



Clinical trial results:

An Exploratory, Randomized, Double-Blind, Placebo-Controlled Study of the Effects of Dupilumab on Airway Inflammation of Adults With Persistent Asthma

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2015-001572-22 |
| Trial protocol | DE GB SE DK |
| Global end of trial date | 03 January 2018 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 20 February 2019 |
| First version publication date | 04 January 2019 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set Data and description for endpoint #8 (Average Change in Fractional Exhaled Nitric Oxide (FeNO) From Baseline to Week 6 Through Week 12) was updated |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | PDY14192 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02573233 |
| WHO universal trial number (UTN) | U1111-1170-7168 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Sanofi aventis recherche & développement |
| Sponsor organisation address | 1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380 |
| Public contact | Sanofi aventis recherche & développement, Trial Transparency Team, Contact-US@sanofi.com |
| Scientific contact | Sanofi aventis recherche & développement, Trial Transparency Team, Contact-US@sanofi.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 | 18 April 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 03 January 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of dupilumab, compared to placebo, on airway inflammation in subjects with persistent asthma

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency.

Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 27 January 2016 |
| 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 | Germany: 6 |
| Country: Number of subjects enrolled | Canada: 6 |
| Country: Number of subjects enrolled | Denmark: 3 |
| Country: Number of subjects enrolled | United Kingdom: 6 |
| Country: Number of subjects enrolled | United States: 21 |
| Worldwide total number of subjects | 42 |
| EEA total number of subjects | 15 |

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 | 0 |

| | |
|---------------------------|----|
| months) | |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 42 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 16 sites in 6 countries . A total of 133 subjects were screened between January 2016 and January 2018. Of which, 42 subjects were randomized. 91 subjects were screen failures mainly due to exclusion criteria met and inclusion criteria not met.

Pre-assignment

Screening details:

Subjects were randomized in 1:1 ratio to receive dupilumab 300 mg every 2 weeks (q2w) and placebo q2w by using Interactive Voice/Web Response System (IVRS). Randomization was stratified by inhaled corticosteroids (ICS) dose (medium and high) and region (North America and Europe).

Period 1

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

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Placebo (for dupilumab), 2 subcutaneous injections on Day 1 (Week 1) as a loading dose followed by a single injection q2w from Week 2 to Week 14 added to stable inhaled corticosteroid/ long-acting beta-agonist (ICS/LABA) therapy. Salbutamol/albuterol or Levosalbutamol/levalbuterol was given as reliever medication.

| | |
|--|--|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subcutaneous injection (2 mL) in abdomen (avoiding navel and waist areas), the upper thighs or the upper arms.

| | |
|------------------|-----------|
| Arm title | Dupilumab |
|------------------|-----------|

Arm description:

Dupilumab, 2 subcutaneous injections on Day 1 as a loading dose for a total of 600 mg, followed by a single 300 mg injection q2w from Week 2 to Week 14 added to stable ICS/LABA therapy. Salbutamol/albuterol or Levosalbutamol/levalbuterol was given as reliever medication.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Dupilumab |
| Investigational medicinal product code | SAR231893 |
| Other name | REGN668 |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subcutaneous injection (2 mL) in abdomen (avoiding navel and waist areas), the upper thighs or the upper arms.

| Number of subjects in period 1 | Placebo | Dupilumab |
|---------------------------------------|---------|-----------|
| Started | 22 | 20 |
| Completed | 22 | 20 |

Baseline characteristics

Reporting groups

| | |
|---|-----------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo (for dupilumab), 2 subcutaneous injections on Day 1 (Week 1) as a loading dose followed by a single injection q2w from Week 2 to Week 14 added to stable inhaled corticosteroid/ long-acting beta-agonist (ICS/LABA) therapy. Salbutamol/albuterol or Levosalbutamol/levalbuterol was given as reliever medication. | |
| Reporting group title | Dupilumab |
| Reporting group description: | |
| Dupilumab, 2 subcutaneous injections on Day 1 as a loading dose for a total of 600 mg, followed by a single 300 mg injection q2w from Week 2 to Week 14 added to stable ICS/LABA therapy. Salbutamol/albuterol or Levosalbutamol/levalbuterol was given as reliever medication. | |

