Combination Sodium Sulfacetamide 10% and Sulfur 5% Cream With Sunscreens Versus Metronidazole 0.75% Cream for Rosacea

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Topical metronidazole and combination sodium sulfacetamide and sulfur commonly are used to treat rosacea. Recently, the relative efficacy and safety of sodium sulfacetamide 10% and sulfur 5% cream with sunscreens (Rosac® Cream) (n=75) and metronidazole 0.75% cream (Metrocream®) (n=77) were compared in an investigator-blinded, randomized, parallel-group study at 6 sites. After 12 weeks of treatment with sodium sulfacetamide 10% and sulfur 5% cream with sunscreens, there was a significantly greater percentage reduction (80%) in inflammatory lesions compared with metronidazole 0.75% cream (72%)(P=.04), as well as a significantly greater percentage of subjects with improved erythema (69% vs 45%, respectively; P=.0007). In addition, the sodium sulfacetamide 10% and sulfur 5% cream with sunscreens group had a significantly greater proportion of subjects with success in global improvement at week 12 compared with the metronidazole 0.75% cream group (79% vs 59%, respectively; P=.01). There was no significant difference between treatment groups in the percentage of subjects with improvement in investigator global severity. Overall tolerance was good or excellent in 85% of subjects in the sodium sulfacetamide 10% and sulfur 5% cream with sunscreens group and in 97% of subjects in the metronidazole 0.75% cream group. Seven subjects had poor tolerance to the sodium sulfacetamide 10% and sulfur 5% cream with sunscreens, possibly caused by a sulfa drug allergy.

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An estimated 14 million Americans are affected by rosacea.[1] Patients with rosacea normally have persistent centrofacial erythema with periodic flares characterized by increased flushing and development of inflammatory lesions (papules and pustules). Patients also frequently experience facial burning, stinging, and pruritus.

The pathologic mechanisms that cause rosacea are not clearly understood.[2] Rosacea is improved by

both topical antibacterial treatments and systemic antibiotics. The efficacy of antibacterial agents in the treatment of rosacea may be related to the anti-inflammatory activity of these agents, as well as to their antibacterial activity.[1,3] Sulfacetamide, a sulfonamide antibiotic, was one of the first effective chemotherapeutic agents discovered in the 1930s to treat bacterial infections. The most widely accepted mechanism of action is the Woods-Fildes theory, because sulfonamides act as competitive antagonists to para-aminobenzoic acid, an essential component in bacterial growth. Sulfacetamide is used mainly as topical therapy, especially in the management of ophthalmic infections. Sulfur has a mild antibacterial and keratolytic effect and has long been used to effectively treat a variety of skin diseases. Several topical formulations containing sodium sulfacetamide 10% and sulfur 5% are available. Other topical therapies available in the treatment of rosacea include metronidazole 0.75% gel, cream, and lotion; metronidazole 1% cream; and azelaic acid 15% gel.

Many triggering factors can exacerbate rosacea, including sunlight.[4,5] One important goal in the management of rosacea, therefore, is to minimize sunlight exposure to the face.[3] This goal could be at least partially achieved by the daily use of a topical broad-spectrum sunscreen. However, only 5% of patients with rosacea report daily sunscreen use.[5] Sodium sulfacetamide 10% and sulfur 5% cream with sunscreens, with a sun protection factor of 18, is a new product in the topical treatment of rosacea that contains 2 sunscreen agents, avobenzone (UVA filter) and octinoxate (UVB filter). The efficacy of sodium sulfacetamide and sulfur products in the topical treatment of rosacea is well-known.[6,7] Topical metronidazole is also an effective treatment for rosacea,[8,9] and topical metronidazole 0.75% cream is a commonly used product. In this study, the results of a recent investigator-blinded, randomized, parallel-group study comparing the relative efficacy and safety of sodium sulfacetamide 10% and sulfur 5% cream with sunscreens and metronidazole 0.75% cream are discussed. This study is the second of 2 studies conducted comparing these treatments.

Methods

The relative efficacy and safety of Rosac® Cream with Sunscreens (sodium sulfacetamide 10% and sulfur 5%) and Metrocream® (metronidazole 0.75%) were evaluated in an investigator-blinded, randomized, parallel-group clinical trial at 6 sites. Inclusion criteria included clinical evidence of rosacea with a minimum of 10 and a maximum of 39 inflammatory lesions (papules and pustules), at least moderate erythema, and at least an investigator global severity of moderate. Subjects had to be at least 16 years of age.

