



Clinical trial results:

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.

Summary

EudraCT number	2017-001765-25
Trial protocol	Outside EU/EEA
Global end of trial date	28 January 2008

Results information

Result version number	v1 (current)
This version publication date	25 March 2018
First version publication date	25 March 2018

Trial information

Trial identification

Sponsor protocol code	CASM981CUS09
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
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Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 January 2008
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 January 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to investigate the atopic disease modifying capabilities of Elidel with early intervention. This study assessed whether, in atopic infants with AD and a family history of atopy, Elidel-LTM provided better control of AD over 36 months than a vehicle/corticosteroid (CS)-based treatment (assessed as proportion of disease-free days without CS/without study medication, and length of AD remissions). This study will also assess whether commencement of Elidel-LTM soon after the first diagnosis of AD, compared with delaying intervention by 3 years, reduces the incidence of asthma at 6 years of age.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 October 2003
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 1087
Worldwide total number of subjects	1087
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	907
Adolescents (12-17 years)	160
Adults (18-64 years)	20
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

546 started in the Elidel arm, but 3 patients did not receive drug. 545 started in the comparator arm, but 1 patient did not receive drug.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Pimecrolimus (Elidel) Treatment Group

Arm description:

Pimecrolimus (Elidel) 1% Cream twice a day/topical corticosteroid rescue

Arm type	Experimental
Investigational medicinal product name	1% cream
Investigational medicinal product code	ASM981
Other name	Elidel
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

patients were dispensed Elidel cream at or between each study visit to apply topically to affected areas twice daily at the first signs and symptoms of AD and continued until clearance was achieved.

Arm title	Control Treatment Group
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Arm description:

Management with vehicle/topical corticosteroid rescue.

Arm type	Experimental
Investigational medicinal product name	vehicle cream
Investigational medicinal product code	vehicle cream
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

patients were dispensed vehicle cream at or between each study visit to apply topically to affected areas twice daily at the first signs and symptoms of AD and continued until clearance was achieved.

Number of subjects in period 1	Pimecrolimus (Elidel) Treatment Group	Control Treatment Group
Started	543	544
Completed	291	273
Not completed	252	271
Consent withdrawn by subject	127	136
Adverse event, non-fatal	3	-
Lost to follow-up	114	120
Lack of efficacy	5	10
Protocol deviation	3	5

Baseline characteristics

Reporting groups

Reporting group title	Pimecrolimus (Elidel) Treatment Group
Reporting group description: Pimecrolimus (Elidel) 1% Cream twice a day/topical corticosteroid rescue	
Reporting group title	Control Treatment Group
Reporting group description: Management with vehicle/topical corticosteroid rescue.	

Reporting group values	Pimecrolimus (Elidel) Treatment Group	Control Treatment Group	Total
Number of subjects	543	544	1087
Age Categorical Units: Subjects			
2 y - <12 y	462	445	907
12y - <18 y	71	89	160
18 y - <65 y	10	10	20
Age Continuous Units: months			
arithmetic mean	7.1	7.4	
standard deviation	± 3.76	± 4.06	-
Gender, Male/Female Units: Subjects			
Female	194	218	412
Male	349	326	675
Study Specific Characteristic Parents' Index of Quality of Life - Atopic Dermatitis Score			
Parents' Index Quality of Life - Atopic Dermatitis (PIQoL-AD) score = (sum of valid items/number of valid items)*28. Scores range from a total possible minimum value of 0 to a maximum value of 28, with a high total overall score indicating poor quality of life.			
Units: Scores on PIQoL-AD Scale			
arithmetic mean	6.5	6.9	
standard deviation	± 4.73	± 4.92	-

End points

End points reporting groups

Reporting group title	Pimecrolimus (Elidel) Treatment Group
Reporting group description:	Pimecrolimus (Elidel) 1% Cream twice a day/topical corticosteroid rescue
Reporting group title	Control Treatment Group
Reporting group description:	Management with vehicle/topical corticosteroid rescue.

Primary: Atopic Dermatitis (AD) disease control over 36 months

End point title	Atopic Dermatitis (AD) disease control over 36 months
End point description:	Proportion of disease-free days in Step 2 or less (per Patient) using total number of days in study as the denominator- double-blind phase. Intent to Treat Population: defined as all randomized patients who were dispensed study medication and had at least one post baseline efficacy measurement.
End point type	Primary
End point timeframe:	36 months

End point values	Pimecrolimus (Elidel) Treatment Group	Control Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	530	523		
Units: Proportion of disease free days				
arithmetic mean (standard deviation)	0.4404 (\pm 0.29876)	0.4346 (\pm 0.29317)		

