CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-302

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

Submission:	NDA 21-302
Product Trade Name:	Elidel®
Product:	Pimecrolimus 1% Cream
Indication:	Atopic Dermatitis
Submission Date:	December 15, 2000
Type of Submission:	Original NDA (1S)
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I. Executive Summary:

Pimecrolimus (SDZ ASM 981) is a novel anti-inflammatory ascomycin macrolactam which selectively inhibits the synthesis of pro-inflammatory cytokines in T-cells and the release of inflammatory mediators from mast cells. When applied topically SDZ ASM 981 exhibits strong anti-inflammatory activity but unlike corticosteroids does not cause skin atrophy. The clinical pharmacology findings of SDZ ASM 981 using SDZ ASM 981 cream 1% formulation (Elidel™) intended for marketing (MF cream) are summarized below:

In adult patients

- Topical applications of SDZ ASM 981 MF cream 1% to adult patients with extensive lesions of atopic dermatitis (AD) for 3 weeks and up to 1 year was well tolerated and resulted in low blood concentrations of pimecrolimus with the majority of the concentrations below the assay LoQ (0.5 ng/ml). The maximum systemic concentration ranged between ——— ng/ml.
- There was no systemic accumulation of pimecrolimus beyond day 2 of treatment over 3 weeks and up to 1 year of treatment.
- There was no evidence for higher blood concentrations of pimecrolimus with increasing body surface area treated.
- Maximal exposure in terms of $AUC_{(0\text{-}24h)}$ (23 ng h/ml) following topical applications of SDZ ASM 981 MF cream 1% to adult patients was considerably lower than the exposure at the No-Adverse-Effect-Level observed in a dermal 104-week carcinogenicity study in mice ($AUC_{(0\text{-}24h)}$: 1040 ng h/ml, ratio of 45) and in the 26-week oral study in rats ($AUC_{(0\text{-}24h)}$: 688 ng h/ml, ratio of 30), and the adjusted $AUC_{(0\text{-}24h)}$ observed in adults following oral administration of a well tolerated dose of 60 mg/day (590 ng h/ml, ratio of 26).
- Efficacy as measured mainly by change in Eczema Area Severity Index (EASI) score in the PK studies showed significant improvement in healing atopic dermatitis lesions during treatment with SDZ ASM 981 MF cream 1%.

In pediatric patients

- Blood concentrations of pimecrolimus in children aged 3 months to 14 years receiving topical treatment with SDZ ASM 981 cream for atopic dermatitis for 3 weeks (up to 12 months in one study extension) were consistently low (typically <1 ng/ml and mainly <LoQ (0.1ng/ml)). However, in contrast to the adult population higher proportion of subjects (30 – 75%) displayed blood concentration above 0.5 ng/ml. In one study (Study # 301, n = 7), 75% of the samples (4.9 – 11 mo) had serum concentration above 0.5 ng/ml.
- The maximum systemic concentration ranged between [redacted] ng/ml with the highest ([redacted] ng/ml) being found in the infant population (4.9 – 11 mo).
- Whether all of the above findings are due to involvement of higher affected body surface area (BSA) and/or higher area mass ratio (AMR) in infants and children compared to adults could not be ascertained. In general, there was no evidence for higher systemic exposure in children with higher proportions of body surface area (%BSA) receiving treatment, with the exception of children < 2 years in study 0304 who showed a statistically significant relationship between their baseline %BSA (ranging from 10-92%) and their blood concentrations ([redacted] ng/ml). However, this involved only a very small increment in blood concentrations over the wide %BSA range.
- As with adults, there was no evidence of systemic accumulation over the 3 weeks of treatment.
- Maximal exposure in terms of $AUC_{(0\text{-}24h)}$ (38 ng h/ml) following topical treatment with SDZ ASM 981 1% cream observed in studies with children was considerably lower than the No-Adverse-Effect-Level exposure observed in a dermal 104-week carcinogenicity study in mice ($AUC_{(0\text{-}24h)}$: 1040 ng h/ml, ratio of 27) and in the 26-week oral study in rats ($AUC_{(0\text{-}24h)}$: 688 ng h/ml, ratio of 18), and the adjusted $AUC_{(0\text{-}24h)}$ observed in adults following oral administration of a well tolerated dose of 60 mg/day of SDZ ASM 981 (590 ng h/ml, ratio of 16).
- Efficacy as measured mainly by change in EASI score in the PK studies showed significant improvement in healing atopic dermatitis lesions during treatment with SDZ ASM 981 MF cream 1%.
- 37% of infants population (< 2 yrs) reported upper respiratory tract and/or flu, cold like symptoms as opposed to 15% of children population 2 – 14 yrs reported similar conditions during 3 weeks of treatment. In the extension of study 301 from 3 weeks to 12 months a total of 7 adverse events were recorded in 4 of the 5 patients who continued their treatment with SDZ ASM 1% cream. In addition, nearly all of the 5 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).

In conclusion, clinical pharmacology studies with the SDZ ASM 981 cream 1% (the final market formulation of pimecrolimus) indicated consistently low systemic exposure and an absence of systemic accumulation in adults, adolescents, children and infants with AD. Within the studied population, infants under 2 years of age were found to have relatively higher blood concentrations of SDZ ASM 981 compared to older children and adults. Whether this is related to the higher affected body surface area (BSA) and/or higher area mass ratio (AMR) in infants compared to children and adults could not be ascertained. Even so these concentrations are generally within the upper range of concentrations seen in older children and adults.

While the clinical significance of these increased blood levels is unknown, an observation was made during the development program that the infants receiving SDZ ADM 981 1% cream had a higher incidence of upper respiratory tract and/or flu, and cold like symptoms.

[

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A. Recommendations:

Based on this review, NDA 21-302 is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. Because of the unanticipated finding of an increased adverse event rate in infants under 2 yrs of age, as outlined above, its use in this population should be restricted. A review of the PK data in this submission has resulted in certain changes in the appropriate sections of the product label. The suggested changes have been incorporated in the section "Labeling Comments" and have been conveyed to the reviewing division.

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III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

The systemic absorption of pimecrolimus (blood concentrations) has been investigated in open label studies following topical application to adults and children aged 3 months to 14 years with atopic dermatitis (AD) and following topical administration to adults with [redacted]. Additional supporting pharmacokinetic studies following [redacted] administration of SDZ ASM 981 to healthy adults and [redacted] patients have also been conducted. However, in this NDA 21-302, the sponsor seeks approval for only atopic dermatitis indication and submitted six studies (2 adults and 4 children/infants) in this regard. These studies have been reviewed thoroughly and overviews have been incorporated in this section. Recommendation is made based on exposure, response and safety (Adverse events) data. Detailed reviews of the individual studies could be found in the Appendix. In this document, pimecrolimus (SDZ ASM 981) is also referred to as ASM 981 or ASM. The final market formulation for pimecrolimus is referred to as ASM cream 1%, or ASM 1%.

The blood pharmacokinetics of pimecrolimus have been characterized after topical administration of SDZ ASM 981 to healthy adult volunteers, adult patients with atopic dermatitis and to pediatric patients aged 3 months to 14 years with atopic dermatitis. The blood pharmacokinetics of pimecrolimus have also been characterized following single and multiple [redacted] administration of SDZ ASM 981 to healthy subjects and [redacted] patients.

Earlier topical studies used [redacted] and [redacted] development formulations. Overall, these studies showed that topical applications of SDZ ASM 981 in various formulations were locally and systemically well tolerated, both in healthy volunteers and patients, without significant adverse events. The pimecrolimus blood concentrations were predominantly below the assay limit of quantitation (LoQ = 0.5 ng/ml).

All subsequent topical studies used the ASM cream 1% formulation intended for marketing (MF cream). Only topical pharmacokinetic studies in which the MF cream 1% was used are presented in this document. Studies involving [redacted] administration of SDZ ASM 981 used [redacted] formulations.

Because the majority of blood concentrations were below the LoQ in both adult and pediatric subjects after topical application, and blood samples collected in pediatric pharmacokinetic studies were few in number, the area under the concentration-time curve (AUC) could only be computed from a few individuals. As a rule, the individual AUC over a dosing interval ($AUC_{(0\text{-}12h)}$) was computed when at least three quantifiable blood concentrations of pimecrolimus were available from the given individual.

Pharmacokinetics Following Topical Administration to Adults

The systemic absorption of pimecrolimus in adult patients was investigated in two open-label studies during short-term and long-term treatment of subjects with moderate to severe AD with ASM cream 1%. Tables I-IV below summarize these studies.

Summary Table I: Demographics and Blood Levels in Adult Patients

Study #	Population		# of Patients (Enrolled/ Completed)	Total # of measured samples	# (%) of Samples above LOQ (0.5ng/ml)				
	Age (yrs/mos)	% BSA Affected			1	4	22	EOS	Total
204	Adult (19-45)	15 - 59	12/12	444	1	17	4	1	23 (5%)
205[a]	Adult (19-59)	13-62	40/13	918	-	-	-	-	18 (2%)

[a] This was a *12-month* study as opposed to rest of the 3-week studies. Of the 918 concentrations determined, only 2% (18 samples) were above the LOQ of 0.5 ng/ml.
na – not applicable

Summary Table II: PK Parameters of Adult Patients

Study # (Duration)	Total # of measured samples	# of samples claimed spurious	Conc. Range (ng/ml)	PK Parameters			
				Max C (ng/ml) claimed		$AUC_{max(0-12h)}$ (ng/h/ml) claimed	
				Normal	Spurious	Normal	Spurious
204 (3 Weeks)	444	1	<0.5 - 1.4	1.4	4.6	11.4	NC
205 (1 –12 mos)	918	0	<0.5 – 0.8	0.8	-	NC	-

- None found; NC – Not calculated due to absence of enough data.

