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ORIGINAL CONTRIBUTION

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Acne RA-1,2, a novel UV-selective face cream for patients with acne: Efficacy and tolerability results of a randomized, placebo-controlled clinical study

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Summary

Background: General skincare measures such as the use of moisturisers and products containing adequate photoprotection are important components of acne patients' management to complement the pharmacological regimen. Acne RA-1,2 is a novel dermato-cosmetic product which contains selective photofilters and active ingredients against the multifactorial pathophysiology of acne.

Objectives: To evaluate the tolerability of Acne RA-1,2 and its effect on the clinical signs of acne.

Methods: This double-blind, placebo-controlled study randomized 40 adult patients with 10-25 comedones per half face to once-daily application of Acne RA-1,2 or placebo for 8 weeks. Evaluations after 4 and 8 weeks included the number of comedones, transepidermal water loss (TEWL), sebum production, and tolerability.

Results: In the Acne RA-1,2 group, there was a significant 35% decrease in the mean number of comedones from 26 at baseline to 17 at Week 8 ($P<.001$), a 7% significant reduction in TEWL (9.32 to 8.66 g/h/m^2; $P<.001$), and a 24% significant reduction in sebum production (154.8 to 117.6 μg/cm^2; $P<.001$). The reductions in TEWL and sebum production were significantly greater than those in the placebo group at Weeks 4 and 8 ($P<0.05$). There were no adverse events.

Conclusions: Acne RA-1,2 was well tolerated and effective at reducing comedones and sebum production and improving epidermal barrier function. These results suggest that Acne RA-1,2 is useful against acne-prone facial skin, particularly as it targets sebum production, which topical pharmacological acne therapies do not address.

KEYWORDS
acne, comedones, dermato-cosmetic, sebum, tolerability

1 | INTRODUCTION

Acne is a multifactorial disease of the pilosebaceous unit involving increased sebum production, altered keratinization, colonization by *Propionibacterium acnes*, and inflammation.[1] An effective acne treatment needs to address as many of these underlying disease factors as possible. In so doing, an optimal acne treatment would quickly reduce the clinical signs of acne and consequently the impairment to quality of life and psychosocial burden that this highly visible disease causes.[2]

In addition to the use of pharmacological treatments for acne, there is increasing interest in the use of dermato-cosmetic products

which can complement the medical regimen such as the use of moisturisers and products with adequate photoprotection.[3] These dermato-cosmetics can help to maintain the integrity of the stratum corneum and to reduce the local skin reactions caused by topical treatments such as retinoids and benzoyl peroxide (BPO).[3-5] They may also improve patients' adherence to their pharmacological acne treatment, which is estimated to be poor in 50% of patients.[6]

Acne RA-1,2 is a new dermato-cosmetic product which was designed to provide selective protection from daily UV light, with additional clinical benefits for acne-prone and acne-affected skin. This randomized, double-blind, placebo-controlled study was carried out to evaluate the effect of Acne RA-1,2 on the clinical signs of acne (number of comedones, transepidermal water loss [TEWL], and sebum production) as well as determining its tolerability. Patients did not use any pharmacological acne medications during this study.

2 | METHODS

2.1 | Patients

Patients were eligible for participation in this study if they were Caucasian adults aged at least 18 years with greasy facial skin and with 10-25 open and closed comedones per half face. Patients had to stop their pharmacological treatment for acne at least 4 weeks before the study start and had to agree not to expose themselves intensively to UV rays during the study. Patients were excluded if they received a systemic treatment for acne, and if pregnant or breastfeeding, if female. Patients were also excluded if they were taking food supplements which could interfere with the study medication, or if they had other skin conditions in the area to be treated. All patients provided written informed consent before participating in the study.

