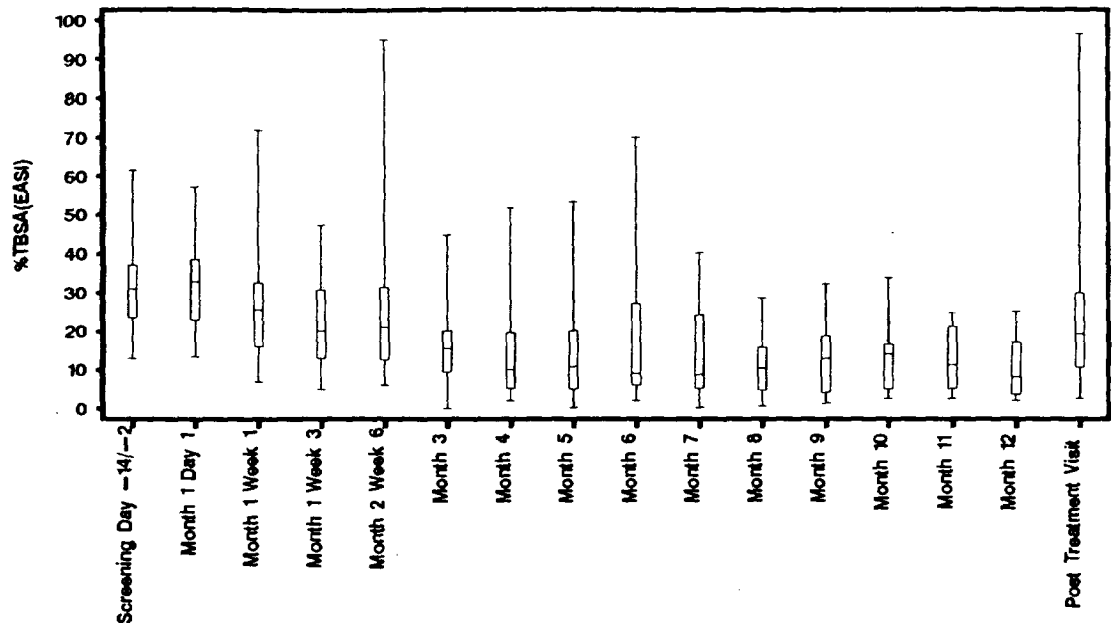
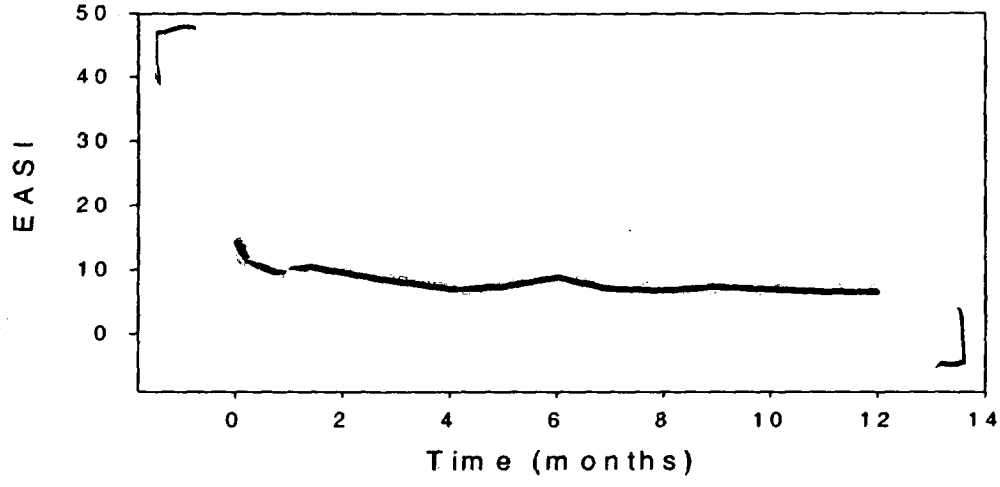
Figure 3: Median and ranges of the affected body surface area determined from the EASI evaluation at each site visit




The individual EASI values and the mean (except 3 protocol violators nos. 7, 17 22) are shown in Figure 4 below.

Figure 4: Eczema area severity index (EASI) over time with mean value (solid line) and individual values (shaded lines); n=37, patients 7, 17 and 22 were excluded (protocol violators)



According to the investigator's overall evaluation of dermatitis, 60% of patients had their eczema cleared by at least 50% at their end-of-study evaluation compared to baseline, 35% had their eczema cleared by less than 50%, and one patient had worsened during the study. For the eczema area severity index (EASI), mean values and ranges at baseline and months 6 and 12 are shown below in Table 2 for the intention-to-treat (ITT) population including the last observation carried forward (LOCF), and for the patient under treatment (PUT) population (excluding patients 7, 17, 22, protocol violators).

**Table 2: EASI: mean values, percentage change from baseline, and minimum/ maximum values for the ITT (including LOCF) and PUT population excluding protocol violators nos. 7, 17, 22 (n=number of patients)**

| Population | Month 1 Day 1 (baseline) | Month 6 | Month 12 |
|---|---|---|---|
| ITT population with LOCF, mean values, min-max | 14.6 | 10.1 | 10.3 |
| | (n=40) | (n=40) | (n=40) |
| PUT population, mean values min-max | 14.2 | 9.0 | 6.5 |
| | (n=37) | (n=16) | (n=12) |
| ITT population with LOCF mean percent change from baseline min-max | NA | - 27.6 | - 25.7 |
| | | (n=40) | (n=40) |
| PUT population mean percent change from baseline min-max | NA | - 34.2 | - 37.2 |
| | | (n=16) | (n=12) |

At baseline, mean EASI scores were similar for both the ITT (with LOCF) and PUT population. At the month 6 visit, the mean EASI score was lower compared to baseline and similar for both populations. At the month 12 visit, the mean EASI score remained stable for the ITT population (with LOCF), whereas it further decreased for the PUT population, indicating that patients with less improvement tended to discontinue the study between month 6 and month 12 of treatment. The mean EASI change from baseline was similar after 6 and 12 months of treatment for both populations; however, the level of disease improvement was consistently better for the PUT population. Thus, it appears that the discontinuations due to an unsatisfactory therapeutic effect occurred mainly during the first 6 months of study treatment

Discussion :

Twice daily application of 1% SDZ ASM 981 cream for up to 12 months in patients with extensive atopic dermatitis lesions (up to 61.5% of body surface area affected at baseline) showed a good local and systemic tolerability. Blood concentrations of SDZ ASM 981 were consistently low with no systemic accumulation over the treatment period. There was no evidence for increases in blood concentrations in patients with larger areas of body surface under treatment.

## Comments:

- *A large proportion of the patients (55%) discontinued the treatment due to unsatisfactory therapeutic effect. Most of the patients discontinued after the first 1 to 3 months. The investigator attributed the high discontinuation rate, which occurred mainly in the first 20 patients due to very hot weather conditions in the study center area during that time. However, given the real life use condition, this can very well be the case. The medical officer is requested to look into this issue.*

- *Interpretation of efficacy data from this pharmacokinetic study was limited due to the open-label, non-controlled study design and because the evaluations were only performed at the visit days. Evaluation should have been performed more frequently.*

NDA: 21-302/Study ASM W202 Study Date: Jan' 98 – Nov' 98

***A STUDY OF THE TOLERANCE, BLOOD CONCENTRATIONS, AND EFFICACY OF SDZ ASM 981 IN 1- TO 4-YEAR-OLD CHILDREN WITH MODERATE TO SEVERE ATOPIC DERMATITIS TREATED TOPICALLY FOR 3 WEEKS WITH THE 1% SDZ ASM 981 FINAL MARKET FORMULATION CREAM***

**Objectives:**

Primary: To evaluate the tolerance of the 1% SDZ ASM 981 FMF cream, administered twice daily for 3 weeks to the lesional skin in pediatric patients with moderate to severe atopic dermatitis and to determine the blood concentrations of SDZ ASM 981 during treatment.

Secondary: To investigate the efficacy of the 1% SDZ ASM 981 FMF cream in pediatric patients with moderate to severe atopic dermatitis

**Study Design:**

The study employed an open-label, multiple topical dose, non-controlled design. It consisted of a one-day to 2-week screening period, a pre-treatment period of 4 days, a treatment period of 22 days and a completion evaluation one week after the last application of SDZ ASM 981. The patients attended a total of 7 visits to the clinic: at screening, day -4, day 1, 4, 10, 22 of treatment and at completion. Each visit was allowed to be made within a window of ±1 day of the protocol specified day.

During the pre-treatment period (day-4 to day 1) the vehicle of the study cream, without active ingredient (placebo; Lot # ZO 250397), was applied twice daily on an affected area of about 100cm$^2$ (other affected areas of skin may be treated with topical corticosteriods during this time). This was included in order to check the skin tolerability to the vehicle prior to applying the 1% SDZ ASM 981 cream itself. If the vehicle was well tolerated and caused no worsening of the eczema on the test area, treatment with the 1% SDZ ASM 981 cream (FMF, Lot # ZO 751097) was pursued twice daily for 3 weeks (first application in the morning of day 1, last application in the morning of day 22), or until complete clearance of the lesions. The 1% SDZ ASM 981 FMF cream was applied by the parents or another care giver onto the dermatitis lesional skin. The individual amount of SDZ ASM981 cream used per application during visits to the clinic (i.e. on days 1, 4, 10 and 22) ranged from 1 to 11g. All lesions were treated, including those on the face. Patients were treated as outpatients throughout.

Blood samples were collected at some of the visits in order to determine the SDZ ASM 981 blood concentrations and perform safety laboratory tests. The SDZ ASM 981 blood concentrations were monitored on line. Treatment was to be discontinued at the next visit if the estimated $AUC_{(0\text{-}12h)}$ was higher than 50ng.h/ml at the day 4 evaluation.

The study population consisted of 10 patients fulfilling the diagnostic criteria of Hanifin and Rajka for atopic dermatitis. The patients were enrolled in two cohorts, A and B according to the extent of lesions as described in the following table. Due to the difficulty in recruiting the target population in Cohort B, only 4 children were included in this cohort of the trial. Cohort B was initiated only after completion of cohort A.

Details of patients included in Cohorts A and B

| Cohort | Age range | % BSA affected | No of patients | | |
|---|---|---|---|---|---|
| | | | Planned | Entered | Completed |
| A | 1-4 year | 10-30% | 4+2[a] | 6 | 4 |
| B | 1-4 year | >30% | 8 | 4 | 3 |

[a] Two additional patients were recruited into cohort 1 as per protocol amendment.

**Demographic characteristics – Mean (Minimum – Maximum)**

| Age [months] | Height [cm] | Weight [Kg] |
|---|---|---|
| 36.9 (14-52) | 96.3 (76-111) | 15.2 (10-22) |

*PK Measurements*: At each time of SDZ ASM 981 determination in whole blood, 1ml (2 ml at screening sample only) venous blood was taken by either direct venipuncture or an indwelling cannula or butterfly needle inserted at a site where no SDZ ASM 981 cream was applied. The blood was drawn into EDTA tubes at the following times:

Screening: one sample at any time during visit, (2ml),
Day 4: 0 (before application), 2, 4 and 6 hours after morning application, (1ml)
Day 22: 0 (before application), 2, 4 and 6 hours after morning application (1ml)
Completion: one sample at any time during the visit.
All samples were processed according to the Study Protocol and kept frozen at ≤ -20°C pending analysis. The investigator shipped blood samples and Sample Log Forms to ——— where the analysis for determination of SDZ ASM 981 concentrations was performed by means of a ——————— method (LOQ 0.5 ng/ml).

Efficacy Measurements: The extent of lesions and of clinical signs was assessed using an adapted Erythema Area Severity Index at screening, day 1, 4, 10, 22, and at completion.

## Results:

*Pharmacokinetics*: All subjects were included in the pharmacokinetic data analysis. Concentrations below the limit of quantitation were treated as zero in summary statistics and for the calculation of pharmacokinetic parameters. Pharmacokinetic parameters were determined using non-compartmental method(s).