Subjects were not allowed to use medicated cleansers containing benzoyl peroxide, sodium sulfacetamide, or salicylic acid for 2 weeks before study entry; rosacea or acne treatments of any type for 2 weeks (topical) or 1 month (systemic) before study entry; retinoids for 1 month (topical) or 6 months (systemic) before study entry; and systemic antibacterials for 1 month before study entry. Moreover, these medications were not allowed throughout the course of the study. In addition, subjects were excluded from study entry if they used cimetidine, lithium, disulfiram, coumarin anticoagulants, or niacin; if they frequently used vasodilators with known flushing activity; or if they used any medication that would interfere with study results. Subjects also were excluded from study entry if their rosacea was known to be therapeutically unresponsive to treatment with topical metronidazole or sodium sulfacetamide and sulfur products.

Subjects were asked to minimize their consumption of spicy foods, very hot foods and drinks, and caffeinated and alcoholic beverages and to minimize their exposure to sunlight, including sunlamps, during the study. The protocol was approved by a central institutional review board, and all subjects gave written informed consent before study entry.

A total of 152 subjects were enrolled at 6 study sites. Subjects were randomly assigned to treatment with either sodium sulfacetamide 10% and sulfur 5% cream with sunscreens or metronidazole 0.75% cream. Subjects were instructed to apply the study medication to their entire face after washing with a mild cleanser twice daily for 12 weeks. Although the identity of the medication was masked, some subjects may not have been blinded as a result of previous use of the products. The investigators or evaluators were kept blinded. At 2 study sites, facial photographs of the subjects were taken at the baseline visit and again at the end of treatment.

Efficacy was evaluated at baseline, and efficacy and safety were evaluated at all subsequent visits (weeks 3, 6, 9, and 12). Evaluation of efficacy was made by counting total facial inflammatory lesions (papules and pustules), grading facial erythema on a scale of 0 to 3 (0=no redness; 1=slight erythema, light red or pink; 2=definite erythema, red; and 3=intense erythema, beet red), and grading investigator global severity at all visits as shown in Table 1. Global severity was based on lesion count; however, severity score was increased

Table 1.

Investigator Global Severity

Score	Grade	Erythema	Lesions
0	Clear	Absent	None
1	Slight	Light red or pink	None
2	Mild	Red	1–5
3	Mild to moderate	Red	6–9
4	Moderate	Red	10–19
5	Moderate to severe	Red	20–39
6	Severe	Beet red	20–39
7	Very severe	Beet red	>39

Table 2.

Overall Tolerance

Score	Grade	Definition
0	Poor	Numerous treatment-related, moderate to severe local signs and symptoms during treatment leading to withdrawal
1	Fair	Numerous treatment-related, mild to moderate local signs and symptoms during treatment
2	Good	Few treatment-related, mild local signs and symptoms during treatment
3	Excellent	No treatment-related local signs and symptoms at the end of treatment, with no or only a few local signs and symptoms during early treatment

if erythema was severe. In addition, subjects assessed global improvement of rosacea relative to their initial condition at weeks 3, 6, 9, and 12 on a scale of 0 to 5 (0=cleared, no evidence of rosacea; 1=excellent, almost cleared; 2=good, substantial improvement; 3=fair, some improvement; 4=poor, little or no improvement; and 5=worsening). Evaluation of safety was made by reporting of adverse events at all visits and scoring of overall tolerance at the end of treatment on a scale of 0 to 3 (Table 2).

Statistical Analysis—Data analyses for efficacy were performed on all subjects after baseline, regardless of whether the protocol was followed, with imputations made by carrying forward the last available observation. All subjects were included in the safety analyses without imputation. Statistical methods included analysis of variance (ANOVA) for lesion count data and the log-rank test for categorical data. Effects considered were site and treatment. All statistical tests were 2 sided at a significance level of $\alpha = .05$.

