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ORIGINAL ARTICLE

Tolerability and effectiveness of a dermocosmetic product containing Silybum marianum fruit extract in adolescents and young adults with acne-prone skin: An international, phase IV, longitudinal study

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Abstract

Background: Dermocosmetic products are often used to maintain or enhance the tolerance and effectiveness of medical anti-acne therapies. Recent discoveries about the pathophysiology of acne-prone skin indicate that skincare products may help maintain homeostasis around the sebaceous gland progenitor cells, thereby preventing microcomedone formation.

Aims: To evaluate the tolerance and effectiveness of a dermocosmetic product containing *Silybum marianum* fruit extract (SMFE) in adolescents and young adults with acne-prone skin.

Patients/Methods: This real-life, international, observational, multicenter study was conducted in patients aged 12–25 years with mild-to-moderate acne. Patients ($N = 4230$) used the product twice daily for 8–12 weeks, either alone before ("initial group") or after an anti-acne therapy ("maintenance group"), or in association with their usual prescribed anti-acne therapies ("association group"). The tolerance, effectiveness, and cosmetic properties of the product were assessed. Patient quality of life (QoL) was also evaluated.

Results: Dermatologists rated the tolerance of the product as "good" or "very good" in about 95% of the patients and the effectiveness of the product as "effective" or "highly effective" in about 80% of the patients, with a significant reduction in the mean global evaluation of acne (GEA) grade (−36% ± 39%, $p < 0.0001$) at study end. The QoL of most patients (80%) improved by the end of the study, and the majority (79% to 94%) appreciated the cosmetic properties of the product. Overall, the product was a clinical success in >84% of patients.

Conclusions: This dermocosmetic product can be used by adolescents and young adults with acne-prone skin to limit the initial or chronic use of medical anti-acne therapies.

KEYWORDS
microcomedone, mild-to-moderate acne, observational real-life study, *Silybum marianum* fruit extract (SMFE), skin free fatty acids (FFA)

1 | INTRODUCTION

Acne vulgaris, hereafter referred to as acne, is a common disease that involves the development of non-inflammatory lesions (comedones) and inflammatory skin lesions (papules, pustules, and nodules) that may heal to leave erythematous and pigmented macules or scars.[1] Acne may have an impact on mental health, leading to a range of symptoms from low self-esteem to depression.[2] Historically, the etiology of the disease included high rates of sebum production, the hyperkeratinization of the pilosebaceous follicle and its colonization by *Cutibacterium acnes* (*C. acnes*, formerly called *Propionibacterium acnes*), and an imbalance of the skin microbiome.[3]

Combined topical and systemic therapies, containing retinoids and antibiotics, are recommended as first-line therapies (USA,[4] Canada,[5] and Europe[6]) to alleviate acne symptoms and improve patient quality of life (QoL).[7,8] Topical dermocosmetic products – such as cleansers and moisturizers containing active ingredients (e.g., salicylic acid and linoleic acid) – are often used either as adjunctive therapies to enhance the effectiveness and tolerance of medical anti-acne therapies and improve treatment adherence, or as monotherapies to prolong remission,[9] but their effectiveness remains to be clearly demonstrated.

Advances in the understanding of the physiological and molecular mechanisms underlying the development of acne over the past 10 years have led to the emergence of new, more targeted, dermocosmetic products for disease management. The analysis of skin lesions induced by exposure to high doses of the comedogenic agent 2,3,7,8-tetrachlorodibenzo-p-dioxin - (TCDD) allowed elucidation of the mechanism of formation of the infra-clinical earliest lesions in the acne lesional cycle called microcomedones. This process, which has been named the "comedone switch",[3,10] involves a loss of homeostasis in the environment of the progenitor cells of the sebaceous glands, for which the niche is located in the epithelium, close to the infundibulum, at the junction with the sebaceous duct.[11] A loss of homeostasis, which may be induced by comedogens (i.e., increased sebum free fatty acid [FFA] levels, *C. acnes*, local vitamin A deficiency, and dioxin-like xenobiotic factors), appears therefore to be involved in the early stages of development of typical acne lesions.[3,12,13,14,15] Maintaining homeostasis during the programmed differentiation of sebaceous stem cells in order to prevent microcomedone formation is a new goal in patients with acne-prone skin.

These findings led to a screening programme of herbal products, which resulted in the identification of *Silybum marianum* fruit extract (SMFE) as a putative anti-comedogenic factor (International patent published in 2018: WO2018002338 A1).

