

Drug Regulatory Affairs**Elidel (pimecrolimus) Cream 1%****NDA 21-302****Briefing Document**

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1 Executive summary

Atopic dermatitis (eczema) is a prevalent skin disease affecting an estimated 35 million Americans, predominantly children. Before the introduction of topical calcineurin inhibitors, studies revealed a significant patient and physician desire for steroid-free topical treatments. Elidel (pimecrolimus) Cream 1% was developed in response to this unmet medical need.

Since the approval of Elidel in December 2001, over 5 million patients have been treated including over 19,000 patients in clinical trials. The average patient prescribed Elidel cream 1% uses 72 g/year and treats their eczema for an average of 45 days of the course of a year.

As of January 15, 2005, a total of 8 malignancies (7 adults, 1 child) have been reported: two malignancies from clinical studies (colon carcinoma and squamous cell carcinoma) and 6 malignancies from post marketing surveillance spontaneous reports. Four out of the six spontaneous reports were lymphomas; two were skin carcinomas (basal cell- and squamous cell-carcinoma). External experts reviewed the available information on the individual lymphoma cases and concluded that there was no evidence for a causal link between the use of Elidel cream and the occurrence of the respective malignancy, based on the type, location, and the time interval between Elidel use and the diagnosis of the lymphoma. Epidemiological analysis shows the number of lymphomas reported with Elidel is below the number typically observed in the general population. The quantitative epidemiological analysis and the qualitative investigation of the spontaneous lymphoma reports do not show a safety signal regarding lymphoma in Elidel treated patients.

Furthermore, data from pharmacokinetic studies, incidence rates of systemic infections and in vivo immunocompetence assessments in humans demonstrate a lack of biological plausibility of a systemic immunosuppressive effect of Elidel cream.

Novartis Pharmaceuticals Corporation remains committed to an on-going post-marketing clinical program to ensure the continued safety of Elidel cream when used to treat atopic dermatitis.

2 Introduction

2.1 Background

Novartis Pharmaceuticals makes this submission in response to the notice of the Food and Drug Administration (FDA) that its Pediatric Advisory Committee will discuss risk evaluation, labeling, risk communication, and dissemination of information on potential cancer risk among pediatric patients treated for atopic dermatitis with topical dermatological immunosuppressants.

This meeting follows a previous meeting held on October 30, 2003, where the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee met to discuss how to approach long-term monitoring for cancer occurrence among patients treated for atopic dermatitis with topical immunosuppressants. At that meeting, the Committee “felt that long term clinical studies would be needed in situations where there is evidence of systemic absorption and systemic effects with potential for serious and long-term complications.”

(Summary minutes: http://www.fda.gov/ohrms/dockets/ac/03/minutes/3999M1_Final.htm) In addition, the Committee recommended information concerning the systemic measure of the immune response to vaccination.

Information in this briefing document details the minimal systemic absorption detected in patients, including children, treated with Elidel, provides evidence that no systemic immunosuppressive effects are observed, and presents data that supports that Elidel has no effect on the vaccination response in children.

Novartis continues to follow through with the post-marketing commitments made with FDA at the time of approval in December 2001. Novartis and the FDA have worked together and are continuing to cooperate on the design of long-term human studies to monitor for cancer occurrence among patients treated for atopic dermatitis with topical immunosuppressants. The first prospective registry was initiated in November 2004 and additional studies are planned to start in 2005.

2.2 Unmet medical need

2.2.1 Key findings

?? Atopic dermatitis (AD), also referred to as eczema, is a common skin disorder affecting an estimated 35 million Americans

?? Ninety percent of eczema patients experience symptoms before the age of five

?? Before the introduction of topical calcineurin inhibitors, studies revealed a significant patient and physician desire for steroid-free topical treatments for atopic dermatitis

As stated above, atopic dermatitis is a disease affecting an estimated 35 million Americans. The prevalence of atopic dermatitis has increased steadily in recent decades, as much as 10-fold in some areas. Based on prevalence data, 90 percent of eczema patients experience symptoms before the age of five, therefore children are particularly likely to suffer from eczema. Up to 20% of infants and young children in the US population will have atopic dermatitis, while the onset of the disease after age thirty is much less common. Children with atopic dermatitis have a 50-80% risk of developing related atopic diseases, such as asthma or allergies.

Atopic dermatitis can have a severe and often under-recognized impact on the quality of life of patients, particularly children, and their caregivers. Eczema can result in distress, embarrassment, anxiety, poor self-esteem, social isolation, and lack of confidence. The itchy skin of atopic dermatitis can lead to significant sleep disturbance and impairment of routine activities, such as participating in sports and social events. Caring for a child with eczema can be stressful for the caregiver.

Studies addressing the patient and physician satisfaction with treatment options (topical corticosteroids mainly) available before the introduction of topical calcineurin inhibitors demonstrated a significant unmet medical need for steroid-free topical treatments:

?? The NEASE study, was conducted by the National Eczema Association of Science and Education (NEASE). This large U.S.-based survey (n=303 for physicians; n=961 for patients) reported that current treatment modalities (i.e., those available in the year 2000) while effective for some, have meaningful limitations with respect to duration of use,

location (e.g., face), and age of patient. The study called for new treatment modalities that better answer the needs of patients in managing AD, especially over the long term.

- ?? In the Charman study, a 200-patient UK study (Charman, 2000), almost 73% of patients admitted being worried about using topical corticosteroids, even though some of the side-effects patients, or their caregivers, were worried about are unlikely to occur with standard topical corticosteroid treatment. One of the most frequent concerns in this study was skin-thinning (35% of respondents). Significantly, almost a quarter (24%) of patients 16 years of age and older and 36% of parents admitted to non-compliance due to safety concerns.

2.2.2 Conclusion

Atopic dermatitis (eczema) is a common skin disorder that affects an estimated 35 million Americans, most often beginning in infancy and childhood. The introduction of topical calcineurin inhibitors for the treatment of atopic dermatitis addresses a clear unmet medical need by offering an important alternative to topical corticosteroids for patients, care-givers and physicians.

3 Patient exposure to Elidel Cream 1%

3.1 Key Findings

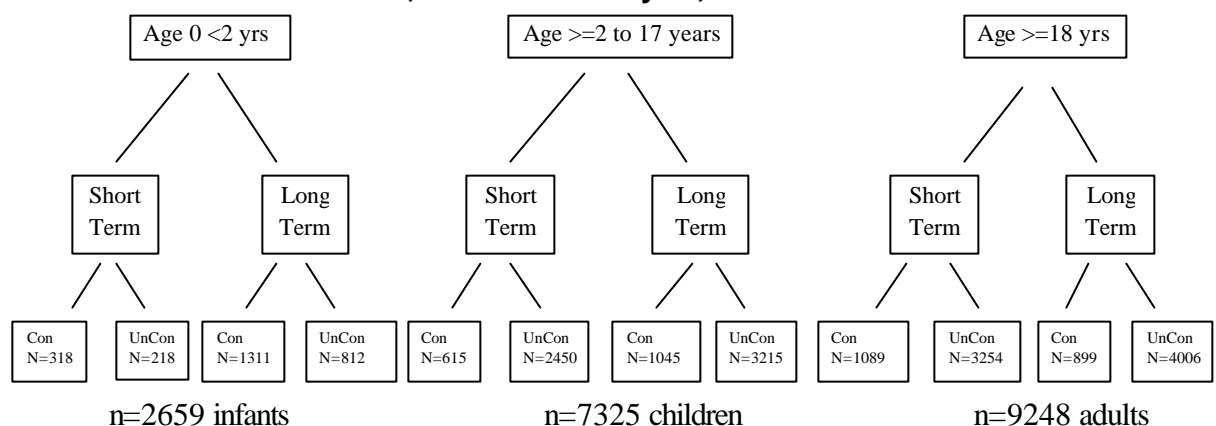
- ?? Extensive clinical experience exists with the use of Elidel Cream in over 5 million patients (including over 19,000 patients in clinical trials)
- ?? More than 50% of patients treated with Elidel Cream are below the age of 10
- ?? Data indicate that the average patient treats for about 45 days over the course of a year and uses on average 72.86 g/year (daily dose= 1.62g/day).
- ?? Estimated world wide patient exposure to Elidel cream is 814,138 person years of which more than 520,000 patient years of exposure occurs in patients below the age 18

3.2 Patient exposure in clinical trials

As of January 15, 2005, more than 19,000 patients have been treated with Elidel Cream 1% in clinical trials worldwide; of these 14% were infants (3 to 23 months), 38% were children (2-17 years), and 48% were adults.

Figure 3-1 below summarizes the total number of patients who have been treated with Elidel Cream in registration and post-registration clinical studies (all indications and all topical formulations) and those who are still participating in studies as of January 15, 2005. Over 23,000 patients participated in clinical trials of which over 19,000 patients have been treated with Elidel Cream (see the Section 9.1 for a full list of studies).

Figure 3-1 Total number of patients exposed to Elidel Cream 1% in clinical trials was over 19,000 as of January 15, 2005



N—number of patients who used Elidel Cream 1% in clinical trials under particular category

Short term—study duration shorter or equal to 6 weeks

Long term—study duration longer than 6 weeks

Con—controlled, studies with control arm

UnCon—uncontrolled, studies without control arm

3.3 Patient exposure with the marketed product

3.3.1 Estimated Defined Daily Dose of Elidel

The defined daily dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication. We estimated Elidel Cream's DDD using market data. The market data estimates that the DDD is 1.62 g/day (i.e., 0.0162 g/day of active substance). This value is attained by dividing the mean amount of cream used per year (72.86g) by the mean number of treatment days (45.2 days).

3.3.2 Age distribution of Elidel Cream 1% users

Based on the analyses of the data from the United Health Care Research Database about 17% of Elidel cream 1% users are infants, 51% are children (aged 2-18yrs) and 32% are adults. United Health Care (UHC) Research Database is a large and geographically diverse health insurance database. UHC has developed a proprietary Research Database with 10 million enrollees dating back to 1990 providing the opportunity to link patient and physician survey data to pharmacy and medical claims, and clinical laboratory results. Ingenix databases house more than 500 million charge records. Underlying information is geographically diverse across the United States. An analysis was conducted to determine the number of patients with AD treated with Elidel Cream and their distribution by gender and age

The age distribution of individuals with AD prescribed Elidel Cream since US launch in 2002 through the March 2004 database update is shown in Table 3-1. Over 54% of the Elidel Cream usage occurs in patients below age 10.

Table 3-1 UHC number of patients with atopic dermatitis with Elidel Cream 1% dispensing by year, sex, and age

		Age group									
Year	Sex	< 2	2-4	5-9	10-14	15-19	20-29	30-39	40-49	50-64	65+
2002	F	318	493	438	250	180	233	260	260	258	23
	M	475	536	367	207	62	109	136	150	158	19
	Total (%)	793 (16.1)	1.029 (20.9)	805 (16.3)	457 (9.3)	242 (4.9)	342 (6.9)	396 (8.0)	410 (8.3)	416 (8.4)	42 (0.9)
2003	F	533	790	747	415	257	408	492	449	370	34
	M	856	949	595	283	112	172	251	216	213	21
	Total (%)	1.389 (17.0)	1.739 (21.3)	1.342 (16.4)	698 (8.6)	369 (4.5)	580 (7.1)	743 (9.1)	665 (8.1)	583 (7.1)	55 (0.7)
2004†	F	264	441	356	211	118	204	223	225	170	22
	M	413	489	328	158	64	69	117	110	94	22
	Total (%)	677 (16.5)	930 (22.7)	684 (16.7)	369 (9.0)	182 (4.4)	273 (6.7)	340 (8.3)	335 (8.2)	264 (6.4)	44 (1.1)
Total (%)§		2.775 (17.2)	3.347 (20.8)	2.595 (16.2)	1.432 (8.9)	734 (4.6)	1.134 (7.0)	1.408 (8.7)	1.329 (8.3)	1.208 (7.5)	125 (0.78)

†Data until first quarter of 2004

§ Totals are calculated avoiding duplication of counts through different years

3.3.3 Estimated patient exposure to Elidel Cream 1% and age distribution (Q3 2002-Q3 2004)

3.3.3.1 Post-marketing patient exposure to Elidel Cream 1% based on commercial sales data

Elidel Cream 1% was first approved in the USA on 13 December 2001. On 15 March 2002, Elidel was registered in the EU and is now approved in over 80 countries. Since launch, 90% of the usage has been in the USA.

Based on post-marketing usage data (Verispan), we have calculated patient exposure considering worldwide sales of active substance (kilograms) divided by the defined daily dose. As of September 30, 2004, total sales since launch of Elidel cream correspond to 4814 kg of substance sold. When translated into exposure data, these numbers yield a total cumulative worldwide exposure of 814,138 person-years worldwide.

Patient Exposure: Methodology & assumptions

Consumption data are derived from Verispan longitudinal data which surveyed 15,000 people to estimate the prevalence of eczema, respondents self-reported the number of days per year they used Elidel Cream. These data track the size and number of prescriptions individual patients filled during a 1-year reporting period. The sample (n=2,987) includes patients suffering from eczema and other dermatitis, and has a representative mix of age and disease severities. Based on these data and assumptions:

?? The average amount of Elidel cream a patient uses per year has been estimated at 72.86g.

- ?? The average number of days per year a patient is treated with Elidel cream was estimated at 45.2 days.
- ?? The estimated Elidel DDD is 1.62g/day (estimated by dividing the mean amount of cream used per year (72.86g) by the mean number of treatment days (45.2).
- ?? The estimated number of patients treatments since launched is more than 5 million (amount of drug sold divided by the amount of drug used per patients in a year = $481,400,000 \text{ g} / 72.86 \text{ g} = 6.6 \text{ million}$. Assuming 25% of patients are treated for more than 1 year with Elidel, the total number of patients treated since launch is over 5 million.)
- ?? The calculated patient exposure is 814,138 person-years worldwide (considering worldwide sales of active substance sold from launch to Sept 30, 2004 (4814 kg) divided by the defined daily dose (DDD) which is 1.62g/day.

4 Malignancies

4.1 Key Findings

- ?? Analysis of the individual case reports (n=8) of malignancies provide no evidence of a causal relationship between the use of Elidel Cream and development of malignancy.
- ?? Two malignancies were reported in clinical trials. Both were classified as not suspected to be associated with Elidel use by the investigators
- ?? Six malignancies have been reported during postmarketing surveillance
 - ?? Of these, 4 case reports were lymphomas (one pediatric case). For cases where enough information was available, they were assessed by external experts as unlikely to be linked to the use of Elidel.
- ?? Epidemiological analysis does not support an increased risk of lymphoma.
- ?? The number of lymphomas observed in Elidel treated patients is below the expected number of lymphomas in both pediatric and adult populations

4.2 Malignancies reported during or after treatment with pimecrolimus in the clinical trials and postmarketing surveillance data

4.2.1 Elidel (pimecrolimus) Cream 1%

To date, 8 cases of malignancies have been reported for Elidel Cream. Six are spontaneous case reports, and two have been reported from clinical trials.

Figure 4-1 provides an overview of the malignancies reported for Elidel Cream. For discussion of key details of these cases, we have separated malignancies into two categories; lymphomas (Table 4-1) and non-lymphoma malignancies (Table 4-2). Following the tables, a more detailed case description, comment from the sponsor, and a medical assessment by external experts (lymphoma cases only) are provided.

Figure 4-1 Malignancies reported for Elidel Cream 1%

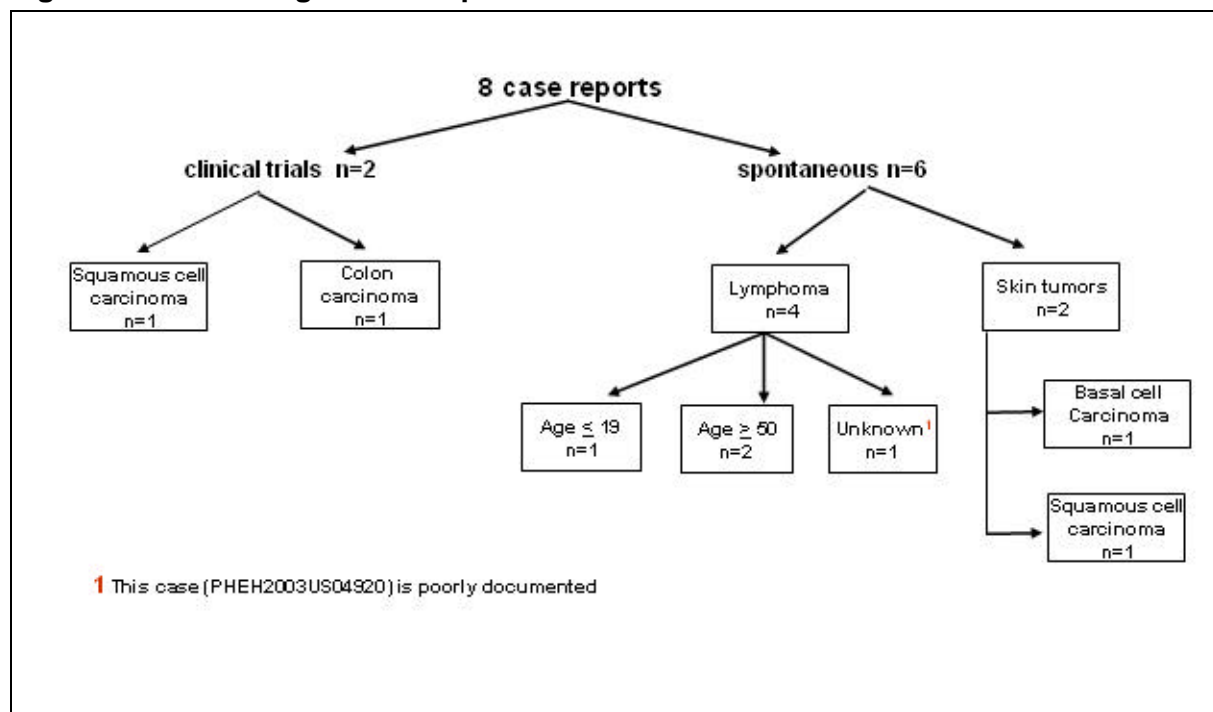


Table 4-1 Lymphomas reported for Elidel Cream 1%

Patient ID source/country	Date reported	Sex/Age	Neoplasm	Localization	Treatment duration and location	Time to treatment start to onset of AE
PHEH2004US01380 Spontaneous/ USA	29 Jan 04	Female /61y	Histiocytic lymphoma	Neck	"few weeks" on arms	"few weeks"
PHEH2004US07674 Spontaneous/USA	14 July 04	Male /2y	Lymphoblastic lymphoma	Mediastinum, Lung	~100g within 6 months on arms and legs (~20% BSA)	6 months
PHBS2004CA12158 Spontaneous/Canada	13 Sep 04	Unknown	Lymphoma	Unknown	Unknown	unknown
PHEH2004US10204 Spontaneous/USA	20 Sep 04	Male /53y	Subcutaneous panniculitis like T-cell lymphoma	Trunk, limbs, left 5th finger leg	6 mo on approx. 60% of BSA	6 months

Table 4-2 Other malignancies reported for Elidel Cream 1%

Patient ID source/country	Date reported	Sex/Age	Neoplasm	Localization	Treatment duration	Time to treatment start to onset of AE
PHBS2004CA06077 Spontaneous/Canada	5 May 04	Male /53 y	Basal cell carcinoma	Nose	14 days on nose	5 months
PHNR2004AU01498	12 Oct 04	Female/71y	Squamous	Vulva	3 weeks	4 weeks

Patient ID source/country	Date reported	Sex/Age	Neoplasm	Localization	Treatment duration	Time to treatment start to onset of AE
Spontaneous/Australia			cell carcinoma			
PHNU2004DE01381 Clin Trial/Germany	30 Mar 04	Male/74y	Colon carcinoma	Colon	Unknown	Unknown
PHHO2004GB03487 Clin Trial/UK	05 Mar 04	Female/65y	Squamous cell carcinoma	Left forearm	ongoing	~1 month

Three external experts evaluated each lymphoma case. All three experts individually concluded that the available evidence does not support a causal relationship between Elidel and lymphoma. The complete report from each expert can be found in Appendix 1.

PHEH2004US01380 - Histiocytic lymphoma

This 61-year-old, otherwise healthy female patient reportedly without remarkable medical history or medication, was diagnosed with histiocytic lymphoma of the neck (confirmation by biopsy). Neither the results of the biopsy, nor the date of the diagnosis of the lymphoma was reported. The patient had been used Elidel Cream for eczema on her arm in an unknown frequency and amount a few weeks prior to the diagnosis of a histiocytic lymphoma. The patient was subsequently administered an unknown type of chemotherapy, is as of March 2004 in remission, and is followed by an oncologist. The reporting physician noted that the patient had been used hair dyes for a very long time and that this in his view might have contributed to the development of the lymphoma.

Sponsor comment: The overall treatment duration with Elidel Cream 1%, the low systemic exposure with topical use of Elidel Cream 1%, but especially the very short interval between Elidel treatment and the diagnosis of lymphoma (only a few weeks) makes a causal relationship of Elidel in the induction of lymphoma in this patient very unlikely. The remark on hair dyes of the reporting physician refers to the hypothesis of a possible relationship between use of hair dyes and occurrence of lymphoma that was controversially discussed in the past. Recent published epidemiological study suggest that there might indeed be a relationship between the use of hair dyes and lymphoma [Zhang Y, 2004]

Background information on histiocytic lymphoma:

Histiocytic lymphoma is a non-Hodgkin lymphoma of intermediate to high malignancy, characterized by the presence of large tumor cells that resemble histiocytes morphologically but are now considered to represent lymphomas of T or B lineage, especially anaplastic large cell lymphoma. The most common sites of involvement are lymph node, gastrointestinal tract, skin, and soft tissue. Regardless of site, this tumor has an aggressive behavior and most often presents with a high stage of disease. Courses with only singular involvement of any of the sites are known, and especially, if only the skin is affected, the prognosis might be much better. The incidence of non-Hodgkin lymphoma has increased during the past decades, making it to one of the most common malignant neoplasms, especially in the elderly. It increases with age, from about 2.5 cases per 100,000 persons in 20-year-old individuals to nearly 44 cases per 100,000 by age 60.

Summary of external experts' assessments

Two of the experts concluded that the description of this case is not consistent with immunosuppression-related lymphoma and therefore concluded that causality is unlikely. A third expert required more information than is available at this time.

