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Safety Assessment of a Novel Topical Vehicle for Personalized Treatments in Acne

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Abstract

Acne vulgaris is a common inflammatory disease of the pilosebaceous unit, with a profound impact on the quality of life of patients. In this work, we aimed to study the safety characteristics of Cleoderm™, a novel functional semisolid vehicle developed for the compounding of treatments for acne and oily skin. The primary and cumulative irritation and sensitization potential were evaluated in 54 healthy volunteers in a comparative single-blinded study, while the acnegenic and comedogenic potential of the product were assessed in 31 healthy volunteers with combination to oily skin through a non-comparative study. Cleoderm™ was applied (0.05 g/cm^2) in filter paper discs in both studies. For the evaluation of the irritation and sensitization potential, the investigational product, or a control (0.9% NaCl) was applied to the right or left scapular area of the study subjects. No clinical reactions were observed during the induction or challenge phases, suggesting that Cleoderm™ presents no irritating or allergenic potential. Regarding acnegenicity and comedogenicity, no significant increase in the number of acne lesions linked to the application of the product in four areas of the face was reported, indicating that Cleoderm™ appears not to display acnegenic and comedogenic potential. Furthermore, over 60% of the study subjects exhibited a decrease in the number of acne lesions after product use. These results show that Cleoderm™ exhibited no irritating, sensitizing, acnegenic or comedogenic potential, and suggest that it can be considered safe under the study conditions and that the claims dermatologically tested, clinically tested, and non-comedogenic/acnegenic can be supported.

Keywords

Acne Vulgaris, Personalized Medicine, Irritation, Sensitization, Comedogenicity

1. Introduction

Acne vulgaris, also referred to as common acne, is a highly prevalent inflammatory skin condition of the pilosebaceous unit. It is most common in 11 - 24-year-olds, affecting up to 85% of this population [1], although it can appear well into adulthood.

Scientific literature and clinical practice have shown that women are more frequently affected by adult acne (12% - 22%) than men (3%) [2] [3]. Additionally, acne in the adult population manifests with more inflammatory lesions and increased scarring, and it is reported to have a more severe impact on the quality of life of adult females than in teenagers [4] [5] [6]. While acne manifests most frequently on the face, it can also occur in other parts of the body rich in sebaceous follicles such as chest and back [7] [8].

The multifactorial etiology of the disease remains unclear, but it is widely accepted that the mechanism of action involves the overproduction of sebum, hyperkeratinization, and colonization by *Cutibacterium acnes* [9] [10] [11]. Moreover, this process is influenced by diverse factors including stress [12] [13] [14] [15], genetics [16]-[22], environmental conditions such as seasonal variations, pollutants, use of cosmetics, medications, and even lifestyle factors like sleep deprivation, exposure to light, or socioeconomic pressure [23] [24].

To this day, acne remains the most recurrent primary diagnosis in the dermatologist's practice [25], and although not a life-threatening condition, the psychological impact of acne can be profound to the patient's mental health and become a significant barrier to social interaction. Psychosocial sequelae linked to acne include increased levels of anxiety, social withdrawal, and unemployment levels; as well as lower levels of self-esteem and life satisfaction [26] [27] [28] [29]. Additionally, clinical depression and even suicidal ideation are frequent comorbidities of acne, underlining the need for effective treatment strategies in this field [30]-[36].

Common therapeutic regimes for the treatment of acne include physical, topical, and oral approaches [37]. In recent times, given the worldwide increase in bacterial resistance, and the rising number of studies reporting the effectiveness of various topical treatments, the interest in this route of administration has significantly grown [38] [39] [40] [41] [42]. Topical treatments for acne can be found in the form of commercial preparations with standardized doses of active pharmaceutical ingredients (APIs), but individualized approaches through the compounding of creams and gels have regained relevance in the era of personalized medicine [43] [44] [45]. In this context, the development of ready-to-use vehicles that can facilitate the compounding of a wide array of APIs and minimize the technical and practical challenges to the compounding pharmacy is paramount. To this effect, Cleoderm™, a semisolid, ready-to-use functional vehicle, can be an important addition to the existing arsenal of topical therapies for acne within the compounding pharmacy, especially given the broad compatibility of this vehicle with a wide range of APIs used in the treatment of acne [46].

