

ORIGINAL ARTICLE

A multicentre, randomized, single-blind, parallel-group study comparing the efficacy and tolerability of benzoyl peroxide 3%/clindamycin 1% with azelaic acid 20% in the topical treatment of mild-to-moderate acne vulgaris

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Abstract

Background Mild-to-moderate acne vulgaris is treated with a range of mono- and combination therapies; however, clinical evidence is still required to optimize treatment recommendations.

Objective To compare the efficacy, tolerability and safety of a combination of benzoyl peroxide 3% and clindamycin 1% (BPO + CLN) with azelaic acid 20% (Aza) for the topical treatment of mild-to-moderate acne vulgaris.

Method This was a randomized, assessor-blinded, parallel-group, multicentre study conducted in Germany. Patients with a confirmed diagnosis of acne vulgaris, aged 12–45 years, were randomized 1 : 1 to once-daily BPO + CLN gel or twice-daily Aza cream for up to 12 weeks. The primary endpoint was the percentage change in inflammatory lesions from baseline at Week 4. Secondary endpoints included total and inflammatory lesion counts and tolerability assessments. For selected secondary endpoints, inductive statistical analysis was performed post hoc. Patient safety was assessed by adverse event (AE) monitoring.

Results Efficacy was assessed in the modified intent-to-treat (mITT) population [patients using ≥ 1 dose of study medication (ITT), plus baseline and ≥ 1 post-baseline lesion count ($n = 215$)]. There was a statistically significant difference in the primary endpoint, with a median decrease of -52.6% for BPO + CLN ($n = 107$) vs. -38.8% for Aza ($n = 108$; $P = 0.0004$). There was also a greater difference in secondary lesion endpoints at Week 12, with a median decrease in inflammatory lesions of -78.8% and -65.3% and total lesions of -69.0% and -53.9% with BPO + CLN and Aza, respectively (both $P < 0.0001$). Tolerability was acceptable for both treatments. Overall, 55.6% (BPO + CLN) and 69.7% (Aza) of patients reported treatment-emergent AEs, and 15.7% and 35.8% of patients experienced application site reactions with BPO + CLN (24 events; 17 patients) and Aza (60 events; 39 patients) treatment, respectively (ITT population).

Conclusion BPO + CLN demonstrated greater efficacy than Aza in the treatment of mild-to-moderate acne vulgaris and has a positive tolerability and safety profile.

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Conflicts of interest

MSch has been a member of the advisory board of Bayer Healthcare and Galderma for the past 2 years and has received lecture fees from AbbVie, Bayer Healthcare, Galderma and La Roche-Posay. MSeb has been an advisor or investigator for AbbVie, Novartis, Janssen-Cilag, Lilly, Amgen, Celgene, Galderma, Leo Pharma, GSK, and Pfizer. CR, DS and MH are employees of GSK and hold stocks/shares in GSK.

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Introduction

Acne vulgaris is a common skin disease, affecting 85% of people at some point in their lives and is particularly prevalent in adolescents.^{1,2} It is characterized by the presence of comedones,

papules and pustules, with both inflammatory and non-inflammatory lesions, and has a multifactorial pathogenesis including increased sebum production, *Propionibacterium acnes* colonization, altered keratinization and inflammation.³ Combination

topical treatments are favoured for the treatment of mild-to-moderate acne in order to address these pathogenic factors. However, despite the availability of a range of combination therapies, there remains a need for further clinical data to improve evidence-based treatment recommendations.

Benzoyl peroxide (BPO) has anti-microbial and keratolytic properties; clindamycin (CLN) has antibiotic and anti-inflammatory properties.⁴ Therefore, a combination of these two agents targets three of the pathogenic factors (inflammation, *P. acnes* and keratinization) of acne vulgaris. Randomized Phase III clinical trials have demonstrated the superior efficacy of BPO 3% + CLN 1% vs. its individual constituents⁵ and BPO 5% + CLN 1% vs. monotherapies such as adapalene 0.1% in the treatment of mild-to-moderate acne vulgaris.⁶

Azelaic acid (AzA) has both keratolytic and anti-microbial properties.⁷ While randomized trials have demonstrated comparable efficacy of AzA 15% with BPO 5% and CLN 1% individually,⁸ and AzA has been shown to be as efficacious as BPO,⁹ there have been no studies to directly compare AzA with a low-dose strength combination of BPO 3% + CLN 1%. The objective of this study was to compare the efficacy, tolerability and safety of a combination of BPO 3% + CLN 1% (Duac® 10 mg/g + 30 mg/g gel) with AzA 20% (Skinoren® 20% cream) for the treatment of mild-to-moderate acne vulgaris.

