

MAS063DP is Effective Monotherapy for Mild to Moderate Atopic Dermatitis in Infants and Children: A Multicenter, Randomized, Vehicle-Controlled Study

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Objective To examine the efficacy and safety of MAS063DP (Atopiclair) cream in the management of mild to moderate atopic dermatitis in infants and children.

Study design One hundred forty-two patients aged 6 months to 12 years were administered MAS063DP (n = 72) or vehicle (n = 70) cream 3 times per day to affected areas and sites prone to develop atopic dermatitis. The primary endpoint for efficacy was the Investigator's Global Assessment at day 22. Secondary endpoints included Investigator's Global Assessment at other time-points, patient's/caregiver's assessment of pruritus, onset, duration of itch relief, Eczema Area and Severity Index, subject's/caregiver's assessment of global response, and need for rescue medication in the event of an atopic dermatitis flare.

Results MAS063DP cream was statistically more effective ($P < .0001$) than vehicle cream for the primary endpoint and all secondary endpoints. Treatment discontinuation as a result of an adverse event occurred in 9.9% of patients using MAS063DP cream and 16% of patients using vehicle cream.

Conclusion MAS063DP cream is effective and safe as monotherapy for the treatment of symptoms of mild to moderate atopic dermatitis in infants and children. (*J Pediatr* 2008;152:854-9)

Atopic dermatitis (AD) is the most common chronic skin disease of young children, with a prevalence approaching 17% in school-aged children in the United States.¹ AD is characterized by intense pruritus with erythema, scaling, vesiculation, weeping, crusting, and lichenification. Importantly, the disease can cause significant sleep disruption and impact the quality of life of patients and families.² Treatment most commonly includes avoidance of triggers, use of moisturizers, as well as topical corticosteroids or topical calcineurin inhibitors.³ Side effects of medications may limit their use, and patients or caregivers are frequently worried about potential side effects.^{4,5} Thus new therapeutic strategies are needed.⁶

Patients with AD have a genetically impaired epidermal barrier, both in clinically affected and nonaffected skin.⁷ A number of studies have now shown that mutations in the filaggrin gene are a major predisposing factor for AD.^{8,9} Filaggrin is a key epidermal protein, essential for the formation of a normal skin barrier. In addition, abnormalities in stratum corneum chymotryptic enzyme, a serine protease localized in the extracellular space of the stratum corneum specific for keratinizing cells undergoing desquamation have also been demonstrated in AD.¹⁰ This results in increased production of the stratum corneum chymotryptic enzyme protease and premature breakdown of the skin barrier. Of note, impaired epidermal barrier function may play a critical role in allergic sensitization, allowing allergen penetration into skin and microbial colonization, eliciting a number of immune responses.^{11,12}

MAS063DP (Atopiclair), a nonsteroidal cream, has been efficacious in several small open-label and vehicle-controlled studies in adults with AD and contact dermatitis.¹³⁻¹⁵ MAS063DP is a hydrolipidic cream that helps maintain a healthy epidermal barrier while providing symptomatic relief of pruritus. Ingredients include glycyrrhetic acid (GrA),

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AD	Atopic dermatitis	IGA	Investigator's Global Assessment
AE	Adverse event	ITT	Intention-to-treat
EASI	Eczema Area and Severity Index	VAS	Visual analogue scale
GrA	Glycyrrhetic acid		

vitis vinifera (grapevine) extract, and telmestine. GrA 2%, the active metabolite in licorice root extract, shows antiinflammatory and antipruritic activity and has been shown to block the degradation of endogenous cortisol through inhibition of 11- β -hydroxysteroid dehydrogenase.¹⁶ Additionally, GrA has been demonstrated to potentiate cutaneous hydrocortisone activity.¹⁷ The standardized *vitis vinifera* (grapevine) extract in MAS063DP has antioxidant and antiprotease activity, which may help protect against breakdown of the epidermis.¹⁸ Telmestine also has antiprotease action and inhibits elastase, collagenase, and matrix metalloproteinase, which are expressed at high levels in patients with AD.¹⁹ Finally, hyaluronic acid in the emollient helps to moisturize the epidermis and restore barrier function.²⁰ Here, we report the results of a multicenter, randomized, placebo-controlled study evaluating the efficacy and safety of MAS063DP in infants and children with mild to moderate AD.