Inflammatory lesion count was analyzed by transformation to the symmetrized percentage reduction ($100 \times$ [baseline − post/baseline + post]), followed by ANOVA with effects for site and treatment, using type 3 sums of squares. Least squares method of symmetrized percentage reduction

obtained from the ANOVA was transformed back to percentage reduction for reporting purposes. The analysis of symmetrized percentage reduction is free of the excessive influence of outliers and low baseline counts.

Investigator global severity score, subject global improvement score, and erythema score were collapsed to a dichotomous classification. Success with investigator global severity was defined as a score at least 2 grades lower than the baseline score. Improvement in erythema was defined as a score at least 1 full grade lower than the baseline score. A score of 0, 1, or 2 indicated success with subject global improvement. These binary variables were analyzed using the log-rank test stratifying on site.

Success with investigator global severity and the percentage reduction from baseline of inflammatory lesion count at week 12 were the primary measures of efficacy. Secondary measures of efficacy variables included success with subject global improvement at week 12 and improvement in erythema score at week 12.

Overall tolerance scores were dichotomized as success (good or excellent) or failure (poor or fair). Success with overall tolerance was the primary safety variable. Secondary safety variables included both the frequency of adverse events and the frequency of adverse events related to treatment to determine relative safety. Fisher exact test was used to analyze the 3 safety variables.

Results

A total of 152 subjects, 75 subjects in the sodium sulfacetamide 10% and sulfur 5% cream with sunscreens group and 77 subjects in the metronidazole 0.75% cream group, were enrolled in the study at 6 sites. At study completion, 138 subjects remained, with 10 dropouts in the sodium sulfacetamide 10% and sulfur 5% cream with sunscreens group and 4 dropouts in the metronidazole 0.75% cream group. Seven of the dropouts, all in the sodium sulfacetamide 10% and sulfur 5% cream with sunscreens group, were due to intolerability of study medication. All subjects were included in the analysis of the study, and this data set was considered primary. There were few protocol violations; most commonly, subjects were either early or late for visits. One subject in the sodium sulfacetamide 10% and sulfur 5% cream with sunscreens group was using a contraindicated medication (Coumadin®) at study entry, and 2 subjects in the metronidazole 0.75% cream group used contraindicated medications (oral and injected corticosteroids) during the study. One subject in the metronidazole 0.75% cream group was enrolled in the study with an exclusionary concurrent disease (polycythemia vera).

The demographic and baseline features of subjects were similar in both groups. The population consisted primarily of white female adults—women comprised 72% of subjects, and 93% of subjects were white. Subjects had a mean age of 47 years (range, 19–77 years). The baseline inflammatory lesion count was 18±1 in the sodium sulfacetamide 10% and sulfur 5% cream with sunscreens group and 17±1 in the metronidazole 0.75% cream group.

Improvement in disease severity, assessed by investigator global severity score and reduction in mean inflammatory lesion counts (Figure 1), was observed in both treatment groups. At the end of the 12-week treatment period, the percentage reduction in inflammatory lesion counts was statistically significantly greater (P=.04) in the sodium sulfacetamide 10% and sulfur 5% cream with sunscreens group (80%) compared with the metronidazole 0.75% cream group (72%)(Figure 2). The sodium sulfacetamide 10% and sulfur 5% cream with sunscreens group also had a significantly greater (P=.0007) proportion of subjects (69%) with improvement in erythema score (reduction by at least one grade) at week 12 compared with the metronidazole 0.75% cream group (45%)(Figure 3). In addition, the sodium sulfacetamide 10% and sulfur 5% cream with sunscreens group had a significantly greater (P=.01) proportion of subjects (79%) with success in global improvement (cleared, excellent, or good) at week 12 compared with the metronidazole 0.75% cream group (59%)(Figure 4). These results are consistent with the first study conducted, which compared both treatments.[7]

At the end of the study, the investigator assessed overall tolerance to the study medication concerning local adverse events. The metronidazole 0.75% cream group had a significantly greater (P=.001) proportion of subjects with good or excellent overall tolerance scores. Overall tolerance was good or excellent in 85% of subjects in the sodium sulfacetamide 10% and sulfur 5% cream with sunscreens group and in 97% of subjects in the metronidazole 0.75% cream group (Table 3). In 7 subjects, tolerability to sodium sulfacetamide 10% and sulfur 5% cream with sunscreens was poor and resulted in discontinuation of study participation. Signs and symptoms included swollen eyes, facial dryness, pruritus, hives, and increased erythema. Although allergy to the sulfa drug was an exclusion criterion, the nature of these adverse events suggested a possible allergy to the sulfa drug.

