ORIGINAL ARTICLE

Tolerance and Efficacy of a Combined Prebiotic and Postbiotic-Based Moisturizer as a Complementary Treatment in Patients with Predominance Phototype IV Diagnosed with Mild to Moderate Acne

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Abstract: Acne is a common skin disorder that has the potential to cause physical scarring and significantly impact the quality of life (QOL). This observational study aims to evaluate the efficacy and tolerance of combined prebiotic and postbiotic- based moisturizer, either alone or as a complement to topical and systemic treatments, in patients with mild to moderate acne. Patients aged 14 years and above, with mild to moderate acne based on a validated Global Evaluation Acne (GEA) score of I to III, received Effaclar Duo (+) for a duration of 60 days. The evaluation of its efficacy, targeting both types of lesions (20.5% retentional, 28.3% inflammatory, 51.2% mixed), and preventing colored marks, was assessed using GEA score, observed seborrhea level, skin-colored marks, Cardiff Acne Disability Index (CADI) scores, and clinical examinations at day 0 (D0) and day 60 (D60). Demographic data, acne onset duration, and skin phototype of patients were collected at D0. Additionally, both patients and assessing dermatologists completed self-administered questionnaires to assess tolerance and acceptability at D60. In this study, a total of 268 patients from the local cohort, with a mean age of 24.4 ±7.8 years, GEA scores ranging from I to III, and 51% of the patients with skin phototype IV, were recruited. The results showed a statistically significant ($p < 0.0001$) improvement of the GEA Grade in 48% of the patients at D60. A significant reduction ($p < 0.0001$) of up to 47% in seborrhea level was observed at D60. Significant improvement in erythematous marks ($p < 0.0001$) and pigmentary marks ($p < 0.0001$), seen in 44% and 42% of patients, respectively. Furthermore, there was a significant ($p < 0.0001$) improvement in the QOL among patients, with 27.5% reduction in CADI score. In conclusion, Effaclar Duo (+), which contains Aqua Posae Filiformis, was proven to reduce acne severity, skin post-inflammatory erythema and pigmentation, and skin seborrhea, thereby enhancing the QOL for local patients with mild to moderate acne.

Keywords: Acne, Effaclar duo (+), Prebiotic Moisturizer

Introduction

Acne is a common, chronic inflammatory skin disorder of the pilosebaceous unit. Its established pathophysiology involves abnormal-ities such as hyperseborrhea, follicular keratin-ization, proliferation of *Propionibacterium acnes* or *Cutibacterium acnes*, and inflammation. Clinically, acne is characterized by seborrhea, noninflammatory, and inflammatory lesions. Alterations in the sebaceous lipid profile, particularly during puberty, stress, irritation, cosmetic use, and potential dietary factors, trigger skin inflammation and the formation of different types of acne lesions [1]. Genetic factors significantly influence the proportion of branched fatty acids found in sebum, with heritability estimates ranging from 50% to 90%.

The pathogenesis of acne also involves the interaction of several host factors, including the stimulation of sebaceous glands by circulating androgens and dysbiosis of the pilosebaceous follicle microbiome. Dysbiosis is a process leading to a disturbed skin barrier and disequ-ilibrium of the cutaneous microbiome [2]. The pro-inflammatory activity of the cutaneous microbiome could result in the proliferation of *P. acnes* strains [3].

Effaclar Duo (+) moisturizing cream contains a unique thermal fragmented bacterial extract (postbiotic) resulting from the prebiotic Aqua Posae Filiformis (APF). The prebiotic APF is derived from the boosted probiotic *Vitreoscilla Filiformis* bacterium in a medium enriched with thermal spring water [4,5]. Aqua Posae Filiformis helps rebalance the skin microbiome and strengthen the skin barrier, ultimately improving acne-prone skin. The cutaneous microbiota on the surface of acne-prone skin is characterized by the overexpression of *Staphylococcus*, which in excess triggers inflammatory cascades, resulting in inflamed skin. Aqua Posae Filiformis's action on the skin microbiome favors the growth of commensal bacteria, reduces the abundance of *Staphylococcus*, and increases the synthesis of antimicrobial peptides (AMP) in the skin. An increased skin innate system, AMP, strengthens the skin barrier through inflammatory regulation.