2.2 | Study design

This randomized, double-blind, placebo-controlled clinical study was conducted from 5 October 2015 to 16 December 2015 at Farcoderm srl facilities (San Martino Siccomario, Italy) in accordance with the latest version of the Declaration of Helsinki. The protocol and informed consent were approved by a local independent ethics committee. Patients were randomized to receive Acne RA-1,2 (Meda Pharma [a Mylan company], Monza, Italy) or matching placebo for 8 weeks. Acne RA-1,2 contains selective photofilters (ethylhexyl methoxycinnamate, 4-methylbenzylidene camphor, ethylhexyl triazone, methylene bis-benzotriazolyl tetramethylbutylphenol, titanium dioxide [nano]) to protect against UVB rays, which may worsen acne, while allowing partial penetration of UVA rays around 400 nm in wavelength, which may be of benefit in treating acne (Table 1).[7-16] The other active ingredients in Acne RA-1,2 target the principal pathogenic factors of acne (Table 1). The *Salix alba* (willow bark extract) component of Acne RA-1,2 provides anti-inflammatory effects,[17-19] whereas its 1,2-decanediol component reduces both *P. acnes* and sebum levels.[20-22] The vitamin B_3 present in Acne RA-1,2 provides anti-inflammatory effects and improves the epidermal barrier,[23,24] and soy isoflavones provide anti-inflammatory and anti-oxidant effects and protect DNA from UV damage.[25-28] The matching placebo contained aqua, dicaprylyl carbonate, polyglyceryl-2 dipolyhydroxystearate, prunus amygdalus dulcis oil, hydrogenated dimer dilinoleyl/dimethyl carbonate copolymer, sodium polyacrylate, dimethicone, phenoxyethanol, cetearyl alcohol, sodium lauryl glucose carboxylate, lauryl glucoside, sodium hydroxide, xanthan gum, and tropolone.

TABLE 1 Components and key activities of Acne RA-1,2[a]

Component	Action
Selective photofilters (ethylhexyl methoxycinnamate, 4-methylbenzylidene camphor, ethylhexyl triazone, methylene bis-benzotriazolyl tetramethylbutylphenol, titanium dioxide [nano])	UVB protection while allowing partial penetration of certain UVA wavelengths
Salix alba (willow bark extract)	Anti-inflammatory effects[17-19] and reduces *Propionibacterium acnes*[22]
1,2-decanediol	Reduces *P. acnes* and sebum production[20-22]
Vitamin B_3	Anti-inflammatory effects and improvement of the epidermal barrier[23,24]
Soy isoflavones	Anti-inflammatory and anti-oxidant effects and protect DNA from UV damage[25-28]
Vitamins C and E	Anti-oxidant effects

[a]Full list of components: aqua, ethylhexyl methoxycinnamate, dicaprylyl carbonate, glycerin, 4-methylbenzylidene camphor, polyethylene glycol-100 stearate, ethylhexyl triazone, glyceryl stearate, methylene bis-benzotriazolyl tetramethylbutylphenol, titanium dioxide (nano), panthenol, polyacrylamide, magnesium aluminum silicate, hydroxyacetophenone, tocopheryl acetate, C13-14 isoparaffin, xanthan gum, decylene glycol, glycine soya extract, niacinamide, *Salix alba* bark extract, caprylyl glycol, 1,2-hexanediol, dimethicone, ascorbyl tetraisopalmitate, laureth-7, silica, disodium ethylenediaminetetraacetic acid, butylated hydroxytoluene, microcrystalline cellulose, magnesium stearate, talc, *Citrus aurantium amara* flower extract.

Patients were also provided with a facial cleanser and a base cream for use during the study. The facial cleanser (Meda Pharma [a Mylan company] R&D, Monza, Italy) contained glycerin, decyl glucoside, zinc gluconate, magnesium aspartate, copper gluconate, and *Camellia sinensis* (leaf extract). The base cream (Meda Pharma [a Mylan company] R&D) contained aqua, *Helianthus annuus* seed oil, and polyglyceryl-3 methylglucose distearate, glyceryl stearate. Patients applied the base cream in the morning onto clean and dry skin, and if necessary, in the evening during a 1-week run-in period prior to the study start. During the 8-week trial, study treatment was applied by patients once daily in the morning after cleaning the skin with the provided facial cleanser. Patients could also apply the base cream in the evening, if necessary. Both the cleanser and base cream do not have any known cosmetic efficacy and were selected to standardize the patients' daily skincare routine.

