primary endpoints was to be demonstrated in both strata combined (IGA=3 and IGA=4; Step 1) before testing in the Severe stratum (IGA=4; Steps 2 and 3). The study was to be considered as positive for efficacy outcome if EF was statistically more effective than Vehicle Gel for Steps 1 and 2. This objective was achieved. According to the statistical reviewer

> The applicant stratified the randomization such that 50% of the subjects had moderate acne (IGA = 3) and 50% of subjects had severe acne (IGA = 4) at baseline. In addition, the applicant pre-specified statistical testing (EPIDUO FORTE gel vs. vehicle gel) for the severe acne subgroup in the multiplicity testing strategy. For the severe acne subgroup, EPIDUO FORTE gel was statistically superior (p-values ≤ 0.029) to vehicle gel for the co-primary and secondary efficacy endpoints…

The third step in the analysis was for comparison of EF vs Epiduo in the severe stratum. This comparison did not achieve statistical significance (according to the applicant the study was not powered to demonstrate significance for this comparison) but did show a positive trend.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary efficacy endpoints for trial 18240 were

- Percent change in inflammatory lesion counts from baseline to Week 12
- Percent change in non-inflammatory lesion counts from baseline to Week 12

The results for the secondary efficacy endpoints are presented in the table below from the statistical reviewer's midcycle review:

Table 10: Secondary Efficacy Endpoints at Week (ITT)

Endpoints	EPIDUO FORTE Gel (N=217)	EPIDUO Gel (N=217)	Vehicle Gel (N=69)	P-value[1]
Percent Change in:				
Inflammatory Lesions: Mean	68.7%	69.3%	39.2%	<0.001[4]
Non-Inflammatory Lesions: Mean	68.3%	68.0%	37.4%	<0.001[4]

(1) EPIDUO FORTE vs. Vehicle
(4) P-value from a CMH test stratified by baseline IGA and analysis center with row mean difference statistic using RIDIT score using MI (Schafer 1997).
*The values displayed are the averages over the 5 imputed datasets (MI).
ITT: Intent-to-Treat

Source: Statistical Reviewer's Midcycle Review

EF was statistically superior to vehicle for both of the secondary efficacy endpoints at week 12 in the ITT population. Epiduo was also statistically superior to vehicle for both of the secondary efficacy endpoints at week 12 in the ITT population.

6.1.6 Other Endpoints

See Section 6.1.4 Analysis of Primary Endpoint(s) for the results for the co-primary efficacy endpoints stratified by baseline severity.

6.1.7 Subpopulations

The efficacy endpoints for trial 18240 were also analyzed by predefined demographic subgroups of gender, race and age group. Examination of success rates in the ITT population for the EF arm of trial 18240 revealed that women achieved a higher success rate than men (33.6% vs 26.9%), caucasians achieved a higher success rate than non-caucasians (31.6% vs 26.1%) and adult subjects achieved a higher success rate than adolescent subjects (34.9% vs 26.1%).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable, a single fixed dose of Epiduo Gel was used in the trial.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable, a 12 week treatment course was used for all subjects in the trial.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

The safety population for trial 18240 was the same as the intent to treat (ITT) population which included 503 subjects who were randomized. No deaths and no related serious adverse events occurred in trial 18240. Three subjects were discontinued from the trial, 2 secondary to adverse events and one at the subject's request due to an episode of irritation suspected by the investigator to represent sensitization. The most common adverse events in the EF arm of trial 18240 were skin irritation (2.8%) and skin burning sensation (0.9%). Assessment of local tolerability revealed erythema, scaling, dryness and stinging/burning in 43-66% of the safety population in both active arms. The majority of reactions were mild to moderate and the incidence decreased over the course of the study.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

See Section 5.1, Table 1: Table of Clinical Trials Conducted for NDA 209719. The majority of this review reports the safety evaluation for trial 18240.

7.1.2 Categorization of Adverse Events

Adverse events were recorded at each visit. In addition, signs and symptoms of local tolerability (erythema, scaling, dryness, and stinging/burning) were evaluated at each visit using a score ranging from "0" (none) to "3" (severe) in Trial 18240.

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

Trials were not pooled due to differences in trial objective and duration.

7.2 Adequacy of Safety Assessments

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

The mean treatment duration for trial 18240 was 79 days for EF, 78.3 days for Epiduo and 78.4 days for the vehicle arm. The mean daily amount of EF used per subject in trial 18240 was .92 g/day vs .94 g/day for Epiduo and .63 g/day for the vehicle arm.

This exposure is adequate to evaluate the safety of EF.

7.2.2 Explorations for Dose Response

No dose exploration was conducted for the development of EF. It was agreed upon with the agency during development that the three proposed trials, one cumulative irritation, one PK and one efficacy and safety were sufficient for the submission of the EF NDA.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed in the development program for EF.