Individual blood concentrations of SDZ ASM 981 measured on day 4, day 22 and at end of study are summarized in Table 1 and 2. Of the total of 63 blood concentrations of SDZ ASM 981 measured in the 10 patients (excluding the screening blank samples) 41 (63% ) were below the Limit of Quantitation (LoQ = 0.5 ng/ml). The individual maximum concentrations ranged from <0.5 to — ng/ml (Figure 1), except for one outlier value of — ng/ml (not shown on Figures) which corresponded to a contaminated sample, documented by the investigator to have been drawn on a skin area freshly treated with the cream. The hypothesis of a contamination was confirmed by the fact that all other concentration values in this patient (No. 4) were below the limit of quantitation of the assay. In three patients having more than 2 quantifiable concentrations at day 4 (Patients 1, 2 and 9), $AUC_{(0\text{-}12h)}$ could be calculated: the respective values were 9.2, 11.0 and 18.8 ng.h/ml. The individual blood pharmacokinetic parameters assessed during the study in the 10 patients included are presented in Table 3. SDZ ASM 981 blood concentration ranges were similar at day 4 and day 22, indicating no systemic accumulation of SDZ ASM 981 over the treatment period. All blood concentrations measured one week after treatment discontinuation were below the limit of quantitation except for Patient 1 who had a value of —ng/mL. Within the range of body surface area affected in patients in this study, there was no evidence for an increase in SDZ ASM 981 blood concentrations with increasing body surface area affected (Figure 2).

Figure 1: Blood concentrations of SDZ ASM 981 on days 4 and 22.

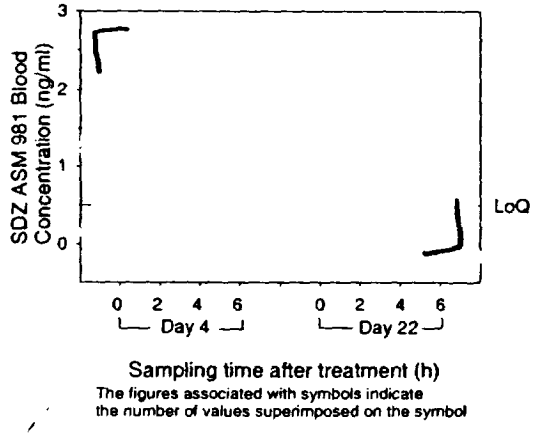



Figure 2: Blood concentrations of SDZ ASM 981 versus Body Surface Area affected on day 1.

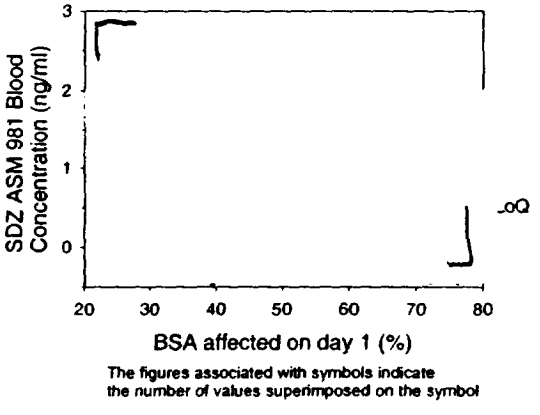



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**Table 1: Blood Concentrations of SDZ ASM 981 following application of the 1% cream twice a day for three weeks to 1-4 years old children with 10-30% body surface area affected by atopic dermatitis at time of screen** (Data expressed as ng/mL)

| Target Time of Blood Sample Collection Post application | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Patient** | **BSA/Day1** | | **Any time** | **0h** | **2h** | **4h** | **6h** |
| 1 | 43.5% | SCR | | | | | |
| | | D4 | | | | | |
| | | EOS | | | | | |
| 2 | 43.5% | SCR | | | | | |
| | | D4 | | | | | |
| | | EOS | | | | | |
| 4 | 23% | SCR | | | | | |
| | | D4 | | | | | |
| | | D4-R | | | | | |
| | | D22 | | | | | |
| | | EOS | | | | | |
| 5 | 26% | SCR | | | | | |
| | | D4 | | | | | |
| | | D22 | | | | | |
| | | EOS | | | | | |
| 6 | 39% | SCR | | | | | |
| | | D4 | | | | | |
| | | D22 | | | | | |
| | | D22-R | | | | | |
| 7 | 24.5% | SCR | | | | | |
| | | D4 | | | | | |
| | | D22 | | | | | |
| | | EOS | | | | | |

SCR = Sample collected at time of screen; D4 = Day 4 samples; D22 = Day 22 samples; EOS = End of study;
INS = Insufficient sample for successful analysis; NSR = No sample received;
* Documented contamination; Samples of concentrations below the LOD were set to zero

**Table 2: Blood Concentrations of SDZ ASM 981 following application of the 1% cream twice a day for three weeks to 1-4 years old children with > 30% body surface area affected by atopic dermatitis at time of screen** (Data expressed as ng/mL)

| Target Time of Blood Sample Collection Post application | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Patient** | **BSA/Day1** | | **Any time** | **0h** | **2h** | **4h** | **6h** |
| 8 | 64.5% | SCR | | | | | |
| | | D4 | | | | | |
| | | D22 | | | | | |
| | | EOS | | | | | |
| 9 | 58.5% | SCR | | | | | |
| | | D4 | | | | | |
| | | D22 | | | | | |
| | | EOS | | | | | |
| 10 | 69% | SCR | | | | | |
| | | D4 | | | | | |
| | | EOS | | | | | |
| 11 | 66.5% | SCR | | | | | |
| | | D4 | | | | | |
| | | EOS | | | | | |

SCR = Sample collected at time of screen; D4 = Day 4 samples; D22 = Day 22 samples; EOS = End of study;
INS = Insufficient sample for successful analysis; NSR = No sample received;
* Documented contamination; Samples of concentrations below the LOD were set to zero

**Table 3: Summary of pharmacokinetic parameters[a]**

| Patient No | Age (Mths) | %BSA (Day1) | Day 4 $AUC_{(0-12h)}$ (ng.h/ml) | $C_{max}$ (ng/ml) | $C_{min}$ (ng/ml) | Day 22 $AUC_{(0-12h)}$ (ng.h/ml) | $C_{max}$ (ng/ml) | $C_{min}$ (ng/ml) | C at end of study (ng/ml) |
|---|---|---|---|---|---|---|---|---|---|
| 0010001 | 45 | 43.5 | 18.8 | 1.8 | 1.3 | NSC | NSC | NSC | 0.5 |
| 0010002 | 45 | 43.5 | 9.2 | 1.1 | 0.0 | NSC | NSC | NSC | 0.0 |
| 0010004 | 17 | 23 | NC[bc] | 0.0[b] | 0.0[b] | NC[cd] | 0.0 | 0.0 | 0.0 |
| 0010005 | 14 | 26 | NC[d] | 0.9 | 0.0 | NC[d] | 0.0 | 0.0 | 0.0 |
| 0010006 | 38 | 39 | NC[d] | 0.7 | 0.0 | NC[d] | 0.8 | 0.0 | NSC |
| 0010007 | 52 | 24.5 | NC[cd] | 0.0 | 0.0 | NC[d] | 1.3 | 0.0 | 0.0 |
| 0010008 | 50 | 64.5 | NC[d] | 0.0 | 0.0 | NC[d] | 1.6 | 0.0 | 0.0 |
| 0010009 | 32 | 58.5 | 11 | 1 | 0.7 | NC[d] | 0.8 | 0.6 | 0.0 |
| 0010010 | 26 | 69 | NC[d] | 0.5 | 0.0 | NSC | NSC | NSC | 0.0 |
| 0010011 | 50 | 66.5 | NC[cd] | 0.0 | 0.0 | NSC | NSC | NSC | 0.0 |

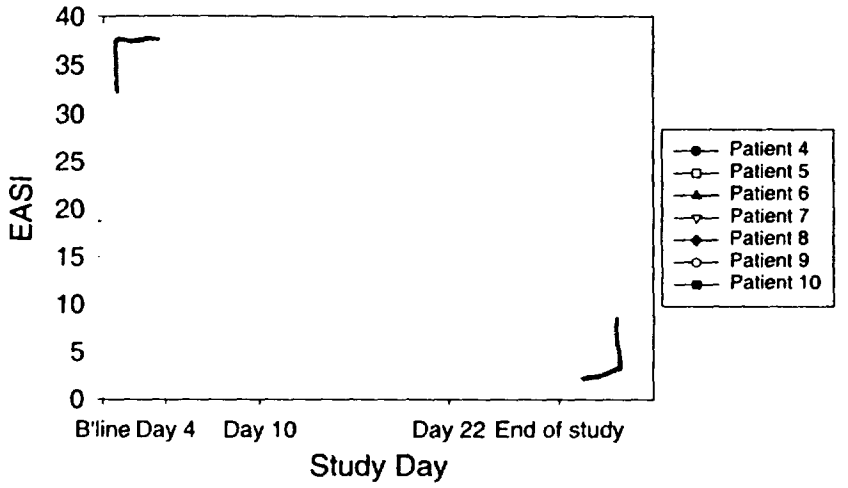
[a]All blood concentrations <LoQ were set to 0.0 ng/ml.
[b] Samples collected on day 9, day 4 concentrations were not used to determine PK parameters due to contamination of the predose sample.
[c] All concentrations <LoQ; [d] Too few (≤2) quantifiable concentrations were available for calculation of AUC; NSC = No sample collected; NC = Not calculated

*Efficacy:* For the seven patients who completed the study according to the protocol, the adapted EASI score at screening, days 1, 22 and completion is listed in Table 4 and at screening, days 1, 4, 10, 22 and completion is shown in Figure 3. Adapted EASI scores were lower in all seven patients on Day 22 when compared to the scores on Day 1. However, when compared with end-of-study scores, the difference seemed to diminish in most of the cases. For patients nos. 5 and 6, the EASI scores were even higher than that on Day 1. Therefore, the efficacy seemed to diminish immediately upon discontinuation of the medication.

**Table 4: Summary of EASI Scores**

| | | | Adapted EASI | | | | | |
|---|---|---|---|---|---|---|---|---|
| Patient No | Age (Mths) | %BSA (Day1) | Screening | Day 1 | Day 22 | (D22-D1) | EOS | (EOS-D1) |
| 0010001 | 45 | 43.5 | | | | | | |
| 0010002 | 45 | 43.5 | | | | | | |
| 0010004 | 17 | 23 | | | | | | |
| 0010005 | 14 | 26 | | | | | | |
| 0010006 | 38 | 39 | | | | | | |
| 0010007 | 52 | 24.5 | | | | | | |
| 0010008 | 50 | 64.5 | | | | | | |
| 0010009 | 32 | 58.5 | | | | | | |
| 0010010 | 26 | 69 | | | | | | |
| 0010011 | 50 | 66.5 | | | | | | |

**Figure 3: Adapted EASI scores for subjects completing the study at screening, days 1, 4, 10, 22, and at completion.**




*Safety and tolerability:* No serious adverse event occurred. The first 2 patients included in the study experienced a flare of atopic dermatitis with severe pruritus that was not controlled by the study medication. They discontinued the study after 13 days of treatment. Another patient experienced moderate and transient pruritus under the study treatment. Such incidents of pruritus were suspected of being due to study drug.

**Discussion :**

An essential safety aspect to be addressed when developing a new topical treatment for young children is systemic absorption of the drug. The main objective for this first paediatric study with SDZ ASM 981 cream was to measure systemic concentrations of the drug over a 3-week treatment period. In all patients, and excluding the value associated with a contaminated sample, the blood concentrations ranged from <0.5 to ~ ng/ml. These values are in the same range as those observed after topical treatment in adult patients with atopic dermatitis (Study ASMW 204). For comparison, in adult ——— patients treated with SDZ ASM 981 by the — route for 4 weeks at doses ranging from 5 to 60 mg per day (Study ASMW 121), the mean peak level and the area under the blood concentration versus time curve over a dose interval ($AUC_{(0\text{-}12h)}$) at steady-state were 54.5 ng/ml and 294.9 ng.h/ml, respectively at the highest dose tested. Thus, exposure in children following topical application of SDZ ASM 981 cream is very low compared to systemic exposure in adults following — administration.

In this first pediatric study, the interpretation of efficacy results is limited by the small sample size and the absence of control treatment. Excluding the patient (#11) who discontinued at day 4 for study independent reasons and patients nos. 1 and 2 who discontinued the study after 13 days of treatment due to a flare of atopic dermatitis with severe pruritus, six of remaining seven patients showed a clinically significant improvement of their eczema score on day 22. Patient # 6 did not show much improvement on Day 22. When adapted EASI scores were compared from baseline on Day 1 to end of study (EOS), the extent of efficacy improvement diminished in all patients except in patient no. 10 who showed continued improvement beyond discontinuation of therapy. For patients 5 and 6, the EOS score even went up much beyond Day 1 score. The reason why the first two patients developed a flare under study treatment is unclear. However, it can be anticipated that systemic exposure in children with milder atopic dermatitis will be lower or at least not higher than in these selected patients. With its low percutaneous absorption properties even in patients with extensive skin lesions, SDZ ASM 981 has the potential to be an effective and safe alternative treatment for the long-term management of atopic dermatitis in children.

