

**Public Assessment Report
for paediatric studies submitted in accordance
with Article 46 of Regulation (EC) No1901/2006, as
amended**

(Clindamycin phosphate with benzoyl peroxide)

Duac[®] Once Daily Gel

UK/W/0061/pdWS/002

| | |
|---|----------------|
| Rapporteur: | United Kingdom |
| Finalisation procedure (day 90): | 10/12/2016 |

ADMINISTRATIVE INFORMATION

| | |
|--|--|
| Invented name of the medicinal product: | Duac® Once Daily Gel |
| INN (or common name) of the active substance(s): | Clindamycin phosphate with benzoyl peroxide |
| MAH: | GlaxoSmithKline |
| Pharmaco-therapeutic group (ATC Code): | Anti-infectives for treatment of acne D10AF51 |
| Pharmaceutical form(s) and strength(s): | Gel for topical use: Clindamycin phosphate 1% / benzoyl peroxide 3% Clindamycin phosphate 1% / benzoyl peroxide 5% |

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ABBREVIATIONS

| | |
|--------|--|
| ADR | Adverse drug reaction |
| AE | Adverse event |
| ANCOVA | Analysis of covariance |
| CDLQI | Children's Dermatology Life Quality Index |
| DLQI | Dermatology Life Quality Index |
| FDA | Food and Drug Administration |
| ISGA | Investigator's Static Global Assessment |
| ITT | Intention to treat |
| LOCF | Last observation carried forward |
| mITT | Modified intention to treat |
| MMRM | Mixed model for repeated measures |
| PAP-Q | Patient product acceptability and preference questionnaire |
| PP | Per protocol |
| QoL | Quality of life |
| SAE | Serious adverse event |
| SD | Standard deviation |
| SGCA | Subject Global Change Assessment |
| TEAE | Treatment emergency adverse event |
| TESAE | Treatment emergent serious adverse event |
| TrAE | Treatment related adverse event |
| UK | United Kingdom |

I. EXECUTIVE SUMMARY

On 18th August 2016, one MAH submitted two completed paediatric studies for clindamycin phosphate with benzoyl peroxide, in accordance with Article 46 of Regulation (EC) No. 1901/2006, as amended, on medicinal products for paediatric use.

Clindamycin phosphate with benzoyl peroxide is licensed as a prescription-only medication in the United Kingdom (UK) for the topical treatment of mild to moderate acne vulgaris in adults and adolescents aged 12 years and older. It is available in gel formulation in strengths of 1% clindamycin / 3% benzoyl peroxide or 1% clindamycin / 5% benzoyl peroxide. Only the lower strength formulation was used in the studies being assessed for this procedure.

Clindamycin is a bacteriostatic lincosamide antibiotic with additional anti-inflammatory effects. Clindamycin inhibits bacterial protein synthesis by binding to the bacterial 50S ribosomal subunit.

Benzoyl peroxide is a bacteriocidal antimicrobial with additional antikeratolytic and comedolytic effect. It is thought to exhibit its broad spectrum antibacterial activity through generation of free radicals.

The SmPC for Duac[®] Once Daily Gel (both the 1%/3% and 1%/5% strengths) provides a posology for adults and adolescents 12 years and older for the topical treatment of mild to moderate acne vulgaris. The SmPC states that *“the safety and efficacy of Duac[®] Once Daily Gel has not been established in children under 12 years of age therefore [it] is not recommended for use in this population”*.

The MAH states that results of the submitted paediatric studies are in line with currently approved product information for Duac[®] Once Daily Gel in the EU and therefore no changes to the Product Information are necessary.

II. RECOMMENDATION

The submitted data are in line with currently approved product information. No changes to the SmPC are required.

Summary of outcome

- ☒ No change
- ☐ New study data
- ☐ New safety information
- ☐ Paediatric information clarified
- ☐ New indication

III. INTRODUCTION

On 18th August 2016, one MAH submitted two completed paediatric studies for clindamycin phosphate with benzoyl peroxide, in accordance with Article 46 of Regulation (EC) No. 1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview and the full study reports were also provided.

The MAH states that results of the submitted paediatric studies are in line with currently approved product information for clindamycin phosphate with benzoyl peroxide in the EU and therefore no changes to the Product Information are necessary.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study

Clindamycin is a bacteriostatic lincosamide antibiotic with additional anti-inflammatory effects. Clindamycin inhibits bacterial protein synthesis by binding to the bacterial 50S ribosomal subunit.

Benzoyl peroxide is a bacteriocidal antimicrobial with additional antikeratolytic and comedolytic effect. It is thought to exhibit its broad spectrum antibacterial activity through generation of free radicals.

Clindamycin phosphate in combination with benzoyl peroxide is available in gel formulation in strengths of 1% clindamycin / 3% benzoyl peroxide or 1% clindamycin / 5% benzoyl peroxide. Only the lower strength formulation was used in the studies being assessed for this procedure.

The SmPC for Duac[®] Once Daily Gel (both 1% / 3% and 1% / 5% strengths) provides a posology for adults and adolescents 12 years and older for the topical treatment of mild to moderate acne vulgaris:

Posology

Adults and adolescents (aged 12 years and above)

The product should be applied once daily in the evening, to the entire affected area. Treatment should not exceed more than 12 weeks of continuous use.

Paediatric population

The safety and efficacy of Duac[®] Once Daily Gel has not been established in children under 12 years of age therefore [it] is not recommended for use in this population.

The SmPC also provides information about undesirable effects and local tolerability:

Undesirable effects

Adverse drug reactions (ADRs) are summarised below for Duac® Once Daily Gel as a combination including any additional ADRs that have been reported for the single topical active ingredients, benzoyl peroxide or clindamycin. Adverse drug reactions are listed by MedDRA system organ class and by frequency. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ and $< 1/10$); uncommon ($\geq 1/1,000$ and $< 1/100$); rare ($\geq 1/10,000$ and $< 1/1,000$) and not known (cannot be estimated from the available data).

| MedDRA SOC | Very Common | Common | Uncommon | Not known** |
|---|---------------------------------|-------------------|--|---|
| Immune system disorders | | | | Allergic reactions including hypersensitivity and anaphylaxis |
| Nervous system disorders | | | Paraesthesia | |
| Gastrointestinal disorders | | | | Colitis, haemorrhagic diarrhoea, diarrhoea, abdominal pain |
| Skin and subcutaneous tissue disorders | Mild erythema, peeling, dryness | Burning sensation | Dermatitis, pruritus, erythematous rash, worsening of acne | Urticaria |
| General disorders and Administration site conditions | | | | Application site reactions including skin discoloration |

* At site of application. ** Based on post-marketing reports. Since these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency however, systemic reactions are rarely seen.