METHODS

Patient Population

Subjects were male or female infants and children between the ages of 6 months and 12 years, diagnosed with AD according to Hanifin and Rajka's criteria.²¹ To be eligible, subjects had to have an Investigator's Global Assessment (IGA) score of mild (IGA = 2) or moderate (IGA = 3) AD and have at least 5% body surface area affected by AD at study entry. Additionally, subjects needed to score at least 40 mm on a Visual Analogue Scale (VAS) for itch out of a total 100 mm, where 0 correlated to no itch and 100 to the worst possible itch. Patients and caregivers agreed to refrain from using other topical and systemic medications (including phototherapy) during the wash-out and study periods. A wash-out period of 7 or 14 days was used for patients on topical and systemic medications, respectively, including topical and systemic corticosteroids, topical calcineurin inhibitors, antihistamines, and phototherapy. If clinically indicated, a low potency rescue topical steroid was prescribed for patients by the study investigator. Patients were excluded from participation if they had severe AD, active skin infection, or another skin condition that could interfere with evaluation of AD. Additionally, patients with intolerance to extract of *butyrospermum parkii* (shea nut), insulin-dependent diabetes, or other systemic disease that could interfere with participation were excluded. Finally, those patients who previously had used MAS063DP and females who had reached menarche were excluded from the study.

Study Design

The study was a randomized, double-blind, parallel-group, vehicle-controlled trial. The protocol was approved by the Institutional Review Board at each participating site. All subjects/caregivers were educated on the study procedures, risks and benefits of participation in the study, and proper application technique of the study medicine. All caregivers signed an informed consent document approved by the Insti-

tutional Review Board at each study center before entering into the study. Determination of sample size was performed such that analysis of the primary endpoint (IGA score at day 22) would have at least 80% power to detect a difference between the 2 groups with a 2-sided test at a 5% significance level. On the basis of data from previous studies and allowing for a 30% attrition rate, it was planned to recruit a total of 126 subjects, with 63 subjects randomized to the MAS063DP group and 63 to the vehicle group.

Eligible subjects were randomized to receive either MAS063DP or vehicle in a 1:1 ratio according to a computer-generated code. This was a 43-day study with visits/assessments at baseline and days 3, 8, 15, 22, 29, and 43. If a wash-out period was not required, the screening and baseline visits were combined. Safety measurements were evaluated through clinical observations and subject/caregiver-reported adverse events.

Treatments

Subjects were instructed to apply the study medication 3 times daily (morning, afternoon, and evening) to areas of their skin that were affected by AD, had been affected by AD in the past, or could reasonably be affected by AD during the course of the study. Investigators identified 1 target lesion to monitor throughout the study for evaluation and photography. The vehicle used in the study was a cream with an emollient base similar to that of MAS063DP, such as ethylhexyl palmitate and glyceryl stearate, without the key ingredients including GrA, *vitis vinifera* extract, and telmestine. MAS063DP contains shea nut butter, and although there are theoretical concerns for using shea nut derivative in patients with tree nut allergy, extensive review of the literature does not support such clinical cross-reactivity. In fact, shea nut butter is used extensively in various topical preparations. In addition, the product used in this study was analyzed and shown not to contain detectable levels of shea nut protein in the batch analyzed (data on file, Sinclair Pharmaceuticals). Previous studies did not report any suspected allergic reactions to shea nut with use of MAS063DP cream.

Study Endpoints

The study's primary endpoint was the IGA at day 22, on a scale of 0 to 5, where 0 correlated to clear and 5 to severe disease. Success of treatment was defined as reaching an IGA score of 0 or 1. Secondary endpoints included IGA scores at other time points, subject/caregivers' assessment of pruritus (100 mm VAS scale and 0-3 ordinal scale), onset and duration of itch relief, Eczema Area and Severity Index (EASI)²² at study visits, subject/caregivers' assessment of global response, and need for rescue medication in the event of an AD flare.