In conclusion, in young children with extensive lesions of atopic dermatitis treated twice daily for 3 weeks with 1% SDZ ASM 981 cream:

- Blood concentrations of SDZ ASM 981 were consistently low, even in the patients with the most extensive surface areas treated (up to 69% BSA).
- SDZ ASM 981 did not accumulate over the treatment period between day 4 and day 22.
- No systemic effects were detected.
- The range of SDZ ASM 981 blood concentrations measured was comparable to that observed in adults.
- Efficacy as measured by Adapted EASI score was significant in nearly all patients during treatment; however, it diminished immediately upon discontinuation of the medication in nearly all patients.

**Comments:**

- *The first 2 patients included in the study experienced a flare of atopic dermatitis with severe pruritus that was not controlled by the study medication. They discontinued the study after 13 days of treatment. Another patient experienced moderate and transient pruritus under the study treatment. Such incidents of pruritus were suspected of being due to study drug. The medical officer should look into these adverse events which occurred in 30% (3/10) of the study population.*

- *The sponsor noted that "Excluding the patient (#11) who discontinued at day 4 for study independent reasons, six of nine patients showed a clinically significant improvement of their eczema score." However, the basis for defining clinically significant improvement is not clear. Therefore the correct statement should be "seven (~~NOT six~~) of nine patients showed a clinically significant improvement of their eczema score when compared between EOS and Day 1 scores." (Figure 3)*

- *While patients 1 and 2 were withdrawn from the study by their parents after 13 days of treatment owing to non-controlled flares of atopic dermatitis and were not asked to give assessment of overall tolerability of cream at the end of study visit, it is not clear how they were brought into the clinic to collect end of study blood samples as indicated in Table 1.*

- *The sponsor noted that "all other concentration values in this patient (No. 5) were below the limit of quantitation of the assay". However it should be "all other concentration values in this patient (No. 4) (~~NOT No. 5~~) were below the limit of quantitation of the assay".*

- *Too many NSRs (No sample received) from a fairly small number of scheduled blood samples makes the PK calculation difficult. However considering the age of the subjects, inability to endure taking too many blood samples is an issue of practical relevance.*

- *The sponsor noted "The % change from baseline at day 22 for EASI ranged from –8% to –89% and the median % change from baseline at day 22 was –58%". However, in absence of reference time points (e.g., D22-D1, EOS-D1 etc), the above figures seem meaningless.*

- *$AUC_{(0\text{-}12h)b}$ should not have been computed unless the blood concentration profile included less than three <u>consecutive</u> quantifiable concentrations. However, some AUCs were calculated though the quantifiable concentrations were not consecutive*

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**NDA : 21-302/Study ASM W206** **Study Date: May '98 – Oct '00**

***A STUDY OF THE TOLERANCE, BLOOD CONCENTRATIONS, AND EFFICACY OF SDZ ASM 981 IN 5- TO 16-YEAR-OLD CHILDREN WITH ATOPIC DERMATITIS TREATED TOPICALLY FOR 3 WEEKS WITH THE 1% SDZ ASM 981 FINAL MARKET FORMULATION CREAM***

**Objectives:**

Primary: To evaluate the tolerance of the 1% SDZ ASM 981 FMF cream, administered twice daily for 3 weeks to the lesional skin in pediatric patients with atopic dermatitis and to determine the blood concentrations of SDZ ASM 981 during treatment.

Secondary: To investigate the efficacy of the 1% SDZ ASM 981 FMF cream in pediatric patients with atopic dermatitis.

**Study Design:**

The study employed an open-label, multiple topical dose design. It consisted of a one-day to 2-week screening period, a treatment period of 22 days, and an end-of-study evaluation one week after the last application of SDZ ASM 981 (FMF, Lot # Z0 250397, Z0 611098). The patients attended a total of 6 visits to the clinic: at screening, days 1, 4, 10, 22 of treatment and at end-of-study. Each visit was allowed to be made within a window of ±1 day of the protocol specified day.

Two consecutive cohorts of children with atopic dermatitis were included according to the criteria as described in the following table:

**Details of Children Included in Cohorts 1 and 2**

| Cohort | Age range | % BSA affected | No. of patients | | |
|---|---|---|---|---|---|
| | | | Planned | Entered | Completed |
| 1 | 5-16 years | ≥20% | 12 | 10 | 9 |
| 2 | 3-35 months | ≥20%[a] | 8 | 8 | 8 |

**Demographic characteristics – Mean (Minimum – Maximum)**

| Cohort | Age | Height [cm] | Weight [kg] |
|---|---|---|---|
| 1 | 10.5 years (8-14) | 141.4 (123-160) | 36.4 (21.8-53.6) |
| 2 | 22.4 months (8-30) | 83.4 (71-92) | 11.6 (8.6-14.1) |

*PK Measurements:* At each time of SDZ ASM 981 determination in whole blood, 1ml (2 ml at screening sample only) venous blood was taken by either direct venipuncture or an indwelling cannula or butterfly needle inserted at a site where no SDZ ASM 981 cream was applied.

For **cohort 1** the blood was drawn into EDTA coated tubes at the following times:

Screening: one sample at any time during visit, (2ml)

Day 4: 0 (before application), 2, 4 and 6 hours after morning application, (1ml)

Day 22: 0 (before application), 2, 4 and 6 hours after morning application (1ml)

End-of-study: one sample at any time during the visit.

For **cohort 2** the following schedule of blood sampling (EDTA coated tubes) was targeted:

Screening: one sample at any time during visit, (2ml)

Day 4: 2 hours after morning application, (1ml)

Day 22: 2 hours after morning application, (1ml)

End-of-study: one sample at any time during the visit only in case a recheck from safety laboratory was performed. Otherwise no sample.

The SDZ ASM 981 blood concentrations were monitored on line. Patients who showed good tolerability and low systemic exposure of SDZ ASM 981 were proposed further inclusion into a 1 year extension study investigating the efficacy and blood concentrations of SDZ ASM 981 during long term management of atopic dermatitis (Study ASM W206E1). Patients were included into the extension study either at day 22, at the end-of-study visit or within 3 months after the end-of-study visit of this initial study. The results of the extension study are scheduled to be reported separately in an addendum to this clinical study report. The SDZ ASM 981 blood concentrations were determined using a [redacted] with a Limit of Quantitation (LoQ) of 0.5 ng/ml. An $AUC_{(0\text{-}12h)}$ was estimated by assuming the SDZ ASM 981 blood concentration at 12 h was equal to the pre-application concentration. $AUC_{(0\text{-}12h)}$ was not computed when the blood concentration profile included less than three quantifiable concentrations.

*Efficacy Measurements*: The extent of lesions and of clinical signs was assessed using an adapted Eczema Area Severity Index at screening, day 1, 4, 10, 22, and at end-of-study.

**Results:**

*Pharmacokinetics:*

Cohort 1: Blood concentrations of SDZ ASM 981 in the children aged 8-14 years (cohort 1; Table 1) were consistently low. Of the total number of concentrations (n = 77) obtained throughout the study (days 4 and 22 and end-of-study sample) 42 (54.5%) were below the LoQ of 0.5 ng/ml (Figure 1). The maximum observed concentration was —

ng/ml. Blood concentration ranges of SDZ ASM 981 were similar at day 4 and day 22, indicating no systemic accumulation of SDZ ASM 981 over the treatment period. Within the range of body surface area affected in patients in this study, there was no evidence for an increase in SDZ ASM 981 blood concentrations with increasing body surface area affected (Figure 2).

**Table 1: Blood Concentration of SDZ ASM 981 9ng/mL) in Children 8 –14 years old (Cohort 1)**

| Subject | Age (yrs) | % BSA Day 1 | Target time of blood sample collection post application | | | | | | | | End Of Study |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Screen | Day 4 | | | | Day 22 | | | |
| | | | | 0 h | 2 h | 4 h | 6 h | 0 h | 2 h | 4 h | 6 h | |
| 1 | 8 | 34 | | | | | | | | | | |
| 2 | 11 | 21 | | | | | | | | | | |
| 3 | 9 | 28.5 | | | | | | | | | | |
| 4 | 11 | 33 | | | | | | | | | | |
| 5 | 12 | 33 | | | | | | | | | | |
| 6 | 14 | 49.5 | | | | | | | | | | |
| 7 | 8 | 34 | | | | | | | | | | |
| 8 | 14 | 37.5 | | | | | | | | | | |
| 9 | 9 | 31 | | | | | | | | | | |
| 10 | 9 | 26.5 | | | | | | | | | | |

NSC = No sample collected; INS = Insufficient sample for analysis;
- = Patient discontinued the study (#4) or visit not completed (#9)

**Figure 1: Blood concentrations of SDZ ASM 981 on days 4 and 22 and at end-of-study (cohort 1).**

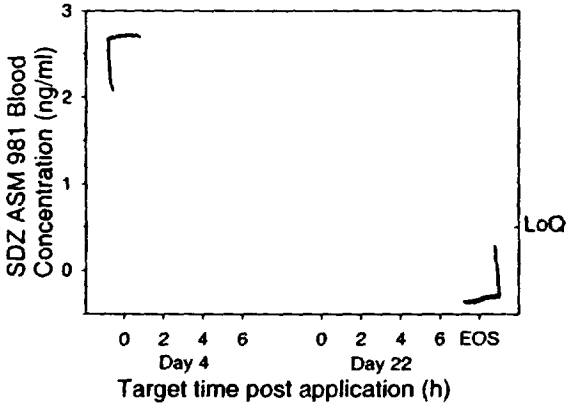
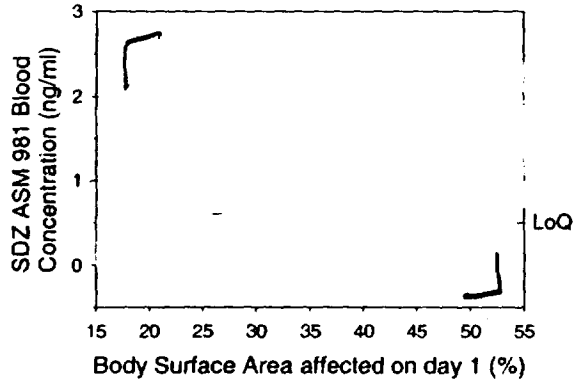



**Figure 2: Blood concentrations of SDZ ASM 981 versus Body Surface Area affected on day 1 (cohort 1).**




As many blood concentrations were below the LoQ, determination of $AUC_{(0\text{-}12h)}$ was only possible in 4 patients of cohort 1 on day 4, and 3 patients of cohort 1 on day 22. ( Table 2). $AUC_{(0\text{-}12h)}$ ranged from 5.4 to 16.4 ng h/ml.

**Table 2: Summary of Pharmacokinetic Parameters[a] (Cohort 1)**

| Subject | Age (years) | % BSA day 1 | Day 4 $AUC_{(0-12)}$ (ng h/ml) | Day 4 $C_{max}$ (ng/ml) | Day 4 $C_{min}$ (ng/ml) | Day 22 $AUC_{(0-12)}$ (ng h/ml) | Day 22 $C_{max}$ (ng/ml) | Day 22 $C_{min}$ (ng/ml) | C at end of study (ng/ml) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 8 | 34 | NC[c] | 0.9 | 0.0 | NC[c] | 0.5 | 0.0 | 0.0 |
| 2 | 11 | 21 | NC[b] | 0.0 | 0.0 | NC[c] | 0.6 | 0.0 | INS |
| 3 | 9 | 28.5 | 8.0 | 1.0 | 0.5 | 7.4 | 1.6 | 0.0 | 0.0 |
| 4 | 11 | 33 | 5.4 | 1.0 | 0.0 | NSC | NSC | NSC | NSC |
| 5 | 12 | 33 | NC[c] | 0.6 | 0.0 | NC[b] | 0.0 | 0.0 | 0.0 |
| 6 | 14 | 49.5 | NC[c] | 0.5 | 0.0 | NC[b] | 0.0 | 0.0 | 0.0 |
| 7 | 8 | 34 | NC[b] | 0.0 | 0.0 | 7.8 | 0.7 | 0.6 | 0.0 |
| 8 | 14 | 37.5 | 13.4 | 1.5 | 1.0 | 15.0 | 1.8 | 0.9 | 0.5 |
| 9 | 9 | 31 | 16.4 | 2.0 | 0.5 | NSC | NSC | NSC | 0.0 |
| 10 | 9 | 26.5 | NC[b] | 0.0 | 0.0 | NC[b] | 0.0 | 0.0 | 0.0 |

[a] All blood concentrations <LoQ were set to 0 ng/ml.
[b] All samples <LoQ
[c] Too few (≤2) quantifiable concentrations were available for calculation of AUC
NSC = No sample collected
INS = Insufficient sample for analysis
NC = Not calculated

Cohort 2: Blood concentrations of SDZ ASM 981 in the children aged 8-30 months (cohort 2, Table 3) were also consistently low. Of the total number of concentrations (n = 21), 11 (52.4%) were below the LoQ (Figure 3). The maximum observed concentration was — ng/ml, apart from one high value ( — ng/ml) associated with a sample suspected to have been contaminated by the cream during venipuncture. The blood concentration of SDZ ASM 981 in this patient was — ng/ml on day 4. Blood concentrations of SDZ ASM 981 were similar on days 4 and 22 and there was no evidence for an increase in blood concentrations of SDZ ASM 981 with increasing body surface area affected (Figure 4). Given the nature of the blood sampling scheme, no AUC was determined.