Materials and methods

Study design

This was a Phase IV, randomized, assessor-blinded, comparator-controlled, parallel-group study (NCT02058628; GSK study identifier: GSK200398) conducted across 11 study centres in Germany to compare the efficacy, safety and tolerability of BPO 3% + CLN 1% gel with 20% AzA cream in the topical treatment of facial acne vulgaris, in accordance with the respective product labels.^{4,7} In total, 220 patients were planned to be randomized 1 : 1 to receive either once-daily BPO 3% + CLN 1% or twice-daily AzA 20% for 12 weeks. This study was approved by the appropriate regulatory and ethics committees in Germany, and performed in accordance with the Declaration of Helsinki of 2008 and Good Clinical Practice guidelines. Written informed consent was obtained from each patient prior to study participation.

Patients

Patient inclusion criteria included being 12–45 years old, having facial acne vulgaris (defined as having 17–60 inflammatory lesions [papules and pustules], ≤1 facial nodular cystic lesion, 20–125 non-inflammatory facial lesions and an Investigator's Static Global Assessment [ISGA] score of 'mild' or 'moderate'). Sunbed or ultraviolet light treatment was not permitted for 4 weeks pre-study. Exclusion criteria included being pregnant (or at risk of becoming pregnant), breastfeeding, a history of non-acne facial disease or severe systemic disease, having

received medications that could interfere with the evaluation of the study treatments within the 6 months pre-study (antibiotics, corticosteroids, retinoids), facial procedures within the last month, or known hypersensitivity or allergy to active constituents of the study drugs. Oestrogen (including hormonal contraceptives), androgen and anti-androgen agents were permitted if used at the same dose for 12 consecutive weeks pre-study and the dose remained unchanged throughout the study.

Treatments

Patients applied a thin film of either BPO 3% + CLN 1% once-daily (evening) or AzA 20% twice-daily (morning and evening), to their entire face after cleansing. Following application, patients were not permitted to wash their faces for 4 h.

Endpoints

The primary endpoint was the percentage change in inflammatory lesion count from baseline at Week 4. Secondary endpoints included inflammatory (papules and pustules, including nasal lesions), non-inflammatory (open and closed comedones) and calculated total lesion counts, speed of therapy onset, physician and patient assessment of disease severity, investigator and subject tolerability assessment, quality of life (QoL) assessment and patient safety assessments. Lesion counts, tolerability and adverse events (AEs) were assessed at baseline, and Weeks 2, 4, 8 and 12 [Week 12 data include both data from patients who attended the Week 12 visit (patients completing the study) and those who attended an Early Withdrawal Visit pre-Week 12]; QoL measures were performed at every study visit. The speed of therapy onset was determined as the time to a 50% reduction in total lesion count. Disease severity was evaluated by physicians using the ISGA, scored on a 6-point rating scale and by patients using the Subject Global Change Assessment (SGCA), scored on a 7-point scale (Appendix). Tolerability was determined by the physician's assessment of erythema, dryness and peeling, and patient assessment of burning/stinging and pruritus using 4-point scales (Appendix). QoL assessment used the 10-question Children's and adult Dermatology Life Quality Indices (CDLQI and DLQI, respectively), scored on a 4-point scale (Appendix). Both questionnaires have been validated as appropriate for assessing the QoL burden of acne vulgaris.^{10,11} Patient safety was evaluated by monitoring of AEs, treatment-emergent AEs (TEAEs) and serious AEs (SAEs) and treatment-emergent SAEs (TESAEs), withdrawals due to TEAEs, vital signs and physical examinations.

Randomization and blinding

Randomization (1 : 1) to treatments was performed using a computer-generated schedule. Acne lesion assessors were blinded to treatment. Patients, site staff responsible for distribution and drug accountability and individuals involved in the conduct, analysis and reporting of clinical study data were not

