 

# Reduction of Erythema in Moderate-Severe Rosacea by a Low Molecular Weight Heparan Sulfate Analog (HSA)

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## ABSTRACT

Rosacea changes are a result of an immune mediated response and the angiogenic properties of the LL-37 peptide. This peptide induces an inflammatory signal that activates the NLRP3-mediated inflammasome, triggering rosacea pathogenesis. Research findings show that LL-37 peptide is inhibited by binding to a cell surface glycosaminoglycan, heparan sulfate. Heparan Sulfate Analog (HSA) is a proprietary low molecular weight analog of heparan sulfate that has been formulated into a Dermal Repair Cream (DRC), specifically to aid in such immune mediated responses. Herein, in vitro studies using human epidermal keratinocytes showed an increase in HSA decreased LL-37 toxicity and IL-8 cytokine release. A single-center, randomized double-blind trial included 16 subjects (Fitzpatrick skin types I-IV) with a clinical diagnosis of type 1 rosacea and moderate to severe facial erythema, who were undergoing Pulsed Dye Laser (PDL) treatment. The clinical improvements of their facial erythema were assessed at baseline, 2 weeks, 4 weeks, and 8 weeks. Results revealed that low molecular weight HSA significantly improves the clinical signs of rosacea during the 8 weeks of use likely resulting from inhibition of LL-37 induced IL-8 cytokine release. These findings support the use of DRC in rosacea topical treatment regimens as it demonstrates visible skin benefits and improves tolerability of PDL therapy in a shorter duration of time as compared with PDL alone.

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## INTRODUCTION

Rosacea is a chronic inflammatory skin condition that affects blood vessels and pilosebaceous units.[1] It is characterized by recurrent flushing, telangiectasia, central facial erythema, and papules/pustules that often present on the nose, cheek, forehead, and chin.[2,3] The clinical signs and symptoms of rosacea vary but may include redness, dryness, edema, and stinging/burning.[3] Rosacea can have a massive impact on patients' quality of life as those with the condition report experiencing increased anxiety, depression, and embarrassment.[4-6] Despite its high burden, the choice of treatment is still challenging. The National Rosacea Society Expert Committee, American Academy of Dermatology, and National Institute of Arthritis and Musculoskeletal and Skin Diseases recommend standard management options which include topical/oral medications and laser/surgical interventions. A study by Baldwin et al[7] has shown that other over-the-counter (OTC) skin care products such as IL-8, cleansers, moisturizers, and sunscreen remain instrumental in rosacea therapy. Although retinoids are recommended for phymatous rosacea, there is a lack of OTC products to tackle the persistent facial redness many patients experience. This highlights a significant need for an efficacious, nonpharmacological treatment for the facial erythema of rosacea that can be integrated seamlessly into patients' treatment skincare regimens.

Research suggests that rosacea's various phenotypes are a result of an immune mediated response as well as the angiogenic properties of the antimicrobial peptide LL-37, which has a high prevalence and expression level in rosacea patients.[8] When bound to lipopolysaccharides (LPS) found in bacteria, LL-37 induces an inflammatory signal cascade that activates the NLRP3-mediated inflammasome, triggering skin inflammation, new blood vessel growth, and rosacea pathogenesis.[9] LL-37 also induces the secretion of Th1-inducing cytokines, IL-8, generation of reactive oxygen species, and inhibition of bacterial growth. This results in a disruption of the skin barrier function which consequently enhances the entry of foreign

substances, decreases the skin's water content, and increases transepidermal water loss (TEWL), all abnormalities seen in rosacea patients.[10]

Heparan sulfate is a naturally occurring glycosaminoglycan that is found in extracellular matrices, basement membranes, and exterior surfaces as receptors/coreceptors.[11,12] Its diverse architecture allows for a variety of proteins, chemokines, and antimicrobial peptides to bind to areas that contain specific saccharide sequences.[13] Interestingly, when LL-37 is bound to heparan sulfate, it prevents the formation of angiogenesis, tissue remodeling, and inflammatory cell responses that cause rosacea.[13]

Although the benefits of heparan sulfate are being used in various anti-inflammatory, wound healing, and periorbital skin rejuvenation strategies,[14-16] to our best knowledge, there is no clinical study that investigated its efficacy in the treatment of rosacea. Heparan Sulfate Analog (HSA) is a proprietary low molecular weight analog of heparan sulfate that has been formulated into a Dermal Repair Cream (DRC) specifically to aid in such immune mediated responses. The aims of this study are to investigate the potential of HSA to attenuate LL-37-induced inflammation and evaluate the clinical benefit and tolerability of DRC containing HSA in rosacea patients.