| Reporting group values | Placebo | Dupilumab | Total |
|------------------------|---------|-----------|-------|
| Number of subjects | 22 | 20 | 42 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--|---------------|-----------------|----|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 41.0 | 45.5 | |
| standard deviation | ± 10.3 | ± 10.6 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 8 | 13 | 21 |
| Male | 14 | 7 | 21 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 1 | 1 | 2 |
| Not Hispanic or Latino | 21 | 19 | 40 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Race | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 1 | 1 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 3 | 3 | 6 |
| White | 19 | 16 | 35 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Baseline Eosinophils Count in Bronchial Tissue | | | |
| Inflammatory cells i.e. eosinophils were counted in the bronchial submucosa of biopsy thin sections using quantitative immunohistochemistry and reported as the number of cells per square millimeter. Data is reported for 40 subjects (Placebo: 21 subjects and Dupilumab: 19 subjects). | | | |
| Units: cells/mm ² | | | |
| median | 12.97 | 34.96 | |
| inter-quartile range (Q1-Q3) | 9.91 to 21.24 | 10.07 to 263.75 | - |

| | | | |
|---|------------------|------------------|---|
| Baseline Mast Cells Count (Chymase Positive) in Bronchial Tissue | | | |
| Inflammatory cells i.e. mast cells were counted in the bronchial submucosa of biopsy thin sections using quantitative immunohistochemistry and reported as the number of cells per square millimeter. | | | |
| Units: cells/mm ² | | | |
| arithmetic mean | 74.36 | 79.17 | |
| standard deviation | ± 58.63 | ± 68.07 | - |
| Baseline Mast Cells Count (Tryptase Positive) in Bronchial Tissue | | | |
| Inflammatory cells i.e. mast cells were counted in the bronchial submucosa of biopsy thin sections using quantitative immunohistochemistry and reported as the number of cells per square millimeter. Data is reported for 41 subjects (Placebo: 22 subjects and Dupilumab: 19 subjects). | | | |
| Units: cells/mm ² | | | |
| arithmetic mean | 80.10 | 105.53 | |
| standard deviation | ± 64.92 | ± 104.68 | - |
| Baseline Total T-Lymphocytes Count in Bronchial Tissue | | | |
| T-Lymphocytes i.e. CD3 positive cells were counted in the bronchial submucosa of biopsy thin sections using quantitative immunohistochemistry and reported as the number of cells per square millimeter. Data is reported for 41 subjects (Placebo: 22 subjects and Dupilumab: 19 subjects). | | | |
| Units: cells/mm ² | | | |
| median | 301.09 | 153.33 | |
| inter-quartile range (Q1-Q3) | 121.01 to 500.43 | 83.81 to 192.40 | - |
| Baseline T-Helper Lymphocytes Count in Bronchial Tissue | | | |
| T-helper i.e. CD4 positive lymphocytes were counted in the bronchial submucosa of biopsy thin sections using quantitative immunohistochemistry and reported as the number of cells per square millimeter. Data is reported for 41 subjects (Placebo: 22 subjects and Dupilumab: 19 subjects). | | | |
| Units: cells/mm ² | | | |
| median | 237.10 | 200.85 | |
| inter-quartile range (Q1-Q3) | 190.17 to 511.48 | 102.49 to 398.08 | - |
| Baseline Mucin-Stained Area in Bronchial Tissue | | | |
| Mucin was identified by staining with Alcian-blue periodic acid-Schiff and/or immunostaining for MUC5AC and then the mucin-positive area was measured and expressed per square millimeter. Data is reported for 41 subjects (Placebo: 22 subjects and Dupilumab: 19 subjects). | | | |
| Units: cells/mm ² | | | |
| arithmetic mean | 561.12 | 520.57 | |
| standard deviation | ± 289.00 | ± 511.69 | - |
| Baseline Fractional exhaled nitric oxide (FeNO) | | | |
| FeNO is a surrogate marker for airway inflammation. FeNO was analyzed using a NIOX instrument or similar analyser using a flow rate of 50 mL/s, and reported in ppb. | | | |
| Units: parts per billion (ppb) | | | |
| arithmetic mean | 41.2 | 36.4 | |
| standard deviation | ± 31.5 | ± 22.8 | - |