In addition, a skincare product containing SMFE, when used alone or in combination with anti-acne therapies, has been found to be well tolerated and effective in open-label[13,16] and controlled[15,17] studies of small groups of juvenile and adult patients with mild-to-moderate acne presenting inflammatory and/or noninflammatory lesions. This product containing SMFE is the first topical product identified as being able to modulate the comedone-switch mechanism. Indeed, during the most recent open-label study, 1 year of twice-daily use of SMFE by patients with mild-to-moderate facial acne, was found to be well tolerated and to have led to sustained (over months) and highly significant decreases in lesion counts, clinical scores, and other efficacy markers. The need to use any type of acne drug occurred on less than 4% of the days when SMFE was used during the 12 months of follow-up.[16]

Here, we report the results of a real-life, international, prospective, observational, multicenter study, which was conducted to assess the tolerance and effectiveness of this SMFE-containing dermocosmetic product when used twice daily over 8–12 weeks, either as a monotherapy before any anti-acne therapy ("initial group") or after completing an anti-acne therapy ("maintenance group"), or in association with medical anti-acne therapies ("association group"), in a large population of adolescents and young adults with acne-prone skin. Patient-reported outcomes, such as QoL and an evaluation of the cosmetic properties of the study product, were also assessed.

2 | MATERIALS AND METHODS

2.1 | Study design and ethics

This observational, real-life, prospective, comparative (pre–post), longitudinal, multicentric study was conducted from May 26, 2019 to February 03, 2022 in 21 geographical areas (Algeria, Austria, Belgium, China, Colombia, the Czech Republic, the Dominican Republic, Ecuador, France, French Overseas territories, Germany, Greece, Italy, Lebanon, Mexico, Morocco, Paraguay, Portugal, Spain, Switzerland, and Turkey). The study involved two visits, which were part of the usual care for acne patients: an inclusion visit on Day 1 and a follow-up visit 8–12 weeks after inclusion. The study product was a commercially available facial skincare cream, to be applied twice a day (morning and evening) on the whole face for 8–12 weeks. This so-called "non-interventional study" evaluated a cosmetic product being prescribed as part of the usual clinical practice of the dermatologists and involved no constraints or invasive examinations. Approval of the study protocol by an ethics committee was therefore not required (Article L1121-16-2 and Article 1 of the order of May 3, 2017:https://www.legifrance.gouv.fr/eli/arrete/2017/5/3/AFSP1713710A/jo/article_1). Patients received a leaflet in their own language containing details about the study and their rights. Patients could refuse to participate in the study at any time. They were informed that their

data would be stored for the duration of the study, remain strictly confidential, and would be completely anonymized. In accordance with Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016 on the protection of natural persons, patients could access and modify their personal data. In France, because the process was "devoid of risks and performed in the framework of everyday practice", patients could oppose their inclusion in the study and the recording of their data, but signed informed consent was not necessary, as specified by the law Jardé n° 2012–300 of the March 5, 2012 (modified by order n° 2016–800 of the June 16, 2016).

2.2 | Patients

Dermatologists were invited by the Sponsor to participate in the study, and those agreeing to take part were asked to recruit the first five consecutive patients meeting the following eligibility criteria: adolescents or young adults, aged 12–25 years, who had mild-to-moderate acne according to the 6-point global evaluation of acne (GEA) scale.[18] The main study population included three subpopulations: patients who were prescribed the study product alone before starting any anti-acne therapy ("initial therapy"), those who were prescribed the study product with ongoing topical or systemic anti-acne therapies ("associated therapy"), and those who were prescribed the study product after completing their course of anti-acne therapies ("maintenance therapy"). Patients were excluded in case of sensitivity to any of the components of the product, if they had another disease that may have an impact on evaluations of the clinical signs of acne, if they were pregnant or breastfeeding, or if they had participated in another interventional clinical study during the month prior to inclusion.

2.3 | Study product

The study product (Cleanance Comedomed™) was a cream with a light texture containing *Silybum marianum* fruit extract (SMFE: 25%; European Patent EP3478309), isopropyl alcohol, polyethylene glycol 6, silica, polyacrylate-13, polyisobutene, polysorbate 20, sorbitan isostearate, Avène thermal spring water, glycerine, and water (aqua).

