LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Epiduo, 0.3%/2.5%, gel
# (adapalene, benzoyl peroxide)

# SE/H/664/02/DC

**This module reflects the scientific discussion for the approval of *Epiduo*, 0.3%/2.5%, gel. The procedure was finalised on 2016-09-21. For information on changes after this date please refer to the module 'Update'.**

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# I. INTRODUCTION

Galderma Nordic AB has applied for a marketing authorisation for *Epiduo*, 0.3%/2.5%, gel. The active substances adapalene and benzoyl peroxide are the same as in *Epiduo*, 0.1%/2.5%, gel, marketed by Galderma Nordic AB since 2008.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10b (fixed combination) of Directive 2001/83/EC.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

# II. QUALITY ASPECTS

## II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

## II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

# III. NON-CLINICAL ASPECTS

## III.1 Pharmacology

*Epiduo* 0.3%/2.5% Gel contains two active ingredients, benzoyl peroxide and adapalene, with different mechanisms of action which are thought act complementary in the treatment of Acne vulgaris. The pharmacodynamic properties of adapalene and benzoyl peroxide are considered well known and no new pharmacodynamic studies have been performed which is accepted.

## III.2 Pharmacokinetics

The pharmacokinetics of the individual components is considered well known. When applied on the skin only small amounts, if any of adapalene, is absorbed via the skin. Benzoyl peroxide is rapidly conversed to benzoic acid which is excreted in urine. Performed absorption/metabolism studies with the combination of adapalene 0.1% and benzoyl peroxide 2.5% did not demonstrate any different absorption/metabolism properties when the active ingredients are administered together compared to when administered alone.

## III.3 Toxicology

The toxicology of the active ingredients adapalene and benzoyl peroxide is considered well known. In addition to the available data on the individual active substances, the dataset presented by the applicant includes new studies as well as the existing nonclinical studies available for the approved adapalene 0.1% / benzoyl peroxide 2.5% gel (Decentralised Procedure SE/H/664/01/DC and subsequent extensions) that have established the safety profile of the fixed-dose combination by the intended route of administration.

Two dermal toxicity studies have been conducted in minipigs to complete the safety package from the previously marketed adapalene 0.1% and benzoyl peroxide 2.5% product. The animals were treated with the new formulation proposed for marketing, adapalene 0.3% and benzoyl peroxide 2.5%, on approximately 10% of the body surface area. The gel base was used as control.

There were no signs of systemic toxicities in either sex after topical exposure to adapalene 0.3% and benzoyl peroxide 2.5% for 13 weeks. Local reactions were noted which included acanthosis, parakeratosis and/or hyperkeratosis, exocytosis / spongiosis and minimal dermal inflammatory infiltrates. These effects are expected, considering the irritant properties of both adapalene and benzoyl peroxide when administered alone.

Toxicokinetic data of adapalene demonstrate systemic uptake from the formulation proposed for marketing in only 3 of 8 minipigs. The absorption of CD0271 was slow with maximum plasma concentration observed between 3h and 24h. The exposure margin calculated for adapalene 0.3% / benzoyl peroxide 2.5% gel is relatively high. Despite the proportional increase of the adapalene concentrations when compared to the already marketed fixed-dose combination (adapalene 0.1% / benzoyl peroxide 2.5%) the exposure margin obtained remained sufficiently high (around 30 except one study with exposure margin of just 6) and

there are no safety concerns when the product is used clinically with the currently proposed dosing regimen.

The absence of new genotoxicity or carcinogenicity studies on adapalene and benzoyl peroxide is accepted considering the well-known profiles of the active ingredients. The profiles are not considered to be altered when the active substances are administered together.

The reprotoxic potential of the fixed-dose combination is related to the teratogenic potential of adapalene identified in animal studies and consistent with its retinoid-like pharmacological activities. The lack of new studies is acceptable, since the reproductive and developmental toxicity of the drug products are well-known. However, since the concentration of adapalene in this product is increased by a factor 3 compared to the already approved adapalene 0.1% and benzoyl peroxide 2.5% product, the Applicant was asked to discuss the relation of this increase to an increased risk of developmental toxicities. This discussion should address relevant animal data on reproductive toxicity, including on systemic exposure, in relation to the systemic exposure achieved following the intended use of the product applied for. In this context, the Applicant was also asked to consider appropriate changes in the product information.

The Applicant provided a discussion to support the position that there is a low risk of developmental toxicities if women are exposed to *Epiduo* 0.3%/2.5% during pregnancy. This included both pre-clinical exposure margins from reproduction toxicity studies in rat and rabbit as well as clinical data where the mother has been exposed to adapalene during early pregnancy.

Regarding the clinical data, there are currently too few exposed pregnancies to evaluate the developmental effects of clinical adapalene use with topical application. However, it is well known that all retinoids are teratogenic at sufficient systemic exposures, and that adapalene produces malformations that are consistent with those expected for retinoids. It is thus important that the lowest exposure margins possible after topical exposure are still wide enough to be able to conclude that the risks for a foetal malformation attributed to adapalene are low or negligible.

While the preclinical data used for the exposure margin calculations are identical for the adapalene 0.1% and 0.3% products, there are (as expected) obvious differences in exposure margins. In the SRE.2690 study, the exposure margin was as low as 6, which, according to the Applicant, was due to one individual PK profile with an $AUC_{0\text{-}24h}$ of 36.1 ng.h/mL (mean+SD=8.94+8.99 ng.h/mL). While the data is from one individual, and the mean is considerably lower, it shows that relatively high exposures are possible also with topical exposure to adapalene at the higher strength dose.

Considering that pregnancies are often realized by the mother several weeks into organogenesis, and that there is a risk that levels of adapalene exposure can be sufficiently high to pose a risk to the developing foetus, the Applicant was asked to introduce a

recommendation in the SmPC and PL that women of childbearing potential should use an effective method of contraception when using Adapalene 0.3% / BPO 2.5%.

The local tolerance studies were performed with adapalene 0.3% / benzoyl peroxide 2.5% gel and its placebo gel to evaluate single-dose dermal irritation in rabbits, eye irritation potential in vitro and sensitization in guinea pigs.
Skin irritation was observed in the rabbits treated with adapalene 0.3% / benzoyl peroxide 2.5% gel. The new strength of the fixed-dose combination was classified as 'irritant', whereas the already approved adapalene 0.1% / benzoyl peroxide 2.5% gel was previously classified 'slightly irritant' in the same test. Thus, the increased concentration of adapalene in the new formulation increased the local irritation in the rabbit skin irritation test.
Adapalene 0.3% / benzoyl peroxide 2.5% gel did not show irritant or corrosive properties in the Bovine Corneal Opacity and Permeability test, but the gel did show a strong sensitizing potential in a 9-application Bühler test in guinea pig.
Adapalene 0.3%/ benzoyl peroxide 2.5% gel is considered to have a strong sensitizing potential. This is consistent with the results obtained with the lower strength gel and is also expected in a combination product containing benzoyl peroxide.
To summarize the findings in the local tolerance studies, the submitted studies show that the profile of the fixed combination adapalene 0.3% / benzoyl peroxide 2.5% gel are in accordance with the local tolerance profiles of the individual drug substances.

To conclude, the non-clinical studies performed with adapalene 0.3% / benzoyl peroxide 2.5% gel indicate that the toxicological profile is similar to that of the individual active substances and the already approved adapalene 0.1% / benzoyl peroxide 2.5% gel. There are no systemic safety concerns, and the local effects are within what would be expected from topical application of adapalene and benzoyl peroxide. However, considering that pregnancies are often realized by the mother several weeks into organogenesis, and that there is a risk that levels of adapalene exposure can be sufficiently high to pose a risk to the developing foetus, the MAH was asked to introduce a recommendation in the SmPC and PL that women of childbearing potential should use an effective method of contraception when using Adapalene 0.3% / BPO 2.5%.

## III.4 Ecotoxicity/environmental risk assessment

An ERA has been submitted by the Applicant, but several key studies that are needed to come to a conclusion regarding the environmental impact of the product are missing. The applicant was thus asked to revise and update the ERA with the appropriate study documentation in accordance with the currently adopted Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use. In the D160-response, the Applicant has committed to perform the required Phase IIA and Phase IIB studies and complete the ERA (submission date scheduled for Q4 2018, including full reports). In response to the suggestion from the Applicant, it is the Assessor's view that OECD 301 and OECD 308 studies should be performed.

# IV. CLINICAL ASPECTS

## IV.1 Introduction

Acne vulgaris is the single most common skin disease affecting up to 85% of adolescents. The primary site of acne is the face followed by the back, chest, and shoulders. Clinically, acne vulgaris presents with several types of lesions, both inflammatory (papules, pustules and nodules) and non-inflammatory (open and closed comedones – 'blackheads' and 'whiteheads', respectively). Acne may be grouped into different categories both based on severity (the terms "mild, moderate and severe" are not always the best terms to use) and by clinical signs and presentation. Commonly used categories are presented below, with typical treatment regimens (Nast et al., JEADV 2012):

1. Comedonal acne: topical retinoids

2. Mild–moderate papulopustular acne: topical retinoids, benzoyl peroxide, azelaic acid, topical antibiotics; combination of topical treatments

3. Severe papulopustular acne, moderate nodular acne: oral retinoids (isotretinoin), systemic antibiotics, often combined with topical treatments. Hormonal treatment in females.

4. Severe nodular acne, conglobate acne: oral retinoids (isotretinoin)

The active substances adapalene and benzoyl peroxide are currently approved for the treatment of acne in several products. Adapalene is available as a 0.1% gel and cream (Differin) and as a 0.1% gel in combination with benzoyl peroxide in *Epiduo* 0.1%/2.5%. Benzoyl peroxide is available in several topical acne products and in combination products, e.g. *Epiduo* 0.1%/2.5% gel and Duac (benzoyl peroxide and clindamycin).

## IV.2 Pharmacokinetics

The pharmacokinetic documentation comprises one *in vivo* study (RD.06.SRE.18229) to determine the systemic exposure of adapalene during dermal application of either *Epiduo* (adapalene 0.3%/benzoyl peroxide 2.5% gel) or Differin (adapalene 0.3% gel). From an EU-perspective, the comparison with Differin 0.3% gel is of limited value since this product is not approved in the EU. The study was performed in adolescent and adult patients with acne vulgaris and involved application of the gel once daily for four weeks. The doses used in the study were higher than doses expected to be used in clinical practice and could thus be considered as "worst-case" doses from a safety perspective. Plasma concentrations of adapalene were determined with a validated LC/MS/MS method with a LLOQ of 0.1 ng/ml.