In study W204, blood samples for determination of pimecrolimus concentrations were collected on Days 1 to 4, up to 12 h following the morning application, on day 6 up to 8 h post-dose, on days 10 and 17 up to 6 h post-dose, and 1 and 7 days (single sample) after the last application. Of the total 444 blood concentrations measured, 77.5% were below the assay LoQ (0.5 ng/ml) and 99% were below or at 1 ng/ml (see Tables I-III). Only two concentrations were above 1 ng/ml (——— ng/ml), excluding one outlier value of — ng/ml. On the whole, the concentrations were quantifiable from day 2 of treatment and did not show any further accumulation of pimecrolimus concentrations beyond day 2 over the 3 weeks of treatment. In the 8 patients presenting at least 3 consecutive quantifiable concentrations in the PK profile, the individual $AUC_{(0-12h)}$ ranged from 2.5 to 11.4 ng h/ml (not including the outlying concentration of — ng/ml).

In study W205, blood samples for determination of pimecrolimus concentrations were collected on Days 1, 7, 21, 42 and once monthly (months 3-12), before and 2 and 4 h after the morning cream application. Of the 40 patients included in the study, 13 have completed 1 year in the study, and 27 patients completed between 7-21 days (8 patients), 2-5 months (13) and 6-9 months (6) in the study. Generally blood concentrations of pimecrolimus were very low and of the 918 concentrations measured, 98.0% (900 concentrations) were below the assay LoQ (0.5 ng/ml). Individual quantifiable maximum concentrations ranged from ——— ng/ml (Table II). There was no evidence for higher

pimecrolimus blood concentrations in subjects with higher proportion of their body surface area affected at baseline. In the 2 patients presenting at least 3 consecutive quantifiable concentrations in the PK profile, the individual $AUC_{(0\text{-}12h)}$ were 8.2 and 7.0 ng h/ml respectively.

In summary, these studies in adult patients with atopic dermatitis have demonstrated that systemic absorption following topical application of ASM cream 1% is consistently either below or close to LoQ (0.5 ng/ml) in comparison with systemic exposure observed in animal studies and repeated administration of oral SDZ ASM 981 in man. Blood concentrations remain low without any sign of systemic accumulation even on prolonged and unrestricted bid use. About 25% (all in study 205) of the population showed flu like adverse events. However as study 205 was a 12-month study and all the flu-like symptoms were observed round the year, linking these symptoms with the study drug is not justifiable.

Summary Table III. Blood concentrations of pimecrolimus in adults with AD under treatment with ASM cream 1% bid

Concentration range (ng/ml)	% of total samples collected		
	Study W204*	Study W205	Total
<0.5	77.5	98.0	91.3
0.5-1.0	21.8	2.0	8.4
>1.0-2.0	0.5	0	0.1
>2.0	0.2*	0	0.1
Total samples (N)	444	918	1362

- Includes one high value (— ng/ml) in a sample documented to have been contaminated with the cream during venipuncture (see section 3.3)

Summary Table IV: PK and Overall Comments in Adult Patients

Study # (n)	Population	PK Comments	Overall Comments
204 (12)	Adult (19-45)	The blood concentrations ranged from —— ng/ml with 1 spurious concentration of — ng/ml measured in patient # 2 on Day 3 , 2 h postdose.	Other than a feeling of warmth/burning sensation at the site of application reported by most of the patients, 2 patients developed diarrhea claimed not likely to be due to study drug. However no SAE was observed.
205 (40)	Adult (19-59)	The blood concentrations ranged from —— ng/ml	13 patients reported flu and cold like symptoms and 1 reported diarrhea over 12-month period. None of the symptoms was claimed to be study drug related. However no SAE was observed.

Pharmacokinetics Following Topical Administration to Children

The systemic absorption of pimecrolimus after topical treatment with the ASM cream 1% was investigated in patients aged 3 months to 14 years (see Tables V - VIII below). Blood concentrations of pimecrolimus were consistently low; however the upper range in this population was higher than that measured in adults.

Table V: Demographics and Blood Levels in Children and Infants

Study #	Population		# of Patients (Enrolled/ Completed)	Total # of measured samples	# (%) of Samples above LOQ									
	Age (yrs/mos)	% BSA Affected			Above 0.5 ng/ml on Day					Above 0.1 ng/ml on Day				
					1	4	22	EOS	Total	1	4	22	EOS	Total
202	Children (1 – 4)	20 - 70	10/7	63	-	13	5	1	**19 (30%)**	na	na	na	na	**na**
206A	Children (8 – 14)	20 - 50	10/9	77	-	20	15	1	**36 (47%)**	na	na	na	na	**na**
206B	Children (8–30 mo)	8 - 80	8/8	21	-	4	6	0	**10 (48%)**	na	na	na	na	**na**
301	Infants (4.9-11 mo)	25 - 58	8/7	16	-	6	6	-	**12 (75%)**	-	8	8	-	**16 (100%)**
304	Infants (3-23 mo)	40 - 95	22/21	100	7	15*	7	-	**29 (29%)**	12	38*	19	-	**69 (69%)**

* Day 10 instead of Day 4

[a] This was a 12-month study as opposed to rest of the 3-week studies. Of the 918 concentrations determined, only 2% (18 samples) were above the LOQ of 0.5 ng/ml.

na – not applicable

Table VI: PK Parameters of Children and Infants

Study # (Duration)	Total # of measured samples	# of samples claimed spurious	Conc. Range (ng/ml)	PK Parameters			
				Max C (ng/ml) claimed		$AUC_{max(0-12h)}$ (ng/h/ml) claimed	
				Normal	Spurious	Normal	Spurious
202 (3 Weeks)	63	1	<0.5- —	1.8	31.7	18.8	NC
206 A (3 Weeks)	77	0	<0.5- —	2.0	-	16.4	-
206B (3 Weeks)	21	1	<0.5- —	2.0	> 50	NC	NC
301 (3 Weeks)	16	1	——	2.6	36.6	NC	NC
301 (12 Mo)	10	0	<0.1 – —	1.94	-	NC	NC
304 (3 Weeks)	100	2	<0.1- —	2.26	8.67, 42.2	NC	NC

\- None found

NC – Not calculated due to absence of enough data.

In study W202, blood concentrations of pimecrolimus were measured before and at 2, 4, and 6 h after ASM cream 1% application on days 4 and 22 (last day) of treatment. Of the 63 concentrations measured in the 10 patients, 63.5% were below the assay LoQ (0.5 ng/ml). The maximal concentration observed was — ng/ml, apart from an isolated concentration of — ng/ml in a contaminated sample taken on an area of skin freshly treated with the cream. Because of the majority of samples with concentrations below the LoQ, $AUC_{(0\text{-}12h)}$ was computed in 3 patients only. However in 2 patients with at least 3 consecutive quantifiable concentrations in the PK profile, the individual $AUC_{(0\text{-}12h)}$ were 11.0, and 18.8 ng h/ml. There was no evidence of accumulation between day 4 and day 22.

In study W206 (cohort 1, similar PK design as W202), 54.5% of the the 77 pimecrolimus blood concentrations measured in the 10 patients were below the assay LoQ and the maximal concentration observed was —ng/ml. The $AUC_{(0\text{-}12h)}$ computed in 5 patients having 3 or more quantifiable consecutive concentrations ranged from 5.4 to 16.4 ng h/ml. There was no accumulation between day 4 and day 22.

In cohort 2 of study W206, involving younger patients aged 8-30 months, a single blood concentration was measured 2 h after the morning application on days 4 and 22. The blood concentrations observed were consistently low and in a range similar to those measured in children 1-4 years old (study W 202) and 8-14 years old (W 206, cohort 1). Of the total number of concentrations (n = 21), 52.4% were below the LoQ. The maximal blood concentration measured was — ng/ml, apart from a single isolated high value of — ng/ml which could not be quantified within the assay calibration curve (maximum calibration concentration was — ng/ml). This outlying high value was suspected to result from contamination of the sample by the cream during venipuncture. Similar to the results in study W202, no accumulation of SDZ ASM 981 in blood was observed between days 4 and day 22 (last day) of treatment.

In study 0301, blood concentrations of pimecrolimus measured 2 h after the morning application of the cream on days 4 and 22 ranged from —— ng/ml, apart from one isolated concentration of — ng/ml attributed to sample contamination by the cream. The blood concentrations measured in the 8 children were in a range similar to that measured in older children. In this study extension for 12 months (301E1), blood concentrations of pimecrolimus measured after the morning application of the cream on days 183 and 366 ranged from <0.1 to — ng/ml.