## MATERIALS AND METHODS

This randomized, double-blind, placebo study was approved by the Institutional Review Board and conducted at the Wilmington Dermatology Cosmetic and Research Center, PLLC from January 2022 to March 2022. All participants were provided written informed consent and photo release forms prior to participation.

### Study Participants

Eligible participants were female adults older than 18 with a clinical diagnosis of type 1 rosacea accompanied by persistent facial erythema; moderate to severe facial erythema associated with rosacea in accordance with the Clinician Erythema Assessment (CEA) scale (Table 1); no evidence of bumps or pustules in the previous 6 months; and planned to undergo Pulsed Dye Laser (PDL) treatment. Key exclusion criteria included evidence of bumps or pustules associated with rosacea or inflammatory disease, or any uncontrolled systemic disease; history of immunosuppression (eg, immune/deficiency disorders) or current use of oral/systemic immunosuppressive medications; or pregnant/intended to become pregnant or breastfeeding.

A sample size of 16 patients (Fitzpatrick skin types I-IV) met the inclusion criteria and were assigned interventions by the clinical investigator. All study participants were undergoing PDL treatment for their rosacea but were then, by 1:1 randomization, assigned to one of two groups, Group A-*control* included PDL plus Cetaphil cleanser, Cetaphil moisturizer, and Cetaphil sunscreen (SOC) (n=8), or Group B-*test product* included PDL plus SOC with DRC in place of control moisturizer (n=8). Baseline assessments including digital photographs, investigator CEA gradings, and telangiectasia severity scores were recorded. Facial erythema was assessed at baseline, 2 weeks, 4 weeks, and 8 weeks using the following assessment measurements: Investigator Assessment (CEA scale), and Self-Assessments (SAT-RFR) (Table 1 and Table 2, respectively), as well as Tolerability, and Satisfaction.

**TABLE 1.**

| The Clinical Erythema Assessment (CEA) Visual Assessment Scale Used to Grade Rosacea | |
|---|---|
| **Erythema** | **Grade Description** |
| 0 = Clear | Clear skin with no signs of erythema |
| 1 = Almost clear | Almost clear, Slight redness |
| 2 = Mild | Mild erythema, Definite redness |
| 3 = Moderate | Moderate erythema, Marked redness |
| 4 = Severe | Severe erythema, Fiery redness |

**TABLE 2.**

| Satisfaction Assessment Tool for Rosacea Facial Redness (SAT-RFR) | |
|---|---|
| **Erythema** | **Grade Description** |
| 0 | Very Dissatisfied |
| 1 | Dissatisfied |
| 2 | Neither Satisfied or Dissatisfied |
| 3 | Satisfied |
| 4 | Very Satisfied |

### Study Design

The study was conducted over 8 weeks and consisted of 4 visits. All patients were provided product use instructions and were asked to track product application in a diary for the study's duration. Specifically, patients were instructed to use Cetaphil cleanser two times daily and Cetaphil sunscreen one time daily. Patients in the treatment group (Group B) were asked to use DRC (Senté, Inc. Carlsbad, CA, USA) 2 times daily (8-weeks in combinations with the Cetaphil cleanser and Cetaphil sunscreen) and patients in the control group (Group A) were asked to use Cetaphil moisturizer 2 times daily for the same duration (8-weeks in combinations with the Cetaphil cleanser and Cetaphil sunscreen). At each visit, the IntelliStudio® Imaging System (Canfield Scientific, Parsippany, NJ) was utilized to obtain high-resolution digital photographs (front/right/left side of face). Subjects were also directed to complete a questionnaire that included subjective tolerability and redness assessment questions of their skin at each follow-up visit. Participants were asked on a scale of 0 (none) to 3 (severe) if they had any dryness, scaling, itching, or stinging/burning using a 4-point scale. Moreover, using a 5-point scale for Satisfaction-Assessment

of Rosacea Facial Redness (SAT-RFR) (Table 2), the participants rated how satisfied they were with the effect of their study topical product. After each visit, clinical investigators graded erythema, redness, and adverse events on a CEA 5-point scale (Table 1). Additionally, investigators also confirmed participant adherence to treatment by a review of subject diary at the end of each visit.

**Study Endpoints**

The primary outcome was to determine if DRC (with HSA) clinically reduces severe erythema in rosacea, as an adjunct to PDL therapy. This was measured by at least a 1-point improvement on the 5-point CEA scale or percentage (%) improvement of erythema from baseline to weeks 2, 4, and 8 after starting the test product. Secondary outcome measures included image-based analysis of facial erythema, participant-evaluated SAT-RFR for tolerability/even skin tone, and clinician-reported adverse events throughout the course of the study.