After four weeks treatment with *Epiduo* 0.3%/2.5%, 62% of the subjects had quantifiable plasma concentrations. In these subjects mean (range) AUC was 3.03 (1.79-6.41) ng*h/ml and Cmax 0.19 (0.10-0.38) ng/ml. In a previous study included in the *Epiduo* 0.1%/2.5% dossier (i.e. the lower strength), 2 out of 10 patients in the *Epiduo* 0.1%/2.5% group and 4 of 10 patients in the Differin 0.1% control group had detectable plasma concentrations with AUCs within the range 1.26-2.65 ng*h/ml and Cmax 0.11-0.21 ng/ml. As expected, the exposure of

adapalene appears to be slightly higher after administration of *Epiduo* 0.3%/2.5% than after a formulation containing 0.1% adapalene (*Epiduo* 0.1%/2.5% or Differin 0.1%). Since this is a between-study comparison, the data should however be interpreted with caution. Nevertheless, plasma concentrations of adapalene were in general low after four weeks administration of *Epiduo* 0.3%/2.5%.

## IV.3 Pharmacodynamics

The two active components in *Epiduo* 0.3%/2.5%, adapalene and benzoyl peroxide, are previously approved and well known substances in the treatment of acne. Their use, both as single agents and in combination is considered well-established. No additional pharmacodynamic data were submitted for this line extension application, which is acceptable.

## IV.4 Clinical efficacy

The efficacy and safety of *Epiduo* 0.3%/2.5% is based mainly on one pivotal phase 3 study (study 18240). The application also contains a Dermal Tolerance (Cumulative Irritancy) study and a PK study (described above). Reference is also made to previous studies and clinical experience for the lower strength combination product *Epiduo* (Adapalene 0.1%/Benzoyl Peroxide 2.5% Gel) and Adapalene 0.3% Gel. This is adequate, however, it should be noted that Adapalene 0.3% Gel is not approved in the EU, only Adapalene **0.1%** Gel (Differin). The studies referred to by the applicant are summarized in the table below.

**Table List of clinical studies supporting Adapalene 0.3%/Benzoyl Peroxide 2.5% Gel**

| Study Number | Objective(s) of the Study | Study Population | Number of Subjects | Duration of Treatment |
|---|---|---|---|---|
| **Adapalene 0.3%/Benzoyl Peroxide 2.5% Gel** | | | | |
| RD.06.SRE.18242 | Dermal Tolerance (Cumulative Irritancy) | Healthy subjects | 36 | 3 Weeks |
| RD.06.SRE.18229 | Pharmacokinetics | Subjects with acne vulgaris | 58 | 4 Weeks |
| RD.06.SRE.18240 | Efficacy/Safety | Subjects with acne vulgaris | 503 | 12 Weeks |
| **Adapalene 0.3% Gel** | | | | |
| RD.03.SRE.2644 | Dermal Tolerance (Cumulative Irritation and Contact Sensitization) | Healthy subjects | 215 | Induction: 3 Weeks<br>Rest: 2 Weeks<br>Challenge: Single 48 Hour Application |
| RD.03.SRE.2645 | Dermal Tolerance (Photosensitivity) | Healthy subjects | 30 | Induction: 3 Weeks<br>Rest: 2 Weeks<br>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<br>Rest: 2 Weeks<br>Challenge: Single 24 Hour Application |
| RD.03.SRE.2683 | Dermal Tolerance (Cutaneous Sensitization) | Healthy subjects | 251 | Induction: 3 Weeks<br>Rest: 2 Weeks<br>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 |

Dose response studies

The applicant has not performed any dose response studies to support the chosen concentrations of active substances in *Epiduo* 0.3%/2.5%. For the Adapalene component, the choice to use a 0.3% concentration was based on data with Adapalene 0.3% Gel, for which clinical studies are available, although Adapalene 0.3% Gel is not approved in the EU. For the benzoyl peroxide component, the same concentration as in *Epiduo* 0.1%/2.5% is used, since higher concentrations can cause more irritation. This is acknowledged. To conclude, the applicant has provided a rationale for their choice of concentrations of the active components of *Epiduo* 0.3%/2.5% and no further studies were requested.

Main study(ies)

**Study 18240**

Study18240 was a multi-center, randomized, double-blind, parallel-group, vehicle- and active-controlled study in subjects with acne vulgaris, aged at least 12 years. The inclusion and exclusion criteria were overall acceptable and the population included was defined as having moderate to severe acne, with an IGA score of 3 or 4, at least 20 inflammatory lesions (papules and pustules) and at least 30 non-inflammatory lesions (comedones). Subjects with more than two acne nodules on the face or very severe forms, e.g. nodulo-cystic acne or acne requiring systemic treatment, were excluded. Subjects on already ongoing systemic treatments were not included as this would have necessitated long washout periods. The treatment restrictions for other topical and systemic treatments and the respective washout periods were acceptable.

The patients were randomised in a 3:3:1 ratio to receive once daily treatment for 12 weeks with Adapalene 0.3%/Benzoyl Peroxide 2.5% Gel (*Epiduo* 0.3%/2.5%), Adapalene 0.1%/Benzoyl Peroxide 2.5% Gel (*Epiduo* 0.1%/2.5%) or Vehicle Gel. Inclusion of the lower strength combination, *Epiduo* 0.1%/2.5%, as a reference treatment in the study is endorsed. If a subject experienced persistent dryness or irritation, a reduced application frequency (every other day) could be used temporarily. Overall there were more interruptions for the 0.3% Adapalene vs. the 0.1% Adapalene combination (21 vs. 6, out of 217 subjects in each group) and also more interruptions in the moderate vs. severe stratum. Thus, *Epiduo* 0.3%/2.5% seemed more tolerable in a population with more severe acne. Whether this is due to a larger tendency to tolerate a treatment in subjects with more severe acne or whether those with less severe acne have less sebum production (and hence get more problems with dry, scaling skin) was not clear.

The randomisation and blinding procedures were overall adequate. The measures used to maintain blinding seem largely acceptable. The two formulations containing active substances were identical both in composition, manufacturing process, container closures and appearance.

There were three sets of efficacy objectives, specified in a hierarchical order. The trial was to be considered positive regarding efficacy if objectives (1) and (2) were met, i.e. (1) to demonstrate superiority in efficacy of CD0271 0.3%/CD1579 2.5% Gel versus Vehicle Gel in the treatment of acne vulgaris for up to 12 weeks in the full population of moderate and severe acne, and (2) to demonstrate superiority in efficacy of CD0271 0.3%/CD1579 2.5% Gel versus Vehicle Gel in the subgroup of subjects with severe acne. The third objective was to assess the superiority of CD0271 0.3%/CD1579 2.5% Gel versus *Epiduo* 0.1%/2.5% Gel in the subgroup of subjects with severe acne. The study objectives are considered acceptable. There were three co-primary end-points in the study (assessed in the ITT population):

- Success Rate, defined as 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)
- Change in Inflammatory Lesion Count from Baseline to Week 12
- Change in Non-inflammatory Lesion Count from Baseline to Week 12

Acne severity was assessed by using the IGA scale at each visit (see table below). The IGA is dichotomized, such that the Success is clearly defined as 0=Clear or 1=Almost Clear. The co-primary end-points are commonly used in acne clinical trials and are acceptable.

**Table Investigator's Global Assessment**

| | | |
|---|---|---|
| 0 | Clear | Clear skin with no inflammatory or noninflammatory 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. |

Results

A total of 554 subjects were screened and 503 subjects were randomized and included in the ITT population. All randomized subjects were included in the Safety Population and 459 subjects (91%) were included in the PP population. Within each treatment group, a majority of subjects completed the study, and completion rates were comparable among groups; 88-91%.

Concerning baseline demographic characteristics, no major differences were observed between treatment groups in the ITT population. Gender distribution was balanced between males and females and the majority of subjects were White (77%). The mean age was 20 years (median 17 years), ranging from 12 to 57 years, and approximately half of the subjects (54%) were 12 to 17 years of age. Similarly, for the acne and skin type characteristics, no major differences were observed between treatment groups. The proportions of subjects with moderate and severe acne according to IGA were about equal. The median numbers of inflammatory and non-inflammatory lesions were around 32 and 50, respectively. In accordance with the exclusion criteria, the number of nodules per patient was two or less. In the overall population, 67.6% had no nodules at baseline, 20.5% had one nodule and 11.9% had two nodules. In the severe stratum, 50.4% had no nodules at baseline, 26.6% had one nodule and 23% had two nodules. Thus, even if some subjects, especially in the severe stratum, had a few nodules, the majority had none. Almost 50% of the subjects had lesions on the trunk. A total of 309 (about 62%) subjects received treatment on the face only (65% for *Epiduo* 0.3%/2.5%, 61% for *Epiduo* 0.1%/2.5% and 55% for the Vehicle).

*Co-primary end-points*

For the first objective of the study, efficacy was demonstrated for all three co-primary endpoints for step 1 of the statistical analysis in the overall population with both moderate and severe acne. *Epiduo* 0.3%/2.5% was statistically more effective than Vehicle Gel ($p<0.001$, ITT-MI) with a difference from Vehicle Gel of 22.7% for the Success Rate at Week 12. For the Change in Inflammatory Lesion Count from Baseline (ITT-MI, Week 12), *Epiduo* 0.3%/2.5% was also statistically more effective than Vehicle Gel ($p<0.001$). The LS mean difference from Vehicle Gel was -12.6 lesions. Similarly, for Change in Non-inflammatory Lesion Count from Baseline (ITT-MI, Week 12), *Epiduo* 0.3%/2.5% was statistically more

effective than Vehicle Gel (p<0.001) with a LS mean difference from Vehicle Gel of -21.7 lesions.

Looking at the comparison of *Epiduo* 0.3%/2.5% and the marketed, lower strength *Epiduo* (0.1%/2.5%) in the overall (moderate and severe) population, no major differences were observed. For the Success Rate, there was a difference of about 6% between the two active treatments at week 12, but at earlier time points the two treatments were very similar. For the changes in lesion counts, the time courses for the two strengths were almost superimposable. Thus, a gain in efficacy with *Epiduo* 0.3%/2.5% compared with *Epiduo* 0.1%/2.5% is not obvious in the overall population.