**Table 3: Blood Concentration of SDZ ASM 981 9ng/mL) in Children 8 –30 months old (Cohort 2)**

| Subject | Age (mos) | % BSA Day 1 | Target time of blood sample collection post application | | | End Of Study |
|---|---|---|---|---|---|---|
| | | | Screen | Day 4 | Day 22 | |
| | | | | 2 h | 2 h | |
| 201 | 27 | 35 | | | | |
| 202 | 29 | 28 | | | | |
| 203 | 30 | 29 | | | | |
| 204 | 28 | 60 | | | | |
| 205 | 8 | 80 | | | | |
| 206 | 15 | 79 | | | | |
| 207 | 15 | 38 | | | | |
| 208 | 27 | 44 | | | | |

NSC = No sample collected; INS = Insufficient sample for analysis
*Additional samples were colected from this subject on day 4 at predose and 4 and 6 h post dose, concentrations were below LoQ in all these samples.

**Figure 3: Blood concentrations of SDZ ASM 981 post application on days 4 and 22 and at end-of-study (cohort 2).**

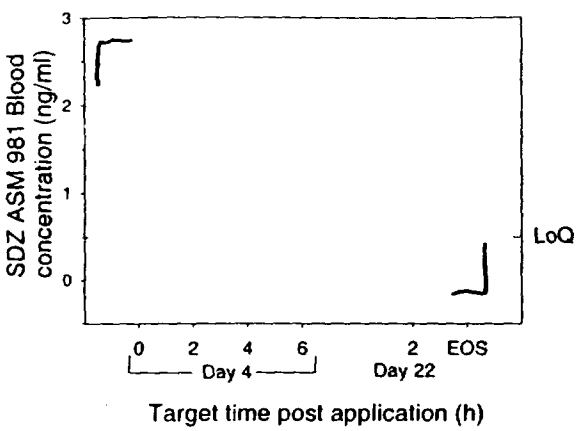
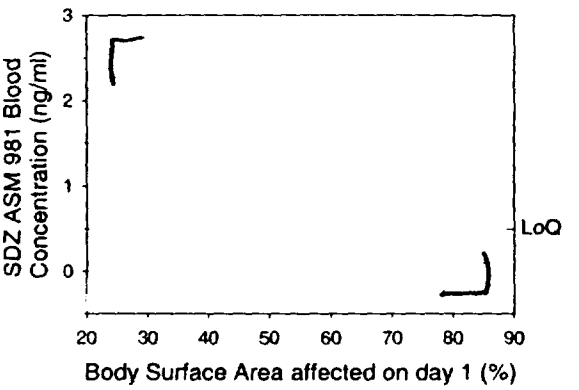



**Figure 4: Blood concentrations of SDZ ASM 981 versus BSA affected on day 1 (cohort 2)**




There was no clear evidence for an increase in blood concentrations with increasing body surface area affected by atopic dermatitis on day 1 in both cohorts. However all samples collected from patients in cohort 2 with more than 60% body surface area affected contained quantifiable concentrations of the drug (Table 3).

In both cohorts 1 and 2, SDZ ASM 981 blood concentration ranges were similar at day 4 and day 22, indicating no systemic accumulation of SDZ ASM 981 over the treatment period. The range of blood concentrations measured in the two cohorts was similar (Figure 1 and 3).

*Efficacy:* The individual adapted Eczema Area Severity Index (EASI) values are given in Tables 4 and 5 below:

Cohort 1: For the nine patients who completed the study according to the protocol, the adapted EASI at screening, days 1 (baseline), 4, 10, 22 and end-of-study is shown in Figure 5. Selected values are also shown in Table 4 as well as the % change from baseline at day 22.

Table 4: Adapted EASI (study days 1, 4 and 22) and % change from baseline at day 22 (cohort 1)

| Patient | Day 1 | Day 4 | Day 22 | % change from baseline at day 22 |
|---|---|---|---|---|
| 1 | | | | -40.4 |
| 2 | | | | -42.2 |
| 3 | | | | -44.2 |
| 4[a] | | | | |
| 5 | | | | -91.0 |
| 6 | | | | -70.9 |
| 7 | | | | -38.1 |
| 8 | | | | -65.3 |
| 9[b] | | | | |
| 10 | | | | -80.8 |

[a] Patient 4 discontinued on day 11 of treatment due to an infective exacerbation of her atopic dermatitis

[b] Patient 9 discontinued on day 16 of treatment as his atopic dermatitis was clear. The patient attended the scheduled day 22 visit, however, since no cream had been applied, this visit was classified as end-of-study

For patients completing the study, the % change from baseline at day 22 for EASI ranged from –38% to –91%.

Cohort 2: All eight patients completed the study according to the protocol. The adapted EASI at screening, days 1 (baseline), 4, 10, 22 and end-of-study is shown in Figure 6 and again selected values are shown in Table 5 with the % change from baseline at day 22. The % change from baseline at day 22 for EASI ranged from –5% to –87%. For patient # 207, the EASI scores were erratic.

**Table 5: Adapted EASI (study days 1, 4 and 22) and % change from baseline at day 22 (Cohort 2)**

| Patient | Day 1 | Day 4 | Day 22 | % change from baseline at day 22 |
|---|---|---|---|---|
| 201 | | | | -14.8 |
| 202 | | | | -57.8 |
| 203 | | | | -67.7 |
| 204 | | | | -35.1 |
| 205 | | | | -83.3 |
| 206 | | | | -75.3 |
| 207 | | | | -4.6 |
| 208 | | | | -87.1 |

In general, infants and children with relatively stable atopic dermatitis, treated twice daily with SDZ ASM 981 cream showed improvement in their EASI, with rapid onset of action by day 4 and a sustained response throughout the treatment period.

**Figure 5: Adapted EASI at baseline, days 4, 10, 22, and at end-of-study.**

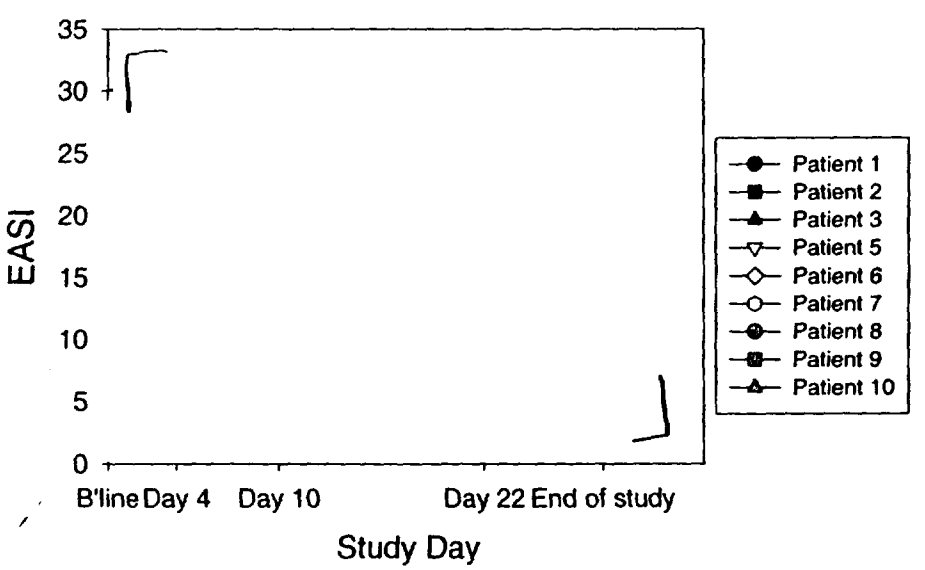
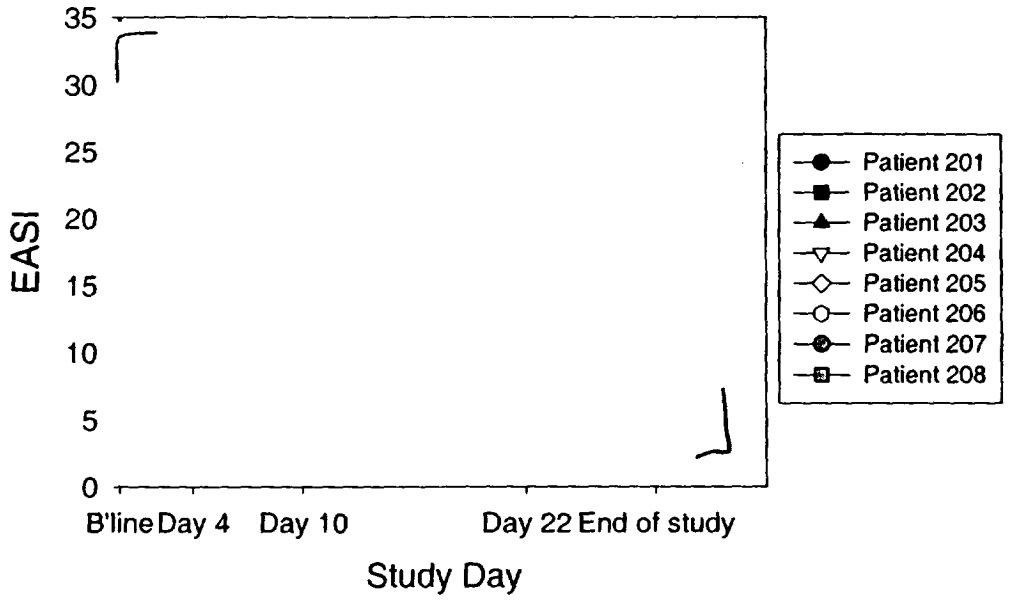


Figure 6: Adapted EASI at baseline and days 4, 10, 22 (and end-of-study for those subjects not continuing onto the extension study).




**Discussion**:

Blood concentrations of SDZ ASM 981 measured in both the older children and the younger children were low and in a range of <0.5 to — ng/ml. There was apparently no difference in exposure between the older and younger children and blood concentrations of both groups were similar to those measured in other studies in children (1-4 years old, Study ASMW 202 and 4-11 months old, study CASM981 0301), and in adults (Study ASMW 204) treated under the same dosing regimen for 3 weeks. In the present study the maximum $AUC_{(0\text{-}12h)}$ observed (16.4 ng h/ml) was considerably lower than the mean exposure observed in adults at steady state following — administration of a well tolerated dose of 60 mg/day of SDZ ASM 981 (mean $AUC_{(0\text{-}12h)}$: 294.9 ng.h/ml, ratio of 18, study ASMW121).

Also consistent with other studies with SDZ ASM 981 in children and adults, there was no evidence for accumulation of SDZ ASM 981 in blood from day 4 to day 22. It has been observed in studies in adult patients with — formulations of SDZ ASM 981 (Study ASM W121) that steady state pharmacokinetics are achieved after about 6 days of administration and this is consistent with the data presented here in which steady state appears to have been reached by day 4 of application.

Despite large areas of skin under treatment (up to 80% of body surface area) there did not appear to be a significant increase in blood concentrations of SDZ ASM 981 with increasing area treated.

The assessment of EASI showed improvement in the atopic dermatitis for all patients with a rapid onset of action, usually within 4 days. The response was generally shown to be sustained throughout the entire treatment period suggesting that SDZ ASM 981 cream is likely to be an effective treatment for atopic dermatitis in this patient population.
In conclusion, in young children (aged 8-30 months and 8-14 years) with extensive lesions of atopic dermatitis treated twice daily for 3 weeks with 1% SDZ ASM 981 cream:

- Blood concentrations were consistently low, even in patients with the most extensive body surface area treated (up to 80% BSA affected at baseline).
- SDZ ASM 981 did not accumulate over the treatment period between day 4 and day 22.
- No adverse systemic effect was detected.
- The range of SDZ ASM 981 blood concentrations measured was comparable to that observed in adults.
- Efficacy as measured by Adapted EASI score was significant in nearly all patients during treatment; however, it diminished immediately upon discontinuation of the medication in nearly all patients.