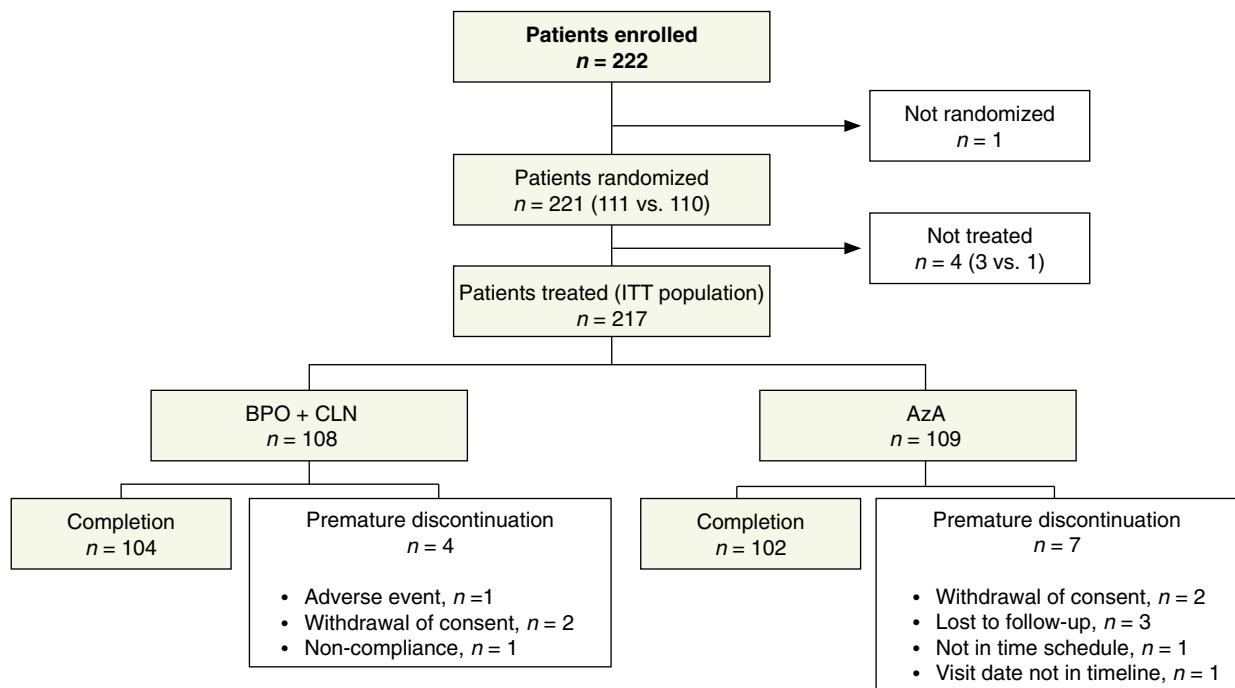


Figure 1 Summary of patient disposition. Note: The treatment group data are consistently reported in the order: BPO + CLN vs. AzA. AzA, azelaic acid; BPO, benzoyl peroxide; CLN, clindamycin; ITT, intent-to-treat.

blinded to treatment assignment. Patients were instructed not to use the study treatments in the presence of the acne assessor.

Statistical analysis and patient populations

The following null hypothesis was tested, using a two-sided Mann–Whitney *U*-test for superiority: the two samples of patients treated with BPO + CLN and AzA have the same distributions for the primary endpoint. Sample size was calculated as follows: 110 patients required per treatment to detect a 12.5% difference between treatment groups based on two-sided significance level of $\alpha = 5\%$, a power of 80%, standard deviation (SD) = 32, using a Mann–Whitney *U*-test. Descriptive statistics were reported for all endpoints and all inductive statistical analyses on secondary endpoints were introduced post hoc and were exploratory in nature and non-confirmatory. The intent-to-treat (ITT) population was defined as all patients randomized and receiving ≥ 1 dose of study medication and was used in safety analysis. The modified ITT (mITT) population was defined as all patients in the ITT set and having a baseline inflammatory lesion count and ≥ 1 post-baseline inflammatory lesion count and was used for all efficacy analyses.

All available data were included in the analyses and summarized as the data permitted. All withdrawals, along with the reasons, were recorded. For first step ‘observed cases analysis’, missing data were not replaced, but were treated as ‘missing’ for all endpoints. Analyses using imputation strategies to handle

missing data were also performed. For the primary endpoint, patients without data on inflammatory lesions at Week 4 had missing data imputed using the last available value before Week 4 or if data on inflammatory lesions were available after Week 4 only, missing data were imputed using linear interpolation between the baseline value and the first value after Week 4. For secondary endpoints, the last observation carried a forward (LOCF) approach that was used to impute data from the last available assessment in cases of early study withdrawal. If no post-baseline assessment was available, the missing LOCF data were imputed from the baseline value. In case of patient withdrawal, where informed patient consent was not withdrawn, patients were to attend the Early Withdrawal Visit and these data were included in Week 12 analysis.

Results

Study population and patient disposition

Of the 222 patients enrolled, between 21 February 2014 and 2 June 2014, 221 were randomized (111 in the BPO + CLN group and 110 in the AzA group), 217 included in the ITT population and 215 in the mITT population. The drop-out rate was low, with only 15 out of 221 (6.8%) patients leaving the study post-randomization. Patient disposition and the reasons for withdrawal are shown in Fig. 1. Patient demographics and baseline characteristics were similar between the treatment groups and are shown in Table 1.

Treatment adherence was higher in the BPO + CLN than the AzA treatment group, with 48.1% and 34.9% of patients, respectively, stating that they had not missed any treatment applications.