**Statistical Analysis**

Data were analyzed for statistical significance at $P<0.05$ using paired-samples *t*-tests.

**In Vitro Study**

*Specimen Preparation*

Primary normal human epidermal keratinocytes (NHEK) were cultured on a flask containing keratinocyte growth medium (KGMc). The sample was collected and then seeded on 96 test wells at a rate of 6 wells per condition and per plate. When cells reached 80% confluence, the medium was replaced by 3 different concentrations of LL-37: 2 µg/mL, 5 µg/mL, and 10 µg/mL prepared in KGMc or by the KGMc for the negative control. The cell plates were then incubated for 24h or 48h at 37°C (5% of CO2). Cultures were then placed in a -80°C freezer to further analyze interleukin-8 (IL-8) cytokine release, which was conducted using the viability test by Thiazolyl blue tetrazolium bromide (MTT) (Sigma Aldrich – M5655).

*Viability Test*

Thiazolyl blue tetrazolium bromide (MTT) assays were used to determine the minimal dose of LL-37 and time (24h or 48h) required to induce inflammation, specifically IL-8 production, without cell toxicity. Immediately after the cultures were removed from the freezer a viability test was performed. A 1 mg/mL solution of MTT was prepared from stock solution at 5 mg/mL then added to each cellular well and intubated in CO2 for a 3-hour duration. The MTT solution was then replaced with isopropanol after 30 minutes under orbital agitation. The optical density (DO) was then measured at 570 nm.

*IL-8 ELISA*

IL-8 assay was performed on KGMc culture medium to measure the expression of IL-8 release. To assess the effects of HSA on cytokine release, 5 µg/mL of LL-37 was placed into 4 different concentrations of HSA: 0 µM (negative control), 10µM, 100µM, and 1mM prepared in KGMc and cell plates were incubated for 48h at 37°C (5% of CO2). Changes in IL-8 were quantitated by a human enzyme-linked immunosorbent assay (ELISA) kit (Sigma Aldrich – RAB0319-1KT). The culture media, diluted in DPBS, and the standards were incubated into the coated wells containing the immobilized IL-8 antibody for 2.5 hours at room temperature. The coated wells were incubated with a biotinylated anti-human IL-8 antibody and HRP-conjugated streptavidin with 3,3',5,5'-tetramethylbenzidine (TMB) for 30 minutes according to the manufacturer's instructions. The reaction was stopped and the absorbance at 450 nm was measured using the M200Pro Tecan microplate reader and Magellan7 software. From this, the mean and the variation percentage between the different wells with the same treatment were recorded. The average percentage of variation was calculated compared to the control wells (ng/ml) and the significance was determined by a student's *t*-test.

## RESULTS

In vitro - At 24h, there was a significant increase (60%) in the release of IL-8 compared with the control when the human epithelial keratinocytes were exposed to LL-37 at a concentration of 10 µg/mL. At 48h, a significant increase in the release of IL-8, compared with the control, 37% and 96%, respectively when the keratinocytes were exposed to LL-37 at concentration of 5 and 10µg/mL, respectively (Figure 1A). The results of the MTT test showed cytotoxicity of LL-37 at 10 µg/mL with viability results at 24h and 48h, respectively of 32.8 ± 6.5% and 37.0 ± 8.1%. The optimal results were observed using LL-37 at 5 µg/mL at 48 hours (cell viability of 70.2 ± 5.7% and 37% IL-8 release). Therefore, this concentration was utilized for the remainder of the testing. The results indicated a decrease in the release of IL-8 in the KGMc culture, indirectly proportional to the concentration of HSA. Specifically, at 48h HSA (concentration of 1000 µM) significantly decreased the release of IL-8 by 40% compared to the control with 0 µM HSA (Figure 1B). Taken together, higher concentrations of HSA lead to a greater decrease in IL-8 release from cells, reducing inflammation.

*Demographics and Baseline Characteristics*

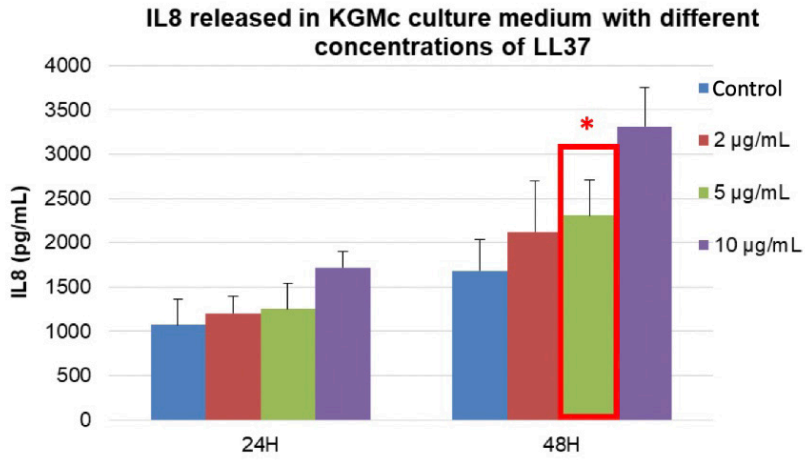
A total of 16 patients (Fitzpatrick skin types I-IV), who received PDL treatment for their rosacea, met the enrollment criteria (Table 3). Participants were randomized in a double-blind fashion to receive one of the two interventions: control (Group A), continuing PDL plus Cetaphil cleanser, Cetaphil moisturizer, and Cetaphil sunscreen (SOC), or treatment (Group B), continuing PDL plus SOC with DRC in place of Cetaphil moisturizer.

*Clinician Erythema Assessment*

Using the CEA scale (Table 1), clinical investigators (all blinded) graded participants in the control (Group A) and treatment

**FIGURE 1. In vitro analysis of HSA effect on LL-37 release from human epidermal keratinocytes.** Keratinocytes were first cultured on a flask containing KGMc medium, then collected and seeded in two 96 wells plates, at a rate of 6 wells per conditions/per plate. When the confluence reached about 80%, the culture medium was replaced by 3 different concentrations of LL37: 2µg/mL, 5 µg/mL, and 10 µg/mL prepared in KGMc, or by KGMc for the negative control. The average percentages of variation between treated and control wells were determined, and data was analyzed with student's t-test for statistical analysis. (A) The most favorable contact time chosen is 48h. And, the minimal dose of LL-37 inducing the best IL-8 release with the weakest cell toxicity is 5µg/mL. (B) HSA blocks LL-37-mediated inflammatory IL-8 cytokine release.

(A)




(B)

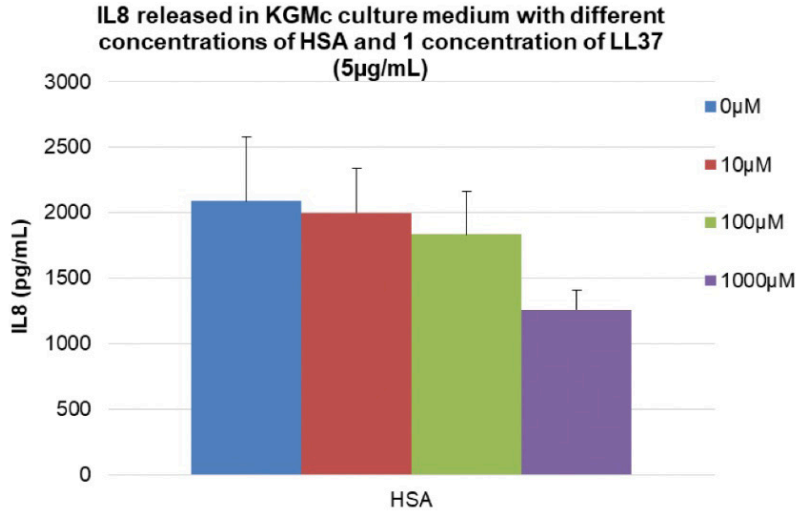


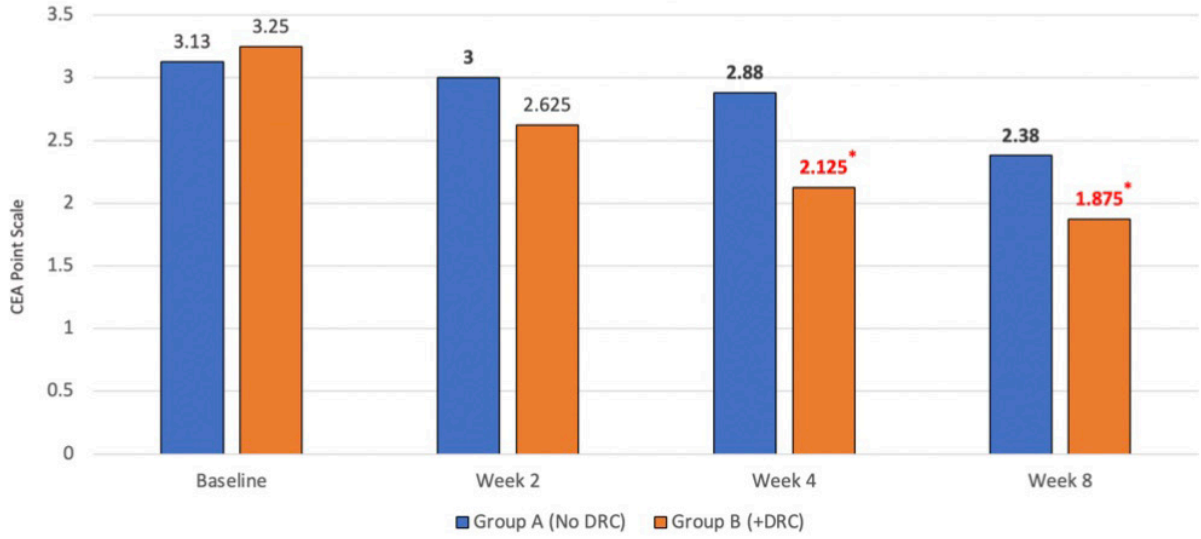

**TABLE 3.**

| Participant Distribution and Demographics | |
|---|---|
| **Participant Distribution and Demographics** | **N** |
| Subjects | |
| Enrolled | 16 |
| Completed | 16 |
| Age | |
| Mean | 46.2 |
| Minimum | 22 |
| Maximum | 66 |
| Sex | |
| Female | 16 |
| Male | 0 |
| Race | |
| White (Fitzpatrick skin types I-IV) | 16 |

(Group B) groups. The criterion of at least a 1-point reduction in CEA was used to determine a reduction in redness from baseline to week 2, week 4, and week 8 (Figure 2A). At week 2, a 19.23% (CEA - 3.25 to 2.625) improvement in facial erythema was noticed for the DRC group (Group B) as compared to 4.15% (CEA – 3.13 to 3) in the control group (Group A). At week 4, there was a 34.61% (CEA - 3.25 to 2.125) reduction in redness for DRC (Group B) vs 7.98% (CEA – 3.13 to 2.88) in the control group (Group A). At 8 weeks, the DRC group (Group B) exhibited a 42.3% (CEA – 3.25 to 1.875) reduction in erythema compared to 23.96% (CEA - 3.13 to 2.38) in the control group (Group A) (Figure 2B). Importantly, control group (Group A) did not achieve the required endpoint of a 1-point improvement in CEA throughout the study (Figure 2A). Compared to baseline, at week 4 and week 8, 100% of subjects in the DRC group (Group B) had a 1-point

**FIGURE 2. (A) Visual redness evaluation by Clinical Erythema Assessment (CEA). (B) (CEA) – Percent (%) Change from baseline.** Using CEA 5-point scale, clinical investigators graded participants in the control (Group A) and treatment (Group B) groups.

(A)




(B)

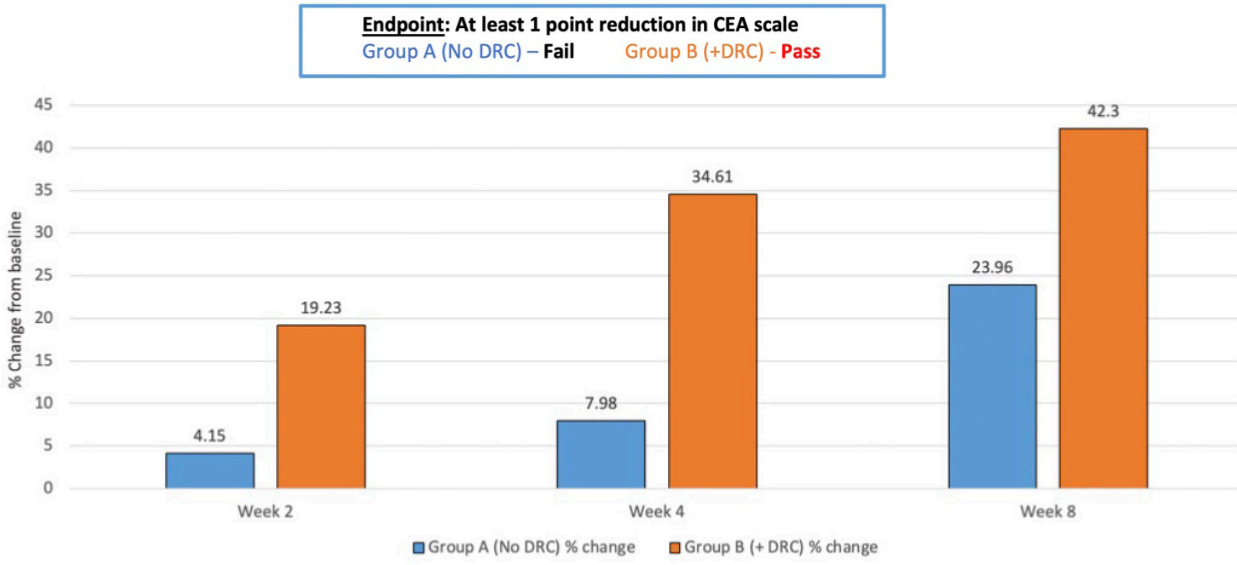



**FIGURE 3. Satisfaction-Assessment of Rosacea Facial Redness (SAT-RFR) - Percent (%) subjects satisfied or very satisfied with facial redness.** Using the SAT-RFR 5-point scale, clinical investigators (all blinded) graded participants in the control (Group A) and treatment (Group B) groups.

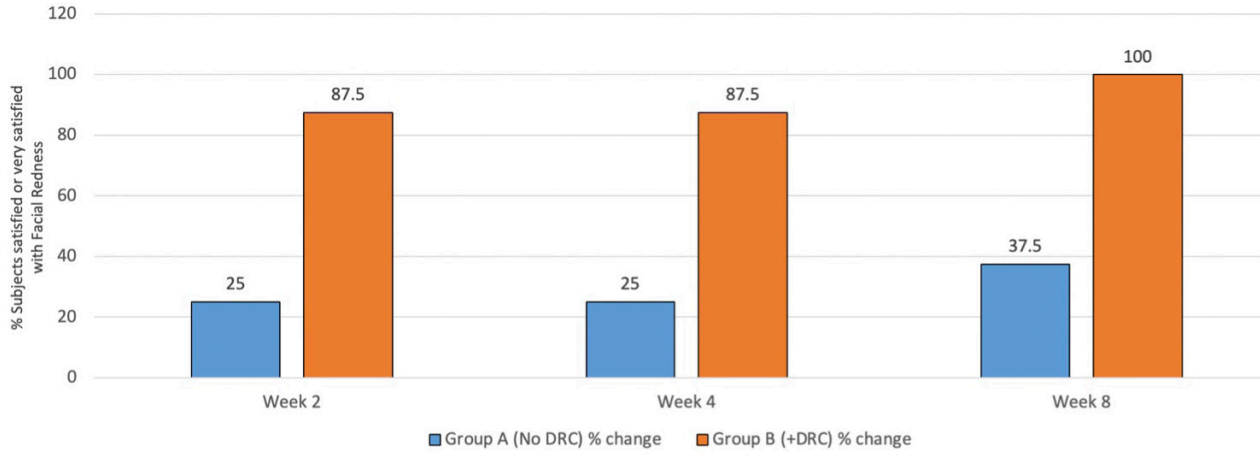


**FIGURE 4. Tolerability Assessments – Percent (%) subjects experiencing irritation by week 8.** Scaling, itching, and burning was not experienced by any patients in the treatment group (Group B), but was experienced in the control group (Group A). Dryness was experienced by both groups; however, only 12.5% of patients experienced dryness in the treatment group (Group B) compared to 62.5% in the control group (Group A).