**Comments:**

- *The study is entitled "A Study of.....SDZ ASM 981 in 5- to 16-year-old children....Cream". However Cohort B scheduled to recruit children in the age between 3- 35 months. It is not clear why the sponsor did not change the title of the study during amendment to include younger children.*
- *While the scheduled 3-month study of Cohort B completed on March, 23, 2000, the result of the 12-month extension study (Study ASM W206E1) should be available by now.*
- *According to the study design Cohort 1 was composed of children in the ages between 5 – 16 years and Cohort B was of children in the age between 3- 35 months. However, in the actual study, Cohort 1 had children in the age between 8-14 years and Cohort 2 had children in the age between 8 – 30 months. Therefore, there was a gap in recruiting children in the age between 3 – 7 months and 30 months to 7 years.*
- *All samples collected from patients in cohort 2 with more than 60% body surface area affected contained quantifiable concentrations of the drug (Table 3). Clinical significance of this observation is not apparent.*
- *The sponsor noted one high value [ — ng/ml; patient # 205 (8 mo)] associated with a sample suspected to have been contaminated by the cream during venipuncture. The blood concentration of SDZ ASM 981 in this patient was — ng/ml on day 4. However, there can be a big difference between day 4 and day 22 concentrations. No documentation was provided in support of the suspicion and no follow-up measure was also undertaken. The EOS sample from the patient also could not be measured due to insufficient sample volume. A similar incidence happened in patient # 4 (17 months) also in study W202 which apparently was documented to be a contamination case. Within a very limited number of subjects and samples, these incidences signal concern over systemic level.*

NDA: 21-302/Study CASM981 0301 Study Date: Jun' 98 – Dec' 99

*A STUDY OF THE TOLERANCE, BLOOD CONCENTRATIONS, AND EFFICACY OF SDZ ASM 981 IN INFANTS WITH ATOPIC DERMATITIS TREATED TOPICALLY FOR 3 WEEKS WITH THE 1% SDZ ASM 981 FINAL MARKET FORMULATION CREAM*

**Objectives:**

Primary : To evaluate the tolerance of the 1% SDZ ASM 981 FMF cream, administered twice daily for 3 weeks to the lesional skin in infants with atopic dermatitis

To determine the blood concentrations of SDZ ASM 981 when applied as the 1% FMF cream twice daily for 3 weeks to the lesional skin in infants with atopic dermatitis

Secondary: To investigate the efficacy of the 1% SDZ ASM 981 FMF cream in infants with atopic dermatitis

**Study Design:**

The study employed an open-label, multiple topical dose, non-controlled design. It consisted of a one-day to 2-week screening period, a treatment period of 22 days, and an end-of-study evaluation one week after the last application of SDZ ASM 981. The patients attended a total of 6 visits to the clinic: at screening, day 1, 4, 10 and 22 of treatment and at end-of-study. Each visit may have been attended within a window of ± 1 day around the day specified by the protocol.

On the morning of day 1, the parent applied the cream at the outpatient clinic in presence of the investigator or authorized staff. The patients were treated as outpatients with the 1% SDZ ASM 981 FMF cream (Batch No.:Z025 0397) applied twice daily for 3 weeks (first application in the morning of day 1, last application in the morning of day 22). The 1% SDZ ASM 981 FMF cream was applied by the parents or another care giver onto the dermatitis lesional skin. All lesions were treated, including those on the face. The frequency of applications performed at home as well as adverse events were recorded by the parents on a diary card.

A blood sample was collected at screening (blank sample) and on days 4 and 22 in order to determine the SDZ ASM 981 blood concentrations and perform safety laboratory tests. The SDZ ASM 981 blood concentrations were monitored on line throughout the study. Patients who showed good tolerability and low systemic exposure of SDZ ASM 981 were proposed further inclusion into a 1 year extension study investigating the efficacy and blood concentrations of SDZ ASM 981 during long term management of atopic dermatitis (Study CASM981 0301E1). Patients were included into the extension study either at day

22, at the end-of-study visit or within 3 months after the end-of-study visit of this initial study. The results of the extension study will be reported separately in an addendum to this clinical study report.

Eight (8) patients, 3 male and 5 female, aged from 4.9 months to 11 months with a diagnosis of atopic dermatitis (AD) entered the study. Seven (7) patients completed the study, one patient (No 7) was discontinued on day 13 of treatment based on a high blood SDZ ASM 981 concentration — ng/ml). These patients presented atopic lesions on 25% to 58% of their body surface area (BSA) at baseline (day 1) as calculated from the EASI.

The individual demographic data and descriptive statistics at screening are summarized below:

**Demographic characteristics at screening – Mean (Minimum – Maximum)**

| Age [months] | Height [cm] | Weight [kg] |
|---|---|---|
| 8.0 | 67.3 | 7.6 |
| (4.9 – 11.0) | (62.0 – 74.0) | (5.5 – 10.0) |

*PK Measurements:* At each time of SDZ ASM 981 determination in whole blood, 1 ml (2 ml at screening only) venous blood was taken by direct venipuncture at a site where no SDZ ASM 981 cream was applied. However, application of an anesthetic product, Ametop® was permitted prior to puncture.

The blood was drawn into EDTA coated tubes at the following times:

Screening: one sample at any time during the visit

day 4: 2 hours after morning application

day 22: 2 hours after morning application

End-of-study: one sample at any time during the visit only if sampling was performed to recheck safety laboratory tests.

All samples were processed as described in the Study Protocol and kept frozen at ≤ -20°C pending analysis. Whole blood samples were analyzed by ——— in the Bioanalytics and Pharmacokinetics (BAPK) Department, Novartis, Basel, Switzerland.The SDZ ASM 981 blood concentrations were determined by ——— with a limit of quantitation (LoQ) of 0.1 ng/ml.

Efficacy Measurements: The extent of lesions as evaluated using the Lund and Browder chart, the Investigator's Global Assessment (IGA), and the Eczema Area Severity Index (EASI), were evaluated at each visit,

**Results:**

Safety and tolerability: Twice daily application of 1% SDZ ASM 981 FMF cream for 3 weeks was well tolerated, both locally and systemically. No serious adverse event occurred during the study.

Pharmacokinetics: All completed subjects were included in the pharmacokinetic data analysis. 1. As only one blood sample was collected from each patient on each of study days 4 and 22 determination of standard pharmacokinetic parameters was not possible. The individual blood concentrations of SDZ ASM 981 measured 2 h after the morning cream application on day 4 and day 22 of treatment in the 8 patients enrolled in the study are presented in Table 1. All predose blood concentrations were below the limit of quantitation and were treated as zero in summary statistics. The mean (± SD) blood concentration of SDZ ASM 981 was 1.04 ± 0.77 ng/ml on day 4 and 0.94 ± 0.42 ng/ml on day 22. The blood concentrations measured during study treatment were consistently low. They ranged from [redacted] ng/ml (Figure 1), apart from one isolated concentration of [redacted] ng/ml due to possible sample contamination by the cream during venipuncture. In patient 7 who presented the highest concentration of [redacted] ng/ml at day 4, subsequent samples were collected on day 13 and day 22 and treatment was stopped from day 13 until evaluation of the results. The blood concentrations measured on days 13 and 22 were within the range of those measured in the 7 other children. Therefore, a possible contamination of the sample by the cream was suspected. This patient entered the 1 year study extension and subsequent blood concentrations measured at day 15 of this extension, before and 2 h after the morning application were found to be low (<0.7 ng/ml). In patient 1 who presented the blood concentration of [redacted] ng/ml at day 4, the concentration measured at day 22 was [redacted] ng/ml.

Table 1: Concentrations of SDZ ASM 981 (ng/mL) following application of SDZ ASM 981 1% cream to infants for 3 weeks

| | Sample day/ target sample time | | |
|---|---|---|---|
| Subject number | Screen | Day 4 2h | Day 22 2 h |
| 1 | [redacted] | | |
| 2 | | | |
| 3 | | | |
| 4 | | | |
| 5 | | | |
| 6 | | | |
| 7 | | | |
| 8 | | | |
| **n** | 8 | 7 | 7 |
| **Mean** | 0.00 | 1.04 | 0.94 |
| **SD** | 0.00 | 0.77 | 0.42 |

| | Additional samples | | |
|---|---|---|---|
| | Day 13* 8 h | Day 15*¶ | Day 15* 2 h |
| 7 | [redacted] | [redacted] | [redacted] |

§ Application ceased 7 days prior to sample collection
* Days after the end of the scheduled dose period (extension)
¶ Sample collected pre-application (extension)

In order to investigate the suspicion of contamination, analysis of the suspected sample for the peak area ratio of SDZ ASM 981 metabolites to SDZ ASM 981 was performed. The peak area ratios were compared to those found after — administration of the drug (samples from study ASMW122). It was assumed that the peak area ratio of metabolites to the parent drug would be reasonably constant in the blood once SDZ ASM 981 is systemically absorbed. The peak areas ratios of the SDZ ASM 981 metabolites to SDZ ASM 981 after — administration were all in the range of 3 to 9% independent of the post-dose sampling time. In contrast, the possibly contaminated sample from subject 7 showed no measurable signals of the metabolites (signal ratios below 0.8), indicating therefore that the high level of —— ng/ml was very likely the result of a contamination, probably during venipuncture, and did not represent systemic exposure to SDZ ASM 981.

There was no clear correlation between blood concentrations of SDZ ASM 981 measured throughout the study and total body surface area affected by atopic dermatitis on day 1.

Blood concentrations remained low even in the patients with the largest body surface area treated (up to 58% BSA affected on day 1) (Figure 2).

Figure 1.: Blood concentrations of SDZ ASM 981at 2 h post application on days 4 and 22

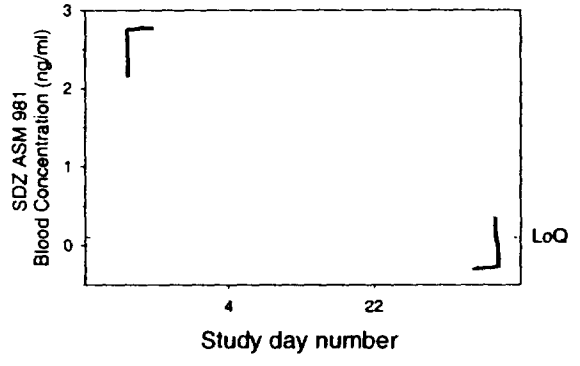
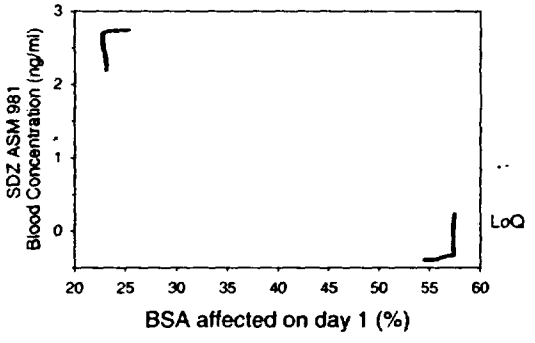



Figure 2.: Blood concentrations of SDZ ASM 981 versus body surface area (BSA) as recorded on day 1




Efficacy: The results of the Eczema Area Severity Index (EASI) evaluation are shown in Table 2 below. Evaluations were made at screening, day 1, day 4, day 10, day 22 and at the end-of-study. All patients improved markedly in their EASI with a rapid onset of action at day 4 of treatment (see Figure 3). For the 7 patients who completed the study according to the protocol, the EASI change from baseline at day 22 ranged from -65.2% to -100% (median was -82.8%).

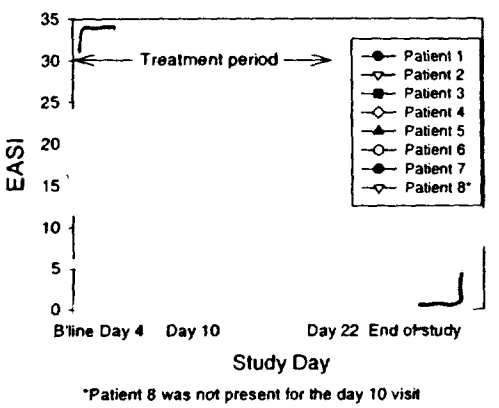
**APPEARS THIS WAY ON ORIGINAL**

Table 2: Adapted EASI (study days 1, 4, and 22)

| Patient | Day 1 | Day 4 | Day 22 | % change from baseline at day 22 |
|---|---|---|---|---|
| 1 | | | | -86.6 |
| 2 | | | | -88.6 |
| 3 | | | | -81.3 |
| 4 | | | | -65.2 |
| 5 | | | | -100 |
| 6 | | | | -82.8 |
| 7 | | | | -81.5 |
| 8 | | | | -80.3 |

[a]: Patient 7 stopped 1% SDZ ASM 981 cream application at day 13

**Figure 3: Adapted EASI at screening, day 1, 4, 10, 22, and at end-of-study.**




## Discussion

This study was designed to explore the tolerability and the blood concentrations of SDZ ASM 981 after repeated topical application of the 1% FMF (Final Market Form) cream in infants with moderate to severe atopic dermatitis.