PHEH2004US07674 - Lymphoblastic lymphoma

A 2.5 year-old boy received from 10 Apr 2003 for 2 weeks Elidel twice daily (1 sample tube of 2g daily) for the treatment of atopic dermatitis of mainly legs and arms, covering approx. 20% of the body surface. After two weeks of daily use, the application was reduced to an intermittent use until 13 Oct 2003. The total amount of Elidel Cream used during this timeframe was ~100g. Respiratory distress, poor oral intake, weight loss, sweats and fever for 5 days led to referral to a pediatric oncologist on 13 Oct 2003. A CT scan was performed on [] which showed a mediastinal mass, measuring 11.0 x 12.6 x 9.0 cm involving the anterior mediastinum, infiltrating the carina and anterior trachea with no obstruction of the great vessels; airway was patent. There were small bilateral pleural effusions but no nodules were visible in the lungs. Diagnosis of a lymphoblastic lymphoma was made by biopsy. A bilateral bone marrow aspirate and biopsy was performed on [] which was negative. The metastatic workup did not show any metastatic lesions or hepatosplenomegaly. Immunophenotyping confirmed the lymphoma was of T cell origin. No specific viral serologies were performed. The patient was started on chemotherapy thereafter, to which the patient reportedly responded well.

The diagnosis of atopic dermatitis was made at 1.5 years of age, and both the family history and medical history of the patient are unremarkable.

Sponsor comment: It is not know whether the patient had an underlying (heredity) immunodeficiency or was EBV-positive. From the medical point of view, it seems unlikely that an intermittent use of a topical calcineurin inhibitor for 6 months would induce the development of a lymphoma.

Background information:

Lymphoblastic lymphoma belongs to the rapid growing non-Hodgkin lymphomas (NHL), and occurs mainly in children and adolescents, where it accounts for about 30% of childhood lymphoma. Numerous risk factors, especially different types of hereditary immunodeficiency syndromes have been identified, but also immunosuppressive therapy, e.g., after transplantation may pose the patient at risk developing lymphoproliferative disorder especially of Burkitt lymphoma type.

Summary of external experts' assessments

The experts concluded that this T-cell lymphoblastic lymphoma is typically seen in this age group, and that it is unlikely that this patient developed lymphoma as a result of Elidel therapy.

PHBS2004CA12158 - Lymphoma

Initial physician report received via sales representative: This patient experienced lymphoma 5 months after starting Elidel Cream for vitiligo. Follow-up of the case revealed that a physician had a question about Elidel Cream link with lymphoma because she heard from someone who heard from someone else about a patient who has lymphoma who was or is being treated with Elidel Cream 1%. Out of curiosity and safety she wanted more information.

Sponsor comment: Doubtful case. No clear information is available on the reporter, on the patient, on the diagnosis, on the use of Elidel Cream 1%, and if Elidel Cream was used, in which dose or duration, and in what timely relationship to the diagnosis of the reported lymphoma. The case is not assessable.

Summary of external experts' assessments

The experts concluded that there was insufficient data to comment on causality.

PHEH2004US10204 - Subcutaneous panniculitis like T-cell lymphoma

This 53-year-old patient with a long-standing history of severe generalized atopic dermatitis developed subcutaneous panniculitis like T-cell lymphoma. Treatment of his severe atopic dermatitis consisted over the years primarily of topical corticosteroids and other topics, incl. Protopic ointment. Patient used Protopic ointment intermittently from 18-Dec-2003 to 23-Mar-2004 and Elidel Cream 1% was used intermittently from 14-Mar-2004 to 17-Sep-2004 to the trunk and limbs on approximately 60% of body surface. In early [], the patient developed swollen tender and superinfected masses on fingers, trunk and limbs. Morphologic and immunophenotypic features were assessed as being most consistent with subcutaneous panniculitis-like T-cell lymphoma. CT scans of the chest, abdomen and pelvis revealed only mild axillary lymphadenopathy. The patient is receiving an unspecified chemotherapy for the T-cell lymphoma. The immune histopathology and histopathology is described as follows:

"Sections show skin with dermis and subcutaneous adipose tissue. The surface is ulcerated and intact epidermis is not seen. The dermis and subcutaneous adipose tissue is extensively infiltrated by lymphoma composed of medium sized cells with markedly irregular nuclear contours and a moderate amount of cytoplasm. Occasional cells contain nucleoli. There are several areas with necrosis and adjacent acute inflammation. The neoplastic cells extend into the subcutaneous adipose tissue and from rimming around individual fat cells "necklace."

Immunohistochemical stains were done and show that neoplastic cells are positive for CD3, CD43, some cells for CD7 and a few cells for CD4. There is a loss of CD5, CD2, CD8 and most cells lost CD4 and some cells lost CD7. The neoplastic cells are positive for TIA-1 and Granzyme B. There is no expression by B-cell markers. Morphologic and immunophenotypic features are most consistent with subcutaneous panniculitis-like T-cell lymphoma. The T-cell gene rearrangement studies done was negative."

Sponsor comment: This type of non-Hodgkin lymphoma is a rare lymphoma of adulthood not usually associated with systemic immunosuppression.. Not very much is known about the individual risk factors in this patient. Considering the overall short treatment duration with Elidel Cream 1% on the one hand, and the timeframe in which lymphoma develops, it seems unlikely that Elidel Cream 1% has contributed to the event.

Summary of external experts' assessments

The experts concluded that the presentation of this case is consistent with the usual presentation, morphology and immunophenotype of this rare type of lymphoma. In addition, the interval between duration and development of lymphoma is relatively short. Therefore, a causal relationship with Elidel is unlikely.

PHBS2004CA06077 – Two basal cell carcinomas on the nose

The 53-year-old male patient reportedly used for 14 days Elidel Cream for rosacea in August 2003. He was diagnosed with two basal cell carcinoma on the nose in January 2004. The reporter added a remark that two nodules were already present prior to treatment with Elidel.

Sponsor comment: Treatment dates, duration of therapy and onset of the events are not clearly given in the report. However, basal cell carcinoma is an extremely slow developing and growing tumor, mainly located in sun-exposed areas. Even assuming a worst-case for therapy dates and diagnosis of the tumor (5 months), a causal relationship between the administration of Elidel Cream 1% and the basal-cell carcinoma is very unlikely. The note of the reporter that two nodules were already present prior to treatment supports indicates that the condition was most probably already present prior to therapy start.

PHNR2004AU01498 - Squamous cell carcinoma

This 71 year old female patient developed low grade squamous cell carcinoma of the vulva. The patient had approx 2 year history of hypertrophic vulvar lichen sclerosis, and presented to her physician with superimposed itchy and inflammatory vulvitis. Her condition had not responded to a variety of potent topical corticosteroids including betamethasone valerate, betamethasone dipropionate and methylprednisolone aceponate. Two vulvar biopsies were consistent only with lichen sclerosis. In March 2004, she presented with a suspicious lichenified paraclitoral lesion. She was admitted to hospital for excision of the lesion, which showed only an area of benign hyperplasia. It was noted at this time that the vulvitis improved, and this was attributed to temporary suspension of her topical corticosteroids. A provisional diagnosis of allergy to or intolerance of topical corticosteroids was made. Topical corticosteroids were ceased and she was commenced on Elidel Cream. This was applied twice daily for 3 weeks without improvement. One week after cessation of treatment in Jun 2004 a lesion erupted in the vicinity of the previously excised paraclitoral skin. On examination there was a 1cm nodule on the right labium minor lateral to the clitoris. There was no

lymphadenopathy. The lesion was excised and reported to be a well differentiated squamous cell carcinoma. At the time of reporting, the patient was well and her lichen sclerosis was now well controlled with betamethasone dipropionate 0.05% ointment.

Sponsor comment: Lichen sclerosis is a chronic inflammatory skin disorder which mainly affects the vulvar and perianal areas. There is a 4-6% risk of squamous cell carcinoma for patients with Lichen sclerosis. It is highly unlikely, that the use of Elidel Cream could have led to tumor formation in that short timeframe.

PHNU2004DE01381 - Colon carcinoma

This 74-year-old male patient was included in the post-marketing Elidel patient self observation study with Elidel Cream on 9 Feb 2004. After treatment start the patient was diagnosed as having a colon carcinoma and was hospitalized for a surgery and a subsequent chemotherapy. The physician excluded a causal relationship between the event and Elidel.

Sponsor comment: Co-incident treatment start and diagnosis of colon cancer make a causal link unlikely.

PHHO2004GB03487 - Squamous cell carcinoma

This 65-year-old female patient is taking part in protocol CASM981C2316, a 26-week, randomized, multicenter, double-blind, vehicle-controlled study to evaluate the incidence of atopic dermatitis flares when Elidel Cream is used at the first signs and/or symptoms of atopic dermatitis in adults of 18 years of age and older.

The patient commenced study medication on 1 Dec 2003. The application area was limited to the hands. On 29 Dec 2003, the patient noticed a lesion on her left forearm which was unusual in appearance. It was initially thought this might be an insect bite with associated infection, however the lesion did not resolve. The dermatologist diagnosed probable squamous cell carcinoma and the lesion was excised. The histology confirmed squamous cell carcinoma. The microscopy findings showed a well differentiated squamous cell carcinoma invading the dermis (3.8 mm thick). No vascular invasion was seen. The tumor was 4.2 mm from the deep margin and at least 5.7 mm from the closest lateral margin. The investigator confirmed that the event was not suspected to be related to study medication.

Sponsor comment: In concordance with the investigator, a causal relationship is not suspected. Elidel was not applied to the area where the squamous cell carcinoma was detected.

4.2.2 Oral pimecrolimus (in development)

An oral formulation of pimecrolimus is in clinical development for different indications including severe asthma.

In a completed study in severe bronchial asthma, two malignancies were reported for patients assigned to oral pimecrolimus 30 mg bid. Both case reports involve breast cancer, and for both cases the causal relationship of the drug was assessed as not suspected by the investigators. An overview of the cases is provided in Table 4-3, followed by a case description and the medical assessment of the sponsor.

Table 4-3 Malignancies reported for oral pimecrolimus

Patient ID source/country	Date reported	Sex/Age	Neoplasm	Localization	Treatment duration	Time to onset
PHHO2004IT15765 CT / Italy	04 Nov 04	Female /49y	Breast cancer, bone metastasis	Breast, Bone	89 days	unknown
PHHO2003AR14862 CT / Argentina	17 Nov 03	Female /58y	Breast cancer	Breast	unknown	unknown

PHHO2004IT15765 - Breast cancer, bone metastasis

This 49-year-old patient was taking part in study protocol CASM981D2201, a randomized, double-blind, placebo controlled, parallel group, multi-center study, to assess the efficacy and safety of 12 weeks' treatment with oral ASM981 30 mg bid in patients with severe bronchial asthma. The patient commenced study medication on 7 Mar 2003. In Dec 2003, the patient presented with breast cancer and bone metastases. Treatment included chemotherapy in Sept 2004. At the time of this report the patient's condition had deteriorated. The investigator assessed that this event was not related to study medication.

Sponsor comment: Study case of breast cancer with bone metastasis. In concordance with the investigator, a causal relationship is not suspected due to the short interval between administration of study drug and diagnosis of breast cancer with bone metastasis.

PHHO2003AR14862 - Breast cancer

This 58-year-old female patient was taking part in study protocol CASM981D2201, a randomized, double-blind, placebo controlled, parallel group, multi-center study, to assess the efficacy and safety of 12 weeks' treatment with oral ASM981 30 mg bid in patients with severe bronchial asthma. The patient's relevant medical history included hypercholesterolemia (2000), diet treatment and menopause (1998), no hormonal replacement therapy. The patient commenced study medication on 17 Jun 2003. On 3 Sep 2003, following self-examination, the patient discovered a lump in her right breast. She was referred to a gynecologist. A breast ultrasonography, indicating that the lump was a cyst, was performed on []. A mammography performed on [] showed two areas: a lump in the right breast (inferior) and microcalcification area (superior) in the right breast. The patient was admitted to hospital for breast surgery on []. The surgery was performed on [] and a diagnosis of breast carcinoma was made. A histiopathic report showed ductal carcinoma (2.2 cm) with anatomic borders free of pathology. Axillary lymphatics were also free of pathology. Radiotherapy will be performed over the next weeks. The patient is in apparent good health.

The investigator assessed that this event was not related to study medication as the replication time of the tumor cells is usually longer than 3 months.

Sponsor comment: Study case of breast cancer. In concordance with the investigator, a causal relationship is not suspected due to the very short interval (3 months) between administration of study drug and diagnosis of the event.

4.3 Epidemiological data on the risk of lymphoma in the general population

If we take into consideration the 4 cases of lymphoma reported to date in patients treated with Elidel, the crude estimated reporting rate based on the current exposure data would be 0.49 cases per 100,000 patient-years (95% CI 0.16-1.17). This reporting rate is below the incidence rates for any age group reported for NHL according to the Surveillance, Epidemiology and End Results Program (SEER), USA (Table 4-4).

To assess the risk of lymphoma in patients treated with Elidel Cream, we performed an epidemiological analysis comparing the observed number of cases of lymphoma among Elidel users with the expected number of cases applying the specific cancer rates from the SEER data.

4.3.1 Incidence rates of non-Hodgkin lymphoma in the US general population

The age adjusted incidence rate of non-Hodgkin lymphoma (NHL), all ages, all races, male and female, using 9 SEER cancer registries (1973-2001) is 16.7 cases per 100,000 patient-years. Rates increase with age as shown in table 4-4.

Table 4-4 Incidence rates of non-Hodgkin lymphoma, all ages, all races, male and female, SEER (1973-2001)

Age group	Incidence rate [per 100,000 patient years] (95%CI)
00-19 years	1.0 (1.0 – 1.1)
20-29 years	2.7 (2.6 – 2.8)
30-39 years	6.7 (6.5 – 6.9)
40-49 years	12.7 (12.5 – 13)
>50 years	47.4 (47.1 – 47.8)
50-59 years	23.5 (23.1 – 23.9)
60-69 years	44.2 (43.6 – 44.8)
70-79 years	74.4 (73.4 – 75.3)
>80 years	86.8 (85.4 – 88.3)

In the US, approximately 1,700 children and adolescents younger than 20 years of age are diagnosed with lymphomas each year of which approximately 850-900 are cases of Hodgkin's disease and 750-800 are cases of NHL. NHL incidence increases up until age 4 years where it reaches a plateau of approximately 10 per million which is maintained until the second decade of life when rates increase again.

The table below describes the incidence rates in groups under 19 years with data from the report on lymphomas and reticuloendothelial neoplasms from the US SEER database.

Table 4-5 Incidence rates of non-Hodgkin lymphoma, pediatric ages, all races, male and female, SEER (1990-1995)

Age group	Incidence rate ?
?5 years	0.64
5-9 years	0.82
10-14 years	1.07

Age group	Incidence rate ?
15-19 years	1.63

? Average annual rate per 100,000 adjusted to the 1970 US standard population

4.3.2 Expected incidence of non-Hodgkin lymphoma in Elidel Cream 1%-treated patients

The number of NHL cases reported were below the expected number of cases in both pediatric and adult age groups.

When considering the geographic distribution, more than 90% of usage of Elidel Cream took place in the US. For this reason that we have considered the data on Elidel Cream utilization from a large US claims database and the population incidence rates of lymphoma generated by US cancer registries as appropriate to estimate the expected number of cases of lymphoma in the estimated population exposed to Elidel Cream. We have considered US person-time of exposure to be 90% of the total exposure worldwide according to the DDD.

If we consider the defined daily dose for Elidel Cream to be 1.62 g/day (i.e., 0.0162 g/day active substance), person-time of exposure amounts to 732,724 person-years in the US out of a total of 814,138 p-y worldwide.(Table 4-6).

If we assume that the distribution of person-time of Elidel Cream follows the distribution of prescriptions by age obtained from UHC database (Table 3-1) and apply the age specific incidence rates of non-Hodgkin lymphoma from SEER to that person-time of exposure, we can estimate the expected number of cases of non-Hodgkin lymphoma in the population of patients treated with Elidel Cream. In this calculation, the fourth case could not be included, as no age was provided.

Table 4-6 Person time distribution of Elidel Cream 1% users and observed-expected cases (DDD=1.62 g/day)

Age (years)	?5	5-9	10-14	15-19	20-29	30-39	40-49	=50
Person time of exposure (person-years) ^a	278,842	118,196	65,224	33,431	51,651	64,131	60,532	60,714
% of person time per age group ^b	38	16	8.9	4.6	7.0	8.7	8.3	8.3
Expected Number of cases ^c	1.78	0.96	0.69	0.54	1.39	4.29	7.68	28.77
Reported cases	1	0	0	0	0	0	0	2
One (1) unsubstantiated case of unknown age								
Reporting Rate per 100,000 ^d (95% CI)	0.36 (0.03-1.67)	-	-	-	-	-	-	3.29 (0.66-10.56)

^a (Total person-time based on commercial sales of Elidel Cream 1% x proportion of patient in same age group prescribed Elidel Cream 1% in UHC)/100

^b% of person time per age group according to UHC data (table 3-1)

^c Person time of exposure per age group x SEER Incidence rate of non-Hodgkin lymphoma in the age group per 100,000

^d Reporting Rate per 100,000 persons (Number of cases/ Person time per age group) x 100,000

We specifically studied the age group under 5 years. Lymphoma in this age group is a rare event and the assumption was made that it follows a Poisson distribution. The number of cases expected with such frequency and person time of exposure is 1.78 cases. From a statistical point of view the occurrence of 5 or more cases in this age group would be significant ($p < 0.05$).

The number of cases reported was below the number of expected cases in all age groups after considering the market exposure and age distribution of Elidel Cream users.

4.4 Risk assessment in patients treated with Elidel Cream

The post-approval clinical experience with Elidel Cream 1% is extensive. More than 19,000 patients have been studied in clinical trials since 1996. In addition, post-marketing safety data encompassing 814,138 patient-years since launch are available. With this amount of clinical exposure, it is expected that there will be coincident adverse events reported to Elidel Cream.

Up until December 2004, there have been three documented cases and one non-documented case of lymphoma in Elidel Cream-treated patients, as well as three cases of skin cancer and one case of colon cancer. Individual assessment of cases of malignancies provides no evidence of causal relationship.

The observed number of lymphoma cases in Elidel users is below the expected number of lymphomas cases we would expect considering the amount of Elidel Cream exposure and the incidence rates of lymphoma in the general population.

Because of underreporting in post-marketing surveillance, definite conclusions can not be made. However, the analysis of spontaneous reports do not show a safety signal regarding lymphoma in Elidel treated patients.

5 Assessment of the risk of systemic immunosuppression with Elidel Cream

In humans, an increased risk of skin and systemic malignancies has been reported in patients receiving a combination of systemic immunosuppressants such as oral corticosteroids, azathioprine or calcineurin inhibitors in the context of organ transplantation. The evidence indicates that the risk of malignancy in the setting of immunosuppression for organ transplantation is associated with the overall degree of systemic immunosuppression rather than with a specific immunosuppressive drug [Fortina, 2004; Sheil, 2001]. The increased risk of malignancy in these patients is also considered to be related to the profound and continuous systemic immunosuppression.

Although chronic use of oral corticosteroids have been associated with an increased risk of skin malignancies and lymphoma [Karagas, 2001; Sorensen, 2004], there is no data available on the risk of cancer in patients treated with topical corticosteroids. However, given the limited systemic absorption of topical corticosteroids, it is unlikely that the use of topical corticosteroids is associated with systemic immunosuppression, which is thought to be the basis for increased risk of malignancy associated with such drugs.

Based on this hypothesis, the following section reviews the evidence on the risk of systemic immunosuppression (and thus the potential for malignancy related to immunosuppression) associated with topical application of Elidel Cream.

5.1 Preclinical data

5.1.1 Key Findings

- ?? No evidence for carcinogenic, photocarcinogenic, or mutagenic potential exists in animals with Elidel Cream
- ?? Lymphoma related to systemic immunosuppression has only been observed in animals treated with doses resulting in high systemic exposure to pimecrolimus.

5.1.2 Preclinical studies with Elidel Cream

Topical treatment with Elidel Cream resulted in very low blood drug levels in all species investigated (mostly below 1 ng/mL). The cream formulations were well tolerated by rats, adult and juvenile minipigs. No organ toxicity was observed in any animal species in dermal toxicity studies and no effects on the immune system, such as reduction in lymphocyte counts or medullary atrophy in the thymus, were noted.

There were no carcinogenic effects in the dermal carcinogenicity study in rats with Elidel cream. Pimecrolimus was devoid of photocarcinogenic potential as compared to its vehicle, which shortened the time to appearance of skin papillomas in hairless mice. Such shortening effect of the vehicle on time to onset of skin papilloma has been observed with several excipients and drugs in the mouse model.

5.1.3 Preclinical studies with other formulations of pimecrolimus

Lymphomas were observed in mouse studies with ethanolic solutions of pimecrolimus, which resulted in much higher levels of systemic drug exposure compared with the cream formulation. Systemic exposures (AUC) at doses showing no evidence of systemic immunosuppression in these mouse studies with ethanolic solutions were at least 28 times higher than the highest exposure observed in the dermal clinical studies with adult and pediatric subjects.

Oral toxicity studies testing high doses of pimecrolimus producing high systemic exposures were used for identification of hazard, target organs and for safety considerations. Results indicated that the main target organs at high blood levels of pimecrolimus for extended periods of time were the immune system, reproductive system, kidney, and pancreas. Experience with other calcineurin inhibitors indicates that these are the target organs and toxicities associated with exaggerated pharmacological activity of this drug class.

There was no evidence of a mutagenic or clastogenic potential. In the oral carcinogenicity study in mice, atrophy of lymphoid tissues and an increased incidence of lymphomas was observed. These findings constitute an expression of exaggerated pharmacological activity of pimecrolimus at high dosages for extended periods of time. In the oral carcinogenicity study in rats, an increased incidence of benign thymomas was observed. A finding considered to be rat specific.

Table 5-1 provides a list of comparative systemic exposures of orally administered pimecrolimus in animals, effects related to immunosuppression observed at these exposures, and exposure multiples based on the maximum observed level after topical administration in a pediatric atopic dermatitis patient.