2.3 | Evaluations

The effects of study treatments were evaluated after 4 and 8 weeks of their daily use. The number of facial open and closed comedones was determined by the investigator at each study visit by visual inspection and, if necessary, by palpation. TEWL was measured using a Tewameter 300® (Courage + Khazaka electronic GmbH, Cologne, Germany) to evaluate the effect of the treatments on the epidermal barrier. Sebum production was assessed using a Sebumeter® (Courage + Khazaka electronic GmbH), for which the reference scale is as follows: <70 dry skin, 70-180 normal skin, >180 oily skin.[29] Patients assessed the severity of their acne at baseline and after 8 weeks of treatment on a scale of 0 (no acne) to 10 (serious acne). Adverse events, including local skin reactions such as erythema, edema, dryness, and desquamation, were recorded by the investigator at each study visit.

2.4 | Statistical analyses

All statistical tests were carried out using NCSS 10—PROFESSIONAL, version 10.0.7 (Kaysville, UT, USA). The number of comedones at Weeks 4 and 8 was compared to baseline using a Wilcoxon signed-rank test, and the number of comedones in the Acne RA-1,2 vs the placebo group was compared using a Mann-Whitney *U* test. TEWL and sebum production at Weeks 4 and 8 were compared to those at baseline using repeated-measures analysis of variance (ANOVA) followed by Tukey-Kramer post-test. These parameters were compared in the two treatment groups using a bilateral Student's *t* test for unpaired data.

3 | RESULTS

3.1 | Patients

In total, 40 acne patients were enrolled into this study: 20 into the Acne RA-1,2 group and 20 into the placebo group. The baseline demographics and clinical characteristics of the two treatment groups were similar, with no significant differences in any of the baseline parameters. The mean age (range) of patients was 28 years (18-47) in the Acne RA-1,2 group and 29 years (20-47) in the placebo group. Most of the patients in both groups were female (Acne RA-1,2: 19/20; placebo: 18/20). According to the system of classification of acne severity of Plewig and Kligman,[30] 45% of patients in the Acne RA-1,2 group had grade 1 and 55% had grade 2 comedonal acne. By comparison, 25% of patients in the placebo group had grade 1 and 75% had grade 2 comedonal acne.

3.2 | Clinical improvement in acne

There was a significant 35% reduction in the mean number of comedones in the Acne RA-1,2 group from 26 at baseline to 17 at Week 8 ($P<.001$; Figure 1A). The mean number of comedones in the two treatment groups was not significantly different at any time point during the study.