SDZ ASM 981 was previously shown to be well tolerated after repeated topical application in adults and children with atopic dermatitis (studies ASMW204, ASMW202, ASMW206). Even after treatment of extensive lesions in moderate to severe adult and pediatric (over 1 y) atopic patients, the SDZ ASM 981 blood concentrations remained low and well below levels at which systemic effects, in particular signs of immunosuppression, were observed in the toxicology studies.

It was expected that systemic absorption through the skin would also be low in infants below 1 year of age, providing an adequate safety margin. Since the areas of skin treated related to body weight increase inversely with age, it was essential to assess the tolerance and the systemic exposure to the drug in a well-controlled setting before allowing for enrollment of this age group in large clinical trials. To minimize invasiveness for pharmacokinetic evaluation in the infant population, blood samplings were limited to one per evaluation so that it was not necessary to leave a catheter in place. Based on the

results from the previous pharmacokinetic studies in adults and children, one blood sample 2 hours after topical application should provide a reasonable indication on systemic exposure since there is no proper peak over a dosing interval but rather a plateau. The day 4 sample aimed at capturing the potential maximum exposure to the drug, after repeated applications but at a stage when most lesions still remain. The day 22 sample aimed at capturing a potential accumulation after prolonged treatment.

Twice daily application of 1% SDZ ASM 981 FMF cream for 3 weeks onto the lesional skin of 8 male and female infants aged 4.9 to 11.0 months at screening with atopic dermatitis affecting from 25% and 58% of their BSA at baseline was well tolerated. No serious adverse event occurred. The SDZ ASM 981 blood concentrations measured in the 8 patients included in the study were low and in a range similar to those measured in children 1-4 years old (Study ASMW 202) and 8-14 years old (Study ASMW 206), and in adults (Study ASMW 204) treated under the same dosing regimen for 3 weeks. Also consistent with these other studies with SDZ ASM 981 in children and adults, there was no evidence for accumulation of SDZ ASM 981 in blood from day 4 to day 22. For comparison, in the highest dose group of adult —— patients treated with the — dose of 30 mg bid (Study ASMW 121), the mean peak level and the area under the blood concentration versus time curve over a dose interval ($AUC_{(0-12h)}$) at steady-state were 54.5 ng/ml and 294.9 ng.h/ml, respectively. The efficacy assessments showed a substantial improvement of the atopic dermatitis most pronounced in the Eczema Area Severity Index. in all patients during therapy with SDZ ASM 981 FMF 1% cream for 3 weeks twice daily with a rapid onset of action.

**Comments:**

- *Though particular attention was taken to avoid contamination by the SDZ ASM 981 cream of the blood samples for pharmacokinetics, a high (— ng/ml) SDZ ASM 981 blood concentration value measured from the day 4 sample in patient 7. There was no documentation for such contamination. The sponsor attempted to address the issue with follow-up tests. However, in spite of the fact that no cream was applied between days 13 and 22 to this patient, Day 22 sample had a concentration of — ng/ml. —*

- *In order to investigate the suspicion of contamination, analysis of the suspected sample for the peak area ratio of SDZ ASM 981 metabolites to SDZ ASM 981 was performed. The sponsor mentioned that the peak areas ratios of the SDZ ASM 981 metabolites to SDZ ASM 981 after — administration were all in the range of 3 to 9% independent of the post-dose sampling time. In contrast, the possibly contaminated sample from subject 7 showed no measurable signals of the metabolites (signal ratios below 0.8), indicating therefore that the high level of — ng/ml was very likely the result of a contamination, probably during venipuncture, and did not represent systemic exposure to SDZ ASM 981. However, still the reviewer believes that 2 h post dose sampling time was too short to detect metabolites in the blood following permeation through the skin.*

**NDA: 21-302/Study CASM981 0301E1** **Study Date: Oct' 99 – Dec' 00**

***AN OPEN-LABEL STUDY OF THE SAFETY, BLOOD CONCENTRATIONS, AND EFFICACY OF SDZ ASM 981 IN INFANTS WITH ATOPIC DERMATITIS TREATED WITH THE 1% SDZ ASM 981 FINAL MARKET FORMULATION CREAM: EXTENSION TO 1-YEAR TREATMENT***

**Objectives:**

Primary : To investigate the safety of 1% SDZ ASM 981 FMF cream in the long-term management of atopic dermatitis in infants

Secondary: To determine SDZ ASM 981 blood concentrations during long-term management of atopic dermatitis in infants

To investigate the efficacy of 1% SDZ ASM 981 cream in the long-term management of atopic dermatitis in infants

**Study Design:**

In the initial core study CASM981 0301, 8 infants with atopic dermatitis lesions affecting at least 10% of their body surface were included and completed 3-week treatment with SDZ ASM 981 cream 1%. All showed good tolerability and low systemic exposure to SDZ ASM 981. They were proposed for further inclusion for this 1-year extension. The study extension was open-label, non-controlled, as was the initial study. It started after completion of the 3-week treatment period of the initial study, i.e. at day 22.

Seven scheduled visits were planned: day 1 (which was combined with the day 22 visit of the 3-week initial study), week 3, 7, 15, 27, 39, and completion at week 53. In addition, the subject's primary care giver was contacted by the investigative center by telephone 4 times (at week 11, 21, 33, and 45) during the course of the study for the purpose of monitoring adverse events, concomitant medication, and any other clinically relevant information.

The study medication was applied twice daily in a thin film to affected areas by the primary care giver. As far as possible, the study medication was applied at approximately the same time each day and 12 hours apart (e.g. at 8:00 am and at 8:00 pm). A short-lived, transient feeling of warmth at the site of study medication application was considered to be normal.

With the exception of the 7-day mandatory application of study medication following each treatment with second-line medication when the application of study medication was used to reduce the likelihood of "rebound" of the AD flare, the primary care giver had to stop treatment on cleared areas while continuing to apply study medication to persistent lesions. Skin treated with study medication was not to be washed for at least 3 hours after application of the medication.

Five (5) patients (no. 4, 5, 6, 7, 8 of the core study CASM981 0301) with moderate to severe atopic dermatitis, 2 male and 3 female, out of which 4 were Caucasian and 1 patient's race was classified as 'other' continued on the extension study. At start of the 3-week core study these patients were aged 4.9 to 11.0 months and presented atopic lesions on 39% to 52% of their body surface area (BSA). The individual demographic data and descriptive statistics at screening are shown in Table below.

**Table: Demographic characteristics at screening* – Mean (Minimum – Maximum)**

| Age [months] | Height [cm] | Weight [kg] |
|---|---|---|
| (N=5) | (N=4) | (N=5) |
| 7.6 | 68.8 | 7.5 |
| (4.9 – 11.0) | (64.0 – 75.0) | (5.9 – 10.8) |

*PK Measurements:* For determination of SDZ ASM 981 in whole blood, 1 ml venous blood was taken by direct venipuncture at a site where no SDZ ASM 981 cream was applied. The blood was drawn into EDTA coated tubes at the following times:

Week 27: 2 hours after morning application if the cream was being used, otherwise at any time during the visit

Week 53 (study completion): one sample at any time during the visit

All samples were processed as described in the Study Protocol and kept frozen at ≤ -20°C pending analysis.

Whole blood samples were analyzed by [redacted] LOQ = 0.1 ng/mL) in the Bioanalytics and Pharmacokinetics (BAPK) Department, Novartis, Basel, Switzerland.

*Efficacy Measurements:* At each visit, the Investigator's Global Assessment (IGA), the Eczema Area Severity Index (EASI) and pruritus severity were evaluated.

**Results:**

Safety and tolerability: A total of 7 adverse events were recorded in 4 of the 5 patients who continued their treatment with SDZ ASM cream in the study extension. The adverse events consisted of severe asthma (1x) and asthma exacerbation (1x), mild viral upper respiratory tract infection (1x) and febrile convulsion (1x), mild coryza (1x), mild fever (1x), and moderate infective exacerbation of eczema (1x). All adverse events disappeared spontaneously (duration 2-7 days) and were not present at study completion. None of these events were considered by the investigator to be related to study treatment. In addition, nearly all patients showed slight to moderate abnormalities from the normal range for the individual biochemistry and hematological parameters recorded at month 6 of study treatment (week 27) and at the end of the study (week 53). However, none of them were judged clinically relevant.

Pharmacokinetics: As only one blood sample was collected from each patient on each of study during weeks 27 and 53 (end-of-study) determination of standard pharmacokinetic parameters was not possible. Individual blood concentrations of SDZ ASM 981 were

tabulated and plotted versus week to explore any relationships between exposure and long-term treatment duration.

The individual blood concentrations of SDZ ASM 981 measured at a target time of 2 h after the morning cream application at week 27 (day 183, month 6) and at end (week 53) of treatment (total of 10 concentrations) in the 5 patients who continued in the study extension are presented in Table 1. The mean (± SD) blood concentrations of SDZ ASM 981 were 0.32 ± 0.35 ng/mL at week 27 and 0.68 ± 0.76 ng/mL at end-of-study. The individual blood concentrations measured during the 1-year treatment extension were consistently low (Figure 1) and in a range (below assay LoQ (0.1 ng/mL) to — ng/ml) comparable to that measured in the initial 3-week study —— ng/ml, source: core study report CASM981 0301). Apart from 1 subject (no. 7) who presented an increased blood concentration at study completion ( — ng/mL), blood concentrations measured at week 53 were in a comparable range to those measured at week 27 (Figure 1). Compared to the results of the initial 3-week treatment period, there was no evidence for systemic accumulation of SDZ ASM 981 over the 1-year treatment extension. Blood concentrations measured in patient 7, 2h after the morning cream application at day 15 (additional samples, see core study CASM981 0301 report) and day 183 were —ng/mL and — ng/mL.

**Table 1** **Blood concentrations of SDZ ASM 981 on days 183 and 366 following application of SDZ ASM 981 1% cream to infants for 1 year**

| | Sample day/ target sample time | |
|---|---|---|
| Subject number | Day 183 2h | Day 366 anytime |
| 4 | — | — |
| 5 | — | — |
| 6 | — | — |
| 7 | — | — |
| 8 | — | — |
| | | |
| n | 5 | 5 |
| Mean | 0.32 | 0.68 |
| SD | 0.35 | 0.76 |

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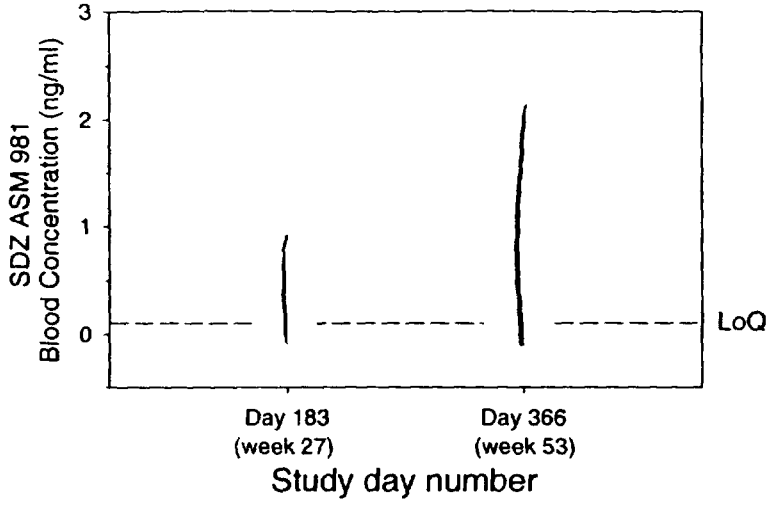
Figure 1.: Blood concentrations of SDZ ASM 981 at 2 h post application at week 27 and at end-of-study (week 53) (n=10; LoQ=0.1 ng/mL)




**Efficacy:**

The results of the Eczema Area Severity Index (EASI) evaluation are presented in Table 2 below. In the study extension, evaluations were performed at day 1 (day 22 of initial 3-week core study), weeks 3, 7, 15, 27 (day 183, month 6), 39 and at the end-of-study.