Efficacy

Inflammatory lesions at Week 4 (primary endpoint) At Week 4, BPO + CLN treatment resulted in a median percentage change in inflammatory lesion counts from baseline of

Table 1 Baseline demographics and characteristics

ITT population	BPO + CLN <i>n</i> = 108	AzA <i>n</i> = 109	Total <i>n</i> = 217
Age (years)			
Mean (SD)	20.1 (7.1)	20.0 (6.9)	20.1 (7.0)
Gender, <i>n</i> (%)			
Male	47 (43.5)	51 (46.8)	98 (45.2)
mITT population	<i>n</i> = 107	<i>n</i> = 108	
Lesions, mean (SD)			
Total	79.8 (31.9)	84.0 (32.2)	-
Inflammatory	27.2 (10.1)	26.7 (8.8)	-
Non-inflammatory	52.6 (28.5)	57.2 (29.5)	-
Median			
Total	69.0	78.0	-
Inflammatory	23.0	24.0	-
Non-inflammatory	46.0	52.0	-

AzA, azelaic acid; BPO, benzoyl peroxide; CLN, clindamycin; ITT, intent-to-treat; mITT, modified ITT; SD, standard deviation.

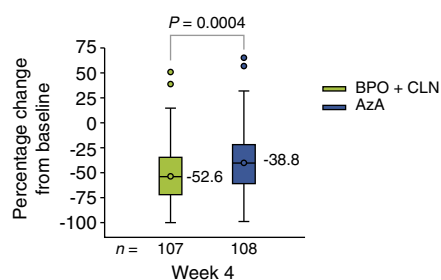


Figure 2 Percentage change in inflammatory lesions from baseline at Week 4 (LOCF) (mITT population). Box and whisker plots summarize data as follows: a box extends from the 1st to the 3rd quartile and the median is displayed inside this box by a white horizontal line. Above the box a vertical line (whisker) indicates the region from the 3rd quartile to the maximum value below the upper fence, and below the box a vertical line indicates the region from the 1st quartile to the minimum value above the lower fence. The upper fence lies 1.5 interquartile-ranges above the 3rd quartile; the lower fence lies 1.5 interquartile-ranges below the 1st quartile. Values outside these fences are displayed by a distinct marker. Mean data are represented by a circle. Data were analyzed by the two-sided Mann–Whitney *U*-test for independent samples. AzA, azelaic acid; BPO, benzoyl peroxide; CLN, clindamycin; LOCF, last observation carried forward; mITT, modified intent-to-treat.

–52.6% vs. AzA, –38.8% (mITT population). The difference between the two treatment groups was statistically significant ($P = 0.0004$; Fig. 2). Therefore, the study met the primary endpoint, showing superiority in the efficacy of BPO + CLN vs. AzA.

Inflammatory, non-inflammatory and calculated total lesion counts The number of inflammatory, non-inflammatory and calculated total lesion counts demonstrated numerically greater reductions with BPO + CLN vs. AzA across all time points (mITT population) (Table 2). At Week 12 and at the LOCF, the median change in inflammatory lesion counts was –78.8% and –65.3% ($P < 0.0001$) with BPO + CLN and AzA, respectively. Similarly, non-inflammatory lesion counts at Week 4 were changed by –39.3% and –30.4% with BPO + CLN and AzA, respectively ($P = 0.0052$). At Week 12 and at the LOCF, lesions were changed by –68.8% with BPO + CLN and –51.0% (Week 12) and –48.8% (LOCF) with AzA ($P < 0.0001$ for the between group comparison at Week 12).

Table 2 Summary of inflammatory, non-inflammatory and total lesion counts over time (mITT population)

	BPO + CLN <i>n</i> = 107		AzA <i>n</i> = 108	
	Mean (SD)	Median	Mean (SD)	Median
Inflammatory lesions				
% change from baseline				
Week 2*	-37.3 (27.7)	-38.5	-24.2 (30.3)	-24.0
Week 4†	-52.2 (27.7)	-52.8	-38.1 (31.1)	-37.5
Week 8‡	-65.0 (26.3)	-71.4	-49.1 (30.9)	-51.8
Week 12§	-72.3 (25.0)	-78.8	-55.0 (29.8)	-65.3
LOCF	-72.3 (25.0)	-78.8	-55.0 (29.4)	-65.3
Non-inflammatory lesions				
% change from baseline				
Week 2*	-23.5 (25.3)	-25.5	-14.9 (23.4)	-16.1
Week 4†	-38.1 (27.8)	-39.3	-27.0 (28.2)	-30.4
Week 8‡	-48.5 (39.8)	-52.1	-35.5 (31.2)	-37.2
Week 12§	-60.6 (35.3)	-68.8	-42.1 (37.5)	-51.0
LOCF	-60.6 (35.3)	-68.8	-42.1 (37.0)	-48.8
Calculated total lesions				
% change from baseline				
Week 2*	-28.7 (22.3)	-30.0	-18.4 (20.3)	-17.3
Week 4†	-43.8 (23.3)	-45.5	-30.8 (23.0)	-30.6
Week 8‡	-55.2 (30.5)	-58.6	-40.1 (27.4)	-39.8
Week 12§	-64.6 (26.9)	-69.0	-46.1 (31.8)	-53.9
LOCF	-64.6 (26.9)	-69.0	-46.1 (31.3)	-53.9

AzA, azelaic acid; BPO, benzoyl peroxide; CLN, clindamycin; LOCF, last observation carried forward; mITT, modified intent-to-treat; SD, standard deviation.