Acne is commonly associated with seborrhea, with hormonally responsive sebaceous glands abundant on the face, neck, chest, upper back, and upper arm areas. Inflammatory acne presents with erythematous lesions, such as papules, pustules, or nodules. Resolving acne lesions may manifest with post-inflammatory hyperpigmentation, more common in individuals with darker skin (phototypes IV to VI). Management of acne aims to resolve active lesions and prevent new ones, requiring at least 2 to 3 months of treatment compliance for complete resolution. An effective treatment response should involve a noticeable reduction in active lesions rather than complete clearance, along with a reduction in seborrhea and post-inflammatory signs (erythema, pigmentation).

Effaclar Duo (+) is prescribed as part of the treatment protocol in inflammatory acne and can be used alone in retentional non-inflammatory acne. It also contains glycerin (humectant moisturizer). To date, there is a lack of clinical data on the efficacy and tolerability of Effaclar Duo (+) in our local cohort. This study aims to evaluate the tolerance and efficacy of Effaclar Duo (+) as a complement to topical treatment, associated with systemic treatment (except isotretinoin), or used alone in patients with mild to moderate acne in a Malaysian cohort.

Methodology

Study Design and Patients

This observational, prospective cross-sectional, open label study analysed 268 patients **(Figure 1)**. The study was conducted with institutional ethical approval (REC12/2021;MR/1051) from Univer-siti Teknologi MARA (UiTM). The patients were recruited using universal sampling. Informed consent was obtained from the patient or their parent/guardian if the patient is under 18 years old before the study commenced. The inclusion criteria were individuals aged 14 years or above,

diagnosed with mild to moderate acne based on validated Global Evaluation Acne (GEA) scoring system **(Table 1)**, ranged from 1 to 3 (hardly any lesions to moderate), prescribed with topical or systemic acne treatment, or both, or otherwise prescribed with Effaclar Duo (+) alone. The appropriate existing treatments before patient study enrolment will be continued with the addition of Effaclar Duo (+). Acne-treatment-naive patients at study enrolment will be given either Effaclar Duo (+) alone or with other appropriate treatment according to standard practice. Patients undergoing isotretinoin treatment and those treated with isotretinoin in the past three months were excluded from the study.