In addition to the ADRs reported in the table above, in the pivotal trial conducted with topical clindamycin 1%/benzoyl peroxide 3% gel, application site photosensitivity reaction was also reported commonly. Also in addition to the ADRs reported above, in studies conducted with topical clindamycin alone, headache and application site pain were reported commonly.

Local Tolerability

During the five clinical trials with Duac® Once Daily Gel, all patients were graded for facial erythema, peeling, burning, and dryness on the following scale: 0 = absent, 1 = mild, 2 = moderate and 3 = severe. The percentage of patients that had symptoms present before treatment (at baseline) and during treatment were as follows:

Local Tolerability Assessments for Subjects (N=397) in the Duac® Once Daily Gel Group during the Phase 3 Studies

| | Before Treatment (Baseline) | | | During Treatment | | |
|-----------------|-----------------------------|----------|--------|------------------|----------|--------|
| | Mild | Moderate | Severe | Mild | Moderate | Severe |
| Erythema | 28% | 3% | 0 | 26% | 5% | 0 |
| Peeling | 6% | <1% | 0 | 17% | 2% | 0 |
| Burning | 3% | <1% | 0 | 5% | <1% | 0 |
| Dryness | 6% | <1% | 0 | 15% | 1% | 0 |

IV.2 Clinical aspects

IV.2.1 Introduction

The MAH submitted final study reports for:

Study A: *A multi-centre, single-blind, parallel group clinical evaluation of the efficacy and safety of clindamycin 1% / benzoyl peroxide 3% and azelaic acid 20% in the topical treatment of mild to moderate acne vulgaris.*

Study B: *Clinical evaluation of efficacy at 2 weeks of [clindamycin 1% / benzoyl peroxide 3%] fixed dose combination gel in treatment of facial acne vulgaris in Japanese Subjects.*

IV.2.2 Clinical studies

IV.2.2.1 Clinical study - Study A

“A multi-centre, single-blind, parallel group clinical evaluation of the efficacy and safety of clindamycin 1% / benzoyl peroxide 3% and azelaic acid 20% in the topical treatment of mild to moderate acne vulgaris”

➤ Description

A multi-centre, Phase 4 study to compare the efficacy, safety and tolerability of clindamycin 1% / benzoyl peroxide 3% with azelaic acid 20%, for topical treatment of mild to moderate acne vulgaris.

➤ Methods

- Objective(s)
 - Primary objective: To compare efficacy, safety and tolerability of clindamycin 1% / benzoyl peroxide 3% with azelaic acid 20%
- Study design
- Study population /Sample size

12 week prospective, randomised, single-blind, comparator-controlled, parallel-group clinical study across 11 centres in Germany, enrolling between 2 and 36 patients each.

A planned study population of 220 male and female patients aged 12 to 45 years of age with confirmed acne vulgaris. Randomised 1:1 to each treatment arm.

Inclusion criteria:

- Confirmed acne vulgaris.
- Baseline Investigator's Static Global Assessment (ISGA) score 2 or 3.
- 17-60 inflammatory facial lesions (papules and pustules).
- 20-125 non-inflammatory facial lesions (open and closed comedones).
- No more than 1 facial nodular cystic lesion.
- No use of sun-beds or IV light treatment for 4 weeks prior to study inclusion.

Exclusion criteria:

- Female patients who were pregnant, breastfeeding or sexually active and not using reliable contraception or not prepared to do so for the duration of the study.
- Patients with clinically relevant history or findings at baseline of severe systemic disease or skin diseases other than acne vulgaris.
- Patients who had facial hair that could obscure the accurate assessment of their ISGA score.
- Patients with a history of regional enteritis or inflammatory bowel disease.
- Patients receiving specific therapies prior to baseline: 6 months; systemic retinoid, 4 weeks; systemic antibiotics, investigational drug, facial procedures, topical corticosteroids, topical anti-acne preparations, 1 day; high dose vitamins, haloperidol, halogens, neuromuscular blocking agents, photosensitisers.
- Patients unwilling to stop using specified over-the-counter facial products during the study.
- Patients with known sensitivity or allergy to any active component or excipient.
- Patients using oestrogens or anti-androgens for less than 12 consecutive weeks prior to first dose.

Rapporteur's comment:

Assessment of efficacy of a topical treatment for acne vulgaris over 12 weeks is in keeping with other studies and wider literature for the condition ([Purdy & de Berker, 2011](#)). Safety exclusion criteria included the presence of serious gastrointestinal pathologies, which could potentially be exacerbated by systemic absorption of a topical antibiotic.

- **Treatments**

Endpoint assessors were blinded to the treatment received. Patients were not blinded to the treatment received.

Patients were randomised by computer-generated schedule 1:1 to topical treatment to the face with once daily (evening) clindamycin 1% / benzoyl peroxide 3% or twice daily azelaic acid 20% for 12 weeks. Randomisation was stratified by site.

All patients were instructed to wash their face with a soap free cleanser and rinse with warm water and dry with a towel prior to applying the study product. Following application, the patient was not allowed to wash the face again for 4 hours. Preferably, the study product was to be left on for 7 hours before washing the face again.

The use of oil-free moisturiser and oil-free makeup during the study period was permitted but had to be documented. Makeup had to be removed at least 1 hour prior to assessments.

Rapporteur's comment:

This was an active comparator study with no placebo arm. azelaic acid 20% is licensed in the UK in adults and adolescents 12 years and older for the topical treatment of acne vulgaris.

The main limitation of this study is the single-blind design. The report states that the single-blind design was chosen on the basis that the two products have different appearances and application frequencies, making it impossible to blind patients to the treatment received. The study staff assessing acne lesion counts were blinded to the treatment received.

- Outcomes/endpoints

If possible, the same efficacy assessor performed all the efficacy assessments on the same patient at all study visits.

Photographs of the front and lateral views were taken at each assessment to illustrate any visible changes in acne lesions.

The *primary efficacy endpoint* was %-change from baseline of the inflammatory lesion count at week 4 (superiority analysis).

The *primary safety endpoints* were the number of treatment-related AEs (TrAE) and Serious AEs (SAE). Clinical laboratory tests were not performed as part of this study. A urine pregnancy test for female patients of childbearing potential was performed at each assessment visit.

The *secondary endpoints* were:

- Lesion count (inflammatory, non-inflammatory and total) weeks 0, 2, 4, 8 and 12.
- ISGA score at weeks 0, 2, 4, 8 and 12.
- Time to 50% reduction in total lesion count.
- Investigator tolerability assessment at weeks 0, 2, 4, 8 and 12.
- Subject Global Change Assessment (SGCA) at weeks 2, 4, 8 and 12.
- Subject tolerability assessment at weeks 0, 2, 4, 8 and 12.
- Patient product acceptability and preference questionnaire (PAP-Q) at week 12.
- Adherence at week 12 (as measured by weight remaining in tube).
- Dermatology Life Quality Index (DLQI) or Children's Dermatology Life Quality Index (CDLQI, for children ≤16 years) at weeks 0, 2, 4, 8 and 12.