7.2.4 Routine Clinical Testing

No laboratory testing (other than urinary pregnancy testing) was performed in the efficacy and safety trial #18240.

7.2.5 Metabolic, Clearance, and Interaction Workup

No metabolic, clearance or interaction work-up was performed in the development program for EF.

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

See original clinical review for Epiduo Gel.

7.3 Major Safety Results

The safety population for trial 18240 was the same as the intent to treat (ITT) population which included 503 subjects who were randomized.

7.3.1 Deaths

No deaths occurred in the development program for EF.

7.3.2 Nonfatal Serious Adverse Events

There was one serious adverse event (SAE) in trial 18240. This occurred in a subject in the Epiduo group who experienced a generalized anxiety disorder of moderate severity that was not felt by the investigator to be related to the product. I agree with this interpretation.

7.3.3 Dropouts and/or Discontinuations

Three subjects discontinued from trial 18240, 2 due to AEs and one at the subject's request due to an episode of irritation suspected by the investigator to represent sensitization.

Table 11: Summary of Overall Adverse Events Trial 18240

Category	CD0271 0.3%/ CD1579 2.5% Gel (N=217)	CD0271 0.1%/ CD1579 2.5% Gel (N=217)	Vehicle Gel (N=69)	Total (N=503)
Subjects With At Least One Adverse Event	**50 (23.0%)**	**42 (19.4%)**	**13 (18.8%)**	**105 (20.9%)**
Related AE	12 (5.5%)	1 (0.5%)	0	13 (2.6%)
Unrelated AE	41 (18.9%)	41 (18.9%)	13 (18.8%)	95 (18.9%)
Subjects With At Least One Serious Adverse Event	**0**	**1 (0.5%)**	**0**	**1 (0.2%)**
Unrelated AE	0	1 (0.5%)	0	1 (0.2%)
Subjects With At Least One Adverse Event Leading to Discontinuation	**1 (0.5%)**	**1 (0.5%)**	**0**	**2 (0.4%)**
Related AE	1 (0.5%)	0	0	1 (0.2%)
Unrelated AE	0	1 (0.5%)	0	1 (0.2%)
Subjects With At Least One Mild Adverse Event	**44 (20.3%)**	**33 (15.2%)**	**9 (13.0%)**	**86 (17.1%)**
Related AE	7 (3.2%)	1 (0.5%)	0	8 (1.6%)
Unrelated AE	37 (17.1%)	32 (14.7%)	9 (13.0%)	78 (15.5%)
Subjects With At Least One Moderate Adverse Event	**15 (6.9%)**	**17 (7.8%)**	**5 (7.2%)**	**37 (7.4%)**
Related AE	6 (2.8%)	0	0	6 (1.2%)
Unrelated AE	10 (4.6%)	17 (7.8%)	5 (7.2%)	32 (6.4%)
Subjects With At Least One Severe Adverse Event	**0**	**0**	**1 (1.4%)**	**1 (0.2%)**
Unrelated AE	0	0	1 (1.4%)	1 (0.2%)
Subjects With At Least One Adverse Event of Special Interest	**1 (0.5%)**	**0**	**0**	**1 (0.2%)**
Related AE	1 (0.5%)	0	0	1 (0.2%)

Subjects might be counted twice, once in Related AE category and once in Unrelated AE category for having more than one AE.
MedDRA version 15.0.
Data source: Table 14.3.2.1

Source: Applicant's Study Report pg. 107

In the EF arm, subject 8340-006, a 12 year old female, experienced an AE of atopic dermatitis on day 4 assessed as moderate and related by the investigator and discontinued the trial as a result. In the Epiduo arm subject 8009-018, a 16 year old male, experienced an AE of worsening acne on day 29 assessed as moderate and related by the investigator and discontinued the trial as a result.

7.3.4 Significant Adverse Events

One subject experienced an adverse event of special interest (AESI) in the EF arm of trial 18240. Subject 8056-011 a 14 year old white female reported mild skin irritation with "puffy eyes, erythema, itching and burning" on day 19 of treatment, and the investigator suspected sensitization to the investigational product, rated the event as

mild and related. The subject refused patch testing and was terminated from the study on day 28 at the subject's request.

7.3.5 Submission Specific Primary Safety Concerns

There were no submission specific safety concerns in the development program for EF.