Table 5-1 Comparative systemic exposures of orally administered pimecrolimus in animals and exposure multiples based on topical levels in pediatric atopic dermatitis patients

Study type, route of administration	Species	Dose (LOAEL) mg/kg/day	Effect	AUC(0-24h) [ng·h/mL]	Cmax [ng/mL]	EM based on AUC	EM based on Cmax
Oral carcinogenicity study	Mouse	45	Lymphoma	9821 (m) 12911 (f)	2053 (m) 2204 (f)	261 (m) 343 (f)	790 (m) 848 (f)
26-week oral toxicity	Rat	25	Malignant reticulosis and encephalitis	6012 (m) 11368 (f)	1408 (m) 2524 (f)	160 (m) 302 (f)	542 (m) 971 (f)
26-week oral toxicity	Minipig	30	Arteritis, lymphoid tissue modulation and infections	2455 (m) 2641 (f)	183 (m) 145 (f)	65 (m) 70 (f)	70 (m) 56 (f)
39-week oral toxicity	Cynomolgus monkey	15	IRLD ^{a)}	1480 (m) 1090 (f)	146 (m) 104 (f)	39 (m) 29 (f)	56 (m) 40 (f)
Max observed in AD patients (pediatric, ≥ 40% TBSA)				AUC _{0-24h} 37.6	2.6		

a) The literature seems to suggest that LPD rates in cynomolgus monkeys might be higher than those in man, e.g., for HIV-infected individuals, fatalities caused by LPD account for 5.7% of all HIV-related deaths [Selik, 1995], while some 30-40% of SIV-infected monkeys die by LPD [Habis, 1999; Rezikyan, 1995]. For kidney transplanted patients, the first year post-transplant incidence of LPD is 0.3% [Opelz, 2003] while for monkeys with a kidney allograft, the incidence of LPD is 4-6% in the first 160 days post surgery and for heart and/or lung grafts it is 12%, using a variety of therapeutic immunosuppressive regimes [Schmidtko K, 2002; McInnes, 2002; Reitz, 1982]. To the best of our knowledge, no long term studies in cynomolgus monkeys comparing directly the activity of immunosuppressive drugs such as cyclosporine and tacrolimus have been published.

EM – Exposure margin

In a 39-week monkey oral toxicity study, a dose-related immunosuppressive-related lymphoproliferative disorder (IRLD) associated with lymphocryptovirus (LCV) and other opportunistic infections was observed, beginning at 15 mg/kg/day, corresponding to a mean AUC₍₀₋₂₄₎ value of 1193 ng·h/mL (equivalent to 31 times the maximum individual exposure observed in a pediatric patient in clinical trials). Recovery and/or at least partial reversibility of the effects were noted upon cessation of dosage. This was evidenced by the facts that the 3 animals from the dose group 120 mg/kg/day (AUC₍₀₋₂₄₎ value of 7485 ng·h/mL), which

survived to the end of the 20-week recovery period, showed normalized body weight gain, food consumption, clinical signs and hematology parameters, the absence of visible swellings, and did not have IRLD or LCV-related epithelial lesions. Additionally, studies for hybridization for Epstein-Barr virus-encoded RNA (EBER) and opportunistic infections were negative at recovery.

5.2 Systemic absorption of Elidel Cream in humans

5.2.1 Key Findings

- ?? Minimal systemic absorption was detected in PK studies
 - ?? Even in the youngest patients with the most extensive disease (3 months of age; 92% BSA)
 - ?? Most patients had levels below limit of quantification
- ?? No systemic accumulation was observed during prolonged use
- ?? Large margins in terms of exposure from topical application compared to the lowest oral doses producing immunosuppression in animals
 - ?? Highest transient blood level measured in humans after topical application is about 30 times below the level producing immunosuppression after oral administration in animal studies

5.2.2 Methods

As an assessment of systemic safety, blood concentrations of pimecrolimus and systemic exposure were examined after topical application of the 1% cream in healthy volunteers, as well as in pediatric and adult patients with atopic dermatitis. Since the skin barrier is impaired in patients with AD as compared to healthy volunteers (HV), results in HV have limited clinical relevance. Therefore, this section will focus on results in patients with AD.

In order to provide a worst case scenario concerning systemic absorption of pimecrolimus from Elidel cream, pharmacokinetic studies included patients with moderate to severe atopic dermatitis and extensive body surface area involvement. In addition, attention was paid to include patients as young as 3 months of age, who are known to be more susceptible to systemic absorption of topical drugs because of high body surface area to mass ratio and thinner skin.

During the studies, there was no limitation regarding the amount of total body surface area (TBSA) affected and in the amount of cream to be applied and patients used up to 40g of Elidel cream per application.

Blood concentrations of pimecrolimus were determined by radioimmunoassay (RIA) with a limit of quantification (LoQ) of 0.5 ng/mL or by liquid chromatography/tandem mass spectrometry (LC/MS) with a LoQ of 0.1 ng/mL to 0.25 ng/mL.

5.2.3 Overview of pharmacokinetic studies in patients

Eight studies were performed to evaluate blood levels of pimecrolimus in pediatric (as young as 3 months) and adult AD patients with b.i.d topical administration of the 1% cream. Seven

studies in AD were open-label and non-controlled; one study included a topical tacrolimus ointment 0.1% (Protopic) control group (Table 5-2).

Table 5-2 Pharmacokinetic studies with Elidel Cream 1%

Study	N =	Age	Treatment duration	%TBSA affected at baseline
W202	10	14-52 mo	3 weeks	23-69%
W206 Cohort 1	10	8-14 yrs	3 weeks	21-50%
W206 Cohort 2	8	8-30 mo	3 weeks	28-80%
0301	8	4.9-11.0 mo	3 weeks	25-58%
0301E1	5 out of 301	4.9-11.0 mo	Up to 12 mo, as needed	39-52%
0304	22	3.4-22.7 mo	3 weeks	10-92%
CJP01	17	3 mo-11 yr	22 days	10-48%
W204	12	adults	3 weeks	15-59%
W205	40	adults	1-12 mo	14-62%
C2401	18	adults*	13 days	33-97%
6 mo follow-up				

* In addition 19 patients were treated with tacrolimus ointment 0.1%.

In total 145 AD subjects with 10 to 97% of their body surface area affected at baseline were enrolled. Most of the subjects (70 pediatric and 12 adults) were treated with Elidel Cream 1% for 21-22 days; 18 adults were treated for 13 days, and 5 pediatric (infant) patients and 40 adults were treated for up to 1 year.

5.2.4 Blood concentrations of pimecrolimus in adults and children

In adult AD subjects treated for up to 1 year (W204, W205, C2401), blood concentrations were constantly low (below the LoQ). The single highest blood concentration of pimecrolimus was 1.51 ng/mL (Table 5-3). There was no increase of blood concentration over time in any patient during the 12 months of treatment.

Table 5-3 Pimecrolimus blood concentrations in subjects treated with Elidel Cream 1%

Study	Pop.	Concentration mean*, ng/mL	Pimecrolimus blood Concentration range, ng/mL	Number blood Concs measured	<0.5 ng/mL [†]
W204	adults	0.16	<0.5 - 1.4 [‡]	444	77.5%
W205	adults	0.01	<0.5 - 0.8	900	98.0%
C2401	adults [§]	0.061	<0.25 - 1.51	141	95.7%
W202	peds	0.35	<0.5 - 1.8 [‡]	63	63.5%
W206 Cohort 1	peds	0.38	<0.5 - 2.0 [‡]	77	54.5%
W206 Cohort 2	peds	0.43	<0.5 - 2.0 [‡]	21	52.4%
0301	peds	0.87	0.28 - 2.6	19	21.1%
0301E1	peds	0.50	<0.1-1.94	10	60.0%
0304	peds	0.40	<0.1 - 2.26	100	71.0%
CJP01	peds	0.22	<0.1 - 4.14	76	94.7%

Study	Pop.	Concentration mean*, ng/mL	Pimecrolimus blood Concentration range, ng/mL	Number blood Concs measured	<0.5 ng/mL [†]
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* Overall mean, concentrations below the LoQ were set to 0 for calculation

[†] Assay LoQ (0.5 ng/mL (RIA): W202, W204, W205, W206; 0.1 ng/mL (LC/MS): 0301, 0301E1, 0304)- Assay LoQ 0.25 ng/mL (LC/MS): C2401, 0.1 ng/mL (LC/MS): CJP01

[‡] Excluding a high value associated with a sample documented or suspected to have been contaminated by the cream during venipuncture (4.6 ng/mL [W204], 31.7 ng/mL [W202], >50 ng/mL [W206, 2nd cohort], 36.6 ng/mL [0301], 8.67 ng/mL and 42.18 ng/mL [0304]).

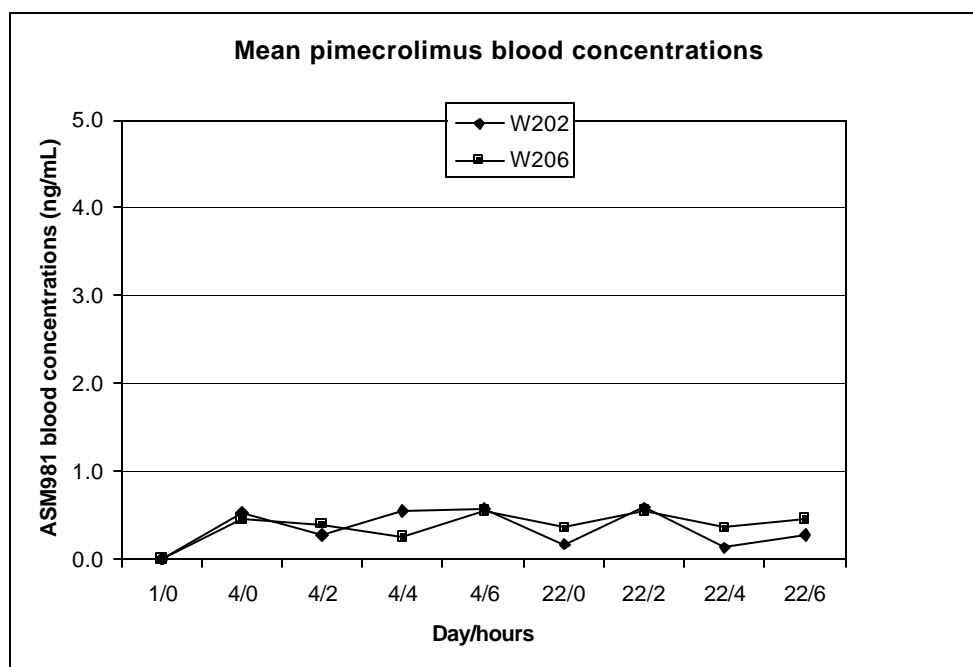
[§] In addition 19 patients were treated with tacrolimus ointment 0.1%. Results presented here are only for pimecrolimus In the tacrolimus group, 36% of samples had drug concentrations above the LOQ of 0.3 ng/mL, and 14% of samples contained more than 1 ng/mL tacrolimus (concentration range <0.3 to 2.39 ng/ml).

In registration studies in pediatric patients (W202, W206, 0301, 0304) from 3 months to 14 years of age blood concentrations were consistently low, typically below 0.5 ng/mL. The single highest blood concentration measured in these studies in pediatric patients was 2.6 ng/mL.

In an additional study CJP01 conducted in pediatric AD patients of Japanese descent (age 3 mo to 11y), blood concentrations were consistently low (94.7% below 0.5 ng/mL). Blood concentrations were not related to body surface area affected. One patient had a blood level of 4.14 ng/mL 3 hr after drug application on Day 10. This patient was a 3 mo old girl with mild AD and only 4% TBSA involved at Day 10 (11% TBSA at baseline). Sample contamination could not be ruled out.

Analysis of the blood concentration over time in studies W202 and W206 (Figure 5-1) showed that the mean blood concentration of pimecrolimus remained below 1 ng/mL with no accumulation over time.

Figure 5-1 Mean Blood concentrations measured in studies W202 and W206



Concentrations below the LoQ were set to 0 for calculation of mean

Excludes suspected sample contamination

5.2.4.1 Blood concentrations of pimecrolimus in infants 23 months of age or below

Very young patients with extended atopic lesions present the highest challenge with regard to safety and efficacy of a treatment. Minimal systemic absorption is an important goal in these patients.

Overall, pharmacokinetic data showed a low exposure of infants to pimecrolimus that was comparable to that in older children under the same Elidel treatment regimens.

The systemic absorption (blood concentrations) of pimecrolimus after topical treatment with Elidel Cream 1% was investigated in 30 infants aged 3 months to 23 months (Table 5-4).

Table 5-4 Summary of pharmacokinetic studies in infants with atopic dermatitis under treatment with Elidel Cream 1% bid for 3 weeks

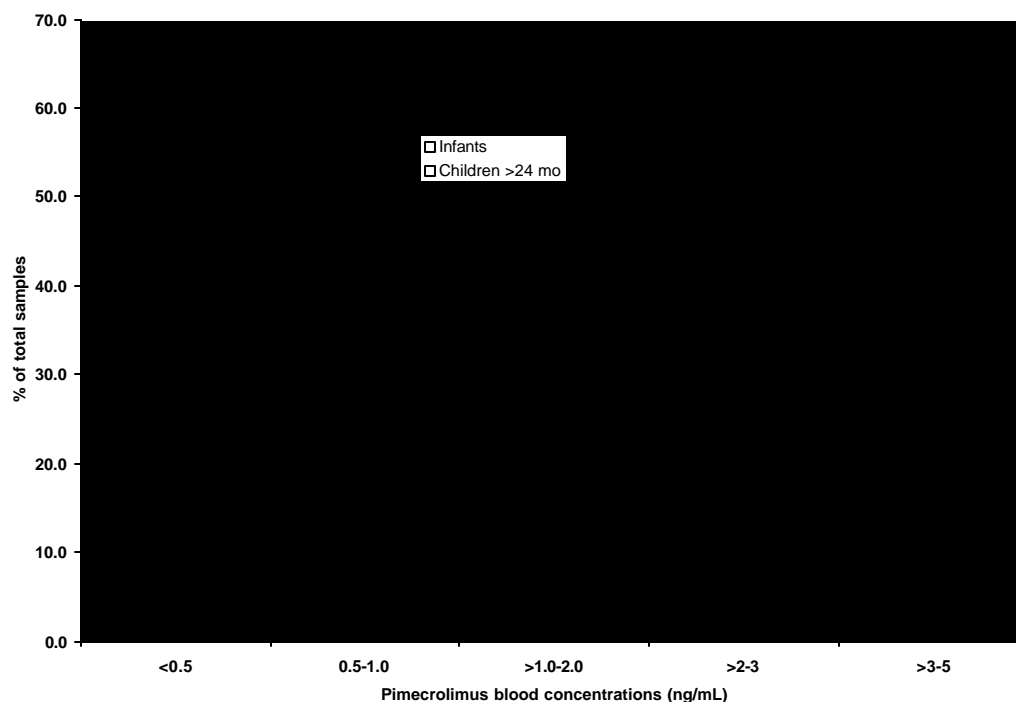
Study	No. of subjects	Age (months)	% BSA affected, day 1	g cream used per application (range)	Assay LoQ (ng/mL)	Pimecrolimus concentration range (ng/mL)
0301	8	4.9-11.0	25-58	0.72-11.2	0.1b	0.28 – 2.6
0301E1	5 from 0301	4.9-11.0	39-52	N/A	0.1b	<0.1 – 1.94
0304	22	3.4-22.7	10-92	N/A	0.1b	< 0.1 - 2.26

a: RIA; b: LC/MS

All infant patients included in the study had moderate to severe AD with up to 92% of TBSA affected. The pimecrolimus blood concentrations were low in all patients and in a range similar to older children (Table 5-3).

Looking separately at the pimecrolimus blood concentrations in infants (up to 23 months of age) and children (24 months of age and older), a similar frequency distribution of the concentrations can be observed (Figure 5-2, pooled data from trials W202, W206, 0301, 0301E and 0304). This shows a similarly low exposure of infants to pimecrolimus compared to older children under the same Elidel treatment regimens.

Figure 5-2 Frequency distribution of pimecrolimus blood concentrations in infants and children (Infants: N=145, Children N=140)



*excluding 5 samples suspected of contamination see footnote ‡ Table 5-3

In summary, these studies in infants and children with AD demonstrated that systemic exposure following topical application of Elidel Cream 1% is consistently low irrespective of age or disease severity. All patients had blood concentrations which were either not detectable or very low in comparison to blood concentrations observed in adults after oral use of pimecrolimus. Even the single highest pimecrolimus blood concentration measured (4.14 ng/mL) in a pediatric patient (3 month old) was only 8% of the mean maximum blood concentration (C_{max}) after oral administration of pimecrolimus showing efficacy in adult psoriasis patients (30 mg b.i.d.).

Based on this minimal systemic absorption, the risk for systemic adverse events with topical use of Elidel cream in pediatric patients is highly unlikely.

5.2.4.2 Effect of body surface area involvement (TBSA) on systemic absorption

In order to assess the effect of body surface area involvement on systemic absorption, we compared the blood concentrations of pimecrolimus between patients who had less than 40% TBSA and patients who had 40% TBSA or more (Table 5-5).

Table 5-5 Summary of systemic exposure by <40% and ≥ 40% TBSA and age group, AD subjects treated with Elidel Cream 1% in registration trials

Age [†]	%TBSA	Concentration mean* (range [§]) ng/mL
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Age [†]	%TBSA	Concentration mean* (range [§]) ng/mL
< 2yrs	<40%	0.26 (<0.1 – 1.0) [§]
		0.09 (<0.5 – 0.9) [§]
	≥ 40%	0.62 (<0.1 – 2.6) [§]
		1.07 (<0.5 – 2.0) [§]
2-<12 yrs	<40%	0.31 (<0.5 – 2.0)
	≥ 40%	0.55 (<0.5 – 1.8)
12-<18 yrs	<40%	0.61 (<0.5 – 1.8)
	≥ 40%	0.06 (<0.5 – 0.5)
≥ 18 yrs	<40%	0.08 (<0.5 – 1.1)
	≥ 40%	0.26 (<0.5 – 1.4)

[†]<2 yrs, Studies 0301, 0301E1, 0304, W206 cohort 2, W202; 2-<12 yrs, Studies W206 cohorts 1 and 2, W202; 12-<18 yrs, Study W206 cohort 2; and ≥ 18 yrs, Study W204.

* Overall mean, concentrations below the LoQ were set to 0 for calculation

[§]Separate ranges of blood concentrations for studies measured with LC/MS (LoQ: 0.1 ng/mL, 0301, 0301E1, 0304) and RIA (LoQ: 0.5 ng/mL, W202, W206 cohort 2, W204).

The analysis shows that the amount of body surface area involved had a very limited effect on the blood concentrations of pimecrolimus after topical application. In three age groups the mean blood concentrations were slightly higher in patients with at least 40% TBSA affected as compared to those patients with less than 40% TBSA affected. In the 12 to <18 years age group, however, the opposite was observed.

5.2.5 Systemic exposure as calculated by AUC in adults and children

Given the majority of blood concentrations below the LoQ observed in both adult and pediatric subjects after topical application, and the limited number of blood samples collected in individual pediatric patients, the area under the blood concentration-time curve (AUC) could only be calculated from a few individuals. As a rule, the individual AUC over a dosing interval (AUC) was computed when at least three consecutive quantifiable blood concentrations of pimecrolimus were available from the individual at a given visit.

In 8 pediatric patients aged 2-14 years presenting at least three consecutive measurable blood concentrations per visit day, AUC_(0-12h) ranged from 5.4 to 18.8 ng·h/mL. In 8 adult AD subjects (W204) the AUC_(0-12h) values ranged from 2.5 to 11.4 ng·h/mL. In another adult study (C2401) systemic exposure, could be calculated for 2 of the 18 patients treated with pimecrolimus, The AUC_(0-10h) for these patients were 2.04 and 2.34 ng·hr/mL.

These results show that the systemic exposure as measured by the AUC was minimal in pediatric and adult patients treated with Elidel cream. For the few patients in whom an AUC could be measured, the systemic exposure was much less as compared to the mean AUC_(0-10h) (295 ng·hr/mL) observed in adult patients treated with 30mg bid oral pimecrolimus for psoriasis, indicating that the systemic exposure after topical application of Elidel is minimal. For the pediatric patient with the highest AUC measured with Elidel Cream, the exposure was only 6% of that observed after oral administration of pimecrolimus in adults, which was associated with clearance of psoriasis.

5.2.6 Exposure based comparison in animals and humans

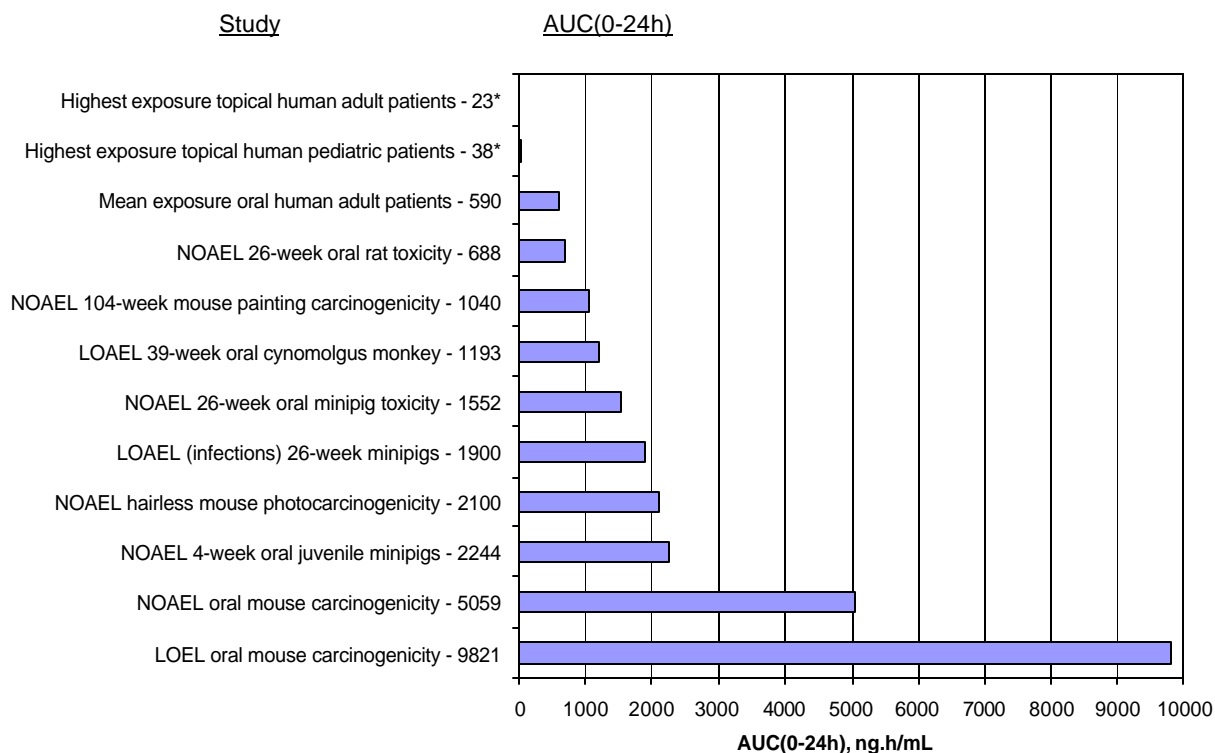
Animal studies with Elidel cream provided no evidence of a safety signal regarding malignancies. However, animals treated with high oral doses of pimecrolimus showed an increased risk of lymphoma associated with high systemic exposure.