Statistical Analysis

The IGA was dichotomized into either successes (IGA: 0-1) or failures (IGA: 2-5). Statistical analysis of IGA score

was performed with Fisher's exact test. IGA was measured at day 22 or the last post-baseline efficacy measure in case of early discontinuation or use of rescue medication. Statistical analysis of change in subject/caregiver's assessment of itch (both VAS and ordinal scale) over time was performed using the Student's *t* test. IGA scores (dichotomized as they were at day 22) were analyzed at all other time points with Fisher's exact test, and the frequency distribution was presented by frequency tables. All subjects were considered for standard safety analysis, which was presented in frequency tables. Where appropriate, a comparison between treatments was performed with a χ^2 test. All significant tests were 2-sided, with a 5% significance level. In general, the statistical analysis was performed on an Intention-to-Treat (ITT) population, with a confirmatory analysis performed with a Per Protocol population. The Last Observation Carried Forward method was used where data were missing (eg, when rescue medication was prescribed or when a patient missed a visit). All statistical analysis was carried out by SAS, System for Microsoft Windows (Release 8.2-SAS Institute, Inc., Cary, NC).

RESULTS

Study Patients

A total of 142 subjects were enrolled at 7 study centers in the United States. Of these, 72 (50.7%) were randomized to receive MAS063DP, and 70 (49.3%) were in the vehicle group. The first patient was enrolled on November 17, 2005, and the last patient completed the study on May 19, 2006. Of 142 subjects, 106 completed the study; 36 subjects terminated early or were withdrawn, 19 (26.3%) in the MAS063DP group and 17 (24.2%) in the vehicle group. A total of 139 of 142 subjects (97.9%) were therefore evaluated for efficacy (ITT population), and all subjects were included in the safety analysis. The primary reasons for discontinuation included the following: "poor control of AD" (5 subjects in the MAS063DP group and 10 in the vehicle group), "withdrawal of consent" (5 subjects in the MAS063DP and 3 in the vehicle group), "side effects" (3 subjects in each group attributable to study cream, primarily burning/discomfort on application), and "failure to follow up" (3 subjects in the MAS063DP group). One subject in each group discontinued the treatment because of an adverse event (1 asthma exacerbation and 1 tonsillectomy, both considered unrelated to study treatment) and 2 subjects in the MAS063DP group did not complete the study, 1 because of a protocol deviation and 1 because of moving out of state. All subjects were included in the safety analysis.

Baseline Characteristics

Of 142 enrolled subjects, 52% were female and 48% male, with ages ranging from 6 months to 12 years (Table). Of the subjects, 49% were Caucasian, 25% were black, 16% were Hispanic, and 10% were from other ethnic groups. The disease history showed a "constant" pattern in 66 (60.6%) subjects, "frequent" in 35 (24.6%), and "intermittent" in 21

Table. Subject demographics and disease characteristics

	MAS063DP (n = 72)	Vehicle (n = 70)
Sex		
Female	36 (50.0%)	38 (54.2%)
Male	36 (50.0%)	32 (45.7%)
Age (years)		
No. of patients	72	70
Mean (SD)	4.89 (3.35)	5.10 (3.29)
Min:Median:Max	0.5:4.1:11.9	0.6:4.5:12.5
Ethnic origin		
Black	16 (22.2%)	19 (27.1%)
Hispanic	12 (16.6%)	10 (14.2%)
Caucasian	39 (54.1%)	30 (42.9%)
Other	5 (6.8%)	11 (22.4%)
Pattern of disease		
Constant	44 (61.1%)	42 (60.0%)
Frequent	15 (20.8%)	20 (28.6%)
Intermittent	13 (18.0%)	8 (11.4%)
IGA of AD (score)		
Mild	37 (51.3%)	37 (52.8%)
Moderate	35 (48.6%)	33 (47.1%)
Itch (VAS score, mm)		
No. of patients	72	70
Mean (SD)	61.89 (16.99)	67.41 (17.24)
Min:Median:Max	40:60:100	40:70:100

*Data missing for 1 patient.

