



## Clinical trial results:

### A Randomized, Double-Blind, Placebo-Controlled, Repeat-Dose Study of the Efficacy, Safety, Tolerability, and Pharmacodynamics of Subcutaneously-Administered REGN668 in Adult Patients With Extrinsic Moderate-to-Severe Atopic Dermatitis

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2011-003836-29 |
| Trial protocol           | HU DE CZ       |
| Global end of trial date | 25 June 2013   |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1           |
| This version publication date  | 07 June 2017 |
| First version publication date | 07 June 2017 |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | R668-AD-1117 |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01548404 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Regeneron Pharmaceuticals, Inc.   |
| Sponsor organisation address | 777 Old Saw Mill River Rd., Tarrytown, United States, 10591                                 |
| Public contact               | Clinical Trial Management, Regeneron Pharmaceuticals, Inc.,<br>clinicaltrials@regeneron.com |
| Scientific contact           | Clinical Trial Management, Regeneron Pharmaceuticals, Inc.,<br>clinicaltrials@regeneron.com |

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? | No |

Notes:

## Results analysis stage

|  |              |
|--|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 25 June 2013 |
| Is this the analysis of the primary completion data? | No           |

|                                  |              |
|----------------------------------|--------------|
| Global end of trial reached?     | Yes          |
| Global end of trial date         | 25 June 2013 |
| Was the trial ended prematurely? | No           |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to assess the clinical efficacy of repeated subcutaneous (SC) doses of Dupilumab in adult subjects with moderate-to-severe atopic dermatitis (AD).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 15 March 2012 |
| 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 | Poland: 23         |
| Country: Number of subjects enrolled | Czech Republic: 11 |
| Country: Number of subjects enrolled | France: 19         |
| Country: Number of subjects enrolled | Germany: 45        |
| Country: Number of subjects enrolled | Hungary: 11        |
| Worldwide total number of subjects   | 109                |
| EEA total number of subjects         | 109                |

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)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 106 |

|                     |   |
|---------------------|---|
| From 65 to 84 years | 3 |
| 85 years and over   | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 25 sites in Europe between 03 April 2012 and 25 June 2013. A total of 153 subjects were screened in the study.

### Pre-assignment

Screening details:

Out of 153 subjects, 109 were randomized and enrolled treated into the study. Out of 153 subjects, 109 were randomized and treated in the study. Subjects were randomized in 1:1 ratio to receive either Dupilumab 300 mg or placebo.

### Period 1

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

### Arms

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

Arm description:

Placebo (for Dupilumab) once weekly for 12 weeks.

|  |                         |
|--|-------------------------|
| Arm type                               | Placebo                 |
| Investigational medicinal product name | Placebo (For Dupilumab) |
| Investigational medicinal product code |                         |
| Other name                             |                         |
| Pharmaceutical forms                   | Solution for injection  |
| Routes of administration               | Subcutaneous use        |

Dosage and administration details:

Single subcutaneous injection altered between back of arms, abdomen and upper thighs.

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Dupilumab 300 mg |
|------------------|------------------|

Arm description:

Dupilumab 300 mg once weekly for 12 weeks

|  |                        |
|--|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Dupilumab 300 mg       |
| Investigational medicinal product code | REGN668/SAR231893      |
| Other name                             | Dupixent               |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

Single subcutaneous injection altered between back of arms, abdomen and upper thighs

| <b>Number of subjects in period 1</b>  | Placebo | Dupilumab 300 mg |
|--|---------|------------------|
| Started                                | 54      | 55               |
| Completed                              | 24      | 41               |
| Not completed                          | 30      | 14               |
| Other than specified above             | -       | 2                |
| Physician decision                     | 2       | 1                |
| Consent withdrawn by subject           | -       | 3                |
| Inadequate response to study treatment | 23      | 7                |
| Adverse event                          | 3       | 1                |
| Lost to follow-up                      | 2       | -                |