**Table Summary of Co-primary Analyses, ITT Population**

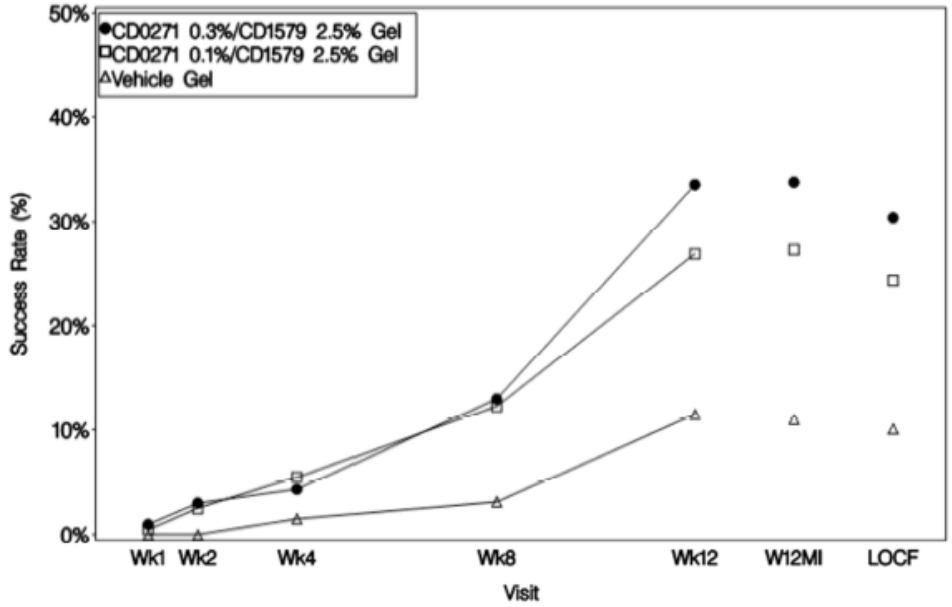
| Visit | CD0271 0.3%/ CD1579 2.5% Gel (N=217) | CD0271 0.1%/ CD1579 2.5% Gel (N=217) | Vehicle Gel (N=69) |
|---|---|---|---|
| **Success Rate** | | | |
| Week 12 | 66/197 (33.5%) | 52/193 (26.9%) | 7/61 (11.5%) |
| Week 12, MI | 33.7% | 27.3% | 11.0% |
| Difference from Vehicle [a] | 22.7% | 16.3% | - |
| 95% CI [a] | [12.8%, 32.6%] | [6.1%, 26.4%] | - |
| P-value vs. Vehicle [b] | <0.001 | 0.014 | - |
| **Change from Baseline in Inflammatory Lesion Count** | | | |
| Week 12 | | | |
| N | 197 | 193 | 61 |
| Mean | 12.2 | 11.7 | 25.1 |
| SD | 10.23 | 9.62 | 21.58 |
| Week 12, MI | | | |
| N (Change) | 217 | 217 | 69 |
| Mean (Change) | -27.79 | -26.46 | -13.19 |
| LS Mean Change from Baseline | -27.04 | -26.72 | -14.40 |
| SE (LS Mean) | 0.846 | 0.822 | 1.460 |
| LS Mean Difference from Vehicle | -12.64 | -12.32 | - |
| 95% CI [c] | [-15.82, -9.46] | [-15.56, -9.07] | - |
| P-value vs. Vehicle [c] | <0.001 | <0.001 | - |
| **Change from Baseline in Noninflammatory Lesion Count** | | | |
| Week 12 | | | |
| N | 197 | 193 | 61 |
| Mean | 19.3 | 20.6 | 43.8 |
| SD | 17.28 | 19.25 | 34.01 |
| Week 12, MI | | | |
| N (Change) | 217 | 217 | 69 |
| Mean (Change) | -40.46 | -40.03 | -19.70 |
| LS Mean Change from Baseline | -40.18 | -39.00 | -18.47 |
| SE (LS Mean) | 1.332 | 1.277 | 2.270 |
| LS Mean Difference from Vehicle | -21.71 | -20.54 | - |
| 95% CI [c] | [-26.66, -16.76] | [-25.59, -15.49] | - |
| P-value vs. Vehicle [c] | <0.001 | <0.001 | - |

a) The method was based on 'Combining Analysis Results from Multiply Imputed Categorical Data' (Ratitch 2013).
b) P-value vs. Vehicle was from the CMH test stratified by Baseline IGA and analysis center with general association statistic using MI Methodology (Schafer 1997).
c) The 95% CI and P-value vs. Vehicle were from the LS mean differences between each treatment group and vehicle using ANCOVA with terms for treatment, baseline IGA severity, analysis center, and Baseline lesion count as covariate using MI Methodology.

CD0271=Adapalene, CD1579=Benzoyl Peroxide, SD=Standard deviation; SE=Standard error

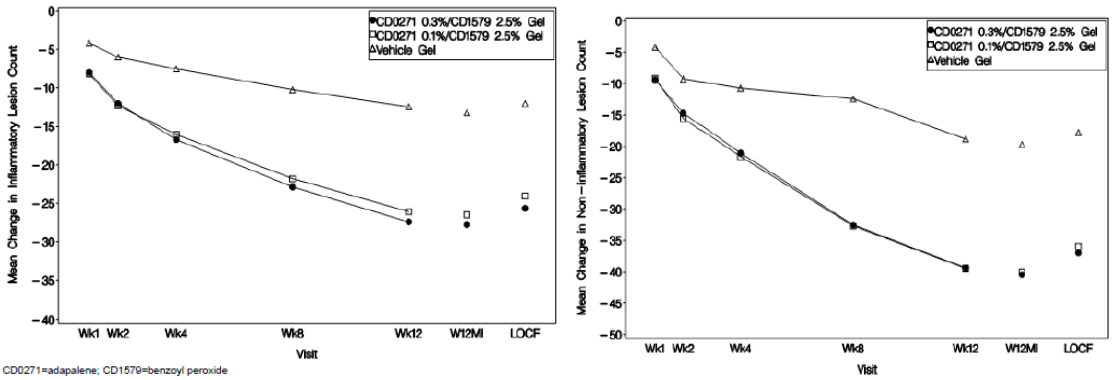
Success rates and changes in inflammatory lesion counts for each of the 3 study drugs at each study visit to Week 12 and endpoints (MI, LOCF) are shown in the following figures.

**Figure Success Rate over time (Observed, MI, and LOCF), Study 18240, ITT Population**




CD0271=adapalene; CD1579=benzoyl peroxide; Wk=W=week; MI=Multiple Imputation; LOCF=Last Observation Carried Forward
Success was defined as '0 = Clear' or '1 = Almost Clear' on IGA (0 to 4 scale).

**Figure Change in Inflammatory Lesion Counts (Left panel) and Change in Non-inflammatory Lesion Counts over time (Right panel) (Observed, MI, and LOCF), Study 18240, ITT Population**




CD0271=adapalene; CD1579=benzoyl peroxide
Mean changes [±SE] in inflammatory lesion counts are shown.

CD0271=adapalene; CD1579=benzoyl peroxide

For the second step of the analysis, in the Severe stratum (IGA=4), the primary efficacy analyses (MI, ITT) were also statistically significant for Adapalene 0.3%/Benzoyl Peroxide 2.5% Gel versus Vehicle Gel for all 3 co-primary endpoints at Week 12. For Success rate, the difference from the vehicle Gel was about 20%. For the Change in Inflammatory Lesion Count from Baseline, the LS mean difference from Vehicle Gel was almost 20 lesions and for Non-Inflammatory Lesion Count the mean difference was 28 lesions. Thus, also for Step 2 of the statistical analysis, the study was successful.

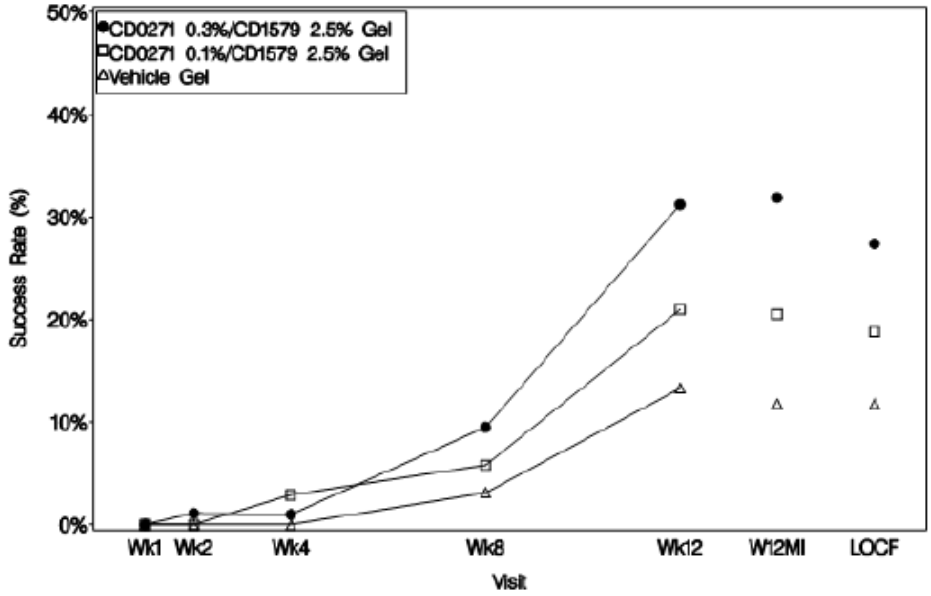
**Table Summary of Co-primary Analyses in Severe Stratum (Baseline IGA=4), Study 18240, ITT Population**

| Visit | CD0271 0.3%/ CD1579 2.5% Gel (N=106) | CD0271 0.1%/ CD1579 2.5% Gel (N=112) | Vehicle Gel (N=34) |
|---|---|---|---|
| **Success Rate** | | | |
| Week 12 | 29/93 (31.2%) | 21/100 (21.0%) | 4/30 (13.3%) |
| Week 12, MI | 31.9% | 20.5% | 11.8% |
| Difference from Vehicle [a] | 20.1% | 8.8% | - |
| 95% CI [a] | [6.0%, 34.2%] | [-4.6%, 22.1%] | - |
| P-value vs. Vehicle [b] | 0.029 | 0.443 | - |
| Difference from Epiduo | 11.4% | - | - |
| 95% CI [a] | [-0.5%, 23.2%] | - | - |
| **Change from Baseline in Inflammatory Lesion Count** | | | |
| Week 12 | | | |
| N | 93 | 100 | 30 |
| Mean | 12.8 | 13.8 | 33.0 |
| SD | 9.60 | 10.56 | 24.02 |
| Week 12, MI | | | |
| N (Change) | 106 | 112 | 34 |
| Mean (Change) | -37.25 | -30.24 | -14.28 |
| LS Mean Change from Baseline | -35.17 | -31.92 | -15.46 |
| SE (LS Mean) | 1.407 | 1.320 | 2.297 |
| LS Mean Difference from Vehicle | -19.71 | -16.46 | - |
| 95% CI [c] | [-24.81, -14.62] | [-21.70, -11.22] | - |
| P-value vs. Vehicle [c] | <0.001 | <0.001 | - |
| LS Mean Difference from Epiduo | -3.25 | - | - |
| 95% CI [c] | [-7.15, 0.64] | - | - |
| **Change from Baseline in Noninflammatory Lesion Count** | | | |
| Week 12 | | | |
| N | 93 | 100 | 30 |
| Mean | 19.2 | 21.5 | 49.5 |
| SD | 15.54 | 17.57 | 37.96 |
| Week 12, MI | | | |
| N (Change) | 106 | 112 | 34 |
| Mean (Change) | -46.33 | -43.89 | -17.82 |
| LS Mean Change from Baseline | -45.61 | -43.10 | -17.25 |
| SE (LS Mean) | 2.058 | 1.847 | 3.337 |
| LS Mean Difference from Vehicle | -28.36 | -25.85 | - |
| 95% CI [c] | [-35.64, -21.08] | [-33.42, -18.28] | - |
| P-value vs. Vehicle [c] | <0.001 | <0.001 | - |
| LS Mean Difference from Epiduo | -2.51 | - | - |
| 95% CI [c] | [-8.08, 3.06] | - | - |

a) The method was based on 'Combining Analysis Results from Multiply Imputed Categorical Data' (Ratitch 2013).
b) P-value vs. Vehicle, was from the CMH test stratified by analysis center with general association statistic using MI Methodology (Schafer 1997).
c) The 95% CI and P-value vs. Vehicle were from the LS mean differences between each treatment group and vehicle using ANCOVA with terms for treatment, analysis center, and Baseline lesion count as covariate using MI Methodology.
CD0271=Adapalene, CD1579=Benzoyl Peroxide