**Table 2: Adapted EASI (study days 1, 43, 183 (month 6), 267 and end-of-study) and % change from baseline at days 183 and end-of-study**

| Patient/ Day | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|
| 1[a)] | | | | | |
| 22[b)] | | | | | |
| 43 | | | | | |
| 183 | | | | | |
| % change day 183/day 1 | -80.8% | -81.4% | -37.8% | -71.6% | -79.2% |
| 267 | | | | | |
| EOS | | | | | |
| % change EOS/day 1 | -75.8% | -100% | -56.5% | -81.5% | -100% |

[a)]: baseline of the initial 3-week core study (source: study report CASM981 0301)

[b)]: day 22 of the initial 3-week core study (source: study report CASM981 0301)

[c)]: patient 7 stopped 1% SDZ ASM 981 cream at day 13 of the core study and restarted on day 1 of study extension

Following a markedly improvement of EASI with a rapid onset of action at day 4 of treatment during the initial 3-week treatment period in the core study (see Figure 2 and

day 22 results in Table 2), the 5 patients who continued their treatment in the 1-year extension showed a sustained response to the study treatment as indicated by the EASI values at day 183 (month 6) and end-of-study (see Figure 3). The EASI scores at the end of the 1-year study treatment were in a comparable range to those recorded at the end of the initial 3-week treatment period (day 22). The EASI change from baseline (day 1 of the initial 3-week study) ranged from –37.8% to –80.8% (median: -79.2%) at day 183 (month 6) and from –56.5% to -100% (median: -81.5%) at the end of the 1-year treatment.

Figure 2.: EASI at days 1, 4, 10, 22, and at end-of-study

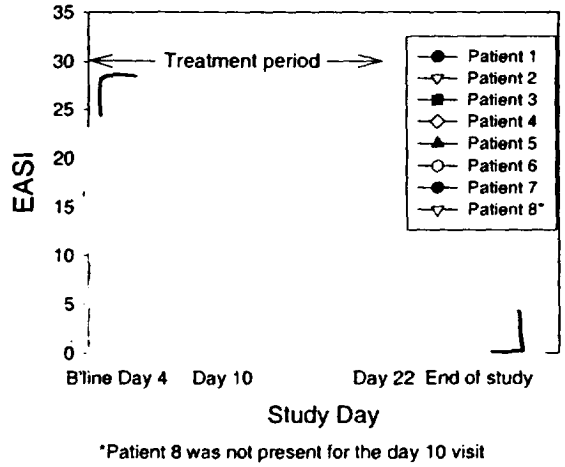
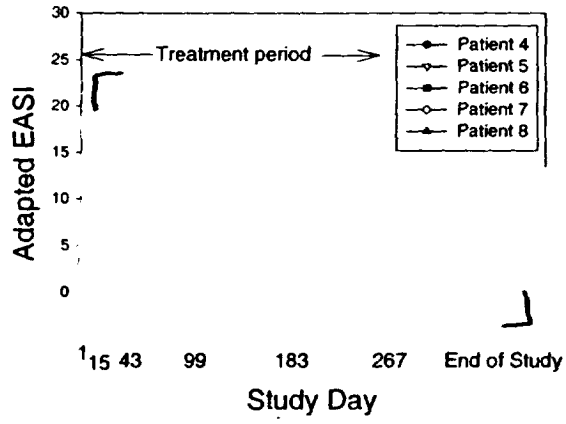



Figure 3.: EASI at days 1, 15, 43, 99, 183, 267, and at end-of-study

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## Discussion

Five of the 8 patients who completed the initial 3-week study treatment with 1% SDZ ASM 981 cream continued and completed the 1-year treatment extension. In these patients aged 4.9 to 11.0 months and presenting with 39% to 52% of the BSA affected at baseline, twice daily application of the SDZ ASM 981 cream was tolerated, both locally and systemically with some adverse events. Serious adverse events which occurred in 2 patients (severe asthma exacerbation and mild febrile convulsion during viral infection, both requiring ≤2 days hospitalization) were not considered by the investigator to be related to study drug, and did not lead to discontinuation from the study.

The SDZ ASM 981 blood concentrations measured in the 5 patients included in the study extension were consistently low and in a range similar to those measured during the initial 3-week treatment period. They were also in a comparable range to those measured in a separate infant population (study CASM981 0304), in children 1-4 years old (Study ASMW 202) and 8-14 years old (Study ASMW 206), and in adults (Study ASMW 204) treated under the same dosing regimen for 3 weeks or up to 1 year (study ASMW 205). Also consistent with these other studies with SDZ ASM 981 in children and adults, there was no evidence for accumulation of SDZ ASM 981 in blood over 1 year.

The efficacy assessments performed during the course of this 1-year study extension showed a sustained effect of the substantial improvement of the atopic dermatitis initially showed during the 3-week treatment period in all 5 patients (core study CASM981 0301), most pronounced in the Eczema Area Severity Index. However, due to the uncontrolled, open design of the study, and due to the limited number of patients studied, this finding cannot be interpreted further in the context of this study.

In view of the low blood concentrations of SDZ ASM 981 in this study, the open uncontrolled study design, the limited patient sample size and the very good tolerability/safety results, no attempt was made to correlate the blood concentration data with the results of the efficacy and/or tolerability/safety analyses.

## Comments:

- *Occurrence of 7 adverse events recorded in 4 of the 5 patients raises concern on the long-term safety of the drug in infants population. In addition, nearly all patients showed slight to moderate abnormalities from the normal range for the individual biochemistry and hematological parameters recorded at month 6 of study treatment (week 27) and at the end of the study (week 53). Though none of them was judged clinically relevant, medical officer is requested to look into that.*

**NDA: 21-302/Study CASM 981 0304** **Study Date: Jan' 00 – Jun' 00**

***AN OPEN-LABEL STUDY OF THE SAFETY, BLOOD CONCENTRATIONS, AND EFFICACY OF SDZ ASM 981 IN INFANTS WITH ATOPIC DERMATITIS TREATED TOPICALLY FOR 3 WEEKS WITH THE 1% SDZ ASM 981 FINAL MARKET FORMULATION CREAM***

**Objectives:**

Primary : To evaluate the safety of the 1% SDZ ASM 981 FMF cream, administered twice daily for 3 weeks to the lesional skin in infants with atopic dermatitis

To determine the blood concentrations of SDZ ASM 981 when applied as the 1% FMF cream twice daily for 3 weeks to the lesional skin in infants with atopic dermatitis

Secondary : To investigate the efficacy of the 1% SDZ ASM 981 FMF cream in infants with atopic dermatitis

**Study Design:**

This study employed an open-label, multiple topical dose design. It consisted of a one-day to 2-week screening period, a treatment period of 22 days, and a completion evaluation one week after the last application of SDZ ASM 981. 1% SDZ ASM 981 cream (Batch # Z0611098) was applied twice daily to the affected areas throughout the study. The patients had a total of 6 visits to the clinic: at screening, days 1, 4, 10 and 22, and at completion (day 29). Two blood samples were collected at some of the visits to determine the SDZ ASM 981 blood concentrations and to perform safety laboratory tests. Efficacy evaluations were conducted at each visit. SDZ ASM 981 blood concentrations were closely monitored throughout the study.

Twenty-two (22) patients, 16 male and 6 female of whom 12 were Caucasian, 7 were Black and 3 were Oriental, diagnosed with atopic dermatitis were enrolled in the study. The mean patients presented atopic lesions on 10% to 92% of their body surface area (EASI) on day 1 (mean 50%). Thirteen (13) of these 22 patients presented with at least 40% atopic lesions on day 1. All of the twenty-one (21) patients, (15 male and 6 female) that completed the study were under 24 months of age. Fifty percent of those enrolled were below 12 months of age. The individual demographic data and descriptive statistics are summarized below :

**Demographic characteristics – Mean (Minimum – Maximum)**

| Group | Number | %TBSA [EASI] | Age [months] | Height [cm] | Weight [Kg] |
|---|---|---|---|---|---|
| 2-23 months | 22 | 50 (10-92) | 11.7 (3.4-22.7) | 72.5 (53-91) | 9.8 (5.5-15.9) |
| 2-<12 months | 11 | 53 (24-83) | 7.2 (3.4-11.2) | 68.9 (61-84) | 8.0 (5.5-12.5) |
| 12-23 months | 11 | 46 (10-92) | 16.7 (12.5-22.7) | 76.2 (53-91) | 11..5 (10.0-15.9) |

*PK Measurements:* At each time of SDZ ASM 981 determination in whole blood, 1ml venous blood was taken by either direct venipuncture or an indwelling cannula or butterfly needle inserted at a site where no SDZ ASM 981 cream was applied. Application of an anesthetic product, such as ELA-MAX® was permitted prior to puncture. The blood was drawn into EDTA tubes at the following times:

Screening: blank sample at any time during the visit

Day 1: 1 and 2 hours (or 2 and 3 hours)* after the morning application

Day 10: 1 and 2 hours (or 2 and 3 hours)* after the morning application

Day 22: one sample at any time during the visit

*: In order to provide a balanced set of data points, ie. 50 % of the patients in each sampling time group, the 1- and 2-hour sampling times were applied to the patients with an odd patient number (No. 1, 3, 5, ...) and the 2- and 3-hour sampling times were applied to the patients with an even patient number (No. 2, 4, 6, ...).

All samples were processed according to the Study Protocol and kept frozen at ≤ -20°C pending analysis. Whole blood samples were analyzed by [redacted] in the Bioanalytics and Pharmacokinetics (BAPK) Department, Novartis, Basel, Switzerland with a limit of quantitation (LoQ) of 0.1 ng/ml.

*Efficacy Measurements:* At each visit, the extent of lesions was evaluated using the Lund and Browder chart, the Investigator's Global Assessment (IGA), and the Eczema Area Severity Index (EASI).

**Results:**

*Safety and tolerability*: Twice daily treatment with 1% SDZ ASM 981 cream for 21 days was well tolerated by children aged 3 to 23 months. One patient discontinued study participation due to an adverse event not considered however to be related to study drug. Patient #6 of center 5 experienced a worsening of eczema during the study.

*Pharmacokinetics:* Individual blood concentrations are reported in Table 1. Concentrations below the limit of quantitation (0.1 ng/ml) were treated as zero in summary statistics and for the calculation of pharmacokinetic parameters. As only two blood samples were collected from each patient on each of study days 1 and 10, only $C_{max}$ and $C_{min}$ were determined. Blood concentrations of SDZ ASM 981 were plotted versus time/day and %TBSA (EASI) affected by atopic dermatitis at baseline (day 1) to explore any relationships between exposure and these parameters. In addition, the relationship between the baseline area-mass ratio (AMR, ratio of the area involved to the mass/weight of the subject) and blood concentrations of SDZ ASM 981 was also investigated.

Of the 42 samples collected on day 1 a total of 30 (71.4%) had concentrations of SDZ ASM 981 below the limit of quantitation (Table 2 and Figure 1). On day 10, 36 of the 37 collected samples had concentrations above the LoQ. With the exception of the two high values ( ——— ng/ml) which were suspected to be a result of contamination by cream at the venipuncture site, the maximum concentration observed was — ng/ml. On day 22 all concentrations were above the LoQ and were in a range of ——— ng/ml. Overall, 31% of the total blood concentrations measured during this study (n=100), were below the LoQ (0.1 ng/ml). Seventy-one (71) percent of these concentrations were below the LoQ (0.5 ng/ml, —— that was used in previous studies (ASMW204, W205, W202 and W206).