In study 0304, two blood concentrations of pimecrolimus were measured at 1 and 2 h or 2 and 3 h after the morning application on days 1 and 10 and a single concentration was measured on the last day of a 3-week treatment. Blood concentrations of pimecrolimus were consistently low and in a range similar to that measured in other children and adult studies. Eighty-six percent (86.0%) of the total of 100 concentrations measured were less than or equal to 1 ng/ml, and 31.0 % of the concentrations were below the LoQ (0.1 ng/ml). The individual maximum blood concentrations ranged from <LoQ (0.1 ng/ml) to — ng/ml, apart from two isolated high values of —— ng/ml attributed to sample contamination by the cream during venipuncture.

In each of the above 4 pediatric studies, one or more spurious samples were identified. However upon further investigation, no correlation was found between % affected BSA of the patients with those high spurious concentrations (Table VIII).

In all pediatric studies presented above, compared to NOAEL exposures in animals and safe systemic exposure after oral administration in man, the blood concentrations were consistently low, even in the patients with a baseline percent body surface area affected greater than 40%. 13 out of 35 (37%) infants (< 2 yrs) and 2 out of 13 (15%) children reported upper respiratory tract and/or flu, cold like symptoms.

Table VII: Blood concentrations of pimecrolimus in children with AD under treatment bid with ASM cream 1%

Concentration range (ng/ml)	% of total samples collected					
	Study W202	Study W206 cohort 1	Study W206 cohort 2	Study 0301	Study 0304	Total
< 0.1				0.0	31.0	11.1
0.1-<0.5				21.1	40.0	15.7
<0.5	63.5	54.5	52.4	21.1	71.0	60.0
0.5-1.0	23.8	37.7	28.6	47.4	15.0	26.4
>1.0-2.0	11.1	7.8	14.3	21.1	10.0	10.7
>2.0	0.0	0.0	0.0	5.3	2.0	0.7
Other samples*	1.6	0.0	4.8	5.3	2.0	2.1
Total samples (N)	63	77	21	19	100	280

*Including high values attributed to contamination of the samples by the cream during venipuncture: — ng/ml, (W202), — ng/ml (W206, 2nd cohort), — ng/ml (0301), — ng/ml and — ng/ml (0304)

Summary Table VIII: PK and Overall Comments in Children and Infants

Study #	# of Patients					
	< 2yrs	PK comments	> 2yrs	PK Comments	Total	Comments
202	2	Patient # 4 (23% BSA) had spurious blood concentration of — ng/ml on Day 4 at 0 h	8	-	10	The blood concentrations ranged from <0.5 to — ng/ml with no apparent difference between infants (< 2yrs) and children (> 2yrs) in terms of exposure, response and safety. **Patient # 5 (14mo) had moderate chest infection.** Patient #s 1 and 2 (both 45 mo) also showed similar symptoms. None of the symptoms was claimed to be study drug related. However, no SAE was observed.
206B	3	Patient # 205 (80% BSA) had spurious blood concentration of — ng/ml on Day 22 at 2 h	5	-	8	The blood concentrations ranged from <0.5 to — ng/ml with no apparent difference between infants (< 2yrs) and children (> 2yrs) in terms of exposure, response and safety. **Nobody except patient # 205 (8 mo) showed mild upper respiratory tract infection claimed not related to the study drug.** However, no SAE was observed.
301	8	Patient # 7 (44% BSA) had spurious blood concentration of — ng/ml on Day 4 at 2 h	0	-	8	The blood concentrations ranged from — to — ng/ml. **Patient # 2 (6.6mo) showed mild upper respiratory tract infection claimed not related to the study drug.** However no SAE was observed.
304	22	Patient # 3 (of center 5, 40% BSA) and patient # 1 (of center 6, 45% BSA) had spurious blood concentration of — ng/ml on Day 10 at 2 h and — ng/ml on Day 10 at 3 h respectively	0	-	22	The blood concentrations ranged from — to — ng/ml. **10 patients showed cold symptoms, 5 showed gastroenteritis, 1 ottis media, and 2 emesis.** None of the symptoms was claimed to be study drug related. However no SAE was observed.

A summary of exposure to pimecrolimus in AD pediatric and adult subjects treated with SDZ ASM 981 1% cream for 3 weeks is given in Table IX.

Table IX: Summary of systemic exposure to pimecrolimus in AD pediatric and adult subjects treated with ASM cream 1% for 3 weeks - Studies W202, W206, 0301, 0304, W204

Age	%BSA	Conc. range ng/ml	*$AUC_{(0-12h)}$ range ng h/ml	<0.1† ng/ml	<0.5† ng/ml
< 2yrs	<40%	<0.1 -		14 (22.9)	
		<0.5 -			50 (81.9)
	≥40%	<0.1 -		17 (21.5)	
		<0.5 -			38 (48.1)
2-<12 yrs	<40%	<0.5 -	5.4; 7.4; 8.0; 16.4		49 (62.8)
	≥40%	<0.5 -	9.2; 11.0; 18.8		15 (42.9)
12-<18 yrs	<40%	<0.5 -	7.8; 13.4; 15.0		7 (38.9)
	≥40%	<0.5 -			8 (88.9)
≥18 yrs‡	<40%	<0.5 -	2.5 - 6.8		225 (89.3)
	≥40%	<0.5 -	3.8 - 11.4		117 (60.9)

* Values quoted only when concentrations were sufficiently high to enable calculation of $AUC_{(0-12)}$
† n(%) of blood concentration measured below the assay LoQ of 0.1 ng/ml —— or 0.5 ng/ml ——
‡ study W204

In general, there was no evidence for higher systemic exposure in children with higher proportions of body surface area (%BSA) under treatment, with the exception of children < 2 years in study 0304 (Page 86) who showed a statistically significant relationship (p=0.013) between their baseline %BSA (ranging from 10-92%) and their blood concentrations (<0.1 —— ng/ml). The estimated coefficient (slope) was 0.005 implying that a 10% increase of %BSA affected would be associated with a 0.05 ng/ml increase in pimecrolimus blood concentrations. A patient with 90% BSA would have on average pimecrolimus concentrations of 0.4 ng/ml higher than a subject with 10% BSA.

In summary, these studies in pediatric patients with atopic dermatitis have demonstrated that systemic absorption following topical application of ASM cream 1% is consistently low irrespective of age, body surface area, or disease severity. The number of concentrations >0.5 ng/ml ——LoQ:0.5 ng/ml) appears to be higher in young children than in adults. This is consistent with the fact that the surface to body weight ratios in children are greater than in adults.

Reviewer's Comments:

- *Out of six pharmacokinetic studies submitted and reviewed, four (204, 205, 202 and 206) used — and remaining two (301 and 304) used —— as bioanalytical methods respectively. During review of the method validation report for — a few issues —— from 13th Jan, 1998 to 13th Jan, 2001) were raised and communicated to the sponsor via fax. In absence of further clarification, the reviewer initially decided to consider results from the first four studies (204, 205, 202 and 206) as "supportive" and results from the last two studies (301 and 304) as "pivotal". As the last two studies were conducted in infants*

population and in absence of adequate number of samples, AUCs (exposure) could not be calculated, any discussion pertaining to measure of AUC in these studies was scheduled to be modified in the label. The sponsor addressed those issues promptly. However, the reviewer believes that:

- *13 out of 35 (37%) infants (< 2 yrs) reported upper respiratory tract and/or flu, cold like symptoms as opposed to 2 out of 13 (15%) children (2 – 14 yrs) reported similar conditions over a 3-week study period. In contrast, no adult reported similar conditions in 3-week study period. However, 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 301E1. Also, 13 out of 52 (25%) adults (> 18 yrs) also reported similar conditions in 12-month study 205 beyond 3 weeks. Because of the duration (12 months) of the last two studies (205, 301E1), linking those adverse events with the study drug is not justifiable.*

- *Out of 6 high and spurious concentrations reported (mostly undocumented) in all the studies combined, 5 were found in infants.*

IV. Question-Based Review

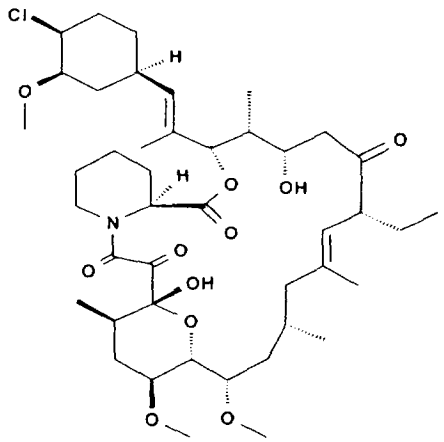
A. General Attributes

1. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product? What is the proposed mechanism of drug action and therapeutic indications? What is the proposed dosage and route of administration?

SDZ ASM 981 (Pimecrolimus), the 33-epi-chloro-derivative of the macrolactam ascomycin, is a novel ascomycin derivative under development for the topical treatment of , atopic dermatitis. These diseases are thought to be related to a dysfunction of the immune system in which activated CD4 T-cells play a crucial role, providing a rationale for the well-established therapeutic use of oral cyclosporin A. Despite impressive efficacy, the systemic long-term use of cyclosporin A is limited by side effects like renal dysfunction, tremor, hirsutism, hypertension etc. Also, topical cyclosporin A is ineffective in

dermatitis, most likely because of insufficient percutaneous penetration of the drug. Beside corticosteroids, there is still only a limited number of topical treatments available.