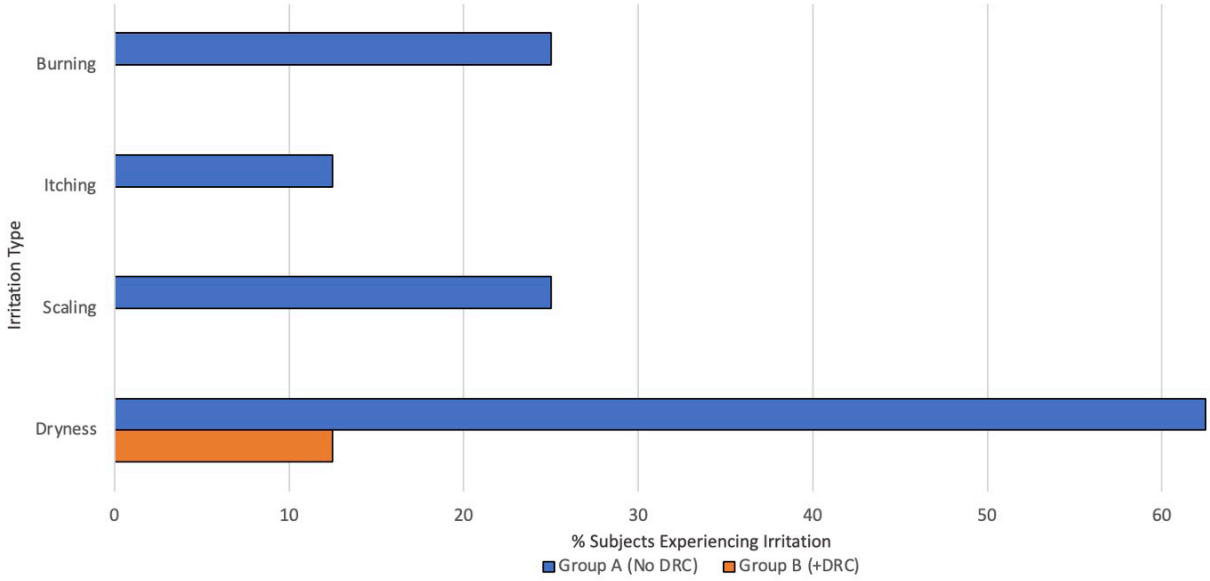



**FIGURE 5. Photographs depicting subject responses – Treatment group (Group B).** A subject from the treatment group (Group B - PDL + Cetaphil SOC + DRC) from baseline to 8 weeks in digital (*upper panel, A*) and under cross-polarized red channel imaging (*lower panel, B*). There is significant improvement in erythema.

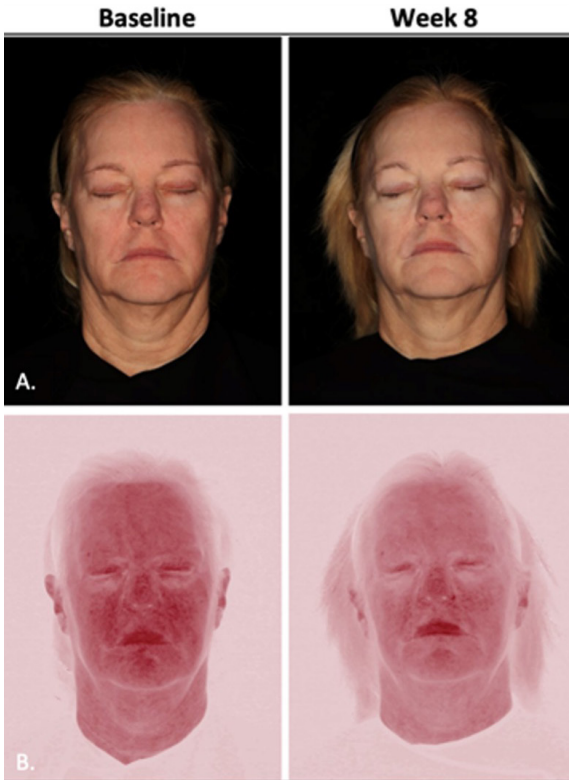
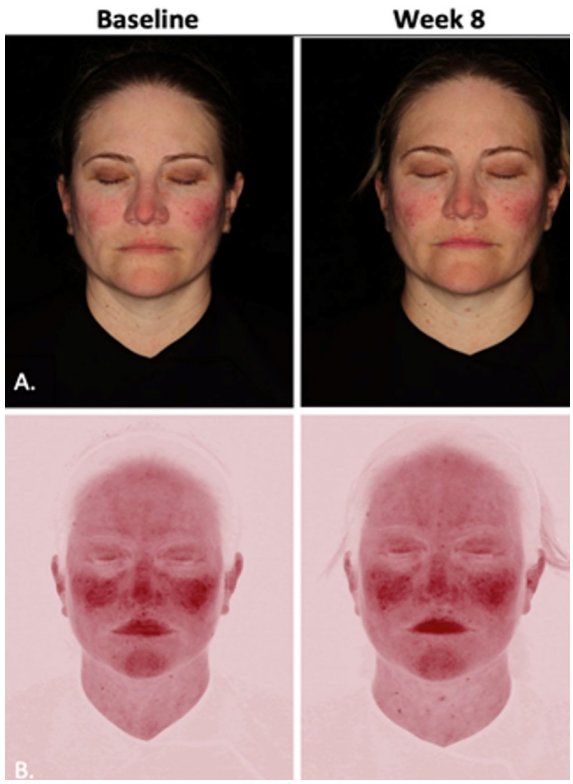



**FIGURE 6. Photographs depicting subject responses – Control group (Group A).** A subject from the control group (Group A - PDL + Cetaphil SOC) from baseline to 8 weeks in digital (*upper panel, A*) and under cross-polarized red channel imaging (*lower panel, B*). There is no improvement in erythema.



reduction in CEA, which was not seen in the control group (Group A). Taken together, DRC (Group B) improves redness in subjects with rosacea undergoing PDL more significantly than the control (Group A).