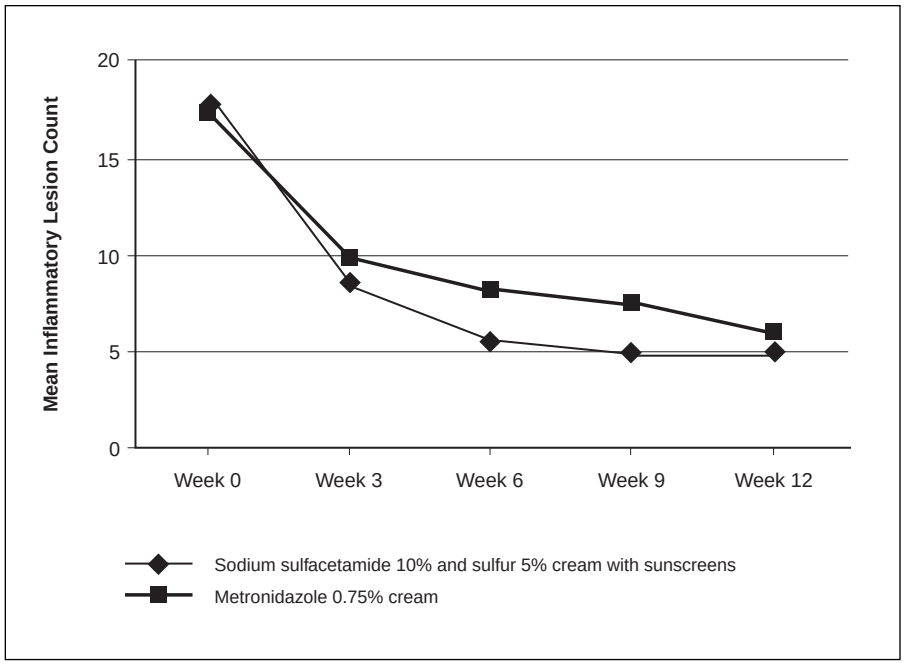

Figure 1. Mean inflammatory lesion counts over 12 weeks of treatment with either sodium sulfacetamide 10% and sulfur 5% cream with sunscreens or metronidazole 0.75% cream.

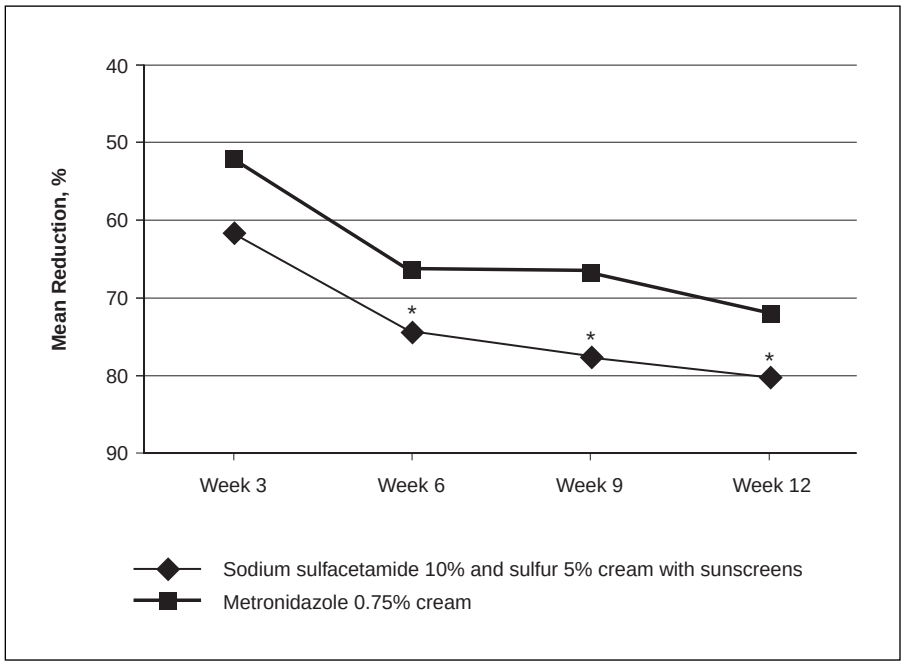

Figure 2. Mean percentage reduction in inflammatory lesion counts after 3, 6, 9, and 12 weeks of treatment with either sodium sulfacetamide 10% and sulfur 5% cream with sunscreens or metronidazole 0.75% cream. Asterisk indicates significantly greater ($P<.05$) vs the metronidazole 0.75% cream group.