Rapporteur's comment:

There is no single, standardised and reproducible system for grading the severity of acne. Several grading systems exist, almost all using an ordinal scale for assessing global severity of acne ([Lehmann et al., 2002](#)).

The primary efficacy endpoint in this study is intended to be an objective, quantitative measure of the number of active lesions. In fact, precision lesion counts can be difficult and may vary between clinicians ([Lucky 1996](#); [Tan, Fung & Bulger 2006](#)). Reduction in counts may be perceived differently by patient and assessor, depending on the baseline lesion count. Finally, this quantitative assessment fails to reflect other important aspects such as size, location, appearance and pain of individual lesions.

For this reason, the primary efficacy endpoint is supported by several subjective, ordinal efficacy and tolerability endpoints. Used alone, these scales and questionnaires are limited

by their simplicity and subjectivity. However, combination of the two assessment types aims to provide an overall impression of acne severity, including some assessment of the impact on quality of life.

The ISGA is a standardised 6-point rating scale for skin conditions:

Figure 1. Investigator's Static Global Assessment (ISGA)

| Score | ISGA Assessment Scale |
|-------|---|
| 0 | Clear skin with no inflammatory or noninflammatory lesions |
| 1 | Almost clear: rare noninflammatory lesions with no more than rare papules |
| 2 | Mild severity: greater than Grade 1, some noninflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions) |
| 3 | Moderate severity: greater than Grade 2, up to many noninflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion |
| 4 | Severe: greater than Grade 3, up to many noninflammatory and inflammatory lesions, but no more than a few nodular lesions |
| 5 | Very severe: many noninflammatory and inflammatory lesions and more than a few nodular lesions. May have cystic lesions |

It is commonly used in trials for acne vulgaris and has been endorsed by the US Food and Drug Administration (FDA) ([draft guidance, Acne vulgaris: Developing drugs for treatment](#)) as a static, qualitative evaluation of overall acne severity. The FDA recommends the blinding of assessors to any previous or baseline scores which may impact their assessment, but the study protocol for the submitted study asserts that the same assessor should complete all assessments for any one patient (if possible), which would preclude blinding assessors to previous scores. It is not clear from the study report to what extent this was adhered to for the submitted study.

The SGCA is an 8 point score used by the patient, defined as: “not applicable”, “no change”, “minimally improved”, “much improved”, “very much improved”, “minimally worse”, “much worse”, “very much worse”.

The study's Investigator Tolerability Score is a 4-point rating scale used by the study investigator, based on erythema, dryness and peeling of the face, defined as: “erythema and dryness” 0=none, 1=slight, 2=some, 3=very red/dry and “peeling” 0=none, 1=slight, 2=moderate, 3=strong.

The study's Subject Tolerability Score is a 4-point rating scale used by the patient, defined as: “burning/stinging and pruritus” 0=none, 1=slight, 2=moderate, 3=strong.

The patient PAP-Q is a questionnaire which was delivered at one time point only (week 12). It comprises questions relating to facial acne signs and symptoms, ease of application, comfort of skin, satisfaction with study agent, prevention of new acne lesions, control of existing acne lesions, everyday use of study agent, hydration and moisturisation of skin, study agent continuation, easy use of make-up.

DLQI and CDLQI are validated, well established quality of life measures used widely in dermatology, including acne vulgaris ([Finlay & Khan, 1994](#); [Lewis-Jones & Finlay, 1995](#); [Finlay, 2004](#); [Basra et al. 2008](#); [Reljić et al. 2014](#)).

- Statistical Methods

Superiority analysis using a two-sided Mann-Whitney U-test for independent samples.

The sample size of 220 patients was calculated to provide 80% power to detect a relative difference of 12.5% between the groups for the primary efficacy endpoint, with a two-sided significance level of 5%, using an estimate of the standard deviation of the primary efficacy endpoint (32%) as measured in a previously completed study.

The approach to missing data was described in detail. Missing lesion count data were imputed where previous values were available. Missing secondary endpoint data were handled with a Last Observation Carried Forward (LOCF) approach.

➤ **Results**

- Recruitment/ Number analysed

222 patients were screened for the study, of which 221 patients were randomised to treatment (111 clindamycin 1% / benzoyl peroxide 3% vs 110 azelaic acid 20%). 4 randomised patients (3 vs 1) did not receive a single dose of study drug, resulting in an intention-to-treat (ITT) subset of 217 patients.

2 further patients received the drug but were “*not available for efficacy evaluation*”, resulting in a total of 215 evaluable patients as a modified intention-to-treat (mITT) subset (107 vs 108).

Overall, minor and/or major protocol violations occurred in 166 of the 221 randomised patients (75.1%, 80 vs 86). The most common reasons for minor and major protocol violations related to compliance issues, including “*compliance mistake*” and “*time window violation*”.

63 of the 221 randomised patients (28.5%, 30 vs 33) had major protocol deviations that led to their exclusion from per protocol analysis, resulting in a per protocol (PP) subset of 158 patients (81 vs 77).

15 of the 222 screened patients (7.0%, 7 vs 8) terminated the study prematurely. Only one of these withdrawals (an adult) occurred following a treatment-related AE that prompted permanent discontinuation of the study medication.

Rapporteur's comment:

The drop-out rate was low and similar between treatment groups (3.7% vs 6.4%). One (adult) patient is cited as having terminated the study prematurely because of adverse event, although in the adverse event results section the study report states that two (adult) patients discontinued study medication due to treatment-emergent AE (TEAE).

The generally high rate of minor and major protocol deviations due to compliance issues was similar between groups, but is not further discussed in the study report. This might suggest that topical regimens for the treatment of acne are generally difficult to comply fully with.

92 patients aged 12 to 16 years were included in the mITT subset. (Note that a different age cut-off is used in the study report for mITT analysis than for the baseline demographic data).

- Baseline data

In the ITT population, 54.8% of patients were female. 47.9% of patients were less than 18 years old. Age ranged from 12 to 44 years with mean 20.1±7 years. 90.3% of patients were Caucasian.

The demographic data shows that 104 paediatric patients aged 12 to 17 were included in the ITT population (48 vs 56).

Demographics, previous / concomitant diseases, concomitant skin therapies, vital signs, physical examination, duration of exposure, baseline inflammatory lesion count and skin type were comparable between the groups at baseline, and between the ITT, mITT and PP subsets. The most frequently listed concomitant disease findings were allergies and other, minor skin diseases.

Rapporteur's comment:

104 paediatric patients (48 clindamycin 1% / benzoyl peroxide 3% vs 56 azelaic acid 20%) aged 12 to 17 years were included in this Phase 4 randomised, single-blind, comparator-controlled trial. Further breakdown by age was not provided. This study does not provide information on use of the product in paediatric patients less than 12 years old.

The slight female preponderance was balanced between groups and not expected to affect analysis.

- Efficacy results

Primary efficacy endpoint (mITT subset)

Superiority analysis of 217 mITT patients by 2-sided Mann-Whitney U-test for independent samples demonstrated a statistically significant greater % reduction in the primary efficacy endpoint (inflammatory lesions at 4 weeks) in patients treated with clindamycin 1% / benzoyl peroxide 3% (-52.6%) vs azelaic acid 20% (-38.8%, p=0.0004).

The same trend was demonstrated in sub-analysis stratified by age subset (12-16 years vs 17-45 years) and when stratified by skin type (sensitive vs not).

Secondary efficacy endpoints (mITT subset)

All statistical analyses for secondary endpoints were exploratory in nature.

ISGA score demonstrated a trend towards improvement for both products, but with better assessments for clindamycin 1% / benzoyl peroxide 3% vs azelaic acid 20% at all assessment time points. Exploratory p-values demonstrated that this difference between groups became (and remained) statistically significant from 4 weeks.

A slightly higher frequency of patients reporting “very much improved” in the SGCA score was noted at 12 weeks, favouring clindamycin 1% / benzoyl peroxide 3% vs azelaic acid 20%.

Exploratory p-values for secondary endpoints supported statistically significant superiority of clindamycin 1% / benzoyl peroxide 3% vs Skinoren at all assessment time points for absolute- and %-change in non-inflammatory lesions and calculated total lesions. Exploratory p-values also supported statistically significant superiority of clindamycin 1% / benzoyl peroxide 3% vs azelaic acid 20% for ISGA score at assessment time points from 4 weeks onwards. The same trend was demonstrated in sub-analysis stratified by age subset (12-16 years vs 17-45 years) and by skin type (sensitive vs not).

The average time to 50% reduction of total lesion count was shorter in clindamycin 1% / benzoyl peroxide 3% vs azelaic acid 20% (46.3 ± 26.9 days vs 51.3 ± 26.5 days). The same trend was demonstrated in sub-analysis stratified by age subset (12-16 years vs 17-45 years) and by skin type (sensitive vs not). This secondary endpoint analysis included 91/107 (85%) of clindamycin 1% / benzoyl peroxide 3% patients who achieved 50% reduction by the end of the study period, vs 60/108 (55.6%) of azelaic acid 20% patients who achieved the same, demonstrating that statistically significantly more patients in the clindamycin 1% / benzoyl peroxide 3% group reached this milestone during the study duration ($p < 0.0001$).

Answers to the quality of life questionnaires (DLQI and CDLQI) showed a trend towards mean better improvement for clindamycin 1% / benzoyl peroxide 3% vs azelaic acid 20% throughout the duration of the study.

- Sensitivity analysis (PP subset)

Statistical evaluation of demographics, baseline variables and efficacy variables did not reveal any major differences between the per protocol and mITT subsets, supporting the statistical significance of the above results. Exploratory analysis of the primary endpoint in the PP subset also supported statistically significant superiority of clindamycin 1% / benzoyl peroxide 3% vs azelaic acid 20% ($p = 0.0009$).

Rapporteur's comment:

This study presents a number of efficacy sub-analyses that have been stratified by age subgroup, allowing us to draw at least some conclusions specific to the paediatric population aged 12-16 years. A statistically significant greater % reduction (-13.8%, $p = 0.0004$) in the primary efficacy endpoint (inflammatory lesions at 4 weeks), and a greater positive trend in secondary efficacy endpoints, was demonstrated for clindamycin 1% / benzoyl peroxide 3% vs azelaic acid 20%. This trend was first demonstrated for the entire mITT population and was

maintained in sub-analysis of the adolescent subset (92 patients, aged 12 to 16 years). (Note that a different age cut-off is used in the study report for mITT analysis than used for the demographic data). This suggests that both treatments were associated with a reduction in the number of inflammatory acne lesions in children 12-16 years by 4 weeks, with clindamycin 1% / benzoyl peroxide 3% being associated with the greatest improvement.

Interestingly, age-stratified analysis demonstrated that while clindamycin 1% / benzoyl peroxide 3% was associated with comparable change from baseline at 4 weeks in both the 12-16 years and 17-45 years subgroups, by contrast, azelaic acid 20% was associated with a noticeably smaller improvement in the 12-16 years group than the 17-45 years group, suggesting the superiority of clindamycin 1% / benzoyl peroxide 3% vs azelaic acid 20% may be even more marked in the paediatric population than their adult counterparts.

The same pattern was noted for calculated total lesion count, where the paediatric population demonstrated a larger difference between treatment arms than their adult counterparts at week 4. However, the reverse is true for non-inflammatory lesions, where the paediatric population demonstrated a smaller difference between treatment arms than their adult counterparts at week 4.

Although mean change in CDLQI score was indeed greater at 12 weeks for clindamycin 1% / benzoyl peroxide 3% vs azelaic acid 20%, the distribution of scores in both groups was significantly skewed, which may over-emphasise the apparent difference between groups. The paediatric population subgroup achieved a greater mean improvement in quality of life (QoL) score at week 4 with clindamycin 1% / benzoyl peroxide 3% vs azelaic acid 20% (absolute difference -23.9%, -60.7% vs -36.8%) than their adult counterparts (absolute difference -13.4%, -53% vs -39.6%).

Overall these results suggest that the superiority of clindamycin 1% / benzoyl peroxide 3% vs azelaic acid 20% demonstrated in this study is at least comparable, and possibly greater, in the paediatric population aged 12-16 years vs the adult population.

Although the study report states that a higher frequency (vs baseline) of “very much improved” SGCA score was demonstrated for clindamycin 1% / benzoyl peroxide 3% vs azelaic acid 20% at 12 weeks, the raw data demonstrates a wide distribution of scores in both groups during the study period, and in fact an increased frequency (vs baseline) of “very much worse” scores by the end of the study. This suggests a variability in patient-perceived response to both treatments that is not highlighted or discussed in the study report.

- Tolerability results (mITT subset)

There were no significant differences between treatment groups for Investigator or Subject Tolerability Assessments throughout the study period.