*Patient Self Assessments (SAT-RFR)/Tolerability*

Using the SAT-RFR scale (Table 2), clinical investigators graded participants in the control (Group A) and DRC treatment (Group B) groups. At week 2 and week 4, 87.5% of subjects in the DRC group (Group B) were satisfied/very satisfied with their facial redness improvement compared to 25% of subjects in the control group (Group A). By week 8, 100% of subjects in the DRC group (Group B) were satisfied/very satisfied with their outcomes in facial redness reduction compared to only 37.5% in the control group (Group A) (Figure 3). By week 8, scaling, itching, and burning was not experienced by any patients in the DRC group (Group B), but was experienced in the control group (Group A). Dryness was experienced by both groups; however, only 12.5% of patients experienced dryness in the DRC group (Group B) compared to 62.5% in the control group (Group A) (Figure 4). Multiple photographic examples are also shown demonstrating results at baseline and week 8 between subjects using DRC (Group B) (Figure 5) and those using the control (Group A) (Figure 6). There is an apparent reduction in redness in the DRC group (Group B) compared to the control group (Group A) depicting the reduction of inflammation and redness by DRC.

## LIMITATIONS

One limitation of this study was its relatively small sample size and non-inclusiveness of skin of color subjects which can affect the generalization of presented results. Ideally, more than 16 participants would allow for more precise confidence intervals. Moreover, our trial utilized the CEA scale to identify redness in our patients, as it has been largely used in other clinical trials. However, the CEA may lack specificity and reliability when assessing skin of color patients as traditional clinical features of rosacea may be less obvious in richly pigmented skin.[17] It is also important to note the challenges that arise when using redness as a clinical assessment in skin of color. Redness and other potential inflammation are often overlooked in dark skin due to the observers' inability to notice alterations in skin tone during visual assessments.[18] Since rosacea often goes unrecognized and underdiagnosed in skin of color,[17,19] it is important to consider the need for validated scales that are precise and consistent in assessing typical rosacea features in all skin tones.

## CONCLUSION

The in vitro study demonstrates the ability of HSA to block LL-37-mediated inflammatory IL-8 cytokine release, one of the critical cytokines responsible for rosacea-based erythema. This mechanism of action may be one of the key pathways associated with the clinical outcomes observed when using HSA based topical products. Recent studies have shown that rosacea patients have a barrier deficiency that leads to increased transepidermal water loss, decreased skin hydration, and increased skin pH.[11] The lack of a protective barrier could potentially allow the entry of irritants into the skin and cause hypersensitivity and inflammation leading to rosacea. To combat this, dermatologists recommend the use of products that target skincare barrier repair to minimize inflammation. They consider it essential to use skin cleansers that are able remove noxious stimuli from the face while keeping the lipids and proteins necessary to maintain a healthy skin barrier. Moreover, they recommend avoiding products that contain alcohol, acetone, propylene-glycol, and other acidic substances that could irritate the skin surface.[11]

Herein, HSA (a proprietary formulated heparan sulfate), the key ingredient in DRC, maintains skin homeostasis and skin barrier function while simultaneously mediating the inflammatory cascade at a cellular level. This study shows DRC is an efficacious adjunct to PDL therapy in reducing moderate to severe erythema associated with rosacea. This study also demonstrates that DRC improves the tolerability of PDL therapy as well as reduces post therapy irritation. The inclusion of HSA in topical creams, such as DRC, has been proven through fluorescence to penetrate the different skin layers and hence relieve rosacea symptoms caused by inflammation (*unpublished data not shown*). HSA and this mechanism of action may be beneficial to reduce the potential inflammatory response and redness observed in many inflammatory skin conditions. Future studies are warranted to better understand the full potential of this unique molecule.

## DISCLOSURES

RG is an Investigator- Senté, Inc., AbbVie, Galderma, Merz, Aclaris, Symbio, Amgen, Innovaderm, Eli Lilly, Consultant for Abbvie, Cartessa; RLG is a consultant for and has equity interest in MatriSys bioscience and Senté; JLC – Senté, Inc., Allergan, Galderma, Revance, Sciton, Pulse, Biopelle, Merz, CROMA, InMode, Accure; ASB is a consultant for Senté, inc. All other authors declare no conflict of interest.

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