In order to provide an assessment of safety margins, a comparison between systemic exposure associated with Elidel cream and systemic exposure in oral pimecrolimus animal studies was made. To assume the “worst case”, the highest systemic exposure observed in an individual pediatric or adult patient was taken as a reference for Elidel cream treatment. As described in section 5.2.5 the highest AUC_(0-12h) in pediatrics and adults patients was 18.8 ng·hr/mL and 11.4 ng·hr/mL, respectively. Thus, the extrapolated AUC_(0-24h) for a b.i.d. dose regimen is 2 x 18.8 = 38 ng·hr/mL in children and 2 x 11.4 = 23 ng·hr/mL in adults.

High safety margins in terms of exposure (AUC) were observed for children compared to Lowest Observed Adverse Effect Levels (LOAEL) in animal studies in cynomolgus monkeys and minipigs (Figure 5-3).

The highest systemic exposure in children treated with Elidel is only 6% of the exposure observed after clinical use of oral pimecrolimus in humans and 3% of the exposure associated with the development of lymphoma in primates.

Figure 5-3 Comparative systemic exposures in animals and man after topical and oral administration



* AUC extrapolated to 24h

5.2.6.1 Conclusions

These data provide evidence that topical treatment with Elidel is associated with minimal systemic exposure compared to the exposure in animals associated with immunosuppression.

5.3 Incidence of infections in patients treated with Elidel Cream

5.3.1 Key Findings

- ?? In clinical trials, no clinically significant differences in the incidence of systemic infections between Elidel cream treated patients and control treated patients were observed.
- ?? When differences were observed in individual studies, no consistent pattern of imbalances was observed
- ?? In a 2-year infant study the incidence of infections was similar in Elidel and vehicle treated patients and did not increase over time.
- ?? No evidence for risk of systemic opportunistic infection was seen with the use of Elidel cream
- ?? The data show an overall increased risk of viral skin infections in Elidel treated children as compared with vehicle patients. This information is conveyed in the prescribing information. The relative risk versus vehicle is 1.6 and the difference between groups is 6.4 events per 1000 patient-months.

5.3.2 Summary of infectious adverse event data from Elidel clinical trials

A critical early indicator of systemic immunosuppression is an increased incidence of systemic infections. Therefore a comprehensive analysis of infections in Elidel clinical trials was performed. In this section, the safety data on infections is summarized for the Elidel cream registration studies (which will be presented in detail later) as well as the long-term post-registration trials with Elidel Cream 1% clinical program following registration. These pooled data encompass an extensive experience with Elidel and provide the quantitative reflection of the infection experience to date.

Data is presented on the incidence density of infections in children ages 2-17 from the following studies:

Registration studies: B305, B307, and B313

Post-registration studies: 2405, 2405E1, 2420, US04, and C2315

Data is also presented on the incidence density of infections in infants less than 2 years of age from the following studies:

Registration studies: 0316 and 0315

Post-registration studies: 2405, 2405E1, 2420, US-04, and DE-04

Data on adult trials are not presented in this document. However a pooled safety analysis from adult trials with Elidel cream was performed and can be found in Appendix 2.

Detailed information on each post-registration study is found in Section 9.3.

Data are presented as the incidence density of infections. This technique takes into account the exact time spent on study. The differences in time on study between the two treatment arms was very high (7114 months for Elidel treated children and 3674 months for vehicle). In addition, because incidence density analysis allows for combination of data from studies of different durations and to look also at the number of events instead of number of patients like in the crude incidence analysis. The incidence density is the number of observed events divided by the number of months of follow-up and is reported as the number of events per 1000 person-months.

Table 5-6 presents the incidence density of the most frequent systemic and skin infections in children 2-17 years of age.

Table 5-6 Incidence density (per 1000 patient-months of follow-up) of the most frequent systemic and skin infections in children 2-17 years of age

Primary system organ class Preferred term	ELIDEL 1% CREAM DB(N=1135) month follow-up=7114 AEs Per 1000 months of follow up	Vehicle DB (N=707) month follow-up=3674 AEs Per 1000 months of follow up	Relative risk	95%CI (1)	p-value (1)	Total Elidel 1% Cream (N=2825) month follow-up=18809 AEs Per 1000 months of follow up
Systemic infections						
Total	189	178	1.060	0.97,1.16	0.224	164
Nasopharyngitis	57.1	56.1	1.018	0.86,1.21	.0836	47.9
Upper respiratory tract infection	20.1	17.7	1.136	0.85,1.53	0.393	21.4
Bronchitis	15.9	17.1	0.926	0.68,1.27	0.626	11.3
Influenza	15.5	10.6	1.457	1.02,2.12	0.044	13.1
Pharyngitis	9.8	5.7	1.721	1.08,2.87	0.029	6.9
Tonsillitis	9.3	9.8	0.947	0.64,1.43	0.792	8.0
Otitis Media	9.0	11.4	0.787	0.54,1.17	0.228	6.3
Gastroenteritis	7.7	5.2	1.495	0.90,2.58	0.131	5.2
Viral infection	7.5	4.6	1.610	0.95,2.86	0.087	4.1
Ear Infection	6.5	4.6	1.397	0.82,2.51	0.238	6.5
Sinusitis	4.8	3.0	1.596	0.84,3.30	0.178	4.1
Gastroenteritis Viral	2.5	3.5	0.715	0.35,1.49	0.357	1.9
Pharyngitis Streptococcal	2.4	1.6	1.463	0.61,4.06	0.423	2.3
Rhinitis	2.2	4.4	0.516	0.26,1.04	0.062	5.5
Enterobiasis	1.5	0.5	2.840	0.76,18.4	0.174	0.6
Pneumonia	1.5	1.9	0.812	0.32,2.21	0.666	1.6
Respiratory tract infection	1.5	3.8	0.406	0.18,0.89	0.025	2.2
Conjunctivitis	1.1	0.8	1.377	0.40,6.29	0.636	0.4
Otitis Externa	1.0	2.2	0.452	0.16,1.26	0.125	0.7

Primary system organ class Preferred term	ELIDEL 1% CREAM DB(N=1135) month follow-up=7114 AEs Per 1000 months of follow up	Vehicle DB (N=707) month follow-up=3674 AEs Per 1000 months of follow up	Relative risk	95%CI (1)	p-value (1)	Total Elidel 1% Cream (N=2825) month follow-up=18809 AEs Per 1000 months of follow up
Urinary tract infection	0.8	2.4	0.344	0.12,0.95	0.043	1.2
Laryngitis	0.7	0.8	0.861	0.21,4.20	0.837	1.3
Lower respiratory tract infection	0.7	0.3	2.582	0.42,49.5	0.386	0.3
Tooth Abscess	0.3	1.1	0.258	0.04,1.32	0.118	0.3
Tracheitis	0.3	1.1	0.258	0.04,1.32	0.118	0.5
Eye infection Bacteria	0	0.8				0
Skin infections						
Total	52.7	45.7	1.153	0.96,1.39	0.126	46.3
Bacterial						
total	25.4	23.4	1.087	0.84,1.41	0.524	22.2
Impetigo	10.5	10.3	1.019	0.69,1.52	0.924	9.6
Folliculitis	3.8	3.0	1.268	0.65,2.67	0.507	3.3
Bacterial infection	3.0	3.0	0.986	0.48,2.12	0.970	1.5
Superinfection	2.4					1.3
Abscess	1.1	0.8	1.377	0.40,6.29	0.636	0.5
Dermatitis infected	1.1	1.4	0.826	0.28,2.73	0.738	1.4
Staphylococcal infection	1.1	2.2	0.516	0.19,1.40	0.186	1.0
Skin bacterial infections	0.4	1.1	0.387	0.08,1.76	0.214	1.1
Fungal						
total	1.7	2.7	0.620	0.27,1.47	0.264	1.9
Skin fungal infection	0.6	0.5	1.033	0.20,7.45	0.970	0.6
Body tinea	0.1	1.1	0.129	0.01,0.87	0.067	0.3
Viral						
total	17.0	10.6	1.602	1.13,2.33	0.010	14.3
Herpes simplex	5.5	2.2	2.518	1.24,5.81	0.017	4.5
Chickenpox	4.2	4.1	1.033	0.56,1.97	0.918	3.7
Molluscum contagiosum	2.8	3.0	0.939	0.46,2.03	0.867	3.1
Skin papilloma	2.0	0.5	3.615	1.01,23.0	0.089	1.6
Herpes simplex dermatitis	1.1	0.3	4.132	0.76,76.6	0.181	0.6

Primary system organ class Preferred term	ELIDEL 1% CREAM DB(N=1135) month follow-up=7114 AEs Per 1000 months of follow up	Vehicle DB (N=707) month follow-up=3674 AEs Per 1000 months of follow up	Relative risk	95%CI (1)	p-value (1)	Total Elidel 1% Cream (N=2825) month follow-up=18809 AEs Per 1000 months of follow up
Skin infection non specified						
total	7.7	8.4	0.916	0.59,1.44	0.697	7.4
Skin infection	6.6	7.9	0.837	0.53,1.34	0.451	4.2
Localized infection	0.7	0.3	2.582	0.42,49.5	0.386	0.4
Parasitic						
total	0.8	0.5	4.549	0.36,10.6	0.592	0.5
Scabies infestation	0.8	0.5	4.549	0.36,10.6	0.592	0.5

Incidence density in 1000 person months=(1000 * number of events during the study / total months of monitoring)

(1) p-value: Poisson regression, 95% CI: log likelihood ratio based confidence interval

Source: Safety summary children and adults PTT 5.1-9a and b (located in Appendix 2)

DB=patients included from double blind phase of the studies

Most frequent defined as incidence density of = 0.7 event in either DB group per 1000 patient-months

These data are inclusive of all data available from the controlled registration and post-registration trials. The large number of patients included for analysis should mitigate against any study-specific factors that might influence an event rate in any given study. The data also provide an insight into the natural history of infections in children with AD.

The most frequent systemic infectious adverse event in children is nasopharyngitis. Nasopharyngitis is the dictionary preferred term for the common cold. Thus it is not surprising that it is the most common infectious event in many of these clinical studies. The rate of nasopharyngitis is 57.1 per 1000 person months in the Elidel-treated patients and 56.1 per 1000 person months in the vehicle control-treated patients. These rates are essentially identical.

The rate for any systemic infection was 189 per 1000 in Elidel-treated patients and 178 for vehicle control. These rates are indistinguishable. Otitis media is another event that occurs with a high frequency in children. For Elidel-treated patients, the rate is 9.0 per 1000 person-months. For vehicle treated patients, 11.4 per 1000 person months.

Four systemic infections showed statistical significant differences between treatment groups. Two (pharyngitis and influenza) were more frequent in the Elidel group and two (respiratory tract infection and urinary tract infections) were more frequent in the vehicle group. This apparent statistical significance is probably more a reflection of a random association due to the high number of statistical tests performed at the 0.05 alpha level without adjustment for multiplicity rather than any clinically meaningful trend.

No other clinically or statistically significant differences were observed for any of the systemic infectious adverse events. This comprehensive analysis supports the premise that any imbalances seen in an individual study are probably random occurrences. Elidel treatment is not associated with a clinically significant increase in systemic infectious adverse events.

For skin infections, the rate for any skin event is 52.7/1000 for Elidel-treated patients and 45.7/1000 for vehicle control. The most common skin infection is impetigo and the event rates are almost identical (10.5 per 1000 for Elidel treated patients and 10.3 for the vehicle control). This also applies to all skin bacterial infections combined (25.4 per 1000 for Elidel treated patients and 23.4 for the vehicle control) and skin fungal infections combined (1.7 per 1000 for Elidel treated patients and 2.7 for the vehicle control).

The category of viral skin infections was significantly increased in Elidel-treated patients. This translates into a difference of 6 cases of these infections per 1000 months (relative risk 1.6). The only individual skin infection to reach statistical significance was that of “herpes simplex”. For these studies, this preferred coding term primarily included the reported event of cold sores. The rates indicate that 5.5 herpes infections would be expected per 1000 person months for patients receiving Elidel and that 2.2 herpes infections would be expected in control patients. Because of the size of the data base, this small difference in event number is statistically significant. However, clinically, this translates into a difference of 3 events per 1000 months of treatment (in predisposed patients). The prescribing information for Elidel Cream contains a precaution regarding viral skin infections.

Table 5-7 presents the incidence density of the most frequent systemic and skin infections in infants less than 2 years of age.

Table 5-7 Incidence density (per 1000 patient-months of follow-up) of the most frequent systemic and skin infections in infants 3-23 months of age

Primary system organ class Preferred term	ELIDEL 1% CREAM DB(N=495) month follow-up=2581 AEs Per 1000 months of follow up	Vehicle DB (N=193) month follow-up=596 AEs Per 1000 months of follow up	Relative risk	95%CI (1)	p-value (1)	Total Elidel 1% Cream (N=1098) month follow-up=7686 AEs Per 1000 months of follow up
Systemic infections						
Total	356	351	1.015	0.88,1.18	0.842	303
Nasopharyngitis	128	114	1.121	0.87,1.47	0.392	105
Upper respiratory tract infection	60.1	65.4	0.918	0.65,1.32	0.632	47.9
Ear infection	30.2	23.5	1.287	0.75,2.37	0.385	18.9
Bronchitis	28.7	33.6	0.854	0.53,1.44	0.532	26.3
Otitis media	21.7	20.1	1.078	0.60,2.11	0.814	20.7
Gastroenteritis	14.7	16.8	0.877	0.46,1.86	0.713	11.7
Tonsillitis	10.5	8.4	1.247	0.52,3.68	0.650	8.2
Influenza	8.1	11.7	0.693	0.31,1.76	0.400	7.3
Lower respiratory tract infection	6.2	6.7	0.924	0.34,3.22	0.887	2.5

Primary system organ class Preferred term	ELIDEL 1% CREAM DB(N=495) month follow-up=2581 AEs Per 1000 months of follow up	Vehicle DB (N=193) month follow-up=596 AEs Per 1000 months of follow up	Relative risk	95%CI (1)	p-value (1)	Total Elidel 1% Cream (N=1098) month follow-up=7686 AEs Per 1000 months of follow up
Pharyngitis	5.8	3.4	1.732	0.49,11.0	0.466	4.2
Conjunctivitis	5.4	1.7	3.233	0.65,58.6	0.257	2.6
Sinusitis NOS	3.9	5.0	0.770	0.24,3.43	0.691	2.3
Viral infection	2.7	10.1	0.269	0.09,0.84	0.018	3.0
Pneumonia	2.3	3.4	0.693	0.16,4.73	0.653	2.3
Gastrointestinal infection	1.2	5.0	0.231	0.04,1.25	0.073	2.3
Bronchiolitis	0.8	3.4	0.231	0.03,1.92	0.143	0.9
Skin infections						
Total	71.3	63.8	1.118	0.80,1.61	0.531	46.6
Bacterial						
total	25.6	25.2	1.016	0.60,1.85	0.956	15.6
Impetigo	10.8	13.4	0.808	0.39,1.90	0.595	7.2
Bacterial infection	6.2	6.7	0.924	0.34,3.22	0.887	3.3
Fungal						
total	14.3	6.7	2.136	0.86,7.13	0.149	8.1
Oral candidiasis	5.4	3.4	1.616	0.45,10.3	0.525	3.0
Skin fungal infection	3.5	3.4	1.039	0.27,6.82	0.961	2.1
Parasitic						
total	1.9	3.4	0.577	0.12,4.03	0.511	0.8
Scabies infestation	1.9	3.4	0.577	0.12,4.03	0.511	0.8
Viral						
total	19.0	11.7	1.616	0.78,3.91	0.235	15.0
Chickenpox	10.8	8.4	1.293	0.54,3.81	0.596	7.5
Viral rash	4.3	1.7	2.540	0.49,46.4	0.372	2.2
Skin infection non specified						
total	10.5	16.8	0.623	0.31,1.35	0.202	7.2
Skin infection	5.8	11.7	0.495	0.21,1.30	0.124	2.9
Superinfection	2.7	3.4	0.808	0.20,5.42	0.791	2.7

Incidence density in 1000 person months=(1000 * number of events during the study / total months of monitoring)
(1) p-value: Poisson regression, 95% CI: log likelihood ratio based confidence interval

Primary system organ class	ELIDEL 1% CREAM DB(N=495)	Vehicle DB (N=193)	Relative risk	95%CI (1)	p-value (1)	Total Elidel 1% Cream (N=1098)
Preferred term	month follow-up=2581	month follow-up=596				month follow-up=7686
	AEs Per 1000 months of follow up	AEs Per 1000 months of follow up				AEs Per 1000 months of follow up

Source: Safety summary children and adults PTT 5.1-9 (located in Appendix 2)

DB = patients included from double blind phase of the studies

Most frequent defined as incidence density of =3.4 event in either DB group per 1000 patient-month

For the infant patient population, nasopharyngitis is the most common infectious adverse event. The rate is more than twice that seen in children in both Elidel and control groups. Respiratory and ear infections occur with more frequency in infants and this is borne out in this analysis.

The rates for all frequent systemic infections are comparable, with rates for some individual terms higher in the Elidel group and others higher in the control group. The only event to reach statistical significance is non-specific viral infection, with incidence higher in the vehicle group.

The same is true for the rates of the skin infections.

This review of pooled data for systemic and skin infectious adverse events from these Elidel clinical trials demonstrates that:

- ?? No overall differences in the incidence of systemic infections between Elidel cream-treated and control groups were observed in these analyses. The few statistically significant imbalances were equally distributed between Elidel and vehicle group.
- ?? Skin infections are common in patients with AD. There is no indication that the overall frequency of these events is increased in patients treated with Elidel
- ?? The data show a increased risk of viral skin infections, mostly herpes simplex skin infections, in Elidel treated children as compared to vehicle treated patients. This information is currently conveyed in the US prescribing information. The relative risk versus vehicle is 1.6 and the difference between groups is 6.4 events per 1000 patients-months.

5.3.3 Summary of infectious adverse event data from Elidel registration trials

The pediatric registration program for Elidel cream involved five trials:

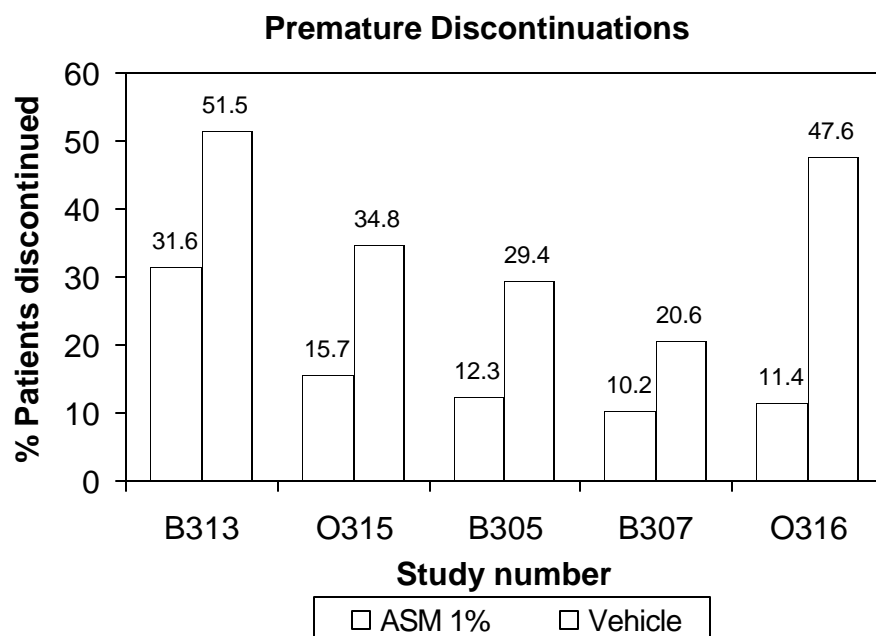
- ?? Two identical short-term six-week studies in children ages 2-17 (Studies B305 and B307)
- ?? One short-term six-week study in infants 3-23 months of age (Study 0316)
- ?? One long-term one-year study in children 2-17 months of age (Study B313)
- ?? One long-term one-year study in infants 3-23 months of age (Study 0315).

5.3.3.1 Systemic infections in registration trials

In order to understand the context of the infectious adverse event data for these trials, it is important to note that there was an appreciably longer time on study for Elidel-cream treated patients versus those in the vehicle control group in these registration studies. Patients in the control groups did not experience the same improvement in symptoms and signs as patients treated in the Elidel cream cohorts. Thus, there was a higher discontinuation rate in the vehicle groups as compared to the Elidel groups, as shown in Fig. 5-4. Premature discontinuations in the vehicle group were on average 2-3 times higher as compared to the Elidel cream group. The main reason (and the only one showing differences between groups) for premature discontinuations was unsatisfactory therapeutic effect.

Consequently and especially in the long-term studies, the mean duration of observation was reduced for patients in the control groups. In Study B313, the mean duration of observation was 304 days for patients in the Elidel cream group versus 235 days in the control group. In Study O315, the mean observation time was 321 days for patients treated with Elidel versus 263 days in the control. Thus, total time on study was 23% less for control patients in Study B313 and 18% less for control patients in Study O315. For adverse events that are very common such as common colds and ear infections, less observation time leads to less overall occurrence for these events.

Figure 5-4 Premature patients discontinuations in studies: B305, B307, B313, O315, O316



The implication of the difference in observation time between treatment groups in these trials is that adverse event data can only be fully evaluated when time on study is also taken into account. In this document, there are two statistical methods that have been utilized for these analyses.

