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Efficacy of 7% Ectoine Cream for Facial Seborrheic Dermatitis: A Randomized Controlled Trial of Acute and Maintenance Phases

Nirynya Jitarayameth, Nanticha Faromkao, Chotinij Lertphanichkul, Chantalck Muennarong and Montree Udompataikul *

Department of Dermatology, Faculty of Medicine, Srinakharinwirot University, Bangkok 10110, Thailand
* Correspondence: umontree@gmail.com

Abstract

Background: Seborrheic dermatitis is a chronic, relapsing inflammatory condition requiring acute and maintenance treatment. Ectoine, a natural extremolyte with barrier-supportive and anti-inflammatory properties, offers a potential non-steroidal option. **Methods:** In this double-blind randomized controlled trial, 40 participants received 7% ectoine or 1% hydrocortisone cream twice daily for up to 4 weeks. Responders entered a 12-week maintenance phase and were re-randomized to ectoine or placebo. Outcomes included change in Seborrheic Dermatitis Area and Severity Index (SEDASI) from baseline, Investigator's Global Assessment (IGA), remission and relapse rates, time to relapse, and adverse events. **Results:** SEDASI decreased from baseline in both groups. The reduction was larger with hydrocortisone, but the between-group mean difference at Week 4 was −2.01 (95% CI, −4.81 to 0.78; $p = 0.151$). Median time to relapse was 56 versus 28 days with ectoine and placebo, respectively (log-rank $p = 0.066$). Adverse events were mild. **Conclusions:** Overall, 7% Ectoine reduced disease severity during the acute phase, though numerically less than 1% hydrocortisone; the non-significant difference does not exclude a clinically relevant advantage of hydrocortisone. Ectoine showed a non-significant trend toward longer time to relapse.

Keywords: ectoine; hydrocortisone; randomized controlled trial; seborrheic dermatitis

1. Introduction

Seborrheic dermatitis is a common chronic inflammatory dermatosis, with a global pooled prevalence of approximately 4.4% [1]. It typically presents with erythematous patches and fine scaling in sebaceous-rich areas, particularly on the face [2]. Although benign, the disease often significantly impairs patients' quality of life due to its recurrent nature and cosmetic burden [3]. Flares are commonly triggered by stress and dry and cold weather [4].

The exact pathogenesis of seborrheic dermatitis remains unclear. However, current evidence suggests a complex interplay between *Malassezia*-associated microbial dysbiosis and dysregulated immune responses, resulting in recurrent inflammation [2,5]. Current management of facial seborrheic dermatitis in the acute phase primarily involves topical corticosteroids and antifungal agents [6]. Low- to mid-potency corticosteroids, such as hydrocortisone, provide effective short-term control but they are not suitable for prolonged use due to adverse effects including skin discoloration, acne, and skin atrophy. During

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the maintenance phase, antifungal agents and topical calcineurin inhibitors are commonly used. However, the use of topical calcineurin inhibitors is limited by local irritation, high cost, and concerns regarding long-term safety [7].

Given the chronic and relapsing nature of seborrheic dermatitis, long-term treatment strategies are essential. In recent years, there has been a shift toward non-steroidal and cosmeceutical formulations, particularly for long-term use. This approach is based on the understanding that the disease involves multiple factors, including *Malassezia* overgrowth, inflammation, and impaired skin barrier function.

During the acute phase, multi-ingredient non-steroidal formulations containing various combinations of agents such as zinc PCA, piroctone olamine, glycyrrhetinate, biosaccharides, lactoferrin, and *Aloe vera* have shown effectiveness in reducing erythema, scaling, and pruritus [8]. These ingredients work together through different mechanisms, including antifungal effects, reduction of inflammation, regulation of sebum, and improvement of skin barrier function [9,10].

During the maintenance phase, continued use of non-steroidal dermocosmetic formulations may help maintain disease control and reduce recurrence. Barrier-supportive ingredients may also contribute to restoration of skin barrier function and control of low-grade inflammation. These properties are particularly relevant for facial seborrheic dermatitis, where tolerability and suitability for long-term use are important considerations [11,12]. However, current evidence remains limited. Most studies are small and non-randomized, and the formulations used vary widely, making it difficult to compare results. Therefore, well-designed randomized controlled trials are needed to confirm the effectiveness and long-term benefits of these treatments.

Ectoine is an extremophile-derived molecule and cyclic amino acid derivative that plays a crucial role in protecting cells from environmental stress, particularly in microorganisms inhabiting extreme environments. Its zwitterionic structure enables strong water-binding capacity, facilitating the formation of a "water shell" around cellular components. This property enhances membrane stability, reduces water loss, and protects cells from external damage. Experimental studies have shown that, at the in vitro level, ectoine stabilizes cellular membranes and reduces surfactant-induced cell lysis [13,14].

Ectoine also induces *hsp70* expression in keratinocytes, inhibiting IκB-α degradation and NF-κB activation, thereby downregulating proinflammatory cytokines including IL-1, IL-6, and TNF-α [15]. In addition, ectoine suppresses UVA-induced activation of transcription factor AP-2 and prevents the upregulation of intercellular adhesion molecule-1 (ICAM-1), a cell-surface protein that mediates leukocyte adhesion to the vascular endothelium and amplifies cutaneous inflammatory cascades [16]. Some in vivo studies demonstrated that ectoine decreased transepidermal water loss (TEWL), improved skin hydration, and reduced inflammatory responses [17]. It is classified as a moisturizer with an anti-inflammatory property. Clinical studies of ectoine in inflammatory skin conditions, such as atopic dermatitis [18–20] and retinoid-induced dermatitis [17], have demonstrated improvements in erythema, pruritus, and overall disease severity, with excellent tolerability even in infants [17]. Taken together, the membrane-stabilizing and anti-inflammatory properties are particularly relevant to inflammatory dermatoses such as atopic dermatitis and retinoid-induced dermatitis, both of which are characterized by epidermal barrier dysfunction, inflammation, and impaired water retention. However, evidence regarding its role in seborrheic dermatitis, particularly in acute management and relapse prevention, remains limited. Therefore, this study aimed to evaluate the efficacy and safety of 7% ectoine cream in patients with mild-to-moderate facial seborrheic dermatitis during both the acute and maintenance phases. We hypothesized that 7% ectoine cream would reduce disease

severity during the acute phase compared with 1% hydrocortisone cream, and would help maintain remission during the maintenance phase, with a comparable safety profile.

