

## Efficacy of a Corticosteroid-Free, 5% Hyaluronic-Based Facial Cream in the Treatment of Seborrheic Dermatitis. A Proof-of-Concept Study

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### Abstract

**Introduction:** Seborrheic Dermatitis (SD) is a very common skin disease. This papulo-squamous disorder characterized by erythema, itch, and flaking, affects sebum-rich areas such as scalp, trunk and face. Topical steroids are commonly used as first line therapy of SD but their long-term use, especially when face is involved, could have untoward side effects like skin atrophy, acne and telangiectasia. Local tolerability and long-term safety concerns limit the use of calcineurin inhibitors. Hyaluronic acid topical formulations, thanks to its hydrating and several skin cellular modulation effects have shown to reduce skin inflammation and improve the clinical course of SD. A new cream formulation of HA 5% (Eutrosis DS, Difa Cooper, IFC Group; EDS) has been recently developed.

**Study aim:** To evaluate in a proof-of-concept study the efficacy and tolerability of EDS in the treatment of facial SD in adult subjects.

**Subjects and Methods:** A total of 20 out-patient male subjects (mean age 46) with moderate-severe facial SD were enrolled, after their informed consent, prospective 6-week assessor-blinded study. EDS cream was applied twice daily on the most affected areas (mainly face and chest). The primary outcome was the evolution of the Investigator Global Assessment (IGA) score evaluating erythema, scale/flaking, grade of seborrhea and itch, all measured on a five-point scale, from 0: absence of sign/symptom to 4: very severe sign/symptom. Subjects were assessed at baseline, after 3 and 6 weeks of treatment by an investigator unaware of the type of treatment. Local tolerability was evaluated checking self-reported side effects at each visit.

**Results:** All 20 subjects concluded the study. Baseline IGA scores (mean  $\pm$  SD) was  $9 \pm 3$  (range: 5-13). The use of EDS reduced significantly IGA score by 67% at week 3 and by 83% at week 6. EDS was effective in reducing erythema, scale, seborrhoea, and itch. The product was very well tolerated. No local side effects were reported.

**Conclusion:** EDS applied twice daily for 6 consecutive weeks has been shown to be effective in reducing signs and symptoms of SD of the face and chest. The product was found to be well tolerated. Future controlled trials are warranted to confirm the efficacy and safety of this new therapeutic corticosteroid-free, hyaluronic acid-based product for the treatment of facial SD.

**Keywords:** Seborrheic Dermatitis; Hyaluronic acid; Assessor-blinded study

### Introduction

Topical steroids are frequently used as first line therapy of Seborrheic Dermatitis (SD) but their long-term use, especially when face is involved, could have untoward side effects like skin atrophy, acne and teleangectasia [1]. Calcineurin inhibitors like pimecrolimus and tacrolimus are considered effective in SD but their local tolerability and the concerns of their safety profile in the long-term have limited their use in this skin condition [2,3]. Some trials conducted with hyaluronic acid topical formulations, using different concentrations or type of HA molecule, have shown that this compound could reduce skin inflammation in SD subjects [4,5]. This positive effect of topical HA could be linked to its skin hydrating action [6], anti-oxidant action

and skin barrier function improvement [7]. In addition, topical HA can modulate several skin cells function inducing an anti-inflammatory effect [8]. Finally, topical HA could have beneficial effect on innate skin immunity [9]. Skin effects of HA could be dependent on its molecular weight [10]. A new cream formulation of sodium hyaluronate 5% (Molecular weight 400.000-600.000 Da) (Eutrosis DS; EDS) has been recently developed. The cream contains also xylitol and dimethicone. The complete formulation of the product is under patent. No clinical data regarding its efficacy in the treatment of SD are so far available.