Secondary safety variables included the frequency of adverse events and treatment-related adverse events. Forty-eight subjects in the sodium sulfacetamide 10% and sulfur 5% cream with sunscreens group and 41 subjects in the metronidazole 0.75% cream group reported adverse events. Of these, 38 subjects in the sodium sulfacetamide 10% and sulfur 5% cream with sunscreens group and 20 subjects in the metronidazole 0.75% cream group had adverse events related to treatment. While there was no statistical difference between treatments in the number of subjects reporting adverse events, the sodium sulfacetamide 10% and sulfur 5% cream with sunscreens group had a statistically significant ($P=.003$) number of subjects reporting treatment-related adverse events compared with the metronidazole 0.75% cream group. Most adverse events were mild and resolved by the end of treatment. Of the treatment-related adverse events in both groups,

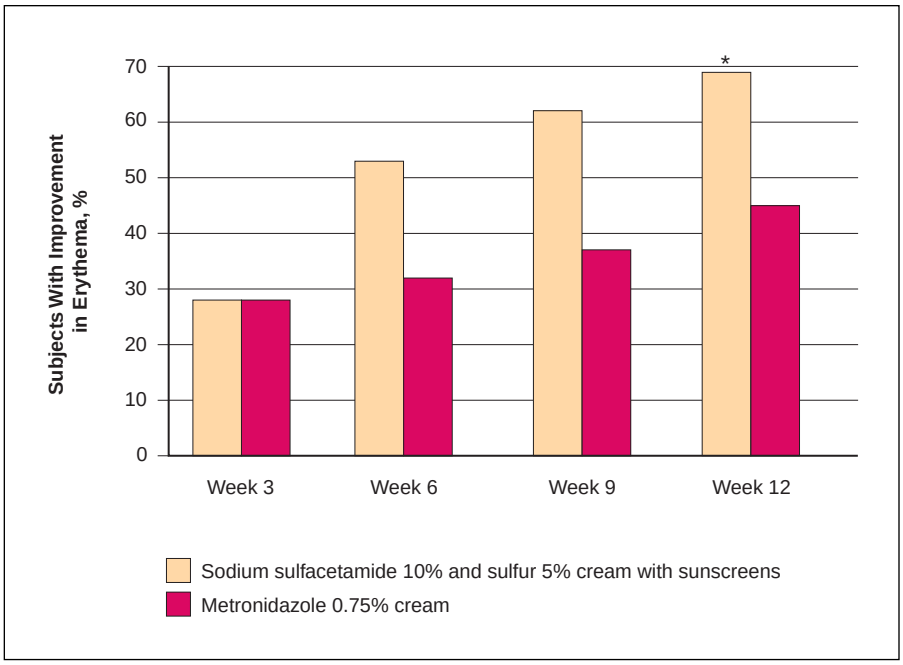

Figure 3. Percentage of subjects with at least a one grade improvement in erythema score graded on a scale of 0 to 3 over 12 weeks of treatment with either sodium sulfacetamide 10% and sulfur 5% cream with sunscreens or metronidazole 0.75% cream. Asterisk indicates *P*=.0007 vs the metronidazole 0.75% cream group.