2. Materials and Methods

2.1. Participants

This single-center trial was conducted at the outpatient dermatology clinic of the Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand. A total of 40 adult participants aged ≥18 years with mild-to-moderate facial seborrheic dermatitis (SEDASI score 1–29) during the acute phase were enrolled in this study. Participants were excluded if they had other facial dermatoses (e.g., psoriasis, rosacea, or acne), concomitant facial skin conditions that could interfere with clinical evaluation, known hypersensitivity to study-related medications, immunocompromised status, or were pregnant or breastfeeding. Participants who had received topical or systemic treatment for seborrheic dermatitis within 1 month prior to enrollment were also excluded.

After completing the 4-week treatment during the acute phase, participants who achieved remission, defined as an Investigator's Global Assessment (IGA) score of 0 or 1, were subsequently enrolled in the maintenance phase.

Sunscreen and makeup products were permitted during both study phases; however, non-medicated topical moisturizers were permitted only during the acute phase.

2.2. Study Design

This was a two-group parallel, double-blind randomized controlled trial with a 1:1 allocation ratio and a superiority framework (Figure 1). The trial was reported in accordance with the CONSORT 2025 guidelines (See Supplementary Table S1). A non-blinded pharmacist generated the random allocation sequence using a computer-generated block randomization schedule with a block size of four, prepared coded, identical medication packs accordingly, and assigned participants to the intervention. Participants were enrolled by the investigators, who had no access to the allocation sequence at any point. Allocation codes were held by non-blinded study personnel throughout.

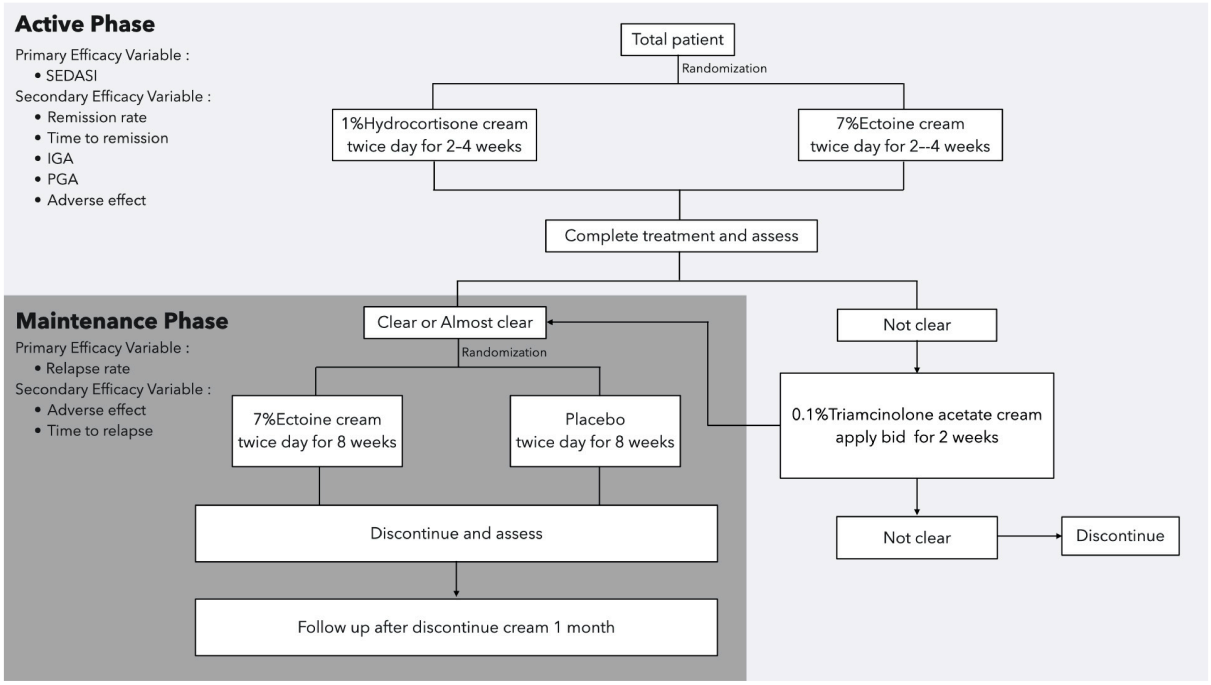


Figure 1. Study protocol illustrating the acute and maintenance phases, treatment allocation, follow-up schedule, and outcome assessments throughout the study.

Participants, investigators, outcome assessors, and the data analyst were blinded to treatment allocation. All study creams were dispensed in identical, unlabeled containers bearing only the allocation code. The two creams used in the acute phase were identical in appearance, color, and texture. In the maintenance phase, the placebo used the same vehicle formulation as the ectoine cream and was therefore sensorially identical.

Assessments were conducted online weekly to monitor remission and relapse and on-site every 2 weeks during the acute phase and every 4 weeks during the maintenance phase.

There were no important changes to the trial design, eligibility criteria, or outcomes after the trial commenced. The outcomes and analyses reported here are those specified in the protocol approved by the ethics committee before enrollment began.

2.2.1. Acute Phase

Participants were randomized 1:1 to 7% ectoine cream (E; Qualimed Co., Ltd., Bangkok, Thailand) or 1% hydrocortisone cream (H; provided by Qualimed Co., Ltd., Bangkok, Thailand), self-applied twice daily for 2–4 weeks according to written and verbal instructions. During the acute phase, participants were instructed to apply the assigned cream as a thin film to the affected facial areas, using a rule-of-thumb approach for topical application. At each study visit, participants were provided with a 10-g tube of the assigned study cream. Treatment adherence was assessed at subsequent visits based on the amount of study medication remaining in the returned tube.

The 7% ectoine cream contained Aqua, Hydrogenated Phosphatidylcholine, Caprylic/Capric Triglyceride, Pentylene Glycol, *Butyrospermum Parkii* Butter, Glycerin, Squalane, Ceramide 3, 7% ectoine, *Olea Europaea* Fruit Oil, *Cardiospermum Halicacabum* Flower/Leaf/Vine Extract, *Oryza sativa* Bran Cera, Glycine, Alanine, Butylene Glycol, Hydroxyphenyl Propamidolbenzoic Acid, Hydroxyethylcellulose, Sodium Carbomer, Carbomer, and Xanthan Gum. The 1% hydrocortisone cream was a commercially available formulation containing 1% hydrocortisone. The complete excipient composition was not available to the investigators.