## Baseline characteristics

### Reporting groups

|   |                  |
|---|------------------|
| Reporting group title   | Placebo          |
| Reporting group description:<br>Placebo (for Dupilumab) once weekly for 12 weeks. |                  |
| Reporting group title   | Dupilumab 300 mg |
| Reporting group description:<br>Dupilumab 300 mg once weekly for 12 weeks         |                  |

| Reporting group values             | Placebo | Dupilumab 300 mg | Total |
|------------------------------------|---------|------------------|-------|
| Number of subjects                 | 54      | 55               | 109   |
| Age categorical<br>Units: Subjects |         |                  |       |

|   |                 |                 |    |
|---|-----------------|-----------------|----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation   | 39.4<br>± 12.29 | 33.7<br>± 10.41 | -  |
| Gender categorical<br>Units: Subjects   |                 |                 |    |
| Female  | 27              | 24              | 51 |
| Male  | 27              | 31              | 58 |
| Eczema Area and Severity Index (EASI)<br>Score  |                 |                 |    |
| The EASI score was used to measure the severity and extent of AD and measures erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD.   |                 |                 |    |
| Units: units on a scale<br>arithmetic mean<br>standard deviation  | 30.8<br>± 13.63 | 28.4<br>± 13.57 | -  |
| Investigator's Global Assessment (IGA)<br>Score   |                 |                 |    |
| IGA was an assessment scale used to determine severity of AD and clinical response to treatment on a 5-point scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe) based on erythema and papulation/infiltration. Therapeutic response was an IGA score of 0 (clear) or 1 (almost clear).   |                 |                 |    |
| Units: Units on a scale<br>arithmetic mean<br>standard deviation  | 4<br>± 0.69     | 3.9<br>± 0.67   | -  |
| Scoring Atopic Dermatitis (SCORAD)<br>Score   |                 |                 |    |
| SCORAD is a clinical tool for assessing the severity of atopic dermatitis developed by the European Task Force on Atopic Dermatitis (Severity scoring of atopic dermatitis: the SCORAD index). Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology (Basel) 186 (1): 23-31. 1993. Extent and intensity of eczema as well as subjective signs (insomnia, etc.) are assessed and scored. Total score ranges from 0 (absent disease) to 103 (severe disease). |                 |                 |    |
| Units: Units on a scale<br>arithmetic mean<br>standard deviation  | 69.1<br>± 13.38 | 66.7<br>± 13.82 | -  |
| Body Surface Area (BSA)   |                 |                 |    |
| BSA affected by AD was assessed for each section of the body (the possible highest score for each region was: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs  |                 |                 |    |

|   |                 |                 |   |
|---|-----------------|-----------------|---|
| [36%], and genitals [1%]). It was reported as a percentage of all major body sections combined.   |                 |                 |   |
| Units: Percentage of BSA<br>arithmetic mean<br>standard deviation   | 50.8<br>± 24.13 | 46.8<br>± 24.55 | - |
| 5-D Pruritus Scale  |                 |                 |   |
| The 5-D Pruritus was a 5-question tool used in clinical trials to assess 5 dimensions of background itch: degree, duration, direction, disability, and distribution. Each question corresponded to 1 of the 5 dimensions of itch. Subjects rated their symptoms over the preceding 2-week period on a scale of 1 (least affected) to 5 (most affected).   |                 |                 |   |
| Units: Units on scale<br>arithmetic mean<br>standard deviation  | 18.7<br>± 3.5   | 18.4<br>± 3.04  | - |
| Pruritus Numerical Rating Scale (NRS) Score   |                 |                 |   |
| Pruritus NRS scale is an assessment tool that is used to report the intensity of subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0= no itch; 10= worst itch imaginable]). |                 |                 |   |
| Units: units on a scale<br>arithmetic mean<br>standard deviation  | 5.8<br>± 1.93   | 6.1<br>± 1.34   | - |

## End points

### End points reporting groups

|   |                  |
|---|------------------|
| Reporting group title   | Placebo          |
| Reporting group description:<br>Placebo (for Dupilumab) once weekly for 12 weeks. |                  |
| Reporting group title   | Dupilumab 300 mg |
| Reporting group description:<br>Dupilumab 300 mg once weekly for 12 weeks         |                  |

### Primary: Percent Change From Baseline in Eczema Area and Severity Index (EASI) Score at Week 12- Last Observation Carried Forward (LOCF)

|                 |  |
|-----------------|--|
| End point title | Percent Change From Baseline in Eczema Area and Severity Index (EASI) Score at Week 12- Last Observation Carried Forward (LOCF) <sup>[1]</sup> |
|-----------------|--|