?? Kaplan-Meier analysis. This technique accounts for the first occurrence and timing of an adverse event. All patients are included in the analysis and patients are censored at the time they drop out of the study. Adverse event estimates (Kaplan Meier estimates) are provided for every study time point. In addition, a p-value comparing the rate of occurrence of first infections over time between the two treatment groups is provided based on the log-rank test.

?? Incidence density analysis. This is a technique that uses as the denominator the exact time on study as the denominator expressed in person-months of observation. It allows for comparison between treatment groups with different duration of exposure as well as combination of data from studies of different lengths to increase the power to detect a signal across studies. The incidence density is the number of observed events divided by the number of months of follow-up and is reported as the number of events per 1000 person-months.

Table 5-8 presents the incidences of the most common systemic infectious adverse events in the two identical short-term trials in children, Studies B305 and B307. The left hand columns provide the actual crude incidence data for these events. The right hand columns provide the same data, adjusted for time on study using the Kaplan-Meier estimates.

All of the events listed are infections that are commonly seen in children, including upper respiratory tract infections, nasopharyngitis (common colds), influenza, and ear infections. The only event with a statistically significant difference between groups was viral gastroenteritis, with a higher incidence in the vehicle control group.

Table 5-8 **Crude and adjusted incidence of systemic infections, short term pediatric studies, B305 and B307 (= 1% for any group)**

	Crude incidence %			Adjusted incidence %		
	Elidel 1% (N=267)	Control (N=136)	p-value (1)	Elidel 1% (N=267)	Control (N=136)	p-value (2)
Preferred term						
Upper respiratory tract infection NOS	14.6	13.2	0.764	15.6	15.4	0.915
Nasopharyngitis	10.1	7.4	0.466	11.2	8.6	0.520
Influenza	3.0	0.7	0.283	3.2	0.8	0.174
Ear infection NOS	2.6	1.5	0.724	5.5	1.5	0.514
Otitis media NOS	2.2	0.7	0.431	2.5	0.9	0.329
Pneumonia NOS	1.1	0.7	1.000	1.2	0.8	0.748
Sinusitis NOS	1.1	0.7	1.000	1.2	0.9	0.752
Pharyngitis NOS	0.7	1.5	0.606	0.8	1.7	0.435
Pharyngitis streptococcal	0.7	1.5	0.606	0.9	1.7	0.438
Bronchitis NOS	0.4	2.2	0.114	0.4	2.6	0.061
Gastroenteritis viral NOS	0	2.2	0.038	<0.1	2.5	0.011

	Crude incidence %			Adjusted incidence %		
	Elidel 1% (N=267)	Control (N=136)	p-value (1)	Elidel 1% (N=267)	Control (N=136)	p-value (2)
Preferred term						
(1) p-value from Fisher's exact test (Elidel 1% vs vehicle) (2) p-value from log-rank test comparing the rate of occurrence of 1 st infection over time. Adjusted incidence (Kaplan Meier estimate) refers to specific incidence at Day 56. Source: 120 day safety update PTT REQ 3 and PTT 5.1-7 NOS = not otherwise specified in the coding dictionary						

Table 5-9 presents the incidences for the most common systemic infectious adverse events in the long-term trial in children, Study B313. Only one event, gastroenteritis, was of significantly increased incidence in the Elidel group in the crude incidence analysis. However, when adjusted for time on study, the event rate was not significantly increased. Note that in the short-term studies, the event rate for viral gastroenteritis was higher in the vehicle control group. No other events reached statistical significance.

It is reasonable to conclude that there are no clinically significant differences between the study groups for these events.

Table 5-9 **Crude and adjusted incidence of systemic infections, long term pediatric study, B313 (= 2% for any group) for all patients**

	Crude incidence %			Adjusted incidence %		
	Elidel 1% (N=474)	Control (N=237)	p-value (1)	Elidel 1% (N=474)	Control (N=237)	p-value (2)
Preferred term						
Nasopharyngitis	23.0	20.7	0.504	28.9	27.1	0.944
Influenza	10.1	5.9	0.067	14.6	9.5	0.083
Bronchitis NOS	8.2	8.0	1.000	13.2	13.7	0.794
Viral infection NOS	5.3	3.0	0.183	6.8	5.3	0.352
Gastroenteritis NOS	5.1	1.7	0.039	6.3	4.4	0.214
Tonsillitis NOS	5.1	2.5	0.164	7.2	5.2	0.249
Pharyngitis NOS	4.9	2.5	0.163	8.3	4.1	0.073
Upper respiratory tract infection NOS	3.4	3.8	0.830	5.7	6.4	0.760
Ear infection NOS	3.4	3.0	0.827	4.4	4.8	0.89
Otitis media NOS	1.5	2.1	0.547	4.0	22.0	0.144
(1) p-value from Fisher's exact test (Elidel 1% vs vehicle) (2) p-value from log-rank test comparing the rate of occurrence of 1 st infection over time. Adjusted incidence (Kaplan Meier estimate) refers to specific incidence at Day 393. Source: ISS PTT 5.1-8 and study ASMB 313 PTT 10.1-16 NOS = not otherwise specified in the coding dictionary						

Table 5-10 presents the incidence of the most common systemic infectious adverse events in the long-term trial in infants, Study 0315. The overall incidences for many of the individual events are higher in infants than children. This is especially true for the respiratory and ear infections which occur at higher incidence rates in infants.

The most common infection adverse event in the study was nasopharyngitis (common cold). Although the crude incidence rate was higher in Elidel-treated patients, the time-adjusted rates are clinically comparable with no significant difference present. The common cold (nasopharyngitis) was the most common infectious adverse event in many of the clinical trials. It was discussed previously in the section on the pooled clinical data. As seen above in section 5.3.2, when data from all registration studies and available post-registration studies are pooled, the rate of nasopharyngitis is essentially identical between Elidel and control-treated patients.

Some of the events associated with respiratory infections were of increased incidence in the vehicle control group including lower respiratory tract infection, influenza, and non-specific viral infection. There were four events of very low incidence with a significantly higher rate of incidence in the Elidel group in the crude analysis but these differences were not significant when the data were adjusted for time on study. The increased incidence in the vehicle group for non-specific viral infection was significant in the adjusted analysis.

Table 5-10 **Crude and adjusted incidence of systemic infections, long-term study, in infants, Study 0315 (= 2% for any group)**

	Crude incidence %			Adjusted incidence %		
	Elidel 1% (N=204)	Control (N=46)	P-value (1)	Elidel 1% (N=204)	Control (N=46)	p-value (2)
Preferred term						
Nasopharyngitis	49.5	37.0	NS	56.9	46.2	0.612
Upper respiratory tract infection NOS	25.0	19.6	NS	27.3	25.3	0.710
Ear infection NOS	18.1	15.2	NS	21.7	20.8	0.832
Otitis media NOS	12.7	10.9	NS	14.9	15.5	0.931
Bronchitis NOS	12.3	10.9	NS	14.6	16.2	0.826
Gastroenteritis NOS	10.8	10.9	NS	4.5	14.9	0.617
Lower respiratory tract infection NOS	6.4	8.7	NS	7.3	14.2	0.383
Tonsillitis NOS	6.9	4.3	NS	7.7	6.6	0.701
Influenza	3.9	6.5	NS	4.3	9.4	0.320
Eye infection NOS	3.9	2.2	NS	4.4	3.6	0.661
Viral rash NOS	3.9	2.2	NS	4.4	3.4	0.704
Viral infection NOS	2.0	10.9	NS	2.4	16.4	0.0004
Pharyngitis NOS	2.9	0	<0.05	3.3	0	0.291
Oral candidiasis	2.5	2.2	NS	2.7	3.0	0.947
Laryngitis NOS	2.5	0	<0.05	3.1	0	0.348
Respiratory Tract infection NOS	2.5	0	<0.05	2.7	0	0.332
Urinary tract infection NOS	2.5	0	<0.05	2.9	0	0.334
Sinusitis NOS	2.0	2.2	NS	2.1	3.6	0.818

	Crude incidence %			Adjusted incidence %		
	Elidel 1% (N=204)	Control (N=46)	P-value (1)	Elidel 1% (N=204)	Control (N=46)	p-value (2)
Preferred term						
Pneumonia NOS	1.5	2.2	NS	1.8	3.4	0.569
Broncholitis	0.5	2.2	NS	0.6	3.6	0.173
Fungal infection NOS	0.5	2.2	NS	0.6	2.3	0.200
Gastrointestinal infection NOS	0.5	2.2	NS	0.6	5.3	0.152
(1) 95%CI treatment difference: NS not including 0. (2) p-value from log-rank test comparing the rate of occurrence of 1 st infection over time. Adjusted incidence (Kaplan Meier estimate) refers to specific incidence at Day 393. Source: PTT 10.1-3 and 10.1-16 of CSR NOS = not otherwise specified in the coding dictionary						

This review of the data on systemic infections demonstrates that:

- ?? No consistent differences in the incidence of common infections between Elidel Cream-treated and control groups were observed when time on study was taken into consideration
- ?? There is no evidence from these data for a risk of systemic opportunistic infections with Elidel cream use, as one would expect with systemic immunosuppression.

5.3.3.2 Skin infections in registration trials

Because skin infections are common in patients with AD and because Elidel Cream 1% is a topically administered product, skin infections were analyzed carefully as part of the registration program.

5.3.3.2.1 Controlled long-term pediatric studies B313 and 0315

The crude incidence of skin infections greater than 1% for the controlled long-term pediatric studies B313 and 0315 can be found in Table 5-11. There were no statistically significant between-group differences with respect to specific infection types (e.g., impetigo, folliculitis, molluscum contagiosum, herpes simplex and herpes zoster), although superinfection was significantly more common in the Elidel Cream 1% group. However, this event was of low incidence.

The adjusted incidences are not different between treatment groups (Table 5-12) for these events with the exception of superinfection. It is important to note that in study B313 only one of 10 subjects (031_0001) had superinfection rated as severe and none of the events required hospitalization. Also, the kinds of events grouped under this term were captured in other preferred terms as well. Note that the incidence of “skin infection NOS” was higher in the vehicle control group. Overall, the types of infections reported are common in pediatric subjects with AD.

Table 5-11 Crude incidence at 12 months of skin infections, B313 and 0315 (= 1% for any group)

	Elidel Cream 1%	Control	
Preferred term	(N=678)	(N=283)	p-value (1)
Impetigo NOS	7.5%	8.5%	0.600
Skin infection NOS	5.5%	7.1%	0.369
Herpes simplex	2.2%	1.8	0.807
Folliculitis	2.2%	2.8%	0.644
Superinfection	1.9%	0	0.014
Molluscum contagiosum	1.9%	1.1%	0.420
Skin papilloma	1.8%	0.4%	0.123
Bacterial infection NOS	1.8%	0.7%	0.254
Herpes simplex dermatitis	1.3%	0.4%	0.296

(1) p-value from Fisher's exact test (Elidel 1% vs vehicle)

Source: ISS 120 Day update PTT 5.1-8a

Table 5-12 Adjusted incidence at 12 months of skin infections, B313 and 0315

		Elidel Cream 1%	Control	
Infection Class	Preferred Term	(N=678)	(N=283)	p-value ¹
Bacterial	Total	13.6%	42.1%	0.338
	Impetigo NOS	8.5%	20.1%	0.161
	Folliculitis	2.2%	3.5%	0.315
	Bacterial infection NOS	1.7%	0.9%	0.471
	Stye	0.6%	0	0.219
	Otitis externa (exc boil of meatus) NOS	0.2%	0.7%	0.336
	Staphylococcal infection NOS	0.3%	0	0.364
	Cellulitis	0.2%	0	0.550
	Erysipelas	0	0.4%	0.116
	Furuncle (exc genital)	0.1%	0	0.518
	Genital infection bacterial NOS	0.2%	0	0.589
	Streptococcal infection NOS	0.1%	0	0.524
Skin infection	Total	9.6%	11.0%	0.427
	Skin infection NOS	6.3%	8.7%	0.116
	Superinfection	2.2%	0	0.035
	Infection NOS	0.5%	0.5%	0.979
	Localised infection	0.5%	0.7%	0.940
	Abscess NOS	0.3%	0.6%	0.758
	Paronychia	0.2%	1.4%	0.068
	Wound infection NEC	0.1%	0	0.517
Viral infection	Total	9.6%	6.5%	0.163
	Herpes simplex	2.5%	2.9%	0.952
	Molluscum contagiosum	2.2%	1.5%	0.688
	Skin papilloma	2.1%	0.5%	0.147
	Herpes simplex dermatitis	1.6%	0.6%	0.293

Infection Class	Preferred Term	Elidel Cream 1%	Control	p-value ¹
		(N=678)	(N=283)	
	Herpes zoster	0.7%	0	0.239
	Pityriasis rosea	0.4%	0	0.433
	Viral rash NOS	0	1.0%	0.017
	Flat warts	0.2%	0	0.588
	Herpes viral infection NOS	0.2%	0	0.590
Fungal infections	Total	1.4%	1.0%	0.701
	Fungal infection NOS	0.4%	0.5%	0.705
	Candida nappy rash	0.3%	0	0.377
	Body tinea	0	0.6%	0.069
	Candida NOS	0.1%	0	0.525
	Fungal rash NOS	0.2%	0	0.578
	Tinea cruris	0.2%	0	0.560
	Tinea NOS	0.2%	0	0.588
Parasitic infections	Total	1.2%	0.4%	0.547
	Scabies infestation	1.2%	0.4%	0.547

¹p-value from log-rank test comparing the rate of occurrence of 1st infection over time. Adjusted incidence (Kaplan Meier estimate) refers to specific incidence at Day 393.

Source: ISS 120 Day update PTT 5.1-205 CDS

A special analysis was performed in the infant Study 0315 to evaluate if long-term application of Elidel Cream could induce local or systemic immunosuppression over time. The variation in the incidence of infections over time was evaluated in the cohort of 76 patients from Study 0315 treated for up to 2 years. Table 5-13 displays the incidence of skin and systemic infectious adverse events over time for the Elidel treated patients comparing the first 12 months with the second 12 months. In a study in which infants were treated for 2 years, the incidence of infections was similar in Elidel and vehicle treated patients and did not increase over time.

Table 5-13 Crude Incidence of skin and systemic infections in infants treated for 2 years (Study CASM981 0315E1)

Primary system organ class Preferred term	First Year (N=76) %	Second Year (N=76) %
At least 1 AE	100	92.1
At least one skin or systemic infection	92.1	80.3
Impetigo	5.3	9.2
Tonsillitis	11.8	7.9
Superinfection	0	1.3
Chickenpox/ Varicella	13.2	7.9
Herpes simplex	1.3	0
Herpes simplex dermatitis	0	2.6
Molluscum contagiosum	0	0
Gastroenteritis	18.4	10.5
Bronchitis	19.7	15.8
Influenza	2.6	3.9

Primary system organ class	First Year (N=76)	Second Year (N=76)
Preferred term	%	%
Nasopharyngitis	60.5	47.4
Upper respiratory tract infection	19.7	7.9
Ear infection	22.4	15.8
Otitis media	13.2	7.9

5.3.3.2.2 Controlled short-term pediatric studies (B305, B307)

The most common skin infections in these studies were skin infection, impetigo, bacterial infection, folliculitis, molluscum contagiosum, and staphylococcal infection (source: US package insert).

Calculation of the adjusted incidence of skin infections (using Kaplan-Meier) to account for differences in time on study showed significantly higher rates of 'skin infection NOS', and 'staphylococcal infection NOS' in the vehicle group (source: Integrated Safety Summary). In the US prescribing information, it is noted that the crude incidences for these events were higher in the vehicle group as well. There were no other statistically significant between-group differences and most other infections occurred at similar rates in both treatment groups for both the crude incidence and Kaplan-Meier data. The skin infections seen in this population were qualitatively similar to those seen in the long-term pediatric studies.

5.3.3.2.3 Eczema herpeticum – an important skin infection

One of the clinically most important skin infections observed in the clinical trials is eczema herpeticum.

Patients with disorders such as AD are at risk for developing extensive herpes simplex infections. The terms 'eczema herpeticum' or 'Kaposi's varicelliform eruption' (KVE) refers to an unusually extensive cutaneous herpes infection of an eczematous skin disease. This cutaneous dissemination can accompany primary episodes or recurrences of herpes simplex infection. Clinical experience indicates that the incidence of eczema herpeticum is higher in patients who have more severe and uncontrolled forms of atopic dermatitis although there is little published evidence on this.

In the registration studies, the investigator terms 'eczema herpeticum', 'KVE', and 'herpes simplex general cutis' were coded to 'herpes simplex dermatitis' as the preferred term. For the remainder of this discussion, the disease is referred to as 'eczema herpeticum'. The term 'eczema herpeticum' should be reserved for events that involve a spreading eruption that continues to spread over several days. For the current discussion, a conservative approach was adopted and all events identified by the terms 'eczema herpeticum', 'KVE', or 'herpes simplex general cutis' are included even though some of these patients may not have had actual disseminated disease.

In total, 16 patients in the Elidel Cream 1% registration development program experienced clinically diagnosed eczema herpeticum; 6 cases were reported as SAEs. Thirteen of the patients affected were using Elidel Cream 1% and 3 were control patients. Five cases, 4 in Elidel patients (2 SAEs, 2 AEs) and one in a control patient (AE) were suspected to be treatment-related. In one Elidel-treated patient, review of the narrative indicates that the investigator questioned whether eczema herpeticum was indeed present as the diagnosis was

based on reports from the patient. The majority of cases occurred on the face. Confirmation of the diagnosis was performed in only one patient by means of a Tzanck smear test. In none of the patients was there confirmation of the diagnosis via virological culture, PCR or immunofluorescence analysis using virus specific antibodies.

In all but one of the 16 patients, the events resolved without sequelae and without recurrence during the period of observation. In one patient, the event was uncomplicated but ongoing at study end. After the event, the majority of patients went on to complete their time on study. Only one patient received intravenous antiviral therapy and two patients did not receive any antiviral therapy, again suggesting that these disease events were uncomplicated and not of the nature seen in immunocompromised patients.

In order to compare incidence of eczema herpeticum in Elidel Cream 1% and vehicle treated patients in the Elidel Cream 1% registration clinical program, incidence density rates were estimated for all AD patients, for adults, and for pediatric patients (Table 5-14). There was no statistical difference in incidence rates between Elidel Cream 1% and control for any population. However, the relative risk of eczema herpeticum in patients with Elidel was 2.2 (0.6-7.8) indicating a modest increased risk of about 1 additional case of eczema herpeticum for every 2000 patient-months.

Table 5-14 Incidence rates for eczema herpeticum in registration trials

Population	No. of cases	Patient-months of follow up	Incidence rate (cases/1000patient-months) (95% CI)	Relative risk Elidel Cream 1% vs. comparator (95% CI)	P-value
All AD studies on Elidel Cream 1%	13	12596	1.032 (0.473, 1.591)	2.226 (0.634,7.812)	0.212
All AD studies on comparators	3	6471	0.464 (-0.060, 0.987)		
Adults on Elidel Cream 1%	2	2938	0.681 (-0.260, 1.622)	1.364 (0.192, 9.680)	0.757
Adults on comparators	2	4006	0.499 (-0.191, 1.190)		
Pediatric patients on Elidel Cream 1%	11	9658	1.139 (0.469, 1.809)	2.806 (0.362, 21.738)	0.323
Pediatric patients on vehicle	1	2464	0.406 (-0.389, 1.200)		

In the literature, the incidence of all herpes simplex virus skin episodes, including eczema herpeticum and severe initial infections, and first recurrences in children with atopic dermatitis, has been estimated at 4.7 per 1,000 patient-months of observation (95% CI: 2.6-7.7) [Reltien, 2001]. When all herpes simplex events are considered for all children and adult registration vehicle-controlled studies, there were 29 events in 1113 patients in the Elidel Cream group and six events in 525 patients in the vehicle group. Incidence density calculations for these events indicate an incidence rate of 6.01 (3.96-8.73) per 1,000 patient-months of follow-up in the Elidel Cream group and an incidence rate of 3.87 (95% CI 1.42-8.40) events per 1,000 patient-months of follow-up in the vehicle group. These figures correlate well with data from literature.

5.3.3.3 Conclusions – systemic and skin infections in registration trials

This review of these data demonstrate that:

- ?? No differences in the incidence of common infections between Elidel Cream-treated and control groups were observed when time on study was adjusted for
- ?? No evidence for a risk of systemic opportunistic infection was seen with the use of Elidel Cream
- ?? Skin infections are common in patients with AD, with no indication that the overall frequency of these events is increased in patients treated with Elidel
- ?? For viral skin infections and eczema herpeticum, there is a numerical increase in events in Elidel-treated patients. However, this effect was not statistically significant. It should be noted that a precaution regarding viral skin infections is currently in the US prescribing information.

5.3.4 Infections reported in postmarketing surveillance safety reports

A search in the Novartis Elidel Cream 1% adverse drug reaction (ADR) database was carried out with a cut-off date of December 3, 2004 for all serious and non-serious spontaneous reports with the primary or secondary MedDRA SOC (System Organ Class) "Infections and Infestations" (MedDRA version 7.0).

Until December 3, 2004 Novartis Clinical Safety and Epidemiology received 47 serious spontaneous case reports including 61 AEs, and 200 non-serious case reports including 212 AEs linked either primary or secondary to the System Organ Class (SOC) 'Infections and Infestations'. Cases not confirmed by a health care professional (8 serious and 93 non-serious cases) are included in these numbers. There were no cases with a fatal outcome.

The infections can be grouped into three categories: Systemic infections, skin- and application site infections, and musculoskeletal and connective tissue infections. In case of unclear or generic terms as e.g., "infection" the events were counted in the group of systemic infections, unless the case description allowed the assignment to any of the two other groups.