Participants achieving remission (IGA score of 0 or 1) at Week 2 entered the maintenance phase immediately; the remainder continued their assigned treatment until Week 4. Those who had not achieved remission at Week 4 discontinued the assigned treatment and received rescue treatment with 0.1% triamcinolone acetonide cream (Qualimed Co., Ltd., Bangkok, Thailand) twice daily for 2 weeks, to minimize prolonged disease activity and patient discomfort. Participants who failed to achieve remission after rescue treatment were excluded from the maintenance phase but remained in the acute-phase efficacy analysis.

2.2.2. Maintenance Phase

Participants achieving remission were re-randomized 1:1 to 7% ectoine cream or placebo (P; Qualimed Co., Ltd., Bangkok, Thailand), applied twice daily over the entire face as a thin film using the same rule-of-thumb approach for 8 weeks, followed by a 4-week treatment-free follow-up period. The placebo contained the same vehicle formulation and ingredients as the ectoine cream, except that ectoine was omitted. As in the acute phase, participants received a 10-g tube at each study visit, and treatment adherence was assessed based on the amount of study medication remaining in the returned tube. Participants who relapsed, defined as an IGA score ≥ 2, were withdrawn according to the study protocol.

2.3. Primary Variable of Efficacy

During the acute phase, the primary efficacy outcome was the change in Seborrheic Dermatitis Area and Severity Index score (SEDASI) [21] from baseline to Week 4.

Clinical assessments were performed using standardized facial images captured with the OBSERV 520x system (Canfield Scientific, Parsippany, NJ, USA), which provides stan-

dardized illumination and dedicated imaging modes for enhanced visualization of erythema and scaling. Images were obtained from three standardized positions: frontal, left 45°, and right 45° views. This approach was intended to support consistent assessment across study visits.

The SEDASI score is a composite severity index evaluating lesion extent, presentation pattern, scaling, and erythema across four facial regions (nose, forehead, left cheek, and right cheek). Disease severity was classified as mild (1–14), moderate (15–29), severe (30–44), or very severe (>45) (Table 1).

Table 1. Seborrheic Dermatitis Area and Severity Index (SEDASI).

Area	Lesion Extension	Presentation Pattern	Scaling	Erythema
Nose Forehead Left cheek Right cheek	0 = none 1 = 1–9% 2 = 10–29% 3 = 30–49% 4 = 50–69% 5 = 70–89% 6 = 90–100%	0 = absence of lesions 1 = few scattered patches 2 = multiple/clustered patches 3 = large/confluent patches	0 = none 1 = tiny scales 2 = medium thicker scales 3 = large thickened scales	0 = none 1 = pink 2 = pink-red 3 = intense red

The total SEDASI score = the composite score of lesion extension, presentation pattern, scaling, and erythema across four facial areas (nose, forehead, left cheek, and right cheek). Disease severity was classified as mild (1–14), moderate (15–29), severe (30–44), or very severe (>45).

2.4. Secondary Variables of Efficacy

During the acute phase, secondary outcomes included comparisons of Investigator's Global Assessment (IGA), Patient Global Assessment (PGA), remission rate, time to remission, and adverse events between the ectoine (E) and hydrocortisone (H) groups from baseline to Week 4. Overall clinical improvement was assessed by investigators using the IGA and by participants using the PGA (Table 2).

Table 2. Investigator's Global Assessment (IGA) and Patient Global Assessment (PGA) in acute phase.

IGA and PGA Score in Acute Phase	Description
0	completely clear
1	minimal residual lesions (≥10% to <25% of baseline)
2	lesions ≥ 25% to <50%
3	lesions ≥ 50% to <100%
4	equal to baseline
5	worsening beyond baseline severity

During the maintenance phase, outcomes included changes in SEDASI, IGA, and PGA scores from maintenance-phase baseline, as well as relapse rate, time to relapse, and adverse events (Table 3).

Table 3. Investigator's Global Assessment (IGA) and Patient Global Assessment (PGA) in maintenance phase.

IGA and PGA Score in Maintenance Phase	Description
0	completely clear skin with no recurrence
1	minimal recurrence involving ≥10% to <25% of baseline severity
2	recurrence of ≥25% to <50%
3	recurrence of ≥50% to <100%
4	full recurrence equivalent to baseline
5	worsening beyond baseline severity

2.5. Adverse Event Assessment

Adverse events were defined as any untoward local or systemic event occurring after the first application of the study medication, regardless of causal relationship. Harms were assessed systematically using a structured questionnaire administered at every onsite visit, which asked participants about symptoms. Any reported event was further evaluated by the investigator, who recorded its onset, duration, severity, relationship to the study medication, and whether it led to treatment discontinuation.

2.6. Sample Size

The sample size was calculated for a superiority comparison of the primary outcome. As no prior trial of ectoine in seborrheic dermatitis was available, assumptions were derived indirectly from two published trials in atopic dermatitis that used the SCORAD index (SCORing Atopic Dermatitis). Canpolat et al. [22] reported a mean reduction in SCORAD of 4.00 units from baseline to day 8 in participants treated with 1% hydrocortisone cream alone, while Marini et al. [19] reported a mean reduction of 2.19 units (standard deviation 1.76) from baseline to day 7 in participants treated with 7% ectoine cream. These figures yielded an anticipated between-group mean difference of 1.81 units, with an assumed common standard deviation of 1.76 units. With a two-sided α of 0.05 and 80% power, 16 participants per group were required (PS: Power and Sample Size Calculation, version 3.1.2 (Vanderbilt University, Nashville, TN, USA)). Because the follow-up period extended to 12 weeks, a 20% dropout rate was anticipated, and the target sample size was therefore increased to 20 participants per group (total N = 40).

2.7. Statistical Analysis

Statistical analyses were performed using Stata version 14.0 (StataCorp LLC, College Station, TX, USA). All randomized participants were included in the analysis according to their originally assigned group (intention-to-treat). Continuous variables were compared using Student's *t*-test or the Mann–Whitney U test, and categorical variables using the Chi-square or Fisher's exact test, including for adverse events. Longitudinal continuous outcomes were analyzed using linear mixed-effects models, which include all available observations under a missing-at-random assumption; no imputation was performed. For binary outcomes, participants with missing data were counted as not having achieved the event. Time-to-remission and time-to-relapse were analyzed using Kaplan–Meier survival analysis and compared between groups using the log-rank test. A two-sided p-value < 0.05 was considered statistically significant. No interim, subgroup, or sensitivity analyses were performed.