*BPO + CLN, *n* = 105.

†BPO + CLN, *n* = 105; AzA, *n* = 107.

‡BPO + CLN, *n* = 104; AzA, *n* = 102.

§AzA, *n* = 104.

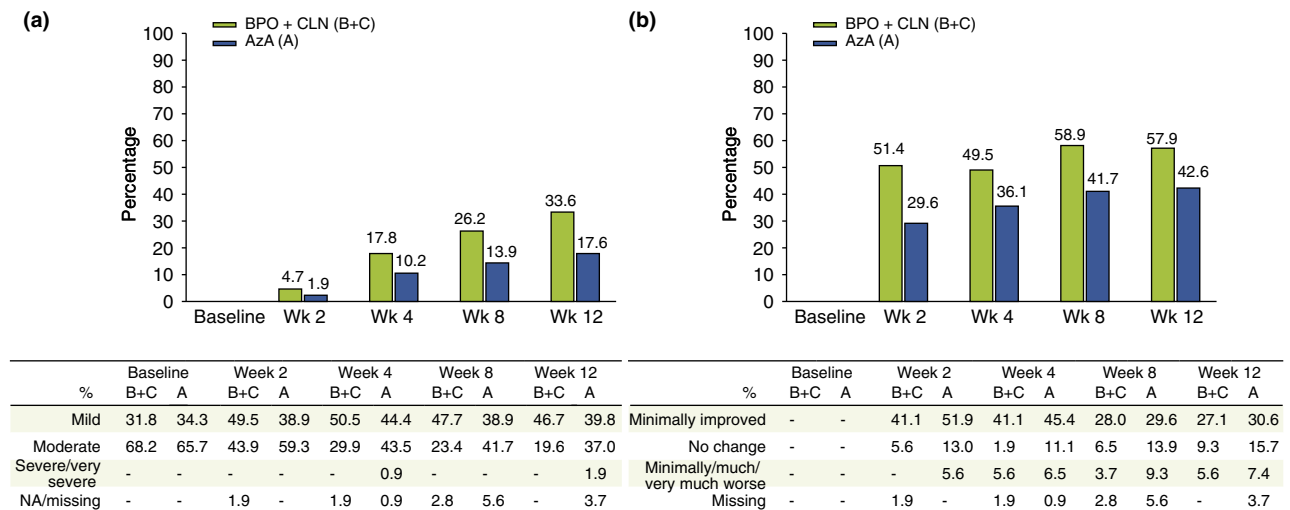


Figure 3 Summary of (a) ISGA 'clear'/'almost clear' and (b) SGCA 'very much improved'/'much improved' scores over time (mITT population). AzA or A, azelaic acid; B+C, benzoyl peroxide + clindamycin; BPO, benzoyl peroxide; CLN, clindamycin; ISGA, investigator's Static Global Assessment; mITT, modified intent-to-treat; NA, not applicable; SGCA, Subject Global Change Assessment.

Calculated total lesion counts at Week 4 were changed by -45.5% and -30.6% ($P < 0.0001$), and at Week 12 the LOCF by -69.0% and -53.9% ($P < 0.0001$) with BPO + CLN and AzA, respectively.

Speed of onset The mean (SD) time to a 50% reduction in calculated total lesion scores from baseline was lower with BPO + CLN: 46.3 (26.9) days vs. 51.3 (26.5) days with AzA. A higher proportion of patients achieved a 50% reduction in calculated total lesion count by Week 12 with BPO + CLN (85.0%) vs. AzA (55.6%; $P < 0.0001$).

ISGA and SGCA BPO + CLN continuously increased the proportion of patients (mITT population) with an ISGA rating of 'clear'/'almost clear' until Week 12. However, AzA treatment did not increase the proportion of patients with an ISGA rating of 'clear'/'almost clear' to the same extent (Fig. 3a). At baseline, no patients had an ISGA rating of 'clear'/'almost clear'. By Week 12, the proportion of patients with ratings of 'clear'/'almost clear' in the BPO + CLN and AzA groups increased to 33.7% and 17.6% ($P = 0.0080$), respectively (Fig. 3a). Patient assessment of disease severity by SGCA at Week 12 revealed that ratings of 'very much improved'/'much improved' were given by 57.9% and 42.6% of patients with BPO + CLN and AzA, respectively (Fig. 3b).