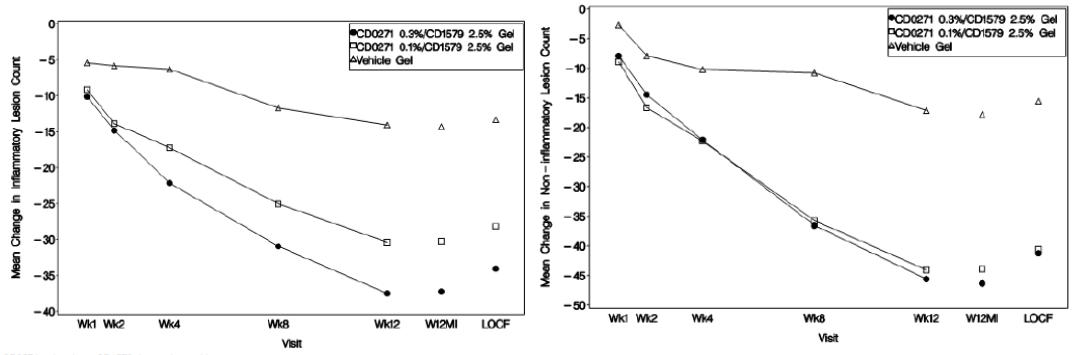
Success rates and changes in inflammatory lesion counts for each of the 3 study drugs at each study visit to Week 12 and endpoints (MI, LOCF) for the Severe stratum are shown in the following figures.

**Figure Success Rate over time (Severe, IGA = 4), Study 18240, ITT Population**




CD0271=adapalene; CD1579=benzoyl peroxide
Success was defined as '0 = Clear' or '1 = Almost Clear' on the IGA (0 to 4 scale).

**Figure Change in Inflammatory Lesion Count (left panel) and Non-inflammatory Lesion Count (right panel) over time (Severe stratum, IGA = 4), Study 18240, ITT Population**

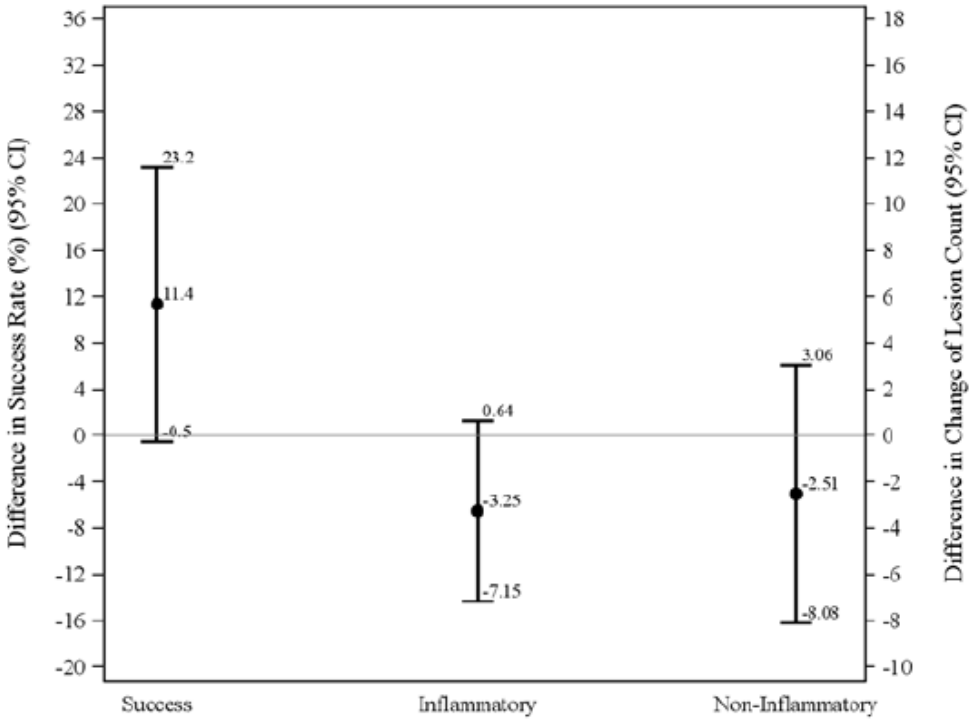



CD0271=adapalene; CD1579=benzoyl peroxide;

CD0271=adapalene; CD1579=benzoyl peroxide

For the comparison of *Epiduo* 0.3%/2.5% and *Epiduo* 0.1%/2.5% in the Severe stratum, no formal hypothesis testing was planned, as the sample size was deemed to be too small for comparison of the two active treatments. As could be expected, statistically significant differences between *Epiduo* 0.3%/2.5% (containing 0.3% Adapalene) and *Epiduo* 0.1%/2.5% (containing 0.1% Adapalene) were not achieved in this study. However, for all 3 co-primary endpoints, *Epiduo* 0.3%/2.5% was numerically better compared with *Epiduo* 0.1%/2.5% in the severe stratum and the differences approached statistical significance. The difference in Success rate was approximately 11% between the two products, whereas the differences in changes in lesion counts were smaller, i.e. about 3 lesions.

**Figure Co-primary endpoint comparison at Week 12 (MI) between Adapalene 0.3% Gel/Benzoyl Peroxide 2.5% Gel and Adapalene 0.1% Gel/Benzoyl Peroxide 2.5% Gel in Severe stratum (IGA=4), ITT Population**




Co-primary endpoints: Success Rate, Change from Baseline in Inflammatory Lesion Count, and Change from Baseline in Noninflammatory Lesion Count
Difference in Success Rate and difference in Change in Inflammatory and Noninflammatory Lesion Count between Adapalene 0.3%/Benzoyl Peroxide 2.5% Gel and Adapalene 0.1%/Benzoyl Peroxide 2.5% Gel.

Analyses of the effect of treatment of *Epiduo* 0.3%/2.5% also in the Moderate stratum are considered of interest and such analyses have been requested by several authorities in national scientific advice. In this respect, it is also of interest to compare the results of the two strengths in this sub-group. The results showed that *Epiduo* 0.3%/2.5% was statistically superior to the Vehicle Gel for all 3 co-primary endpoints at Week 12. The difference in Success rate vs. Vehicle was approximately 25%, which was similar to the difference for *Epiduo* 0.1%/2.5% (24%). Thus, *Epiduo* 0.3%/2.5% was superior to the Vehicle Gel also in the sub-group with moderate acne, whereas there was virtually no difference in comparison with the lower strength, *Epiduo* 0.1%/2.5%. For inflammatory lesions, *Epiduo* 0.1%/2.5% was even slightly better than *Epiduo* 0.3%/2.5%. There was no difference in the time course of response, i.e. use of the higher adapalene strength fixed dose combination did not lead to a faster improvement. Thus, for patients with moderate acne, there is no efficacy advantage with the use of *Epiduo* 0.3%/2.5% compared with *Epiduo* 0.1%/2.5%.

**Table Summary of Co-primary Analyses in Moderate Stratum (Baseline IGA=3), Study 18240, ITT Population**

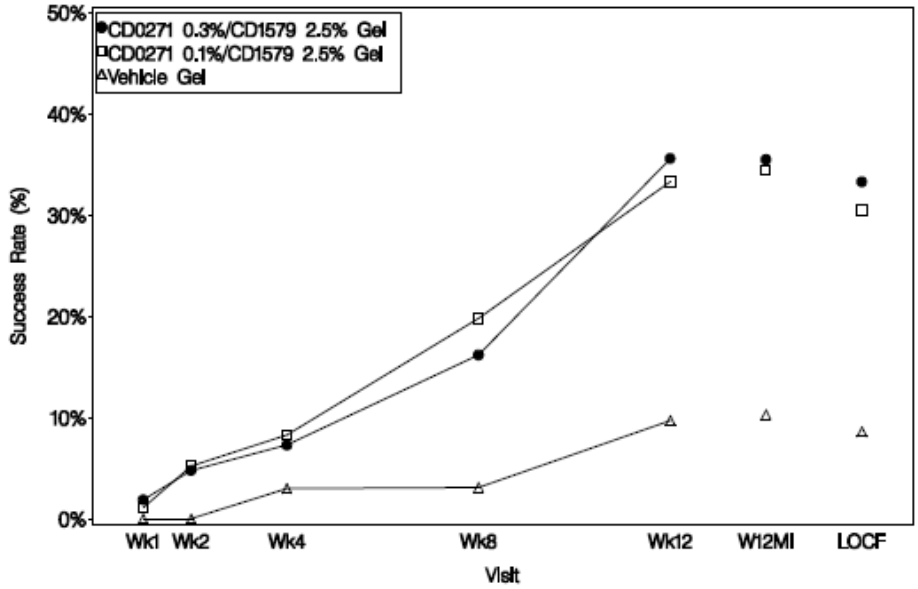
| Visit | CD0271 0.3%/ CD1579 2.5% Gel (N=111) | CD0271 0.1%/ CD1579 2.5% Gel (N=105) | Vehicle Gel (N=35) |
|---|---|---|---|
| **Success Rate** | | | |
| Week 12 | 37/104 (35.6%) | 31/93 (33.3%) | 3/31 (9.7%) |
| Week 12, MI | 35.5% | 34.5% | 10.3% |
| Difference from Vehicle [a] | 25.2% | 24.2% | - |
| 95% CI [a] | [10.8%, 39.6%] | [9.2%, 39.2%] | - |
| P-value vs. Vehicle [b] | 0.004 | 0.014 | - |
| Difference from Epiduo | 1.0% | - | - |
| 95% CI [a] | [-11.8%, 13.9%] | - | - |
| **Change from Baseline in Inflammatory Lesion Count** | | | |
| Week 12 | | | |
| N | 104 | 93 | 31 |
| Mean | 11.6 | 9.6 | 17.5 |
| SD | 10.78 | 8.00 | 15.83 |
| Week 12, MI | | | |
| N (Change) | 111 | 105 | 35 |
| Mean (Change) | -18.76 | -22.42 | -12.14 |
| LS Mean Change from Baseline | -18.60 | -21.33 | -12.23 |
| SE (LS Mean) | 0.978 | 1.030 | 1.838 |
| LS Mean Difference from Vehicle | -6.37 | -9.11 | - |
| 95% CI [c] | [-10.33, -2.41] | [-13.19, -5.03] | - |
| P-value vs. Vehicle [c] | 0.002 | <0.001 | - |
| LS Mean Difference from Epiduo | 2.74 | - | - |
| 95% CI [c] | [-0.04, 5.52] | - | - |
| **Change from Baseline in Noninflammatory Lesion Count** | | | |
| Week 12 | | | |
| N | 104 | 93 | 31 |
| Mean | 19.4 | 19.8 | 38.3 |
| SD | 18.78 | 20.97 | 29.24 |
| Week 12, MI | | | |
| N (Change) | 111 | 105 | 35 |
| Mean (Change) | -34.85 | -35.92 | -21.51 |
| LS Mean Change from Baseline | -33.97 | -34.53 | -18.81 |
| SE (LS Mean) | 1.756 | 1.854 | 3.220 |
| LS Mean Difference from Vehicle | -15.16 | -15.72 | - |
| 95% CI [c] | [-22.17, -8.15] | [-22.97, -8.47] | - |
| P-value vs. Vehicle [c] | <0.001 | <0.001 | - |
| LS Mean Difference from Epiduo | 0.56 | - | - |
| 95% CI [c] | [ -4.46, 5.57] | - | - |

a) The method was based on 'Combining Analysis Results from Multiply Imputed Categorical Data' [Ratitch 2013].
b) P-value vs. Vehicle was from the CMH test stratified by analysis center with general association statistic using MI Methodology [Schafer 1997].
c) The 95% CI and P-value vs. Vehicle were from the LS mean differences between each treatment group and vehicle using ANCOVA with terms for treatment, analysis center, and baseline lesion count as covariate using MI Methodology.

CD0271=Adapalene, CD1579=Benzoyl Peroxide

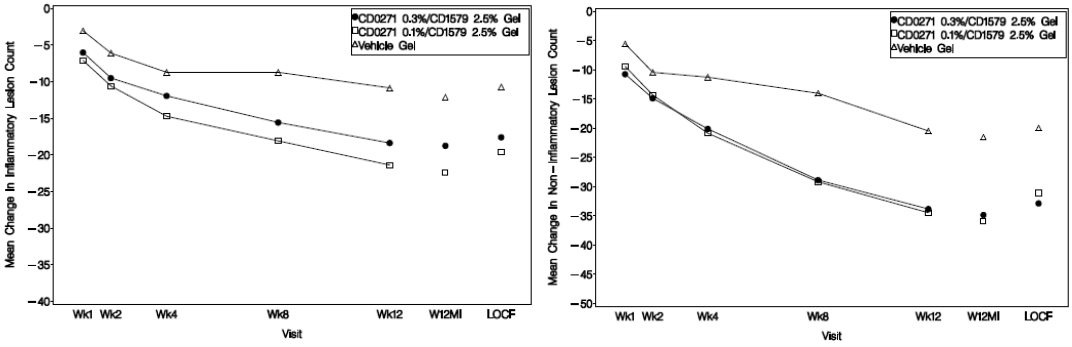
Success rates and changes in inflammatory lesion counts for each of the 3 study drugs at each study visit to Week 12 and endpoints (MI, LOCF) for the Moderate stratum are shown in the following figures.

**Figure Success Rate over time (Moderate, IGA = 3), Study 18240, ITT Population**




CD0271=adapalene; CD1579=benzoyl peroxide
Success was defined as '0 = Clear' or '1 = Almost Clear' on the IGA (0 to 4 scale).

**Figure Change in Inflammatory Lesion Count (left panel) and Non-inflammatory Lesion Count (right panel) over time (Moderate stratum, IGA = 3), Study 18240, ITT Population**




*Secondary endpoints, other end-points and other analyses*
Results for secondary endpoints (% changes in lesion counts) supported the results of the co-primary end-points, as expected.

For patient-reported outcomes (DLQI, CDLQI, EQ-5D-3L), the population included in this study did not have a particularly impaired quality of life due to their acne condition and the effects of the treatments studied were modest or absent compared with Vehicle gel. Other questionnaires completed by patients (Subject's Assessment of Acne Improvement and an Appreciation Questionnaire) generally showed favorable results for *Epiduo* 0.3%/2.5% and *Epiduo* 0.1%/2.5% vs. Vehicle gel. Both active treatment groups reported more skin irritation compared with the Vehicle gel group. There was no relevant difference between *Epiduo* 0.3%/2.5% Gel and *Epiduo* 0.1%/2.5%Gel concerning skin irritation in this assessment.

Subgroup analyses evaluating the effect of treatment with respect to age, gender and race gave no cause for concern.

Supportive data were provided from studies performed with *Epiduo* 0.1%/2.5% and for Adapalene 0.3%. The population included in these studies generally had moderate acne and the results were largely as expected.

Long-term efficacy data are available from open-label 1-year studies with *Epiduo* 0.1%/2.5% and Adapalen 0.3% while no long-term efficacy data are available with *Epiduo* 0.3%/2.5%. Also in these studies, the subjects included appeared to have mainly moderate acne. The studies indicated that treatment with *Epiduo* 0.1%/2.5% or with Adapalene 0.3% gel resulted in continued or sustained improvement over 12 months, based on lesion counts.

Conclusions on clinical efficacy

The submitted study was successful, since both primary objectives were fulfilled; to show superior efficacy of *Epiduo* 0.3%/2.5% vs. Vehicle Gel for all three co-primary endpoints in the overall population and in the stratum with severe acne, respectively. It has not been shown that *Epiduo* 0.3%/2.5% is superior to the lower strength *Epiduo* (0.1%/2.5%), neither in the total population, nor in the subgroup with severe acne. However, in the severe stratum, *Epiduo* 0.3%/2.5% was numerically better than *Epiduo* 0.1%/2.5%. The relevant target group for *Epiduo* 0.3%/2.5% was therefore not completely clear and this was discussed during the procedure.

The indication initially proposed for *Epiduo* 0.3%/2.5% included moderate to severe forms of *Acne vulgaris* (such as inflammatory acne which may be associated with a risk of scarring). The indication for the marketed lower strength product *Epiduo* 0.1%/2.5% reads: “Cutaneous treatment of *Acne vulgaris* when comedones, papules and pustules are present (See section 5.1)”. Thus, the indication for the lower strength does not specify severity grade, e.g. “moderate acne”. In comparison with *Epiduo* 0.1%/2.5%, *Epiduo* 0.3%/2.5% was numerically better in the severe stratum, but not in the overall population (except for somewhat higher success rate) or in the moderate stratum. Thus, for patients with moderate acne, there is no apparent advantage with the use of *Epiduo* 0.3%/2.5% vs. *Epiduo* 0.1%/2.5%.

On the other hand, a claim for treatment of “severe acne including inflammatory acne which may be associated with a risk of scarring” was not considered justified either. This group is generally treated with oral antibiotics (often combined with topical treatment) and in the most severe cases (nodular, nodulocystic acne) with oral isotretinoin. The initially proposed indication wording may imply that very severe, possibly nodulocystic, acne may be treated with *Epiduo* 0.3%/2.5% since scarring was mentioned. The inclusion criteria for study 18240 stipulated that the patients included should have an IGA score of 3 or 4, at least 20 inflammatory lesions and at least 30 non-inflammatory lesions while subjects with more than two acne nodules on the face or very severe forms, e.g. nodulocystic acne or acne requiring systemic treatment, were excluded. For lesion counts, subjects had an average of 98 total lesions (range: 51-226), of which the mean number of inflammatory lesions was 38 (range: 20-99) and the mean number of non-inflammatory lesions was 60 (range: 30-149). However, it

was considered important that the indication should not imply that too severe cases of acne may be adequately treated with *Epiduo* 0.3%/2.5%. Furthermore, the strict division of acne as "moderate" or "severe" is not always relevant and helpful for the prescriber. A classification based on the clinical picture (type and number of lesions) is generally more appropriate, e.g. comedonal acne, papulopustular acne and nodulocystic acne (Nast et al., JEADV 2012). Hence, it was considered more appropriate to include information about the type of acne to be treated and make reference to section 5.1 for a more detailed description of the population studied.

The Applicant pointed out that since *Epiduo* 0.3%/2.5% was not developed as a replacement for the approved *Epiduo* 0.1%/2.5% Gel (indicated for a different acne population compared to *Epiduo* 0.3%/2.5%), a head-to-head Phase 3 study with demonstration of 'therapeutic equivalence' was not aimed for. It was also claimed that it was not strictly necessary to have a head-to-head comparison with *Epiduo* 0.1%/2.5% Gel for the evaluation of benefit-risk profile of this new strength. This view could be endorsed, but for a product existing in several strengths it is of interest to know how the strengths relate to each, both for efficacy and safety. It is agreed that some incremental clinical benefit for *Epiduo* 0.3%/2.5% Gel vs. *Epiduo* 0.1%/2.5% Gel has been shown in the severe acne stratum, even if strict superiority vs. the lower strength has not been shown. This was mainly reflected in the IGA end-point, though (success rate 31.9% vs. 20.5%), whereas the differences are smaller for the lesion counts.

When discussing the "severe stratum" and the proposed indication, it should be remembered that the "severe stratum" in this study represents patients with large numbers of inflammatory and non-inflammatory lesions, but no or few nodules (a maximum of 2 nodules were allowed). The Applicant proposed a new indication wording with no mentioning of "moderate" or "severe" acne. Instead, the types of lesions were described, which is in line with *Epiduo* 0.1%/2.5% and other similar products. The applicant added the word "numerous", when papules and pustules are described. This was endorsed since the study included subjects with large numbers of such lesions and more details (numbers) are provided in section 5.1.

To conclude, the indication wording finally accepted reads: "*Epiduo* 0.3% / 2.5% gel is indicated for the cutaneous treatment of *Acne vulgaris*, when comedones, numerous papules and pustules are present (see sections 4.2 and 5.1)".