3. Results

3.1. Baseline Characteristics in the Acute Phase

Participants were recruited between 10 June 2024 and 3 February 2025. Follow-up for both efficacy and harm outcomes was completed on 12 March 2025. The trial ended after the planned sample size had been recruited and the prespecified follow-up period had concluded.

A total of 40 participants were enrolled and block-randomized 1:1 to the H group (n = 20) or the E group (n = 20) in the acute phase. Remission was achieved directly, without rescue treatment, in 16 participants in the H group and 11 in the E group. Nine participants who did not achieve remission (3 in the H group and 6 in the E group) received rescue treatment with 0.1% triamcinolone acetonide; of these, remission was achieved in 1 (H) and 4 (E) participants, while the remaining 2 in each group failed to achieve remission and were excluded from the maintenance phase, although they were retained in the acute-phase efficacy analysis. A further 4 participants (1 in the H group and 3 in the E group) were lost to follow-up before Week 4 and did not receive rescue treatment; all cited inconvenience in attending scheduled follow-up visits. No participant was lost to follow-up or discontinued treatment because of an adverse event.

Overall, 17 participants in the H group and 15 in the E group achieved remission and entered the maintenance phase, giving 32 participants in the maintenance phase analysis (Figure 2). Baseline characteristics in the acute phase were comparable between groups, as shown in Table 4.

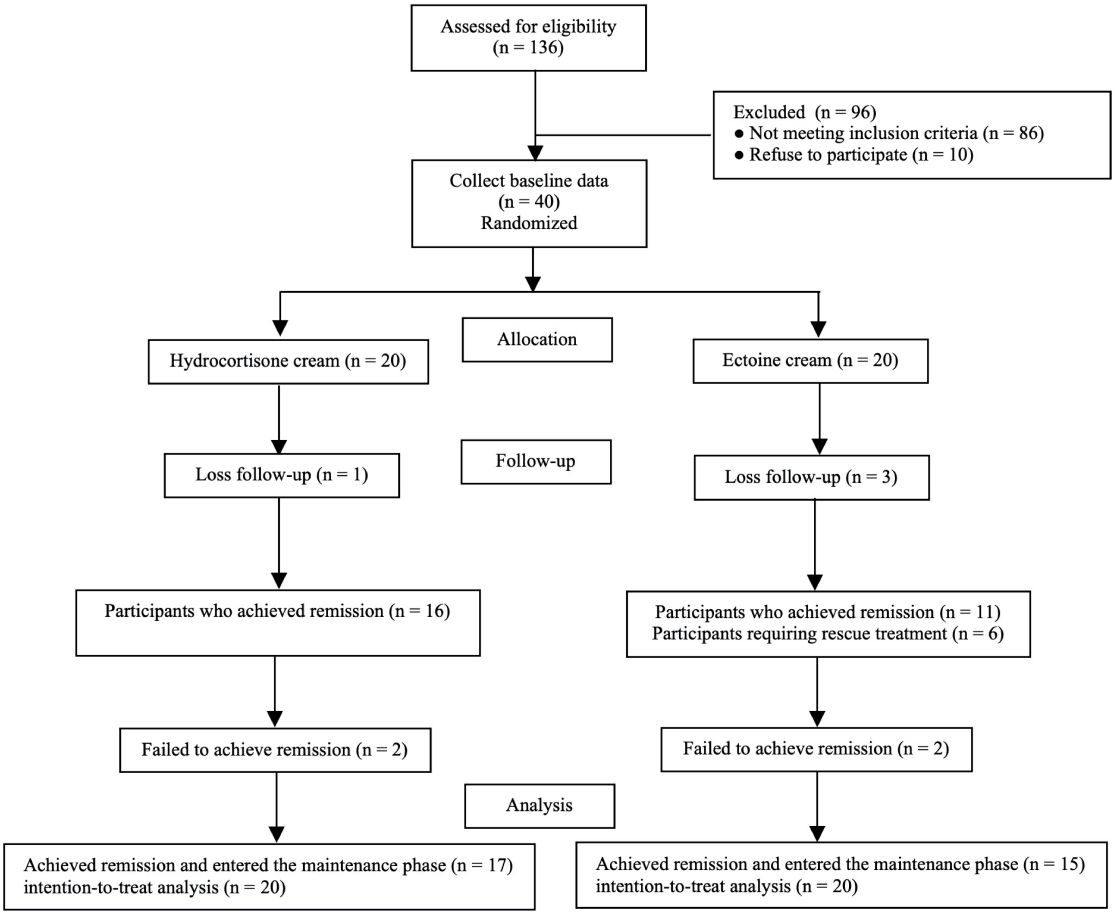


Figure 2. CONSORT flow diagram of the acute phase. Forty participants with mild-to-moderate facial seborrheic dermatitis were randomized to receive either 1% hydrocortisone cream or 7% ectoine cream. Participant enrollment, allocation, follow-up, and analysis are presented.

Table 4. Baseline characteristics of participants enrolled in the study during the acute phase.

Baseline Demographic	1% Hydrocortisone (N = 20)	7% Ectoine (N = 20)	*p*-Value
Sex (*n*,%) Male Female	 15 (75.00%) 5 (25.00%)	 12 (60.00%) 8 (40.00%)	0.311
Age (median, IQR)	30.5 (29.0, 38.5)	33 (28.0, 36.5)	0.978
Interval of active phase (weeks)	3 (2, 4)	2 (1, 4)	0.28
Past treatment history Yes	 8 (40%)	 9 (45%)	0.749
SEDASI score	11.75 ± 5.40	9.25 ± 4.82	0.131

3.2. Baseline Characteristics in the Maintenance Phase

A total of 32 participants who achieved remission after the acute phase were enrolled in the maintenance phase (Figure 3). Two participants in the ectoine group were lost to follow-up during the maintenance phase because they were unable to continue attending the scheduled follow-up visits. The E group had a lower median age (29.5 years) compared with the P group (34.5 years), showing a statistically significant difference ($p = 0.038$). Other baseline clinical severity parameters were comparable between groups, as shown in Table 5.