2.4 | Study procedures

At inclusion, the dermatologists collected patient demographic and clinical data. The study product was then prescribed according to usual clinical practice as an initial, associated or maintenance therapy. It could be prescribed in association with a cleanser, which could be of the same product range (Cleanance®), or combined with physical treatment modalities (peeling, light, or laser therapy). All current treatment and skincare product details were recorded. When combined with a conventional topical treatment, patients were instructed to apply the study product first, and the conventional acne treatment 15 min later. Patients also filled in a self-assessment questionnaire to assess their initial level of QoL. At the follow-up visit, 8–12 weeks after inclusion, the same dermatologists re-assessed the clinical signs, recorded any potential adverse events (AEs), serious AEs (SAEs), or any relevant reactions, and the patients filled in a follow-up self-assessment questionnaire.

2.5 | Evaluation criteria

The evaluation criteria were the global tolerance and global effectiveness of the study product as assessed by the dermatologists in the whole study population after 8–12 weeks of use. Other evaluation criteria included analyses of the global tolerance and global effectiveness of the study product according to the initial GEA grade and type of treatment, and the evaluation of any AEs/SAEs related to the study product. Dermatologists also rated the overall clinical success of the study product. Subjective evaluation criteria included patient assessments of the global effectiveness of the product in the whole study population and according to initial GEA grade and type of therapy, assessments of patient QoL over the course of the study, and an evaluation of the cosmetic properties of the product.

2.6 | Assessment methods

2.6.1 | Global tolerance and adverse events

Dermatologists rated the global tolerance of the study product according to dermatological signs at the follow-up visit using a 4-point scale (1 = very good, 2 = good, 3 = moderate, and 4 = poor). Patients were asked to report any discomfort they experienced when applying the study product and dermatologists evaluated any AEs.

2.6.2 | Clinical effectiveness of the study product

Acne severity was assessed at the inclusion and follow-up visits according to the GEA scale: 0 = no lesions; 1 = almost no lesions; 2 = mild, with a few easily recognizable lesions on less than half of the face; 3 = moderate, with numerous lesions on more than half of the face and ≤1 nodule; 4 = severe, with numerous lesions on the whole face and a few nodules; and 5 = very severe, with highly inflamed lesions on the whole face, including nodules.[18] Dermatologists also identified the type of acne lesions (non-inflammatory, inflammatory, or both). Clinical effectiveness was determined by comparing

the GEA grades for each patient between the two visits and rating whether they had improved, not changed or had worsened.

2.6.3 | Global effectiveness of the study product

The global effectiveness of the study product was evaluated at the follow-up visit using a 4-point scale (1 = very effective, 2 = effective, 3 = moderately effective, 4 = ineffective). The same scale was used by both the dermatologists and the patients, and was included as part of the follow-up self-assessment questionnaire.

2.6.4 | Clinical success

Use of the study product was considered a clinical success if the global effectiveness evaluated by the dermatologists or the patients was rated as "very effective" or "effective", or if the GEA score decreased over the study period, and if the global tolerance was considered as "very good" or "good" by the dermatologists.

2.6.5 | Subjective evaluations by the patients

Patient QoL was assessed at the inclusion and follow-up visits using the 5-item Cardiff Acne Disability Index (CADI)[19] self-assessment questionnaire. The CADI scores at each visit were then compared for each patient to determine if QoL had improved, not changed, or had worsened at the end of the study.

As part of the follow-up questionnaire, patients were asked to evaluate the cosmetic properties of the product according to the following five parameters: texture, fragrance, mattifying effect, moisturizing effect, and absorption time.

2.7 | Statistical analyses

Analyses were performed by Quanta Medical (Rueil-Malmaison) using the SAS software, version 9.4. The tolerance population included all patients who had applied the product at least once, and the efficacy population included all patients who completed the study without any major protocol deviations. Quantitative variables were expressed as the mean and standard deviation (SD), and as the minimum, maximum, and median for these values. Qualitative variables were expressed as the number and percentage of patients in the different groups, and the confidence intervals (CIs) for these percentages. No imputation of missing data was performed. Between-visit differences were expressed as absolute changes (initial value-final value) and relative changes (initial value-final value/initial value*100). Comparisons were analyzed using the paired Student's *t*-test or the Wilcoxon signed-rank test, depending on the normality of the data, or using the chi-squared (χ^2) test or the Fisher's exact test for independent variables. p values of ≤0.05 were considered statistically significant.

3 | RESULTS

3.1 | Study population and patient demographic and clinical characteristics

At total of 5344 patients from 21 geographical areas were enrolled in the study, and 4230 of these patients were included in the study population (Figure 1).