Chemically, pimecrolimus is (1R,9S,12S,13R,14S,17R,18E,21S,23S,24R,25S,27R)-12-[(1E)-2-{(1R,3R,4S)-4-chloro-3-methoxycyclohexyl}-1-methylvinyl]-17-ethyl-1,14-dihydroxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone. The compound has the empirical formula $C_{43}H_{68}ClNO_{11}$ and the molecular weight of 810.47. The structural formula is:



Pimecrolimus is a white to off-white fine crystalline powder. It is soluble in methanol and ethanol and insoluble in water. Each gram of Elidel cream 1% contains 10 mg of pimecrolimus in a whitish cream base of benzyl alcohol, cetyl alcohol, citric acid, mono- and di-glycerides, oleyl alcohol, propylene glycol, sodium cetostearyl sulphate, sodium hydroxide, stearyl alcohol, triglycerides, and water in the following proportions:

Composition	**Cream formulation (%,w/w)**
Water	
Propylene glycol	
Citric acid	
Sodium hydroxide	
Benzylalcohol	
Sodium cetostearylsulfate	
Cetyl alcohol	
Stearyl alcohol	
Triglycerides	
Oleylalcohol	

2. What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology and biopharmaceutics study data (e.g., if disparate efficacy measurements or adverse event reports can be attributed to intrinsic or extrinsic factors that alter drug exposure/response relationships in patients)?

In all the clinical pharmacology studies, Physician's Global Assessment and/or Eczema Area Severity Index (EASI) scores were used as measures of efficacy and Adverse Events data were used as measures of safety. Frequency and stratification of adverse events by age group in consultation with medical officer has been used to draw final recommendation about pediatric labeling in this review.

B. General Clinical Pharmacology

Pimecrolimus is an anti-inflammatory ascomycin macrolactam derivative and a selective inhibitor of the production and release of pro-inflammatory cytokines and mediators in T cells and mast cells. Pimecrolimus binds with high affinity to macrophilin-12 and inhibits the calcium-dependent phosphatase, calcineurin. As a consequence, it inhibits T cell activation by blocking the transcription of early cytokines. In particular, pimecrolimus inhibits at nanomolar concentrations Interleukin-2 and interferon gamma (Th1-type) and Interleukin-4 and Interleukin-10 (Th2-type) cytokine synthesis in human T cells. In addition, pimecrolimus prevents the release of inflammatory cytokines and mediators from mast cells in vitro after stimulation by antigen/IgE. Pimecrolimus does not affect the growth of, or Interleukin-8 release from, keratinocyte, fibroblast, and endothelial cell lines.

Pimecrolimus exhibits high anti-inflammatory activity in animal models of skin inflammation after topical and systemic application. Pimecrolimus is as effective as the ultrapotent corticosteroid clobetasol-17-propionate after topical application in the pig model of allergic contact dermatitis. In contrast to its efficacy in skin inflammation models, the potential of pimecrolimus for affecting systemic immune responses is low. This has been demonstrated in comparative studies with the immunosuppressants cyclosporin A and tacrolimus. Based on its mechanism of action, pimecrolimus is not expected to have any effect on the HPA-axis.

Studies on the effect of various anti-inflammatory immunomodulatory drugs in the topical treatment of allergic contact dermatitis in pigs gave evidence that ascomycin derivatives, in contrast to cyclosporin A, might be effective in the topical treatment of skin diseases in man. The clinical efficacy of SDZ ASM 981 has been confirmed by proof-of-concept studies in atopic dermatitis for a 1% cream and in established

1. **What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?**

Healing of atopic dermatitis lesions was used as the basis for selecting the response or efficacy endpoints. In all the clinical pharmacology studies, Physician's Global Assessment and/or change of EASI scores were used as measures of efficacy.

2. **Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

Individual blood concentrations of ASM 981 following topical application were determined using ——————————— Again, because of lack of enough PK parameters, establishment of a relationship between exposure and response (i.e, PK and PD) was not possible

3. **What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?**

The pharmacokinetic studies of ASM cream 1% conducted in patients have shown consistently low blood concentrations, with the majority of the levels measured below the assay LoQ. Therefore, no formal PK/PD evaluation was performed in Clinical Pharmacology studies.

4. **How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?**

Four Clinical Pharmacology studies have been performed after single administration of — doses of SDZ ASM 981 in *healthy* volunteers and after repeated — doses in patients with moderate to severe ——————— . However, because of the differences in routes (—vs topical) and diseases ——————— vs atopic dermatitis), comparison of data obtained from these studies with the data obtained from six topical studies under review in this application with *atopic dermatitis* patients will not be very relevant. In absence of any head to head comparison, the following section may provide the best answer to the above question:

Maximal systemic exposure in terms of extrapolated $AUC_{(0\text{-}24h)}$ observed in adults and pediatric patients treated topically with ASM cream 1% for 3 weeks was 23 ng h/ml (W204) and 38 ng h/ml (W202), respectively. This is about 26 and 16 times lower, respectively, than the adjusted $AUC_{(0\text{-}24h)}$ observed at steady state during —— treatment of ——————— with a well tolerated — dose of 60 mg/day of pimecrolimus (590 ng h/ml).

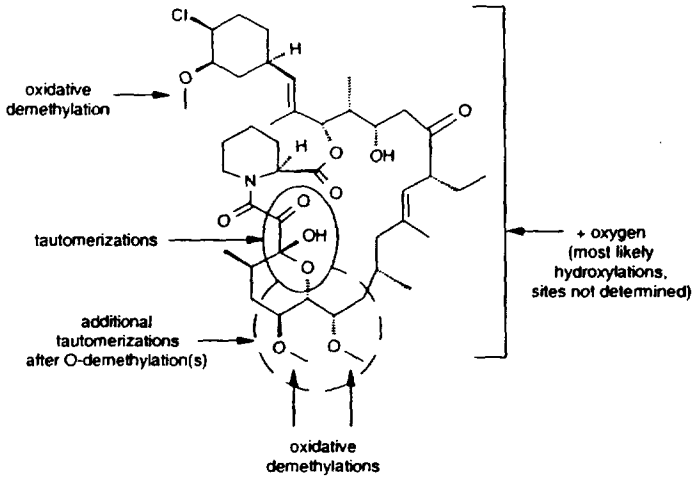
What are the basic PK parameters?

Limited by the low number of samples > LoQ, only AUCs and blood concentrations were used as basic PK parameters.

Does mass balance study suggest renal or hepatic the major route of elimination?

Up to 24 h after an oral dose of 15 mg of [^{3}H]-radiolabeled pimecrolimus to healthy subjects (W124), unchanged pimecrolimus was the major drug related component in blood. The remaining drug related material in blood was comprised of numerous minor metabolites of moderate polarity which appeared to be products of O-demethylations and oxygenation (Figure 1).

Figure 1: Metabolic pathways of pimecrolimus



Drug related radioactivity was excreted principally via the feces, 78% with 2.5% appearing in the urine. The mean total recovery of radioactivity was 80.9%. Parent compound was not detected in urine and <1% of radioactivity in feces was accounted for by unchanged pimecrolimus.

Pimecrolimus was not metabolized or degraded during skin permeation as investigated *in vivo* in the minipig skin and *in vitro* in human skin. The radioactivity recovered in the "stripped" skin at the application site (epidermis and dermis) consisted exclusively of unchanged drug. Studies with human liver microsomes *in vitro* have demonstrated that the metabolism of pimecrolimus is catalyzed principally by members of the CYP3A subfamily (Preclinical data/ Pharm/Tox review).

5. How does the PK of the drug in man compare to that in animals?

The main toxicological studies, i.e. the dermal carcinogenicity study in mice and oral chronic-dose toxicity studies in rats were used to compare the systemic exposure in terms of AUC of pimecrolimus at no-adverse-effect-levels (NOAEL) with that observed in man after topical applications of ASM cream 1% (adult and children).

In a 104-week dermal (painting) carcinogenicity study in mice, no lymphoproliferative disorders were observed up to the highest dose of 4 mg/kg/day corresponding to a mean C_{max} value of 64 ng/mL and mean $AUC_{(0\text{-}24h)}$ value of 1040 ng h/ml. According to Pharm/Tox review, this exposure was about 45 and 27 times higher than the maximum systemic exposure in terms of adjusted $AUC_{(0\text{-}24h)}$ observed in adults and children patients treated topically with ASM cream 1% for 3 weeks, 23 ng h/ml (W204) and 38 ng h/ml (W202), respectively.

In the 26-week oral toxicity study in rats, the most sensitive species, the NOAEL was associated with a mean $AUC_{(0\text{-}24h)}$ of 688 ng h/ml. This exposure was about 30 and 18 times higher than the maximum exposure observed in adult and pediatric patients treated topically with ASM cream 1% for 3 weeks, respectively. These results summarized in Figure 2 provide evidence for a large safety factor for topical use of SDZ ASM 981 cream 1% in adult and children patients.