7.4 Supportive Safety Results

7.4.1 Common Adverse Event

Table 12: Related TEAEs by SOC and Preferred Term Trial 18240 (ITT)

System Organ Class/Preferred Term[a]	CD0271 0.3%/ CD1579 2.5% Gel (N=217)	CD0271 0.1%/ CD1579 2.5% Gel (N=217)	Vehicle Gel (N=69)	Total (N=503)
Total Number of AE(s)	**15**	**2**	**0**	**17**
Total Number (%) of Subjects with AE(s)[b]	**12 (5.5%)**	**1 (0.5%)**	**0**	**13 (2.6%)**
Skin and subcutaneous tissue disorders	**11 (5.1%)**	**1 (0.5%)**	**0**	**12 (2.4%)**
Skin irritation	6 (2.8%)	0	0	6 (1.2%)
Pruritus	1 (0.5%)	1 (0.5%)	0	2 (0.4%)
Skin burning sensation	2 (0.9%)	0	0	2 (0.4%)
Dermatitis atopic	1 (0.5%)	0	0	1 (0.2%)
Eczema	1 (0.5%)	0	0	1 (0.2%)
Erythema	0	1 (0.5%)	0	1 (0.2%)
Rash	1 (0.5%)	0	0	1 (0.2%)
Skin hypopigmentation	1 (0.5%)	0	0	1 (0.2%)
Eye disorders	**1 (0.5%)**	**0**	**0**	**1 (0.2%)**
Erythema of eyelid	1 (0.5%)	0	0	1 (0.2%)
Nervous system disorders	**1 (0.5%)**	**0**	**0**	**1 (0.2%)**
Paraesthesia	1 (0.5%)	0	0	1 (0.2%)

a) A subject was counted only once for multiple occurrences within a System Organ Class or Preferred Term.
b) A subject was counted once even if the subject experienced more than one adverse event during the study.
MedDRA version 15.0.
Data source: SRE.18240, Table 14.3.2.3.1

Source: Applicant's ISS pg.65

In the EF arm, the most common related AE that was more frequent than in the vehicle arm was skin irritation (2.8%). Skin irritation did not occur in either the Epiduo or the vehicle arm. This was followed in order of frequency by skin burning sensation (0.9%), pruritus (0.5%), atopic dermatitis (0.5%), eczema (0.5%), rash (0.5%) and skin hypopigmentation (0.5%).

The table of adverse events to be included in labeling is still under discussion at the time of this review.

Assessment of local tolerability was performed at each visit in trial 18240. The number of subjects experiencing erythema, scaling, dryness and stinging/burning was similar between the active arms of trial 18240 and exceeded that in the vehicle arm. The following table depicts the findings based on highest local tolerability score.

Table 13: Highest Local Tolerability Score Worse than Baseline, Safety Population

Highest Local Tolerability Score Worse Than Baseline	CD0271 0.3%/ CD1579 2.5% Gel (N=217)	Epiduo Gel (N=217)	Vehicle Gel (N=69)
Erythema	**104/213 (48.8%)**	**93/212 (43.9%)**	**25/68 (36.8%)**
1 = Mild	59/213 (27.7%)	58/212 (27.4%)	20/68 (29.4%)
2 = Moderate	43/213 (20.2%)	32/212 (15.1%)	4/68 (5.9%)
3 = Severe	2/213 (0.9%)	3/212 (1.4%)	1/68 (1.5%)
Scaling	**116/213 (54.5%)**	**101/212 (47.6%)**	**21/68 (30.9%)**
1 = Mild	78/213 (36.6%)	75/212 (35.4%)	17/68 (25.0%)
2 = Moderate	36/213 (16.9%)	25/212 (11.8%)	4/68 (5.9%)
3 = Severe	2/213 (0.9%)	1/212 (0.5%)	0/68 (0.0%)
Dryness	**137/213 (64.3%)**	**132/212 (62.3%)**	**27/68 (39.7%)**
1 = Mild	100/213 (46.9%)	102/212 (48.1%)	23/68 (33.8%)
2 = Moderate	32/213 (15.0%)	27/212 (12.7%)	3/68 (4.4%)
3 = Severe	5/213 (2.3%)	3/212 (1.4%)	1/68 (1.5%)
Stinging/burning	**141/213 (66.2%)**	**138/212 (65.1%)**	**19/68 (27.9%)**
1 = Mild	88/213 (41.3%)	88/212 (41.5%)	16/68 (23.5%)
2 = Moderate	40/213 (18.8%)	30/212 (14.2%)	2/68 (2.9%)
3 = Severe	13/213 (6.1%)	20/212 (9.4%)	1/68 (1.5%)

n/N: n = Number of subjects with data worse than baseline; N = Total number of subjects with data available.
Worst Score: The highest severity score observed during post-Baseline period for a subject.
Data source: Table 14.3.3.3.1, Table 14.3.3.3.2, Table 14.3.3.3.3, Table 14.3.3.3.4

Source: Applicant's Clinical Study report 18240, pg.125

The majority of the highest scores were in the mild to moderate categories with only 0.5-2.3% in the severe category for erythema, scaling and dryness. A higher percentage of subjects (6.1-9.4%) scored in the severe category for stinging and burning. Over the 12 week course of the trial, erythema, scaling, dryness and stinging/burning decreased with the peak for all 4 occurring in the first 1-2 weeks.