The adequacy of a single pivotal trial was also discussed. This is a new strength of a previously approved product but it does not constitute an entirely new product or combination, or a new pharmacological principle that needs to be proven. Thus, requirements for replication of the results may not be as strict as for a completely new product or indication. With the revised indication, the degree of "novelty" was reduced compared with the initial proposal, making claims for "severe acne with risk of scarring". The new indication mainly relates to a subset of papulopustular acne with somewhat higher severity (i.e. more lesions) but not a different type of acne (e.g. nodular/nodulocystic).

The phase 3 study was performed in the US and Canada and no European data are available. However, the results are deemed applicable also to a European population.

No long-term data are available on the efficacy of *Epiduo* 0.3%/2.5%. Reference is made to open-label long-term studies with *Epiduo* 0.1%/2.5% gel and Adapalene 0.3% Gel. There is no reason to believe that the efficacy of *Epiduo* 0.3%/2.5% would drastically change with long-term treatment and no long-term study was requested. However, related to the condition as such, recurrence and/or worsening may occur and topical treatment may not be sufficient.

## IV.5 Clinical safety

Safety data from three studies performed with the applied *Epiduo* adapalene 0.3%/benzoyl peroxide 2.5% gel, were retrieved- please see efficacy section III for further study details. Study 18242 included only healthy subjects and studies 18229 and 18240 included patients with moderate to severe acne. There were 245 patients exposed to the study drug for 12 weeks. Long-term studies above this have not been performed for the applied product. The pivotal vehicle- and active comparator efficacy and safety study exposed a total of 217 patients with moderate to severe acne to adapalene 0.3%/benzoyl peroxide 2.5% gel for a maximum of 12 weeks.

The major adverse events were skin related and clearly more commonly seen in the group treated with adapalene 0.3%/benzoyl peroxide 2.5% gel (9.2 %) as compared to the lower concentration, adapalene 0.1%/benzoyl peroxide 2.5% gel (3.7% ) and the gel vehicle ( 2.9% ) See tables a/ and b/ below.

### a/ **TEAEs in any group by System Organ Class, Study 18240, Safety Population**

| 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)** | 82 | 66 | 19 | 167 |
| **Subjects With At Least One Adverse Event; n (%) [b]** | 50 (23.0%) | 42 (19.4%) | 13 (18.8%) | 105 (20.9%) |
| **Infections and infestations** | 23 (10.6%) | 24 (11.1%) | 8 (11.6%) | 55 (10.9%) |
| **Skin and subcutaneous tissue disorders** | 20 (9.2%) | 8 (3.7%) | 2 (2.9%) | 30 (6.0%) |
| **Gastrointestinal disorders** | 5 (2.3%) | 6 (2.8%) | 0 | 11 (2.2%) |
| **Injury, poisoning and procedural complications** | 4 (1.8%) | 4 (1.8%) | 0 | 8 (1.6%) |
| **Nervous system disorders** | 4 (1.8%) | 2 (0.9%) | 2 (2.9%) | 8 (1.6%) |
| **Respiratory, thoracic and mediastinal disorders** | 3 (1.4%) | 3 (1.4%) | 2 (2.9%) | 8 (1.6%) |
| **Musculoskeletal and connective tissue disorders** | 2 (0.9%) | 3 (1.4%) | 0 | 5 (1.0%) |
| **Metabolism and nutrition disorders** | 1 (0.5%) | 2 (0.9%) | 1 (1.4%) | 4 (0.8%) |
| **General disorders and administration site conditions** | 1 (0.5%) | 1 (0.5%) | 1 (1.4%) | 3 (0.6%) |
| **Eye disorders** | 2 (0.9%) | 0 | 0 | 2 (0.4%) |
| **Immune system disorders** | 1 (0.5%) | 1 (0.5%) | 0 | 2 (0.4%) |
| **Psychiatric disorders** | 1 (0.5%) | 1 (0.5%) | 0 | 2 (0.4%) |
| **Blood and lymphatic system disorders** | 0 | 1 (0.5%) | 0 | 1 (0.2%) |
| **Cardiac disorders** | 1 (0.5%) | 0 | 0 | 1 (0.2%) |
| **Ear and labyrinth disorders** | 0 | 0 | 1 (1.4%) | 1 (0.2%) |
| **Reproductive system and breast disorders** | 0 | 1 (0.5%) | 0 | 1 (0.2%) |
| **Vascular disorders** | 0 | 1 (0.5%) | 0 | 1 (0.2%) |

a) A subject was counted only once for multiple occurrences within a System Organ Class or Preferred Term.

a) A subject was counted once even if the subject experienced more than one adverse event during the study.

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## b/ TEAEs of SOC Skin and subcutaneous tissue disorders, preferred terms , Study 18240, Safety Population

| 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) |
|---|---|---|---|---|
| **Skin and subcutaneous tissue disorders** | **20 (9.2%)** | **8 (3.7%)** | **2 (2.9%)** | **30 (6.0%)** |
| Skin irritation | 9 (4.1%) | 1 (0.5%) | 0 | 10 (2.0%) |
| Dermatitis allergic | 1 (0.5%) | 3 (1.4%) | 0 | 4 (0.8%) |
| Eczema | 3 (1.4%) | 0 | 0 | 3 (0.6%) |
| Dermatitis atopic | 2 (0.9%) | 0 | 0 | 2 (0.4%) |
| Pruritus | 1 (0.5%) | 1 (0.5%) | 0 | 2 (0.4%) |
| Rash | 1 (0.5%) | 0 | 1 (1.4%) | 2 (0.4%) |
| Skin burning sensation | 2 (0.9%) | 0 | 0 | 2 (0.4%) |
| Urticaria | 1 (0.5%) | 0 | 1 (1.4%) | 2 (0.4%) |
| Acne | 0 | 1 (0.5%) | 0 | 1 (0.2%) |
| Dandruff | 0 | 1 (0.5%) | 0 | 1 (0.2%) |
| Dermatitis contact | 1 (0.5%) | 0 | 0 | 1 (0.2%) |
| Dry skin | 1 (0.5%) | 0 | 0 | 1 (0.2%) |
| Erythema | 0 | 1 (0.5%) | 0 | 1 (0.2%) |
| Intertrigo | 1 (0.5%) | 0 | 0 | 1 (0.2%) |
| Rash pruritic | 0 | 1 (0.5%) | 0 | 1 (0.2%) |
| Skin hypopigmentation | 1 (0.5%) | 0 | 0 | 1 (0.2%) |

Data from the submitted documentation of the total number of study discontinuations from studies investigating 0.3%/benzoyl peroxide 2.5% gel demonstrates a low number. However, it is noted that the (limited) number of discontinuations from 0.3%/benzoyl peroxide 2.5% gel were due to skin problems.

The applicant has in addition presented extensive safety data from historical clinical trials and from post-authorisation surveillance of the approved adapalene 0.1%/benzoyl peroxide 2.5% gel and of the monad adapalene 0.3% gel with a similar safety profile.

The following studies were included for safety analyses of adapalene 0.1 %/BPO 2.5 %:

| 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<br>Rest: 2 Weeks<br>Challenge: Single<br>24 Hour Application |
| RD.03.SRE.2683 | Dermal Tolerance (Cutaneous Sensitization) | Healthy subjects | 251 | Induction: 3 Weeks<br>Rest: 2 Weeks<br>Challenge: Single<br>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-see below |

## Overview of AEs in studies with Adapalene 0.1%/Benzoyl Peroxide 2.5% Gel

| AE Category | 18097 | 18094 | | 18087 | | 18089 |
|---|---|---|---|---|---|---|
| | Adapalene 0.1%/ BPO 2.5% Gel (N=12) n (%) | Adapalene 0.1%/ BPO 2.5% Gel (N=149) n (%) | Vehicle Gel (N=71) n (%) | Adapalene 0.1%/ BPO 2.5% Gel (N=415) n (%) | Vehicle Gel (N=418) n (%) | Adapalene 0.1%/ BPO 2.5% Gel (N=452) n (%) |
| Any AE | 10 (83.3) | 57 (38.3) | 19 (26.8) | 142 (34.2) | 117 (28.0) | 288 (63.7) |
| Dermatologic | 5 (41.7) | 25 (16.8) | 4 (5.6) | 58 (14.0) | 24 (5.7) | 131 (29.0) |
| Related AEs | 6 (50.0) | 26 (17.4) | 4 (5.6) | 55 (13.3) | 17 (4.1) | 147 (32.5) |
| Dermatologic | 5 (41.7) | 22 (14.8) | 3 (4.2) | 44 (10.6) | 15 (3.6) | 110 (24.3) |
| Deaths | 0 | 0 | 0 | 0 | 0 | 0 |
| SAEs | 0 | 1 (0.7) | 0 | 2 (0.5) | 1 (0.2) | 5 (1.1) |
| AEs Leading to Discontinuation | 0 | 1 (0.7) | 0 | 11 (2.7) | 2 (0.5) | 9 (2.0) |
| Dermatologic | 0 | 0 | 0 | 6 (1.4) | 2 (0.5) | 7 (1.5) |

**Historical safety data is also presented from the following studies of adapalene 0.3%/ gel:**

| Adapalene 0.3% Gel | | | | |
|---|---|---|---|---|
| RD.03.SRE.2644 | Dermal Tolerance (Cumulative Irritation and Contact Sensitization) | Healthy subjects | 215 | Induction: 3 Weeks<br>Rest: 2 Weeks<br>Challenge: Single<br>48 Hour Application |
| RD.03.SRE.2645 | Dermal Tolerance (Photosensitivity) | Healthy subjects | 30 | Induction: 3 Weeks<br>Rest: 2 Weeks<br>Challenge: Single<br>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 |

**Overview of AEs in studies with Adapalene 0.3% Gel**

| Category of Subjects | 2690 | 18115 | 18060 | | 18081 | | 18082 |
|---|---|---|---|---|---|---|---|
| | Adapalene 0.3% Gel (N=16) n (%) | Adapalene 0.3% Gel (N=26) n (%) | Adapalene 0.3% Gel (N=70) n (%) | Vehicle Gel (N=74) n (%) | Adapalene 0.3% Gel (N=258) n (%) | Vehicle Gel (N=134) n (%) | Adapalene 0.3% Gel (N=551) n (%) |
| Any AE | 3 (18.8) | 9 (34.6) | 36 (51.4) | 30 (40.5) | 104 (40.3) | 42 (31.3) | 244 (44.3) |
| Dermatologic | 0 | 4 (15.4) | 31 (44.3) | 5 (6.8) | 69 (26.7) | 12 (9.0) | 142 (25.8) |
| Related AEs | 0 | 1 (3.8) | 28 (40.0) | 5 (6.8) | 57 (22.1) | 6 (4.5) | 119 (21.6) |
| Dermatologic | 0 | 1 (3.8) | 28 (40.0) | 5 (6.8) | 55 (21.3) | 42 (31.3) | 117(21.2) |
| Deaths | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| SAEs | 0 | 0 | 0 | 0 | 1 (0.4) | 0 | 6 (1.1) |
| AEs Leading to Discontinuation | 0 | 1 (3.8) | 4 (5.7) | 0 | 5 (1.9) | 1 (0.7) | 15 (2.7) |
| Dermatologic | 0 | 0 | 4 (5.7) | 0 | 4 (1.6) | 1 (0.7) | 15 (2.7) |

*Long term safety*

There are no long-term studies of adapalene 0.3% /BPO 2.5 %. However, the applicant is referring to safety data retrieved in studies 18089 and in 18082 of adapalene 0.1%/BPO 2.5 % and the monad adapalene 0.3 % resp. in addition to an extensive post-authorisation safety follow up of adapalene 0.1%/BPO 2.5%.