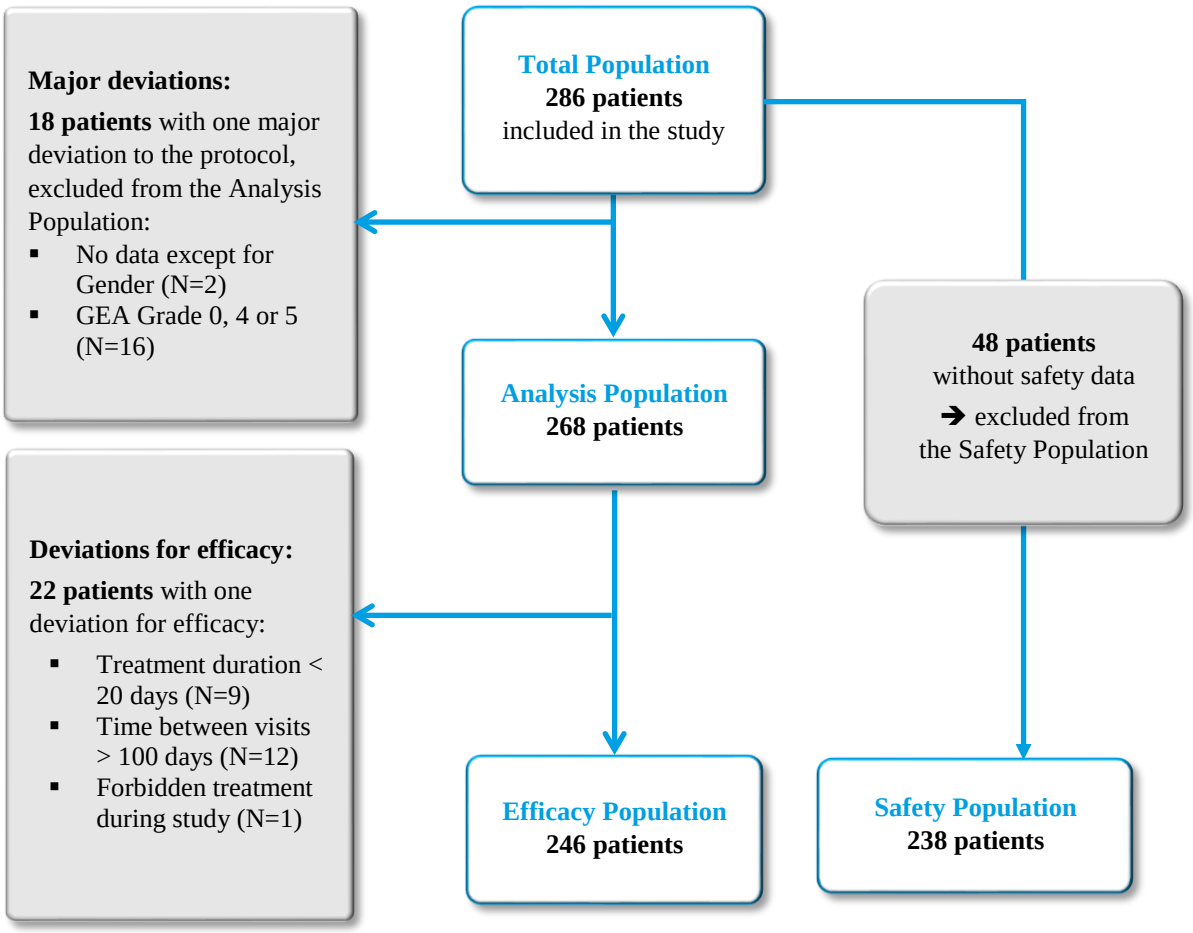

Figure 1 Number of patients and deviations.

Study Protocol

All patients enrol in the study were given a combined prebiotic and postbiotic-based moisturizer (CPPM) cream of which trade name, Effaclar duo (+). They were prescribed to apply the cream twice a day for 60 days on the affected area on the face or other body area (if necessary). Patient was advised to used sunscreen daily during study period. The evaluation of tolerance and efficacy of Effaclar Duo (+), targeting both inflammatory and retentional types of lesions, and preventing colored marks, was assessed at inclusion (D0) and on the evaluation day (D60) using various outcome parameters. These parameters included acne severity (evaluated

Table 1 Global Evaluation Acne (GEA) scoring system.

Description	Score
No lesions, residual pigmentation may exist.	0
Hardly any lesion, rare dispersed open or closed comedones and rare papule.	1
Mild, easily identifiable: less than of the face is affected, some open or closed comedones and some papulo-pustules.	2
Moderate, more than half of the face is affected, numerous papulo-pustules, numerous open or close comedones, one nodule may exist.	3
Severe, the whole face is affected, covered with numerous papulo-pustules, open or closed comedones and rare nodules.	4
Very severe, very inflammatory acne covering the whole face with nodules.	5

using the GEA scoring system), the level of seborrhea (on a scale from 0 indicating absence to 10 indicating high presence), skin-colored marks (both erythema and pigmentation on a scale from 1 to 10), and the Cardiff Acne Disability Index (CADI) obtained through questionnaires to measure the patients' quality of life (QOL). The patient demographic profile, data on acne onset duration, and skin phototype were collected at D0, and a skin clinical examination was performed on both D0 and D60. Patients' compliance with the treatment was assessed using a study questionnaire at D60. Tolerance to the investigational product (IP) was evaluated by both the treating dermatologist and the patient through questionnaires, which were rated on a scale from low to excellent. Additionally, global satisfaction with the IP was assessed by both the dermatologist and the patient, ranging from very satisfied to very unsatisfied. Mean reduction rate for quantitative variables is calculated as (mean v0 - mean v1) /mean v0) *100. The response rate for qualitative variables was calculated as the percentage of patients with improvement. Response rate for tolerance is the percent of patients declaring the tolerance high or excellent.

Results

Demographic and Clinical Profile

A total of 268 patients were included in the study with female patients (76.4%) were predominance over male patients (23.6%). The mean age was 24.4±7.8 years old, ranged from 14 to 45 years old and 54.9% aged 24 years old and below. The mean duration acne from onset was 4.5±5.8 years and the mean age of acne onset was 20.3±7.3 years old. The Fitzpatrick skin type (FPT) distribution among cohort was 34.2 % with I-III, 51.3% with IV and 14.6% with phototype V. Majority (51.2%) were diagnosed with mixed type of acne followed by inflammatory (28.3%) and retentional acne (20.5%). Patient demographic and clinical data of the study is shown in **Table 2.**

Treatment of Acne

A total of 176 patients (71.5%) received Effaclar duo (+) cream as an adjunctive therapy to a topical or oral treatment while 70 patients (28.5%) received Effaclar duo (+) cream alone, as seen in **Figure 2**. The majority (58.9%) had already received at least one topical treatment, including topical retinoids (32.1%) and topical benzoyl peroxide (21.5%). Additionally, a few patients (2%) had received chemical peeling. At least one oral treatment was prescribed to 43.5% of the patients, with the majority receiving tetracycline/ doxycycline (39%), while some received other types of antibiotics (3.7%). Only a few (0.4%) received oral contraceptive pill. The mean duration of Effaclar duo (+) cream application among patients was 51.7±10.4 days, with 86.2% applying it twice a day to the face while the rest applied once per day, either in the morning

(10.2%) or at night (3.6%). Recommended concomitant daily sunscreen application was adhered in 88% of patients.