Statistical analyses

Statistical analysis title	Atopic Dermatitis Disease Control
Statistical analysis description:	A disease-free day in Step 2 or less was defined as a diary day with variable "No or almost no eczema?"=yes and "medication used variable "=no except emollients, yellow label medication 2X day, or medication deviation of yellow label medication 1x day.
Comparison groups	Pimecrolimus (Elidel) Treatment Group v Control Treatment Group
Number of subjects included in analysis	1053
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7901
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.0046

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.029
upper limit	0.0381

Secondary: Long term safety in infants and young children

End point title	Long term safety in infants and young children
End point description:	
Note: The results of this secondary outcome is not reported due to early termination of the study.	
End point type	Secondary
End point timeframe:	
6 years	

End point values	Pimecrolimus (Elidel) Treatment Group	Control Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[1]	0 ^[2]		
Units: Participants				
number (not applicable)				

Notes:

[1] - The results of this secondary outcome is not reported due to early termination of the study.

[2] - The results of this secondary outcome is not reported due to early termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of allergic rhinitis, allergic conjunctivitis and food allergies

End point title	Incidence of allergic rhinitis, allergic conjunctivitis and food allergies
End point description:	
Percentage of Patients who had allergic rhinitis, allergic conjunctivitis and food allergies at the end of the 36 month double blind study. Note: The results at six years are not reported due to early termination of the study.	
End point type	Secondary
End point timeframe:	
6 years (36 month Double-Blind Phase)	

End point values	Pimecrolimus (Elidel) Treatment Group	Control Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	533	532		
Units: Percentage of Participants				
number (not applicable)				
Diagnosis of Food Allergy	16.1	13.2		
Diagnosis of Allergic rhinitis	18.6	16.4		
Diagnosis of Allergic conjunctivitis	12.4	10.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Corticosteroid and Pimecrolimus drug use

End point title	Corticosteroid and Pimecrolimus drug use
End point description: Corticosteroid and pimecrolimus study medication days of exposure during the 36 month double-blind phase. Note: Although the double-blind phase was designed to be 36 months (3 years) in length, the last double-blind visit for some patients occurred after 36 months.	
End point type	Secondary
End point timeframe: 48 months	

End point values	Pimecrolimus (Elidel) Treatment Group	Control Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	530	523		
Units: Days of Exposure				
arithmetic mean (standard deviation)				
Double -blind phase	264.8 (± 259.49)	249.6 (± 251.71)		
0-12 months (Year 1)	146.6 (± 105.75)	147.6 (± 112.69)		
13-24 months (Year 2)	75.0 (± 105.08)	65.0 (± 97.42)		
25-36 months (Year 3)	42.2 (± 83.65)	36.6 (± 76.31)		
37-48 months (Year 4)	1.1 (± 5.74)	1.0 (± 5.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Atopic Dermatitis (AD) remission time

End point title	Atopic Dermatitis (AD) remission time
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End point description:

Longest duration of atopic dermatitis (AD) remission during the 36 month double-blind treatment phase. A remission day was defined as a diary day with a positive response ("yes") to the question "No or almost no eczema?" and a response of no treatment except emollients to the question "Medication used".

End point type	Secondary
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End point timeframe:

36 month Double-Blind Phase

End point values	Pimecrolimus (Elidel) Treatment Group	Control Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	530	523		
Units: Days				
arithmetic mean (standard deviation)	105.9547 (± 137.61350)	117.1071 (± 150.33993)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient/Caregiver quality of life

End point title	Patient/Caregiver quality of life
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End point description:

Change from Baseline in the total Parents' Index of Quality of Life-Atopic Dermatitis (PIQoL-AD) score in the double-blind phase. PIQoL-AD Score = (sum of valid items/number of valid items) * 28. Scores range from a minimum value of 0 to a maximum value of 28 with a high total overall score indicating poor quality of life.

End point type	Secondary
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End point timeframe:

From Baseline to Visit 5 , 6, 8, 10, 12, and 14

End point values	Pimecrolimus (Elidel) Treatment Group	Control Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	533	523		
Units: Scores on PIQoL-AD Scale				
arithmetic mean (standard deviation)				
Change in Baseline to Visit 5 (Week 14)	-2.6 (± 3.67)	-2.3 (± 3.37)		
Change in Baseline to Visit 6 (Week 27)	-2.7 (± 3.84)	-2.7 (± 3.83)		
Change in Baseline to Visit 8 (Week 53)	-2.9 (± 3.97)	-3.1 (± 4.23)		

Change in Baseline to Visit 10 (Week 88)	-3.1 (± 4.13)	-3.5 (± 4.23)		
Change in Baseline to Visit 12 (Week 122)	-3.3 (± 4.15)	-3.6 (± 4.39)		
Change in Baseline to Visit 14 (Week 158)	-3.5 (± 4.28)	-3.8 (± 4.35)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	9.1
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Reporting groups