Topical treatments for acne, as is the case for any personal care and hygiene products that come directly in contact with the skin or hair (e.g. soap, creams, shampoo, deodorants, and toothpaste) must be safe for human health when used under normal or reasonably foreseeable conditions. Furthermore, the concern and attention to the allergenic effects of components found in consumer products have grown over the years, emphasizing the relevance of conducting appropriate studies to assess the safety characteristics of cosmetics, and in particular, dermal irritation and sensitization [47] [48] [49] [50]. For products to be used in the field of acne, the assessment of the comedogenic potential is of special interest [51].

To the best of our knowledge, this is the first study to assess the safety of Cleoderm™, including its potential to elicit irritation and sensitization, as well as its acnegenic and comedogenic potential.

2. Materials and Methods

2.1. Investigational Product

The investigational product studied was Cleoderm™ (Fagron, The Netherlands) whose main functional ingredients are *Cleome gynandra* L. leaf extract, palmitoyl tripeptide-8, bisabolol, hyaluronic acid, tocopheryl acetate and a combination of 8 functional oils (*Persea gratissima*, *Simmondsia chinensis*, *Rosa canina*, *Cocos nucifera*, *Lavandula angustifolia*, *Melaleuca alternifolia*, *Rosmarinus officinalis*, and *Vitellaria paradoxa*) [46].

2.2. Skin Primary and Cumulative Irritation and Skin Sensitization Potential Study

The skin primary and cumulative irritation and skin sensitization potential of the investigational product were examined through a comparative, single-blinded, controlled clinical study, conducted between March 28th and May 5th, 2022. Healthy male and female subjects between 18 and 70 years of age with phototypes I to IV according to the Fitzpatrick Skin Phototype Classification [52] and intact skin on the test area were eligible for the study.

Exclusion criteria included skin marks that could interfere with the evaluation of possible skin reactions, history of allergic reactions to topical products, concomitant medications (including immunosuppressants, antihistamines, anti-inflammatory medicines, and corticosteroids), pre-existing conditions such as pathologies aggravated or triggered by ultraviolet radiation or immunodeficiencies and lifestyle factors related to sunlight or bathing.

The patch test methodology [53] was employed for the assessment. Cleoderm™ (0.05 g/cm^2 at 100% concentration) and control (sterile 0.9% NaCl) were distributed uniformly on filter paper discs and applied to the same respective duly protected area (right or left scapular area of the study subjects) in a sequence of three weekly applications for three consecutive weeks during the induction period. The investigational product remained in contact with the skin for 48 hours

during the week and for 72 hours during weekends.

The induction period was followed by a rest period of at least 10 days without product use, after which the challenge period started, applying the investigational product and control to the right or left back of the subjects on a virgin area, that is, where no patches had been previously applied. Thereafter, the product was removed after approximately 48 hours of contact with the skin.

For the duration of the study, the areas of product application and control were examined and, if clinical signs were observed, they would be classified according to the standardized scale by the International Contact Dermatitis Research Group [54].

The assessment of clinical signs was performed immediately and 24 hours (72 h reading) after product removal. If clinical signs were to be observed at the time of removal, the readings would be carried out after a minimum of 30 minutes and a maximum of 60 minutes to prevent possible false-positive results caused by skin reactions to the removal of the adhesive paper disks rather than to the investigational product.

2.3. Acnegenic and Comedogenic Potential Study

The acnegenicity and comedogenicity of the product were investigated in a non-comparative clinical study, performed between March 7th and May 5th, 2022. Healthy male and female subjects between 18 and 45 years old were selected. The study subjects were to present combination or oily skin prone to acne, and intact skin on the site of testing, with the exception of comedones and occasional inflammatory lesions.