### Study Aim

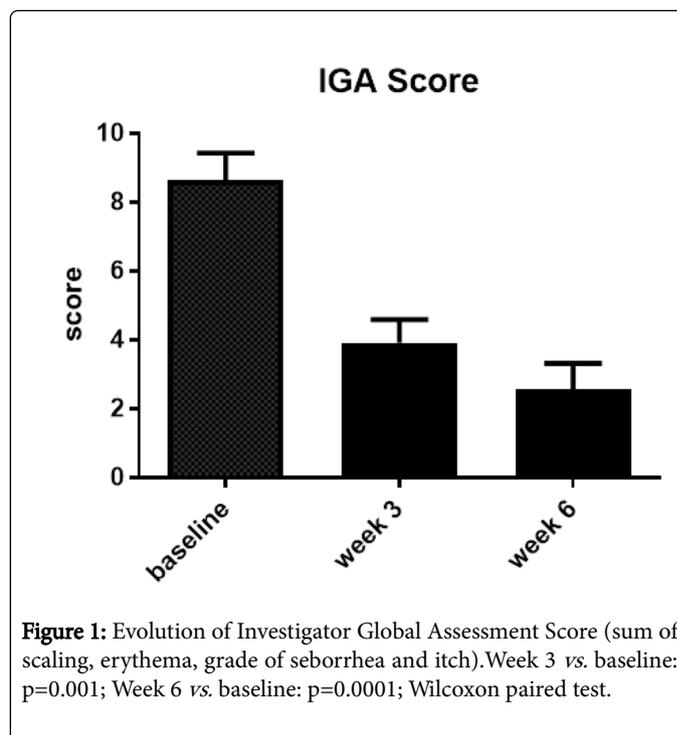
To evaluate in an assessor-blinded study the efficacy and tolerability of EDS in the treatment of facial SD in adult subjects.

## Subjects and Methods

This was a proof-of-concept, open, prospective, assessor-blinded 6-week trial. A total of 20 outpatient male subjects (mean age 46) with moderate-severe facial SD were enrolled, after their written informed consent. SD history lasted on average 20 years. The trial was conducted in two Dermatology out-patient clinics in Italy between June 2016 and February 2017. The study was conducted in accordance with Good Clinical Practices guidelines [11]. The Ethical Committee of each participating center approved study protocol before the start of the trial. Eligible participants were adult subjects aged 18 or over, skin type I to IV with a clinical diagnosis of moderate/severe SD involving face and/or trunk. Exclusion criteria were: a specific oral or topical treatment of SD in the previous month; HIV infection or other immunosuppressive conditions; an acute skin condition other than SD, pregnancy or breast feeding, a known history of allergy to one of the components of the tested product and unlikelihood of complying with protocol procedures. EDS cream was applied twice daily (2 Finger Tip Units per application and per area treated) on the most affected areas (mainly face and chest) in the morning and evening. Subjects were instructed to use non-aggressive cleansing facial products before the application of the cream. The primary study outcome was the evolution of the Investigator Global Assessment (IGA) score assessing erythema, scale/flaking, grade of seborrhea and itch, all measured on a five-point scale, from 0: absence of sign/symptom to 4: very severe sign/symptom. If SD process involved more than one area (i.e. face and trunk) an IGA average score was calculated. Subjects were assessed at baseline, after 3 and 6 weeks of treatment by an investigator unaware of the type of treatment. High definition digital photographs were also taken at each visit. Local tolerability was evaluated checking self-reported side effects. In view of the proof-of-concept nature of the study, no sample size calculation was needed. However, we decided to enroll at least 20 subjects to have a meaningful sample population. Statistical analysis was performed using GraphPad™ statistical software (GraphPad Software, Inc. La Jolla, CA 92037 USA). The main outcome (IGA score) was evaluated comparing week 3 and week 6 versus baseline value using Wilcoxon test for paired comparison. A p-value <0.05 was considered statistically significant.

## Results

All 20 subjects concluded the study. Baseline IGA score (mean ± SD) was  $9 \pm 3$  (Range 5 to 13). All subjects demonstrated clinical improvement starting from week 3. The use of EDS reduced significantly IGA score by 67% ( $p=0.01$ ) at week 3 and by 83% ( $p=0.0001$ ) at week 6 (Figure 1). EDS was effective in reducing each item of erythema, scale, seborrhea and itch (Table 1). After 6 weeks of treatment in comparison with baseline erythema score was reduced by 75%; scale by 58%; seborrhea by 70% and itch by 75%. All these reductions were statistically significant. The product was very well tolerated. Figure 2 shows some subjects' pictures at baseline and after 6 weeks of treatments. No local or systemic side effects were reported by the subjects at all study visits. Interestingly, both investigators and subjects reported the absence of blanching effect, which is quite common when topical corticosteroids are used on the face [12], after the application of the product.