(14.8%). The duration of the "current episode" ranged from 2 days to 12 years (median 5 months), and 43% of subjects/caregivers reported a seasonal pattern of AD. There was no statistical difference between treatments used by subjects in these different categories. Among children in the study, 80% reported a family history of atopy, and 45% had a history of another atopic disorder (asthma or allergic rhinitis) at study initiation. The IGA score for AD was "mild" (50.7%) or "moderate" (49.3%) in all subjects, and the mean VAS score for itch was 62 mm and 67 mm in the MAS063DP and vehicle groups, respectively. The mean VAS scores for itch $\pm$ standard deviation at baseline were 66.24 ± 17.53 mm in the vehicle group versus 60.28 ± 16.88 mm in the MAS063DP group ($P = .04$). Target lesions were most commonly identified on the extremities, with 40% on the lower and 32% on the upper limbs.

Efficacy

PRIMARY ENDPOINT: IGA AT DAY 22. A highly significant difference was found in the IGA scores at day 22 between MAS063DP and vehicle treatment groups (analysis of covariance: $P < .0001$). In the ITT analysis, 53 of 69 (77%) subjects receiving MAS063DP reached an IGA score of 0 and 1. By contrast no treatment successes were recorded in the vehicle group. Mean value of treatment difference was -1.636 in favor of MAS063DP, with a 95% confidence interval ranging from -1.928 to -1.344 .

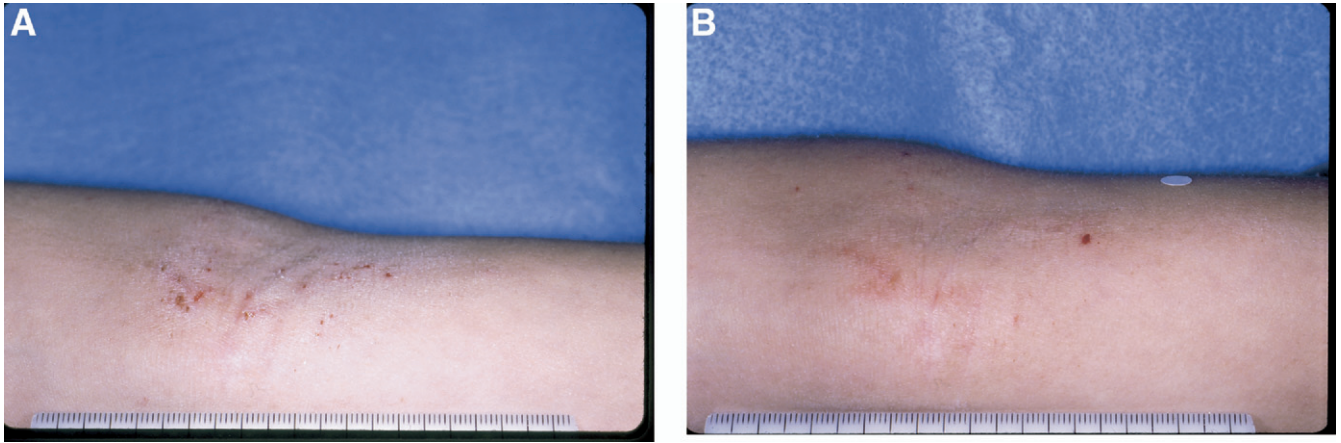


Figure 1. Representative atopic dermatitis skin lesions at day 1 (A) and day 8 (B) of treatment with MAS063DP.

SECONDARY ENDPOINT: IGA OF AD AT OTHER TIME POINTS.