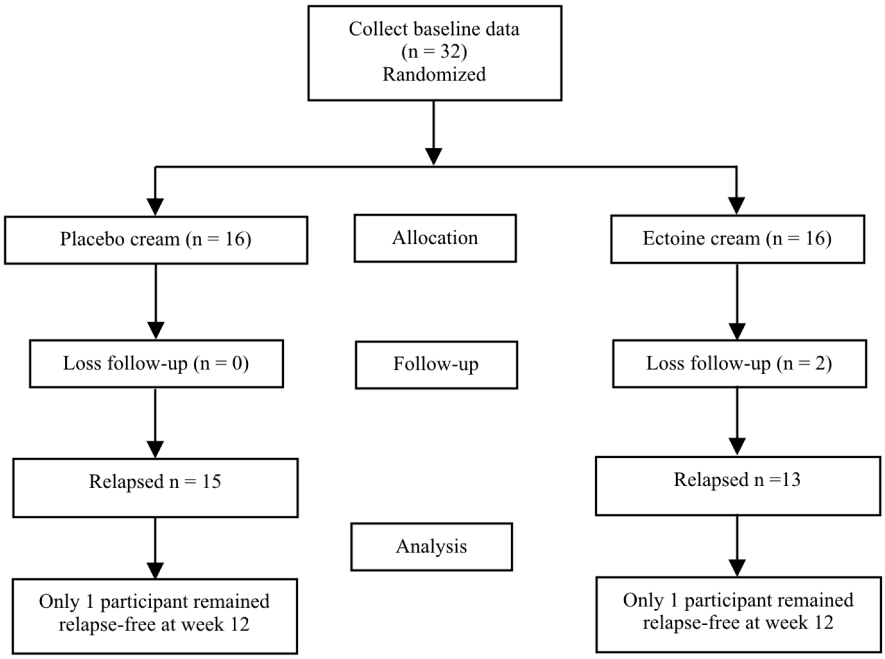


Figure 3. CONSORT flow diagram of the maintenance phase. Participants who achieved remission after the acute phase were re-randomized to receive either 7% ectoine cream or placebo. Participant allocation, follow-up, and analysis during the 12-week maintenance phase are shown.

Table 5. Baseline characteristics of participants enrolled in the study during the maintenance phase.

Baseline Demographic	Placebo (N = 16)	7% Ectoine (N = 16)	*p*-Value
Sex (*n*,%) Male Female	 10 (62.50%) 6 (37.50%)	 13 (81.25%) 3 (18.75%)	0.433
Age (median, IQR)	34.5 (29.5, 40.0)	29.5 (27.5, 33.0)	0.038
Interval of active phase (weeks)	3 (2, 4)	2 (2, 4)	0.751
Past treatment history Yes	7 (43.75%)	8 (50.00%)	0.723
SEDASI score	3.88 ± 2.92	3.88 ± 1.67	1.000
IGA	0.63 ± 0.50	0.69 ± 0.48	0.721
PGA	0.50 ± 0.52	0.56 ± 0.51	0.734

3.3. Outcome in Acute Phase

3.3.1. SEDASI, IGA and PGA in Acute Phase

SEDASI scores decreased from baseline at Weeks 2 and 4 in both treatment groups. Although a larger reduction in SEDASI was observed with hydrocortisone, the between-group mean difference in SEDASI change at Week 4 was −2.01 (95% CI, −4.81 to 0.78; $p = 0.151$). IGA and PGA scores also decreased in both groups, with no significant between-group differences (Tables 6–8; Figure 4).

Table 6. Mean change in SEDASI from baseline during the acute phase.

	1% Hydrocortisone (N = 20) Mean Difference ± SD	7% Ectoine (N = 20) Mean Difference ± SD
Week 2	−6.25 ± 5.33	−2.45 ± 4.80
Week 4	−5.76 ± 3.29	−3.75 ± 4.52

Table 7. IGA of participants enrolled in the study during the acute phase.

IGA	1% Hydrocortisone (N = 20)	Cumulative Remission N (%)	*p*-Value (Within Group)	7% Ectoine (N = 20)	Cumulative Remission N(%)	*p*-Value (Within Group)	*p*-Value
Week 0	0	0	0	0	0	0	
Week 2	1.65 ± 1.23	9 (45.00%)	Ref	2.25 ± 1.52	8 (40.00%)	Ref	0.190
Week 4	1.18 ± 1.29	16 (80.00%)	0.195	1.63 ± 1.36	11 (55.00%)	<0.001	

Table 8. PGA of participants enrolled in the study during the acute phase.

PGA	1% Hydrocortisone (N = 20)	Cumulative Remission N(%)	*p*-Value (Within Group)	7% Ectoine (N = 20)	Cumulative Remission N(%)	*p*-Value (Within Group)	*p*-Value
Week 0	0	0	0	0	0	Ref	
Week 2	1.40 ± 1.27	9 (45.00%)	Ref	2.00 ± 1.89	8 (40.00%)	Ref	0.263
Week 4	1.24 ± 1.09	16 (80.00%)	0.652	1.63 ± 1.75	11 (55.00%)	0.014	

At Week 4, the between-group mean difference in change (hydrocortisone−ectoine) was −2.01 (95% CI, −4.81 to 0.78; $p = 0.151$).

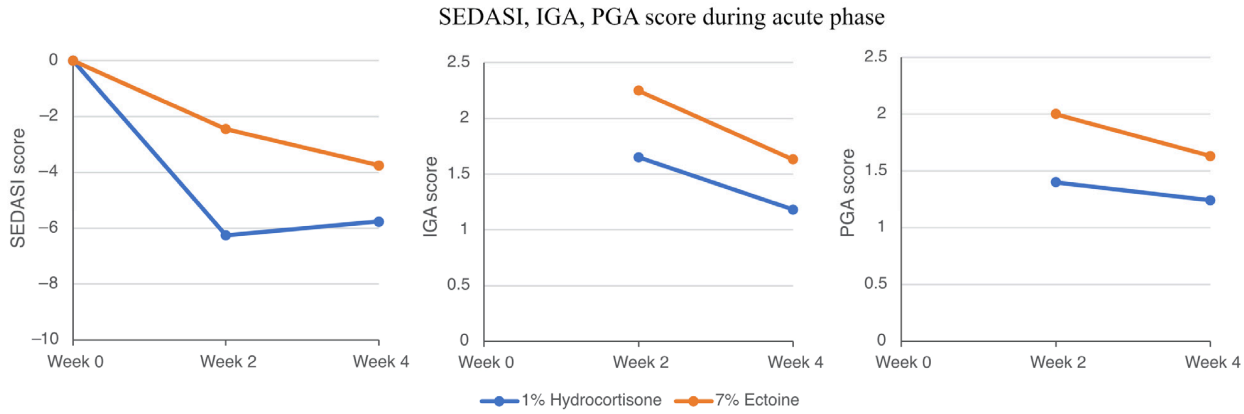


Figure 4. Changes in clinical outcomes during the acute phase. Changes in SEDASI, IGA, and PGA scores were evaluated at baseline, Week 2, and Week 4 in the hydrocortisone and ectoine groups.

