



## 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 |
|-----------------------|--------------|

#### 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,                                  |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |
| 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                | Investigator, Subject          |

### Arms

|                              |                                       |
|------------------------------|---------------------------------------|
| Are arms mutually exclusive? | Yes                                   |
| <b>Arm title</b>             | 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.

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Control Treatment Group |
|------------------|-------------------------|

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<br>(Elidel) Treatment<br>Group | Control Treatment<br>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:<br>Pimecrolimus (Elidel) 1% Cream twice a day/topical corticosteroid rescue |                                       |
| Reporting group title                                                                                    | Control Treatment Group               |
| Reporting group description:<br>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<br>Units: Subjects                                                                                                                                                                                                                                    |                                       |                         |       |
| 2 y - <12 y                                                                                                                                                                                                                                                           | 462                                   | 445                     | 907   |
| 12y - <18 y                                                                                                                                                                                                                                                           | 71                                    | 89                      | 160   |
| 18 y - <65 y                                                                                                                                                                                                                                                          | 10                                    | 10                      | 20    |
| Age Continuous<br>Units: months                                                                                                                                                                                                                                       |                                       |                         |       |
| arithmetic mean                                                                                                                                                                                                                                                       | 7.1                                   | 7.4                     |       |
| standard deviation                                                                                                                                                                                                                                                    | ± 3.76                                | ± 4.06                  | -     |
| Gender, Male/Female<br>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 <sup>[1]</sup>                      | 0 <sup>[2]</sup>        |  |  |
| 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:<br>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:<br>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 |
|-----------------|---------------------------------------|

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 |
|----------------|-----------|

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 |
|-----------------|-----------------------------------|

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 |
|----------------|-----------|

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

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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 |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |     |
|--------------------|-----|
| Dictionary version | 9.1 |
|--------------------|-----|

### Reporting groups

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Pimecrolimus (Elidel) Treatment Group |
|-----------------------|---------------------------------------|

Reporting group description:

Pimecrolimus (Elidel) Treatment Group

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Control Treatment Group |
|-----------------------|-------------------------|

Reporting group description:

Control Treatment Group

| <b>Serious adverse events</b>                                       | 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 %

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

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