Exclusion criteria included pathologies in the area of product application, history of skin reactions to the category of the product tested, concomitant medications and treatments (e.g. corticosteroids, immunosuppressants, antihistamines, anticonvulsants, hormones, acne treatment with topical or systemic medication), pre-existing medical conditions (e.g. Type 1 diabetes and complications related to it, dermatosis, immunological insufficiency) or lifestyle factors including pregnancy or breastfeeding.

The inflammatory and non-inflammatory lesions in four areas of the face were counted, both at the time of the initial dermatological clinical assessment, prior to the application of the product, as well as after 28 ± 2 days of product use, following the aforementioned patch test methodology and applying Cleoderm™ uniformly in the filter paper discs (0.05 g/cm^2) at a 100% concentration.

The counting was performed utilizing a surface magnifying glass and templates with fixed examination areas. The right and left malar (a 7.0 cm × 5.0 cm template placed according to the nasal wing fold in each half-face) as well as the right and left front (a 5.0 × 4.0 cm template laterally placed to the glabella) were evaluated. The scoring of the acne lesions observed the following categories: Open comedones (corneo-sebaceous masses with a visible surface without signs of inflammation), closed comedones (slightly papulous corneo-sebaceous masses, with

whitish or normal surface coloring), papules (skin bumps with pinkish or reddened coloration, which might be painful), and pustules (skin bumps with visible pus secretion in the center).

The data relating to the acnegenic and comedogenic potential of the investigational product (n = 31) are expressed as descriptive statistics in terms of mean ± SEM of the percent change in acne lesion formation from baseline at the first dermatological clinical assessment (reduction, no difference or increase), employing the Wilcoxon signed-rank test with one-sided increase hypothesis as the statistical method of choice. The confidence level considered in the analyses was 95% and MINITAB14 and XLSTAT2021 software packages were used.

2.4. Ethics

The two independent studies were conducted in accordance with the Declaration of Helsinki Ethical Principles [55] and according to Good Clinical Practices (Document of the Americas and ICH E6: Good Clinical Practices) [56] [57].

3. Results

3.1. Assessment of the Primary and Cumulative Irritation Potential and Sensitization Potential

Eighty-nine (89) volunteers signed the informed consent documents to be included in the skin irritation and sensitization potential study. Four volunteers did not meet the inclusion criteria or presented any of the non-inclusion criteria. No volunteers withdrew from the study. Therefore, a total of eighty-five (85) subjects were approved to be included in this study group. Nevertheless, twenty-six (26) subjects were absent from the study (twenty-five [25] during the induction period and an additional one during the challenge period), and five subjects were removed from the study by the study investigator. Out of the initial 89 volunteers recruited, 85 were included as study subjects and fifty-four (54) participated until the end of the study.

During the induction period, five study subjects presented skin irritation after continuous exposure to the patch test adhesive tape. The dermatological clinical assessment did not find a direct link between the skin reaction and patches containing the investigational product, and rather attributed the irritation to individual predisposition to adhesive contact sensitivity. Subsequently, further applications were interrupted, the five subjects were removed from the study and their data were not used further (**Figure 1**).

Among the fifty-four (54) subjects that finished the study, no clinical signs or reactions were reported in the investigational product application area, neither during the induction nor the challenge phases. Additionally, no subjects presented clinical signs in the control site.

3.2. Assessment of the Acnegenic and Comedogenic Potential and Skin Acceptance

Thirty-five (35) volunteers recruited by the study site signed the informed consent