3.3.2. Remission Rate and Time to Remission

At Week 4, remission was achieved in 16/20 participants (80.0%) in the H group and 11/20 participants (55.0%) in the E group. Participants who had not achieved remission by Week 4 received rescue treatment for an additional 2 weeks. By Week 6, remission rates increased to 85.0% and 75.0%, respectively (Table 9).

Table 9. Cumulative remission rate.

Remission Rate	1% Hydrocortisone N(%)	7% Ectoine N(%)
Week 2	9 (45.00%)	8 (40.00%)
Week 4	16 (80.00%)	11 (55.00%)
Week 6	17 (85.00%)	15 (75.00%)

Although the hydrocortisone group showed a tendency toward higher remission rates, no statistically significant difference in remission outcomes was observed between the two groups. The median time to remission was similar between groups (28 days in both groups; log-rank $p = 0.173$) (Figure 5).

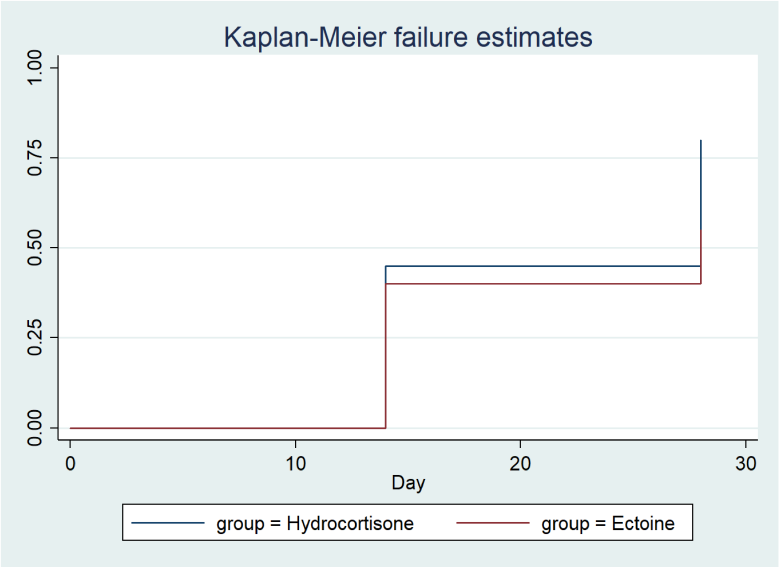


Figure 5. Kaplan–Meier curves showing time to remission during the acute phase in the hydrocortisone and ectoine groups. Remission was defined as an IGA score of 0 or 1. Differences between groups were compared using the log-rank test.

3.4. Outcome in Maintenance Phase

3.4.1. SEDASI, IGA and PGA in Maintenance Phase

During the maintenance phase, similar trends were observed across SEDASI, IGA, and PGA scores. In the P group, scores significantly increased at Week 4, suggesting early relapse, followed by lower observed scores at later time points; however, the Week 12 placebo estimate was based on only one remaining relapse-free participant and should be interpreted with caution.

In contrast, all three scores increased significantly in the E group at Week 4. By Week 8, only a slight increase in IGA scores was observed, while SEDASI and PGA scores showed a reduction. However, by Week 12, all three scores increased again, indicating a fluctuating pattern over time (Figure 6).

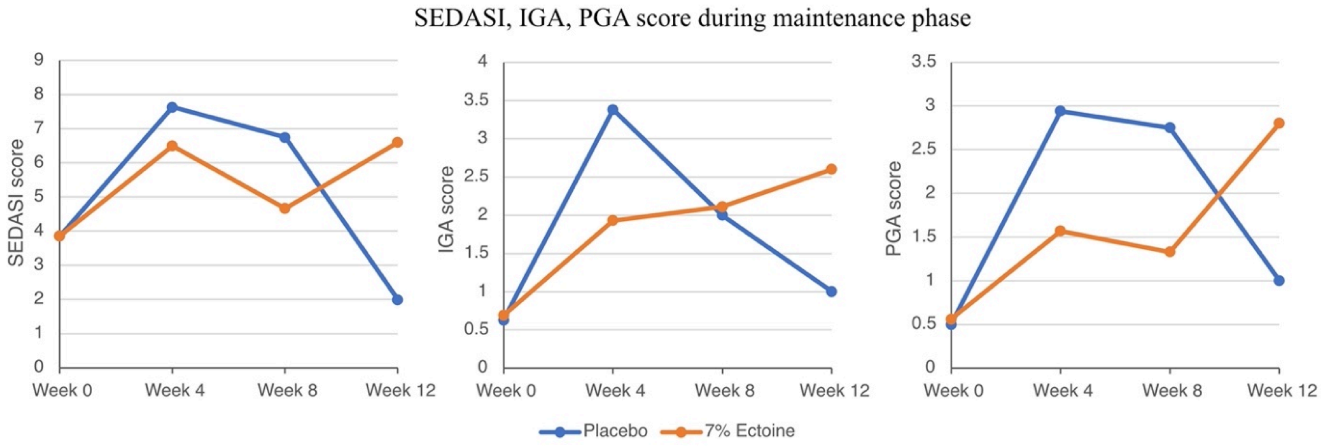


Figure 6. Changes in clinical outcomes during the maintenance phase. Mean SEDASI, IGA, and PGA scores were evaluated throughout the 12-week maintenance period in the ectoine and placebo groups.