Table 5-15 Serious events of infections and infestations (N= 61)

Preferred Term	No. of events
Skin- and application site infections	N= 36
Application site infection	1
Application site abscess	1
Dermatitis infected	1
Eczema impetiginous	1
¥ Erythema multiforma	2
Herpes simplex	4
Herpes virus infection	13
including Eczema herpeticum	9
Herpes zoster	4
Herpetic stomatitis	1

Preferred Term	No. of events
Oral candidiasis	1
Skin infection	5
¥ Skin papilloma (viral warts)	1
Varicella	1
Musculoskeletal and connective tissue infection	N= 7
Abscess	1
Cellulitis	3
Muscle abscess	1
Osteomyelitis	1
Soft tissue infection	1
Systemic infections	N= 18
Bronchitis	1
Ear infection	1
Epiglottitis	1
Gastroenteritis	2
Infection	1
Lung infection	1
Nasopharyngitis	1
Pharyngitis	1
Pharyngitis streptococcal	1
Pneumonia	1
Respiratory tract infection	1
Staphylococcal infection	3
Staphylococcal sepsis	1
Upper respiratory tract infection	1
Viral upper respiratory tract infection	1

(¥) Adverse events that linked secondarily to the SOC Infections and Infestations

Table 5-16 Non-serious events of infections and infestations (N= 212)

Preferred term	No. of events
Skin- and application site infections	N=146
Application site abscess	1
Application site infection	3
Application site pustules	5
Bacterial infection	1
Condyloma acuminatum	1
Conjunctivitis infective	1
¥ Erythema multiforme	1
Folliculitis	4
Fungal infection	1
Furuncle	2

Preferred term	No. of events
Herpes simplex	21
Herpes simplex ophthalmic	1
Herpes virus infection	13
<i>including LLT Eczema herpeticum</i>	4
Herpes zoster	17
Impetigo	5
Molluscum contagiosum	29
Oral candidiasis	2
Papilloma viral infection	1
¥ Pyoderma	3
Rash pustular	8
Skin bacterial infection	1
Skin infection	3
¥ Skin papilloma (viral warts)	17
Tinea infection	1
Tinea versicolour	1
Vaginitis	1
Varicella	2
Musculoskeletal and connective tissue infection	N= 2
¥ Erythema nodosum	1
Subcutaneous abscess	1
Systemic infections	N= 64
Bronchitis	3
Coxsackie viral infection	1
Ear infection	6
Eye infection	1
Gastroenteritis	1
Gastroenteritis rotavirus	1
Gastroenteritis viral	1
Infection	5
Infectious mononucleosis	1
Influenza	1
Laryngitis	1
Lower respiratory tract infection	1
Nasopharyngitis	19
Oral infection	1
Otitis media	4
Pharyngitis	2
Pharyngitis streptococcal	1
Rhinitis	1
Sinusitis	1

Preferred term	No. of events
Staphylococcal infection	3
Tonsillitis	1
Upper respiratory tract infection	4
Urinary tract infection	1
Viral infection	3

(¥) Adverse events that linked secondarily to the SOC Infections and Infestations

Table 5-17 provides a summary of all serious and non-serious events of the three categories (skin infections, musculoskeletal- and connective tissue infections, and systemic infections) with the reporting rates based on the estimated worldwide patient exposure to date.

Further analysis is performed on the number and reporting rates of the most common reported infections: Herpes viral infections (PTs: herpes simplex, herpes virus infections, herpes zoster, varicella-zoster), Viral warts and mollusca (PTs: skin papilloma, papilloma viral infection, molluscum contagiosum, condylomata acuminata), bacterial skin infections (PTs: Application site infections, -abscess, -pustules, Dermatitis infected, Eczema impetiginous, skin infection, bacterial infection, folliculitis, furuncle, impetigo, pyoderma, rash pustular, skin bacterial infection, skin infection), and Ear/Nose/Throat (ENT) infections (PTs: ear infection, laryngitis nasopharyngitis, oral infection, otitis media, pharyngitis, pharyngitis streptococcal, rhinitis, sinusitis, tonsillitis).

Table 5-17 Reporting rates of serious and non-serious infections

	No. of cases Total no. =273	Reporting rate per 100.000 ^a
Skin- and application site infections including :	182	22,3
<i>Herpes simplex viral infections</i>	53	6,5
<i>(incl. Eczema herpeticum n=13)</i>		
<i>Varicella zoster virus infections</i>	24	2,9
<i>(incl. Varicella n=3, H. zoster n=21)</i>		
<i>Warts and mollusca</i>	49	6,0
<i>Bacterial infections</i>	45)	5,5
Musculoskeletal- and connective tissue infection	9	1,1
Systemic infections including:	82	10,0
<i>Ear/nose/throat infections</i>	41	5,0

a: Considering a DDD based on IMS data, i.e., market exposure worldwide is 814138 person-years (see chapter 3.3)

5.3.5 Conclusion

The vast majority of all spontaneously reported events are on skin- and application site infections with herpes viral infections being most frequent, followed by reports on viral warts and mollusca contagiosa, and bacterial skin infections. The predominance of viral skin infections is supported by the notion that such infections have an increased prevalence in atopic patients.

Bacterial infection is a known cause of exacerbation of atopic eczema. A study followed 190 children with atopic eczema for two and a half years. Seventy six children (40%) had episodes of exacerbation of eczema due to bacterial infection, and in 32% infection recurred within three months of a previous infection [David, 1986].

Evaluating the nature of the reported systemic infections, ear/nose/throat (ENT) infections account for half of all reports, which is in accordance with general population background data. The incidence rate of group A streptococcal (GAS) pharyngitis has been estimated around 14 per 100 person-years for children of general population between 3 and 12 years [Danchin, 2004].

5.3.6 Risk assessment

Since registration, substantial data has been accumulated regarding the safety of Elidel Cream 1%. This has included experience both in clinical trials as well as the marketplace. Although commonplace infections have been observed in patients using Elidel Cream 1%, the statistical data from the clinical trials and the epidemiological data of the background incidence do not provide evidence to support a linkage between systemic infections and the use of Elidel Cream 1%.

The clinical program involves more than 19,000 patients and the postmarketing experience in the population is extensive and has been described.

It is important to distinguish common systemic infections from those that would be indicative of systemic immunosuppression related to the compound. All observed infections in the program are common infections. There is no evidence they are related to Elidel Cream 1% as the rates in the control groups are similar.

Although no increase in overall incidence of skin infections has been observed with Elidel, analysis of individual types of skin infections shows an increased incidence of viral skin infections mostly accounted for by herpes simplex. The current label includes precautions with regard to superficial skin infections including those due to herpes simplex virus and varicella-zoster virus. There is no indication from postmarketing experience, where there has been high exposure to Elidel Cream 1%, of an abnormally high frequency of spontaneous reports of herpes virus infections.

These findings pertain to the infant population as well.

No opportunistic infections, that would indicate the presence of systemic immunosuppression, with the use of topical Elidel have been seen in any Elidel Cream 1% clinical study or in the general population post-approval.

5.4 Assessment of immunocompetence in patients treated with Elidel Cream 1%

5.4.1 Key Findings

- ?? As assessed in a 2-year study in infants, Elidel treated patients developed a normal protective immune response to vaccination
- ?? Elidel treatment did not interfere with the development of a normal skin immune response to microbial antigens

5.4.2 Evaluation of Elidel Cream 1% on the antibody response to vaccination

The effect of Elidel Cream 1% on the developing immune system was determined by assessing the antibody response to childhood vaccinations in treated children. Elidel treatment showed to have no influence on the ability of young children to develop a protective antibody response to childhood vaccination.

5.4.2.1 Study design

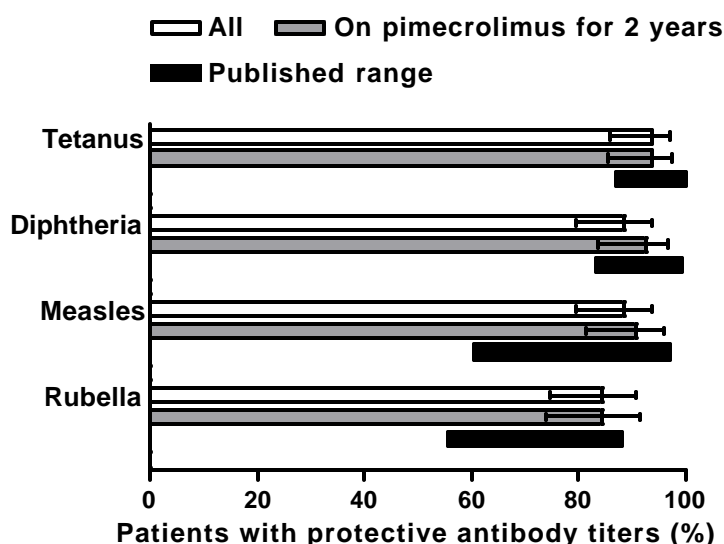
In order to evaluate the magnitude of the antibody response of infants being treated with Elidel Cream 1% following immunizations, the response to vaccines was assessed by measuring antibody titers from sera obtained during the second year of treatment with Elidel Cream 1%. A combined total of 123 blood samples were analyzed from 79 patients. All patients had been vaccinated before titer measurements. This design, using a population based approach is clinically relevant because it is close to clinical practice where patients have frequently long-term exposure to topical therapy (i.e., corticosteroids) before they receive their vaccination. The overall proportion of patients with protective antibody titers against tetanus, diphtheria, measles and rubella, was compared with the seroprevalence reported in general, age-matched pediatric populations, irrespective of the vaccination history. The potential relationship between the antibody response to vaccinations and the following study variables was also analyzed: exposure to Elidel at the time of vaccination, defined as treatment with Elidel in the 28 days preceding and/or following the vaccination day; treatment received during the first year of the study (either Elidel or vehicle); use of topical corticosteroids before measurement of serum antibody titers (yes/no); number of doses of toxoids and vaccines administered before measurement of antibody titers; time (in days) elapsed between vaccination and measurement of serum antibody titer; age; gender; race; country.

5.4.2.2 Results

Most patients had protective antibody titers against major vaccination antigens, whether they were anatoxins, such as tetanus and diphtheria toxoids, or live, attenuated viruses, such as measles and rubella vaccines.

The proportions of patients with protective antibody titers against tetanus, diphtheria, measles and rubella irrespective of the vaccination history were similar to those observed in pediatric populations of similar age (Figure 5-5). For each antigen tested, most patients had positive antibody titers. In total, 84% (rubella), 89% (diphtheria), 89% (measles) and 94% (tetanus) of patients had protective antibody titers to vaccination, compared with 61–80% (rubella) [Pebody, 2000], 79–92% (diphtheria) [Edmunds, 2000] and 76–82% (measles) [de Melker, 2000] 87–100% for tetanus [Gold, 1973] in the general population.

Figure 5-5 Overall seropositivity rate to tetanus, diphtheria, measles and rubella



Error bars indicate the 95% CI.

There were no differences in the rates of positive responses to vaccinations between patients who had received Elidel treatment within 4 weeks before or after the vaccination and those who had not (Table 5-18).

Table 5-18 Relationship between exposure to Elidel at time of vaccination* and response to vaccination

Exposure to Elidel at vaccination	Rubella vaccination (% positive)	Diphtheria vaccination** (% positive)	Measles vaccination (% positive)	Tetanus vaccination** (% positive)
No	91.2%	85.7%	96.8%	100%
Yes	100%	96.2%	94.4%	92.3%

*Exposure defined as receiving Elidel in a window of 4 weeks before and/or after the vaccination

**For diphtheria and tetanus, the booster 3 data was taken as this involved the largest number of patients

The results of the multivariate analysis on vaccination response show that the response to vaccination was not affected by number of vaccinations (tetanus and diphtheria), race, age, gender, country of origin, corticosteroids intake, number of days on Elidel Cream 1% around vaccination, duration between last vaccination and date of titration (response to vaccination) for the four vaccinations rubella, diphtheria, measles and tetanus (Papp 2005).

In summary, a cohort of infants treated with Elidel Cream 1% for up to 2-years show a normal antibody response to childhood vaccinations. There is no association between exposure to Elidel Cream 1% and lack of development of protective response to vaccination.

5.4.3 Skin hypersensitivity reactions to bacterial and fungal antigens

The assessment of the ability to demonstrate a normal cell-mediated, delayed type hypersensitivity (DTH) reaction against a range of antigens is a common method of assessing immunocompetence. A total of 112 subjects (82 Elidel Cream 1%; 30 vehicle) completing one year of treatment were tested against a range of re-call antigens. The results are summarized in Table 5-19.

Table 5-19 Frequency table of positive antigens (safety population)

	Pimecrolimus	Vehicle	Total	p-value
	(N=82)	(N=30)	(N=112)	
	n(%)	n(%)	n(%)	
Tetanus	52 (63.4)	18 (60.0)	70 (62.5)	0.826
Diphtheria	35 (42.7)	7 (23.3)	42 (37.5)	0.079
<i>Streptococcus</i>	6 (7.3)	0	6 (5.4)	0.190
Tuberculin	14 (17.1)	4 (13.3)	18 (16.1)	0.776
<i>Candida</i>	11 (13.4)	1 (3.3)	12 (10.7)	0.176
<i>Trichophyton</i>	7 (8.5)	3 (10.0)	10 (8.9)	0.726
<i>Proteus</i>	15 (18.3)	2 (6.7)	17 (15.2)	0.151
Negative control	3 (3.7)	0	3 (2.7)	0.563

Source: 12-month CSR Post-text table 10.4-4

These results indicate that there is no statistically significant difference between the treatment groups in response to re-call antigens, suggesting that use of Elidel Cream 1% has no effect on the ability to develop a normal T-cell mediated immune response to microbial antigen in children treated.

6 Ongoing studies investigating the long-term safety of Elidel Cream 1% and its effects on the immune system and future plans

6.1 Key Findings

- ?? Novartis has developed a comprehensive and ongoing program to further assess long-term safety of Elidel
- ?? All Phase IV commitments agreed with FDA are being implemented
- ?? In addition, Novartis has voluntarily initiated 2 long-term safety studies (5+ years) involving over 3 000 infants.

6.2 Postmarketing and Phase 4 commitment studies overview

Novartis has developed a program to examine the risk of developing systemic malignancies and cutaneous malignancies (specifically melanoma and non-melanoma skin cancer) following long-term continuous or intermittent exposure to Elidel Cream and to evaluate the drug in immunocompromised patients. Proposals for the program were submitted to FDA in 2002. Comments on the studies were received from the Agency in 2004. The program and status are outlined in Table 6-1.

Novartis also initiated 2 large studies in infants: a 5 year study to assess long-term safety in infants, as well a 6 year study to follow atopic disease progression (Table 6-1).

The following section briefly describes the studies and provides a status update

Table 6-1 Summary of long-term safety studies with Elidel cream 1%

Study	Design	Population	Status
C2311	10-year prospective observational cohort study (registry) to assess risks of systemic cancer (lymphoma) with patient reported outcomes obtained every 6 months	Pediatrics 2-17 yr of age who have used Elidel cream 1% for at least 6 wk	First patient enrolled in Nov 2004
C2308	Case-Control Study to Estimate the Risk of Non-Melanoma Skin Cancer following exposure to Elidel Cream 1%.	Adults (age =40 years) with eczema	Final protocol; initial study execution, 2005; long-term (second) execution, 2010
C2312	A Cohort with a Nested Case-Control Study to estimate the Risk of Melanoma Skin Cancer following exposure to Elidel Cream 1%.	Adults (age =40 years) with eczema	Protocol finalization; study executions in June 2007 and 2017
C2309	Randomized, vehicle control study to assess efficacy, safety, tolerability (final design TBD)	HIV positive adult and pediatric patients with atopic dermatitis	Protocol revision following comments from FDA FPFV target 2005
CUS09	A 6-year investigation into the safety and efficacy of Elidel Cream 1% in atopic disease modification, consisting of a 3-year randomized, double-blind, vehicle-controlled phase, following by an open-label phase of up to a further 33 months duration.	Infants 3-18 months; AD for no longer than 3 months at enrollment; no other atopic diseases; first-degree relative with history of atopy.	Recruitment completed 30-Dec-2004 (1091 patients randomized).
C2306	A 5-year open-label, randomized, active-controlled to demonstrate short and long-term safety of Elidel Cream 1% in mild-to-moderate AD.	Infants, 3 - <12 months; diagnosis of AD; IGA of 2 or 3.	Recruitment ongoing.

6.3 Pediatric registry (2311):

Title

A prospective 10-year observational registry of pediatric subjects (age =2 years to age = 17 years) with atopic dermatitis who have used Elidel Cream 1%.

Status

Novartis submitted a protocol for a 10 year prospective observational Pediatric Registry (Study C2311) to the FDA in August 2004. Final comments were received from the Agency December 2004. The study design is similar to that proposed for evaluations of the long-term risks of medications by the FDA Office of Drug Safety and reviewed by the newly-constituted Drug Safety and Risk Management panel of the FDA. The first patient was enrolled in November 2004.

Objectives

The primary objective of the study is to estimate the rate of lymphoma in a cohort of pediatric patients who have used Elidel Cream 1% for at least 6 weeks to treat their atopic dermatitis. Secondary objectives include reviewing the rates of thyroid cancers in the population under study, and to review the total number of reported systemic malignancies in the Registry population looking for specific patterns of malignancies in these reports. The study also will determine the standardized incidence ratio (SIR) comparisons for lymphoma and all systemic cancers between the Registry population and SEER.

Design

The Registry will enroll approximately 4000 male or female pediatric subjects (age ≥ 2 years to age ≤ 17 years) who have used Elidel Cream 1% for at least 6 weeks (continuous or intermittent) within 6 months prior to enrollment. Patients from all regions across the United States will be enrolled in the Registry to ensure an ethnically diverse population is studied. Patients will be treated according to their local physician and are not required or restricted to use any medication to treat their disease. The patient's parent or caregiver will complete a questionnaire at enrollment and at subsequent 6-month intervals over a 10-year observation period whether or not AD persists or Elidel cream is used. In addition to information on systemic cancers, the Registry will collect information on AD status and severity, exposure to Elidel Cream 1% and other medications/therapies (topical, oral, inhaled, etc.) used for the treatment of AD, general health (including asthma, hay fever, allergies), and risk factors for malignancy. Patients will be encouraged to undergo annual physician check-ups, with emphasis on examinations of skin and lymph nodes.

The total number of lymphomas or systemic malignancies in the Registry will be compared to that in the SEER database. The comparison of observed and expected malignant neoplasms will be made using the Standardized Incidence Ratio (SIR), which is the ratio of observed to expected cases. The expected number of cancers will be calculated by applying the gender and age (by 5-year intervals) specific cancer rates from SEER to the time at risk (person years) in the Registry program using the indirect age standardization method. If at anytime, the total number of cases exceeds the expected number of cases for the corresponding number of person years of observation, a statistical decision point (signal of concern) will have been reached and the health authorities will be notified immediately. Clinical follow-up information, including assessments by an outside panel of experts (DSMB), will also be presented to put the statistical findings into context and provide information on the potential relevance of the cases identified. A similar analysis will be made for all systemic cancers.

Reporting

Novartis will provide summary and descriptive statistics of database characteristics annually beginning Dec 2005. Incidence rate reports will be provided for lymphoma and thyroid cancer. Systemic malignancies will be listed. Novartis will provide this annual update in the NDA annual report and the PSUR annual report. If at any time a signal of concern is detected, the respective health authorities will be notified immediately.

Full reports will be prepared at year 5 and year 10 after inception of the registry.

6.4 Non-melanoma case-control study (2308):

Title

A case-control study of adults (age \geq 40 years) with atopic dermatitis to estimate the risk of non-melanoma skin cancer following exposure to Elidel Cream 1%.

Status

Novartis submitted a proposal for a case controlled study to the FDA in July 2002. Comments were received from the Agency in July 2003. The protocol has been finalized, with the first execution of the study targeted for 2005. The study will be repeated in 2010, after Elidel Cream 1% has been on the market for 8 years, to provide a more long-term assessment of risk.

Objectives

The primary objective of this study is to assess the risk of developing NMSC in adult subjects (age \geq 40 years) with selected chronic inflammatory dermatoses who have used Elidel Cream 1% for treatment of their disease. The study will also explore the odds of developing specific NMSC (basal cell carcinoma or squamous cell carcinoma), and examine the impact of extent or duration of therapy, as well as various patient categorizations on the results. The first execution of the study (2005) will provide an early estimate of risk. The second execution of the study (2010) conducted after Elidel Cream 1% has been on the market for 8 years will provide a risk assessment with a more long-term perspective.

Design

This is a case-control study nested within a cohort of subjects who were seen by dermatologists at the University of Pennsylvania Medical School. Selection of cases as well as controls will be from the PICARD database that contains information on all outpatient-subjects seen by dermatologists at the Department of Dermatology, University of Pennsylvania Medical School. Since dermatologists are practitioners most experienced in recognizing skin cancer, this unique database should circumvent issues derived from the lack of consistent identification, reporting and diagnosis of NMSC.

The subjects will be selected from the database strictly from ICD-9 codes and the selection will be independent of medication exposure status. Information regarding patient demographics, disease, exposure to Elidel Cream 1% and other medications of interest, and potential risk factors will be obtained using a self-administered questionnaire written in English and/or Spanish.

Potential cases will initially consist of a random sample of both male and female subjects over the age of 40 with an ICD-9 CM codes consistent with selected inflammatory dermatoses and with a NMSC in the PICARD database. The control group will also be selected from the PICARD database. Like the cases, the controls will be from a random sample of the population of subjects seen by the Dermatology group at the University of Pennsylvania, and will have ICD-9 codes consistent with a diagnosis of the selected chronic inflammatory dermatoses.

The exposure of interest for this study is Elidel Cream 1%. We will ascertain the subject's exposure (duration, frequency and extent) by a series of written questions via a mail questionnaire. Exposure to other medications of interest (Protopic and topical corticosteroids) will be ascertained in the same manner.

Questionnaires will be sent to approximately 1000 cases and 4000 controls. Sample size estimates are based on a clinically important detectable odds ratio of 2.0, a two-sided alpha error of 0.05, and power of 80%. Given a 20% uptake of Elidel Cream 1% in the population, and a 4:1 ratio of controls to cases, a final sample size of 699 cases and 2796 controls will be required.

Time points for study execution were selected which ensured sufficient exposure in the population for evaluation. They were based on the expected lag time between exposure to drug and development of cancers as described in transplant literature, and the expected exposure of the population to Elidel based on sales. Two time points were selected: the first, 3 years after Elidel was launched onto the market (2005), and the second 8 years post-launch (2010).

Reporting

A report for the first execution of the study should be available by the end of 2005, while a report for the second execution should be available in 2010.

6.5 Melanoma case-control study (2312):

Title

A cohort with a nested case-control study of male and female adults (age ≥ 40 years) with atopic dermatitis to estimate the risk of melanoma skin cancer following exposure to Elidel Cream 1%.