## Discussion

Seborrheic Dermatitis (SD) is a very common skin disease, affecting 1–3% of the general population [13]. Immunosuppressive, like HIV infection and some neurological conditions like Parkinson disease increase the risk of SD [14]. SD is inflammatory chronic condition, characterized by erythema, flaking and itching papulo-squamous lesions [15]. Sebaceous gland rich areas are mainly involved in SD. SD commonly affects face, scalp, and trunk. The most supported pathogenetic theory of SD points out the main role of the yeasts of the genus *Malassezia* [16]. It is well known that *Malassezia* can alter the skin barrier through the degradation of sebum to free fatty acid (FFA) [17]. However more recent studies [18] shown that an alteration in skin microbioma is observed in SD with an over presence of bacteria like *Streptococcus epidermis*.

The authors concluded that, in contrast to other studies, SD is not only associated to the higher incidence of one particular *Malassezia* species but also to differences in the balance between the fungal and bacterial populations on the affected skin areas. SD is also associated to abnormal immune response with an alteration in T helper functions [19]. Finally, qualitative modifications in sebum have been demonstrated in SD. *Malassezia* lipases can alter the composition of sebum increasing the presence of free fatty acids like oleic acid [20]. Boelsma et al. [21] have demonstrated that small amount of oleic acid is sufficient to cause local skin irritation modulating cytokine production. In addition, oxidation of squalene has been detected in the sebum of affected SD skin area [22]. This oxidative stress could be a trigger factor starting the inflammatory process of SD and *Malassezia* could be considered a major source of squalene peroxidation in SD [23]. These data show that the pathogenetic mechanisms of SD are very complex and so far, not completely understood.



**Figure 2:** 5 subjects (1,2,3,4 and 5) at baseline (A) and after 6 weeks (B) of treatment with EDS. Normal light images.

	Baseline	After 3 weeks	After 6 weeks	P value Baseline vs. V6(Wilcoxon paired T test)
Scaling	1.9 (1.1)	0.8 (0.55)	0.8 (0.77)	0.025
Erythema	2.8 (1.0)	1.2 (0.6)	0.7 (0.8)	0.0018
Seborrhea	2.6 (0.9)	1.1 (0.8)	0.8 (0.8)	0.0055
Itch	1.6 (1.2)	0.8 (1.5)	0.4 (0.5)	0.06

**Table 1:** Evolution of single items score: Mean (SD).

Hyaluronic acid is a polysaccharide found in skin's tissue [24]. Some trials conducted with hyaluronic acid topical formulations, using different concentrations or type of HA molecule, have shown that this compound could reduce skin inflammation in SD subjects [4,5]. This positive effect of topical HA could be linked to its skin hydrating action [25] and skin barrier function improvement [26]. Topical HA could exert also anti-oxidant activity [27]. In addition, topical HA can modulate several skin cells functions: topical HA can have relevant effects on cell proliferation, recognition, and cell migration [28]. Interesting HA can stimulate the production of beta-defensin 2, strengthening the antibacterial potential of the skin [29]. This latter mechanism could be useful in view of the new evidences regarding skin microbioma alteration detected in SD skin affected areas [9]. Topical HA therefore could have several beneficial effects counteracting different pathogenetic mechanisms involved in skin alteration during SD. The clinical studies performed so far with HA in SD have used low molecular weight molecules (i.e. 800.000 Da) [4,5]. In our study we use very low molecular weight HA (i.e. 400.000-600.000 Da). It is well known that biological effect of HA could be influenced by its molecular size [30]. In the trial of

Schlesinger IGA score improved by 65.5% (4 weeks of treatment). Our proof of concept study has shown that 5% topical hyaluronic acid markedly improves facial SD with an IGA score improvement of 83% (6 weeks of treatment). Some limitations should be taken in account in evaluating our study results. The main limitation was that this study was an open non-comparative trial. However, to increase the internal validity of our results, we adopted an assessor blinded evaluation of the primary outcome of the trial (i.e. the evolution of IGA score.). Furthermore, this was a proof-of-concept trial and the results we have obtained should be confirmed by future controlled studies with an adequate sample size.

### Conclusion

In this study EDS applied twice daily for 6 consecutive weeks has been shown to be effective in reducing signs and symptoms of SD of the face and chest. The product was found to be well tolerated. Future controlled trials are warranted to confirm the efficacy and safety of this new therapeutic corticosteroid-free product for the treatment of facial SD.

## Acknowledgement

MM is an employee of Difa Cooper; a pharma company, producing and marketing Eutrosis DS. MM participated to the study protocol preparation and was involved in the final version of the manuscript. MM was not involved in data analysis and statistical evaluation. AB and MP were involved in the conduction of the trial (selection of subjects, visits, medical evaluation, data collection and data analysis). AB and MP declare no conflicts of interest.

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