The PAP-Q was performed only once, at study termination. Answers demonstrated higher overall satisfaction with for clindamycin 1% / benzoyl peroxide 3% vs azelaic acid 20% for. Some specific PAP-Q questions demonstrated rating differences in favour of clindamycin 1% / benzoyl peroxide 3% vs azelaic acid 20%, namely; “burning”, “itching”, “comfort of skin”, “satisfaction with study agent” and “continuation of treatment with study agent”. However, remaining questions demonstrated no differences between treatment groups.

The proportion of patients who did not miss any study product applications was higher for clindamycin 1% / benzoyl peroxide 3% vs azelaic acid 20% (48.1% vs 34.9%). Treatment compliance, as determined by weight change of the dispensed product, was deemed acceptable for both treatment groups in this study.

Rapporteur's comment:

Overall satisfaction according to the PAP-Q score was rated higher at 12 weeks for clindamycin 1% / benzoyl peroxide 3% vs azelaic acid 20%. No differences were seen in the Investigator or Subject Tolerability Assessments, although both treatments were generally well tolerated.

About half (48.1%) of patients treated with clindamycin 1% / benzoyl peroxide 3% did not miss any applications, vs one third (34.9%) of patients treated with azelaic acid 20%. This might suggest that the clindamycin 1% / benzoyl peroxide 3% regimen is marginally easier to comply with.

- Safety results (ITT subset)

Safety analysis was performed on the ITT subset. AE data were not presented stratified by age.

No pathological changes or trends were noted at evaluation of blood pressure, heart rate, body temperature, respiratory rate or physical examination at baseline or final visit.

A total of 293 (123 vs 170) TEAEs were reported in 136 of 217 ITT patients (62.7%) during the treatment period, the vast majority of which were grade 1 or 2. The rate of TEAEs was higher in the azelaic acid 20% group, with a difference between treatment arms of 14.2% (95% CI: 0.5-26.8%). The most common TEAE SOC were general disorders and administration site disorders (25.8%), infections and infestations (22.6%) and nervous system disorders (17.5%).

TEAEs considered related to the study medication (TrAE) were less frequent with clindamycin 1% / benzoyl peroxide 3% vs azelaic acid 20% (13.9% vs 33.5%). None were serious. Nearly all TrAEs were related to application site complaints such as pain, pruritus, erythema, dryness and exfoliation.

Two (adult) patients discontinued the study medication due to TrAEs, one in each treatment arm (both non-serious dermatological reactions).

Six treatment-emergent serious adverse events (TESAEs) occurred in 5 patients (2 vs 3). None were considered related to the study medication. None led to discontinuation of the study. Two of these TESAEs occurred in paediatric patients, both in the azelaic acid 20% treatment arm and neither of which was considered related to study drug administration.

Rapporteur's comment:

AE data have not been presented stratified by age in this study, and therefore only conclusions about safety in the overall study population can be drawn. Both treatments were generally well tolerated. clindamycin 1% / benzoyl peroxide 3% was associated with fewer TrAEs than azelaic acid 20%. Nearly all TrAEs related to application site complaints such as pain, pruritus, erythema, dryness and exfoliation. These were reported at frequencies consistent with those listed in the "*Undesirable effects*" section of the current SmPC. Such effects are expected to some extent for a topical treatment with this mechanism of action. There was a low rate of SAEs (five patients, two of whom were 16 years of age, none considered related to study medication). There was a low rate of TrAEs leading to discontinuation of the study medication (one adult patient in each treatment arm).

IV.2.2.2 Clinical study – Study B

“Clinical evaluation of efficacy at 2 weeks of [clindamycin 1% / benzoyl peroxide 3%] fixed dose combination gel in treatment of facial acne vulgaris in Japanese subjects.”

➤ Description

A 12 week, randomised, active-controlled, investigator-blind, parallel-group, multi-centre Phase 4 study to compare the efficacy, safety and tolerability at 2 weeks of fixed dose clindamycin 1% / benzoyl peroxide 3% with combination therapy (clindamycin 1% / adapalene 0.1%, hereafter referred to in this assessment as combination therapy) for topical treatment of facial acne vulgaris.

➤ Methods

- Objective(s)
 - Primary objective: To compare efficacy, safety and tolerability of clindamycin 1% / benzoyl peroxide 3% with combination therapy.
 - Secondary objectives:
 - To compare efficacy and Global Improvement of clindamycin 1% / benzoyl peroxide 3% with combination therapy.
 - To evaluate safety and tolerability of clindamycin 1% / benzoyl peroxide 3% with combination therapy.
 - Exploratory endpoints:
 - To compare compliance clindamycin 1% / benzoyl peroxide 3% with combination therapy.
 - To compare patient preference for clindamycin 1% / benzoyl peroxide 3% vs combination therapy.
 - To compare the Quality of Life effect of clindamycin 1% / benzoyl peroxide 3% vs combination therapy.

- Study design

12 week prospective, randomised, investigator-blind, active-controlled, parallel-group study across 15 centres in Japan.

- Study population /Sample size

Planned study population of 350 male and female patients aged 12 to 45 years of age with confirmed acne vulgaris. Randomised 1:1 to each treatment arm.

Inclusion criteria:

- Confirmed acne vulgaris.
- Baseline Investigator's Static Global Assessment (ISGA) score 2 or more.
- 17-60 inflammatory facial lesions (papules and pustules).
- 20-150 non-inflammatory facial lesions (open and closed comedones).

Exclusion criteria:

- Any nodulo-cystic lesions at baseline.
- Female patients who were pregnant, breastfeeding or sexually active and not using reliable contraception or not prepared to do so for the duration of the study.

- History of presence of regional enteritis, inflammatory bowel disease or similar symptoms.
- History suggestive of immunocompromised status.
- History of substance abuse or dependence within last 12 months.
- Patients receiving specific therapies prior to baseline:
 - 6 months; systemic retinoid.
 - 4 weeks; facial procedures (e.g. laser), topical corticosteroids.
 - 2 weeks; topical (face) or systemic antibiotics, topical anti-acne medications, abrasives, facial peels, masks containing glycolic or other acids.
- Plan to use medications known to exacerbate acne (vitamin D, vitamin B12, corticosteroids, androgens, haloperidol, halogens, lithium, hydantoin, phenobarbital).
- Patients with known sensitivity or allergy to any active component or excipient.
- Patients using oestrogens, androgens or anti-androgens for less than 12 consecutive weeks prior to first dose.
- Use of any investigational therapy in the last 12 weeks.
- Participation in another GSK Japanese clinical study for acne vulgaris.
- Employee, investigator, contract research organisation or family member connected to GSK.
- Use of any medication that in the opinion of the investigator could affect the clinical study or evaluation.
- Any other condition that would put the subject at unacceptable risk for participation in the study.