Status

Novartis submitted a proposal for a case controlled study to the FDA in July 2002. Comments were received from the Agency in July 2003. The final protocol will be submitted to the Agency in 2005. Given the lower incidence of melanoma in the population compared with NMSC, and the potential for a longer lag between exposure to Elidel Cream 1% and development of a melanoma compared with NMSC, the study will be executed first after Elidel Cream 1% has been on the market for 5 years (2007). A second execution (different patient selection) is scheduled for 2017 (after Elidel Cream 1% has been on the market for 15 years).

Objectives

The primary objective of this study is to estimate the risk of developing melanoma skin cancer for individuals with atopic dermatitis and exposure to Elidel Cream 1% as compared to those with atopic dermatitis and no exposure to Elidel Cream 1%. Secondary objectives include estimation of the incidence rate of melanoma in a cohort of patients with a diagnosis of atopic dermatitis, and examination of the association between the risk of melanoma and the use of

Elidel Cream 1% considering other therapies, such as topical and oral treatments, in the cohort of patients with atopic dermatitis.

Design

The study is a retrospective cohort study with a nested case-control analysis to be performed using data from a large, fully adjudicated medical and pharmaceutical claims database.

The selection of the cohort patients will be performed in the aforementioned database containing information on all subjects over the age of 40 with an ICD-9 CM code consistent with AD. Cases will be those patients within the cohort with an ICD-9 CM code consistent with melanoma skin cancer. The control group will be selected from the same database. Like the cases, the controls will be from a random sample of the population of subjects with AD codes and without melanoma skin cancer ICD-9 CM codes.

The exposure of interest for this study is Elidel Cream 1%. The subjects will be selected without knowledge of their exposure status. We will ascertain the subject's exposure status and duration of treatment to this medication and other topicals of interest.

For estimating sample size, we propose to use a 1:4 case-control ratio, a detectable odds ratio (OR) of 2, and an assumption of a 20% uptake of Elidel Cream 1% in the population. Therefore, our study will require 121 cases and 484 controls.

Time points for study execution were selected which ensured sufficient exposure in the population for evaluation. They were based on the expected lag time between exposure to drug and development of cancers as described in transplant literature, and the expected exposure of the population to Elidel based on sales. Two time points were selected: the first, 5 years after Elidel was launched onto the market (2007), and the second 10 years post-launch (2017).

Reporting

A report for the first execution of the study should be available in 2007. That for the second execution should be available in 2017.

6.6 Immunocompromised patients (Study 2309)

Title

Safety, tolerability and efficacy study in immunocompromised patients with atopic dermatitis treated with Elidel Cream 1% BID

Status

Novartis submitted a study proposal to the FDA in April, 2002. The Agency provided comments on the proposal on December 7, 2004. These comments are being incorporated into the study design. Study initiation is targeted for 2005.

Objectives

The study will be designed to determine efficacy of Elidel Cream 1% in an immunocompromised population (HIV-infected adults and children [inclusive of all levels of viremia and CD4 counts]) that will also be followed off-treatment for additional evaluation of safety.

Design

The final design of the study is under discussion.

Reporting

Final timelines and reporting schedule are under evaluation.

6.7 Long-term safety in infants (ASM981C2306):

Title

A 5-year, multicenter, open-label, parallel group, randomized study to demonstrate the short and long-term safety of Elidel (pimecrolimus, ASM981) cream 1% in treatment of mild to moderate atopic dermatitis in infants (3 ? < 12 months of age)

Status

The first patient was randomized on 5 April 2004 and currently, there are 1189 patients randomized out of 2350 planned patients. The recruitment is scheduled to end June 2005.

Objectives

To demonstrate the safety of Elidel Cream 1% vs. TCS in the treatment of infants 3 months to less than 12 months of age with mild to moderate AD:

1. when used for 6 weeks during the acute state of the disease by assessing adverse events (AEs).
2. when used for up to 5 years by assessing AEs and any potential effect on the developing immune system and growth velocity.

Design

This is a multicenter, randomized, open-label, active-controlled (topical corticosteroids), parallel-group, comparative study in 2350 children with mild to moderate AD. Skin care with emollients is recommended for all patients. Elidel or topical corticosteroids (TCS) cream are started at randomization and continued until clearance of disease signs and symptoms. The treatment is restarted again upon reappearance of first signs and/or symptoms as outlined and illustrated in caregiver brochure. In the event that disease worsens despite use of Elidel Cream 1%, patients in Elidel Cream 1% arm will use a low or medium potency TCS. If a patient in TCS arm experiences disease worsening despite the use of low or medium potency TCS, the patient will need to come back to the clinic and be evaluated. The TCS arm is the control arm

and it represents the current standard of care. Elidel treatment group reflects the envisioned paradigm for the use of this drug in infants.

Efficacy: Since this is a safety study, efficacy will only be documented by assessing IGA and body surface area affected. No formal analyses for efficacy are planned.

Safety: Safety monitoring is extensive in this study and includes: SAEs and AEs, physical exams, growth velocity assessments in all patients and immune system tests (candida skin test, vaccination response to measles, hepatitis B, tetanus, varicella and Hib vaccines, assessment of T cell function, immunoglobulin levels and B and T cell cytometry) in a subset of about 700 patients. An independent safety monitoring board will review the data on a quarterly basis for the first 2 years, and then every 6 months until study completion.

Reporting

The final clinical study report will be available in 2010 however, there will be an interim analysis at the end of 2 years in 2006.

6.8 Atopic disease modification in infants (ASM981CUS09):

Title

An investigation of the safety and efficacy of Elidel 1% cream in atopic disease modification, assessed in a 3-year randomized double-blind vehicle controlled phase to evaluate effects on atopic dermatitis in infants, and a 2-3 year open-label phase to evaluate the effect of early intervention versus delayed intervention with Elidel on the incidence of asthma in children

Status

Recruitment closed on 30-Dec-2004. In total, 1091 patients were randomized.

Objectives

To investigate the atopic disease modifying capabilities of Elidel Cream 1%. This study will assess whether, in atopic infants with AD and a family history of atopy, Elidel Cream 1% long-term management (LTM) provides better control of AD over 36 months than a conventional, TCS-based treatment; and whether commencement of Elidel Cream 1%-LTM soon after the first diagnosis of AD reduces the incidence of asthma at 6 years of age compared with delaying intervention by 3 years.

Design

This is a randomized, vehicle-controlled, multicenter, parallel-group study consisting of a 36-month DB phase, followed by an open-label (OL) extension with all patients receiving Elidel Cream 1%. Patients, 3-18 months of age, were recruited. Patients were randomized in a ratio of 1:1 to either:

- The Elidel Cream 1%-LTM schedule, or
- Conventional management with study medication vehicle plus TCS rescue medication

Following the 36-month DB phase, an interim-analysis will be performed to assess the efficacy of Elidel Cream 1%-LTM vs conventional management. Provided the analysis shows superiority of the Elidel Cream 1%-LTM, patients will enter an OL phase during which all patients will receive treatment with Elidel Cream 1%-LTM for up to a further 33 months.

Safety will be monitored by review of adverse events using electronic data capture. Safety results will be reviewed annually by an independent data safety monitoring board (DSMB). The DSMB will recommend whether to continue the trial or to stop for safety concerns. If the trial continues, only blinded results may be published.

Reporting

The final clinical study report will be available in 2011. Additionally, there will be an interim analysis at the end of 3 years, in 2008, which will ascertain whether Elidel Cream 1%-LTM provides better control of AD over 36 months than a conventional, TCS-based treatment.

7 Conclusion

- ?? Extensive safety experience exists with Elidel both in clinical trials (more than 19,000 patients) and with general clinical use in the population (estimated to be over 5 million patients totalizing 814,000 patient years of treatment)
- ?? Individual cases of malignancies (n=8) have been reported in patients. However, no causality between Elidel use and occurrence of malignancies has been established. Epidemiological analysis shows that there is no increase in lymphoma in Elidel treated patients over background rate in the normal population
- ?? Data from pharmacokinetic studies, the analysis of infections incidence, and *in vivo* immunocompetence assessments in humans demonstrate a lack of systemic immunosuppressive effect with Elidel Cream. The only signal observed is an increase in viral skin infection (relative risk of 1.6 versus vehicle), mainly herpes simplex, which is already mentioned in the US prescribing information.
- ?? A comprehensive clinical program is in place to continue to assess the long-term safety of Elidel Cream in pediatric and adult patients. The post-marketing safety surveillance continues to monitor adverse events of clinical significance.

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Zhang Y, Holford TR, Leaderer B et al. Hair coloring Products Use and Risk on Non-Hodgkin's Lymphoma: A Population-based Case-Control Study in Connecticut. Am J Epidemiol 2004; 159:148-154.

9 Other information

9.1 Number of patients who have participated in clinical trials

Table 9-1 below summarizes the total number of patients who have participated in registration and post-registration clinical trials (all indications) and those who are still participating as of January 15, 2005.

Table 9-1 Total number of patients who participated or are participating in clinical trials

Study number(s)	Patient population	Study duration	No. patients	No. patients who received PIM 1%
B005	adults	3 weeks	34	34
B202	adults	3 weeks	260	45
B305/B307/0316	B305/B307 (pediatric) 0316 (infants 3-23 months)	6 weeks double-blind (DB) followed by 20-week open label (OL) extensions	589	DB 389 OL 153
B313/0315	B313 (pediatric) 0315 (infants 3-23 months)	12 months DB, 0315 followed by 12 month open label extension	961	682
B308	adults	12 months	628	328
B009 (chronic hand dermatitis)	adults	6 weeks	48	24
B306 (chronic hand dermatitis)	adults	3 weeks followed by 23 weeks open label	294	151
B002/B010/B203/B204/B206 (allergic contact dermatitis)	adults	2-3 days	197	197 (1)
B001/B003/B004/B006/B007/ASQ0105 (chronic plaque psoriasis)	adults	14-21 days	103	103 (1)
C2306	Infants 3 to less than 12 months	5 years	1189	Approx. 594
C2314	Pediatric age =2 years– =17years	22 weeks	85	85

C2315	pediatric	6 months	524	252
C2316	adults	6 months	543	271
C2322	Pediatric and adults 2-65 years of age	4 weeks	336	168
C2401	adults	13 days	37	18
C2402	Pediatric and adult patients	6 weeks followed by 12 weeks open label	73	47
C2405	Infants > 3 months, pediatric and adults	6 months followed by 6-18 month extension	947	947
C2406	pediatric	6 weeks followed by 20 weeks open label	141	71
C2420	Infants > 3 months, pediatric and adults	3-12 months	2034	2034
C2434	adults	7 days followed by 5-week extension	198	100
C2435	= 2 years of age	6 weeks	41	41
C2442	Pediatric = 12 and adults	6 weeks followed by 6 weeks open label	66	Approx. 38
M2301 (chronic hand dermatitis)	Adults = 18 years of age	6 weeks followed by 6-week open label phase	620	Approx. 310
CA 01	Pediatric = 3 months and adults	6 months followed by extension study	516	516
CA 03	Adults	5 months	200	200
DE 01	adults	6 months	192	96
DE 04	Pediatric including infants	4 weeks DB followed by 12 weeks open label	196	DB 128 OL 59
DE 06	Adults	2 weeks	20	20
DE 07	Pediatric = 2 years and adults	3-5 weeks	5652	5652
DE 10	Pediatric = 2 < 18 years	6 months	184	92
DE 11	Pediatric = 2 years and adults	15 weeks	3588	3588

EG-01	Infants > 3 months, pediatric and adults	12 weeks	308	308
ES 01	Infants 3-23 months	3 weeks followed by 23 weeks open label	102	68
ES 02	Pediatric 2-11 years of age	3 weeks	117	78
GB 01	adults	12 months	202	202
JP 01	Infants = 3 months, pediatric = 12 years	3 weeks	18	18
MEX 01	Infants/pediatric	3 weeks followed by 24 weeks open label	108	108
US 01	= 11 years	3 weeks	49	49
US 02	adults	8 weeks	22	22
US 03	Adults 18-65 years of age	6 months	264	176
US 04	Infants = 3 months, pediatric = 11 years	6 months	275	183
US 05 (inverse psoriasis)	adults	8 weeks	57	28
US 08	pediatric	2 weeks	175	87
US 09	infants 3-18 months	6 years	945	Approx. 472
Total number of patients			23,138	19,232

(1) other pimecrolimus concentration were also used (eg. 0.03%, 0.1%, 0.2%, 0.3%, 0.6%)

PIM 1% = pimecrolimus 1%

9.2 List of studies including infants

Table 9-2 Summary of infant (< 24 months at baseline) data

Study	Type	Duration	Population	Treatment arms	N <24 months
0315 0315-E1	DB, randomized + OL extension	12 months + 12 months extension	3-23 months mild to severe	ELIDEL Cream 1% + TCS if needed Vehicle + TCS if needed	204 + 4 46
0316	DB, randomized + OL phase	6 weeks DB 20 weeks OL	3-23 months mild to severe	ELIDEL Cream 1% (DB +OL) Vehicle (DB)	122 + 51 63
2405 C2405E1	OL	6 months (6 months extension)	3 months to 17 years All severities	ELIDEL Cream 1% + CS if needed	177

Study	Type	Duration	Population	Treatment arms	N <24 months
US-04	DB, randomized	6 months	3 months to 11 years mild to severe	ELIDEL Cream 1% + TCS if needed in combination Vehicle +TCS if needed in combination	41 21
DE-04	DB, randomized + OL Phase	4 weeks DB 12 weeks OL	3-23 months mild to severe	ELIDEL Cream 1% (DB +OL) Vehicle (DB)	128+ 59 63
C2420 German patients only	OL	3 months	= 3 months almost clear to severe	ELIDEL Cream 1% + TCS if needed	312

Table 9-3 Summary of children and adults data (= 2 years at baseline)

Study	Type	Duration	Treatment arms	Population	N	N >18 years
					2 to 17 years	
B305	DB, randomized + OL phase	6 weeks DB 20 weeks OL	ASM (DB + OL) Vehicle (DB)	2 to 17 years	130 + (OL 48) 68	0
B307	DB, randomized + OL phase	6 weeks DB 20 weeks OL	ASM (DB + OL) Vehicle (DB)	2 to 17 years	137 + (OL 54) 68	0
B313	DB, randomized	12 months	ASM + CS if needed Vehicle + CS if needed	2 to 17 years	474 237	
DE-01	DB, randomized	6 months	ASM + CS if needed Vehicle + CS if needed	= 18 years		96 96
2405 + 2405E1	OL	6 months (6 months extension)	ASM + CS if needed	=3 months All severities	489	281
US-03	DB, randomized	6 months	ASM + CS if needed in combination Vehicle + CS if needed in combination	= 18 years		176 88
US-04	DB, randomized	6 months	ASM + CS if needed in combination Vehicle + CS if needed in combination	3 months to 11 years mild to severe	142 41	
C2315	DB, randomized	6 months	ASM + CS if needed Vehicle + CS if needed	2 to 17 years	256 265	
C2316	DB, randomized	6 months	ASM + CS if needed Vehicle + CS if needed	= 18 years		277 266
C2420	OL	3 months	ASM + CS if needed	= 3 months almost clear to severe	1099	623

ASM = Elidel (pimecrolimus) Cream 1%

9.3 Incidence of infections in post-registration global clinical trials (2315, 2316, 2405, 2420, US03, US04)

The next generation of Elidel studies has been able to build on some of the observations in the registration studies by incorporating a couple of key features:

- Increasing emphasis on precision for adverse event description and coding at the level of the study center, monitor, and Novartis personnel
- Study designs that minimize differences in time on study

In this section, the safety data on infections is summarized for six studies that are representative of the Elidel clinical program following registration. These six studies were chosen for this review because they have a robust number of patients, have been (or will be submitted) for publication, and have made contributions to our understanding of the clinical biology of Elidel. However, none of these studies was designed to focus solely on safety issues.

The objectives and basic information for each study will be presented, followed by a short summary of the infectious disease safety findings. For each study, the systemic infections and skin infections will be presented in the same table, but the different types of infections will be discussed separately if appropriate.

9.3.1 Study ASM981C2315

Title: A 26-week, randomized, multicenter, parallel-group, double-blind, vehicle-controlled study to evaluate the incidence of atopic dermatitis flares when ASM981 (pimecrolimus) cream 1% is used at the first signs and/or symptoms of atopic dermatitis and its safety and tolerability in children and adolescents 2-17 years of age.

Objectives:

Primary Objective: To demonstrate that the therapeutic efficacy of Elidel Cream 1% administered b.i.d. is superior to vehicle cream administered b.i.d. in preventing flares (as defined by reducing resultant reactive topical corticosteroid use) in AD over a 26-week period in children and adolescents 2-17 years of age.

Secondary Objectives: To demonstrate that the therapeutic efficacy of Elidel Cream 1% administered b.i.d. is superior to pimecrolimus vehicle cream administered b.i.d. in preventing flares of AD in children and adolescents as primarily demonstrated by ranking patients with regard to the number of flares they experience while participating in the 26-week study.

To evaluate the safety of Elidel-based treatment in AD.

Sample size: 521 patients randomized

Treatment duration: 26 weeks

Patient population (Age): children and adolescents 2-17 years of age

Table 9-4 **Number (%) of patients with most frequent infections and infestations
(? 2% for any group, rounded)**

	Elidel Cream 1% (N=246)	Vehicle cream (N=260)
	%	%
Nasopharyngitis	23.2	15.0
Influenza	6.9	6.2
Otitis media	6.1	6.5
Bronchitis	4.9	5.8
Rhinitis	4.5	5.4
Gastroenteritis	4.1	3.8
Upper respiratory tract infection	4.1	4.2
Gastroenteritis viral	3.7	2.7
Impetigo	3.7	2.3
Pharyngitis streptococcal	3.7	0.8
Varicella	3.7	3.1
Pharyngitis	3.3	3.1
Tonsillitis	2.8	3.1
Enterobiasis	2.4	0.4
Molluscum contagiosum	2.4	3.1
Respiratory tract infection	2.4	2.3
Otitis media acute	2.0	1.9
Sinusitis	2.0	0.8
Bacterial infection	1.6	1.2
Otitis externa	1.6	1.2
Pneumonia	1.6	0.4
Eczema infected	1.2	1.5
Skin bacterial infection	1.2	1.5
Acute tonsillitis	0.8	1.5

This table includes only patients who received at least 1 dose of study medication since study medication was usually not started at randomization (patients entered the study clear or almost clear of AD) or not used at all during the study.

Source: PTT 10.1-1

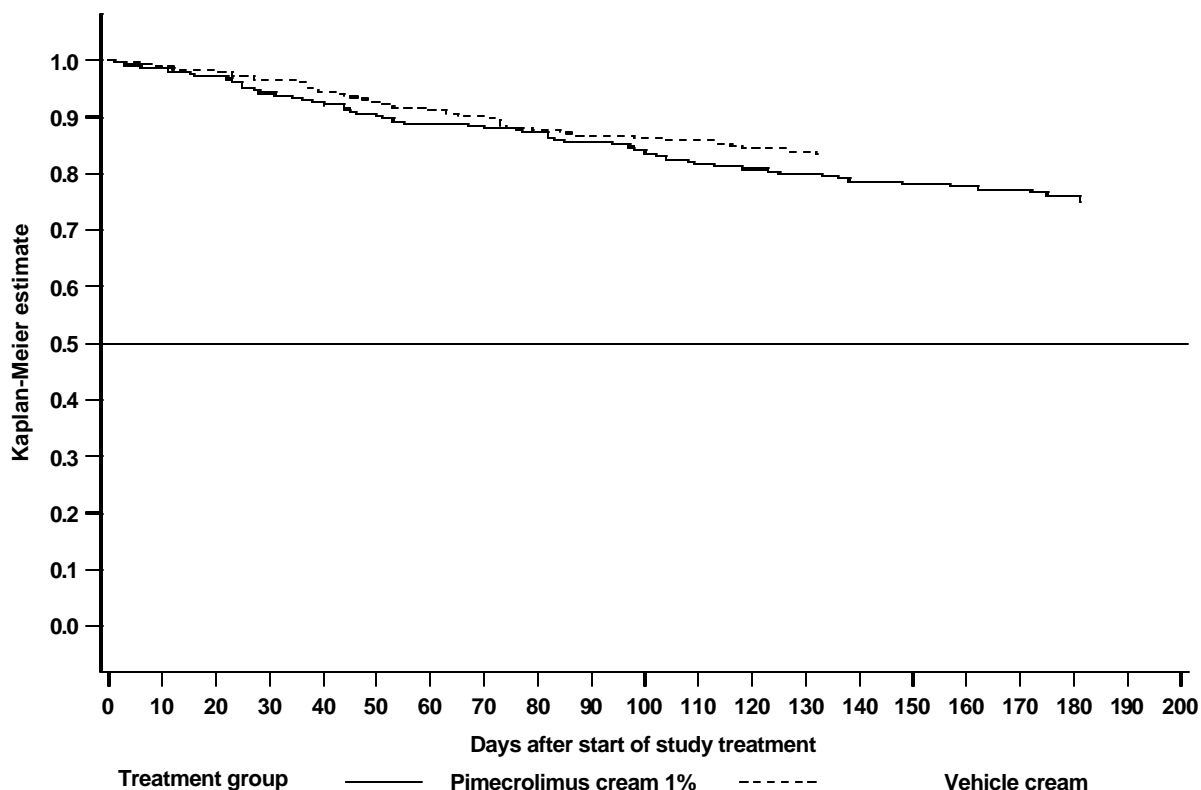
This table includes only patients who received at least 1 dose of study medication since study medication was usually not started at randomization (patients entered the study clear or almost clear of AD) or not used at all during the study.

Source: PTT 10.1-1

Summary:

Table 9-4, Infections and infestations were reported in a greater proportion of patients treated with pimecrolimus than in patients treated with vehicle. This was related to a higher incidence of nasopharyngitis in patients receiving pimecrolimus. Events of nasopharyngitis were generally mild to moderate in severity and few of these events were considered related to study medication by the investigator. Kaplan-Meier estimates for the time from start of study treatment to the first occurrence or worsening of nasopharyngitis showed no statistically significant differences between the treatment groups (Figure 9-1). In fact, approximately 80 days after the start of the study, the Kaplan-Meier displays completely overlap.