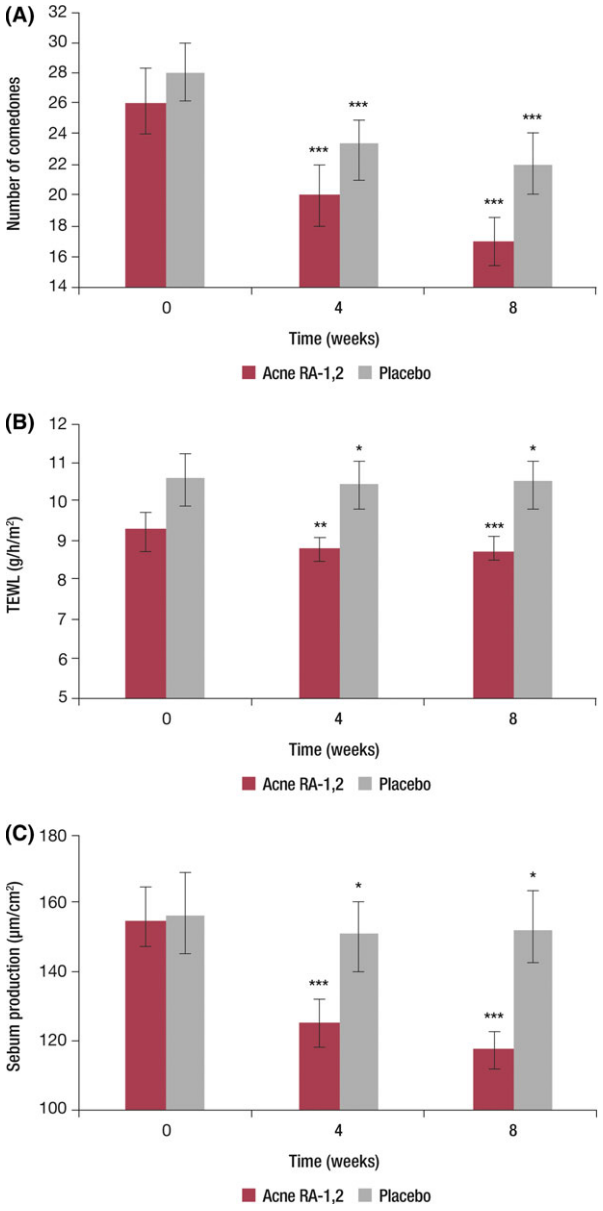

FIGURE 1 Clinical effects of Acne RA-1,2 on (A) comedones, ***$P<.001$ vs baseline (Wilcoxon signed-rank test); (B) TEWL, *$P<.05$ vs Acne RA-1,2 (bilateral Student's *t* test for unpaired data), **$P<.01$ vs baseline, *** $P<.001$ vs baseline (repeated measures ANCOVA followed by Tukey-Kramer post-test); (C) sebum production, *$P<.05$ vs Acne RA-1,2 (bilateral Student's *t* test for unpaired data), ***$P<.001$ vs baseline (repeated-measures ANCOVA followed by Tukey-Kramer post-test). Data are means ± SEM. TEWL, transepidermal water loss

3.3 | TEWL and sebum production

Mean TEWL was significantly reduced by 7% from 9.32 g/h/m^2 at baseline to 8.66 g/h/m^2 after 8 weeks of Acne RA-1,2 treatment ($P<.001$; Figure 1B). Mean sebum production was significantly reduced by 24% from 154.8 µg/cm^2 at baseline to 117.6 µg/cm^2 after 8 weeks of Acne RA-1,2 treatment ($P<.001$; Figure 1C). Both TEWL and sebum production were significantly lower in the Acne RA-1,2 and placebo groups at Weeks 4 and 8.

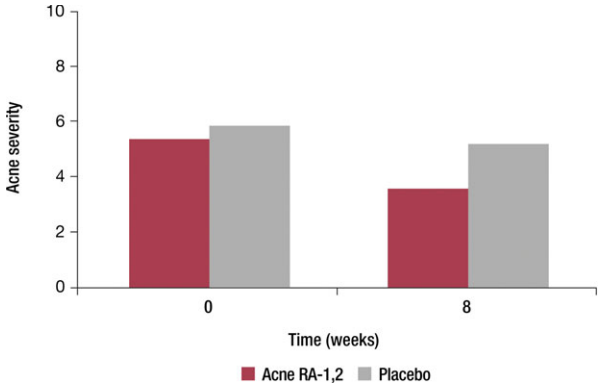

FIGURE 2 Patient assessment of acne severity. Data are means. Acne severity scores range from 0 (no acne) to 10 (serious acne)

3.4 | Patient evaluations

In the Acne RA-1,2 group, there was a 36% improvement in patient's rating of their acne from a mean of 5.3 at baseline to 3.4 after 8 weeks of treatment (Figure 2). In contrast, in the placebo group, there was only a 12% improvement in patient's rating of their acne from a mean of 5.8 at baseline to 5.1 at Week 8 (Figure 2). Two examples of the clinical improvement experienced by patients in the Acne RA-1,2 group are shown in Figure 3.

3.5 | Tolerability

There were no adverse events during the study.

4 | DISCUSSION

This is the first placebo-controlled study to evaluate the tolerability and effect of Acne RA-1,2 against the clinical signs of acne. The results of this study showed a significant reduction in comedones in the Acne RA-1,2 group compared with baseline as assessed by the investigators and a significant improvement in acne as evaluated by patients. Clinical improvements in epidermal barrier function and reduced sebum production were also observed. Furthermore, Acne RA-1,2 was shown to be noncomedogenic and well tolerated by patients with no adverse events occurring during the study. This is important, because to be appropriate for use in acne patients, dermato-cosmetic products must not lead to worsening of acne and must not irritate the already sensitive skin.[31]

The efficacy of Acne RA-1,2 against acne reported in this study may be due to this treatment selectively filtering UV rays and due to its active ingredients which target several of the underlying components of the disease including *P. acnes*, inflammation, and sebum