Withdrawal criteria:

- Lost to follow up.
- Withdrawal from study.
- Pregnancy.
- Premature termination of study.
- Difficulty continuing in study due to AEs.
- Protocol deviation.
- Other reasons deemed necessary by the investigator.

Rapporteur's comment:

Assessment of efficacy of a topical treatment for acne vulgaris over 12 weeks is in keeping with other studies and wider literature for the condition ([Purdy & de Berker, 2011](#)). Safety exclusion criteria included the presence of serious gastrointestinal pathologies, which could potentially be exacerbated by systemic absorption of a topical antibiotic.

- Treatments

Endpoint assessors were blinded to the treatment received. Patients were not blinded to the treatment received.

Patients were randomised by computer-generated schedule 1:1 to topical treatment to the face with once daily clindamycin 1% / benzoyl peroxide 3% or daily combination therapy for 12 weeks. Randomisation was stratified by site.

Patients randomised to clindamycin 1% / benzoyl peroxide 3% were told to apply “2 fingertip units” of the gel over the entire face once daily (evening) for 12 weeks. Patients randomised to combination therapy were told to apply “1 fingertip unit” of adapalene 0.1% gel over the entire face once daily (evening) for 12 weeks, and to apply clindamycin 1% gel to inflammatory lesions (if any) twice daily (morning, evening).

The use of moisturiser was permitted but had to be documented and was then categorised as “constant” ($\geq 80\%$ of days), “temporary” (1-80% of days) or “no” use, for the purposes of analysis. Astringents and toners could be used as long as the subject had been using the same regimen for more than 2 consecutive weeks prior to the start of the study, and continued the same regimen during the conduct of the study. Facial procedures, peels, abrasives, scrubs and medicated masks, washes and soaps were not permitted. Non-comedogenic sunscreen and cosmetics were permitted.

Rapporteur's comment:

This is an active comparator study with no placebo arm. The combination therapy used here as active comparator was chosen because at the time of the study it was recommended as standard first line for treatment of acne patients with inflammatory lesions, in the Japanese Acne Treatment Guidelines ([Hayashi, 2008](#)).

The main limitation of this study is the single-blind design. The report states that the single-blind design was chosen on the basis that the two products have different appearances and application frequencies, making it impossible to blind patients to the treatment received. The study staff assessing acne lesion counts were blinded to the treatment received.

- Outcomes/endpoints

The *primary efficacy endpoint* was %-change from baseline of the total lesion count at week 2.

The *primary safety endpoints* were the number of AEs and SAEs, pregnancy and local tolerability (erythema, dryness, peeling, itching assessed by the investigator at each visit; burning/ stinging assessed by the subject at each visit). Non-serious AEs of special interest were predefined. These were categorised as signs and symptoms of skin irritation, colitis or systemic hypersensitivity.

The *secondary endpoints* were:

- %-change from baseline in total lesions at weeks 1, 4, 8 and 12.
- %-change from baseline in inflammatory lesions at weeks 1, 2, 4, 8 and 12.
- %-change from baseline in non-inflammatory lesions at weeks 1, 2, 4, 8 and 12.
- Absolute change from baseline of all lesion counts (inflammatory, non-inflammatory, total) at weeks 1, 2, 4, 8 and 12.
- Proportion of subjects with ISGA score of 0 or 1 at weeks 1, 2, 4, 8 and 12.
- Proportion of subjects with 2-grade improvement from baseline in ISGA score at weeks 1, 2, 4, 8 and 12.
- Proportion of subjects with a 50% reduction from baseline in lesion count (inflammatory, non-inflammatory, total) at weeks 1, 2, 4, 8 and 12.

The *exploratory endpoints* were:

- Compliance at weeks 1, 2, 4, 8 and 12.
- The proportion of subjects continuing treatment at weeks 1, 2, 4, 8 and 12.

- Patient preference at weeks 1, 2, 4, 8 and 12.
- Quality of life score (Skindex-16) at baseline, weeks 2, 4, 8 and 12.

Rapporteur's comment:

The previous comments regarding the primary efficacy endpoint apply also to the choice of assessments for this second study.

As in the first study, the ISGA was used as a standardised 6-point rating scale for skin conditions.

Compliance was defined as the percentage of the planned number of application times for which the product was actually applied.

The Patient Preference score consisted of 5 categories (ease of application, comfort, satisfaction with treatment, comparison with previous therapies, willingness to continue use) as scored by patients.

Skindex-16 is a well-known and validated dermatology-specific QoL score used to assess the impact of a variety of dermatological conditions on quality of life ([Chren et al. 2001](#)).

- Statistical Methods

Superiority analysis was planned using a two sample t-test with a two-sided 5% significance level.

The sample size of 220 patients was chosen to provide 90% power to detect a relative difference of 10% between the groups for the primary efficacy endpoint with a two-sided significance level of 5%, using an estimate of standard deviation of the primary efficacy endpoint (28%) as measured in a previously completed study.

All “%-change from baseline” endpoints were analysed using a mixed model for repeated measures (MMRM). The primary efficacy endpoint was also analysed using analysis of covariance (ANCOVA), with treatment, baseline total lesion count and centre as fixed effects. Sub-group ANCOVA analysis of the primary efficacy endpoint was then performed by centre.

All “proportion of subjects” endpoints were analysed using the Cochran-Mantel-Haenszel test, stratified by centre, using a two-sided 5% significance level.

Patient preference score, Skindex-16 score and skin tolerability scores were presented descriptively as average scores in each treatment group per visit. Compliance was presented descriptively as average % of application times complied with in each treatment group across the total study duration.

Rapporteur's comment:

The approach to missing data was not described in the study report.

➤ Results

- Recruitment/ Number analysed

360 subjects were screened for this study, of which 9 failed to meet eligibility criteria. 351 patients were therefore enrolled in the study and randomised to treatment (174 clindamycin 1% / benzoyl peroxide 3% vs 177 combination therapy). 2 patients were later excluded before dosing (withdrew consent, lost to follow up; both clindamycin 1% / benzoyl peroxide 3% group), resulting in an intention to treat (ITT) population of 349 patients.

15 of 349 patients (4%, 7 vs 8) prematurely terminated the study. The most common reason for this was adverse event (6 vs 5).

34 of 349 patients (10%, 18 vs 16) reported protocol deviations, of which 26 led to exclusion from per protocol analysis, resulting in a per protocol (PP) population of 323 patients. The most common reason for exclusion from the PP population was “wrong study treatment”.

Rapporteur's comment:

The drop-out rate was low and comparable between the groups (4% vs 5%). 11 patients (3%, 6 vs 5) withdrew from the study secondary to AEs.