7.4.2 Laboratory Findings

The only laboratories assessed in trial 18240 were urine pregnancy tests. One subject in the vehicle group tested positive at day 57 and was discontinued from the trial. One subject in the Epiduo group reported a pregnancy after completing the trial at her one month post-termination phone call. Her week 12 pregnancy test was negative on Jan 2, 2014 but the start date of the pregnancy was estimated to be Dec 23, 2013 so there

was a possible 9 days of exposure. Subject asked not to be contacted again and did not respond to subsequent letters so was considered lost to follow-up.

7.4.3 Vital Signs

No treatment emergent clinically significant abnormalities in vital signs were noted in trial 18240.

7.4.4 Electrocardiograms (ECGs)

No EKGs were performed in trial18240.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies reviewed.

7.4.6 Immunogenicity

Not applicable, as the drug products are small molecule drugs, and not therapeutic proteins.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable, a single fixed dose combination was used in trial 18240.

7.5.2 Time Dependency for Adverse Events

Adverse events decreased in incidence over the 12 week duration of trial 18240.

7.5.3 Drug-Demographic Interactions

Subgroup summaries of AE data by gender, race, and age were provided. With regard to gender, female subjects' experienced higher rates of treatment related AEs (TRAEs) than male subjects for both active arms of trial 18240. In the EF arm AEs were seen in 8.0% of female subjects vs 2.9% of male subjects, in the Epiduo arm AEs were seen in 0.9% of female subjects' vs 0% of male subjects. No TRAEs were seen in the placebo group.

With regard to race, white subjects' experienced higher rates of treatment related AEs (TRAEs) than non-white subjects for both active arms of trial 18240. In the EF arm AEs were seen in 5.8% of white subjects' vs 4.3% of non-white subjects, in the Epiduo arm

AEs were seen in 0.6% of white subjects' vs 0% of non-white subjects. No TRAEs were seen in the placebo group.

With regard to age, younger subjects (ages 12-17) experienced a higher rate of TEAEs than adult subjects in the EF arm of trial 18240 with 6.3% vs 4.7% seen in these groups respectively. In the Epiduo group, however, TEAEs were seen more often in the adult subgroup (1% in adults vs 0% in the younger age group). No TRAEs were seen in the placebo group.

7.5.4 Drug-Disease Interactions

Evaluation of the impact of baseline severity of disease (moderate vs severe) on safety was assessed in trial 18240. The scores for highest local tolerability in the subjects with severe acne were very similar to those in the overall safety population. The majorities were mild to moderate and as with the overall population they decreased over the course of the trial.

7.5.5 Drug-Drug Interactions

No specific studies of potential drug interactions were performed. See original clinical review for NDA 22320 for discussion of this subject.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See original clinical review for NDA 22320 for discussion of this subject.

7.6.2 Human Reproduction and Pregnancy Data

See section 7.4.2 for discussion of the 2 pregnancies reported in trial 18240. Also, see original clinical review for NDA 22320 for discussion of this subject.

7.6.3 Pediatrics and Assessment of Effects on Growth

No assessment has been made on the effects of EF on growth.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

7.7 Additional Submissions / Safety Issues

The 120 day update was submitted for NDA 209719 on Jan 13, 2015. There was no information in the 120 day update that changed the safety profile for EF.

8 Postmarket Experience

There is no postmarketing data for EF.

9 Appendices

9.1 Literature Review/References

No literature was reviewed for this efficacy supplement.

9.2 Labeling Recommendations

Labeling review is ongoing at the time of this review. Final labeling will be appended to the action letter, if approved.

9.3 Advisory Committee Meeting

No advisory committee meeting was held for this product.

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 207917

Submission Date(s): Sept 17, 2014

Applicant: Galderma Laboratories LP

Product: Epiduo Forte (adapalene and benzoyl peroxide Gel, 0.3%/2.5%)

Reviewer: Jane Liedtka, MD

Date of Review: Feb25, 2015

Covered Clinical Study (Name and/or Number): 18240

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: 31		
Number of investigators who are sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): one		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none Significant payments of other sorts: one Proprietary interest in the product tested held by investigator: none Significant equity interest held by investigator in sponsor of covered study: none		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) none		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

(b) (6)

- Consulting and Research Fees (including travel costs) totaling $52,692

Minimization of Potential Bias

Study RD.06.SRE.18240 was a multi-center, randomized, double-blind, vehicle and active controlled clinical trial that involved 31 investigational sites and enrolled 217 subjects. (b) (6) (b) (6) enrolled relatively few patients for this study (b) (6) 217; (b) (6) % and as such, there is little potential for bias resulting from these disclosed financial arrangements.

[1] See [web address].

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

/s/

JANE E LIEDTKA
06/02/2015

JILL A LINDSTROM
06/02/2015
Concur.