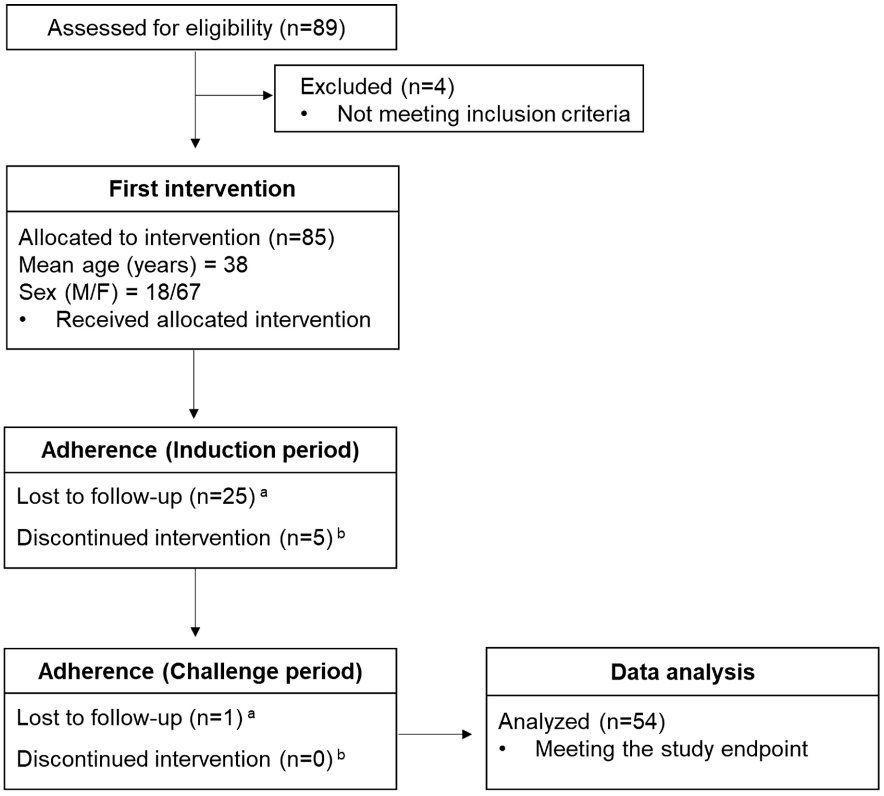

Figure 1. Primary and cumulative irritation and sensitization potential study adherence. [a]Lost to follow up: Subjects who were absent during the study for personal reasons unrelated to the study and to the investigational product. [b]Discontinued intervention: Subjects removed from the study due to skin irritation unrelated to the use of the investigational product. Caption: M: male/F: female.

document and complied with the inclusion and exclusion criteria. No volunteers withdrew or were excluded from the study. A total of thirty-one (31) subjects finished the study following the reported absence of four subjects (**Figure 2**).

For the duration of the study, no subjects exhibited product-use-related skin clinical signs or discomfort in the dermatological clinical evaluations. Additionally, no significant increase in the total number of acne lesions (inflammatory and non-inflammatory) was observed after 28 ± 2 days of product use compared to the initial time-point.

Furthermore, a reduction in the number of acne lesions was reported in a majority of the study subjects (**Figure 3(A)**).

Taking into consideration non-inflammatory lesions alone, 64.5% of the subjects presented a reduction in the number of lesions after the 28 ± 2 days of application, whereas in 32.3% of the subjects no difference was measured, and in 3.2% of cases an increase was detected. With regard to the total number of lesions (inflammatory and non-inflammatory), in 61.3% of the subjects, a reduction in the number of lesions was observed, while 29% of the subjects exhibited no difference and 9.7% showed an increase in the total number of lesions (**Figure 3(B)**).

