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ORIGINAL RESEARCH

A Randomized, Double-Blind, Placebo-Controlled, Multicentric Study to Evaluate the Efficacy and the Tolerability of a Class II Medical Device in the Treatment of Mild and Moderate Acne

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ABSTRACT

Introduction: Several options are available to treat acne lesions, including topical benzoyl peroxide, topical retinoids, topical antibiotics, oral antibiotics, hormonal therapy, isotretinoin, and procedural therapies, such as light and laser therapies, although these cause side effects. This study aimed to establish the efficacy and tolerability of a class IIa medical device containing lactic acid, azelaic acid/polyglyceryl-3 copolymer, azelamidopropyl dimethyl amine, and bifida ferment lysate for the treatment of mild and moderate acne lesions.

Methods: A randomized, double-blind, placebo-controlled, multicentric study was carried out in which 60 persons of both genders aged $\geq$ 16 years affected by mild or moderate acne were enrolled. Each person used the product twice daily for 2 months. The clinical score (classified as absent, mild, moderate, and severe) of lesions such as blackheads, whiteheads, papules and pustules, erythema, desquamation, sebum secretion, and porphyrins production by a wood lamp was evaluated on the basis of a dermatologist's visual assessment at baseline (t_0) and after 2 months of treatment (t_1), and the results were compared between groups. Digital photographic images were also taken.

Results: Sixty subjects concluded the trial. It was observed that subjects treated with the medical device (group I) showed overall improvement in the analyzed acne lesions compared with placebo (group II) after 2 months of treatment. The efficacy of the treatment was also expressed as partial and total clearance. The medical device produced higher percentages of both partial and total clearance in all analyzed parameters, compared with the placebo group. The study was safe and well tolerated.

Conclusions: It was observed that the participants showed an overall improvement of the analyzed lesions in comparison with the placebo group, without adverse events during the trial. Hence, the medical device was found to be safe and effective in the treatment of mild or moderate acne.

Keywords: Mild acne; Moderate acne; Lactic acid; Bifida ferment lysate; Azelaic acid/polyglyceryl-3 copolymer; Azelamidopropyl dimethyl amine

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Key Summary Points

Why carry out this study?

Several options are available to treat acne lesions, including topical benzoyl peroxide, topical retinoids, topical antibiotics, oral antibiotics, hormonal therapy, isotretinoin, and procedural therapies, such as light and laser therapies, although these cause side effects.

The study aimed to establish the efficacy and tolerability of a topical product containing lactic acid, azelaic acid/polyglyceryl-3 copolymer, azelamidopropyl dimethyl amine, and bifida ferment lysate for mild and moderate acne.

What was learned from the study?

In this randomized, double-blind, placebo-controlled, multicentric study, subjects affected by moderate and mild acne were educated to use the tested treatment twice daily for 2 months showing an overall reduction of acne lesions compared with the placebo group.

The results prove the efficacy of lactic acid, azelaic acid/polyglyceryl-3 copolymer, azelamidopropyl dimethyl amine, and gel-based bifida ferment lysate to treat mild and moderate acne. During the study, no side effects were highlighted.

INTRODUCTION

Acne, also known as *acne vulgaris*, is a skin disease that impacts the pilosebaceous units of the face, neck, back, and upper part of the chest [1]. It has been estimated that more than 85% of teenagers are affected by mild to moderate acne [2]; up to 8% have been reported with severe disease [3]. Previous studies reported that severe acne is more common in males than females [4]

It is characterized by blackheads or whiteheads (noninflammatory lesions), also known as comedones, papules, pustules (inflammatory lesions), and secretion of oily sebum by the skin (seborrhea), cysts, nodules, and possible scars [5]. The etiology of acne includes four main factors [6, 7]: (i) the obstruction of sebaceous follicles; (ii) follicular hyperkeratinization; (iii) androgen-induced excessive sebum production, and the resulting proliferation of *Cutibacterium acnes*; (iv) inflammation [9]

Demographics, genetics, hormones, bacterial infection, diet/lifestyle, stress, environmental factors, and the use of contraceptives represent possible risk factors for the development of acne [7]. According to the Comprehensive Acne Severity Scale (CASS), acne can be categorized into mild, moderate, and severe [8]

The choice of therapy (topical or systemic therapy, monotherapy, or combination therapy) depends on the severity of the clinical picture [8]

Suggested treatments include topical and systemic antibiotics, retinoids, vitamin A derivatives, azelaic acid, oral contraceptives, and spironolactone [9–13] The most common side effects of these therapies include dryness, redness, itchy skin, and sensitivity to sunlight [14]

Complementary therapies such as dermocosmetics, chemical peels, light devices, and lasers can provide further clinical effects in addition to conventional therapy [9] and with better tolerance and safety profiles [15]. In particular, α-hydroxy acids (AHAs), including lactic acid (LA), have been extensively used as superficial peeling agents to treat mild and moderate acne [16].