Table 2 Patients demographic and clinical profile (N=268).

Variable	Mean	Percentage (%)
Age (years)	24.4 ±7.8	
< 18		23.8
18-25		31.1
≥ 25		45.1
Gender		
Male		23.6
Female		76.4
Skin Phototype (Fitzpatrick)		
FPT I -III		34.2
FPT IV		51.3
FPT V		14.6
Acne duration (years)	4.5 ± 5.8	
Age of acne onset (years)	20.3 ±7.3	
Acne type		
Retentional		20.5
Inflammatory		28.3
Mixed		51.2

Clinical Efficacy Outcomes

For the severity of acne, of the 243 patients, at study enrolment or inclusion, 53.5% had mild acne severity (GEA 2), 37.4% had moderate (GEA 3) and 9.1% had hardly any active acne (GEA 1) at D0. However, only 190 patients completed GEA scoring at both visits and such numbers were analysed **(Figure 3)**. At D60, there was statistically significant ($p<0.0001$) improvement of the GEA Grade in 48% of the patients. The mean seborrhea score at D0 was 4.9±2.2. A significant ($p < 0.0001$) reduction of up to 46.9% in the seborrhea level was observed at D60, reaching a score of 2.5±2.1 **(Figure 4)**. At study enrolment, most (95%) patients reported presence of residual-coloured marks on their faces. At D60, a significant reduction ($p=0.0008$) changes of residual-coloured marks on the face, either pigmented or erythematous or both, were observed with 11.4% reported no coloured marks compared to 5.0% at inclusion. Significant improvement and disappearance ($p < 0.0001$) of erythematous and pigmentary marks were seen in 43.5% and 42.0% of patients respectively as seen in **Figure 5** and **Figure 6**.

Quality of Life Outcomes

Analysis of 201 patients showed a significant improvement ($p < 0.0001$) in QOL, with a 27.5% reduction in CADI score, from 5.9±3.2 at D0 to 4.2±3.0 at D60. The percentage of patients expressing non-concern or not at all, not bothered or not a problem for questions in CADI questionnaires increased at D60 compared to D0 **(Table 3)**, as follows: aggressive, frustrated, embarrassed (19.4% to 30.3%); social life impaired (37.8% to 49.8%); avoiding public changing facilities or swimsuit (60.6% to 67.9%); feelings about the appearance of the skin (11.4%to 24.4%); and perception of acne (8% to 15.4%).

Global Satisfaction and Tolerance (Safety) Assessment

The majority of dermatologists (77%, N= 193) and patients (77%, N=183), reported being very satisfied or satisfied with the efficacy of Effaclar Duo (+) cream. In terms of tolerance, 54% (N= 232) of dermatologists and 50% (N=222) of patients reported high to excellent levels.

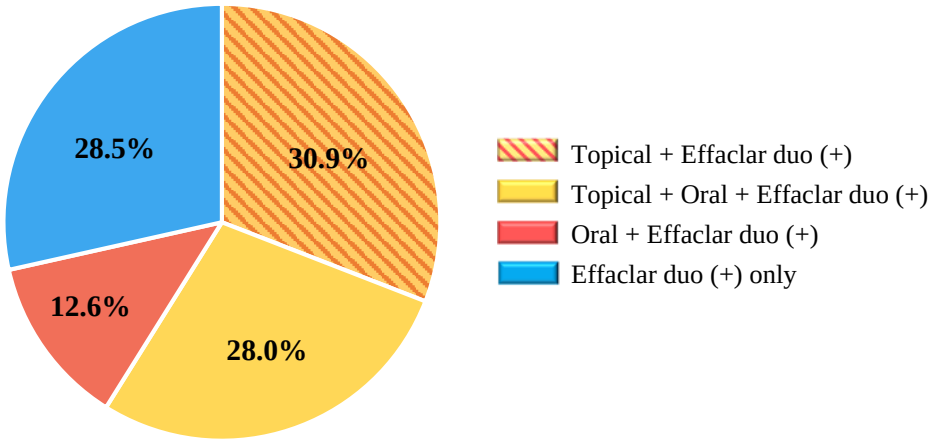

Figure 2 Summary of acne treatments received by patients (N=246).