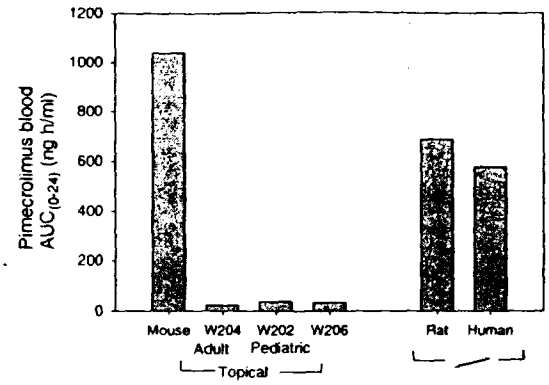


Fig 2: Comparison of maximum $AUC_{(0\text{-}24h)}$ found in adults and children under topical treatment with ASM cream 1% and mean NOAEL $AUC_{(0\text{-}24h)}$ in toxicology species under topical and — ASM treatment and $AUC_{(0\text{-}24h)}$ in adults following — administration of 60 mg/day

6. **What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?**

Due to low systemic absorption and very limited low blood concentrations of pimecrolimus, inter- and intra-subject variability of PK parameters in patients could not be determined.

C. Intrinsic Factors

1. **What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?**

Due to low systemic levels, these factors have not been studied categorically.

2. **Based upon what is known about exposure-response relationships and their variability, and the groups studied (volunteers vs. patients); what dosage regimen adjustments, if any, are recommended for each of these subgroups (examples shown below)? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**

Given the low blood concentrations of pimecrolimus after topical application of the ASM cream 1% and the large safety margin compared with systemic exposure after — administration, pharmacokinetic studies in special subpopulations (e.g., elderly, renal and hepatic impaired subjects) have not been conducted. Also, dose adjustment of pimecrolimus in these subpopulations is not considered to be necessary.

Four studies were conducted in pediatric patients. These studies have demonstrated that systemic absorption following topical application of ASM cream 1% is consistently low irrespective of age, body surface area, or disease severity. The blood concentrations observed were low in comparison to systemic exposure observed in animal studies and in adult patients following — administration at well tolerated doses. The number of concentrations >0.5 ng/ml (— LoQ:0.5 ng/ml) appears to be higher in young children than in adults.

Pregnancy Category C has been suggested for this product by Pharm/Tox reviewer. Because of lack of information in pregnancy and lactation in humans, no suggestion has been given from clinical pharmacology perspective.

D. Extrinsic Factors

1. **What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?**

Due to low systemic levels, these factors have not been studied categorically.

2. **Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.**

Not applicable

3. **Drug-Drug Interactions Studies**

In vitro

In studies with human liver microsomes *in vitro*, pimecrolimus has been demonstrated to be metabolized principally by CYP3A. SDZ ASM 981 was also shown *in vitro* to have small influence on the metabolism of substrates of CYP2C9, CYP2C19 and CYP2D6 (See Pharm/Tox review).

In vivo

Given the consistently low blood concentrations of pimecrolimus and the majority of the levels measured below the assay LoQ after topical application of the cream, no clinically significant interaction of pimecrolimus with co-administered drugs is expected. Similarly, the influence of co-administered drugs on the pharmacokinetics of pimecrolimus is unlikely to be of clinical significance. However because no topical drug-drug interaction studies have been performed with CYP 3A inhibitors during the Clinical Pharmacology development program of the ASM cream 1%, extent and significance of such inhibition

could not be ascertained. Therefore, caution should be exercised during coadministration of CYP 3A inhibitors and ASM cream 1%.

Blood/plasma distribution and protein binding

The moderate binding (70 – 84%) of pimecrolimus to the plasma proteins indicates that a potential drug-drug interaction on the basis of drug-protein binding appears to be very unlikely (See Pharm/Tox review).

E. General Biopharmaceutics

BCS classification system and related issues are not applicable for this topical cream formulation.

F. Analytical Section

1) How are the active moieties identified and measured in the blood in the clinical pharmacology and biopharmaceutics studies?

By ————————————

2) What bioanalytical methods are used to assess concentrations?

Concentrations of pimecrolimus have been determined in blood by a ———— ——— method (Study numbers 202, 204, 205 and 206) and by ——— ———————————— Study numbers 301 and 304).

In Vivo Analytical Methods Summary

Study no:	Biological fluid	Method	Sensitivity of method (range) (ng/mL)
ASMW204	blood	[redacted]	
ASMW205	blood		
ASMW202	blood		
ASMW206	blood		
ASM 0301	blood		
ASM0304	blood		[redacted]

*depending on the run

The high sensitivity afforded by both of these assays is considered to provide sufficient information on blood concentrations of pimecrolimus to enable meaningful evaluation of the systemic safety following topical application to patients. The limit of quantification was 0.5 ng/ml and 0.1 ng/ml for the ———————— methods, respectively. Both assay methods were fully validated. The limit of quantification (LoQ) was based on an accuracy and precision of ———— and of ———————— A brief description of each method is given in the following section.

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V. Detailed labeling recommendations

The following changes are suggested. ~~ABC~~ suggests deletion of text and **ABC** suggests insertion of new text:

Pharmacokinetics

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Labeling

Pharmacokinetics

Absorption

In adult patients being treated for atopic dermatitis (13-62% Body Surface Area (BSA) involvement) for periods up to a year, blood concentrations of pimecrolimus are routinely either at or below the limit of quantification of the assay (<0.5ng/ml). In those subjects with detectable blood levels they are routinely < 2ng/ml and show no sign of drug accumulation with time. Because of the low systemic absorption of pimecrolimus following topical application the calculation of standard pharmacokinetic measures such as AUC, C_{max}, $T_{1/2}$, etc cannot be reliably done.

Distribution

In vitro studies of the protein binding of pimecrolimus indicate that it is 74 – 87% bound to plasma proteins.

Metabolism

Following the administration of a single oral radiolabeled dose of pimecrolimus numerous circulating O-demethylation metabolites were seen. Studies with human liver microsomes indicate that pimecrolimus is metabolized in vitro by the CYP 3A sub-family of metabolizing enzymes. No evidence of skin mediated drug metabolism was identified in vivo using the minipig or in vitro using stripped human skin.

Elimination

Based on the results of the aforementioned radiolabeled study, following a single oral dose of pimecrolimus ~81% of the administered radioactivity was recovered, primarily in the feces (78.4%) as metabolites. Less than 1% of the radioactivity found in the feces was due to unchanged pimecrolimus..

Special Populations

Pediatrics

The systemic exposure to pimecrolimus from Elidel 1% cream was investigated in 26 pediatric patients with atopic dermatitis (20-69 % BSA involvement) between the ages of 2 to 14 yrs. Following twice daily application for three weeks, blood concentrations of pimecrolimus were consistently low < 3ng/ml, with the majority of the blood samples being below the limit of quantification However, the children (20 children out of total 23 children investigated) had at least one detectable blood level as compared to adults (13 adults out of total 25 adults investigated) over a 3-week treatment period. Due to the low and erratic nature of the blood levels observed, no correlation could be made between amount of cream, degree of BSA involvement, and blood concentrations. In general, the blood concentrations measured in adult atopic dermatitis patients were comparable to those seen in the pediatric population.

Renal Insufficiency

The effect of renal insufficiency on the pharmacokinetics of topically administered pimecrolimus has not been evaluated. Given the very low systemic exposure of pimecrolimus via the topical route, no change in dosing is required.

Hepatic Insufficiency

The effect of hepatic insufficiency on the pharmacokinetics of topically administered pimecrolimus has not been evaluated. Given the very low systemic exposure of pimecrolimus via the topical route, no change in dosing is required.

Drug Interactions

VI. Appendices

A. Package Insert (annotated)

B. Clinical Pharmacology and Biopharmaceutics Individual Study Reviews

- Study ASM W204
- Study ASM W205
- Study ASM W202
- Study ASM W206
- Study CASM981 301
- Study CASM981 301E1
- Study CASM 304

C. Cover Sheet and OCPB Filing/Review Form

/S/

Tapash K. Ghosh, Ph.D. 11-30-01
Pharmacokineticist/DPE III

Team Leader: E. Dennis Bashaw, Pharm.D. /S/ 11/30/01

CC: NDA 21-302 (DFS)
HFD-540/Div File
HFD-540/CSO/Wright
HFD-880(Bashaw/Ghosh)
HFD-880 (Lazor/Selen)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tapash Ghosh
11/30/01 10:07:21 AM
BIOPHARMACEUTICS

Dennis Bashaw
11/30/01 11:27:14 AM
BIOPHARMACEUTICS

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Appendix A

Package Insert (annotated)

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Labeling

Appendix B

Clinical Pharmacology and Biopharmaceutics Individual Study Review

- Study ASM W204
- Study ASM W205
- Study ASM W202
- Study ASM W206
- Study CASM981 301
- Study CASM981 301E1
- Study CASM 304

NDA: 21-302/Study ASMW 204 Study Date: April '97 – September'97

DETERMINATION OF SDZ ASM 981 BLOOD CONCENTRATIONS AFTER REPEATED APPLICATIONS OF THE 1% FINAL MARKET FORMULATION CREAM ON THE LESIONAL SKIN OF PATIENTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS

Objectives:

Primary: To determine the blood concentrations of SDZ ASM 981 when applied as the 1% final market formulation (FMF) cream twice daily for 3 weeks to the lesional skin in patients with moderate to severe atopic dermatitis.