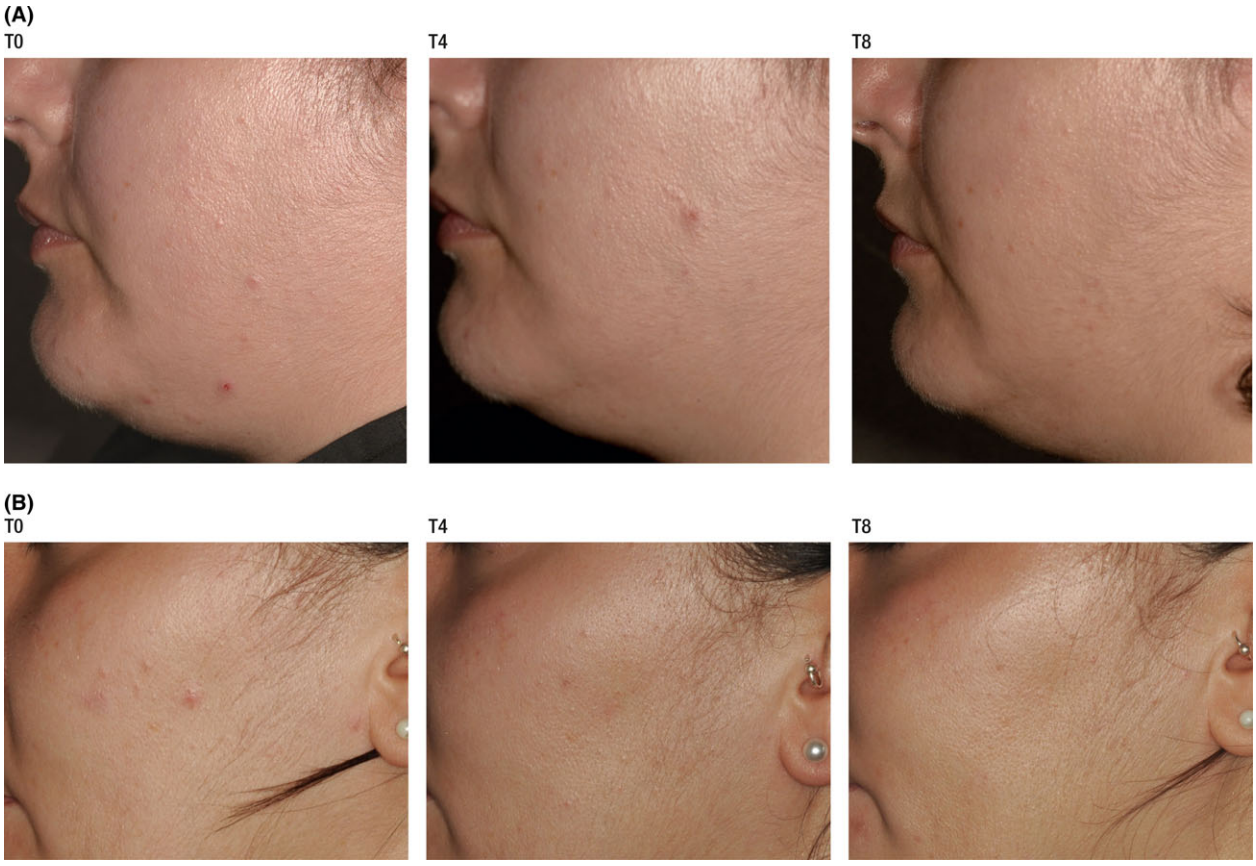

FIGURE 3 Examples of clinical improvement with Acne RA-1,2: (A) Patient 1; (B) Patient 2. T0, baseline; T4, after 4 weeks of Acne RA-1,2 treatment; T8, after 8 weeks of Acne RA-1,2 treatment.

production (Table 1). The selective photofilters present in Acne RA-1,2 provide protection against UVB rays and allow partial penetration of UVA rays around 400 nm in wavelength. UVB rays have multiple detrimental effects on acne such as inducing inflammation,[10-13] increasing proliferation of keratinocytes,[14] and increasing production of sebum.[15,16] In contrast, specific UVA wavelengths around 400 nm may have beneficial anti-inflammatory actions in both acne-prone and acne-affected skin.[7-9] Together, the components of Acne RA-1,2 led to a clinical improvement in the signs of acne and a reduction in the number of comedones in this study.