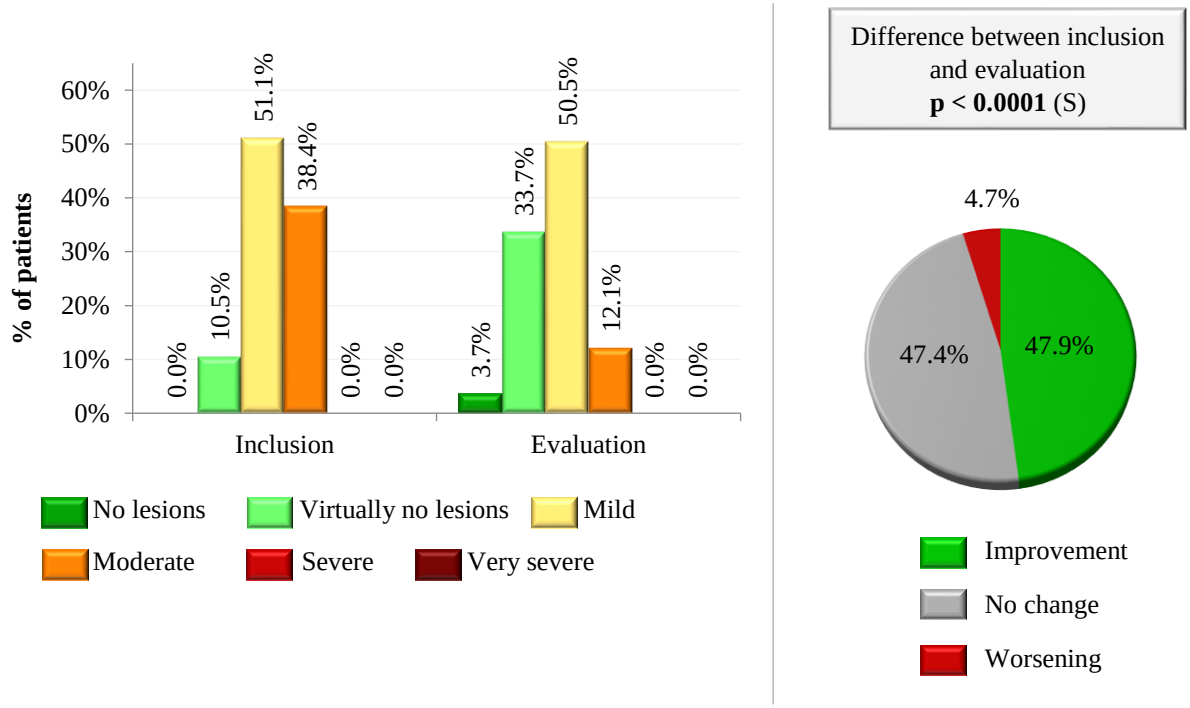

Figure 3 Severity of acne by GEA Score at inclusion (D0) and evaluation (D60); 0-No lesion; 1- Virtually no lesions; 2- Mild; 3- Moderate; 4-Severe; 5- Very severe; N=246.

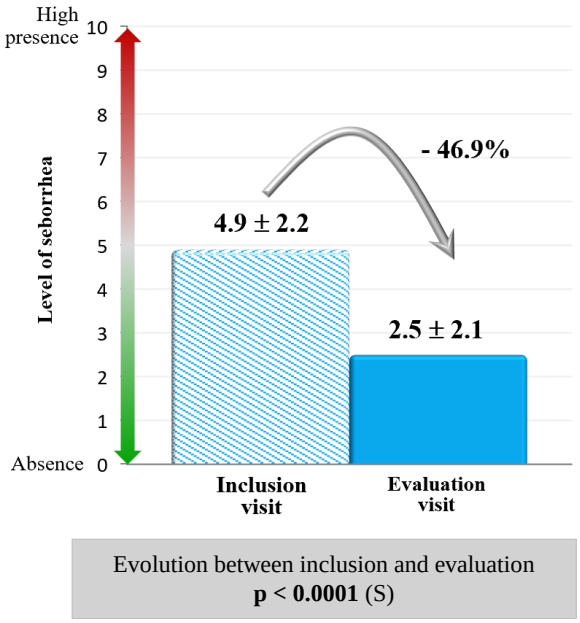

Figure 4 Levels of seborrhea at inclusion (D0) and evaluation(D60); N=246.

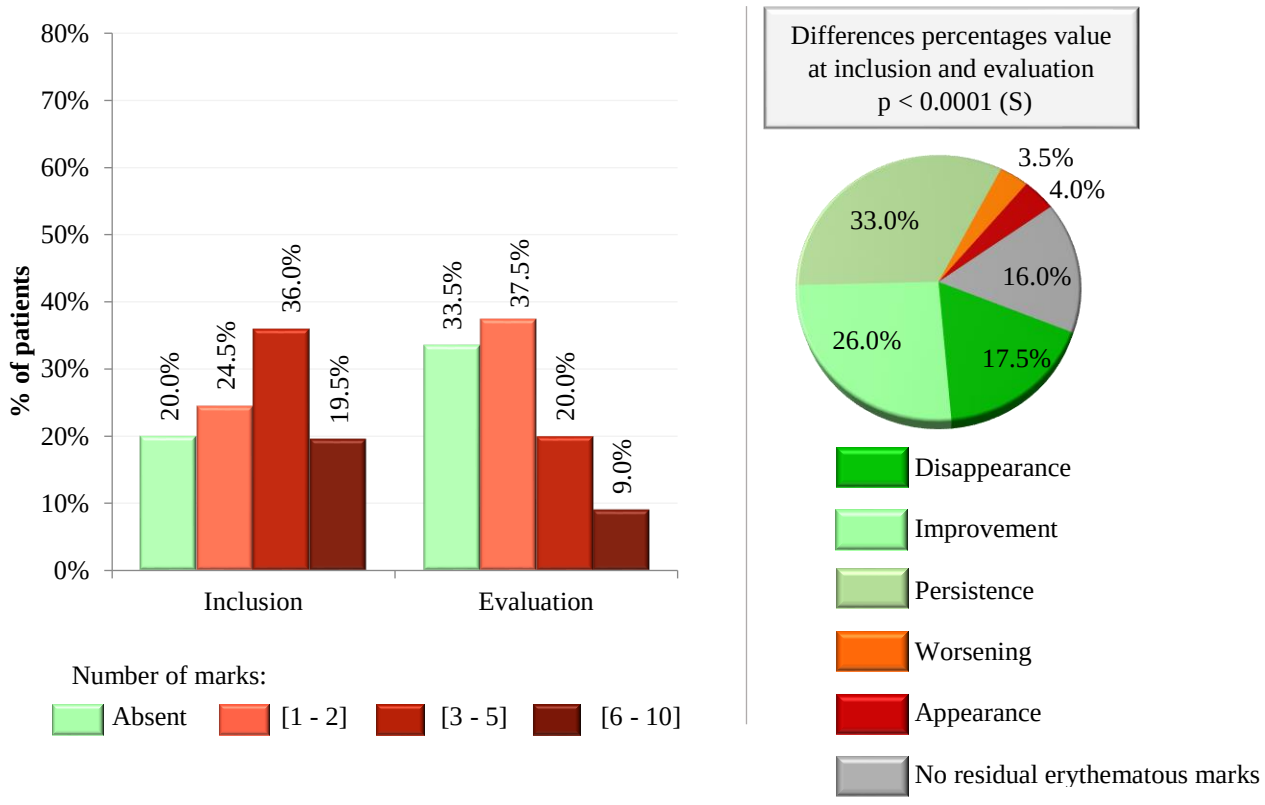

Figure 5 Erythematous marks assessment at inclusion (D0) and evaluation (D60); N=200.