It has also been reported that the increase of skin pH in subjects with acne reflects a state of instability of the chronic stratum corneum, which can predispose the subjects to the recurrence of acne manifestations. Since skin pH can be seen as one of the pathological mechanisms of acne, it is important to maintain the acidity of the stratum corneum during therapy [17]. An acidic pH, moreover, can maintain the resident bacterial flora adhering to the epidermis, while increases in pH, linked for example to a cutaneous occlusion due to the accumulation of

sebum, promote its detachment [18]. In this context, the use of dermocosmetics containing actives able to act as pH modulators can be particularly useful.

In this study, we evaluated the effectiveness of a topically applied gel formulation for the treatment of mild and moderate acne. We carried out a randomized, double-blind, placebo-controlled, multicentric study in patients applying a class IIa medical device twice daily to assess the efficacy and tolerability of this medical device in subjects with mild or moderate acne lesions.

METHODS

Subjects

Sixty male and female subjects (average age 24.77 ± 4.50 years) affected by mild or moderate acne were enrolled in this randomized, double-blind, placebo-controlled, multicentric study. The study was performed in two dermatology clinics in Italy.

The main exclusion criteria included pregnancy and lactation, presence of dermatoses, subjects undergoing topical pharmacological treatment or surgery in the skin area involved in the study up to 3 months before study entry, subjects undergoing treatment with systemic corticosteroids, aspirin, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), and diuretics, and diabetes, endocrinological disorder, liver disease, heart or renal failure, and neoplastic diseases.

Compliance with Ethics

All patients were evaluated and enrolled in the study after signing informed consent. Parental consent was obtained in the case of children.

This study was approved by the Independent Multidisciplinary Ethics Committee at Derming S.r.l. (Milan, Italy) and followed the ethical standards of the Declaration of Helsinki of 1964.

Study Design

A baseline visit (t_0) and a final visit (t_1) after 2 months were planned by the dermatologists. Thirty subjects were randomly assigned to a treatment group (group I), receiving the class II medical device (Primak MED gel trattamento, Giuliani SpA, Milan, Italy), and 30 were randomly assigned to a placebo group (group II). The study was completed between March and September 2021.

All subjects were instructed to self-apply the product, twice daily, in the morning and the evening, to the acne lesions. Blackheads, whiteheads, papules and pustules, erythema, desquamation, and sebum secretion were evaluated on the basis of a dermatological visual assessment describing each lesion type with a clinical score (absent, mild, moderate, and severe). Digital photographs were taken at visits t_0 and t_1. The acne condition of each patient was evaluated according to Table 1.

Table 1 Description of clinical score for lesion assessment

Clinical score	Lesion type
Absent	No comedones
	No inflammatory lesions
	No noninflammatory lesions
Mild	Comedones < 20
	Inflammatory lesions < 15
	Total lesions ≤ 30
Moderate	Papules and pustules > 1
	Comedones 20–100
	Inflammatory lesions 15–50
	Total lesions 30–125
Severe	Nodules and scarring > 1
	Cysts > 5
	Comedones > 100
	Inflammatory lesions > 50
	Total lesions > 125

The medical device was formulated in the form of a gel containing an lactic acid (LA), bifida ferment lysate, and sebum-normalizing actives (azelaic acid/polyglyceryl-3 copolymer and azelamidopropyl dimethyl amine) as active ingredients; the placebo was formulated without the above-mentioned ingredients.

Efficacy Endpoints

The efficacy of the treatment was assessed as the percentage of subjects in each analyzed clinical score at the baseline visit (t_0) and the final visit (t_1).

Moreover, the efficacy of the tested treatment was also expressed in terms of partial clearance or total clearance at the end of treatment. The partial clearance was defined as the reduction of a clinical score from moderate/severe to mild after 2 months of treatments; the total clearance was defined as the resolution of acne lesions after 2 months of treatments. Photographic documentation for each subject was also collected.

Statistical Analysis

All participants included in the study will be randomized in the intention to treat (ITT) group. Statistical analysis was performed using Graph-Pad statistical software version 13.0 (La Jolla, CA, USA).

Categorical variables were presented as absolute numbers and percentages. Continuous variables were assessed for normality by the Shapiro–Wilk test and represented by mean and standard deviation.

The mean changes in lesion clearance between medical device- and placebo-treated groups were tested for significance with a paired Student's *t*-test or the nonparametric Wilcoxon signed-rank test as appropriate.

RESULTS

Sixty of the enrolled subjects (60%) completed the study (30 in group I and 30 in group II). Ten subjects were withdrawn before visit t_1. None of the subjects was terminated because of an adverse event. The demographics of the samples are presented in Table 2.

Table 2 Subject's characteristics at baseline. Thirty subjects were randomly assigned to group I, and 3 were randomly assigned to group II

	Group I (*N* = 30)	**Group II (*N* = 30)**
Women	16.00 (53.33%)	18.00 (60%)
Men	14.00 (46.66%)	12.00 (40%)
Age (years)	25.50 ± 5.05	24.03 ± 4.35
Acne diagnosis (age, years)	16.75 ± 2.98	16.44 ± 2.69

The number of women and men is reported as a percentage in parenthesis; the age of the subjects and the age of acne diagnosis is expressed as mean ± standard deviation (SD)

The results concerning the baseline and final dermatological examination of the two groups are reported in Table 3. The clinical score (classified as absent, mild, moderate, and severe) of acne lesions (blackheads, whiteheads, papules and pustules, erythema, desquamation, and sebum) was evaluated. Changes in porphyrin production were evaluated as absent, mild, moderate, and severe.

Decreases in average clinical lesions, erythema, desquamation, sebum, and porphyrin production were seen with both medical device and placebo treatment (Table 1). Comparing the two groups, at the end of the treatment, the subjects in group I achieved a complete resolution of moderate and severe scores for clinical lesions of acne and a general significant ($p < 0.05$) higher improvement in all endpoints analyzed (Table 1).

Figure 1 shows the partial and total clearance after 2 months of treatment for both treatments. Significantly more patients achieved a significant ($p < 0.05$) partial clearance in all analyzed endpoints at the end of the treatment with medical device compared with placebo (Fig. 1). Therefore, a significantly ($p < 0.05$) greater number of subjects treated with medical device reached a total clearance compared with placebo (Fig. 1).

Table 3 Dermatological examination at baseline (t_0) and after 2 months of treatment (t_1) of two groups

	Group I t_0 (N = 30)	Group II t_0 (N = 30)	Group I t_1 (N = 30)	Group II t_1 (N = 30)
Blackheads score				
Absent	3.00 (10%) ± 0.31	6.00 (20%) ± 0.41	15.00 (50%) ± 0.51	14.00 (46.67%) ± 0.51
Mild	12.00 (40%) ± 0.50	14.00 (46.67%) ± 0.51	15.00 (50%) ± 0.51	13.00 (43.33%) ± 0.50
Moderate	14.00 (46.66%) ± 0.51	10.00 (33.3%) ± 0.48	0.00 (0%) ± 0.00	3.00 (10%) ± 0.31
Severe	1.00 (3.33%) ± 0.18	0.00 (0%) ± 0.00	0.00 (0%) ± 0.00	0.00 (0%) ± 0.00
Whiteheads score				
Absent	0.00 (0%) ± 0.00	3.00 (10%) ± 0.31	20.00 (66.67%) ± 0.48	15.00 (50%) ± 0.51
Mild	21.00 (70%) ± 0.47	20.00 (66.67%) ± 0.48	10.00 (33.33%) ± 0.48	12.00 (40%) ± 0.50
Moderate	7.00 (23.33%) ± 0.43	4.00 (13.33) ± 0.35	0.00 (0%) ± 0.00	3.00 (10%) ± 0.31
Severe	2.00 (6.67%) ± 0.25	2.00 (6.67%) ± 0.25	0.00 (0%) ± 0.00	0.00 (0%) ± 0.00
Papules and pustules score				
Absent	4.00 (13.33%) ± 0.35	6.00 (20%) ± 0.41	20.00 (66.67%) ± 0.48	16.00 (53.33%) ± 0.51
Mild	13.00 (43.33%) ± 0.5	13.00 (43.33%) ± 0.50	10.00 (33.33%) ± 0.48	6.00 (20%) ± 0.41
Moderate	13.00 (43.33%) ± 0.5	11.00 (36.67%) ± 0.49	0.00 (0%) ± 0.00	7.00 (23.33%) ± 0.43
Severe	0.00 (0%) ± 0.00	0.00 (0%) ± 0.00	0.00 (0%) ± 0.00	1.00 (3.33%) ± 0.18
Erythema score				
Absent	6.00 (20%) ± 0.41	7.00 (23.33%) ± 0.44	24.00 (80%) ± 0.41	14.00 (46.67%) ± 0.51
Mild	23.00 (76.67%) ± 0.43	13.00 (43.33%) ± 0.51	6.00 (20%) ± 0.41	13.00 (43.33%) ± 0.50
Moderate	1.00 (3.33%) ± 0.18	9.00 (30%) ± 0.47	0.00 (0%) ± 0.00	3.00 (10%) ± 0.31
Severe	0.00 (0%) ± 0.00	0.00 (0%) ± 0.00	0.00 (0%) ± 0.00	0.00 (0%) ± 0.00
Desquamation score				
Absent	13.00 (43.33%) ± 0.50	10.00 (33.33%) ± 1.83	26.00 (86.67%) ± 0.35	22.00 (73.33%) ± 0.45
Mild	12.00 (40%) ± 0.50	14.00 (46.67%) ± 0.51	4.00 (13.33%) ± 0.35	7.00 (23.33%) ± 0.43
Moderate	5.00 (16.67%) ± 0.38	4.00 (13.33%) ± 0.35	0.00 (0%) ± 0.00	1.00 (3.33%) ± 0.18

Table 3 continued

	Group I t_0 (N = 30)	Group II t_0 (N = 30)	Group I t_1 (N = 30)	Group II t_1 (N = 30)
Severe	0.00 (0%) ± 0.00	1.00 (3.33%) ± 0.18	0.00 (0%) ± 0.00	0.00 (0%) ± 0.00
Sebum score				
Absent	2.00 (6.67%) ± 0.25	3.00 (10%) ± 0.31	18.00 (60%) ± 0.50	12.00 (40%) ± 0.50
Mild	12.00 (40%) ± 0.5	14.00 (46.67%) ± 0.51	11.00 (36.67%) ± 0.49	13.00 (43.33%) ± 0.50
Moderate	16.00 (53.33%) ± 0.51	13.00 (43.33%) ± 0.50	1.00 (3.33%) ± 0.18	5.00 (16.67%) ± 0.38
Severe	0.00 (0%) ± 0.00	0.00 (0%) ± 0.00	0.00 (0%) ± 0.00	0.00 (0%) ± 0.00
Porphyrin production				
Mild	22.00 (73.33%) ± 0.45	21.00 (70%) ± 0.47	8.00 (26.67%) ± 0.45	11.00 (36.67%) ± 0.49
Moderate	8.00 (26.67%) ± 0.45	7.00 (23.33%) ± 0.43	0.00 (0%) ± 0.00	3.00 (10%) ± 0.31
Absent	1.00 (3.33%) ± 0.18	2.00 (6.67%) ± 0.25	22.00 (73.33%) ± 0.45	16.00 (53.33) ± 0.51

Values in the table are presented as a subjects number with the percentage in parenthesis ± SD

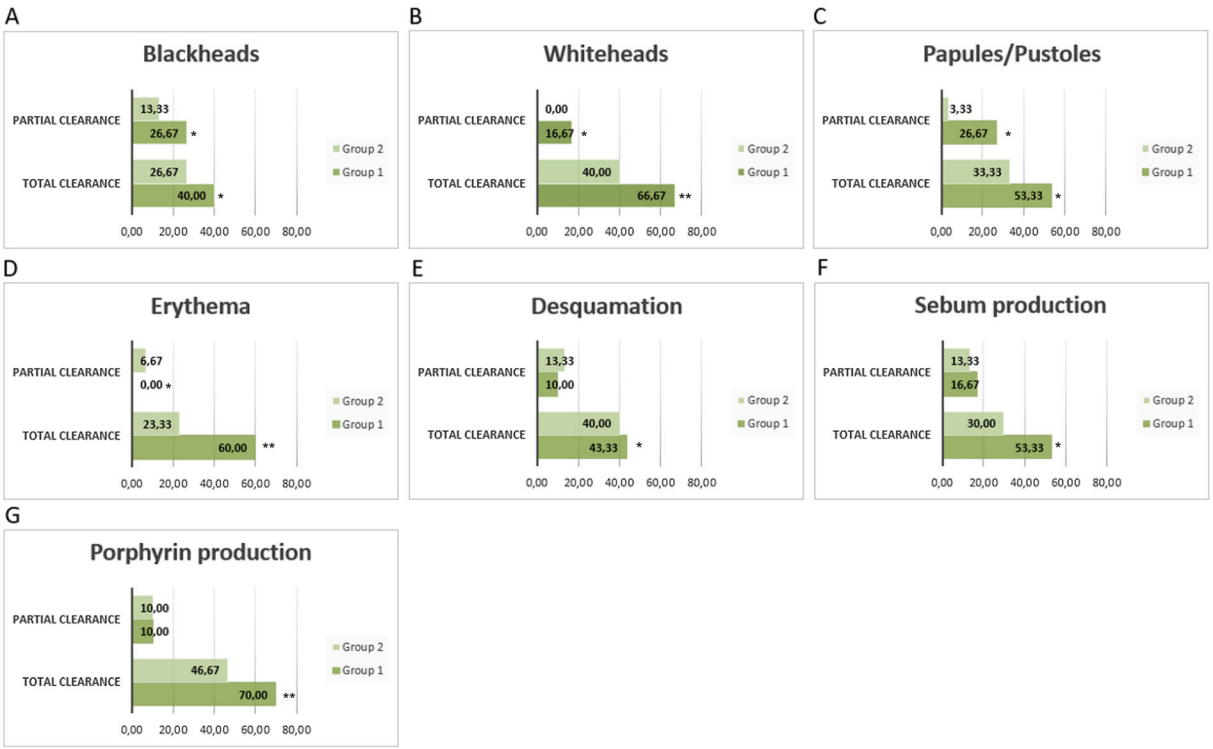

Fig. 1 Partial and total clearance of **A** blackheads, **B** whiteheads, **C** papules and pustules, **D** erythema, **E** desquamation, **F** sebum production, **G** porphyrin production, after 2 months of treatment ($t = 1$). Asterisks indicate a significant difference to the control ($^{*}p < 0.05$;$^{**}p < 0.01$)

The tested product was well tolerated; no adverse events were reported during the study. Some representative photograph images from one subject per group after tested treatment are shown in Fig. 2.

DISCUSSION

To date, several options are available to treat acne [9–13]. Adverse effects associated with the most common treatments [9] and the growing emergence of antibiotic resistance [18] pose the need for safer alternatives in the management of moderate and severe acne [19]

In the present study, subjects with mild or moderate acne, treated with a class II medical device containing as main ingredients lactic acid, azelaic acid/polyglyceryl-3 copolymer, azelamidopropyl dimethyl amine, and gel-based bifida ferment lysate, reported a higher significant improvement of clinical signs of acne, erythema, desquamation, and sebum and porphyrin production compared with subjects in the placebo group, after 2 months of treatment.

The class II medical device tested in the present study, contains LA, azelaic acid/polyglyceryl-3 copolymer, azelamidopropyl dimethyl amine, and bifida ferment lysate.

The obtained results are consistent with previous research. The effectiveness of AHA, including LA, on acne has been confirmed in numerous studies [20–22]. This could be explained by LA's ability to dissolve the intercellular desmosomes, promoting exfoliation, and its antimicrobial and anti-inflammatory properties [23].

Therefore, skin microbiota dysbiosis has been reported to play a crucial role in acne development [24–26], and its modulation could be important for clinical improvement. Recently, there has been a paradigm shift regarding skin microbiome and acne. Indeed, *C. acnes* is no longer considered the only

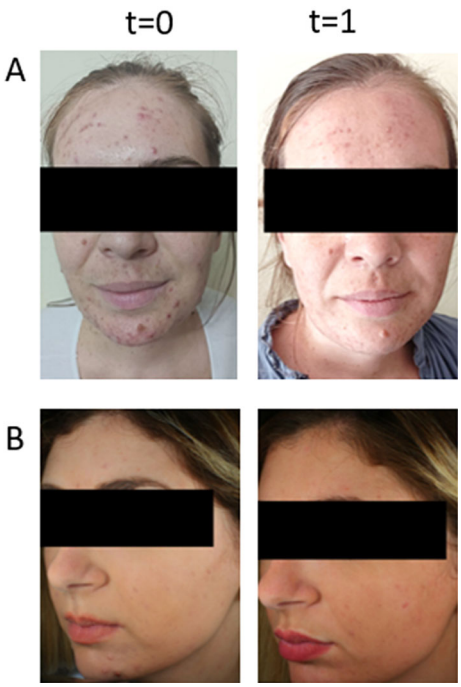

Fig. 2 Photographs from one enrolled subject in group I (**A**) and one in group II (**B**) at baseline ($t = 0$) and after 2 months of treatment ($t = 1$)

microorganism involved in acne development; other bacteria, mainly *Staphylococcus aureus* and *Staphylococcus epidermis*, are also involved [27]. As a consequence of microbial dysbiosis, several inflammatory molecules and chemotactic factors are released that initiate local inflammatory responses and keratinocyte hyperproliferation [28].

To address all the above-mentioned factors involved in acne development, conventional first-line therapy includes topical retinoids as well as anti-inflammatory and antibacterial agent. Among them, azelaic acid is widely used owing to its ability to target the major factors implicated in the pathogenesis of acne [29, 30]. A major issue related to the use of azelaic acid in topical formulations is its irritant potential on the skin; this side effect, which is generally temporary, may manifest itself as itching or tingling [31]. This poses the need for compositions that can deliver azelaic acid, while substantially reducing or eliminating the side effects [32, 33]. One example is that represented by polyglycerol-azelaic acid, a polyester obtained by reacting or condensing azelaic acid with polyglycerols that shows better tolerability compared with azelaic acid [34].

The constant state of subclinical inflammation also leads to changes in the pH of the skin surface, which, as a consequence, promotes the production of inflammatory cytokines by mycoplasma, supporting the vicious cycle of chronic inflammation [35]. Prakash et al. [17] showed that an increase in skin pH predisposes individuals to acne. Indeed, an acidic pH can maintain the resident bacterial flora adhered to the epidermis. The increase in pH, linked to a skin occlusion due to, for example, sebum accumulation, promotes microbial detachment, leading to dysbiosis [36].

Scientists are constantly looking for new solutions that bring good results when it comes to the treatment of acne, including the management of microbial dysbiosis. In this context, the use of internal supplementation and cosmetics with probiotics, prebiotics, postbiotics, and novel microbiome-based ingredients is acquiring importance, and clinical efficacy has been proven [37–39]

In line with these findings, the medical device under study contains a lysate from bifida (bifida ferment lysate) that can regulate bacterial flora modulating the reduction of skin pH [40].

It also contains azelamidopropyl dimethyl amine, a patented active ingredient that imparts outstanding antibacterial properties to help restore the homeostasis of acne-prone skin inhibiting *C. acnes* proliferation, mediating bacteria-induced skin inflammation and controlling facial sebum excretion [41].

Over 8 weeks, treatment with the medical device (Primak MED), led to a higher significant ($p < 0.05$) decrease in the number of total acne lesions in subjects with mild to moderate facial acne, compared with placebo. Subjects showed an average 53% total clearance in acne lesion counts, 60% total clearance in erythema, 43% in desquamation, 53% in sebum production, and 70% total clearance in porphyrin production. The class IIa medical device was well tolerated in the facial area, and no adverse events were reported.

CONCLUSION

The results of this study indicate that the topic application of the class IIa medical device containing lactic acid, azelaic acid/polyglyceryl-3 copolymer, azelamidopropyl dimethyl amine, and bifida ferment lysate, for 2 months, twice daily, in subjects affected by mild or moderate acne is safe and effective. Moreover, the participants showed an overall improvement of the analyzed parameters in comparison with the placebo group, without adverse events during the trial.

Future research should expand upon this work with larger sample sizes.

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Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Author Contributions. G.F. and F.R. conceptualized the study. M.F. and M.D. contributed to the methodology. D.P.and A.P. worked on the formal analysis. G.F., F.R. , M.F. and M.D. carried out the investigation. D.P. and A.P. wrote the original draft. G.F. and F.R. reviewed the manuscript.

Disclosures. Fabio Rinaldi serve as a consultant for Giuliani S.p.A. Daniela Pinto and Angela Papaleare employed by Giuliani S.p.A. Gabriella Fabbrocini, Maria Ferrillo and Marianna Donnarumma have nothing to disclose.

Compliance with Ethics Guidelines. The study was approved by the multidisciplinary independent ethics committee Derming in February 2021, and all procedures were in accordance with the ethical standards of the 1964 Declaration of Helsinki, as revised in 2013, concerning human rights. All patients provided written informed consent prior to inclusion in the study.

Data Availability. The datasets used during and/ or analyzed during the current study are available from the corresponding author on reasonable request.

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