Reporting group title	Pimecrolimus (Elidel) Treatment Group
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Reporting group description:

Pimecrolimus (Elidel) Treatment Group

Reporting group title	Control Treatment Group
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Reporting group description:

Control Treatment Group

Serious adverse events	Pimecrolimus (Elidel) Treatment Group	Control Treatment Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 543 (7.73%)	37 / 544 (6.80%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to lung			
subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephroblastoma			
subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Adverse drug reaction			

subjects affected / exposed	0 / 543 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 543 (0.00%)	2 / 544 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food allergy			
subjects affected / exposed	0 / 543 (0.00%)	2 / 544 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Milk allergy			
subjects affected / exposed	0 / 543 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prepuce redundant			
subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			

subjects affected / exposed	7 / 543 (1.29%)	5 / 544 (0.92%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial hyperreactivity			
subjects affected / exposed	3 / 543 (0.55%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 543 (0.18%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiglottic oedema			
subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 543 (0.18%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status asthmaticus			
subjects affected / exposed	3 / 543 (0.55%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wheezing			

subjects affected / exposed	2 / 543 (0.37%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 543 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 543 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic trauma			
subjects affected / exposed	0 / 543 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 543 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Therapeutic agent toxicity			
subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Von Willebrand's disease			
subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	2 / 543 (0.37%)	2 / 544 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 543 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic thrombocytopenic purpura			
subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal haemorrhage			
subjects affected / exposed	0 / 543 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intussusception			
subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 543 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenovirus infection			

subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Beta haemolytic streptococcal infection			
subjects affected / exposed	0 / 543 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	2 / 543 (0.37%)	3 / 544 (0.55%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 543 (0.00%)	2 / 544 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Croup infectious			
subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema infected			
subjects affected / exposed	0 / 543 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 543 (0.37%)	2 / 544 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	3 / 543 (0.55%)	4 / 544 (0.74%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 543 (0.18%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngotracheo bronchitis			
subjects affected / exposed	0 / 543 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node abscess			
subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 543 (0.18%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 543 (1.10%)	6 / 544 (1.10%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 543 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			

subjects affected / exposed	1 / 543 (0.18%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 543 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	2 / 543 (0.37%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	2 / 543 (0.37%)	2 / 544 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotavirus infection			
subjects affected / exposed	0 / 543 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 543 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis streptococcal			
subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	2 / 543 (0.37%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 543 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	4 / 543 (0.74%)	5 / 544 (0.92%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	1 / 543 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Pimecrolimus (Elidel) Treatment Group	Control Treatment Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	482 / 543 (88.77%)	466 / 544 (85.66%)	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	123 / 543 (22.65%)	123 / 544 (22.61%)	
occurrences (all)	207	173	
Immune system disorders			
Food allergy			
subjects affected / exposed	140 / 543 (25.78%)	118 / 544 (21.69%)	
occurrences (all)	238	194	

Milk allergy subjects affected / exposed occurrences (all)	50 / 543 (9.21%) 52	34 / 544 (6.25%) 34	
Eye disorders			
Conjunctivitis subjects affected / exposed occurrences (all)	50 / 543 (9.21%) 61	44 / 544 (8.09%) 65	
Conjunctivitis allergic subjects affected / exposed occurrences (all)	76 / 543 (14.00%) 85	63 / 544 (11.58%) 66	
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	55 / 543 (10.13%) 64	46 / 544 (8.46%) 53	
Teething subjects affected / exposed occurrences (all)	134 / 543 (24.68%) 169	135 / 544 (24.82%) 189	
Vomiting subjects affected / exposed occurrences (all)	34 / 543 (6.26%) 40	29 / 544 (5.33%) 34	
Respiratory, thoracic and mediastinal disorders			
Asthma subjects affected / exposed occurrences (all)	62 / 543 (11.42%) 76	51 / 544 (9.38%) 62	
Cough subjects affected / exposed occurrences (all)	187 / 543 (34.44%) 420	174 / 544 (31.99%) 312	
Nasal congestion subjects affected / exposed occurrences (all)	52 / 543 (9.58%) 67	43 / 544 (7.90%) 47	
Rhinitis allergic subjects affected / exposed occurrences (all)	122 / 543 (22.47%) 133	107 / 544 (19.67%) 118	
Rhinorrhoea subjects affected / exposed occurrences (all)	68 / 543 (12.52%) 114	63 / 544 (11.58%) 102	