#### End point description:

The EASI score was used to measure the severity and extent of AD and measured erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. The efficacy data were set to be missing after use of rescue medication and after early termination visit for subjects who prematurely discontinued study treatment. Then, all missing values were imputed by simple LOCF. Full analysis set (FAS) population included all randomized subjects who received at least one dose of study drug and had at least 1 post-baseline efficacy assessment.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

#### End point timeframe:

Baseline to Week 12

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

| End point values                     | Placebo         | Dupilumab 300 mg |  |  |
|--------------------------------------|-----------------|------------------|--|--|
| Subject group type                   | Reporting group | Reporting group  |  |  |
| Number of subjects analysed          | 54              | 55               |  |  |
| Units: percent change                |                 |                  |  |  |
| arithmetic mean (standard deviation) | -23.3 (± 49.26) | -74 (± 26.94)    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Investigator's Global Assessment (IGA) Score of "0" or "1" at Week 12- LOCF

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects With Investigator's Global Assessment (IGA) Score of "0" or "1" at Week 12- LOCF |
|-----------------|---|

#### End point description:

IGA is an assessment scale used to determine severity of AD and clinical response to treatment on a 5-

point scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe) based on erythema and papulation/infiltration. Therapeutic response is an IGA score of 0 (clear) or 1 (almost clear). The efficacy data were set to be missing after use of rescue medication and after early termination visit for subjects who prematurely discontinued study treatment. Then, all missing values were imputed by simple LOCF. FAS population.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 12              |           |

| End point values              | Placebo         | Dupilumab 300 mg |  |  |
|-------------------------------|-----------------|------------------|--|--|
| Subject group type            | Reporting group | Reporting group  |  |  |
| Number of subjects analysed   | 54              | 55               |  |  |
| Units: Percentage of subjects |                 |                  |  |  |
| number (not applicable)       | 7.4             | 40               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects Who Achieved at Least a 50% Reduction from Baseline in the EASI Score (EASI 50) at Week 12- LOCF

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects Who Achieved at Least a 50% Reduction from Baseline in the EASI Score (EASI 50) at Week 12- LOCF |
|-----------------|---|

End point description:

The EASI score was used to measure the severity and extent of AD and measured erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. EASI-50 responders were the subjects who achieved  $\geq 50\%$  overall improvement in EASI score from baseline to Week 12. Efficacy data were set to be missing after use of rescue medication and after early termination visit for subjects who prematurely discontinued study treatment. Then, all missing values were imputed by simple LOCF. FAS population.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 12              |           |

| End point values              | Placebo         | Dupilumab 300 mg |  |  |
|-------------------------------|-----------------|------------------|--|--|
| Subject group type            | Reporting group | Reporting group  |  |  |
| Number of subjects analysed   | 54              | 55               |  |  |
| Units: Percentage of subjects |                 |                  |  |  |
| number (not applicable)       | 35.2            | 85.5             |  |  |

## Statistical analyses

**Secondary: Change From Baseline in EASI Score at Week 12- LOCF**

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in EASI Score at Week 12- LOCF |
|-----------------|---|

End point description:

The EASI score was used to measure the severity and extent of AD and measured erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores reflecting the worse severity of AD. The efficacy data were set to be missing after use of rescue medication and after early termination visit for subjects who prematurely discontinued study treatment. Then, all missing values were imputed by simple LOCF. FAS population.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Week 12

| End point values                     | Placebo             | Dupilumab 300 mg     |  |  |
|--------------------------------------|---------------------|----------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group      |  |  |
| Number of subjects analysed          | 54                  | 55                   |  |  |
| Units: Units on a scale              |                     |                      |  |  |
| arithmetic mean (standard deviation) | -6.4 ( $\pm$ 14.85) | -19.9 ( $\pm$ 11.52) |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Percent Change From Baseline in IGA Score at Week 12- LOCF**

|                 |  |
|-----------------|--|
| End point title | Percent Change From Baseline in IGA Score at Week 12- LOCF |
|-----------------|--|

End point description:

IGA is an assessment scale used to determine severity of AD and clinical response to treatment on a 5-point scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe) based on erythema and papulation/infiltration. Therapeutic response is an IGA score of 0 (clear) or 1 (almost clear). The efficacy data were set to be missing after use of rescue medication and after early termination visit for subjects who prematurely discontinued study treatment. Then, all missing values were imputed by simple LOCF. FAS population.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Week 12

| End point values                     | Placebo              | Dupilumab 300 mg     |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed          | 54                   | 55                   |  |  |
| Units: Percent Change                |                      |                      |  |  |
| arithmetic mean (standard deviation) | -14.7 ( $\pm$ 27.37) | -49.5 ( $\pm$ 25.94) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Percent Body Surface Area (BSA) Affected by Atopic Dermatitis at Week 12- LOCF

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Percent Body Surface Area (BSA) Affected by Atopic Dermatitis at Week 12- LOCF |
|-----------------|--|

End point description:

BSA affected by AD was assessed for each section of the body (the possible highest score for each region was: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]). It was reported as a percentage of all major body sections combined. The efficacy data were set to be missing after use of rescue medication and after early termination visit for subjects who prematurely discontinued study treatment. Then, all missing values were imputed by simple LOCF. FAS population.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Week 12

| End point values                     | Placebo         | Dupilumab 300 mg |  |  |
|--------------------------------------|-----------------|------------------|--|--|
| Subject group type                   | Reporting group | Reporting group  |  |  |
| Number of subjects analysed          | 54              | 55               |  |  |
| Units: Percentage of BSA             |                 |                  |  |  |
| arithmetic mean (standard deviation) | -9 (± 21.07)    | -27.4 (± 22.81)  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Scoring Atopic Dermatitis (SCORAD) Score at Week 12- LOCF

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Scoring Atopic Dermatitis (SCORAD) Score at Week 12- LOCF |
|-----------------|---|

End point description:

SCORAD is a clinical tool for assessing the severity of AD developed by the European Task Force on Atopic Dermatitis (Severity scoring of atopic dermatitis: the SCORAD index). Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology (Basel) 186 (1): 23–31. 1993. Extent and intensity of eczema as well as subjective signs (insomnia, etc.) are assessed and scored. Total score ranges from 0 (absent disease) to 103 (severe disease). The efficacy data were set to be missing after use of rescue medication and after early termination visit for subjects who prematurely discontinued study treatment. Then, all missing values were imputed by simple LOCF.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Week 12

| End point values                     | Placebo             | Dupilumab 300 mg   |  |  |
|--------------------------------------|---------------------|--------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group    |  |  |
| Number of subjects analysed          | 54                  | 55                 |  |  |
| Units: Units on a scale              |                     |                    |  |  |
| arithmetic mean (standard deviation) | -9.8 ( $\pm$ 20.53) | -35 ( $\pm$ 19.43) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Pruritus Numerical Rating Scale (NRS) to Week 12- LOCF

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Pruritus Numerical Rating Scale (NRS) to Week 12- LOCF |
|-----------------|--|

End point description:

Pruritus NRS was an assessment tool that was used to report the intensity of a subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). The efficacy data were set to be missing after use of rescue medication and after early termination visit for subjects who prematurely discontinued study treatment. Then, all missing values were imputed by simple LOCF. FAS population. Number of subjects analyzed=subjects with available data for this endpoint.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Week 12

| End point values                     | Placebo            | Dupilumab 300 mg |  |  |
|--------------------------------------|--------------------|------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group  |  |  |
| Number of subjects analysed          | 52                 | 54               |  |  |
| Units: units on a scale              |                    |                  |  |  |
| arithmetic mean (standard deviation) | -0.9 ( $\pm$ 2.07) | -3.5 ( $\pm$ 2)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in 5-D Pruritus Scale at Week 12

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in 5-D Pruritus Scale at Week 12 |
|-----------------|---|

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**End point description:**

The 5-D Pruritus Scale, was a 5-question tool used in clinical trials to assess 5 dimensions of background itch: degree, duration, direction, disability, and distribution. Each question corresponded to 1 of the 5 dimensions of itch. Subjects rated their symptoms over the preceding 2-week period on a scale of 1 (least affected) to 5 (most affected). FAS population.

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|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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End point timeframe:

Baseline to Week 12

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| End point values                     | Placebo         | Dupilumab 300 mg |  |  |
|--------------------------------------|-----------------|------------------|--|--|
| Subject group type                   | Reporting group | Reporting group  |  |  |
| Number of subjects analysed          | 54              | 55               |  |  |
| Units: units on a scale              |                 |                  |  |  |
| arithmetic mean (standard deviation) | -1.9 (± 4.28)   | -7.4 (± 4.33)    |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Day 197) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events (AEs) are treatment-emergent adverse events that is AEs that developed/worsened during the 'on treatment period' (time from first dose of study drug through the end of study [Day 197]).

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 14.0 |
|--------------------|------|

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Dupilumab 300 mg |
|-----------------------|------------------|

Reporting group description:

Dupilumab 300 mg once weekly for 12 weeks by SC injection.

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo (for Dupilumab) once weekly for 12 weeks by SC injection.

| Serious adverse events                            | Dupilumab 300 mg | Placebo         |  |
|---|------------------|-----------------|--|
| Total subjects affected by serious adverse events |                  |                 |  |
| subjects affected / exposed                       | 1 / 55 (1.82%)   | 7 / 54 (12.96%) |  |
| number of deaths (all causes)                     | 0                | 0               |  |
| number of deaths resulting from adverse events    |                  |                 |  |
| Injury, poisoning and procedural complications    |                  |                 |  |
| Facial bones fracture                             |                  |                 |  |
| subjects affected / exposed                       | 1 / 55 (1.82%)   | 0 / 54 (0.00%)  |  |
| occurrences causally related to treatment / all   | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0           |  |
| Cardiac disorders                                 |                  |                 |  |
| Angina pectoris                                   |                  |                 |  |
| subjects affected / exposed                       | 0 / 55 (0.00%)   | 1 / 54 (1.85%)  |  |
| occurrences causally related to treatment / all   | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders   |                  |                 |  |
| Asthmatic crisis                                  |                  |                 |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 55 (0.00%) | 1 / 54 (1.85%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Lung disorder                                   |                |                |  |
| subjects affected / exposed                     | 0 / 55 (0.00%) | 1 / 54 (1.85%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Skin and subcutaneous tissue disorders          |                |                |  |
| Dermatitis atopic                               |                |                |  |
| subjects affected / exposed                     | 0 / 55 (0.00%) | 4 / 54 (7.41%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 5          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal and urinary disorders                     |                |                |  |
| Renal failure                                   |                |                |  |
| subjects affected / exposed                     | 0 / 55 (0.00%) | 1 / 54 (1.85%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Cellulitis                                      |                |                |  |
| subjects affected / exposed                     | 0 / 55 (0.00%) | 1 / 54 (1.85%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Eczema herpeticum                               |                |                |  |
| subjects affected / exposed                     | 0 / 55 (0.00%) | 1 / 54 (1.85%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Skin bacterial infection                        |                |                |  |
| subjects affected / exposed                     | 0 / 55 (0.00%) | 1 / 54 (1.85%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| 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>                     | Dupilumab 300 mg | Placebo          |  |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 38 / 55 (69.09%) | 31 / 54 (57.41%) |  |
| Investigations  |                  |                  |  |
| Neutrophil count increased                            |                  |                  |  |
| subjects affected / exposed                           | 0 / 55 (0.00%)   | 3 / 54 (5.56%)   |  |
| occurrences (all)                                     | 0                | 4                |  |
| White blood cell count increased                      |                  |                  |  |
| subjects affected / exposed                           | 1 / 55 (1.82%)   | 3 / 54 (5.56%)   |  |
| occurrences (all)                                     | 1                | 4                |  |
| Nervous system disorders                              |                  |                  |  |
| Headache  |                  |                  |  |
| subjects affected / exposed                           | 9 / 55 (16.36%)  | 7 / 54 (12.96%)  |  |
| occurrences (all)                                     | 12               | 11               |  |
| Blood and lymphatic system disorders                  |                  |                  |  |
| Eosinophilia  |                  |                  |  |
| subjects affected / exposed                           | 0 / 55 (0.00%)   | 3 / 54 (5.56%)   |  |
| occurrences (all)                                     | 0                | 3                |  |
| Lymphadenopathy                                       |                  |                  |  |
| subjects affected / exposed                           | 0 / 55 (0.00%)   | 4 / 54 (7.41%)   |  |
| occurrences (all)                                     | 0                | 4                |  |
| General disorders and administration site conditions  |                  |                  |  |
| Fatigue   |                  |                  |  |
| subjects affected / exposed                           | 5 / 55 (9.09%)   | 4 / 54 (7.41%)   |  |
| occurrences (all)                                     | 7                | 5                |  |
| Injection site erythema                               |                  |                  |  |
| subjects affected / exposed                           | 4 / 55 (7.27%)   | 1 / 54 (1.85%)   |  |
| occurrences (all)                                     | 7                | 1                |  |
| Injection site induration                             |                  |                  |  |
| subjects affected / exposed                           | 5 / 55 (9.09%)   | 3 / 54 (5.56%)   |  |
| occurrences (all)                                     | 6                | 3                |  |
| Injection site reaction                               |                  |                  |  |
| subjects affected / exposed                           | 3 / 55 (5.45%)   | 1 / 54 (1.85%)   |  |
| occurrences (all)                                     | 6                | 1                |  |
| Eye disorders   |                  |                  |  |
| Conjunctivitis allergic                               |                  |                  |  |

|   |  |  |  |
|---|--|--|--|
| subjects affected / exposed<br>occurrences (all)  | 5 / 55 (9.09%)<br>5  | 0 / 54 (0.00%)<br>0  |  |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)  | 1 / 55 (1.82%)<br>1  | 4 / 54 (7.41%)<br>7  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)  | 3 / 55 (5.45%)<br>4<br><br>3 / 55 (5.45%)<br>3   | 0 / 54 (0.00%)<br>0<br><br>1 / 54 (1.85%)<br>1   |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all)  | 3 / 55 (5.45%)<br>3  | 0 / 54 (0.00%)<br>0  |  |
| Infections and infestations<br>Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Impetigo<br>subjects affected / exposed<br>occurrences (all)<br><br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Oral herpes<br>subjects affected / exposed<br>occurrences (all)<br><br>Rhinitis<br>subjects affected / exposed<br>occurrences (all) | 8 / 55 (14.55%)<br>11<br><br>1 / 55 (1.82%)<br>1<br><br>22 / 55 (40.00%)<br>33<br><br>3 / 55 (5.45%)<br>4<br><br>3 / 55 (5.45%)<br>3 | 2 / 54 (3.70%)<br>2<br><br>3 / 54 (5.56%)<br>3<br><br>10 / 54 (18.52%)<br>15<br><br>0 / 54 (0.00%)<br>0<br><br>2 / 54 (3.70%)<br>3 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 11 November 2011 | Removed the SF-36 questionnaire from the protocol; Allowed the study drug to be administered in multiple SC locations, and split into 2 injections; Updated the AE severity grading to conform to the current safety template; Changed the end of study visit from week 18 (day 127) to week 20 (day 141); Added section for AEs of special interest; Added anti-parasitics and anti-protozoals to description of chronic or acute infection requiring treatment within 4 weeks of screening; Clarified that the efficacy analysis at week 12 was to be the primary efficacy analysis, not the final efficacy analysis; Revised pharmacokinetics sampling and analysis                               |
| 12 March 2012    | Clarified that the study was not limited to subjects with extrinsic AD; Corrected the definition of study drug stopping rules; Increased allowable screening and baseline EASI scores from 12 to 16; Added the collection of a Creatine Phosphokinase (CPK), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Lactate Dehydrogenase (LDH) sample at days 8 and 22; Indicated that collection of the RNA sample (part of the research samples collected during the study) might require separate written informed consent, as required by local regulatory authorities; Clarified that each dose could be administered as a single 2 mL injection, or split into two 1 mL injections |
| 20 August 2012   | Increased the number of subjects in the study from 80 to 100; Extended the follow-up period from 8 weeks to 16 weeks (5 follow-up visits were added; overall study duration was extended from 20 weeks to 28 weeks); Increased the required use of adequate birth control measures following the last dose of study drug from 8 to 16 weeks  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/25006719>