Secondary: To evaluate the topical and systemic tolerability of the 1% SDZ ASM 981 FMF cream, administered twice daily for 3 weeks to the lesional skin in patients with moderate to severe atopic dermatitis.

To collect data on the efficacy of the 1% SDZ ASM 981 FMF cream by recording the score of a target area according to Hanifin, the overall evaluation according to Abrams, and the SCORAD.

Study Design:

This was an Open-label, multiple topical dose pharmacokinetic study. The study consisted of a one-day to 2-week screening period, a one-day baseline period (denoted "Day -1", the day before the first application), a treatment period of 3 weeks (starting on "Day 1", the first day of application), and an end-of-study evaluation one week after the last application of SDZ ASM 981. It was performed in patients with extensive lesions treated in the hospital under controlled conditions and nevertheless as in the normal clinical use. It was therefore expected to provide relevant data about the systemic exposure to SDZ ASM 981 after repeated applications on large surface areas of affected skin. The amount of cream applied on the skin was not predetermined but was measured by weighing of the tubes during the treatment phase. This allowed an estimation of the amount, which was spontaneously applied, in normal clinical use. In extreme conditions of total body involvement and application of 3 mg cream/cm^2, the nominal dose of SDZ ASM 981 applied would have been 600 mg (10 mg/kg). However, since SDZ ASM 981 should induce a clearing of the lesions, the dose applied was expected to be decreased after a few days of application. 12 adult patients (8 males and 4 females) over 18 years of age with moderate to severe atopic dermatitis planned, entered and completed the study. The individual demographic data and descriptive statistics are summarized below.

Demographic characteristics - Mean (Minimum - Maximum)

Age [years]	Height [cm]	Weight [kg]
34.5 (19 - 45)	178.9 (165 - 203)	75.2 (52- 104)

The 1% SDZ ASM 981 FMF (final market formulation) cream (50 g tubes, — #3744737.00.008, Batch #Z062 0996) was applied onto the dermatitis lesional skin. All lesions were treated, including those on the face. The patients were hospitalized for the first week of treatment i.e. from day -1 to day 6. Then, they could pursue the last 2 weeks of treatment as out-patients. The patients were asked to come to the study center for a once a week evaluation visit (days 10 and 17) and on the day following the last application (day 22). From day 1 to the morning of day 6, the cream was applied by the investigator's staff in the morning and in the evening and the amount of cream applied was determined by weighing the tube(s) of cream used before and after each application. From the evening of day 6 to the last application, the cream was applied by the patient herself/himself and the amount of cream applied was determined by weighing the tube(s) of cream used at each visit (on days 10, 17 and 22). On the days of visit (10 and 17), the cream was applied in the morning by the patient herself/himself at the study site and the tubes weighed before and after application.

PK Measurements: Blood samples were collected repeatedly (maximally up to 12 hours after application) in order to determine the SDZ ASM 981 blood concentrations. Treatment had to be discontinued in the first week if the $AUC_{(0\text{-}12h)}$ measured at day 2 was higher than 50 ng.h/ml and in the second week if the $AUC_{(0\text{-}12h)}$ measured at day 6 was higher than 30 ng.h/ml.

Blood samples were collected to measure SDZ ASM 981 blood concentrations on:
Days 1, 2, 3, 4: 0, 2, 4, 6, 8, 12 hours after the morning application
Day 6: 0, 2, 4, 6, 8 hours after the morning application
At outpatient visits (days 10 and 17): 0, 2, 4, 6 hours after the morning application
Day 22 and end-of-study evaluation: single random sample

SDZ ASM 981 blood concentrations were determined using a ———————— (LOQ = 0.5 ng/ml) developed by Novartis Pharma AG. If the SDZ ASM 981 blood concentrations were quantifiable, the following noncompartmental pharmacokinetic parameters were calculated from each blood concentration versus time profile using standard methods: $C_{max,b}$, $C_{min,b}$, t_{max}, $AUC_{(0\text{-}12h)b}$. $AUC_{(0\text{-}12h)b}$ was not computed when the blood concentration profile included less than three quantifiable concentrations.

Efficacy Measurements: The primary efficacy variables of interest, the Hanifin score and SCORAD index scoring were performed at different time points during the study. The Hanifin score is defined as the sum of the six ordinal scales of erythema, oozing/crust, papulation, lichenification, excoriations and pruritus. Each ordinal scale is on a four-point

rating, from 0 (absence) to 3 (severe stage). Overall evaluation was further calculated from the Hanifin score. The SCORAD is a composite scoring index for atopic dermatitis including the evaluation of extent of the atopic lesions (A) using the rule of nine, of the intensity of the disease (B) using a four-point rating, from 0 (absence) to 3 (severe stage), for erythema, edema/papulation, oozing/crust, excoriation, lichenification, and skin dryness, and of subjective symptoms for pruritus and sleep loss (C) recorded on a 10 cm Visual Analog Scale. The SCORAD index is then defined by the following formula: A/5 + 7B/2 + C. Individual and summarized values of the Hanifin score, the SCORAD index, the SCORAD extent score, the SCORAD intensity score, the sum of the SCORAD pruritus and sleep loss scores and the SCORAD pruritus score were tabulated and plotted. For these variables, difference from baseline and percentage change from baseline were summarized. The mean percentage change from baseline was plotted against the evaluation timepoints. The relationship between the extent of lesions and the SDZ ASM 981 blood concentrations ($AUC_{(0\text{-}12h)}$) was explored.

Results:

Pharmacokinetics: Individual blood concentrations of SDZ ASM 981 measured on Day 1 to 4, Day 6, Day 10, Day 17, Day 22 and at end-of-study together with the associated amount of SDZ ASM 981 [mg] applied are listed in Tables 1 and 2. Summary of individual pharmacokinetic parameters (C_{max}, t_{max}, $AUC_{(0\text{-}12h)}$, C_{min}) are presented in Table 3. The doses of SDZ ASM 981 applied on the lesional skin of the 12 patients presenting atopic lesions extending on 15 to 59% of their body surface area at baseline ranged from 5 to 294 mg. From the total 444 blood concentrations of SDZ ASM 981 measured in the 12 patients, 344 (77.5 %) were below the limit of quantitation (0.5 ng/ml) and 441 (99.3%) were below or at 1 ng/ml. Only three values were above 1 ng/ml (——— ng/ml). The highest value (— ng/ml) measured in patient 2 on day 3, 2 h postdose, was isolated within the rest of the profile and associated to a blood sample documented to have been taken on a skin area treated with 1% SDZ ASM 981 cream. Therefore, according to the sponsor, this outlying concentration is very likely due to a contamination of the blood sample with the 1% SDZ ASM 981 cream. In the whole, the concentrations were quantifiable from day 2 of application and did not show much accumulation of SDZ ASM 981 beyond day 2 over the three weeks of treatment. The individual AUCs over a dosing interval ($AUC_{(0\text{-}12h)}$) ranged from 0 (non quantifiable) to 11.4 ng.h/ml (not including the outlying concentration value of — ng/nl). Figure 1 shows the synoptic plot of the quantifiable blood concentrations of SDZ ASM 981 (representing 28% of all measurements) in 12 patients with atopic dermatitis during b.i.d. treatment with the 1% FMF cream for 21 days. Figure 2 shows the concentration versus time profile of patient 2 who had the largest area treated (lesions on 59% of his BSA at the start of treatment) and the highest systemic exposure over the study period. The concentration-time profiles displayed a plateau with no proper peak. For the most severe patients (extent of lesions ranging from 42 to 59% of BSA at baseline), the exposure in terms of $AUC_{(0\text{-}12h)}$ was about 11 ——————— times lower than the No-Adverse-Effect-Level exposure observed in the 13-week carcinogenicity study in mice ($AUC_{(0\text{-}24h)}$ of 642 ng.h/ml at NOAEL, 10 mg/kg/day). Since 77.5% of the SDZ ASM 981 blood concentrations were below the limit of quantitation (0.5 ng/ml), descriptive statistics on pharmacokinetic parameters were restricted to the median, minimum and maximum.

Table1: Blood concentrations of SDZ ASM 981 [ng/ml] measured from day 1-day 6 of in-house treatment after repeated b.i.d. topical applications of 1 % SDZ ASM 981 cream in 12 patients with extensive atopic dermatitis lesions (15 to 59% BSA).

Patient/ Time [h]	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9	No. 10	No. 11	No. 12
BSA treated	17 %	59 %	21 %	52 %	46 %	15 %	27 %	42 %	27 %	21 %	57 %	27 %
Day 1												
ASM [mg]	18	131	38	101	82	40	88	261	80	80	209	30
0												
2												
4												
6												
8												
12												
Day 2												
ASM [mg]	20	118	31	229	79	22	101	159	65	72	133	48
0												
2												
4												
6												
8												
12												
Day 3												
ASM [mg]	5	140	68	150	33	39	57	198	24	70	198	74
0												
2												
4												
6												
8												
12												
Day 4												
ASM [mg]	16	174	42	294	60	19	89	205	46	51	265	68
0												
2												
4												
6												
8												
12												
Day 6												
ASM [mg]	9	44	22	119	38	5	39	55	37	48	139	216
0												
2												
4												
6												
8												

Time of sampling (hours post-application), Extent of the atopic lesions (% of BSA) at baseline. N.S.: no sample drawn; I.S.: insufficient sample for analysis. Note: concentrations below the limit of quantitation (**0.5** ng/ml) were set to zero

Table 2: Blood concentrations of SDZ ASM 981 [ng/ml] measured during the out-patient treatment at days 10, 17, 22 and end-of-study after repeated b.i.d. topical applications of 1 % SDZ ASM 981 cream in 12 patients with extensive atopic dermatitis lesions (15 to 59% BSA).