Figure 9-1 Kaplan-Meier plot for time from start of study treatment to first occurrence or worsening of nasopharyngitis



PTF10_1_01.SAS/DATAMAP/31AUG2004/16:02

<Reference: App 5.1 Output 4.2.2>

The increased incidence of nasopharyngitis (common cold) was not statistically significant, however, there was no clear explanation for the observed trend. One may speculate that the imbalance might have been due to other factors and not necessarily study medication e.g., more children at home or patient attending daycare which were not included in the analysis since such data was not collected during the study.

In addition, the lower rate in the vehicle group could be due to under-reporting. The common cold could be considered a benign (and not adverse) event and undisclosed differences in reporting of this event could be present in the treatment groups.

No clinically or statistically significant trends were observed for any other infectious events.

9.3.2 Study ASM981C2316

Title: A 26-week, randomized, multicenter, parallel-group, double-blind, vehicle-controlled study to evaluate the incidence of atopic dermatitis flares when ASM981 (pimecrolimus) cream 1% is used at the first signs and/or symptoms of atopic dermatitis and its safety and tolerability in adults 18 years of age and older.

Objectives:

Primary Objective: To demonstrate that the therapeutic efficacy of Elidel Cream 1% administered b.i.d. is superior to vehicle cream administered b.i.d. in preventing flares (as defined by reducing resultant reactive topical corticosteroid use) in AD over a 26-week period in adults 18 years of age and older.

Secondary Objectives: To demonstrate that the therapeutic efficacy of Elidel Cream 1% administered b.i.d. is superior to pimecrolimus vehicle cream administered b.i.d. in preventing flares of AD in adults as primarily demonstrated by ranking patients with regard to the number of flares they experience while participating in the 26-week study.

To evaluate the safety of pimecrolimus-based treatment in AD.

Sample size: 543 patients randomized

Treatment duration: 26 weeks

Patient population (Age): adults 18 years of age and older

Table 9-5 **Number (%) of patients with most frequent infections (? 2% for any group, rounded)**

	Elidel Cream 1% (N=264)	Vehicle cream (N=254)
	%	%
Nasopharyngitis	20.5	15.0
Influenza	6.4	6.7
Herpes simplex	3.4	4.7
Rhinitis	3.4	2.0
Sinusitis	3.0	1.6
Upper respiratory tract infection	2.3	4.3
Otitis externa	1.9	0.8
Pharyngitis	1.9	0.4
Urinary tract infection	1.9	0.8
Gastroenteritis	1.5	2.0
Otitis media	1.5	0.4

This table includes only patients who received at least 1 dose of study medication since study medication was usually not started at randomization (patients entered the study clear or almost clear of AD) or not used at all during the study.

Source: PTT 10.1-1

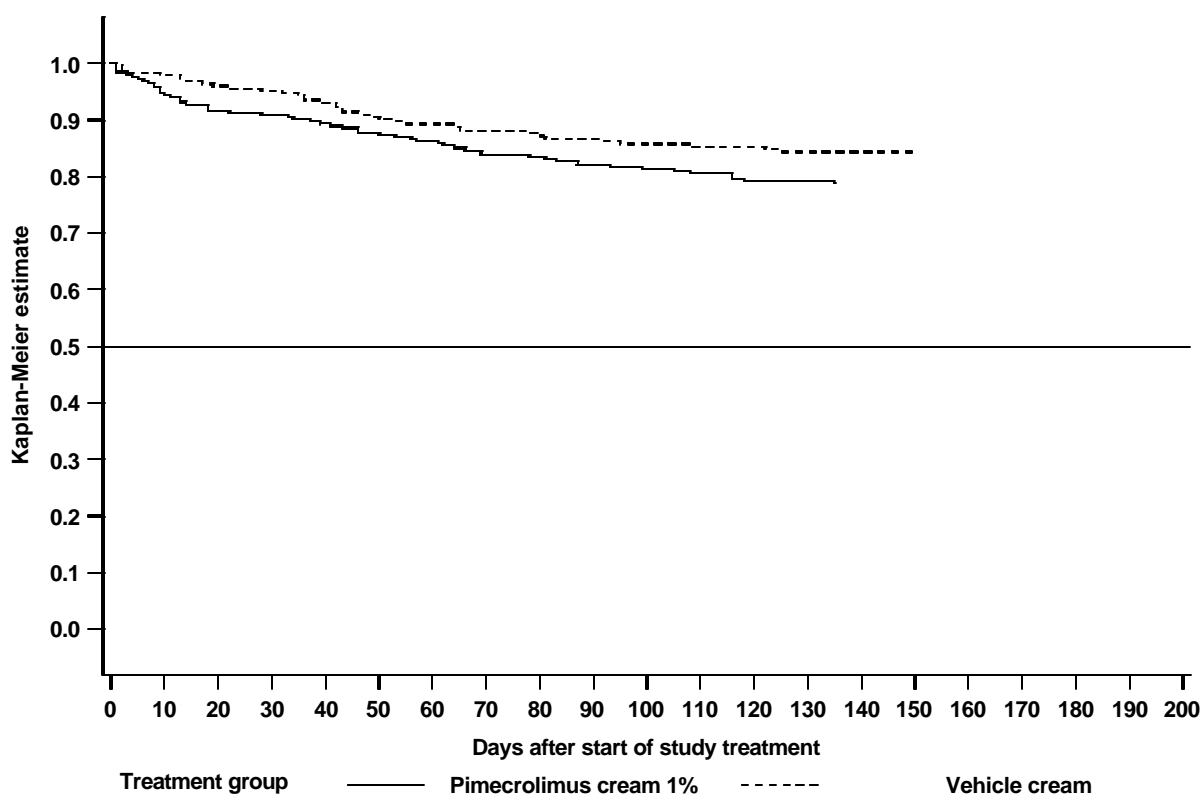
Summary:

Table 9-5, Infections and infestations were the most common AEs reported after the first use of study medication in both treatment groups, but the percentage of patients was higher in the Elidel group than in the vehicle group. As seen in the companion study, this was related to a higher incidence of nasopharyngitis in patients receiving Elidel although the absolute difference in this trial is less. This could signal that the study in adult patients was less influenced by the kind of artifactual factors that could be more prevalent in a pediatric population with AD (e.g., school environment, day care, etc.). Collection of this kind of information was beyond the scope of this trial. Events of nasopharyngitis were generally mild to moderate in severity, and none of the events were considered related to study medication by

the investigator. Kaplan-Meier estimates for the time from start of study treatment to the first occurrence or worsening of nasopharyngitis showed no statistically significant differences between the treatment groups (Figure 9-2). Again, this trend is probably not an Elidel Cream 1%-related effect. The adverse event of nasopharyngitis will be discussed in detail at the conclusion of this section.

No clinically or statistically significant trends were observed for any other infectious events.

Figure 9-2 **Kaplan-Meier plot for time from start of study treatment to first occurrence or worsening of nasopharyngitis**



PTF10_1_01.SAS/DATAMAP/06OCT2004/14:52

<Reference: App 5.1 Output 4.2.2>

9.3.3 Study ASM981C2420

Title: Naturalistic, open-label, multicenter study of long-term management in patients ≥ 3 months of age with mild or moderate atopic dermatitis using Elidel Cream 1%.

Objectives:

The objectives of the study were:

- To monitor the safety of Elidel Cream 1% when used in the long-term management of atopic dermatitis in a naturalistic clinical setting

- To evaluate the effectiveness of the Elidel Cream 1% long-term management in a naturalistic setting by means of the Investigator Global Assessment (IGA)
- To evaluate the effect of Elidel Cream 1% on pruritus
- To evaluate the patient's global satisfaction with therapy

Sample size: 2034 patients enrolled

Treatment duration: at least 3 months and until the time of launch and/or reimbursement of Elidel Cream 1% in the respective country (3 up to 12 months)

Patient population (Age): ≥ 3 months of age

Table 9-6 **Number (%) of patients with most frequent infections (? 2% of patients, rounded)**

	Elidel Cream 1% (N=2034) %
Nasopharyngitis	18.2
Rhinitis	5.4
Influenza	5.0
Bronchitis	4.0
Upper respiratory tract infection	3.5
Impetigo	3.4
Pharyngitis	2.6
Herpes simplex	2.5
Tonsillitis	2.0
Gastroenteritis	1.9
Ear infection	1.8
Varicella	1.8
Application site infection	1.5
Respiratory tract infection	1.5
Source: PTT 10.1-1	

Summary:

Table 9-6 lists infections and infestations AEs including nasopharyngitis (18.2%), rhinitis (5.4%), influenza (5.0%), bronchitis (4%) and upper respiratory tract infections (3.5%).

The infection rates are consistent with other Elidel Cream 1% studies. The infections observed are commonplace infections.

In this study, eczema herpeticum was reported at low rates. Four patients (0.2%) with a total of 8 events were identified, none of which were virologically confirmed.

Local treatment-emergent adverse events occurred in 35.2% of patients. About 15.3% of all patients experienced local treatment-emergent adverse events which coded to the MedDRA system organ class Infections and Infestations. These events included impetigo (3.4%), herpes simplex (2.4%), varicella (1.8%), application site infection (1.5%), folliculitis (1.3%), molluscum contagiosum (1.0%) and skin bacterial infection (0.7%).

9.3.4 Study ASM981US03

Title: A 6 month, randomized, multicenter, parallel-group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of Elidel Cream 1% BID vs standard of care in the management of mild to severe atopic dermatitis in adults.

Objectives:

The primary objective of this study was to compare efficacy and safety of Elidel Cream 1% foundation therapy and conventional therapy over a 6-month treatment period in adults with mild to severe atopic dermatitis. Foundation therapy is emollients for underlying dry skin, Elidel Cream 1% at the earliest signs/symptoms of eczema, and topical corticosteroids for severe flares. Conventional therapy is emollients for underlying dry skin and topical corticosteroids for established flares.

The secondary objectives of this study were to:

- Compare the total corticosteroid exposure of adults treated with Elidel foundation therapy with that of those receiving standard of care therapy
- Evaluate the major signs/symptoms of adults with mild to severe atopic dermatitis treated with Elidel versus standard of care therapy
- Explore the synergic potential of Elidel and topical corticosteroids used during the same time frame to treat atopic dermatitis disease flares
- Assess the quality of life of patients with atopic dermatitis treated with Elidel versus standard of care therapy

Sample Size: A total of 264 patients were randomized in a 2:1 ratio to Elidel Cream or to vehicle (176 patients in the Elidel group and 88 patients in the vehicle group). The safety population consisted of 264 patients, all of whom received at least 1 dose of trial medication.

Treatment Duration: 6 months

Patient Population (Age): adults ages 18-65 years

Table 9-7 Number (%) of patients with most frequent infections (? 2% of patients, rounded)

	Elidel (N=176)	Vehicle (N=88)
	%	%
URI NOS	10.8	6.8
Nasopharyngitis	7.4	13.6
Skin bacterial infection	4.5	1.1
Influenza	4.0	1.1
Ear infection NOS	1.7	1.1
Folliculitis	1.7	1.1
URI viral NOS	1.7	0
Sinusitis NOS	3.4	3.4
Pharyngitis	1.1	6.8

NOS = not otherwise specified, URI = upper respiratory tract infection

Source: PTT 10.1-1

Summary:

Table 9-7 lists the most frequently reported infections and infestations AEs with a crude incidence = 2%. The most frequent type of treatment emergent adverse events reported were URI NOS (10.8% Elidel, 6.8% vehicle) and nasopharyngitis (7.4% Elidel, 13.6% vehicle). Of the infections and infestations AEs reported with a crude incidence = 2%, only pharyngitis showed significance between the 2 treatment groups based on the Fisher exact test ($P=0.018$) and was significantly more frequent in the vehicle group. Only 2 (1.1%; 2/176) patients randomized to the pimecrolimus group reported pharyngitis, while 6 (6.8%; 6/88) patients randomized to vehicle reported an event of pharyngitis. Note that in this study of adults, the incidence of both nasopharyngitis and pharyngitis was higher in the vehicle group.

9.3.5 Study ASM981US04

Title: A 6 month, randomized, multicenter, parallel-group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of ASM 981 (pimecrolimus) cream 1% BID vs standard of care in the management of mild to severe atopic dermatitis in children 3 months to 11 years.

Objectives:

The primary objective of this study was to compare the efficacy and safety of ASM 981 cream 1% foundation therapy and conventional therapy over a 6-month treatment period in children (3 months to 11 years) with mild to severe atopic dermatitis (AD). Foundation therapy is emollients for underlying dry skin, Elidel Cream 1% at the earliest signs/symptoms of eczema, and topical corticosteroids for severe flares. Conventional therapy is emollients for underlying dry skin and topical corticosteroids for established flares.

The secondary objectives of this study were to:

- Compare the total corticosteroid exposure of children treated with ASM foundation therapy with that of those receiving standard-of-care therapy;
- Evaluate the major signs/symptoms of children with mild to severe AD treated with ASM versus standard-of-care therapy;
- Explore the synergistic potential of ASM and topical corticosteroids used during the same time frame to treat atopic dermatitis disease flares;
- Assess the quality of life of pediatric AD patients and their caregivers in each treatment group.

Sample Size: A total of 275 patients were randomized in a 2:1 ratio Elidel to vehicle (183 patients in the ASM 981 cream 1% group and 92 patients in the vehicle group) and 275 patients were included in the analysis. The safety population consisted of 275 patients, all of whom received at least 1 dose of trial medication.

Treatment Duration: 6 months

Patient Population (Age): children ages 3 months to 11 years

Table 9-8 **Number (%) of patients with most frequent infections (? 2% of patients, rounded)**

	Elidel (N=183) %	Vehicle (N=92) %
URI NOS	18.0	17.4
Otitis media NOS	9.3	3.3
Nasopharyngitis	8.7	12.0
Sinusitis	4.9	4.3
Ear infection NOS	4.4	7.6
Impetigo NOS	4.4	5.4
Pharyngitis	4.4	2.2
Pharyngitis NOS	3.3	1.1
Gastroenteritis viral NOS	3.3	2.2
Pharyngitis streptococcal	2.7	2.2
Skin infection NOS	2.2	2.2
Urinary tract infection	2.2	1.1
Viral infection NOS	2.2	1.1
Cellulitis	1.6	0
Furuncle	1.6	0
Influenza	1.6	0
URI viral NOS	1.6	1.1
Viral rash NOS	1.6	0
Bronchitis NOS	0.5	2.2
Body tinea	0.5	2.2
Fungal infection NOS	0	2.2

NOS = not otherwise specified, URI = upper respiratory tract infection

Source: PTT 10.1-1

Summary:

Table 9-8 lists the most frequently reported infections and infestations with a crude incidence $\geq 2\%$. The most frequent type of treatment emergent adverse event reported was consistent with a respiratory infection such as a upper respiratory tract infection NOS (18.0% Elidel, 17.4% vehicle), nasopharyngitis (8.7% Elidel, 12% vehicle), and sinusitis NOS (4.9% Elidel, 4.3% vehicle). Other common adverse events included ear infection (4.4% Elidel, 7.6% vehicle), otitis media (9.3% Elidel, 3.3% vehicle), and impetigo (4.4% Elidel, 5.4% vehicle).

Note that the incidence of nasopharyngitis is higher in the vehicle group. Although the incidence of otitis media is higher in the Elidel Cream 1% group, the incidence of ear infection is higher in the vehicle group. Because the majority of ear infections in this age group are otitis media, the trends balance one another out.

Most skin infections were considered to be of mild to moderate severity. Only one case of impetigo in the Elidel group was considered to be severe. None demonstrated a between-treatment significance based on analysis of the crude incidence.

9.3.6 Study ASM981C2405

Title: A 6 month, open label, multi-national, effectiveness, and safety study of pimecrolimus cream 1% in subjects with atopic dermatitis.

Objectives:

The primary objective was to evaluate the effectiveness of Elidel Cream 1% over a 6-month period of time when it is used as foundation therapy for the treatment of atopic dermatitis (AD).

The secondary objectives were to evaluate the safety of Elidel Cream 1% over a 6-month period of time when it is used as foundation therapy for the treatment of AD; develop an understanding of procedures used by physicians that tend to optimize results with pimecrolimus cream 1% (e.g., use of emollients, bathing practices, etc.); develop a database on prior use/experience with topical corticosteroids, and reasons for desired switch (e.g., safety concerns (real or imaginary)), efficacy issues with topical corticosteroids); evaluate methods for optimal long-term treatment and maintenance regimens according to subject characteristics (data modeling from periodic analyses, generation of treatment algorithms).

Sample Size: 947 patients enrolled

Treatment Duration: 6 months

Patient Population (Age): = 3 months of age

Table 9-9 Number (%) of patients with most frequent infections (? 2% of patients, rounded)

	Elidel (N=947) %
Nasopharyngitis	12.7
Upper respiratory tract infection NOS	10.0
Otitis media NOS	4.6
Ear infection NOS	4.0
Influenza	3.0
Sinusitis NOS	2.7
Bronchitis NOS	2.3
Impetigo NOS	2.2
Herpes simplex	2.1
Pharyngitis streptococcal	1.7
Folliculitis	1.6
Gastroenteritis NOS	1.6
Viral infection NOS	1.6
Rhinitis NOS	1.6

NOS = not otherwise specified

Source: PTT 10.1-1

Summary:

Table 9-9 lists the incidence of infections and infestations. Overall infections and infestations were reported in 45.3% of the patients. The more commonly reported infections AEs included

nasopharyngitis (12.7%), upper respiratory tract infection NOS (10.0%). These events are commonly seen in AD patients. Herpes simplex virus infections were seen in 2.1% of patients. The rates and patterns of infections are similar to those seen in other studies.

In this study, eczema herpeticum was reported in 0.6% of patients and 5 of the 6 cases were suspected to be related to study medication by the investigator and 2 cases were confirmed by viral culture. Two patients required hospitalization for eczema herpeticum and none of them prematurely discontinued from the study.

ASM981C2405 Extension

Title: An open label effectiveness and safety study of pimecrolimus cream 1% in subjects with atopic dermatitis who completed study ASM981C2405.

Objectives:

To assess the long-term efficacy and safety of Elidel Cream 1% beyond the 6 month timeframe of study ASM981C2405.

Sample Size: 361 patients

Treatment Duration: The duration of the Extension study was variable, ranging from about 6 to 18 months, depending on the time of launch and/or reimbursement of Elidel Cream 1% in participating countries.

Patient Population (Age): = 3 months of age

Table 9-10 **Number (%) of patients with most frequent infections (? 2% of patients, rounded)**

	Elidel (N=361)
	%
Nasopharyngitis	13.9
Upper respiratory tract infection	6.4
Influenza	6.1
Ear infection	3.9
Bronchitis	3.0
Tonsillitis	2.8
Gastroenteritis	2.2
Herpes simplex	1.9
Molluscum contagiosum	1.9
Impetigo	1.7
Gastrointestinal infection	1.7

Source: PTT 10.1-1

Summary:

Table 9-10 displays the crude incidence of infections and infestations = 2%. The more commonly reported infections AEs included nasopharyngitis (13.9%), upper respiratory tract infection NOS (6.4%). Molluscum contagiosum and herpes simplex were reported in seven patients each (1.9%). There were 4 patients with varicella (1.1%). The most common events are similar in nature to those seen in the other clinical studies.

9.3.7 Focus on nasopharyngitis – the most common adverse event in clinical trials

Because nasopharyngitis is the most common adverse event in many Elidel Cream 1% clinical trials, it will be examined more closely here.

Table 9-11 displays the incidence of nasopharyngitis in major registration and post-registration studies.

There is no consistent pattern to the incidence trend. In some trials, it is higher in the Elidel Cream 1% group; in others it is higher in the vehicle group. Constancy of pattern from study to study would be expected if the event were related to an actual drug effect.

Table 9-11 Incidence of nasopharyngitis in major registration and post-registration studies

Study (duration; pt. population)	Incidence of nasopharyngitis n (%)	
	Elidel Cream 1%	Vehicle cream (if applicable)
B305 (26 wks; 2-17 yo)	14 (10.8)	3 (4.4)
B307 (26 wks; 2-17 yo)	13 (9.5)	7 (10.3)
B313 (12 months; 2-17 yo)	124 (26.2)	53 (22.4)
0315 (12 months; 3-23 months of age)	101 (49.5)	17 (37.0)
0316 (6 wk DB, 20 wk OL; 3-23 months of age)	18 (14.6)	5 (7.9)
C2315 (26 wks; 2-17 yo)	57 (23.2)	39 (15.0)
C2316 (26 wks; >=18 yo)	54 (20.5)	38 (15.0)
C2405 (6 months; >= 3 months of age)	120 (12.7)	NA
C2405 extension (6-18 months; >= 3 months of age)	50 (13.9)	NA
C2420 (3-12 months; >=3 months of age)	370 (18.2)	NA
US03 (6 months; 18-65 yo)	13 (7.4)	12 (13.6)
US04 (6 months; 3 months—11 yo)	16 (8.7)	11 (12.0)

Some additional data that indicate that nasopharyngitis incidence is not related to Elidel Cream 1% administration comes from the clinical program for oral pimecrolimus tablets. In clinical studies involving pimecrolimus tablets, the compound is absorbed systemically, with systemic exposure on average 16 to 20 higher than the maximum systemic exposure observed with pimecrolimus cream 1%. Pooled data from three Phase II studies are now available. In 175 patients given oral pimecrolimus at a dose of 30 mg bid, the incidence of nasopharyngitis was 15.4%. In a population of placebo patients in the same trials, the incidence of nasopharyngitis was higher, at 16.1%. These data support the assertion that an event such as nasopharyngitis is not related to Elidel Cream 1% use, but rather other factors that might be present in a clinical trial.

9.3.8 Conclusions - infections observed in post-marketing trials

The six studies described above are representative of the Elidel Cream 1% clinical research program following approval. The comprehensive review of the data related to infectious diseases displayed above indicates that no trends regarding the common infections are present that would warrant a change in the labeling or prescribing information for Elidel Cream 1%.

It is also worth noting:

- It is important to distinguish commonplace infections from those that would be indicative of immunosuppression. All infections seen in these studies are common infections. These should be considered side effects, not untoward events. These events are common in the general population and there is no evidence they are related to Elidel Cream 1%.
- The formal clinical program for Elidel Cream 1% involves more than 19,000 patients
- No opportunistic infections, that would indicate immunosuppression, have been seen in any Elidel Cream 1% clinical study or in the marketplace post-approval

10 Appendices

1. Expert reports on lymphoma cases (J. Friedberg, O. Kamel, H. Lazarus)
2. Post-text tables of pooled safety analysis of adults, children, and infants