Improvements in IGA scores were observed as early as day 8 (Figure 1, baseline visit vs day 8 photos of forearm lesions), where 39.1% of subjects in the MAS063DP treatment group reached an IGA of “clear” or “almost clear.” At day 15, 71% of subjects in the MAS063DP group were treatment successes. This number increased to 78.2% at day 29 and remained stable until the end of the study (Figure 2). By contrast, the percentage of treatment successes in the vehicle-treated group did not exceed 7.1% (occurring only at day 43). The difference between treatments was highly statistically significant at all time points (Fisher’s exact test, $P < .0001$).

SECONDARY ENDPOINT: PATIENT/CAREGIVER’S ASSESSMENT OF PRURITUS—VAS SCORE (0–100 MM).

The VAS mean values in the MAS063DP group decreased sharply from baseline to day 43 (from 60 mm at baseline to 13 mm at day 43). Subjects in the vehicle group had a slight decrease in mean VAS score at day 3, sustained until the end of the study (from 66 mm at baseline to 57 mm at day 43). Although the mean values at baseline were significantly different ($P = 0.04$) between the 2 groups, the statistical analysis performed on changes compared with baseline (Figure 3) showed a highly significant difference at all time points (analysis of covariance with baseline value as covariate, $P < .0001$).

SECONDARY ENDPOINT: EASI AT ALL TIME POINTS. The time course of EASI scores recorded during the study showed an important improvement in the EASI scores in the MAS063DP group between baseline and day 22 (64.1%), already noticeable at day 8 (42.8%). Conversely, in subjects treated with vehicle EASI, scores remained substantially the same throughout the study period. In particular, after 22 days of treatment, no changes in the EASI scores were observed in the vehicle treatment group (0.84 ± 3.52), compared with an appreciable improvement in the MAS063DP group (-5.15 ± 7.24). The changes in EASI scores versus baseline showed a highly statistically significant difference between treatments at all time points (t test, $P < .0001$).

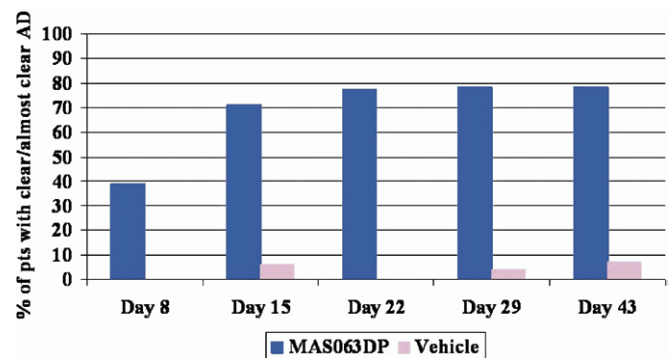


Figure 2. Investigator’s Global Assessment of atopic dermatitis treatment successes (“Clear” or “almost clear” ratings). MAS063DP vs Vehicle: $P < .0001$ at all time points.

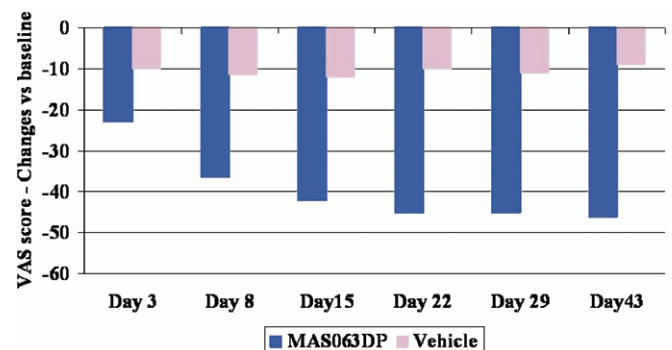


Figure 3. Assessment of pruritus. MAS063DP vs Vehicle: $P < .0001$ at all time points.

SECONDARY ENDPOINT: SUBJECT/CAREGIVER’S ASSESSMENT OF GLOBAL RESPONSE FROM BASELINE.

A good improvement or total resolution was reached in a percentage of subjects ranging from 60.8% at day 8 to 81.1% at day 43 in the MAS063DP group, compared with values not higher than 10% in the vehicle group. The difference between the 2

treatments was highly statistically significant (χ^2 test: $P < .0001$) at all time points.

SECONDARY ENDPOINT: ONSET OF ITCH RELIEF AND DURATION OF ACTION. Complete itch relief was reported by very few subjects treated with vehicle (6% with complete itch relief at day 3 and 7% at day 43); in contrast, 27% reported complete itch relief with MAS063DP at day 3 and 65% at day 43 ($P < .05$, t test). The mean values for the onset of itch relief ranged from 8.16 ± 7.54 SD to 16.25 ± 6.29 SD minutes after application in subjects treated with vehicle, and from $2.42 \pm .24$ SD to 12.24 ± 71.32 SD minutes in subjects treated with MAS063DP. In the MAS063D group, the mean value for the duration of itch relief between each application was 201 minutes ± 153.9 SD at day 8, and it increased steadily to 345 minutes ± 268.9 SD at day 43. By contrast, the mean duration of relief in subjects treated with vehicle was 129 minutes ± 247.9 SD at day 8, and it decreased steadily to 64.4 ± 112.9 SD at day 43. The difference between treatments was statistically significant at all time points ($P < .05$, t test).

SECONDARY ENDPOINT: NEED FOR RESCUE MEDICATION IN THE EVENT OF A FLARE. A total of 26/139 subjects (18.7%) needed rescue medication during the study period, 6 subjects (8.7%) in the MAS063DP group and 20 (28.6%) in the vehicle group. All 6 subjects in the MAS063DP group required rescue medication on only 1 occasion, in contrast to the vehicle group, in which 7 of the 20 subjects (35%) required rescue treatment on 2 occasions ($P = .0041$ by Fisher's exact test). The mean duration of rescue treatment was 4.17 days (range, 3 to 8 days) in the MAS063DP group compared with 5.65 days (range, 2 to 12 days) in the vehicle group.

Adverse Events

All subjects enrolled in the study were included in the safety analysis. Of 142 subjects, 72 (50.7%) reported at least 1 adverse event (AE) during the study, 36 subjects treated with MAS063DP and 36 with vehicle. There were a total of 116 AEs, 60 in the MAS063DP (0.83 events per patient) and 56 in the vehicle (0.80 events per patient) group. Commonly reported AEs in the MAS063DP group included stinging (8.3% of subjects), burning (6.9%), and fever (6.9%). In the vehicle group, common AEs were upper respiratory infections (8.6%), burning (7.1%), fever (7.1%), and colds (7.1%). In the MAS063DP group, 16.6% of the AEs were judged by investigators to be "probably related" to study medicine, compared with 12.5% in the vehicle group. No serious AE was believed related to the medication. Treatment discontinuation (permanent or temporary) as a result of an AE occurred in 9.9% of subjects treated with MAS063DP and 16% of those treated with vehicle. Most AEs (91.3%) resolved without intervention during the study. Two serious AEs (SAEs) required hospitalization during the study. One was a tonsillectomy, scheduled before study enrollment and the other an "acute asthma exacerbation," both judged by the investigator not to

be related to the study treatment. Both subjects completed the study.

DISCUSSION

Children with AD have a defective skin barrier in both lesional and nonlesional skin.^{7,23} These defects allow for transepidermal water loss and leave the skin vulnerable to irritants, allergens, microbes, toxins, and mechanical stresses.¹¹ Patients with AD also display cutaneous hyperreactivity to environmental insults, which aggravates the epidermal abnormalities and leads to the eczematous lesions characteristic of AD. Thus treatment that decreases the signs and symptoms of AD as assessed by the IGA may in fact work by helping to restore the epidermal barrier. Of interest, transepidermal water loss, a marker of barrier function, was shown to improve with use of MAS063DP in a study of contact dermatitis, another chronic inflammatory skin disease with a damaged skin barrier.¹⁴

Many of the current therapies for AD target underlying immunologic defects but fail to adequately address the defective skin barrier. Topical corticosteroids and calcineurin inhibitors may improve function of the epidermis by decreasing cutaneous inflammation but have potential side effects.³ Application of topical corticosteroids may cause skin atrophy, telangiectasias, striae, acne, and even hypothalamic-pituitary axis suppression; these risks have led to concern by patients, caregivers, and physicians about their use.⁴ Topical calcineurin inhibitors can cause application site burning/stinging and have recently received black-box safety warnings by the Food and Drug Administration,⁵ raising patient or parental concerns.