Acne RA-1,2 was associated with a significant improvement in epidermal barrier function in this study—as evidenced by a reduction in TEWL—compared with both baseline and placebo. This is important given that acne itself and many therapies used to treat acne (eg, topical retinoids and BPO) impair the stratum corneum, resulting in increased TEWL, skin sensitivity, and inflammation.[3,32] Acne RA-1,2 contains the active ingredient vitamin B_3, which has previously been shown to lead to improvements in epidermal barrier function including both significant reductions in TEWL and increases in the levels of certain lipids in the stratum corneum.[24]

This study also demonstrated a significant reduction in sebum production with Acne RA-1,2 vs both baseline and placebo. Acne RA-1,2 contains the active ingredient, 1,2-decanediol, which has previously been shown to significantly reduce sebum levels by 20% in acne patients and so is most likely responsible for the reduction in sebum production observed with Acne RA-1,2 in the current study.[20,21] The reduced sebum production with Acne RA-1,2 is a unique and important feature of this dermato-cosmetic product given that no currently available pharmacological option for the topical treatment of acne is able to target this underlying pathogenic factor of acne.

In this study, patients in the placebo group experienced a significant reduction in comedones at Weeks 4 and 8 vs baseline, but no significant changes in TEWL or sebum production. All patients in the study were asked to clean their face every day with the same cleanser, and this may have contributed to the reduction in comedones in the placebo group.

The study was conducted in the autumn season of 2015. This season was selected because sebum production and skin moisture are higher in the autumn compared with other seasons.[33] Consequently, this provided us with the optimal opportunity for evaluating the effects of Acne RA-1,2 on these parameters. The summer season was avoided given that intense sun exposure, heat, humidity, and sweating can aggravate acne in a proportion of patients, whereas others experience an improvement in acne due to the camouflaging effect of tanning.[34] While UVA is present equally throughout daylight hours and seasons, UVB is strongest from April to October. Acne RA-1,2 provides an SPF of 30 (calculated based on UVB protection), which protects patients from normal daily light but not from sunburn. Consequently, the study was conducted outside the seasons of most intense UVB radiation, and patients were also advised to avoid intensive UV exposure during the study to avoid the negative effects that sunburn could have on acneic skin, which is more sensitive and inflamed than normal skin.

The results of this placebo-controlled study complement the data from a previously conducted real-life study in which the effects of Acne RA-1,2 were evaluated when added on to pharmacological acne treatment.[35] The previous study showed that Acne RA-1,2 significantly reduces the skin irritation that topical pharmacological acne treatments such as retinoids and BPO can cause. Acne RA-1,2 also led to a significant increase in adherence to pharmacological acne treatment, and similar to the results of the current study, the combined use of Acne RA-1,2 and pharmacological therapy led to a clinical improvement in acne and epidermal barrier function and a decrease in sebum production.

The main limitations of this placebo-controlled study were the small sample size and short duration of follow-up. The small sample size was considered appropriate for the initial evaluation of the safety and tolerability of Acne RA-1,2 in a randomized, placebo-controlled clinical trial. In the future, studies could assess the efficacy and tolerability of Acne RA-1,2 in larger placebo-controlled studies of longer duration both when used alone and in combination with pharmacological acne treatments. Another limitation was the inclusion of a population comprising mainly adult females with acne. Given that adult female acne may have a different clinical presentation and pathogenesis to adolescent acne,[36] future studies should also evaluate Acne RA-1,2 in different populations including both adolescent and adult males and females.

5 | CONCLUSIONS

Acne RA-1,2 was well tolerated and led to a significant reduction in comedones, a significant improvement in epidermal barrier function and a significant decrease in sebum production. These beneficial effects against the clinical signs of acne suggest that Acne RA-1,2 may be useful in patients with acne-prone facial skin as part of their daily skincare routine. The ability of Acne RA-1,2 to reduce sebum production is particularly noteworthy because this is not targeted by existing topical pharmacological acne treatments.

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