Patient/ Time [h]*	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9	No. 10	No. 11	No. 12
BSA treated**	17 %	59 %	21 %	52 %	46 %	15 %	27 %	42 %	27 %	21 %	57 %	27 %
Day 10												
ASM [mg]	11	46	11	144	37		39	120	UNK	62	57	79
0 2 4 6	[											]
Day 17												
ASM [mg]	11	54	15	138	49		28	102		31	89	65
0 2 4 6	[											]
Day 22												
Any time	[											]
End-of-study												
Any time	[											]

* Time of sampling (hours post-application); ** Extent of the atopic lesions (% of BSA) at baseline; N.S.: No sample drawn
Note: concentrations below the limit of quantitation (0.5 ng/ml) are set to zero

Table 3: Summary of PK parameters [C_{max} (ng/ml), t_{max} (h)*, AUC_{0-12h} (ng.h/mL) and C_{min} (ng/mL)] of SDZ ASM 981 measured after repeated b.i.d. topical applications of 1 % SDZ ASM 981 cream in 12 patients with extensive atopic dermatitis lesions (15 to 59% BSA).

Day	C_{max} (ng/ml)				t_{max} (h)		AUC_{0-12h} (ng.h/mL)[b,c]				C_{min} (ng/mL)]			
	Mean (n)[a]	Med	Min	Max	Min	Max	Mean (n)	Med	Min	Max	Mean (n)	Med	Min	Max
1	0.042(12)	0.00	0.00	0.50	8.0	8.0	0.00(10)	0.00	0.00	0.00	0(12)	0.00	0.00	0.00
2	0.23(12)	0.20	0.00	0.90	6.0	12.0	1.78(8)	0.00	0.00	8.40	0.18(12)	0.00	0.00	0.70
3	0.26(11)	0.20	0.00	4.60[d]	2.0	12.0	1.86(10)	1.50	0.00	8.60	0.21(12)	0.00	0.00	1.10
4	0.23(12)	0.20	0.00	0.90	0.0	8.0	2.12(10)	0.00	0.00	8.30	0.08(12)	0.00	0.00	0.50
6	0.38(12)	0.50	0.00	1.00	0.0	8.0	2.16(8)	0.00	0.00	6.90	0.23(12)	0.00	0.00	1.00
10	0.32(10)	0.00	0.00	0.70	0.0	6.0	2.49(7)	0.00	0.00	6.60	0.24(11)	0.00	0.00	0.70
17	0.44(9)	0.00	0.00	1.40	0.0	6.0	3.71(9)	0.00	0.00	11.4	0.27(11)	0.00	0.00	0.70

[a]: Number of significant figures (above LOQ) used for computation; [b]: The $AUC_{(0-12h)}$ estimated for subject 2 on day 3 does not take into account the contaminated sample concentration at 2 h post-dose — ng/ml).

[c]: $AUC_{(0-12h)}$ not computed when less than 3 quantifiable (≥ LOQ) concentrations.

[d]: Value from presumably contaminated sample, not considered for computation purpose.

Figure 1: Synoptic plot of the quantifiable blood concentrations of SDZ ASM 981 (representing 28% of all measurements) in 12 patients with atopic dermatitis during b.i.d. treatment with the 1% FMF cream for 21 days (Limit of Quantitation, LoQ: — ng/ml)

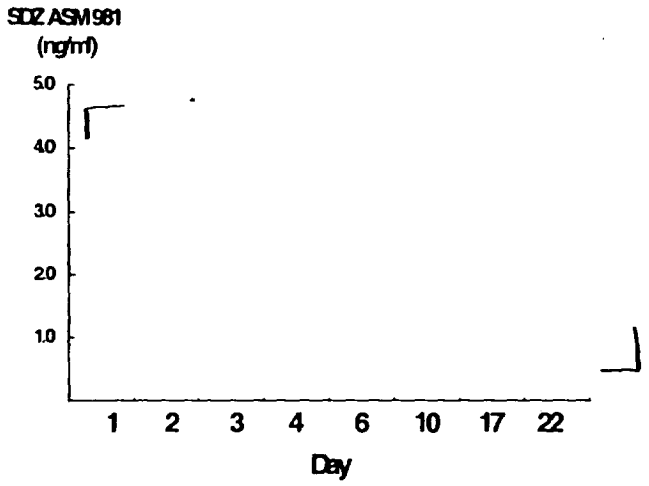
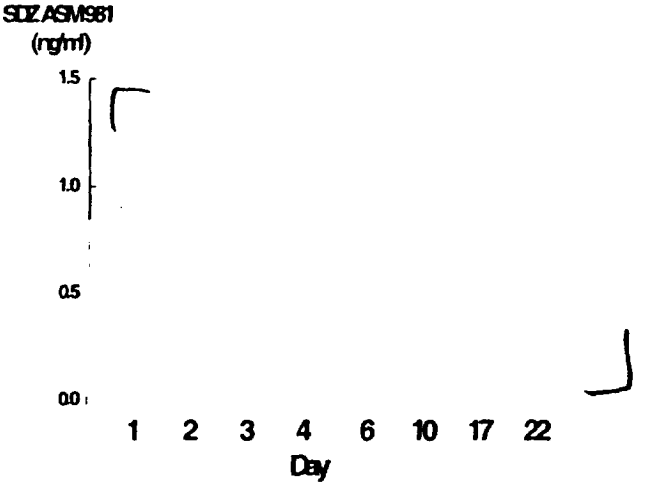


Figure 2: Blood concentrations of SDZ ASM 981 in a patient with extensive atopic dermatitis during b.i.d. treatment for 21 days with the 1% FMF on up to 59% of his Body Surface Area (Limit of Quantitation, LoQ: —ng/ml - Values below the LoQ are set to zero)



Efficacy: In general, the mean percentage change from baseline of the Hanifin score, the SCORAD index and its three components (extent and intensity of the disease, and subjective symptoms of pruritus and sleep loss) showed a rapid decrease (up to 56.9 % for the Hanifin score) during the first 6 days of treatment with SDZ ASM 981 which may be explained by the fact that the patients were hospitalized during this period. This may have reduced the influence of co-factors known to exacerbate atopic dermatitis like stress

and exposure to allergens. Beyond week 1, there was no further decrease of the mean percentage change from baseline scores (showing a plateau with minor fluctuations), except for the extent of disease score which continued to decrease slightly until day 17 indicating that the mean percentage change from baseline was in general maintained. This may reflect the fact that SDZ ASM 981 does not provoke rebound effect (excessive worsening) after discontinuation of treatment, as typically seen with some other treatments like steroids. In light of the low systemic (blood) exposure to SDZ ASM 981, there was no clear relationship between the extent of atopic dermatitis lesions and $AUC_{(0-12h)}$.

Discussion :

Twice daily application of 1% SDZ ASM 981 cream for 3 weeks onto the lesional skin of 12 male and female patients with atopic dermatitis lesions up to 59% of their BSA (baseline) was well tolerated, both locally and generally. No serious adverse event occurred. The most frequent adverse event possibly related to the 1% SDZ ASM 981 cream was a feeling of warmth/burning at the site of application, which was experienced by 6 patients. This event was always rated as mild, and purely subjective. It did not lead to discontinuation of treatment in any of the patients. In conclusion, three weeks b.i.d treatment of atopic patients with extensive lesions (up to 59% of BSA) with the 1% SDZ ASM 981 cream was well tolerated. It resulted in consistently low SDZ ASM 981 blood concentrations, at which no accumulation of concentrations over time was observed.