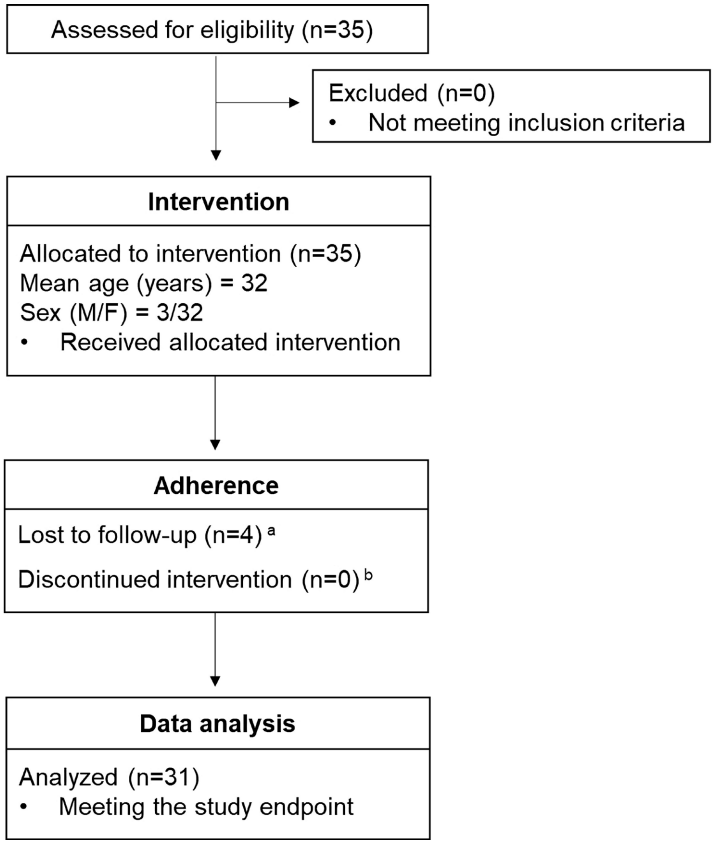

Figure 2. Acnegenic and comedogenic potential study adherence. [a]Lost to follow up: Subjects who were absent during the study for personal reasons unrelated to the study and to the investigational product. [b]Discontinued intervention: Subjects removed from the study due to skin irritation unrelated to the use of the investigational product. Caption: M: male/F: female.

4. Discussion

Therapy adherence remains a challenge in the effective management of acne, with irritation, dryness, and other side effects being some of the reasons associated with this suboptimal treatment compliance [58] [59] [60]. Furthermore, even though there's a growing interest in personalized approaches to medicine, and acne is a highly variable condition in its presentation, as of today, clinical guidelines don't provide a great deal of guidance to enable the personalization of acne treatment [61].

The appropriateness of the vehicle choice is also critical, yet commonly disregarded [62] [63], which represents a missed opportunity in terms of both an improved personalization of treatments, through the compounding of pharmaceutical, cosmeceutical, or cosmetic ingredients in appropriate vehicles, but also by way of using functional vehicles with properties that can potentially improve adherence and even act as adjuvants in the treatment of acne.

To the best of the authors' knowledge, there is currently no vehicle available for patient use developed with the personalization of acne treatment within compounding pharmacies in mind. Presently, formulations of creams, lotions,