Wheezing subjects affected / exposed occurrences (all)	102 / 543 (18.78%) 187	89 / 544 (16.36%) 160	
Skin and subcutaneous tissue disorders			
Dermatitis diaper subjects affected / exposed occurrences (all)	44 / 543 (8.10%) 59	46 / 544 (8.46%) 54	
Urticaria subjects affected / exposed occurrences (all)	41 / 543 (7.55%) 57	31 / 544 (5.70%) 47	
Infections and infestations			
Bronchiolitis subjects affected / exposed occurrences (all)	27 / 543 (4.97%) 34	30 / 544 (5.51%) 35	
Bronchitis subjects affected / exposed occurrences (all)	41 / 543 (7.55%) 53	29 / 544 (5.33%) 36	
Conjunctivitis bacterial subjects affected / exposed occurrences (all)	39 / 543 (7.18%) 42	45 / 544 (8.27%) 55	
Croup infectious subjects affected / exposed occurrences (all)	46 / 543 (8.47%) 64	51 / 544 (9.38%) 81	
Gastroenteritis subjects affected / exposed occurrences (all)	53 / 543 (9.76%) 59	49 / 544 (9.01%) 60	
Gastroenteritis viral subjects affected / exposed occurrences (all)	75 / 543 (13.81%) 108	68 / 544 (12.50%) 101	
Impetigo subjects affected / exposed occurrences (all)	22 / 543 (4.05%) 26	37 / 544 (6.80%) 49	
Nasopharyngitis subjects affected / exposed occurrences (all)	186 / 543 (34.25%) 451	175 / 544 (32.17%) 480	
Otitis media			

subjects affected / exposed	264 / 543 (48.62%)	260 / 544 (47.79%)
occurrences (all)	632	626
Pharyngitis streptococcal		
subjects affected / exposed	35 / 543 (6.45%)	55 / 544 (10.11%)
occurrences (all)	46	79
Pneumonia		
subjects affected / exposed	40 / 543 (7.37%)	39 / 544 (7.17%)
occurrences (all)	48	51
Rhinitis		
subjects affected / exposed	52 / 543 (9.58%)	49 / 544 (9.01%)
occurrences (all)	79	76
Sinusitis		
subjects affected / exposed	75 / 543 (13.81%)	61 / 544 (11.21%)
occurrences (all)	113	98
Upper respiratory tract infection		
subjects affected / exposed	287 / 543 (52.85%)	265 / 544 (48.71%)
occurrences (all)	969	854
Viral rash		
subjects affected / exposed	29 / 543 (5.34%)	29 / 544 (5.33%)
occurrences (all)	34	33
Viral upper respiratory tract infection		
subjects affected / exposed	37 / 543 (6.81%)	38 / 544 (6.99%)
occurrences (all)	50	49

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 November 2005	Amendment 1 resulted in the following changes to the original protocol:• Due to continuing difficulties of a technical nature with the e-CRF used at study sites, a paper-based CRF (p-CRF) was introduced on 08 November 2005 for use in the study. • Difficulty in defining what constitutes an urban as opposed to a rural environment resulted in this question being removed from the allergy history CRF. Typographical errors were corrected.
17 October 2006	Amendment 2 resulted in the following changes to the amended protocol:• Information about the patients' race/ethnicity, breastfeeding history, and the patients' family history of atopy were collected. • An ichthyosis assessment was added. • Pharmacogenetic buccal swab collection procedures were added.
15 January 2008	Amendment 3 resulted in the following changes to the amended protocol:•Clarification of the scale used to define food allergy, allergen components of theCAP-RAST tests, and questions regarding the patient's exposure to food as part of the Family History of Allergy/Atopy Questionnaire. • Changes to the study implementation and conduct. The original protocol had planned to dispense commercial supply of pimecrolimus cream 1% to patients for use in the OL phase. To remain consistent with the size (50 g) and labeling of the tubes used during the DB phase, the supply of pimecrolimus cream 1% was provided to patients in the OL phase from the sponsor's clinical drug supply, not commercial supply. • Removal of an assessment and two secondary efficacy variables from the protocol. At completion of the OL phase, the skin prick test is no longer required. Several reasons contributed to this decision, including potential safety issues regarding conduct of this evaluation at the sites that were not allergy clinics, logistical issues regarding availability of standard extracts to all sites that corresponded to the components of the CAP-RAST tests, and concerns regarding the potential for inconsistent interpretation of skin prick test results and subsequent guidance to caregivers based on these results. Since the skin prick test evaluation was removed from the study design, associated secondary efficacy variable "number of type I hypersensitivities (skin prick test)" was removed. A new CRF called Step 3a Concomitant Medications was used for documentation of Step 3a medication and guidance for interpretation of CAP-RAST results. The CRF accommodated entry of multiple types of mid-potent topical CSs as Step 3a medications, any-potency topical CS used as a Step 3a medication, and allowed entry of Step 3a medications that were not entered in the e-diary. Implementation of direct-mail shipping of study medication and Step 3a rescue medication Cutivate (fluticasone)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

These results are only for the double blind phase of this study,

Notes: