Development of new treatment modalities for atopic dermatitis
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SDZ ASM 981: an emerging safe and effective treatment for atopic dermatitis


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SUMMARY

**Background** SDZ ASM 981 is a selective inhibitor of the production of pro-inflammatory cytokines from T cells and mast cells in vitro. It is the first ascomycin macrolactam derivative under development for the treatment of inflammatory skin diseases.

**Objectives** This study was designed to determine the safety and efficacy of SDZ ASM 981 cream at concentrations of 0.05%, 0.2%, 0.6% and 1.0% in the treatment of patients with atopic dermatitis and to select the concentration to be used in phase III studies.

**Methods** This was a double-blind, randomized, parallel-group, multicentre dose-finding study. A total of 260 patients were randomly assigned to treatment with SDZ ASM 981 cream at concentrations of 0.05%, 0.2%, 0.6%, or 1.0%, matching vehicle cream, or the internal control 0.1% betamethasone-17-valerate cream (BMV). Treatment was given twice daily for up to 3 weeks.

**Results** A clear dose-response relationship for SDZ ASM 981 was evident, with 0.2%, 0.6% and 1.0% SDZ ASM 981 creams all being significantly more effective than vehicle (P = 0.041, 0.001 and 0.008, respectively) in terms of baseline to end-point changes in the Eczema Area Severity Index (EASI) and pruritus score. The 1.0% cream was the most effective SDZ ASM 981 concentration, BMV was more effective than the SDZ ASM 981 creams tested in this study. It appears that the efficacy plateau was not reached with the SDZ ASM 981 creams within 3 weeks treatment. SDZ ASM 981 was well tolerated. Burning or a feeling of warmth were the only adverse events reported more frequently in the 0.6% and 1.0% SDZ ASM 981 treatment groups than in the vehicle treatment group (42.9%, 48.9% and 34.9%, respectively). Few systemic adverse events were reported during the study (headache was the most frequent systemic event reported by 15 of 252 patients) and none was considered to be related to treatment. The local tolerability profile of the 1.0% cream was similar to that of the lower concentrations.

**Conclusions** 1.0% SDZ ASM 981 cream, which was shown to be safe, well tolerated and the most effective concentration in this study, was selected as the concentration to be further developed in phase III studies.
INTRODUCTION

Atopic dermatitis is an increasingly common problem in developed countries.¹ It is part of the atopic syndrome, which includes bronchial asthma, allergic rhinitis and allergic conjunctivitis,² and has a genetic predisposition.³

SDZ ASM 981 is a selective inhibitor of the production of pro-inflammatory cytokines from T cells and mast cells in vitro.⁴ SDZ ASM 981 blocks the synthesis of Th1 (interleukin-2, interferon-?) and Th2 (interleukin-4, -10) type cytokines after antigen-specific stimulation of a human T-helper cell clone isolated from the skin of an atopic dermatitis patient.⁴ Accordingly, inhibition of T-cell proliferation by SDZ ASM 981 is observed after antigen-specific or non-specific stimulation.⁴ SDZ ASM 981 also prevents the release of preformed inflammatory mediators from mast cells after stimulation via the IgE receptor.⁴

In vivo, SDZ ASM 981 exhibits high anti-inflammatory activity in mouse and pig models of allergic contact dermatitis after topical application.⁵ In the pig model, SDZ ASM 981 is as effective as the corticosteroid clobetasol-17-propionate.⁵ Topical activity is also observed with SDZ ASM 981 in a murine model of irritant contact dermatitis.⁵ Unlike steroids, SDZ ASM 981 does not cause skin atrophy when applied under occlusion to the skin of pigs.⁵ SDZ ASM 981 has a low potential for affecting the systemic immune responses, as demonstrated in rat models of localized graft-vs.-host reaction and allogeneic kidney transplantation.⁵

A previous proof-of-concept study⁶ suggested that 1.0% SDZ ASM 981 in a cream formulation, applied twice daily, was effective and well tolerated in atopic dermatitis. A pharmacokinetic trial⁷ in atopic dermatitis patients with moderate to severe lesions proved systemic exposure to be very low after twice daily application of 1% SDZ ASM 981 cream for 3 weeks.

This study was designed to investigate the efficacy and safety of four concentrations of SDZ ASM 981 cream in the treatment of atopic dermatitis. The aim was to select for clinical use the optimal concentration in terms of safety and efficacy.

METHODS

In total, 260 patients were recruited in 14 centres in Belgium, Denmark, Finland, Germany, the Netherlands, Norway and the U.K. Male and female adults (aged >18 years) who had given their written informed consent, suffering from atopic dermatitis according to the diagnostic criteria of Hanifin and Rajka,⁸ were enrolled into the study. The severity of the patients' atopic dermatitis was evaluated according to the grading system of Rajka and
Langeland \(^9\) and had to be of at least moderate severity at baseline. The disease affected between 5% and 30% of the total body surface area. The use of other treatments for atopic dermatitis (including emollient use at treated sites), or corticosteroids (inhaled or oral) for the treatment of asthma during the treatment phase of the study was prohibited.

Patients with concomitant medical conditions that could interfere with the evaluation of the study were excluded, as were women who were pregnant, breast feeding, or not using medically approved contraception if they were of child-bearing potential.

Four concentrations of SDZ ASM 981 cream were selected for this study (0.05%, 0.2%, 0.6% and 1.0%), the 0.05% being the highest concentration expected to have no therapeutic effect and 1.0% being the highest possible concentration for galenical reasons. The treatment duration of 3 weeks was set as an appropriate duration to demonstrate superiority to vehicle and to distinguish between the therapeutic effects of the four concentrations; it was not anticipated that this would show the maximum effect (efficacy plateau) of any of the medications tested. Included in the study as an internal control, 0.1% betamethasone-17-valerate cream (BMV) was selected as the highest potency topical steroid that could be used for 3 weeks in this study setting.

The study utilized a double-blind, parallel-group design. Patients were randomly assigned to treatment with 0.1% BMV cream, one of the four concentrations of SDZ ASM 981 cream, or a corresponding vehicle cream. Study medication was applied by the patients twice daily to all affected areas of skin (excluding the face) for up to 3 weeks. If complete clearance of atopic dermatitis occurred before the end of the treatment period (evaluated by the investigator at each scheduled visit), treatment with the study medication was stopped. Assessments of the patients were made at a screening visit, at baseline (immediately prior to treatment), after 1 and 2 weeks' treatment (days 8 and 15) and after 3 weeks' treatment (post-treatment evaluation on day 22). In the event of premature discontinuation from the study, final assessments were made the day after the last application of study medication.

The patients' dermatitis was assessed at each study visit, days 1, 8, 15 and 22 according to an adapted Eczema Area Severity Index (EASI).\(^{10}\) The EASI was adapted to take into account that the head and neck were not treated with trial medication because the internal control, 0.1% BMV cream, was not regarded as safe for treating these areas. The method for calculating EASI assigns proportionate body surface areas to four body regions: the head (10%) (omitted in this trial), trunk (30%), upper extremities (20%) and lower extremities (40%). The area of involvement of each body region is assigned a numerical score, which represents the proportion of the total area within the region (Table 1). The key signs of atopic dermatitis: erythema (E), infiltration or papules (I),
excoriation (Ex) and lichenification (L), were assessed on a scale from 0 to 3 indicating none (0), mild (1), moderate (2) and severe (3) expression of each clinical sign, with half-value scores being permitted. The total adapted EASI was then calculated, to take into account the severity of each key clinical sign, the involvement within each body region, and the proportion of the whole body represented by each area (Table I). The adapted EASI, therefore, could theoretically vary between 0 and 64.8. Pruritus was assessed separately using a score ranging from 0 to 3, representing none (0), mild (1), moderate (2) and severe (3). Pruritus was assessed as the intensity of itch in the previous 24 h.

Patients were asked to assess their atopic dermatitis separately at the end of the study using a score ranging from 0 to 6 (representing normal or 100% clear) (0), almost clear or 90-99% clear (1), marked improvement or 75-89% clear (2), moderate improvement or 50-74% clear (3), slight improvement 25-49% clear (4), unchanged or <25% clear (5) and worsened (6).

All reported adverse events were recorded. Determination of vital signs (blood pressure and pulse rate), physical examination and laboratory assessments of routine haematology and blood chemistry parameters were performed before treatment, on day 8 of treatment, and post-treatment on day 22.

Statistical methodology
The efficacy analysis was performed on an intent-to-treat (ITT) basis. All patients who received at least one application of study medication were included in the ITT population. The efficacy analysis was based on the EASI at end-point.

An analysis of covariance with centre and baseline EASI as covariates was performed for each concentration level starting with 1.0% SDZ ASM 981. In the analysis the dependent variable was the last EASI recorded (end-point analysis) for the ITT population. A 95% confidence interval for the adjusted mean difference was calculated for the highest selected concentration showing superiority to vehicle. The frequency distribution of patients with pruritus assessment rated 'absent' or 'mild' were performed over all visit days.
RESULTS

In total, 260 patients were randomized to treatment. Of these patients, 61 discontinued treatment prematurely, primarily due to adverse events or lack of therapeutic effect. In 15 of the 61 cases worsening of dermatitis at treated areas, leading to discontinuation, was reported as an adverse event, when this could also have been considered lack of therapeutic effect. One patient discontinued after using a topical steroid following worsening dermatitis (protocol violation). The rate of premature discontinuation increased with decreasing SDZ ASM 981 concentration. This was due to a higher rate of discontinuations due to lack of therapeutic effect in the groups treated with vehicle and lower SDZ ASM 981 concentration. All 260 patients randomized were evaluable for both safety and efficacy (ITT analysis). The disposition of patients is shown in Table 2.

The six treatment groups were not significantly different with respect to demographic characteristics, baseline severity or history of dermatitis (Table 3). The patients were predominantly young caucasian adults, evenly distributed between the sexes, with moderate or severe atopic dermatitis, and a long history of illness; in each treatment group the median time since first occurrence of atopic dermatitis was at least 22 years.
Efficacy

The median EASI decreased over the course of treatment in the 0.2%, 0.6%, 1.0% and BMV treated groups (Fig. 1). The greatest decrease was seen in the BMV-treated patients, followed by the SDZ ASM 981 1.0% and 0.6% groups. The testing procedure showed that the differences at end-point between vehicle and 1.0%, 0.6% and 0.2% SDZ ASM 981 were statistically significant (P = 0.008, 0.001 and 0.041, respectively). As predicted, the 0.05% SDZ ASM 981 cream failed to show a significant therapeutic effect.

As anticipated, all treatments were less effective in the more severe patients (stratified by baseline EASI, Table 4). The 1.0% cream showed the greatest improvement of any SDZ ASM 981 concentration in patients with a baseline EASI of 8-12 and > 12. Improvements in pruritus were seen in all groups. SDZ ASM 981 1.0%, 0.6% and 0.2% were associated with a greater increase from baseline to end-point in the number of patients with pruritus rated as 'absent' or 'mild' compared with vehicle. BMV was more effective than any SDZ ASM 981 concentration in reducing pruritus (Table 5). The patients' assessment of their atopic dermatitis at the end of the study showed a higher proportion of patients to be moderately clear or better (> 50% improvement) in the SDZ ASM 981 1.0%, 0.6% and 0.2% (53.3%, 54.8% and 32.6%, respectively), compared with vehicle (16.3%). The BMV treatment group had the highest rate of moderately clear or better patients (88.1%).

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**Table 1. Baseline demographic characteristics of patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vehicle 0%</th>
<th>0.2%</th>
<th>0.6%</th>
<th>1.0%</th>
<th>BMV 0.4%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41-45</td>
<td>41-42</td>
<td>40-42</td>
<td>40-42</td>
<td>40-42</td>
</tr>
<tr>
<td>Age (months)</td>
<td>13-19</td>
<td>13-19</td>
<td>13-19</td>
<td>13-19</td>
<td>13-19</td>
</tr>
<tr>
<td>Mean baseline EASI</td>
<td>27.21</td>
<td>27.21</td>
<td>27.21</td>
<td>27.21</td>
<td>27.21</td>
</tr>
<tr>
<td>Mean sex</td>
<td>Male: 21</td>
<td>21</td>
<td>21</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Female: 24</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
</tbody>
</table>

*Grading of atopic dermatitis according to Rajka and Leqtra, Baseline severity of atopic dermatitis defined as moderate (score: 4 to < 8) and severe (score 8-9). BMV: 0.1% betamethasone-17-valerate cream; EASI: Investigator Area Severity Index.
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### Table 4. Median percentage change of Eczema Area Severity Index (EASI) overall, stratified by EASI at baseline

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Baseline</th>
<th>EASI at baseline</th>
<th>EASI at follow-up</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle (n = 14)</td>
<td>6 (4%)</td>
<td>4 (3%)</td>
<td>6 (4.5%)</td>
<td>4 (3.5%)</td>
</tr>
<tr>
<td>SDZ ASM 981 0.05%</td>
<td>2 (4%)</td>
<td>2 (4%)</td>
<td>2 (4%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>0.2%</td>
<td>5 (11%)</td>
<td>3 (7%)</td>
<td>1 (2.5%)</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>0.6%</td>
<td>3 (7%)</td>
<td>1 (2.5%)</td>
<td>1 (2.5%)</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>1.0%</td>
<td>4 (10%)</td>
<td>3 (8%)</td>
<td>1 (2.5%)</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>BMV</td>
<td>5 (13%)</td>
<td>3 (8%)</td>
<td>1 (2.5%)</td>
<td>1 (2.5%)</td>
</tr>
</tbody>
</table>

### Table 5. Patients with absent and mild (0) and 1) pruritus score at baseline, day 8 and end-point

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Baseline</th>
<th>Day 8</th>
<th>End-point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle (n = 14)</td>
<td>2 (4%)</td>
<td>6 (14%)</td>
<td>8 (18%)</td>
</tr>
<tr>
<td>SDZ ASM 981 0.05%</td>
<td>2 (4%)</td>
<td>3 (7%)</td>
<td>10 (23%)</td>
</tr>
<tr>
<td>0.2%</td>
<td>5 (11%)</td>
<td>4 (9%)</td>
<td>9 (20%)</td>
</tr>
<tr>
<td>0.6%</td>
<td>3 (7%)</td>
<td>1 (2.5%)</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>1.0%</td>
<td>4 (10%)</td>
<td>2 (5%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>BMV</td>
<td>5 (13%)</td>
<td>3 (8%)</td>
<td>4 (9%)</td>
</tr>
</tbody>
</table>

**Safety and local tolerability**

Few systemic adverse events were observed and none were considered by the investigators to be related to treatment, there was no difference between treatment groups in the frequency of the non-local adverse events. There were no clinically significant changes in vital signs or laboratory parameters reported. With respect to haematology parameters, most newly occurring abnormalities were in eosinophil counts as expected in patients with atopic dermatitis. In the vehicle, SDZ ASM 981 0.05%, 0.2%, 0.6%, 1.0% and BMV groups, the frequency of patients with a change from 'normal at baseline' to 'notable abnormality during study' in eosinophil counts, were 2, 6, 6.4, 6 and 1, respectively. Very few biochemical abnormalities occurred after baseline; most were decreased blood glucose (three patients, one in each of the SDZ ASM 0.05% , 1.0% and vehicle treated groups) or increased potassium levels (two patients, one each of the SDZ ASM 0.05 % and 0.2% treated groups). Only five patients had newly occurring vital sign notable abnormalities. In the SDZ ASM 981 0.2% group, one patient had an elevated pulse; in the SDZ ASM 981 0.6% group low diastolic blood pressure was reported in one patient and a weight decrease in one patient. In the vehicle group, low pulse occurred in one patient. One patient in the BMV group had elevated systolic blood pressure. No newly occurring notable abnormalities of vital signs were reported in the SDZ ASM 981 0.05% and 1.0% groups.
The total number of patients reporting one or more adverse events and the frequency of the most commonly occurring adverse events is presented in Table 6. Application site reactions (burning, feeling of warmth, stinging, smarting, pain and soreness) were the most common adverse events reported. These were the only adverse events reported more frequently in the 1.0% (48.9%) and 0.6% (42.9%) SDZ ASM 981 groups than the vehicle group (34.9%). Most application site reactions were of mild to moderate severity (12 of 15, 14 of 18 and 20 of 22 cases in the vehicle, 0.6% and 1.0% SDZ ASM 981 groups, respectively); patients had been informed before entering the study that these reactions might occur. In patients treated with the 1.0% SDZ ASM 981 cream the application site reactions were transient. The majority (13 of 22) of application site reactions began on the first day of treatment and resolved within the first 3 days of treatment. Other treatment groups had a more delayed onset and resolution of application site reactions.

The next most commonly reported adverse events were pruritus and worsening of atopic dermatitis. The overall incidence of study indication (atopic dermatitis) related adverse events was similar in all SDZ ASM 981 treatment groups and the vehicle treatment group. However, the incidence of withdrawal from the study due to such events was higher in the vehicle and 0.05% SDZ ASM 981 groups, as was the frequency of worsening atopic dermatitis, suggesting that these events are related to lack of efficacy.

Table 6. Number of patients reporting adverse events and frequency of most common adverse events

<table>
<thead>
<tr>
<th>% patients</th>
<th>Vehicle (n = 44)</th>
<th>0.2% (n = 44)</th>
<th>0.6% (n = 44)</th>
<th>1.0% (n = 44)</th>
<th>BMV (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one adverse event</td>
<td>16 (36%)</td>
<td>12 (27%)</td>
<td>29 (65%)</td>
<td>24 (57%)</td>
<td>19 (43%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>15 (13%)</td>
<td>10 (23%)</td>
<td>9 (20%)</td>
<td>11 (26%)</td>
<td>14 (33%)</td>
</tr>
<tr>
<td>Worsening atopic dermatitis</td>
<td>9 (21%)</td>
<td>9 (20%)</td>
<td>9 (20%)</td>
<td>5 (12%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Application site reactions</td>
<td>15 (13%)</td>
<td>14 (15%)</td>
<td>11 (24%)</td>
<td>18 (41%)</td>
<td>22 (49%)</td>
</tr>
<tr>
<td>Burning of feeling of warmth</td>
<td>6 (13%)</td>
<td>9 (20%)</td>
<td>10 (23%)</td>
<td>14 (33%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

BMV, 0.5% betamethasone 17-valerate cream

DISCUSSION

This randomized, double-blind, vehicle and positive-controlled multi-centre study in 260 adult patients with extensive moderate to severe atopic dermatitis shows that topical SDZ ASM 981 is well tolerated and effective in improving the key signs and pruritus associated with atopic dermatitis. A clear dose response was observed in this study. The 1.0%, 0.6% and 0.2% SDZ ASM
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981 creams were significantly more effective than the vehicle cream, whereas the 0.05% concentration was not. The 1.0% drug concentration previously shown to be effective in a proof-of-concept study was the most effective concentration but was less effective than the high-potency steroid BMV. As shown in Figure 1 the therapeutic effect did not reach a plateau within the 3-week treatment period of this study, suggesting that with a prolonged treatment duration the therapeutic effect of SDZ ASM 981 will be even greater. The results of this study suggest that the short-term anti-inflammatory activity of the 1.0% SDZ ASM 981 cream in adult patients with moderate to severe atopic dermatitis is comparable with that of steroids with intermediate potency.

Figure 1. EASI: median percentage change from baseline (intent-to-treat population).

使用的 topical medications always raises the question of absorption through the skin and subsequent systemic exposure. A pharmacokinetic trial in atopic dermatitis patients with moderate to severe lesions treated twice daily with 1% SDZ ASM 981 cream for 3 weeks, showed systemic exposure to be consistently low, with 72% of measurements being below the limit of quantification. The low systemic absorption of topical SDZ ASM 981 should minimize the risk of systemic side-effects. In this study SDZ ASM 981 was shown to be safe. No drug-related (as evaluated by the investigators) systemic adverse events were reported.

The higher concentrations of SDZ ASM 981 were similar to the lower concentrations with respect to local tolerability. Burning or feeling of warmth
were the most prominent adverse events. The majority of patients reported these events to be mild or moderate and transient. Other dermatological adverse events were also reported, particularly pruritus and worsening atopic dermatitis. These were most frequent in the vehicle and 0.05% SDZ ASM 981 treated groups. It was concluded that many of these were probably due to lack of efficacy of the lower concentrations of SDZ ASM 981 cream.

With regard to local tolerability, it should be noted that when compared with steroids under similar conditions, SDZ ASM 981 is devoid of atrophogenic activity. The 1.0% SDZ ASM 981 cream exerted the greatest therapeutic effect in terms of reduction in EASI. It was also the most effective in terms of a more rapid resolution of pruritus, had the lowest discontinuation rate due to treatment failure or worsening of dermatitis of any SDZ ASM 981 concentration tested, and was more effective in the patients with more severe dermatitis as stratified by the EASI at baseline. This concentration was therefore selected for future studies.

In this study, the efficacy of SDZ ASM 981 in treating dermatitis on the face and neck was not tested, as the BMV control treatment, due to its atrophogenic potential and potential to induce facial dermatitis, was not regarded as safe for use on the face. As penetration of topical drugs is usually better on the face than on the trunk or extremities, it is anticipated that the therapeutic effect of SDZ ASM 981 on the face will be at least as good as on the trunk and extremities treated in this study.

The emerging safety and efficacy profile of SDZ ASM 981 1.0% cream offers the opportunity to develop SDZ ASM 981 in the long-term management of atopic dermatitis. Phase III clinical trials are currently being performed to evaluate short-term and long-term safety and efficacy of SDZ ASM 981 1% cream in children (3 months and older) and adults with atopic dermatitis.

Acknowledgements

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REFERENCES