Adapalene 0.1%/benzoyl peroxide 2.5% gel

In study 18089, AEs were reported in 288 of 452 subjects (63.7%) treated with Adapalene 0.1%/Benzoyl Peroxide 2.5% Gel. Dermatologic AEs were observed in 29.0% of subjects, and the majority of drug-related AEs were dermatologic (24.3% of subjects).

**Overview of AEs over Time in Long-term Safety Study 18089**

| Category of Subjects | Adapalene 0.1%/Benzoyl Peroxide 2.5% Gel | | | |
|---|---|---|---|---|
| | Baseline to <Month 3 (N=452) n (%) | Month 3 to <Month 6 (N=397) n (%) | Month 6 to <Month 9 (N=366) n (%) | Month 9 to 1 year (N=334) n (%) |
| Any AE | 195 (43.1) | 79 (19.9) | 83 (22.7) | 82 (24.6) |
| Dermatologic AE | 104 (23.0) | 13 (3.3) | 12 (3.3) | 11 (3.3) |
| Related AEs | 127 (28.1) | 16 (4.0) | 11 (3.0) | 5 (1.5) |
| Dermatologic AE | 94 (20.8) | 8 (2.0) | 8 (2.2) | 4 (1.2) |
| SAEs | 1 (0.2) | 2 (0.5) | 1 (0.3) | 1 (0.3) |
| AEs Leading to Discontinuation | 7 (1.5) | 1 (0.3) | 0 | 1 (0.3) |
| Dermatologic AE | 6 (1.3) | 1 (0.3) | 0 | 0 |

Adapalene 0.3 % gel

In Study 18082, AEs were reported in 244 of 551 subjects (44.3%) treated with Adapalene 0.3% Gel. Dermatologic AEs were observed in 25.8% of subjects, and the majority of drug-related AEs were dermatologic (21.2% of subjects).

**Overview of AEs over Time in Long-term Safety Study 18082**

| Category of Subjects | Adapalene 0.3% Gel | | | |
|---|---|---|---|---|
| | Baseline to <Month 3 (N=551) n (%) | Month 3 to <Month 6 (N=362) n (%) | Month 6 to <Month 9 (N=303) n (%) | Month 9 to 1 year (N=174) n (%) |
| Any AE | 161 (29.2) | 57 (15.7) | 48 (15.8) | 37 (21.3) |
| Dermatologic | 111 (20.1) | 23 (6.4) | 18 (5.9) | 10 (5.7) |
| Related AEs | 98 (17.8) | 12 (3.3) | 13 (4.3) | 6 (3.4) |
| Dermatologic | 98 (17.8) | 10 (2.8) | 12 (4.0) | 6 (3.4) |
| SAEs | 3 (0.5) | 1 (0.3) | 1 (0.3) | 1 (0.6) |
| AEs Leading to Discontinuation | 11 (2.0) | 3 (0.8) | 1 (0.3) | 0 |
| Dermatologic | 11 (2.0) | 3 (0.8) | 1 (0.3) | 0 |

The support of the historical safety data is accepted. As demonstrated for the comparator products most adverse events occur during the initial 12 weeks and decrease substantially in number following longer treatment. There are very few SAE with no specific organ profile. There is an ongoing signal of depression being monitored as discussed in the most recent PBERs of adapalene 1%/BPO 2.5%. However, an increased risk of depression has also been associated with the acne disease itself in a number of previous studies in acne patients.

Pregnancy and lactation

There are no controlled trials in pregnant women treated with adapalene 0.3%/benzoyl peroxide 2.5% gel. Like other retinoids, adapalene could induce teratogenicity at sufficiently high systemic exposure levels. Pregnancy testing was performed for females of childbearing potential in all clinical studies conducted in subjects with acne vulgaris. Subjects who became pregnant during the studies were required to withdraw immediately and the pregnancy was to be followed to the final outcome. A total of 19 pregnancies have been reported. For details see table below.

**Summary of pregnancies**

| Study Number | Subject Number | Treatment | Age (years) | Study Completion Status | Treatment Duration (days) | Pregnancy Outcome |
|---|---|---|---|---|---|---|
| 18089 | 126 | Adapalene 0.1%/BPO 2.5% Gel | 29 | Discontinued | 186 | Normal |
| | 557 | Adapalene 0.1%/BPO 2.5% Gel | 21 | Discontinued | 95 | Normal |
| 18087 | 92347 | Adapalene 0.1%/BPO 2.5% Gel | 22 | Discontinued | 13 | Normal |
| | 92404 | Adapalene 0.1%/BPO 2.5% Gel | 14 | Discontinued | 31 | Normal |
| | 91727 | Adapalene 0.1%/BPO 2.5% Gel | 17 | Discontinued | 22 | Normal |
| | 92490 | Adapalene 0.1%/BPO 2.5% Gel | 17 | Completed[a] | 84 | Normal[a] |
| | 91897 | Adapalene 0.1% Gel | 24 | Discontinued | 28 | Normal |
| | 92017 | BPO 2.5% Gel | 26 | Discontinued | 26 | Normal |
| | 92727 | Vehicle Gel | 16 | Discontinued | 41 | Elective abortion |
| | 90251 | Vehicle Gel | 18 | Discontinued | 6 | Normal |
| | 90965 | Vehicle Gel | 27 | Completed[b] | 86 | Miscarriage |
| | 91524 | Vehicle Gel | 19 | Completed[b] | 80 | Unknown, Lost to follow-up |
| 18094 | 2102-350 | Vehicle Gel | 23 | Completed | 79 | Elective abortion |
| 18082 | 2138-165 | Adapalene 0.3% Gel | 25 | Discontinued | 178 | Normal (4 weeks premature) |
| | 2206-144 | Adapalene 0.3% Gel | 25 | Discontinued | 180 | Normal (5 weeks premature) |
| | 2210-296 | Adapalene 0.3% Gel | 21 | Discontinued | 60 | Lost to follow-up |
| | 2210-288 | Adapalene 0.3% Gel | 32 | Discontinued | 117 | Normal |
| 18240 | 8039-033 | Adapalene 0.1%/BPO 2.5% Gel | 26 | Completed[c] | 84 | Ongoing, Lost to follow-up |
| | 8039-001 | Vehicle Gel | 29 | Discontinued | 56 | Normal |

Considering the higher systemic exposure obtained with this new strength of adapalene an increased risk of developmental toxicities cannot be completely ruled out, taking systemic exposure into account. This is addressed in the approved SmPC and PL stating that women of childbearing potential should use an effective method of contraception when using Adapalene 0.3% / BPO 2.5% and the updated RMP reflecting the SmPC wording and including teratogenicity classified as an important potential risk and amended to the summary of safety concerns (part II module SVIII).

In general, there are no major findings in the analyses of special patient groups. Although the product is recommended to be used with caution in renal or hepatic impairment since this was not studied, this may not be a great concern due to the expected low systemic exposure to adapalene and benzoyl peroxide. Children below the age of 12 years should not be treated with the product.

The skin reactions addressed in the SmPC are skin irritation, skin burning sensation, eczema, rash, dry skin, atopic dermatitis, pruritus but also tingling at application site (paraesthesia) and oedema of the eyelid. As long term safety data relied mainly on the trials and post-authorisation data of the combination product adapalene 0.1%/BPO 2.5% and the monad 0.3% adapalene gel, the section 4.8 SmPC of *Epiduo* 0.3%/2.5% Table 1 also includes eyelid

oedema, throat tightness, allergic contact dermatitis, swelling face, pain of skin (stinging pain) and blisters, categorized with frequency unknown, in order to be harmonized with adapalene 0.1%/benzoyl peroxide 2.5% gel. Information describing the differences in outcome of skin-related AEs in the pivotal study between subjects in the combined population treated with *Epiduo* 0.3%/BPO 2.5% compared to Adapalene 0.1%/BPO 2.5% Gel is presented in section 4.8 including the statement that approximately 10% of patients can be expected to experience adverse skin reactions. The safety information of the SmPC is considered acceptable.

## IV.6 Risk Management Plans

The MAH submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to *Epiduo*. The submitted updated risk management plan is shared with adapalene 0.1%/benzoyl peroxide 2.5% gel and includes information relating to adapalene 0.3%/benzoyl peroxide 2.5% gel as well. The important potential risk of severe cutaneous reactions following a signal previously identified for adapalene 0.1%/benzoyl peroxide 2.5% safety concerns have been included .

Safety specification

Summary table of safety concerns as proposed in RMP

| | |
|---|---|
| Important identified risks | None identified |
| Important potential risks | Serious allergic potentially systemic reactions<br>Severe cutaneous adverse reactions |
| Missing information | None identified |

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed. There will be a close monitoring of the identified important potential risks.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of Safety Concerns and Planned Risk Minimisation Activities as proposed in RMP

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| **Important Identified Risks** | | |
| None | NA | NA |
| **Important potential risks** | | |
| Serious allergic potentially systemic reactions<br>Severe cutaneous adverse reactions | Close monitoring based on information obtained and update of the labelling as appropriate | NA |
| **Missing information** | | |
| None | None | None |
| | | |

Summary of the RMP

A further update in the RMP that includes “bullous dermatitis” and “teratogenicity” as important potential risks and additional revisions to comply with the “Guidance on format of the risk management plan (RMP) in the EU – in integrated format” has been agreed on and will be submitted according to a commitment.

This commitment should be fulfilled following the finalization of the application procedure SE/H/664/02/DC. The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed updated RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

# V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

# VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

*Epiduo* 0.3%/2.5% gel is a higher strength of a combination of two well-known and marketed components in the treatment of acne.