**Table 1: Blood Concentrations (ng/ml) of SDZ ASM 981 Following Application of SDZ ASM 981 1% Cream to Infants for 3 Weeks**

| | | Time (h) Post Dose | | | Time (h) Post Dose | | | |
|---|---|---|---|---|---|---|---|---|
| Center/ | | Day1 | | | Day 10 | | | Day 22 |
| Subject | Predose | 1 | 2 | 3 | 1 | 2 | 3 | |
| 001 001 | | | | | | | | |
| 001 002 | | | | | | | | |
| 001 003 | | | | | | | | |
| 002 001 | | | | | | | | |
| 002 002 | | | | | | | | |
| 002 003 | | | | | | | | |
| 002 004 | | | | | | | | |
| 002 005 | | | | | | | | |
| 002 007 | | | | | | | | |
| 002 008 | | | | | | | | |
| 003 001 | | | | | | | | |
| 004 001 | | | | | | | | |
| 004 002 | | | | | | | | |
| 005 001 | | | | | | | | |
| 005 002 | | | | | | | | |
| 005 003 | | | | | | | | |
| 005 004 | | | | | | | | |
| 005 005 | | | | | | | | |
| 005 006 | | | | | | | | |
| 005 007 / | | | | | | | | |
| 006 001 | | | | | | | | |
| 006 002 | | | | | | | | |
| Mean | 0.01 | 0.08 | 0.27 | 0.30 | 0.65 | 0.61 | 0.41 | 0.52 |
| SD | 0.06 | 0.13 | 0.51 | 0.55 | 0.56 | 0.60 | 0.23 | 0.53 |
| Min | | | | | | | | |
| Max | | | | | | | | |
| Median | 0.00 | 0.00 | 0.00 | 0.00 | 0.41 | 0.39 | 0.37 | 0.33 |

*Sample suspected to be contaminated by the cream during venipuncture; NS = No Sample

**Table 2: Frequency of blood concentrations of SDZ ASM 981 in specified ranges**

| | Day 1 | Day 10 | Day 22 | Total |
|---|---|---|---|---|
| <0.1 ng/ml (LoQ) | 71.4 | 2.6 | 0.0 | 31.0 |
| 0.1 - <0.5 ng/ml | 11.9 | 59.0 | 63.2 | 40.0 |
| 0.5-1.0 ng/ml | 7.1 | 17.9 | 26.3 | 15.0 |
| >1.0-2.0 ng/ml | 9.5 | 12.8 | 5.3 | 10.0 |
| >2.0 ng/ml | 0.0 | 7.7 | 5.3 | 4.0 |

Blood concentrations of SDZ ASM 981 were plotted versus time/day and %TBSA (EASI) affected by atopic dermatitis at baseline (day 1) to explore any relationships between exposure and these parameters. Blood concentrations of SDZ ASM 981 were higher on day 10 compared to day 1, however, no further increase was noted on day 22, indicating absence of systemic accumulation of SDZ ASM 981.

When blood concentrations of SDZ ASM 981 were plotted versus % TBSA (EASI) affected by atopic dermatitis on day 1 (Figure 2), there was evidence for an increase in blood concentrations with increasing body surface area affected. The statistical analysis showed a significant relationship (p=0.013). The estimated coefficient (slope) was 0.005 implying that a patient with a %TBSA (EASI) of 90% would have on average SDZ ASM 981 blood concentrations of 0.4 ng/ml higher than a patient with a %TBSA (EASI) of 10%.

Similarly, there was a significant relationship between SDZ ASM blood concentrations and baseline AMR ($cm^2$/kg) (ranging from 46.5 to 483.5 $cm^2$/kg) (p=0.005). The estimated coefficient (slope) for the AMR on Day 1 was 0.001 implying that a patient with an AMR of 500 $cm^2$/kg would have on average SDZ ASM 981 blood concentrations of 0.4 ng/ml higher than a patient with an AMR of 100 $cm^2$/kg.

The under-proportional increase in SDZ ASM 981 blood concentrations with increasing baseline % TBSA or AMR was consistent with the fact that the blood concentrations were in a comparable range over the wide % TBSA or AMR range (see Table 3). Further analysis showed that there was no effect of TBSA ($cm^2$) (p=0.137) on the blood concentrations of SDZ ASM 981

**Table 3: SDZ ASM 981 blood concentration range in specified %TBSA (EASI) and AMR ranges**

| %TBSA range | AMR range $cm^2$/kg | Pimecrolimus concentration range (ng/ml) |
|---|---|---|
| 10 - <40% | 46.5 – 198.8 | <0.1 – — |
| 40 - <70% | 194.0 – 332.5 | <0.1 – — |
| 70 – 92% | 326.8 – 483.5 | <0.1 – — |

Figure 1.: Blood concentrations of SDZ ASM 981 on days 1, 10 and 22

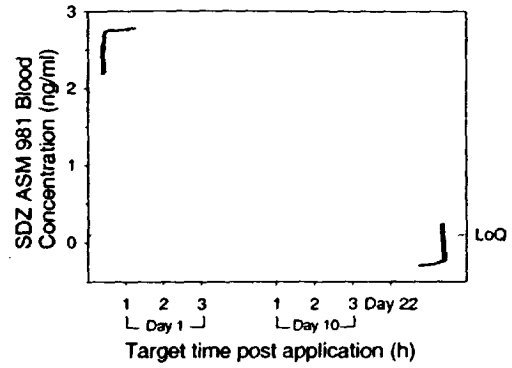
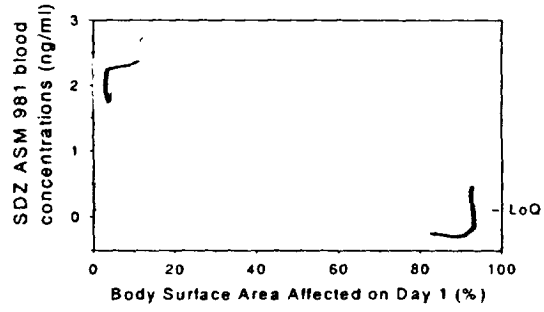
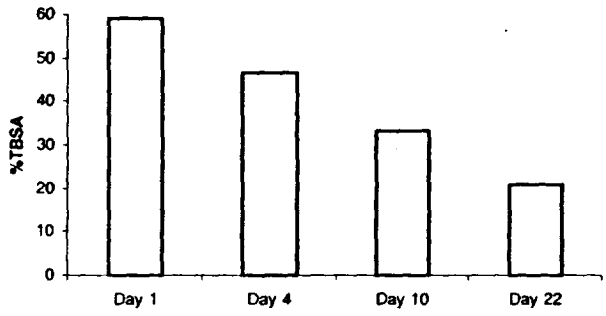



Figure 2.: Blood concentrations of SDZ ASM 981 versus %TBSA (EASI) on day 1




*Efficacy:* Extent of lesions: Evaluations were made at screening, day 1, day 4, day 10, and day 22 and at the end-of-study. Following only 4 days of 1% SDZ ASM 981 cream treatment the median %TBSA was reduced markedly. Furthermore, the extent of improvement increased at each subsequent visit during the SDZ ASM 981 treatment period. The range of total surface area affected was 36% to 95% at screening, 10% to 90% at day 1, 10% to 80% at day 4, 5% to 60% at day 10, and 0% to 50% at day 22. Mean values of % TBSA affected are presented in figure 3, below.

**Figure 3: Mean % TBSA (Lund and Browder) affected by atopic dermatitis on day 1, 4, 10 and 22 of 1 % SDZ ASM 981 cream application**




Overall evaluation (Investigator's Global assessment): Evaluations were made at screening, day 1, day 4, day 10, day 22 and at the end-of-study. Seventy-seven percent of the treated patients showed improvement on day 22 when compared to day 1. In 11 of the

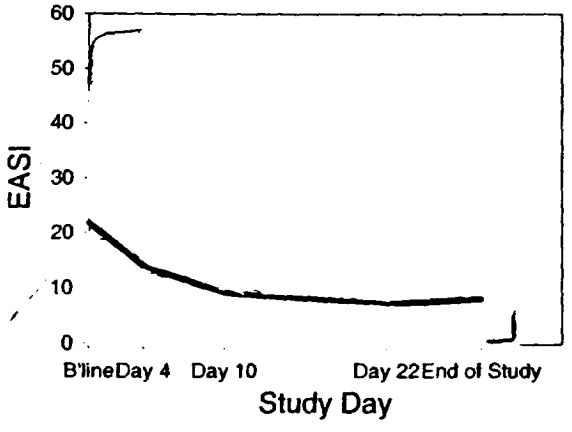
22 patients the improvement was substantial, i.e. they improved by two scores or more in the overall assessment of efficacy whilst comparing the baseline / day 1 scores with the last assessment. Four patients had no improvement and one patient worsened on day 22.

Eczema Area Severity Index (EASI) assessment: The individual EASI data recorded at screening, day 1, 4, 10, 22 and at the end-of-study and the mean curve are presented on Figure 4. For the 21 patients who completed 3 weeks of treatment with 1% SDZ ASM 981 cream, the EASI change from baseline at day 22 ranged from -9% to -100% (median was -78.1%). Sixteen of the 21 (76%) completed patients had a greater than 50 % change from baseline on day 22. Table 4 presents the number of patients that improved by 10% increments. Improvement was rapid with many patients showing an improvement with the first 4 days of initiation of 1 % SDZ ASM 981 therapy.

**Table 4: Adapted EASI (% change)**

| % change from baseline at day 22 (Range of reduction) | N |
|---|---|
| 0 to -10 | 1 |
| -11 to - 20 | 1 |
| -21 to -30 | 1 |
| -31 to -40 | 1 |
| -41 to -50 | 1 |
| -51 to -60 | 1 |
| -61 to -70 | 4 |
| -71 to - 80 | 4 |
| -81 to -90 | 3 |
| -91 to -100 | 4 |

**Figure 4: EASI following 1% SDZ ASM 981 cream application (n=21) Individual (dashed lines) and arithmetic mean data (solid line).**

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**Discussion**

The day 1 sample aimed at capturing the exposure to the drug after a single application, at a stage when the largest (baseline) extent of skin surface area is affected. The day 10 sample evaluated the exposure at steady-state, after repeated applications. The single day 22 sample captured any potential accumulation after prolonged treatment. The SDZ ASM 981 blood concentrations were analyzed on-line throughout the study so that treatment could be discontinued in case unexpectedly high systemic exposure was observed.

Twice daily application of 1% SDZ ASM 981 FMF cream for 3 weeks onto the lesional skin of 22 male and female infants aged 3 to 23 months at screening with atopic dermatitis affecting from 10% to 92% of their TBSA at baseline was well tolerated with no serious adverse event. In all patients, excluding the values associated with the two contaminated samples, the blood concentrations ranged from <0.1 to — ng/ml. This data is consistent with the present understanding of SDZ ASM 981 pharmacokinetics following topical treatment with 1% SDZ ASM 981 cream in adult (Study ASMW 204) and children (Study ASMW 202, ASMW 206 and C ASM 981 0301) patients with atopic dermatitis. For comparison, in adult ——— patients treated with — dose of SDZ ASM 981 ranging from 5 to 60 mg per day for 4 weeks (Study ASMW 121), the mean peak level ($C_{max}$) and the area under the blood concentration versus time curve (AUC) over a 12-h dose interval at steady-state for the highest 60 mg dose were 54.5 ng/ml and 294.9 ng.h/ml, respectively. At this dose no significant adverse events were reported.

Despite the statistically significant correlation between increasing SDZ ASM 981 blood concentrations and increasing %TBSA affected (day 1), overall the blood concentrations were consistently low, even in patients with the highest TBSA involvement. For example, day 22 SDZ ASM 981 blood concentrations were similar for patients with a wide range of total body surface affected.

| Patient #/Center | Day 1 %TBSA (EASI) | Day 22 SDZASM 981 blood concentration |
|---|---|---|
| 4/2 | 11% | — ng/ml |
| 5/2 | 33% | — ng/ml |
| 2/1 | 54% | — ng/ml |
| 2/4 | 86% | — ng/ml |
| 1/5 | 92% | — ng/ml |

Blood concentrations of SDZ ASM 981 were higher on day 10 compared to day 1, however, not further increase was noted on day 22, indicating absence of systemic accumulation of SDZ ASM 981. This is entirely consistent with the pharmacokinetic data obtained from other studies with SDZ ASM 981. Steady state SDZ ASM 981 pharmacokinetics were achieved after 5 days of — administration in adult patients (Study ASM W121). Similarly, steady state appears to have been reached by day 4 of topical application in both adult and child patients (ASMW 204 and ASMW 202, respectively).

The efficacy assessments showed a substantial improvement of atopic dermatitis in most patients with a rapid onset of action within 4 days of treatment, most pronounced in the Eczema Area Severity Index. SDZ ASM 981 clearly reduced the degree of severity of AD in infants under two years of age.

**Comments:**

- *Two high values ——→ and —— ng/ml) were found in this study which were suspected to be a result of contamination by cream at the venipuncture site. However no documentation or further follow-up has been mentioned in the report.*

- *The statistical analysis showed a significant relationship (p=0.013) between blood concentrations of SDZ ASM 981 and % TBSA (EASI) affected by atopic dermatitis on day 1. Similarly, there was a significant relationship between SDZ ASM blood concentrations and baseline AMR ($cm^2/kg$) (ranging from 46.5 to 483.5 $cm^2/kg$) (p=0.005) on day 1. Though the increase in SDZ ASM 981 blood concentrations with increasing baseline % TBSA or AMR is under-proportional, but they are statistically significant.*