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ORIGINAL ARTICLE

A cream containing the sap of oat plantlets and mandarin extract soothes the symptoms of rosacea and improves the quality of life of patients

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Abstract

Background Rosacea is a chronic inflammatory disease of the facial skin that affects all skin types and occurs mostly in adults. The main clinical sign of rosacea is a characteristic and persistent form of centro-facial erythema that is prone to exacerbation and can impair quality of life (QoL). The current therapeutic approach for rosacea is to combine various treatments, use appropriate skincare products and avoid flare-up triggers.

Objective To evaluate the use of a facial skincare product containing protein-free sap extruded from Rhealba® oat plantlets and mandarin extract in subjects with rosacea.

Methods Three clinical studies were conducted in adult subjects with various rosacea phenotypes (erythematotelangiectatic or papulopustular) and treatment histories to assess the dermatological and ophthalmological tolerance of the study product, as well as its clinical effectiveness, after a twice-daily application on the whole face and neck for up to 4 weeks.

Results Tolerance of the product was rated as good to very good by dermatologists across the three studies, which involved a total of 105 evaluable subjects. Subjects with untreated erythematotelangiectatic rosacea reported fewer functional signs and symptoms of the disease and an improved QoL. The evaluation of skin biometric parameters revealed a reduction in transepidermal water loss, indicating that the study product helped to restore skin barrier integrity after 4 weeks, and a higher skin pH, indicating that the cutaneous microbiote was respected. Most subjects (93%) who had either undergone a superficial dermatological procedure for erythematotelangiectatic rosacea or were taking oral/topical treatments for papulopustular rosacea, rated the study product as very good (8/10) and felt it further relieved their symptoms.

Conclusion Overall, the study product was very well tolerated and may be beneficial for subjects with rosacea as an adjunct to superficial dermatological procedures or oral/topical therapies, in line with the current recommendations for rosacea management.

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Conflicts of interest

GF declares no conflicts of interest. CBM and FC are employees of Pierre Fabre Dermo-Cosmétique, France.

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Introduction

Rosacea is a chronic inflammatory disease of the facial skin manifested by a variable combination of persistent centrofacial erythema that is prone to exacerbation, papules and pustules, and phymatous changes.[1–3] Rosacea is a very complex condition, and its aetiology remains to be clearly defined.[4] However, dysregulation of the innate immunity, increased colonization by *Demodex* mites, neurovascular changes and skin barrier impairment appear to be the key underlying mechanisms[1,5] whereas ultra-violet (UV) radiation, temperature variations, hot drinks and spicy food are some of the known rosacea triggers.[6]

Rosacea has long been considered to occur mainly in fair-skinned individuals; however, more recent studies have shown that all skin types may be affected, with delayed diagnosis likely being more common in subjects with darker skin tones.[7]

The four-group clinical classification of rosacea into its erythematous, papulopustular, phymatous and ocular forms[6,8] has now been replaced by a phenotypic approach that focuses on the disease characteristics to help make patient diagnosis more specific and facilitate identification of the most appropriate treatment.[2,3,9] Indeed, proposed treatments for rosacea vary depending on the clinical signs and symptoms presented. Topical alpha agonists (e.g. brimonidine and oxymetazoline) target neurovascular dysregulation, anti-inflammatory treatments target perilesional erythema, and mechanical therapies – involving potassium titanyl phosphate (KTP) lasers or intense pulsed light (IPL) therapy – target telangiectasia and persistent erythema. Other topical treatments may also be used to reduce papules and pustules, whereas surgery may be performed to treat rhinophyma. Recently, a group of American dermatologists who participated in a roundtable discussion organized by the National Rosacea Society proposed to combine different treatments to treat rosacea more effectively and thus minimize its impact on the QoL of subjects.[3] Implementing skincare regimens involving products such as moisturizers and sunscreens, and making lifestyle changes are also recommended to maintain remission.[1,10]

Dermo-cosmetic products contribute to the daily management of rosacea by preventing further disruption of the skin barrier and limiting exacerbation of the vascular phenotype.[11] With the aim of generating skincare products with limited skin reactivity, which would potentially be suitable for use by subjects with conditions such rosacea, Pierre Fabre Dermo-Cosmétique has developed a certified organic facial skincare product (A-Derma, Toulouse, France) containing protein-free sap extruded from Rhealba® oat plantlets, together with mandarin extract.

Here, we report the results of three studies evaluating the effectiveness and tolerance of a facial skincare product from this range in adult subjects. The first study (Study 1) investigated the clinical effectiveness and the dermatological/ophthalmological tolerance of the study product in subjects with untreated erythematotelangiectatic rosacea, then analysed its impact on QoL and conducted a subject-based evaluation of the study product. The dermatological and ophthalmological tolerance of the study product was also assessed in subjects with erythematotelangiectatic rosacea who had undergone a superficial dermatological procedure (Study 2), and in subjects with papulopustular rosacea receiving oral and/or topical treatments (Study 3).