From a non-clinical point of view, the studies performed with adapalene 0.3% / benzoyl peroxide 2.5% gel indicate that the toxicological profile is similar to that of the individual active substances and the already approved adapalene 0.1% / benzoyl peroxide 2.5% gel. There are no systemic safety concerns, except for a potentially higher risk related to teratogenicity, and the local effects are within what would be expected from topical application of adapalene and benzoyl peroxide.

The plasma concentrations of adapalene were in general low after four weeks administration of *Epiduo* 0.3%/2.5% gel. Nevertheless, the systemic absorption of adapalene from the higher strength combination product was somewhat higher after administration of *Epiduo* 0.3%/2.5% gel than after a formulation containing 0.1% adapalene (*Epiduo* 0.1%/2.5% gel or Differin 0.1%), as could be expected.

The clinical efficacy of *Epiduo* 0.3%/2.5% gel in the proposed indication is supported by one pivotal study. The submitted study was successful, since both primary objectives were fulfilled; to show superior efficacy of *Epiduo* 0.3%/2.5% gel vs. Vehicle Gel for all three co-primary endpoints in the overall population and in the stratum with severe acne, respectively. It has not been shown that *Epiduo* 0.3%/2.5% gel is superior to the lower strength *Epiduo* 0.1%/2.5% gel, neither in the total population, nor in the subgroup with severe acne, even if *Epiduo* 0.3%/2.5% gel was numerically better than *Epiduo* 0.1%/2.5% gel in the severe stratum. The relevant target group for this strength of *Epiduo* is further discussed below.

The indication initially claimed for *Epiduo* 0.3%/2.5% included moderate to severe forms of acne, such as inflammatory acne which may be associated with a risk of scarring. The indication for the lower strength does not specify severity grade, e.g. “moderate acne”. The results of the submitted study showed that for patients with moderate acne, there is no apparent advantage with *Epiduo* 0.3%/2.5% vs. *Epiduo* 0.1%/2.5%.

On the other hand, a claim for treatment of “severe acne including inflammatory acne which may be associated with a risk of scarring” was not considered justified either. This group is generally treated with oral antibiotics (often combined with topical treatment) and in the most severe cases (nodular, nodulocystic acne) with oral isotretinoin. The inclusion criteria for study 18240 stipulated that the patients included should have an IGA score of 3 or 4, a minimum of 20 but not more than 100 inflammatory lesions and a minimum of 30 but not more than 150 non-inflammatory lesions while subjects with more than two acne nodules on the face or very severe forms, e.g. nodulocystic acne or acne requiring systemic treatment, were excluded. Thus, it was considered important that the indication would not imply that too severe cases of acne may be adequately treated with *Epiduo* 0.3%/2.5%. Furthermore, the strict division of acne as “moderate” or “severe” is not always relevant and helpful for the prescriber and

a classification based on the clinical picture (type and number of lesions) is generally more adequate. Hence, it was considered more appropriate to include information about the type of acne to be treated and make reference to section 5.1 for a more detailed description of the population studied.

Since *Epiduo* 0.3%/2.5% was not developed as a replacement for the approved *Epiduo* 0.1%/2.5% Gel (indicated for a different acne population compared to *Epiduo* 0.3%/2.5%), a head-to-head Phase 3 study with demonstration of 'therapeutic equivalence' was not aimed for. It was also claimed that it was not strictly necessary to have a head-to-head comparison with *Epiduo* 0.1%/2.5% Gel for the evaluation of benefit-risk profile of this new strength. This view could be endorsed, but for a product existing in several strengths it is of interest to know how the strengths relate to each, both for efficacy and safety. It is agreed that some incremental clinical benefit for *Epiduo* 0.3%/2.5% Gel vs. *Epiduo* 0.1%/2.5% Gel has been shown in the severe acne stratum, even if strict superiority vs. the lower strength has not been shown. This was mainly reflected in the IGA end-point, though (success rate 31.9% vs. 20.5%), whereas the differences are smaller for the lesion counts.

When discussing the "severe stratum" and the proposed indication, it should be remembered that the "severe stratum" in this study represented patients with large numbers of inflammatory and non-inflammatory lesions, but no or few nodules (a maximum of 2 nodules were allowed). A new indication wording was proposed with no mentioning of "moderate" or "severe" acne. Instead, the types of lesions were described, which is in line with *Epiduo* 0.1%/2.5% and other similar products. The word "numerous" was added for description of papules and pustules. This was endorsed since the study included subjects with large numbers of such lesions and more details (numbers) are provided in section 5.1.

To conclude, the indication wording finally accepted reads: "*Epiduo* 0.3% / 2.5% gel is indicated for the cutaneous treatment of *Acne vulgaris*, when comedones, numerous papules and pustules are present (see sections 4.2 and 5.1)".

The adequacy of a single pivotal trial was also discussed. This is a new strength of a previously approved product but it does not constitute an entirely new product or combination, or a new pharmacological principle that needs to be proven. Thus, requirements for replication of the results may not be as strict as for a completely new product or indication. With the revised indication, the degree of "novelty" was reduced compared with the initial proposal, making claims for "severe acne with risk of scarring". The new indication mainly relates to a subset of papulopustular acne with somewhat higher severity (i.e. more lesions) but not a different type of acne (e.g. nodular/nodulocystic).

The phase 3 study was performed in the US and Canada and no European data are available. However, the results are deemed applicable also to a European population.

No long-term data are available on the efficacy of *Epiduo* 0.3%/2.5%. Reference is made to open-label long-term studies with *Epiduo* 0.1%/2.5% gel and Adapalene 0.3% Gel. There is no

reason to believe that the efficacy of *Epiduo* 0.3%/2.5% would drastically change with long-term treatment and no long-term study was requested.

The safety of adapalene 0.3%/benzoyl peroxide 2.5% gel is mainly supported by the pivotal vehicle- and active comparator efficacy and safety study. In this study a total of 217 patients with moderate to severe acne were exposed to adapalene 0.3%/benzoyl peroxide 2.5% gel for a maximum of 12 weeks. The major adverse events were skin related and clearly more commonly seen in the group treated with adapalene 0.3%/benzoyl peroxide 2.5% gel (9.2 %) as compared to the lower concentration, adapalene 0.1%/benzoyl peroxide 2.5% gel (3.7%) and the gel vehicle (2.9%).

There are no long-term studies. However, the applicant has presented extensive safety data from historical clinical trials and from post-authorisation surveillance of the approved adapalene 0.1%/benzoyl peroxide 2.5% gel and of the monad adapalene 0.3% gel with a similar safety profile. The submitted updated risk management plan is shared with adapalene 0.1%/benzoyl peroxide 2.5% gel and now includes information relating to adapalene 0.3%/benzoyl peroxide 2.5% gel as well. The important potential risk of severe cutaneous reactions following a signal previously identified for adapalene 0.1%/benzoyl peroxide 2.5% has been included. The support of the historical safety data is acceptable. As demonstrated for the comparator, most adverse events occur during the initial 12 weeks and decrease substantially in number following longer duration of treatment. However, as long term safety data is relying mainly on the trials and post-authorisation data of the combination product adapalene 0.1%/BPO 2.5% and the monad 0.3% adapalene gel, there was a need to be better this in the SmPC. Revisions were made and found acceptable.

Like other retinoids, adapalene could induce teratogenicity at sufficiently high systemic exposure levels. Since the concentration of adapalene in this product is increased by a factor 3 compared with the already approved adapalene 0.1% and benzoyl peroxide 2.5% product, this may lead to an increased risk of developmental toxicities. As expected, the systemic absorption of adapalene from *Epiduo* 0.3%/2.5% was somewhat higher after administration of *Epiduo* 0.3%/2.5% than after a formulation containing 0.1% adapalene (*Epiduo* or Differin 0.1%). The initially proposed SmPC contained the same recommendations related to pregnancy as for the lower *Epiduo* strength; that *Epiduo* 0.3%/2.5% should not be used during pregnancy and in case of unexpected pregnancy, treatment should be discontinued. Considering the higher systemic exposure obtained with this strength, that pregnancies are often realized by the mother several weeks into organogenesis, and the risk that levels of adapalene exposure could be sufficiently high to pose a risk to the developing fetus appropriate, additional changes in the product information were requested during the procedure. The applicant was requested to include a warning in 4.4 and an advice on effective anticonception in 4.6 when *Epiduo* 0.3%/2.5% is prescribed. Related to this, the applicant was in addition requested to make relevant updates to the RMP including teratogenicity as an important potential risk. The applicant agreed to fulfil these requests and the issue was thereby resolved.

In conclusion, although the efficacy results for *Epiduo* 0.3%/2.5% gel did not demonstrate statistically significant differences in comparison with the lower strength of *Epiduo*

(0.1%/2.5% gel), the results showed clear superiority vs. vehicle gel for all three co-primary end-points. An incremental clinical benefit (albeit small) for *Epiduo* 0.3%/2.5% gel vs. *Epiduo* 0.1%/2.5% gel has been shown in the "severe acne stratum", even if strict superiority vs. the lower strength was not shown. The target population and indication were discussed and better defined during the procedure and it was considered that a more potent topical treatment can have a place in acne therapy.

The local tolerability profile shows that skin related AEs occur in about 10% of patients, however, they seem manageable in most subjects. A potential larger risk related to teratogenicity cannot be excluded with this higher strength of adapalene, however, with adequate recommendations for pregnancy and contraception measures, this can be handled, similar to other topical retinoids.

The benefit-risk profile for *Epiduo* 0.3%/2.5% gel is positive.

**List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment**

**Post approval commitments**

| **Description** | **Due date** |
|---|---|
| A complete and revised Environmental Risk Assessment document, including full reports, for adapalene. The submission should be made as a type II variation and should encompass the studies discussed in the D180 response AR, including OECD 301 and OECD 308. | Q4 2018 |
| **Description** | **Due date** |
| The applicant should submit an updated RMP modifying the important potential risk of "severe cutaneous adverse reaction" into "bullous dermatitis" and list "teratogenicity" as an important potential risk. In addition the updated RMP should be revised according to the "Guidance on format of the risk management plan (RMP) in the EU – in integrated format":<br><br>a) The introduction text under the heading VI.2 should be deleted.<br>b) Section VI.2.2 should be shortened and revised according to the Guidance Document.<br>c) The standard terms in section VI.2.5 should be added.<br><br>A variation should be submitted to implement these changes. | 31 October 2016 |

**List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC**

N/A

# VII. APPROVAL

The Decentralised procedure for *Epiduo*, 0.3%/2.5%, gel was positively finalised on 2016-09-21.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# Public Assessment Report – Update

| Procedure number* | Scope | Product Information affected | Date of end of procedure | Approval/ non approval | Summary/ Justification for refuse |
|---|---|---|---|---|---|
| | | | | | |

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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