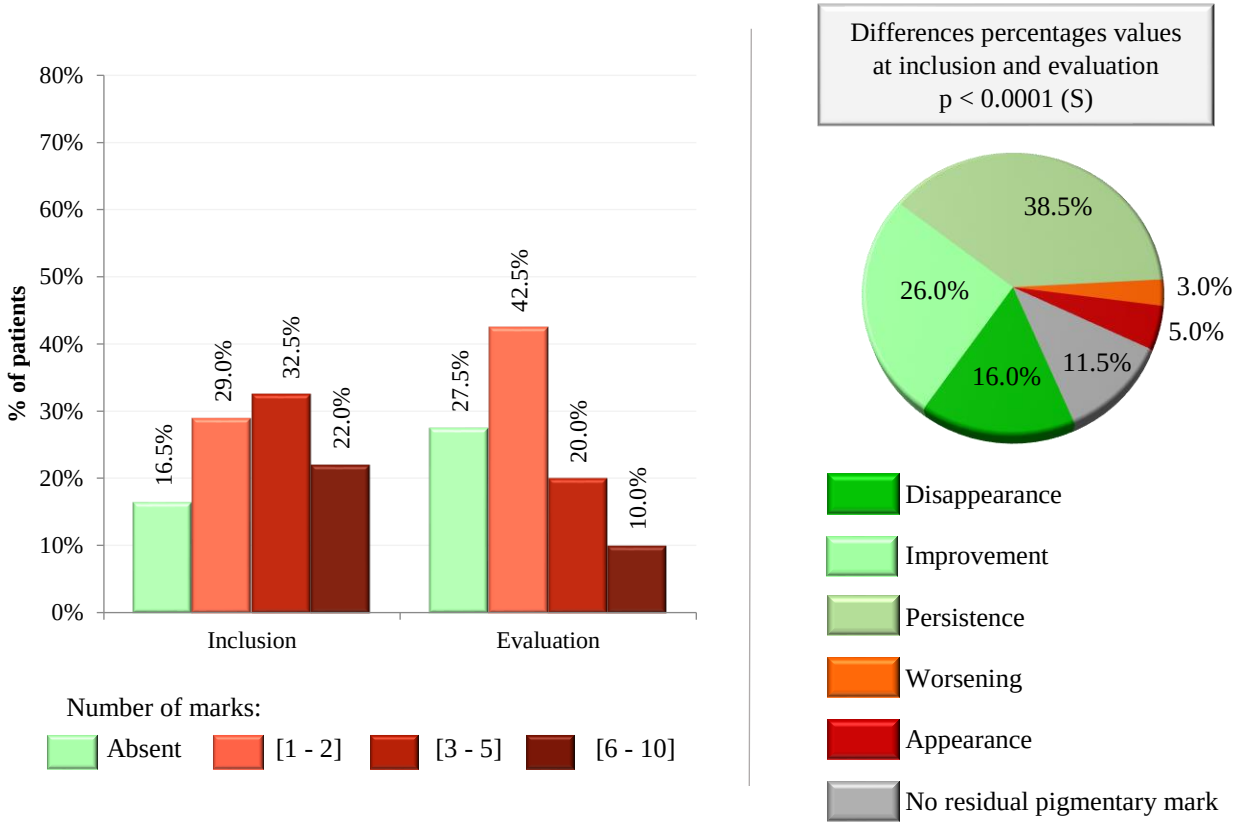

Figure 6 Pigmentary marks assessment at inclusion (D0) and evaluation(D60); N=200.

Table 3 CADI score

	Mean	Percentage (%)	
CADI score (N=201)			
D0	5.9 ± 3.2		
D60	4.2 ± 3.0		
CADI parameters		**Not at all/ Not bothered**	
		D0	**D60**
Aggressive, frustrated, embarrassed (N=201)		19.4	30.3
Social life impaired (N=201)		37.8	49.8
Avoiding public changing, facilities or swimsuit (N=193)		60.6	67.9
Feelings about the appearance of the skin (N=201)		11.4	24.4
Perception of acne (N=201)		8.0	15.4

Discussion

Acne is a chronic inflammatory disease of the pilosebaceous unit. It is divided into two categories, non-inflammatory (closed and opened comedone) and inflammatory (papule, pustule, cystic, nodule). A humid ASEAN country provides a challenge in treating patients with acne-prone skin. Despite the environment humidity, moisturizer application is still important in restoring natural skin barrier. Recent published data had shown the role of cutaneous microbiome

in the pathogenesis of acne [2,6]. Therefore, rebalancing the natural microbiome of the skin is essential in treating inflammatory skin disease. A topical moisturiser that maintains good skin barriers while correcting skin disequilibrium, which do not cause antibiotic resistance, and regulating quantity and quality of sebum, would be an ideal acne adjuvant treatment [6,7-10].

Generally, Asian skin is more prone to irritation to certain topical agents compared to other skin types, most notably, Caucasian skin [7,10]. Asian skin was reported to have an elevated neurosensory response to insults when compared to the skin of Caucasians. Asian skin has also been observed to be more prone to develop post-inflammatory hyperpigmentation, when inflamed or injured due to its relatively increased level of melanin pigmentation. Malaysia has diverse group of individuals, within multi-ethnicities, predominance of Malay ethnicity followed by the Chinese and Indian, resulted in the variability of skin FPT of which mostly ranging from Type III to V. It is unknown whether there are different in skin barrier strength, degree of maturation or degree of skin sensitivity within the different ethnic in Malaysia. Moreover, it is postulated that different subsets of Asian subjects may react differently to topical agents [11]. Despite the climate humidity, moisturising the skin is very essential to Asian skin. The results from this study showed that high tolerance to Effaclar duo (+) were observed, among patients with acne in Malaysia. Effaclar duo (+) with its non-greasy formulation provided the required moisturiser to patient of which help to overcome the side effects of dryness and stinging sensation associated with certain acne treatment such as topical retinoids and benzyl peroxide, thus improving compliance to treatment [12-17]. All patients had complied to minimum daily application, and none had applied more than twice a day.