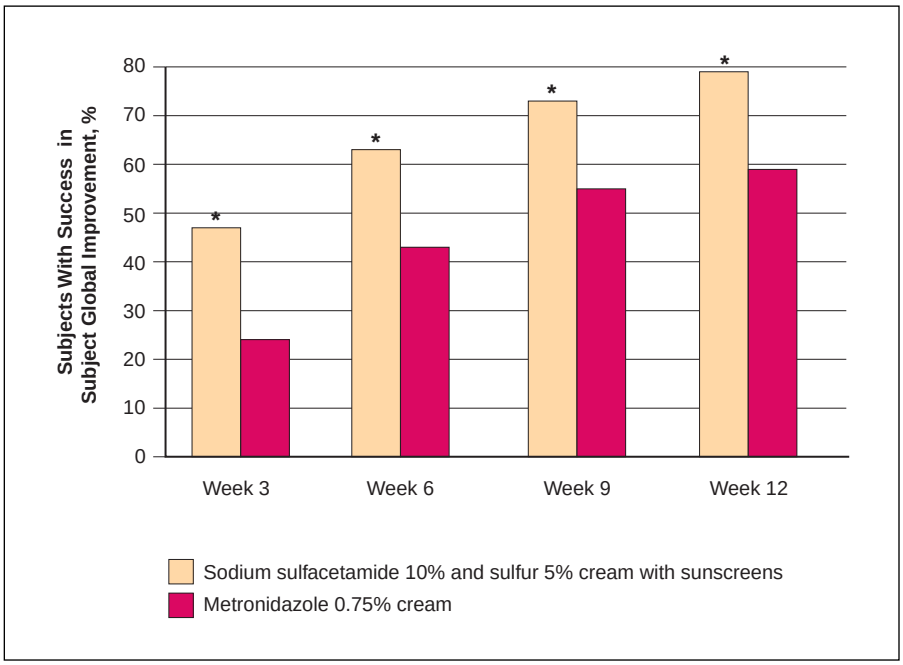

Figure 4. Percentage of subjects with success (cleared, excellent, or good) in global improvement over 12 weeks of treatment with either sodium sulfacetamide 10% and sulfur 5% cream with sunscreens or metronidazole 0.75% cream. Asterisk indicates *P*<.05 vs the metronidazole 0.75% cream group.

most were expected local reactions of dryness, burning, stinging, and pruritus. Other treatment-related local adverse events included erythema, contact dermatitis, desquamation, hyperesthesia, irritation, pain, papules and pustules, paresthesia, urticaria, and perspiration. Seven subjects in the sodium sulfacetamide 10% and sulfur 5% cream with sunscreens group discontinued the study because of treatment-related adverse events, and 1 subject in the metronidazole 0.75% cream group discontinued the study because of an adverse event not related to study medication.

Comment

This 12-week, randomized, investigator-blinded, parallel-group, multicenter study assessed the clinical safety and efficacy of sodium sulfacetamide 10% and sulfur 5% cream with sunscreens. Sodium

Table 3.

Distribution of Subjects by Overall Tolerance

Score	Sodium Sulfacetamide 10% and Sulfur 5% Cream With Sunscreens, n (%) (n=75)	Metronidazole 0.75% Cream, n (%) (n=77)
Fair	2 (3)	0
Good	28 (37)	21 (27)
Excellent	36 (48)	54 (70)

sulfacetamide 10% and sulfur 5% cream contains sunscreens for UVA and UVB protection, which is an important component in the treatment of rosacea. The addition of UVA and UVB protection to a proven sodium sulfacetamide and sulfur combination product may explain the reduction in both erythema and lesion counts compared with metronidazole cream. Patients with rosacea often have increased skin sensitivity. Sodium sulfacetamide 10% and sulfur 5% cream with sunscreens also contains the skin protectant dimethicone, which has been shown to reduce irritation.[10]

A greater number of subjects in the sodium sulfacetamide 10% and sulfur 5% cream with sunscreens group discontinued study participation because of adverse events related to the study medication compared with the metronidazole 0.75% cream group. Because the investigators may have recognized the nature of these adverse events as being suggestive of a sulfa drug allergy, an imperfect investigator blinding may have existed.

After 12 weeks, treatment with sodium sulfacetamide 10% and sulfur 5% cream with sunscreens resulted in both a significantly ($P=.04$) greater percentage reduction (80%) in inflammatory lesions compared with metronidazole 0.75% cream (72%) and a significantly ($P=.0007$) greater proportion of subjects with improved erythema (69% vs 45%, respectively). Overall tolerance was good or excellent in 85% of subjects in the sodium sulfacetamide 10% and sulfur 5% cream with sunscreens group and in 97% of subjects in the metronidazole 0.75% cream group.

It was concluded that in patients without sulfa drug allergies, sodium sulfacetamide 10% and sulfur 5% cream with sunscreens offers greater efficacy than metronidazole 0.75% cream and has the added benefit of sun protection.

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