Overall, no statistically significant differences between the two groups were detected at any time point during the maintenance phase, as assessed by SEDASI, IGA, and PGA (Tables 10–12).

Table 10. SEDASI of participants enrolled in the study during the maintenance phase.

SEDASI	Placebo (N = 16)	Cumulative Relapse N(%)	*p*-Value (Within Group)	7% Ectoine (N = 16)	Cumulative Relapse N(%)	*p*-Value (Within Group)	*p*-Value
Week 0	3.88 ± 2.92	0	Ref	3.88 ± 1.67	0	Ref	0.615
Week 4	7.63 ± 3.77	12 (75.00%)	<0.001	6.50 ± 5.56	5 (31.25%)	0.015	
Week 8	6.75 ± 4.57	15 (93.75%)	0.040	4.67 ± 3.08	9 (56.25%)	0.217	
Week 12	2.00 ± N/A **	15 (93.75%)	0.746	6.60 ± 2.88	13 (81.25%)	0.013	

** At Week 12, only one placebo participant remained relapse-free and contributed to the disease-severity assessment; therefore, an SD could not be calculated.

The number of participants contributing data decreased over time because participants were withdrawn after meeting the predefined relapse criterion. At Week 12, only one placebo participant remained relapse-free and contributed disease-severity data.

Table 11. IGA of participants enrolled in the study during the maintenance phase.

IGA	Placebo (N = 16)	Cumulative Relapse N(%)	*p*-Value (Within Group)	7% Ectoine (N = 16)	Cumulative Relapse N(%)	*p*-Value (Within Group)	*p*-Value
Week 0	0.63 ± 0.50	0	Ref	0.69 ± 0.48	0	Ref	0.153
Week 4	3.38 ± 1.63	12 (75.00%)	<0.001	1.93 ± 1.86	5 (31.25%)	0.009	
Week 8	2.00 ± 0.82	15 (93.75%)	0.023	2.11 ± 2.03	9 (56.25%)	0.003	
Week 12	1.00 ± N/A **	15 (93.75%)	0.705	2.60 ± 1.52	13 (81.25%)	0.001	

** At Week 12, only one placebo participant remained relapse-free and contributed to the disease-severity assessment; therefore, an SD could not be calculated.

Table 12. PGA of participants enrolled in the study during the maintenance phase.

PGA	Placebo (N = 16)	Cumulative Relapse N(%)	*p*-Value (Within Group)	7% Ectoine (N = 16)	Cumulative Relapse N(%)	*p*-Value (Within Group)	*p*-Value
Week 0	0.50 ± 0.52	0	Ref	0.56 ± 0.51	0	Ref	0.068
Week 4	2.94 ± 1.61	12 (75.00%)	<0.001	1.57 ± 1.91	5 (31.25%)	0.031	
Week 8	2.75 ± 2.06	15 (93.75%)	0.001	1.33 ± 1.66	9 (56.25%)	0.052	
Week 12	1.00 ± N/A **	15 (93.75%)	0.597	2.80 ± 2.28	13 (81.25%)	<0.001	

** At Week 12, only one placebo participant remained relapse-free and contributed to the disease-severity assessment; therefore, an SD could not be calculated.

3.4.2. Relapse Rate and Time to Relapse

Relapse rates were consistently lower in the E group across all visits compared with P group. Although the between-group difference did not reach statistical significance ($p = 0.066$), a clear trend toward reduced relapse was observed in the E group. As shown in Figure 7, the time to relapse was longer in the ectoine group (56 days) than in the P group (28 days) (Figure 7).

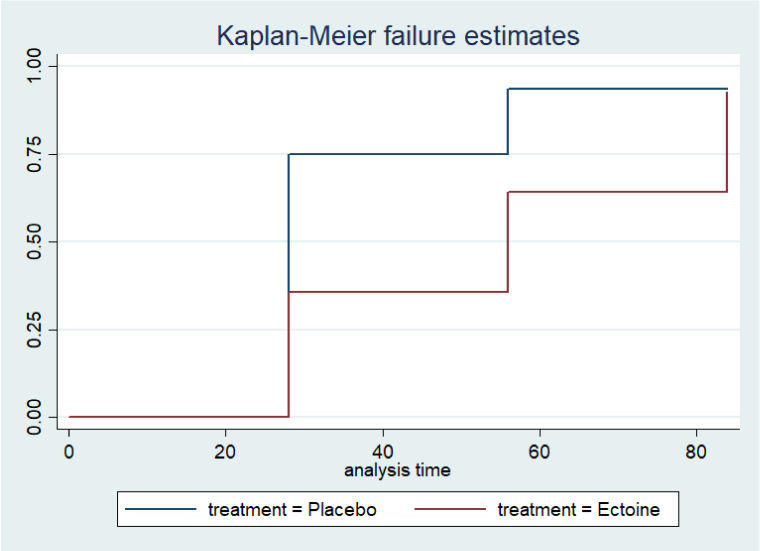


Figure 7. Kaplan–Meier curves showing time to relapse during the maintenance phase in the ectoine and placebo groups. Relapse was defined as an IGA score of ≥2. Differences between groups were compared using the log-rank test.

3.5. Adverse Events

No serious adverse events were observed during either study phase. During the acute phase, mild adverse events, including itching, were reported in both groups, occurring in 2 participants in the H group and 4 participants in the E group ($p = 0.661$). However, all adverse events were mild in severity, and no statistically significant difference was observed between the groups. During the maintenance phase, no adverse events were reported in the E group, while 1 participant in the P group developed mild acne ($p = 1.000$).

4. Discussion

In this study, we evaluated the efficacy and safety of 7% ectoine cream compared with 1% hydrocortisone during the acute phase and with placebo during the maintenance phase, in order to assess its role in both short-term treatment and long-term disease control in seborrheic dermatitis. Previous studies have demonstrated that ectoine is effective in alleviating symptoms of inflammatory skin conditions, particularly atopic dermatitis [17,19,20,22], through its ability to bind water, enhance skin hydration, and improve skin barrier function [23]. In addition, ectoine has been shown to exert anti-inflammatory effects [24]. To our knowledge, this is the first study to evaluate both the efficacy and tolerability of ectoine in acute treatment and maintenance therapy for seborrheic dermatitis.