Here, we report the results of a multicenter, double-blind, vehicle-controlled, randomized clinical trial that shows MAS063DP to be both safe and effective in treating the symptoms of mild to moderate AD in infants and children. Although the treatment groups differed at baseline in severity of pruritus with the vehicle control group scoring higher on VAS ($P = .04$), the clinical relevance of this is uncertain. Improvement of the IGA score at day 22 (primary endpoint) was distinctly superior in children treated with MAS063DP compared with those treated with vehicle alone ($P < .0001$). Skin improvement with MAS063DP was evident as early as day 8, and it continued to improve until day 22, at which time the IGA remained stable for the duration of the study. The clinical benefit of MAS063DP versus vehicle was observed as early as day 3, with significant differences favoring MAS063DP throughout the entire study ($P < .0001$). Itch improved dramatically from baseline in the MAS063DP-treated group. Improvement was noted as early as day 3 (from 60 mm VAS at baseline to 38 mm) and persisted through day 43 (from 60 mm VAS to 13 mm). Subjects in the vehicle group had only a minimal improvement of itch. The difference between MAS063DP and vehicle was highly statistically significant at all time points in favor of the former ($P < .0001$). Finally, a significantly lower number of subjects in the MAS063DP group needed rescue therapy with a topical

corticosteroid compared with those in the vehicle group (8.7% vs 28.6%, $P = .0041$). None of the subjects using MAS063DP needed more than 1 course of rescue therapy, as opposed to 35% of the subjects in the vehicle group who needed 2 courses. The drop-out rate was not considered unusual for a chronic, relapsing disease like AD, where patients or caregivers often have unrealistic expectations of immediate relief. Because patients/caregivers had steroidal and nonsteroidal treatments available to them, this could have contributed to the attrition rate seen in the study, especially when dealing with a disease associated with significant pruritus. Patient withdrawals in the MAS063DP group reflected a spectrum of reasons commonly seen in AD studies including poorly controlled AD (5 patients), withdrawn consent (5 patients), side effects of study cream (3 patients), and other (6 patients) including lost to follow-up, moving, and protocol violation. The results of this study are also notable in that the vehicle-treated group, unlike other studies of AD, showed little or no clinical improvement. Given the complexity of the skin abnormalities described in AD, the combination of antipruritic, antiinflammatory, hydrating, and barrier-restoring activities of MAS063DP resulted in beneficial activity in our population of infants and children with mild to moderate AD. One limitation of our study was the lack of monitoring for any systemic toxicity with use of topical MAS063DP. Oral ingestion of large amounts of licorice-containing glycyrrhetic acid has been associated with pseudohyperaldosteronism with doses of 50 g of licorice (75 mg glycyrrhetic acid) daily for 2 weeks reported to cause a significant rise in blood pressure.²⁴ Because MAS063DP cream contains 2% glycyrrhetic acid, application of large amounts of MAS063DP cream over an extended time period to an abnormal skin barrier could result in systemic absorption. To date, however, no systemic adverse events or laboratory abnormalities have been reported with use of this product in post-marketing surveillance.

A previous study showed the safety and efficacy of MAS063DP in adults with AD.¹³ The results of this study confirm those results and show it to be a safe and effective monotherapy in infants and children with mild to moderate AD. Topical application of MAS063DP 3 times daily resulted in rapid improvement of eczematous lesions with resolution of pruritus and was well tolerated. MAS063DP may help fill the need for additional therapy in patients of all ages with AD.

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