Comments:

- *The sponsor noted that since 77.5% of the SDZ ASM 981 blood concentrations were below the limit of quantitation (0.5 ng/ml), descriptive statistics on pharmacokinetic parameters were restricted to the median, minimum and maximum. However, the reviewer still computed the mean of those parameters accounting only the significant figures above LOQ (Table 3). It shows a good correlation among C_{max}, AUC_{0-12h}, and C_{min}.*
- *$AUC_{(0-12h)b}$ should not have been computed unless the blood concentration profile included at least three consecutive quantifiable concentrations. However, some AUCs were calculated though the quantifiable concentrations were not consecutive. In case of nonconsecutive concentrations, it remains unclear how computer program considered those points.*
- *The sponsor mentioned that the doses of SDZ ASM 981 applied on the lesional skin of the 12 patients presenting atopic lesions extending on 15 to 59% of their body surface area at baseline ranged from 5 to 343 mg. However, the reviewer found the range between 5 to 294 mg (NOT 343 mg).*
- *The sponsor indicated that for the most severe patients (extent of lesions ranging from 42 to 59% of BSA at baseline), the exposure in terms of $AUC_{(0-12h)}$ was 30 times lower than the No-Adverse-Effect-Level exposure observed in the 13-week carcinogenicity study in mice ($AUC_{(0-24h)}$ of 642 ng.h/ml at NOAEL, 10 mg/kg/day). However the reviewer believes that the ratio to be about 11 times [redacted] (NOT 30 times).*
- *Figures 1 and 2 should have been redrawn with new LOQ of 0.5 ng/ml.*

NDA: 21-302/Study ASMW 205 Study Date: March '98 – July ' 00

DETERMINATION OF SDZ ASM 981 BLOOD CONCENTRATIONS DURING LONG-TERM TREATMENT WITH THE 1% FINAL MARKET FORMULATION CREAM APPLIED TWICE-DAILY FOR UP TO 12 MONTHS IN PATIENTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS

Objectives:

Primary : To determine blood concentrations of SDZ ASM 981 when applied as the 1% final market formulation (FMF) cream twice daily intermittently for up to 12 months to the lesional skin in patients with moderate to severe atopic dermatitis

Secondary : To investigate the long-term safety of the 1% SDZ ASM 981 cream when applied intermittently for up to 12 months in patients with moderate to severe atopic dermatitis

To investigate the efficacy of the 1% SDZ ASM 981 FMF cream in patients with moderate to severe atopic dermatitis treated intermittently for up to 12 months

Study Design:

This open-label, multiple topical dose study consisted of a 13-day (day -14 to -2) screening period, a treatment period of up to 12 months and a post-treatment day (day 1 of month 13 or the day after the last application of SDZ ASM 981). The patients attended visits to the clinic at screening, day 1, week 1, 3 and 6 of treatment, then monthly during the treatment period and at study completion (post-treatment day). The patients applied 1% SDZ ASM 981 FMF cream twice daily (50 g tubes, — # 3744737.00.010 Lot # Z025 0397 and — # 3744737.00.050 Lot # Z105 0999) on all their dermatitis lesions, including those on the face, for up to 12 months. During the study, when patients observed complete clearance of their inflammation and did not experience any pruritus, they were asked to stop SDZ ASM 981 treatment and to restart as soon as their dermatitis recurred. Patients were allowed to stop therapy on the cured lesions while continuing to apply study medication on the more severe or persistent inflammatory lesions.

Forty (40) patients (21 males, 19 females) with moderate to severe atopic dermatitis entered the study; 37 were Caucasian and 3 were Oriental. These patients presented atopic lesions on 13.5% to 61.5% of their body surface area at baseline (day 1) as

calculated from the EASI. Individual demographic data and descriptive statistics are summarized below.

Demographic characteristics at screening, mean (minimum – maximum); n=40

Age [years]	Height [cm]	Weight [kg]
33.9 (19 – 59)	176.9 (159 – 203)	75.0 (56 – 150)

Twenty (20) of them completed 6 months and 13 completed 1 year in the study. Of the 27 patients who did not complete the study, 22 patients discontinued due to an unsatisfactory therapeutic effect, 2 patients (nos. 12 and 16) due to adverse events and 3 patients (nos. 18, 29, 42) were lost to follow-up. Blood samples were collected at the site visits to determine SDZ ASM 981 blood concentrations and to perform safety laboratory tests. SDZ ASM 981 blood concentrations were monitored during the study.

PK Measurements: Blood samples were collected to measure SDZ ASM 981 blood concentrations at screening, on Day 1, 1st day each on Weeks 1, 3 and 6 for months 1 and 2, 1st day each on months 3 – 12, and 1st day on month 13 at the end of the treatment. At each sampling time 2 ml (4 ml at screening, only) venous blood was taken at a site where no SDZ ASM 981 cream was applied. The blood was drawn into EDTA coated polypropylene tubes at the following time points:

- at screening: one blank sample
- at 0, 2 and 4 hours after SDZ ASM 981 cream application (if the patient was under treatment at the time of the visit)

OR

- one blood sample at any time during the out-patient visit in that month *(if the patient was **not** under treatment at the time of the visit)*

SDZ ASM 981 blood concentrations were determined using a [redacted] (LoQ = 0.5 ng/ml) developed at Novartis Pharma AG.

Efficacy Measurements: Efficacy of treatment was measured mainly by two parameters: Overall evaluation score and Eczema area severity index (EASI). Overall evaluation score of dermatitis was performed at the week 1, 3 and 6 visit, at each monthly visit, and at study completion. The Eczema Area and Severity Index (EASI) was assessed at screening, baseline (day 1 before application of study medication), at the week 1, 3 and 6 visit, at each monthly visit and at study completion.

Results:

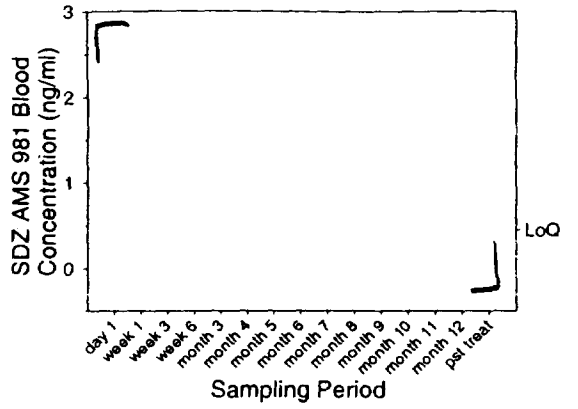
Pharmacokinetics: The individual blood concentrations of SDZ ASM 981 measured between day 1 and month 12 of treatment in the 40 patients enrolled in the study were consistently low. Of the 918 concentrations determined (excluding the blank samples taken at screening), 98% (900 concentrations) were below the limit of quantitation of 0.5 ng/ml. Summary of SDZ ASM 981 blood concentrations > LOQ at various times is reported in Table 1. The maximum concentration observed throughout the entire study was — ng/ml. Concentrations below the limit of quantitation were treated as zero. As the vast majority of blood samples collected contained concentrations of SDZ ASM 981 below the limit if quantitation, determination of standard pharmacokinetic parameters was possible only for patients 1 and 15 on weeks 6 and 15 respectively.

Table 1: Summary of SDZ ASM 981 blood concentrations > LOQ at various times

Patient #	Time [Wk/Mo(Hr)]		Concentration (ng/mL)	$AUC_{(0\text{-}12h)}$ (ng.h/ml)
1	Wk 6	0 hr	—	8.2
		2 hr	—	
		4 hr	—	
3	Post treatment		—	-
6	Wk 6	0 hr	—	-
7	Wk 3	4 hr	—	-
11	Mo 3	4 hr	—	-
12	Wk 6	2 hr	—	-
		4 hr	—	
15	Wk 15	0 hr	—	7.0
		2 hr	—	
		4 hr	—	
	Post treatment		—	
26	Mo 6	0 hr	—	-
28	Wk 3	0 hr	—	-
37	Wk 1	2 hr	—	-
		4 hr	—	
40	Mo 9	0 hr	—	-

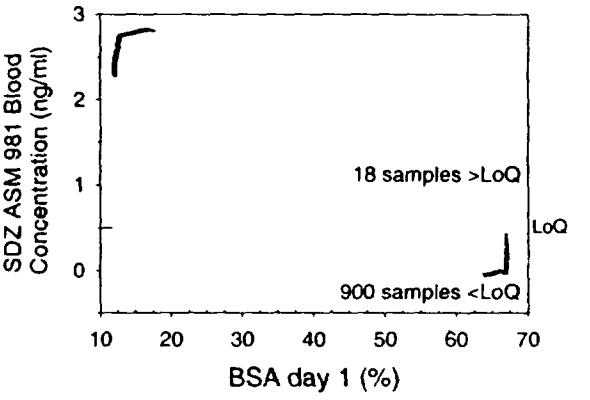
There was no evidence for systemic accumulation of SDZ ASM 981 during multiple topical administration up to 1 year (Figure 1). Blood concentrations remained low even in the patients with the largest body surface area treated (up to 61.5% BSA affected on day 1) (Figure 2). This result was consistent with study ASMW 204.

Figure 1: SDZ ASM 981 blood concentrations at various times during 12 months treatment



(The numbers refer to the number of values superimposed on each symbol)

Figure 2: Body surface area affected on day 1 versus SDZ ASM 981 blood concentrations



The quantifiable blood concentration range —— ng/ml) was similar to or less than the range measured in adults (study ASMW 204) treated under the same dosing regimen for 3 weeks. It was considerably lower than the maximum blood levels observed at steady-state after well tolerated —— administration of 60 mg/day SDZ ASM 981 for 4 weeks in adult —— patients (study ASMW 121, mean C_{max} 54.5 ng/ml).

Given the low blood concentrations measured in these patients, the high proportion of levels below the LoQ, and only with limited number of AUCs, no formal pharmacokinetic/pharmacodynamic (safety-efficacy) analysis was performed in this study.

Efficacy: The efficacy variables were evaluated for the following two populations:

- Intent to treat (ITT) population with the last observation carried forward (LOCF)
- Patients under treatment (PUT) with observed cases, excluding the 3 protocol violators (patients 7, 17 and 22)

The range and median individual body surface area affected by atopic dermatitis as determined from the EASI evaluation at each site visit is represented in Figure 3 below for the PUT population. The range was 13.5% to 57.0% (median 33.0) at baseline (day 1), 2.0% to 70.0% (median 9.0) at month 6, and 2.0% to 25.0% (median 8.0) at month 12.