- Baseline data

In the ITT population, 59% of patients were female. 37% of patients were less than 18 years old. Age ranged from 12 to 44 years, with mean 20 years (SD 5.42). All patients were Japanese ethnicity.

Demographics, baseline total lesion count and baseline use of moisturising agent were all comparable between the groups at baseline.

The use of prior and concomitant medications (not prohibited by study protocol) was similar between the groups. The percentage of subjects who did not use a moisturising agent in the study period was slightly higher in the clindamycin 1% / benzoyl peroxide 3% group (42% vs 24%).

Rapporteur's comment:

A total of 130 of 349 patients (37%) were 12 to <18 years old. The raw data shows that 77 of 349 patients (22%) were aged 12 to <16 years, from which it can be calculated that 53 of 349 patients (15%) were aged 16-17 years.

- Efficacy results (ITT subset)

Primary efficacy endpoint

ITT superiority analysis of 349 patients by two sample t test for independent samples demonstrated a statistically significant greater adjusted mean %-change from baseline at 2 weeks in total lesion count of -42.16% in the clindamycin 1% / benzoyl peroxide 3%

group vs -35.33% in the combination therapy group (-6.83% [95% CIL -11.88, -1.78], p=0.008).

Secondary efficacy endpoints

There were decreases in %-change and absolute-change for both groups in total lesions from baseline to weeks 1, 4, 8 and 12, and in inflammatory lesions from baseline to weeks 1, 2, 4, 8 and 12, with the greater decrease seen in the clindamycin 1% / benzoyl peroxide 3% group from week 2 onwards.

While a similar downward trend was seen in both groups for non-inflammatory lesions from baseline to weeks 1, 2, 4, 8 and 12, there was no apparent difference between groups.

The proportion of subjects with a 2-grade improvement in ISGA score from baseline to weeks 1, 2, 4, 8 and 12 was numerically higher in the clindamycin 1% / benzoyl peroxide 3% group (22% vs 12% by week 12).

The proportion of subjects with an ISGA score of 0 or 1 at weeks 1, 2, 4, 8 and 12 was numerically higher in the clindamycin 1% / benzoyl peroxide 3% group (20% vs 12% by week 12).

The proportion of subjects with a 50% or greater reduction in inflammatory lesions from baseline to weeks 1, 4, 8 and 12 was also numerically higher in the clindamycin 1% / benzoyl peroxide 3% group, although there was no apparent difference between groups for non-inflammatory lesions or total lesions.

The study report concludes that these data demonstrate that once daily clindamycin 1% / benzoyl peroxide 3% was more effective than combination therapy (clindamycin 1% / adapalene 0.1%) in reducing total lesion count in the first 2 weeks of treatment and beyond in the overall study population. It was also more effective at reducing inflammatory lesions and ISGA scores throughout all assessment time points.

- Sensitivity analysis (PP subset)

Analysis of the primary efficacy endpoint in the PP population supported the above result.

Rapporteur's comment:

The raw data include some data stratified by age. In the <16 years subgroup of 77 patients, the mean total lesions decreased in both treatment groups from baseline through all time points, however the treatment difference was not statistically significant.

The same statistically non-significant pattern is seen in the 16-20 years subgroup of 129 patients. (Note that a different age cut-off is used in the study report for sub-analysis than for the baseline demographic data).

The same trend can be seen in the ≥20 years subgroup of 143 patients, with this subgroup achieving a roughly comparable overall improvement by week 12. However, the improvement in this age subgroup is statistically significant from week 2 onwards.

- Tolerability results (ITT subset)

Compliance and treatment continuation was similar between groups, with mean overall compliance >90% and treatment continuation rate >95% at all study visits.

The mean patient preference score for all components was numerically higher in the clindamycin 1% / benzoyl peroxide 3% group throughout the study period. However, the mean score difference was just 0.3-0.4 grades in all categories across all time points. The 95% confidence interval for total Skindex-16 score (ranges -0.40, -0.04 to -0.36, 0.02) suggests that this superiority was marginal across all time points.

The adjusted mean change in total Skindex-16 score from baseline to 2, 4, 8 and 12 weeks was numerically higher in the clindamycin 1% / benzoyl peroxide 3% group, although there was no apparent difference between groups in sub-scores of emotion and functioning.

The % of subjects with “no local tolerability symptoms” remained unchanged in the clindamycin 1% / benzoyl peroxide 3% group throughout the study, but decreased in the combination therapy group after week 1, returning to baseline by week 12.

- Safety results (ITT subset)

The overall incidence of AEs was lower with clindamycin 1% / benzoyl peroxide 3% (31%) than with combination therapy (56%). Most AEs were mild or moderate in intensity.

The incidence of TrAEs was also lower with clindamycin 1% / benzoyl peroxide 3% (17%) than with combination therapy (37%). The most common TrAE across both groups was “application site dryness” (9% vs 24%).

The incidence of AEs specifically on the face was also lower clindamycin 1% / benzoyl peroxide 3% (18%) than with combination therapy (40%).

Severe AEs were reported in 3 subjects: 1 patient in the clindamycin 1% / benzoyl peroxide 3% group (application site erythema) and 2 patients in the combination therapy group (influenza, syncope).

One single SAE, not related to study drug, was reported in an adult in the clindamycin 1% / benzoyl peroxide 3% group (duodenal ulcer). No deaths occurred during the study.

Non-serious AEs of special interest were predefined, based upon potential risks identified: these were categorised as signs and symptoms of skin irritation, colitis or systemic hypersensitivity. Such AEs were reported in 10 subjects in the clindamycin 1% / benzoyl peroxide 3% group (8 skin irritation, 2 systemic hypersensitivity) and 34 subjects in the combination therapy group (29 skin irritation, 5 systemic hypersensitivity). There were no reports of colitis.

Rapporteur's comment:

Both treatments were generally well tolerated. Clindamycin 1% / benzoyl peroxide 3% was associated with fewer TrAEs than azelaic acid 20%. Nearly all TrAEs related to application site complaints such as pain, pruritus, erythema, dryness and exfoliation. These were reported at frequencies consistent with those listed in the “*Undesirable effects*” section of the current SmPC. Such effects are expected to some extent for a topical treatment with this mechanism of action.

The raw data tables include some statistics stratified by age. These show that the incidence of AEs was even lower with clindamycin 1% / benzoyl peroxide 3% (29%) in the <16 years subgroup vs the overall study population, and actually slightly higher with combination therapy (64%) than the overall study population. The incidence of TrAEs was also lower with clindamycin 1% / benzoyl peroxide 3% (12%) in the <16 years age subgroup vs the overall study population, and slightly higher with combination therapy (47%) than the overall study population. The types and frequency of AEs reported were the same as in the other age subgroups. This suggests superior safety and tolerability of clindamycin 1% / benzoyl peroxide 3% vs combination therapy specific to patients <16 years over and above that demonstrated for the overall study population.

- Sub-group analysis

The study reports states that no different patterns or trends in total lesion count or AEs were identified from baseline to week 12 when analysed according to subgroups of age, sex, baseline total lesion count, baseline ISGA, use of moisturising agent.

Rapporteur's comment:

These data demonstrate that once daily clindamycin 1% / benzoyl peroxide 3% was more effective than combination therapy (clindamycin 1% / adapalene 0.1%) in reducing total lesion count in the first 2 weeks of treatment in the overall study population. It was also more effective at reducing inflammatory lesions and ISGA scores throughout the 12 weeks of the study. Finally, clindamycin 1% / benzoyl peroxide 3% was associated with marginally higher SGCA, patient preference and quality of life scores than combination therapy throughout the 12 weeks of the study. The authors conclude that the study demonstrated that clindamycin 1% / benzoyl peroxide 3% has earlier efficacy vs combination therapy for the treatment of acne vulgaris in Japanese subjects.

No new safety concerns were identified and the observed AEs, were generally related to mild application site reactions as recognised and described in the current SmPC. clindamycin 1% / benzoyl peroxide 3% was better tolerated and associated with a lower rate of AEs than combination therapy. AEs occurred at frequencies consistent with those listed in the SmPC under “*Undesirable effects*”.

The study reports states that no different patterns or trends in total lesion count or AEs were identified from baseline to week 12 when analysed according to subgroups of age, sex, baseline total lesion count, baseline ISGA, use of moisturising agent. There was a trend to greater improvement with clindamycin 1% / benzoyl peroxide 3% vs combination therapy in all age subgroups, however, the raw data tables suggest that the treatment difference was only statistically significant in the ≥20 years subgroup. This may be related to smaller patient numbers in the <16 years and 16-20 years subgroups. Nevertheless, there was evidence of

superior safety (in terms of a reduced rate of AEs compared with combination therapy) of clindamycin 1% / benzoyl peroxide 3% specific to patients <16 years, over and above that demonstrated for the overall study population.

As the study population was entirely of Japanese ethnic origin, the results may not necessarily be applicable to patients of all other ethnic origins.

IV.2.3 Discussion on clinical aspects

Both submitted studies used the lower strength preparation of clindamycin 1% / benzoyl peroxide 3% Once Daily Gel (1% clindamycin / 3% benzoyl peroxide). Neither of these studies was designed to provide data on the efficacy or safety of higher strength clindamycin 1% / benzoyl peroxide 3% Once Daily Gel (1% / 5%).

➤ Efficacy

In the first study, the primary efficacy endpoint of % reduction of inflammatory lesions at 4 weeks demonstrated an improvement in both treatment arms, but this improvement was statistically significantly greater (absolute difference 13.8%) for patients treated with clindamycin 1% / benzoyl peroxide 3% vs azelaic acid 20% (mITT subset, $p=0.0004$). The secondary efficacy endpoints also demonstrated a trend towards greater improvements for clindamycin 1% / benzoyl peroxide 3% vs azelaic acid 20% over the entire study duration, although with considerable inter-subject variability. Sub-analysis stratified by age indicated the superiority of clindamycin 1% / benzoyl peroxide 3% vs azelaic acid 20% demonstrated in this study is at least comparable, and possibly greater, in the paediatric population aged 12-16 years vs the adult population. These results support the current use of the product for the treatment of facial acne in the paediatric population.

In the second study, the primary efficacy endpoint of % reduction of total lesions at 2 weeks demonstrated a statistically significant greater improvement (absolute difference 6.83%) for patients treated with clindamycin 1% / benzoyl peroxide 3% vs combination therapy with topical clindamycin 1% and adapalene 0.1% (ITT subset, $p=0.0008$). Secondary efficacy endpoints also demonstrated greater improvements for clindamycin 1% / benzoyl peroxide 3% vs combination therapy over the entire study duration, with the exception of non-inflammatory lesions, where both treatment groups showed an approximately equal improvement. When stratified by age, the trend towards superiority of clindamycin 1% / benzoyl peroxide 3% vs combination therapy was not statistically significant for subgroups of patients <16 years and 16-20 years old. This may have been partly due to small patient numbers in the <16 years and 16-20 years subgroups.

➤ Safety

In the first study, fewer TEAEs were reported with clindamycin 1% / benzoyl peroxide 3% when compared to azelaic acid 20%. The vast majority of TEAEs in both treatment arms were mild. TrAEs were nearly all related to application site findings, which are expected to some extent for a topical treatment with this mechanism of action. They occurred at frequencies consistent with those in the current SmPC under “*Undesirable effects*”. TESAEs were infrequent and none was considered related to study medication.

In the second study, clindamycin 1% / benzoyl peroxide 3% was better tolerated and associated with a lower rate of TEAEs than combination therapy. Similarly, TrAEs were nearly all related to application site findings, which are expected to some extent for a topical treatment with this mechanism of action. They occurred at frequencies consistent with those in the current SmPC under “*Undesirable effects*”. When AE data was stratified by age, there was evidence of superior safety (in terms of a reduced rate of AEs compared to combination therapy) of clindamycin 1% / benzoyl peroxide 3% specific to patients <16 years, over and above that demonstrated for the overall study population. TESAEs were infrequent and none was considered related to study medication. These results support the current product literature.

➤ Overall

These results are in line with the information provided in the current SmPC for clindamycin 1% / benzoyl peroxide 3% Once Daily Gel (1% / 3%).

V. REQUEST FOR SUPPLEMENTARY INFORMATION

No request supplementary information was required.

VI. RAPPORTEUR'S FINAL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

The submitted studies demonstrate that clindamycin 1% / benzoyl peroxide 3% Once Daily Gel (1% / 3%) was superior to two different, licensed active comparators at treating facial acne. It was also well tolerated over a treatment period of 12 weeks, with the majority of AEs being mild to moderate application site findings related to the exfoliative mechanism of action of the product, and consistent with the undesirable effects described in the current SmPC.

➤ Recommendation

The submitted data are in line with currently approved product information. No changes to the SmPC are required.

VII. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

| MAH | Name of the medicinal product | Strength | Class |
|-------------------------------|--|---|-------|
| GlaxoSmithKline UK Limited | Duac [®] Once Daily Gel 10mg/g + 30mg/g | 10mg/g clindamycin + 30mg/g benzoyl peroxide | POM |
| | Duac [®] Once Daily Gel 10mg/g + 50mg/g | 10mg/g clindamycin + 50mg/g benzoyl peroxide | POM |

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