The demographic and clinical characteristics of the whole study population are described in Table 1. The mean age of the patients was 18.5 years and 64% of the population were females (N = 2690). Overall, most patients had GEA grades of 2 (48%) or 3 (35%) and the mean age of acne onset was 14.2 years. Half of the patients had both non-inflammatory and inflammatory lesions, whereas the remaining patients presented either non-inflammatory (36%) or inflammatory (13%) lesions. The study product was prescribed as an initial therapy to 47% of the patients (N = 1981), and in association with recommended first-line anti-acne therapies to 48% of the patients (N = 2044). These recommended therapies included systemic or topical antibiotics (34% and 17% of patients, respectively), retinoids (24%), benzoyl peroxide (20%), and a combination of retinoids and benzoyl peroxide (17%). Most patients (3288/3587, 92%) were also prescribed skincare products from the same product range (Cleanance, Avène) as the study product (mostly a cleansing gel; 76%). Other physical treatment modalities were used by 15% of the patients (613/4168), mostly commonly peeling (63%). Only 5% of the patients (N = 205) were prescribed the study product as a maintenance therapy.

Overall, data were missing for 58 patients (1%) for the assessment of global tolerance and for 47 patients (1%) for the assessment of global effectiveness.

3.2 | Dermatological tolerance

3.2.1 | Global tolerance

The dermatologists evaluated the global tolerance of the study product as good to very good for about 95% (95% CI: 94%–95%) of the patients (Figure 2A). The level of tolerance was dependent on the

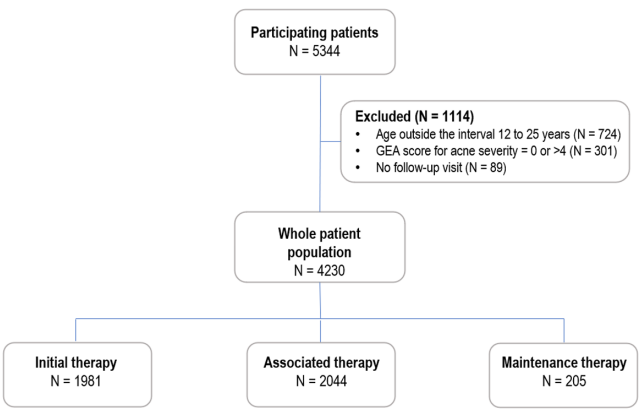


FIGURE 1 Study flowchart. GEA, global evaluation of acne.

TABLE 1 Demographic and acne characteristics of the patients.

Parameters	Main patient population (*N* = 4230)
Age, *n* (%)	*N* = 4230
<18 years	2059 (48.7%)
≥18 years	2171 (51.3%)
Gender	*N* = 4223
Female, *n* (%)	2683 (63.5%)[a]
Acne characteristics	
Age of onset, years	*N* = 4061
Mean ± SD [min-max]	14.2 ± 3.5 [0; 25]
Median [95%CI]	14.0 [14.0; 14.3]
GEA grade, *n* (%)	*N* = 4230
Grade 0	0 (0.0)
Grade 1	703 (16.6%)
Grade 2	2044 (48.3%)
Grade 3	1483 (35.1%)
Grade 4 or 5	0 (0.0)
Lesion type, *n* (%)	*N* = 4156
Non-inflammatory	1506 (36.2%)
Inflammatory	547 (13.2%)
Both	2103 (50.6%)
Therapy type, *n* (%)	*N* = 4230
Initial therapy	1981 (46.8%)
Associated therapy	2044 (48.3%)
Maintenance therapy	205 (4.8%)
Associated therapy[b], *n* (%)	*N* = 2044
Oral antibiotic	684 (33.5%)
Retinoid	484 (23.7%)
Benzoyl peroxide	399 (19.5%)
Topical antibiotic	354 (17.3%)
Retinoid + benzoyl peroxide	337 (16.5%)
Treatment before maintenance therapy, *n* (%)	*N* = 205
Isotretinoin	47 (22.9%)
Topical antibiotic	47 (22.9%)
Retinoids	43 (21.0%)
Benzoyl peroxide	39 (19.0%)
Oral antibiotic	35 (17.1%)
Retinoid + benzoyl peroxide	23 (11.2%)
Azelaic acid	12 (5.9%)
Retinoid + erythromycin	10 (4.9%)
Zinc gluconate	4 (2.0%)
Other	17 (8.3%)
Other prescribed skincare products	*N* = 3587
Cleanance® skincare products, *n* (%)	3288 (92%)
Cleansing gel	2717 (75.7%)
Micellar water	353 (9.8%)
Combination of Cleanance skincare products	197 (5.5%)
Other skincare products	299 (8.3%)
Other prescribed treatments	*N* = 4230
Other prescribed dermocosmetic treatments, *n* (%)	1027 (24.3%)
Other used treatments	*N* = 4168
Other used treatment modalities, *n* (%)	613 (14.7%)
Peeling	384 (62.6%)
Light	104 (17.0%)
Laser	59 (9.6%)
Peeling + light	44 (7.2%)
Peeling + laser	11 (1.8%)
Light + laser	1 (0.2%)
Peeling + light + laser	6 (1.0%)
Not determined	4 (0.7%)