Investigator and patient tolerability assessment Both investigator tolerability assessment of erythema, peeling and dryness and patient tolerability assessment of stinging/burning and pruritus demonstrated a low incidence of symptoms, with mainly

'none' or 'slight' reported for both treatments, throughout the course of the study (mITT population; Fig. 4a–e).

Quality of life A greater mean (SD) change in CDLQI score was reported at Week 12 (-67.4% [56.9] vs. -36.8% [74.8]) and the LOCF (-60.5% [70.6] vs. -36.8% [74.8]) with BPO + CLN vs. AzA, respectively (Fig. 5a). Similarly, greater improvements in DLQI scores were noted with BPO + CLN vs. AzA (Fig. 5b).

Safety In the BPO + CLN and AzA treatment groups, 57.4% and 69.7% of patients, respectively, reported AEs and 55.6% and 69.7% of patients, respectively, reported TEAEs (Table 3). Study treatment-related TEAEs were reported in 13.9% and 33.0% of patients with BPO + CLN and AzA treatment, respectively. Five patients experienced TESAEs [two in the BPO + CLN group (stress and brucellosis, $n = 1$; vulvar haematoma $n = 1$) and three in the AzA group (gastroenteritis, $n = 1$; urinary retention, $n = 1$; type 1 diabetes mellitus, $n = 1$)]. No TESAEs were deemed to be related to study drug administration and none led to study discontinuation. The most common TEAEs in $>2\%$ patients are shown in Table 3. Application site reactions were reported in 15.7% of patients (24 events in 17 patients) in the BPO + CLN group and 35.8% of patients (60 events in 39 patients) in the AzA group, including pruritus (7.4% vs. 22.9%), pain (6.5% vs. 20.2%), erythema (2.8% vs. 4.6%) and dryness (1.9% vs. 2.8%). Two patients withdrew from the study due to TEAEs, one treated with BPO + CLN (experiencing six TEAEs including application site erythema, dryness, pruritus and pain, and left and right eyelid oedema) and one with AzA (two TEAEs including application site pruritus and pain). No clinically

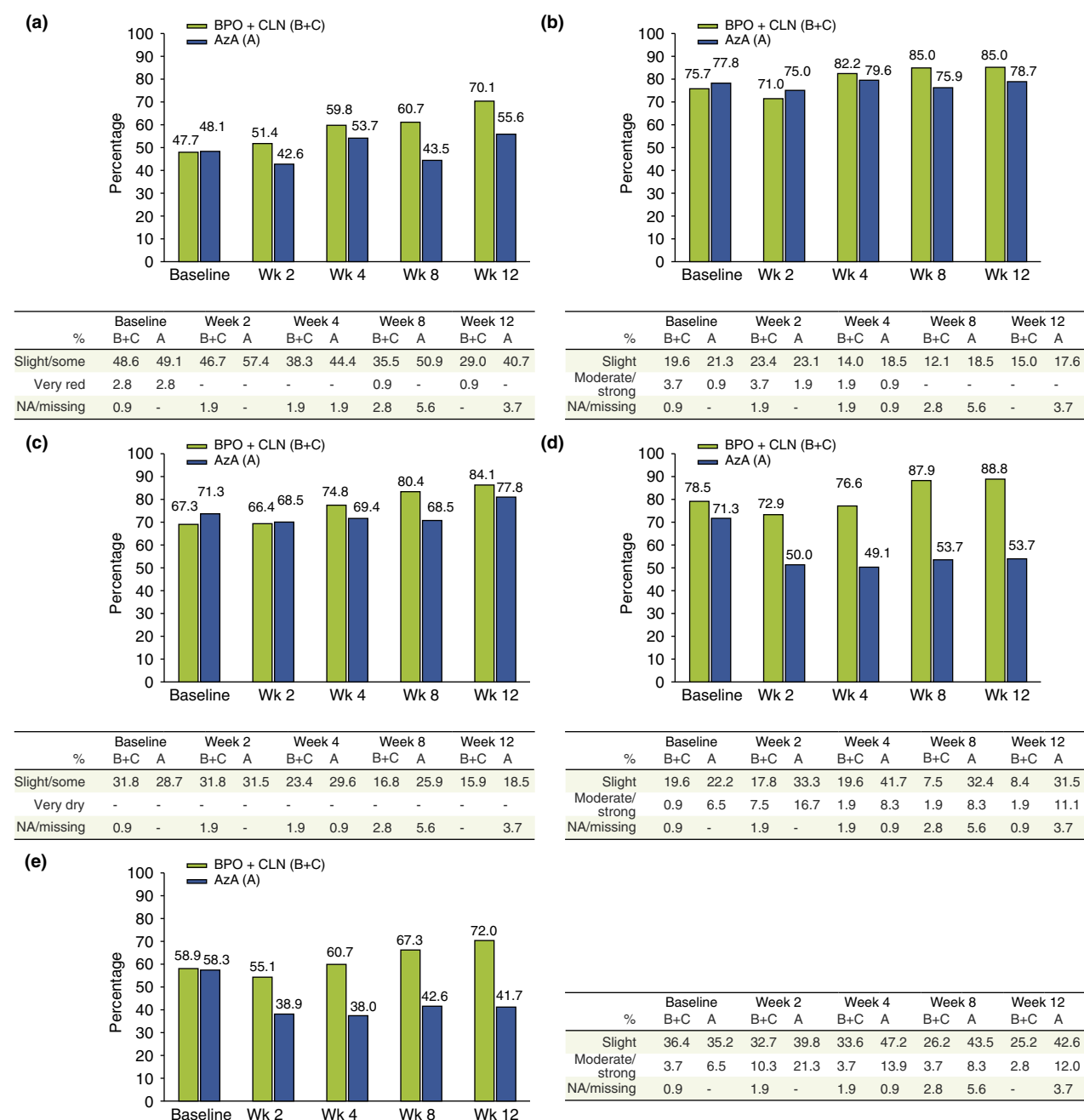


Figure 4 Summary of 'none' scores for (a) erythema, (b) peeling, (c) dryness, (d) stinging/burning and (e) pruritus over time (mITT). AzA or A, azelaic acid; B+C, benzoyl peroxide + clindamycin; BPO, benzoyl peroxide; CLN, clindamycin; mITT, modified intent-to-treat; NA, not applicable.

relevant changes in vital signs were observed in either treatment group.

Discussion

Results from this randomized, single-blind, parallel-group study demonstrate the greater efficacy of BPO + CLN over AzA in the

treatment of mild-to-moderate acne vulgaris, as evidenced by the statistically significant reduction in inflammatory lesion counts at Week 4 (primary endpoint). Further reductions in inflammatory lesion counts, in addition to non-inflammatory lesion counts and calculated total lesion counts were reported until Week 12, with a greater percentage reduction from baseline with

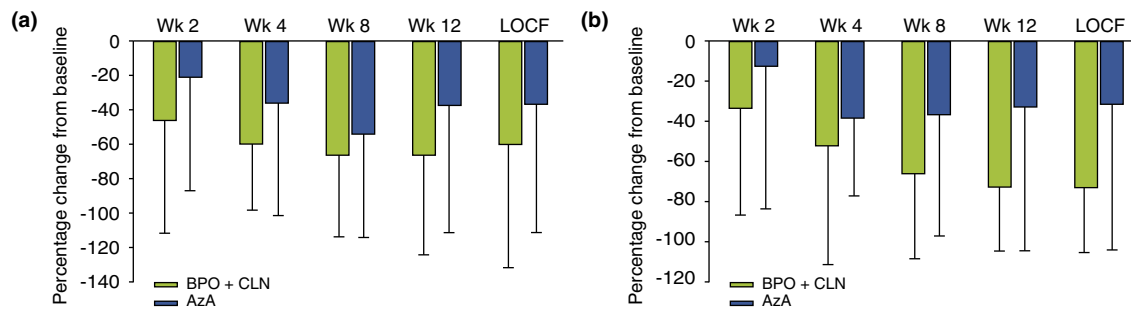


Figure 5 Summary of (a) CDLQI and (b) DLQI scores over time (mITT population). Data presented represent mean (SD). AzA, azelaic acid; BPO, benzoyl peroxide; CDLQI, Children's Dermatology Life Quality Index; CLN, clindamycin; DLQI, Dermatology Life Quality Index; LOCF, last observation carried forward; mITT, modified intent-to-treat; SD, standard deviation.

Table 3 Overview of AEs (ITT population)

	Number (%) of patients		
	BPO + CLN n = 108	AzA n = 109	Total n = 217
Any AEs	62 (57.4)	76 (69.7)	138 (63.6)
TEAEs	60 (55.6)	76 (69.7)	136 (62.7)
Treatment-related TEAEs	15 (13.9)	36 (33.0)	51 (23.5)
Any SAEs	2 (1.9)	3 (2.8)	5 (2.3)
TESAEs	2 (1.9)	3 (2.8)	5 (2.3)
Patient withdrawal due to TEAEs	1 (0.9)	1 (0.9)	2 (0.9)
Patient withdrawal due to TESAEs	-	-	-
TEAEs in ≥2% of patients			
Headache	16 (14.8)	18 (16.5)	34 (15.7)
Application site pruritus	8 (7.4)	25 (22.9)	33 (15.2)
Nasopharyngitis	10 (9.3)	20 (18.3)	30 (13.8)
Application site pain	7 (6.5)	22 (20.2)	29 (13.4)
Application site erythema	3 (2.8)	5 (4.6)	8 (3.7)
Application site dryness	2 (1.9)	3 (2.8)	5 (2.3)
Abdominal pain	4 (3.7)	1 (0.9)	5 (2.3)
Dysmenorrhoea	4 (3.7)	---	4 (1.8)

AE, adverse event; AzA, azelaic acid; BPO, benzoyl peroxide; CLN, clindamycin; ITT, intent-to-treat; SAE, serious AE; TEAE, treatment-emergent AE; TESAE, treatment-emergent SAE.

BPO + CLN vs. AzA treatment. The increased efficacy of BPO + CLN over AzA is further supported by the increased proportion of patients with ISGA ratings of 'clear'/'almost clear' and SGCA ratings of 'much improved'/'very much improved', with BPO + CLN vs. AzA treatment. Exploratory *P*-values of these secondary efficacy endpoints suggested that these differences were statistically significant at Week 12, although these were considered to be non-confirmatory. The increased efficacy of BPO + CLN over AzA may be due to the collective effects of the combination therapy in reducing inflammation, *P. acnes* and keratinization, three pathogenic factors of acne,⁴ whereas the main mechanism of action of AzA is to reduce *P. acnes* and keratinization.⁷

Non-adherence with dosing schedules may be a reason for treatment failure.^{12,13} Patient adherence with acne treatment decreases with increasing treatment time, therefore, an early onset of action may support treatment success. The greater mean reduction in the number of inflammatory lesions at the early study time point (Week 4) and the fewer days required to achieve a 50% reduction in calculated total lesion scores with BPO + CLN vs. AzA treatment may be important factors in the higher patient adherence with BPO + CLN. Additionally, the once-daily application of BPO + CLN compared with the twice-daily application of AzA may have contributed to fewer missed treatment applications in the BPO + CLN group. In other dermatological diseases such as psoriasis, treatment adherence has been reported to almost double (82.3% vs. 44.0%) with once-daily vs. twice-daily treatments.¹⁴

Acne has been demonstrated to impair QoL.¹⁰ The decrease in CDLQI and DLQI scores with both treatments throughout the duration of the study suggests that the treatment of acne not only improves clinical symptoms but also the QoL of patients.

Azelaic acid is perceived to be well tolerated, whereas BPO may cause skin irritation,^{8,9} although lower concentrations demonstrate a trend towards better tolerability.³ However, the combination of BPO 5% + CLN 1% has been found to be well tolerated,^{6,15,16} as has the combination of BPO 3% + CLN 1%⁵; the tolerability results for BPO + CLN in the current study support these findings. Furthermore, the comparable tolerability ratings given by physicians and patients to BPO + CLN and AzA treatment suggest that in the current study BPO + CLN is as well tolerated as AzA. In addition, BPO + CLN was associated with a lower incidence of TEAEs, treatment-related TEAEs and application site reactions than AzA, in accordance with previous trials^{6,15,16}; these factors may have also influenced treatment adherence.

The main limitation of this study was that it was single-blinded, so patients were aware of treatment assignment. Another limitation was that BPO + CLN and AzA have different application frequencies, being applied once- and twice-daily,

respectively. This may have influenced treatment adherence and consequently efficacy. However, these application frequencies are in line with the product label.^{4,7}

In summary, BPO + CLN demonstrated improved efficacy over AzA in the treatment of mild-to-moderate acne vulgaris. Patients reported decreased disease severity, improvements in QoL with treatment with BPO + CLN vs. AzA. Both therapies were rated as having a positive tolerability profile by physicians and patients, and fewer AEs and application site reactions were reported with BPO + CLN compared with AzA. These results suggest that BPO + CLN is an effective therapy in the treatment of mild-to-moderate acne vulgaris.

Authorship contributions

MSch contributed to the study concept and design and was involved in data acquisition, analysis and interpretation. MSeb participated in data acquisition, analysis and interpretation. DS, MH and CR contributed to the study concept and design, and analysis and interpretation. All authors were involved in the preparation and review of the manuscript and approved the final version to be submitted.

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Appendix: Summary of efficacy endpoint rating scales

Endpoint	Scale
ISGA	0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe and 5 = very severe
SGCA	0 = very much improved, 1 = much improved, 2 = minimally improved, 3 = no change, 4 = minimally worse, 5 = much worse, 6 = very much worse
Tolerability: burning/stinging and pruritus	0 = none, 1 = slight, 2 = moderate, 3 = strong
Tolerability: erythema, dryness and peeling	0 = none, 1 = slight, 2 = moderate, 3 = strong
CDLQI	0 = not at all, 1 = a little, 2 = a lot, 3 = very much
DLQI	

CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; ISGA, investigator's Static Global Assessment; SGCA, Subject Global Change Assessment.