Materials and methods

Study design and ethics

The three clinical studies were open-label, monocentric trials conducted from September 2020 to March 2021 in clinical research organizations (Eurofins Dermscan in Gdansk and Malbork -Poland; CIDP in Bucharest-Romania). The studies involved two visits: an inclusion visit on Day 1 (D1) and a follow-up visit after 21 days (Study 2) or 28 days (Studies 1 and 3) of product use (Figure S1). The study product was a facial skincare cream to be applied twice a day (morning and evening) on the whole face (including on the eye contours and eyelids) and neck. Detailed descriptions of each study protocol are provided in Table S1. Each study was performed in accordance with the Declaration of Helsinki and the Good Clinical Practice (GCP) Guideline (EMA/CHMP/ICH/135/1995). The three studies were conducted according to the national regulations in force in Poland and Romania; submission to Ethics Committees was not required. All subjects provided written informed consent for participating in the studies and for the commercial or scientific publication of their clinical photos.

Subjects

Included subjects were adults, aged 18 to 70 years, with a skin phototype of I to III (Fitzpatrick scale).

In Study 1, the subjects included had to present untreated, mild-to-moderate erythematotelangiectatic rosacea, for example, with mild-to-moderate erythema (localized or diffuse) and mild (fine vessels covering <10% of the face) or moderate (several fine vessels and/or a few large vessels covering between 10% to 30% of the face) telangiectasia; and have dry (50%) or normal to combination skin (50%) on the face.

In Study 2, the subjects included had any grade erythematotelangiectatic rosacea requiring treatment with a superficial dermatological procedure, including either KTP laser (50%) or IPL therapy (50%).

In Study 3, the subjects included had mild-to-moderate papulopustular rosacea being treated with a topical (metronidazole, azelaic acid or ivermectine) or an oral (tetracycline [lymecycline]) rosacea therapy, which had been started at least 2 weeks before the inclusion visit and was not scheduled for a change of dosage during the duration of the study.

Subjects who had been exposed to or were planning to be exposed to UV rays or intense sunlight during the previous month or during the study periods were excluded. Exclusion criteria are further detailed in Table S1.

Study product

The study product (BIOLOGY A-R, A-DERMA) was a certified organic (Ecocert) skincare cream, with 99% of the ingredients being of natural origin: water (≈73%), organic Rhealba® oat sap (≈20%), mandarin extract, emollients, hydrating agents, emulsifiers (4%), texturing agents (1.5%) and preservatives (<1%). The study product was to be kept at room temperature.

Study procedures

At inclusion on D1, or just after the KTP/IPL laser procedure for Study 2 subjects, the dermatologist collected patient demographic and clinical data, conducted a dermatological evaluation (including physical and functional signs) of the application areas and weighed the study products before handing them to the

subjects ($D1T_0$). Weights of the study products were not disclosed to the subjects, allowing for blinded compliance assessments. The subjects then performed the first application of the study product under the supervision of a qualified person and the responsibility of the Investigators at the study centres. Ten to 30 min later ($D1T_1$), the dermatologist re-evaluated the application areas and carried out assessments of physical signs and recorded the functional signs reported by the subjects. Potential serious adverse events (SAEs), and any relevant tolerance reactions were recorded. Subjects were also asked to record any functional or physical signs, medication changes and their daily application details in a daily log. No study product was applied on the morning of the last visit. At the last visit on D22 (Study 2) or D29 (Studies 1 and 3), the dermatologist reassessed the clinical signs, recorded any potential AEs, SAEs or relevant reactions, and weighed the returned tubes of study product (used and unused) for compliance assessments.

In addition, in Study 1, biomicroscopy eye examinations were conducted by an ophthalmologist to assess clinical signs and the tear film break-up time (BUT) on D1, before ($D1T_0$) and just after ($D1T_1$) application of the study product, and on D29.

Study constraints

In addition to adhering to the study procedures described above, subjects were instructed to avoid sun exposure or use a sun protection product and maintain a 15-min interval between applying their usual face and body skincare products and applying the study product (e.g. after the topical treatment in Study 3). Subjects were also asked not to use any product similar to the study product, modify their lifestyle or daily habits, change their usual make-up and hygiene habits, or use new products. Use of usual light face make-up (powder and blusher) and eye and lip make-up was allowed for women and use of usual shaving products was allowed for men. On the day of the follow-up visit, usual cleansers and rinsing products were allowed, but subjects were instructed not to shower within the 2 h before the visit.

Tolerance

Evaluation criteria The cutaneous tolerance of the study product was evaluated according to the dermatological signs (clinical and functional) (i) on D1 at T_0 and T_1, and on D22 or D29; (ii) the global tolerance was assessed on D22 or D29; and (iii) the adverse reactions reported during the study. Moreover, ophthalmological tolerance of the study product was evaluated in Study 1, using the following criteria: the ophthalmological physical and functional signs and the relative stability of the precorneal tear film assessed on D1 at T_0 and T_1, and on D22 or D29.

Assessment methods *Dermatological signs.* The intensity of functional signs (burning sensations, sensations of warmth, itching, skin tightness, stinging and other) and physical signs (erythema, eyelid oedema, desquamation, dry skin, vesicles, papules and other) was assessed using a 5-point scale (0 = none, 1 = very mild, 2 = mild, 3 = moderate and 4 = severe) and their location, duration (hours and minutes) and frequency were reported. If any reaction occurred after the first study product application, subjects had to remain under supervision for 30 min.

Ophthalmological signs. The intensity of general physical signs (red eyes, eyelid oedema, desquamation, etc.) and of signs on the eyelashes (e.g. hypotrichosis), the bulbar and tarsal conjunctiva (e.g. conjunctival papillae or pallor), the cornea and the anterior chamber (opacity, hypopyon, etc.), as well as of functional signs (stinging, itching, burning, etc.) on the eye and/or eyelids was assessed by using a 5-point scale (0 = none, 1 = very mild, 2 = mild, 3 = moderate and 4 = severe).

Tear film break-up time. The Ophthalmologist measured the relative stability of the precorneal tear film using the BUT test. A drop of fluorescein was instilled in the conjunctival cul-de-sac. The BUT was then measured after blinking using a chronometer.

Global dermatological and ophthalmological tolerance. The Investigators assessed global tolerance by taking into account the type of reactions (discomfort, irritation, delayed allergic reaction, immediate allergic reaction and other); the intensity, duration, recurrence and time to emergence of the reactions; and the target population. Tolerance of the study product was then rated as bad, moderate, good, very good or excellent (no functional or physical signs related to the study product observed or reported by the subjects).

Effectiveness (study 1 only)

Evaluation criteria Changes in rosacea scores were assessed by rating erythema and telangiectasia severity, the intensity of feelings of discomfort and global flushing severity on D1 at T_0 and T_1, and on D22 or D29. Global changes in rosacea intensity, burning and stinging sensations and QoL, as well as changes in skin biometric parameters (transepidermal water loss [TEWL], skin pH) were assessed on D1 and D29. Changes in the frequency of flushes were assessed every week.

Assessment methods *Clinical scoring of rosacea.* The Investigator scored erythema severity using the clinical erythema assessment (CEA) scale (0 = clear to 4 = severe), telangiectasia severity using a 4-point scale (0 = absent, 3 = severe) and global changes in rosacea using a 5-point scale (0 = worse, 1 = no change, 2 = slight improvement, 3 = marked improvement, 4 = clear to almost clear). The subjects scored the intensity of discomfort using a 11-point scale (0 = none, 10 = very intense), flushing severity using the global flushing severity score (GFSS)[12] on a 11-point scale (none = 0, mild = 1–3, moderate = 4–6,

severe = 7–9 and very severe = 10), and the burning and stinging sensations (mean and maximum) felt during the last 24 h using a scale from 0 (none) to 10 (very intense).

Photographs of the front face were taken using the VISIA-CR system on D1 and D29.

Biometric tests. TEWL was measured with a Tewameter® TM300 probe placed on the left cheek. Subjects were acclimatized to the temperature and humidity of the room (optimum conditions: 23 ± 1°C and 40% to 60% relative humidity) for 30 min before the procedure. Skin pH was measured using the Skin-pH-Meter pH®905.

Quality of life. Subjects assessed their QoL using the RosaQoL questionnaire[13] on D1 and D29.

Subjective evaluation by the subjects (Study 2 and Study 3)

At the end of the study, subjects were asked to fill in a 5-item questionnaire (three answers based on a 1–10-scale, and two answers with multiple choice options) to subjectively evaluate the properties, efficacy and likelihood of future use of the study product.

Statistical analyses

Analyses were performed using SPSS 19.0 (Study 1), or Microsoft Excel −2010 (Study 1) or −2016 (Studies 2 and 3). The tolerance population corresponded to all included subjects who had applied the product at least once, and the efficacy population to those who completed the study without any major protocol deviations. *Descriptive statistics:* quantitative variables were expressed as numbers and percentages, and as the mean and standard deviation (SD) and median and minimum and maximum of these values. *Dermatological and ophthalmological evaluations:* the number and proportion of subjects presenting an improvement/no change/worsened state between T_0 on D1 and D22 or D29 was provided for each sign. A decrease in the score was considered as an improvement, and an increase as a deterioration. *Efficacy variables:* a graphical representation of the means ± 95% confidence intervals (CI) across time was produced. Percentage changes in mean values were calculated as follows:

$$\%\text{change} = Y_t - Y_{\text{baseline/Last Day}} / Y_{\text{baseline/Last Day}} \times 100$$

Changes in each parameter were analysed using the Student's *t*-test for paired data or the Wilcoxon signed-rank test, depending on the normality of the data, which was determined using the Shapiro–Wilk test at a 1% level of significance. The null and alternative hypotheses were: H_0, no difference vs. H_1, a difference between two time points. *Clinical change in rosacea:* a 100% stacked bar chart was generated for each severity category on D29. The frequencies of the responses were compared using a one-sample chi-square test with the following hypotheses: the frequencies of the responses are equal (H_0) vs. different (H_1) across the population. The null hypothesis was rejected when the *P*-value was ≤0.05. *Subjective evaluation:* qualitative data (frequencies and percentages) were calculated on the final day of the study.

Results

Subject demographics and disposition

Subject demographics and clinical characteristics are described in Table 1. Overall, 107 subjects, mostly women with average ages of 43 to 54 years, were enrolled across the three studies (33 in Study 1, 30 in Study 2 and 44 in Study 3). Three subjects withdrew: two stopped applying the study product on D3, either because of a common cold (Study 1) or because of reactions (burning sensation, oedema and papules) (Study 3), and one was lost to follow-up on D22 (Study 2). Subjects in studies 1 and 2 with erythematotelangiectatic rosacea had mostly normal and combination skin, or dry skin; whereas, in Study 3, nearly half of the subjects with papulopustular rosacea had oily skin (Table 1). Except for the two subjects who stopped product application on D3, the overall compliance to the protocol was good.

Dermatological and ophthalmological tolerance

Dermatological tolerance During the three studies, 12 subjects (11%) reported single or multiple immediate cutaneous reactions that were likely or very likely to have been attributable to the study product (Table 2): burning ($N = 5$) or stinging ($N = 4$), erythema ($N = 3$), skin tightness ($N = 2$) and itching ($N = 1$). These common signs of skin sensitivity were of short duration (≤20 min, with most being ≤10 min), and of very mild, mild or moderate intensity. Two exceptions were noticed: a case of erythema around the nose that lasted up to 60 min after each product application in one subject and a burning sensation and skin tightness (both lasting <5 min) rated as severe by another subject. Three other subjects reported reactions that were not clearly attributable to the study product (very mild skin tightness, very mild papules above the upper lip and mild pustules on the chin). In Study 3, one subject modified the study product application regimen for 3 days and later stopped using the study product for 3 days because of a mild tightening of skin on the whole face just after each product application, whereas another subject definitely interrupted using the study product on D3 because of a mild burning sensation on the cheeks, mild oedema on the left eyebrow and mild papules above the right eyebrow on D2. No allergic reactions were reported.

Ophthalmological tolerance (study 1) Three subjects reported very mild reactions but only one of these was considered as very likely/likely to have been attributable to the study product

Table 1 Demographic characteristics of the subjects

Parameters	Study 1, *N* = 33†	Study 2 *N* = 30‡	Study 3 *N* = 44§
Age ± SD, range *(years)*	54 ± 1 (38–65)	43 ± 2 (22–61)	50 ± 2 (25–74)¶
Women, *n* (%)	32 (97%)	30 (100%)	37 (84%)
Skin phototype, *n* (%)	II: 20/33 (63%) III: 12/33 (38%)	II: 21/30 (70%) III: 9/30 (30%)	I: 3/44 (7%) II: 39/44 (89%) III: 2/44 (5%)
Facial skin type, *n* (%)	Normal and combination: 17/32 (53%) Dry: 15/32 (47%)	Normal: 2/30 (7%) Dry: 9/30 (30%) Combination: 19/30 (63%)	Normal: 5/44 (11%) Dry: 21/44 (48%) Oily: 4/44 (9%) Oily and combination: 14/44 (32%)
Disease characteristics	Erythematotelangiectatic rosacea	Rosacea after superficial dermatological procedure††	Papulopustular rosacea requiring pharmacological treatment
Grade	Mild to moderate	Any grade	Mild to moderate
Dermatological procedure, *n* (%)	–	KTP: laser: 16/30 (53%) IPL: 14/30 (47%)	–
Therapy, *n* (%)	–	–	
Oral			Tetracycline: 4/44 (9%)
Topical			Metronidazole:11/44 (25%) Azelaic acid: 5/44 (11%) Ivermectine: 13/44 (30%)
Mixed			11/44 (25%)

†In Study 1, 33 subjects were enrolled, one subject with dry skin could not be analysed.
‡In Study 2, 30 subjects were enrolled, one subject was untraceable on Day 22.
§In Study 3, the test product was applied 15 min after application of the topical drug.
¶In Study 3, two subjects older than 70 years old were enrolled by mistake, but this was considered as minor protocol deviation.
††In Study 2, subjects were treated with potassium titanyl phosphate laser or intense pulse light therapy.
CEA, clinical erythema assessment; D, day; GFS, global flush severity; IPL, intense pulse light; KTP, potassium titanyl phosphate; SD, standard deviation.

Table 2 Dermatological tolerance of the study product throughout studies 1, 2 and 3

Parameters	Study 1 (*N* = 33)	Study 2 (*N* = 30)	Study 3 (*N* = 44)	TOTAL (*N* = 107)
Total subjects with cutaneous reactions†	3 (9%)	4 (13%)	8 (18%)	15 (14%)
Functional and physical signs	*0 (0%)*	*0 (0%)*	*2 (5%)*	*2 (2%)*
Functional signs only	*3 (9%)*	*2 (7%)*	*4 (9%)*	*9 (8%)*
Physical signs only	*0 (0%)*	*2 (7%)*	*2 (5%)*	*4 (4%)*
Subjects with reactions observed by the Investigator	0 (0%)	1 (3%)	0 (0%)	1 (1%)
Subjects with reactions likely or very likely attributable to the study product	3 (9%)	2 (7%)	7 (16%)	12 (11%)
Subjects withdrawn from the study because of the reaction	0 (0%)	0 (0%)	1 (2%)‡	1 (1%)
Subjects who had to modify the application regimen and/or temporary interrupt use of the study product because of the reaction	0 (0%)	0 (0%)	1 (2%)	1 (1%)

†Functional signs (burning sensations, sensations of warmth, itching, skin tightness, stinging or other) or physical signs (erythema, oedema, desquamation, dry skin, vesicles, papules or other) – including both new signs and signs that had worsened compared since the baseline evaluation on D1 – reported by the subjects or observed by the Investigator.
‡Tolerance data and questionnaire responses from this subject were not taken into account for the analyses on D29 because the subject stopped using the study product on D3 as a result of the reaction.

(bilateral oedema on the bulbar and tarsal conjunctiva that lasted for 5 min immediately after product application). No significant differences between tear film BUT results were observed between T_1 and T_0, or between D29 and T_0 (0.0 ± 1.2, $P = 0.747$ and 0.6 ± 2.5, $P = 0.220$ respectively).

Global tolerance Investigators rated the cutaneous tolerance of the study product after 4 weeks of use as good in subjects with papulopustular rosacea treated with oral or topical therapy (Study 3), and as very good in subjects with erythematotelangiectatic rosacea and no prior treatment (Study 1) and in those who had undergone a superficial dermatological procedure (Study 2). In Study 1, the Investigator also rated the ocular and eye contour tolerance of the product as very good after 4 weeks of use.

Adverse events Very few treatment-emergent adverse events (TEAEs) occurred during the three studies (see Table S2). None of these events were related to the study product and none of

them led to study discontinuation. All of the reported TEAEs were of moderate intensity and resolved with corrective therapy (Study 1). There were no SAEs.

Clinical effectiveness of the study product as evaluated in Study 1

The scores for burning sensations (−28%, $P < 0.001$) and skin tightness (−66%, $P < 0.05$) decreased significantly over the 4-week study period (Fig. 1a, b). The mean score for erythema did not change significantly (2.1 vs. 2.2, −5.4%) and the mean score for telangiectasia severity (1.3 vs. 1.3) remained the same after 4 weeks of study product use. However, a significant decrease in erythema was identified through analysis of the CEA scale scores (mean score reduction of −8%, $P < 0.05$; Fig. 1c). Subjects also reported that flushes were of lower intensity (score reduction of −41%, $P < 0.001$) and occurred less frequently (no flushes over a 1-week period in 69% of subjects after 4 weeks, vs. 22% at baseline; Fig. 1e). Global flushing severity score (−41%, $P < 0.001$) (Fig. 1d) and the intensity of discomfort (−35%, $P < 0.05$) were also significantly lower after 4 weeks of study product use. Overall, the Investigator determined that the global change in rosacea over the study period was significant, with a slight improvement for 63% of the subjects and a marked improvement for nearly a third of subjects (28%) (Fig. 2). Furthermore, analysis of the responses to the RosaQoL questionnaire indicated an improvement in the QoL of subjects with mild-to-moderate erythematotelangiectatic rosacea by the end of the study period, with all subjects giving a negative response to some question categories (e.g. 'my rosacea often burns or stings, my rosacea is often irritated, my skin always flushes') after 4 weeks (see Table S3).

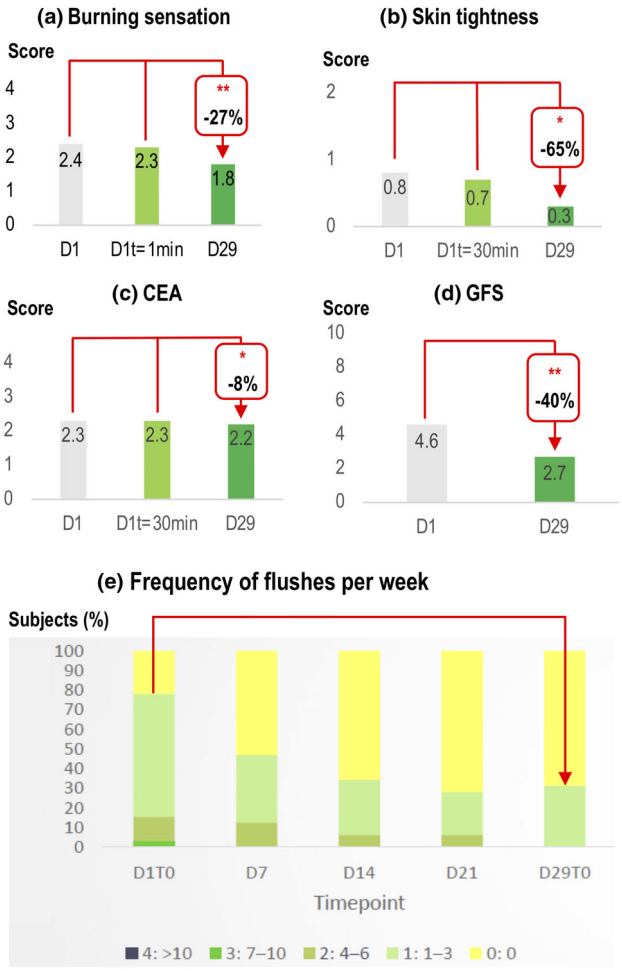

Figure 1 Evaluation of study product effectiveness in subjects with erythematotelangiectatic rosacea after 4 weeks of use (Study 1). Product effectiveness was assessed by analysing the changes in scores over the 4-week study period for (a) burning sensations, (b) skin tightness, (c) clinical erythema assessments, (d) global flush severity and (e) the frequency of flushing episodes in the previous week. Abbreviations: CEA, clinical erythema assessment; D, day; GFS, global flush severity; T0, time0 (*), $P < 0.05$; (**), $P < 0.001$.

Moreover, the TEWL score was significantly lower (12.3 vs. 10.9, −11%, $P < 0.001$; see Fig. S2a), and the skin pH showed a positive variation (5.3 vs. 5.4, +2.6%, $P < 0.001$) at the end of the study (see Fig. S2b).

Altogether the functional and clinical data suggested that use of the study product alone was beneficial for mild-to-moderate erythematotelangiectatic rosacea.

Subjective evaluation of the study product (Studies 2 and 3)

Most subjects with erythematotelangiectatic rosacea who had undergone a superficial dermatological procedure, as well as most of those with papulopustular rosacea, reported reduced redness (83% and 93% respectively) and fast-acting soothing effects (97% and 88% respectively) after using the study product (Table 3). Globally, subjects from both study groups were highly satisfied (93%) with the product and rated it as very good (8/10) (Table 3), with 76% to 85% of subjects indicating that they would be willing to buy the study product (Fig. 3).

Discussion

The tolerance of the newly developed organic skincare product containing Rhealba® oat plantlet sap and mandarin extract, as assessed by a total of 105 evaluable subjects with various rosacea phenotypes and treatments, was rated as good to very good in all three studies. In subjects with erythematotelangiectatic rosacea who used the study product in monotherapy, the skincare regimen led to fewer and less severe functional signs and symptoms of the disease (e.g. less intense and less frequent burning sensations and flushes, and to improvements in QoL). In addition, the reduction in TEWL and the increase in skin pH indicated that the study product promoted reinforcement of the skin barrier after 4 weeks of use. Overall, most subjects (93%) who had

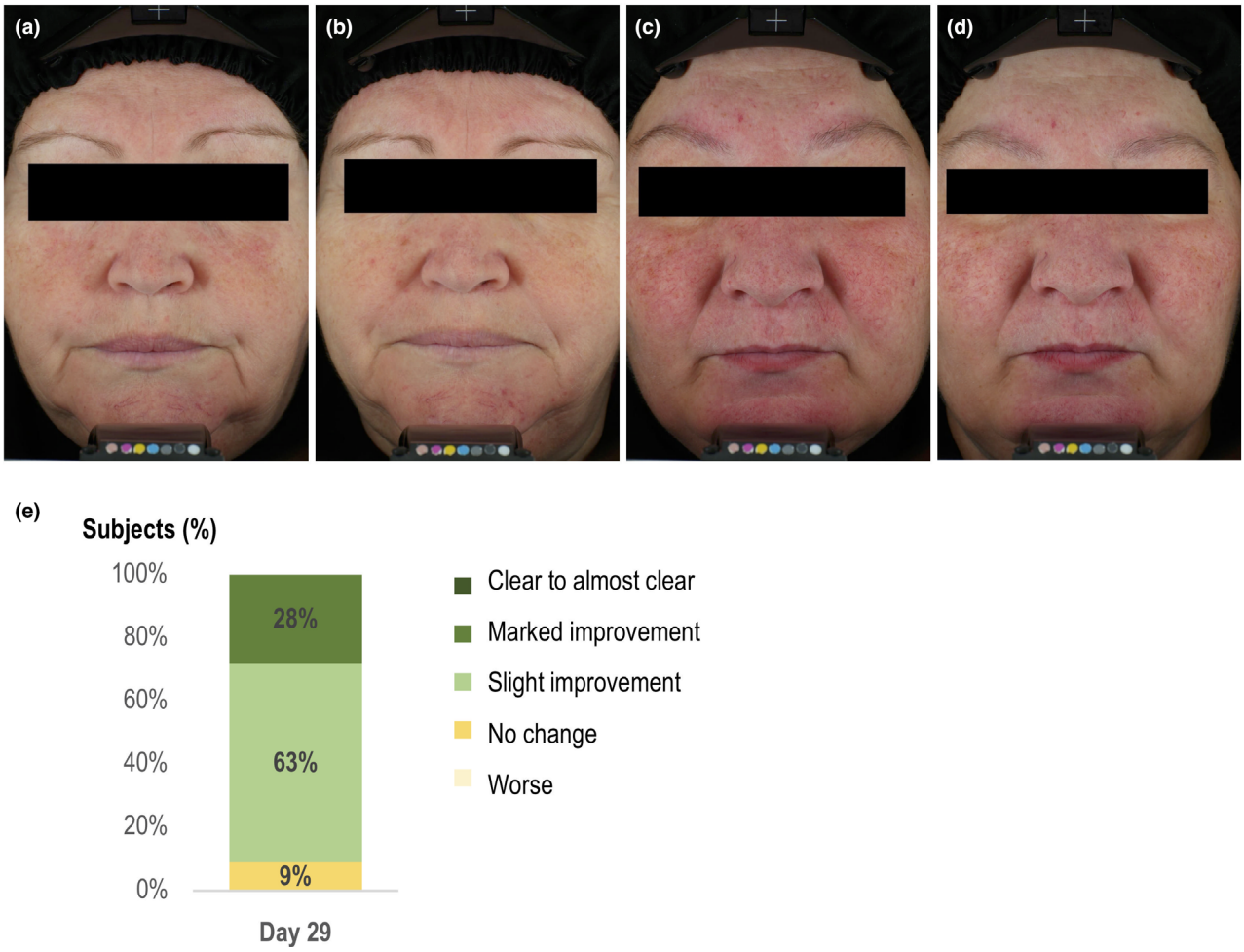

Figure 2 Evolution of rosacea in subjects with erythematotelangiectatic rosacea over the 4 weeks of study product use (Study 1). (a–d) Photographs (VISIA-CR®) illustrating the reduction of the redness phenotype in subjects with rosacea at Day 29 vs. baseline (b vs. a and d vs. c), (e) Global rosacea evolution at Day 29.

Table 3 Evaluation of cosmetic acceptability by the subjects in Study 2 and Study 3

Study product	Study 2 (Day 22)		Study 3 (Day 29)	
	Mean score (×/10)	Subjects (%) with a score ≥ 5/10	Score (×/10)	Subjects (%) with a score ≥ 5/10
Helps to reduce redness	7.4	83	7.4	93
Immediately soothes discomfort	7.9	97	7.5	88
Global acceptability	8.0	93	8.0	93

undergone a superficial dermatological procedure (IPL or KTP) or were using oral/topical treatments, rated the study product as very good (8/10), as they felt that it provided further relief from their symptoms.

The study product mainly induced very mild or mild functional signs of skin reactivity, including burning/stinging and mild-to-moderate transient erythema immediately after application (in only 12 subjects; 11%), indicating that the study product was very well tolerated, even on skin that had undergone laser treatment. The observed discomfort or irritation reactions were expected in the context of the study. The global tolerance assessments conducted by the dermatologists and ophthalmologist confirmed the good to very good cutaneous tolerance and the very good ocular and eye contour tolerance of the

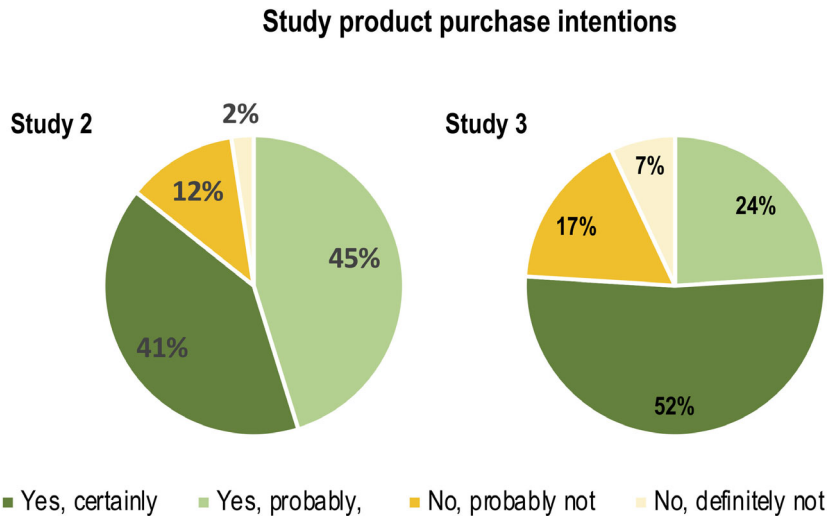

Figure 3 Subjective evaluation of the likelihood of subjects with rosacea buying the study product (Studies 2 and 3). In a subjective evaluation, subjects with erythematotelangiectatic rosacea (Study 2) or papulopustular rosacea (Study 3) responded, respectively, that they would probably (41% and 52%) or certainly (45% and 24%) buy the study product.

study product after twice daily applications for 22 or 28 days. The good tolerance profile of the product is likely related to the process of extrusion of Rhealba® oat plantlet sap (A-Derma patent WO2015040135), which enables the production of a protein-free extract that reduces the risk of reactivity, even for very sensitive skins.

When used alone in subjects with erythematotelangiectatic rosacea, the study product significantly reduced the clinical severity of erythema, with a marked improvement in the redness phenotype. These effects might result from the activity of the mandarin extract, which may have anti-inflammatory properties, as described for other citrus extracts.[14]

Furthermore, the use of the study product led to significant decreases in skin tightness and discomfort, reduces TEWL and increases in skin pH, suggesting that the skincare regimen restored the integrity of the skin barrier and respected its microbiota.[15] The extrusion process helps to preserve the active components of the Rhealba® oat plantlet sap, and thus may allow the study product to have a more potent impact on skin hydration, facilitating recovery of the protective functions of the skin barrier.[16] A similar effect has already been reported for a facial skin moisturizer, which has also been shown to improve stratum corneum hydration and has been found to reduce the facial erythema, dryness and inflammatory lesions of rosacea subjects, but not telangiectasias.[17] Indeed, telangiectasias generally require more invasive therapies, such as physical laser therapy and intravascular polidocanol injections.[4]

Although our studies provided some evidence supporting the effectiveness and good tolerance of the study product in subjects with rosacea, our approach had two main limitations: the absence of a placebo control in all three studies, and the small sample size for evaluating effectiveness in Study 1. However, a placebo-controlled design is not mandatory for the evaluation of dermo-cosmetic products. In addition, the tolerance of the study product was found to be consistently good throughout all three studies, which involved a total of 105 evaluable subjects with different rosacea phenotypes and diverse treatment histories. These tolerance data, combined with our findings indicating that the study product improved QoL and that many of the subjects considered buying the product after participating in the studies, support the routine use of the product by rosacea subjects.

Overall, our studies demonstrated that the 99% organic study product – containing protein-free sap extruded form Rhealba® plantlets and mandarin extract – was a very well tolerated dermo-cosmetic facial skincare cream, which could be combined with various rosacea treatments (IPL, KTP laser and oral/topical therapies) to help limit the reappearance of redness and quickly soothe discomfort in subjects with a range of rosacea phenotypes. The facial skincare regimen used in our studies could therefore help rosacea subjects to better manage their symptoms, and may be used as an adjunct to superficial dermatological procedures or oral/topical therapies to restore the integrity of the skin barrier, in line with the current recommendations for rosacea management.[9,18]

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Data availability statement

The data that support the findings of this study from the Laboratoires A-Derma - Pierre Fabre Dermo-Cosmétique were used under license for the current study, and so are not publicly available. Data are however available from the corresponding author upon reasonable request and with permission of the Laboratoires A-Derma - Pierre Fabre Dermo-Cosmétique.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Overview of the design of the three studies.
Figure S2. Changes in the biometric characteristics.

Table S1. Overview of study design.
Table S2. Treatment-emergent adverse events reported in Studies 1, 2 and 3.
Table S3. Results of the Rosacea Quality of life questionnaire (Study 1).