Abbreviations: GEA, global evaluation of acne; SD, standard deviation.
[a]The mean age of women was 18.5 ± 3.5 years [0; 25].
[b]Please note that the study product is recommended not to be used in association with isotretinoin.

initial GEA score ($p < 0.0001$, χ^2 test; Figure 2B), with more patients with an initial GEA grade of 1 or 2 being reported as having very good or good tolerance than those with an initial GEA grade of 3 (96% and 95% vs. 93%, respectively). The tolerance of the study product was also dependent on the type of therapy ($p < 0.0001$, Fisher's exact test, Figure 2C): a higher proportion of patients in the maintenance group than in the initial or associated therapy groups had a very good or good level of tolerance of the study product (97% vs. 95% and 94%).

3.2.2 | Adverse events

The dermatologists reported 165 AEs among the 4230 patients. The proportion of patients experiencing an adverse event was higher when the study product was used as an initial or an associated therapy than when it was used as a maintenance therapy: 4% (84/1894) and 4% (77/1947), vs. 2% (4/201), respectively.

3.3 | Clinical and global effectiveness of the study product

At follow-up, the dermatologists reported a significant reduction in the overall mean GEA grade over the course of the study (1.4 ± 0.8 vs. 2.2 ± 0.7 at inclusion), with an absolute reduction of 0.8, and a relative reduction of 36% ± 39% ($p < 0.0001$, Wilcoxon signed-rank test). Improvements in the GEA grade were observed in about 69% of the patients (Table 2). The mean reduction in the GEA grade was

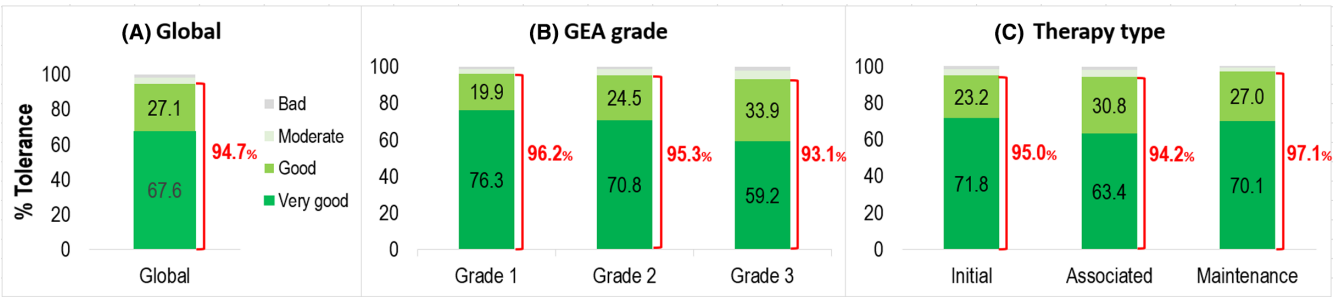


FIGURE 2 Evaluation of tolerance of the product by the dermatologists. Histograms showing the results of the evaluation product tolerance by the dermatologists according to a global analysis (A) in the main patient population ($N = 4172$); or to the initial GEA grade (B) with a significant variation between groups ($p < 0.0001$, χ^2 test); or to the therapy type with a significant variation between groups ($p < 0.0001$, Fisher's exact test). GEA, global evaluation of acne.

TABLE 2 Dermatologist-reported assessments of the clinical effectiveness of the study product in patients with acne.

	Patients with acne	
Acne characteristics	Inclusion $N = 4230$	Follow-up $N = 4183$
GEA, *n* (%)		
Grade 0	0 (0.0%)	514 (12.3%)
Grade 1	703 (16.6%)	1942 (46.4%)
Grade 2	2044 (48.3%)	1366 (32.7%)
Grade 3	1483 (35.1%)	346 (8.3%)
Grade 4	0 (0.0%)	13 (0.3%)
Grade 5	0 (0.0%)	2 (0.0%)
Improvement	-	2865 (68.5%)
No change		1179 (28.2%)
Worsening		139 (3.3%)

Abbreviations: GEA, global evaluation acne; SD, standard deviation.

dependent ($p < 0.0001$, Wilcoxon signed-rank test) on the type of use of the study product, as an initial (0.7 ± 0.7), associated (0.9 ± 0.8) or maintenance therapy (0.8 ± 0.8).

The global effectiveness of the study product was rated by dermatologists as very effective or effective in about 80% (95% CI: 79%–81%) of the patients (Figure 3A) and was also found to be dependent on the initial GEA grade ($p < 0.0001$, χ^2 test, Figure 3B) and on the type of therapy ($p < 0.0001$, Fisher's exact test, Figure 3C). Dermatologists reported that the study product was very effective or effective in 83% of the patients who had an initial GEA grade of 2, in 79% of those who initially graded 3, and in 77% of those who initially graded 1. The study product was rated as very effective or effective in 82% of the patients in the maintenance therapy group and in 80% of patients in the initial and associated therapy groups.

3.4 | Subjective evaluations of the study product

The mean CADI score decreased from 5.2 ± 3.0 at inclusion to 2.9 ± 2.6 at the end of the study. Both the absolute (2.3 ± 2.7) and relative ($40\% \pm 61\%$) mean reductions in CADI score were significant ($p < 0.0001$, Wilcoxon signed-rank test), indicating that the patients experienced a major improvement in their QoL after 8–12 weeks of using the study product. The mean CADI score varied significantly between the three treatment groups (Table 3).

Most patients (3321/4160, 80%) rated the global effectiveness of the study product as very effective or effective and more patients were prone to give this rating if they had an initial GEA grade of 2 than grade 1 or grade 3 (82% vs. 77% or 78% of patients, respectively) and if they belonged to the initial or maintenance therapy groups than to the associated therapy group (81% or 80% vs. 78%).

Overall, 587 patients (15%) experienced discomfort when using the study product. The evaluation of the cosmetic properties of the study product showed that most patients appreciated its texture (94%), fragrance (79%), mattifying effect (83%), moisturizing effect (80%), and absorption time (91%) (Figure 4).

3.5 | Clinical success

Considering the high level of global tolerance, as well as the high rates of global effectiveness evaluated by the dermatologists and by the patients, the use of the study product containing SMFE was considered a clinical success in 3571 out of 4230 of the patients (84% [94% CI: 83%–86%]). Similar rates of clinical effectiveness were reached in the three treatment groups (84%, 85%, and 85% in the initial, associated or maintenance group, respectively, χ^2 $p > 0.05$).

4 | DISCUSSION

This study was conducted in a large population of patients with acne-prone skin ($N = 4230$) presenting a wide range in the age of onset of acne (0–25 years), but which appeared evenly distributed in terms of age (<18 years, 49%), acne severity (mild, GEA grade 2: 48%, and moderate, GEA grade 3: 35%), and the type of acne (36% non-inflammatory and 51% mixed). The higher prevalence of female than male patients (64% vs. 36%) in the study population may reflect that women in the age range chosen for this study (i.e., 12 to 25 years)