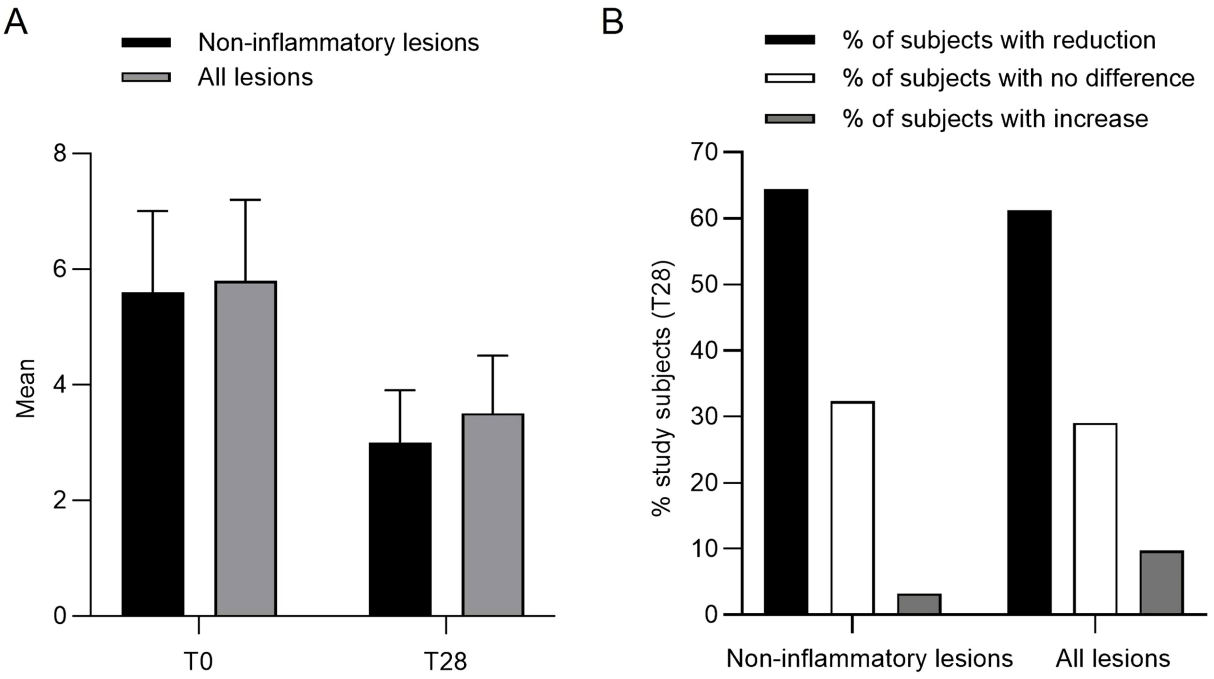

Figure 3. (A) Count of non-inflammatory and total number of acne lesions measured at baseline (T0) and after 28 days of treatment (T28). The data are presented as the mean ± SEM of the number of non-inflammatory and total number of lesions before (T0) and after the application of the investigational product (T28), and also expressed as the percentage of subjects that manifested a reduction, no difference, or an increase in the number of lesions after the period of application of the product. The means of the differences between time-point T28 in relation to the initial time-point were calculated by the difference of the result of the means, according to what is presented in the tables, that is, Mean Δ(T28 – T0) = Mean of T28 – Mean of T0. (B) Difference in the number of acne lesions (non-inflammatory and total number of lesions) at baseline (T0) and after 28 days of treatment with the investigational product (T28), expressed as the percentage of subjects presenting no difference, reduction, or increase in the number of lesions.

and ointments are prepared using available common knowledge on topical vehicles, but given the small scale of the compounding pharmacy, lack the body of evidence to support the appropriateness of the vehicle with regards to the specific application in acne or the compatibility with commonly used APIs for the treatment of this dermatological condition [46].

In terms of studies on the safety and efficacy of cosmetics, cosmeceuticals, compounding vehicles, and related products in the realm of acne treatment are largely performed within the industry, however, despite their generalized use, they often lack sufficient scientific evidence to support claims related to safety [64].

To this end, the present work aimed to evaluate the safety profile of Cleoderm™. The results from the studies performed indicate the absence of irritating and allergenic potential for the investigational product. Moreover, these results show that in a majority of the study subjects the number of acne lesions significantly decreases after the use of Cleoderm™, suggesting that the properties associated with the components of this vehicle may have a beneficial effect on the skin condition of acne patients [46]. These observations are also in line with previous studies on cosmeceuticals showing complementary therapeutic effects

in the treatment of acne and in particular a growing number of them including botanical ingredients [65]-[71].

Taking the results from the two studies into account, Cleoderm™ can be regarded as a dermatologically and clinically tested, safe, non-irritant, and non-comedogenic vehicle for the compounding of active pharmaceutical ingredients for the treatment of acne, particularly given the potentially beneficial attributes of this product in the improvement of skin condition as hinted by the results.

5. Conclusion

Cleoderm™ did not demonstrate irritating or sensitizing potential under the experimental conditions of the study and in the evaluated group of subjects. Additionally, Cleoderm™ did not exhibit acnegenic or comedogenic potential in the relevant study group. Considering the results derived from both study groups, the investigational product Cleoderm™ is considered safe under the evaluated conditions, and the claims dermatologically tested, clinically tested, and non-comedogenic/acnegenic can be supported.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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