Our results demonstrated no significant differences in baseline characteristics between the two groups during the acute phase. Although a statistically significant difference in median age between groups was observed in the maintenance phase (29.5 vs. 34.5 years), both groups fell within the adult age range. Age is not considered a primary determinant of disease severity in seborrheic dermatitis [25], which is more strongly influenced by factors such as sebaceous activity, immune status, and environmental triggers [7]. Therefore, this difference is unlikely to have had a clinically meaningful impact on baseline disease severity or treatment response.

During the acute phase, SEDASI scores decreased from baseline at Weeks 2 and 4 in both treatment groups. The reduction was larger with hydrocortisone, particularly at Week 2. IGA and PGA scores also decreased in both groups, with no statistically significant between-group differences. Similar clinical findings have been reported in previous studies comparing topical calcineurin inhibitors with low-potency corticosteroids in facial seborrheic dermatitis. Papp et al. (2012) [26] reported similar efficacy between tacrolimus 0.1% ointment and hydrocortisone 1% ointment over 12 weeks, as assessed by SASI-F (Seborrhea Area and Severity Index—Face). Additionally, Firooz et al. (2006) [27] similarly found no significant difference between pimecrolimus 1% and hydrocortisone acetate 1% after 2 weeks of treatment.

Although the between-group difference in SEDASI change at Week 4 did not reach statistical significance, the pattern of response differed between treatments. Hydrocortisone produced a faster reduction in SEDASI at Week 2, whereas the difference narrowed by Week 4. The hydrocortisone group also showed a numerically higher remission rate, although no significant difference in remission outcomes was observed between the two groups. A similar response pattern was reported by Balighi et al. (2017) [28], in which hydrocortisone 1% cream demonstrated greater clinical improvement during the early treatment period compared with sertaconazole 2% cream, while between-group differences were no longer statistically significant by Week 4. This finding is consistent with the rapid anti-inflammatory and vasoconstrictive effects of topical corticosteroids.

Notably, the clinical improvement observed in the ectoine group may be explained by the known barrier-supportive and anti-inflammatory properties of ectoine. Ectoine enhances skin hydration, stabilizes cellular membranes, restores barrier integrity, and reduces pro-inflammatory cytokine activity. Although atopic dermatitis and seborrheic

dermatitis are distinct conditions, both are characterized by epidermal barrier dysfunction, cutaneous inflammation, and increased skin sensitivity. Consistent with these shared pathogenic features, Marini et al. (2014) [19] and Kauth et al. (2022) [17] demonstrated that ectoine-based formulations significantly improved erythema, pruritus, and disease severity in atopic dermatitis with an excellent safety profile. These findings may help explain the clinical improvement observed in the ectoine group and support the potential role of ectoine as a steroid-sparing therapeutic option for mild-to-moderate facial seborrheic dermatitis.

In the maintenance phase, disease scores (SEDASI, IGA, and PGA) increased in both groups, with more pronounced worsening observed in the placebo group. Relapse became evident from Week 4 onward in the placebo group, with most participants relapsing by Week 8. The ectoine group demonstrated a nearly twofold longer median time to relapse, which, although not statistically significant, may still be clinically meaningful given the small sample size and limited follow-up duration, which likely reduced statistical power. Despite these limitations, these findings align with previous evidence supporting non-steroidal maintenance therapy in facial seborrheic dermatitis. Kim et al. (2015) [29] showed that proactive twice-weekly tacrolimus 0.1% ointment effectively maintained disease control in stabilized facial SD. While the median time to relapse in the ectoine group exceeded that of both the tacrolimus and vehicle groups in their study (41.17 and 18.20 days, respectively), direct comparisons are limited by differences in baseline severity, maintenance regimens, and study duration. The maintenance benefit observed with ectoine may reflect its barrier-supportive and anti-inflammatory properties, which could help attenuate recurrent inflammation and sustain disease control over time.

Both treatments were well tolerated. During the acute phase, mild local adverse events were observed in a small number of participants and resolved without treatment discontinuation. No adverse events were observed in the ectoine group during the maintenance phase, whereas one participant in the placebo group developed acne. No participants withdrew because of adverse events. These findings are consistent with previous studies of ectoine-based formulations, which have mainly reported mild and transient local reactions [17,30]. Similarly, the corticosteroid used in this study was a low-potency agent administered for a short duration [31]. As corticosteroid-related adverse effects are generally associated with prolonged use and higher potency, the absence of clinically significant adverse events in this study was not unexpected [32].

Limitations

This study has several limitations. The sample size was relatively small, particularly during the maintenance phase where participant withdrawal following relapse progressively reduced the number of evaluable subjects at later time points. Generalizability may be limited, as this was a single-center trial in Thai adults with mild-to-moderate disease, and the trial was registered retrospectively. In addition, the maintenance period was limited to 12 weeks, which may not fully capture long-term relapse patterns in seborrheic dermatitis. Further larger-scale studies with longer follow-up are warranted to better define the role of ectoine in maintenance therapy.

5. Conclusions

In summary, 7% ectoine reduced disease severity in facial seborrheic dermatitis during the acute phase. Although the reduction in SEDASI was numerically greater with 1% hydrocortisone, the between-group difference in SEDASI change at Week 4 did not reach statistical significance. Ectoine also showed a potential benefit for long-term disease control during the maintenance phase and was well tolerated. These findings support

further investigation of ectoine as a potential steroid-sparing option for acute treatment and maintenance therapy.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cosmetics13050264/s1. Table S1: CONSORT 2025 checklist of information to include when reporting a randomised trial.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Human Research Ethics Committee of Srinakharinwirot University (approval number SWUEC-661040) on 8 May 2024, prior to the enrollment of the first participant. The trial was registered with the Thai Clinical Trials Registry (TCTR20260521005) on 21 May 2026, after completion of data collection (https://www.thaiclinicaltrials.org/show/TCTR20260521005 (accessed on 30 September 2026)). The outcomes and analyses reported here are those specified in the protocol approved by the ethics committee before enrollment began.

Informed Consent Statement: Written informed consent was obtained from all participants prior to enrollment.

Data Availability Statement: The datasets generated and analyzed in this study are not publicly available because they contain potentially identifiable clinical information. De-identified data, the trial protocol, statistical analysis plan, data dictionary, and statistical code are available from the corresponding author upon reasonable request, subject to approval by the Human Research Ethics Committee of Srinakharinwirot University (SWUEC-661040) and completion of a data sharing agreement.

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