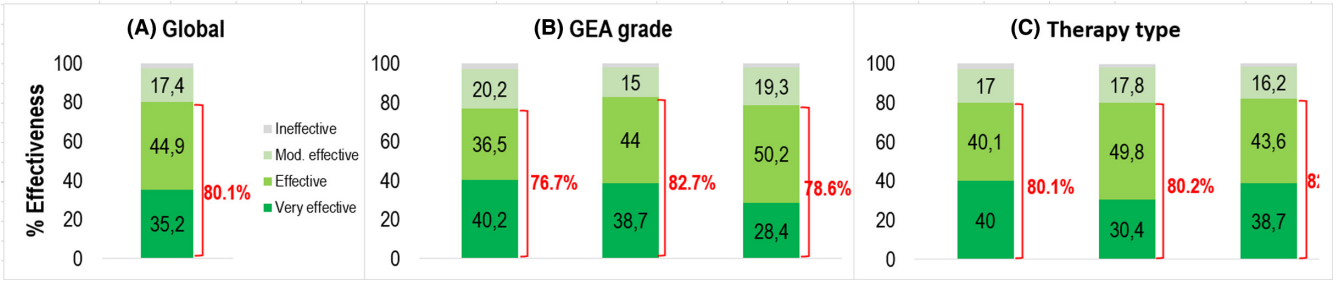


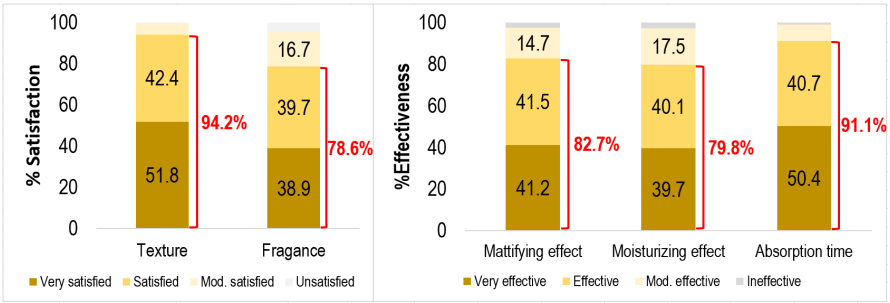
FIGURE 3 Evaluation of the effectiveness of the product by the dermatologists. Histograms showing the results of the evaluation of product effectiveness by the dermatologists according to a global analysis (A) in the main patient population ($N = 4183$); or to the initial GEA grade (B) with a significant variation between groups ($p < 0.0001$, χ^2 test); or to the therapy type with a significant variation between groups ($p < 0.0001$, Fisher's exact test). GEA, global evaluation of acne.

TABLE 3 Evaluation of the quality of life of patients according to therapy type.

CADI mean ± SD (min-max)	Type of therapy		
	Initial $N = 1981$	Associated $N = 2044$	Maintenance $N = 205$
At inclusion	4.6 ± 2.9 (0.0; 15.0) $N = 1963$	5.8 ± 3.1 (0.0; 15.0) $N = 2032$	4.7 ± 2.7 (0.0; 14.0) $N = 202$
At follow-up	2.5 ± 2.5 (0.0; 15.0) $N = 1901$	3.4 ± 2.6 (0.0; 15.0) $N = 1963$	2.6 ± 2.3 (0.0; 11.0) $N = 203$
Change	2.1 ± 2.6 (−13.0; 15.0)*** $N = 1891$	2.4 ± 2.8 (−11.0; 15.0)*** $N = 1956$	2.1 ± 2.7 (−10.0; 14.0)*** $N = 201$

Abbreviations: CADI, Cardiff acne disability index; min, minimum; max, maximum; SD, standard deviation.
***significant variation between groups ($p < 0.0001$, Fisher's exact test).

FIGURE 4 Evaluation of the cosmetic properties of the study product by the patients. Patients evaluated the texture ($N = 4153$), fragrance ($N = 4148$), mattifying effect ($N = 4129$), moisturizing effect ($N = 4078$), and absorption time ($N = 4161$) of the study product after 8–12 weeks of use.



have been found to be more frequently affected by mild-to-moderate acne than men.[20] Almost half of the patients (48%) used the study product in association with medical anti-acne therapies. These medical therapies were representative of the first-line treatments recommended for the management of mild-to-moderate acne.

The dermatologists rated both the global tolerance and the global effectiveness of the study product as good (95%) to very good (80%) in most patients. Furthermore, 59% of the patients had a GEA grade of 0 or 1 at the end of the study, whereas only 17% of them started the study having such low GEA grades. Using cleansers from the same product range as the study product (86% of patients) may have contributed to the effectiveness of the study product, as it has already been shown in a real-life study for another product from the same product range (Cleanance EXPERT® emulsion).[21] The design of our study did not allow to establish the proportion of patients in the initial SMFE group who went on to receive further medical treatment. However, in a recent 1-year real-life use study of a product containing SMFE[16] in teenage and young adults with mild-to-moderate facial acne, prescription drugs were used on less than 4% of the 365 days of follow-up on SMFE. Although both the global tolerance and effectiveness of the study product varied significantly depending on the initial GEA grade of the patients and the type of therapy, most patients presented high to very high levels of global tolerance (93%–97%) and effectiveness (77%–83%) in all patient subpopulations, which was further confirmed by the similar clinical success rates obtained in the three treatment groups.