Other than that, our study results demonstrate that Effaclar duo (+) significantly improved the GEA score and post-inflammatory hyperpigmentation among patients at D60. Similar results were found in a previous single-center, double-blind randomized trial in China, involving individuals with FPT phototype III to IV, which reported a significant reduction in inflammatory acne lesions in 58% of patient and a decrease in post-inflammatory hyperpigmentation by 42% [13]. However, the study conducted on 15 patients, utilized half-face comparisons (Effaclar Duo (+) versus placebo) and assessed outcomes through both clinical scoring and instrumental analysis during a similar study period.

The main bacterium involved in the pathogenesis of acne is *C. acnes* [1,18-19]. An increase in sebum creates an appropriate environment within the pilosebaceous unit for *C. acnes* proliferation. In this study, Effaclar Duo (+), which contains zinc pyrrolidone carboxylic acid (PCA) and niacinamide, has been found to significantly reduce seborrhea levels by up to 47%. This reduction eventually inhibits *C. acnes* proliferation, leading to an improvement in acne. Another noteworthy fact is that *Staphylococcus* is overexpressed on the surface of acne-prone skin [1-2,20-21]. The overexpression of *Staphylococcus* leads to the activation of keratinocyte toll-like receptors, which results in an increase in the production of cytokines and antimicrobial peptides, thus causing an increase in skin inflammation and worsening clinical signs of acne. Effaclar Duo (+) contains an active ingredient, Aqua Posae, in thermal spring water (APF). Aqua Posae is a derived lysate of the non-pathogenic *V. Filiformis* grown in La Roche-Posay thermal spring water [4-5,22-23]. *V. Filiformis* is killed by boiling and fragmented to prevent the risk of bacterial overproliferation, thus having postbiotic properties. The thermal spring water has a unique mineral and microbial composition (ranging from probiotic to prebiotic) and has been reported to significantly decrease *Staphylococcus* colonization in atopic patients with *S. aureus* overproliferation. Aqua Posae favors the growth of commensal bacteria and increases the synthesis of antimicrobial peptides

in the skin.

A significant improvement of 27.5% in the CADI score was reported in our study. This improvement may be attributed to improvement in both the GEA score and seborrhea score within the study cohort. The reduction of skin seborrhea played an important role in improving female QOL, with or without acne. A European study reported that female using regular skincare regime to reduce skin oiliness was able to improve the QOL by 24 % after 2 months of the treatment regime [12]. Seborrhea has been theorized to contribute to the progression of microcomedones into other types of acne lesions. Additionally, it provides a growth medium for *C. acnes*, allowing them to hydrolyze triglycerides in sebum, utilizing it as a nutrient source to produce free fatty acids and glycerol. Regulating both the quantity and quality of sebum presents a significant challenge in the treatment of acne.

Another factor that significantly affects QOL is acne recurrence. Dreno et al [24] reported that acne recurrence has caused 35.2% of subjects to express feelings of fatality. Hence, it is essential to optimize acne treatment, particularly in depressed-prone patients, with systemic and topical treatments. The treatments that ideally incorporate moisturizer regimens with added anti-inflammatory, skin barrier, and microbiota correction such as Effaclar duo (+) will bring benefits to the patients. Moreover, rebalancing the natural microbiome of the skin by restoring the natural skin barrier would eventually limit the proliferation of *P. acnes* on the skin [3,6,23]. Additionally, this study cream does not contain antibiotics, thereby reducing the risk of microbial resistance.

In conclusion, Effaclar Duo (+) cream demonstrated effectiveness and excellent tolerability as a standalone treatment or in combination with topical or systemic approaches for patients with mild to moderate acne in Malaysia. It successfully alleviated skin acne severity, post-inflammatory erythema, pigmentation, and hyper-seborrhea, ultimately improving the quality of life for patients with FPT phototype IV and mild to moderate acne within 60 days of application.

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