The effectiveness of the SMFE-containing product for the management of acne is likely to be associated with the impact of this main active ingredient on several key processes involved in the early stages of comedogenesis and through the maintenance of homeostasis. Homeostasis disruption results in the comedone lineage switch and in the development of the initial, clinically invisible, microcomedones that are present in the non-lesional skin of acne-prone patients.[13,22] The maintenance of homeostasis at the site of differentiation of sebaceous gland progenitor cells (LRIG1$^+$ cells) into sebocytes, sebaceous duct cells, and infundibular keratinocytes, may maintain a low microcomedone index, and would therefore constitute good target for molecules for anti-acne therapies.[3,23] Along these lines, SMFE has been shown to induce the expression of two sebocyte-specific infundibular keratins (K75 and K79)[13] and

two lipid droplet proteins, PLIN2 and CIDEA, in cultured human sebocytes.[15] In skin samples from patients with acne, the levels of K75 and K79[13] and of PLIN2 and CIDEA[15] were found to be lower in samples with higher numbers of microcomedones, whereas using a topical formulation of SMFE resulted in decreased number of microcomedones over time and increased expression of K75 and K79[13] and of PLIN2 and CIDEA.[15] Both K75 and K79 or PLIN2 and CIDEA were therefore identified as potential anti-acne therapy targets as their low levels may participate in the formation of microcomedones in patients with acne-prone skin.[13,15,24] Thus, the currently available evidence indicates that SMFE might have an impact on the processes that participate in the maintenance of a low microcomedone index and healthy skin, given its apparent effectiveness as a maintenance/preventive intervention in comedogenesis in the current study. In addition to SMFE, other plant extracts (e.g., apple polyphenols, lupeol, and lilac) have been found to regulate sebum lipid production in vitro and in vivo,[25,26] but the real-life tolerance and effectiveness of these plant-based products has not yet been reported.

Overall, patients experienced an improvement in their QoL as indicated by the positive variation in the CADI score, with a potentially larger improvement in patients using the study product as an associated therapy. In addition, patients were very satisfied with the various cosmetic properties of the study product, in particular with its moisturizing effect, suggesting that the study product may help to compensate for the skin dryness and irritation that may occur with medical anti-acne therapies.[7] The SMFE-containing study product may therefore contribute to improving treatment compliance.

This observational study provided evidence supporting the effectiveness and tolerance of the study product in patients with mostly mild-to-moderate acne in a real-life setting. Another strength was that the study design allowed the clinical benefits of the product to be evaluated using a validated acne severity scale, and allowed the collection of both dermatologist- and patient-reported evaluations of tolerance and effectiveness, providing a truly global analysis of the use of the product as an adjuvant to anti-acne therapy. Nonetheless, the study design had two major limitations: the absence of a placebo control and the absence of any compliance monitoring. Both of these limitations were associated with the real-life setting of the study. However, the pre–post comparative study design and the large size of the study population reinforced the robustness of the data and provided sufficient statistical power for meaningful comparisons despite wide interpatient variability.

In conclusion, this real-life, international, multicenter study indicated that a skincare product containing SMFE was very well tolerated and might be highly effective for the management of acne-prone skin in adolescent and young adult patients. This dermocosmetic product could therefore be used initially or after an anti-acne therapy to help maintain healthier skin and acne remission in patients with acne-prone skin, who may then be able to limit their use of drug therapies.

AUTHOR CONTRIBUTIONS

F. B., L. L., and C. B. provided data and drafted the manuscript; A. O. B. and J. H. S. established the study concept and design and drafted the manuscript; A. S. managed the study and drafted the manuscript.

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DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are not publicly available because the study product is under a European patent. However, data are available from the corresponding authors upon reasonable request and with permission from Avène, Pierre Fabre Dermo-Cosmétique

MEDICAL WRITING, EDITORIAL, AND OTHER ASSISTANCE

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ETHICS STATEMENT

This study was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments. This so-called "non-interventional study" evaluated a cosmetic product being prescribed as part of the usual clinical practice of the dermatologists and involved no constraints or invasive examinations. Protocol approval by an ethics committee was therefore not required (Article L1121-16-2and Article 1 of the order of May 3, 2017:https://www.legifrance.gouv.fr/eli/arrete/2017/5/3/AFSP1713710A/jo/article_1). Patients received a leaflet in their own language containing the details about the study and their rights. Patients could refuse to participate in the study at any time. They were informed that their data would be stored for the duration of the study, would remain strictly confidential, and would be completely anonymized. In accordance with Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016 on the protection of natural persons, patients could access and modify their personal data. In France, because the process was "devoid of risks and performed in the framework of everyday practice", patients could oppose their inclusion in the study and the recording of their data, but signed informed consent was not necessary, as specified by the law Jardé n° 2012–300 of the March 5, 2012 (modified by order n° 2016–800 of the June 16, 2016).

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