End points

End points reporting groups

| | |
|---|-----------|
| Reporting group title | Placebo |
| Reporting group description: Placebo (for dupilumab), 2 subcutaneous injections on Day 1 (Week 1) as a loading dose followed by a single injection q2w from Week 2 to Week 14 added to stable inhaled corticosteroid/ long-acting beta-agonist (ICS/LABA) therapy. Salbutamol/albuterol or Levosalbutamol/levalbuterol was given as reliever medication. | |
| Reporting group title | Dupilumab |
| Reporting group description: Dupilumab, 2 subcutaneous injections on Day 1 as a loading dose for a total of 600 mg, followed by a single 300 mg injection q2w from Week 2 to Week 14 added to stable ICS/LABA therapy. Salbutamol/albuterol or Levosalbutamol/levalbuterol was given as reliever medication. | |

Primary: Change From Baseline in Eosinophils Cells Count in the Bronchial Submucosa at Week 12

| | |
|--|---|
| End point title | Change From Baseline in Eosinophils Cells Count in the Bronchial Submucosa at Week 12 |
| End point description: Inflammatory cells i.e. eosinophils were counted in the bronchial submucosa of biopsy thin sections using quantitative immunohistochemistry and reported as the number of cells per square millimeter. Analysis was performed on pharmacodynamic (PD) population which consisted of all randomized subjects who underwent baseline and Week 12/end of treatment (EOT) bronchoscopies and have adequate biopsies for analysis at both baseline and EOT. Here, number of subjects analysed = subjects with available data for this endpoint. | |
| End point type | Primary |
| End point timeframe: Baseline, Week 12 | |

| End point values | Placebo | Dupilumab | | |
|---------------------------------------|-----------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 17 | | |
| Units: cells/mm ² | | | | |
| median (inter-quartile range (Q1-Q3)) | 5.80 (-9.18 to 33.41) | -6.04 (-174.71 to 19.41) | | |

Statistical analyses

| | |
|--|-----------------------|
| Statistical analysis title | Dupilumab vs. Placebo |
| Statistical analysis description: Analysis was performed using a rank ANCOVA model stratified by ICS dose level and region. | |
| Comparison groups | Dupilumab v Placebo |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 37 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.84 ^[1] |
| Method | Rank ANCOVA |

Notes:

[1] - Threshold for significance at 0.05 level.

Primary: Change From Baseline in Mast Cells Count (Chymase Positive) in the Bronchial Submucosa at Week 12

| | |
|-----------------|---|
| End point title | Change From Baseline in Mast Cells Count (Chymase Positive) in the Bronchial Submucosa at Week 12 |
|-----------------|---|

End point description:

Inflammatory cells i.e. mast cells were counted in the bronchial submucosa of biopsy thin sections using quantitative immunohistochemistry and reported as the number of cells per square millimeter. Analysis was performed on PD population. Here, number of subjects analysed = subjects with available data for this endpoint.

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

End point timeframe:

Baseline, Week 12

| End point values | Placebo | Dupilumab | | |
|--------------------------------------|------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 17 | | |
| Units: cells/mm ² | | | | |
| arithmetic mean (standard deviation) | -14.80 (± 76.52) | 1.76 (± 62.41) | | |

Statistical analyses

| | |
|----------------------------|-----------------------|
| Statistical analysis title | Dupilumab vs. Placebo |
|----------------------------|-----------------------|

Statistical analysis description:

Analysis was performed using a linear fixed-effect model with treatment, region and ICS dose level as fixed effects, and the baseline value as continuous covariate.

| | |
|---|---------------------------|
| Comparison groups | Dupilumab v Placebo |
| Number of subjects included in analysis | 37 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4795 ^[2] |
| Method | Linear fixed-effect model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 13.89 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -19 |
| upper limit | 46.78 |

Notes:

[2] - Threshold for significance at 0.05 level.

Primary: Change From Baseline in Mast Cells Count (Tryptase Positive) in the Bronchial Submucosa at Week 12

| | |
|-----------------|--|
| End point title | Change From Baseline in Mast Cells Count (Tryptase Positive) in the Bronchial Submucosa at Week 12 |
|-----------------|--|

End point description:

Inflammatory cells i.e. mast cells were counted in the bronchial submucosa of biopsy thin sections using quantitative immunohistochemistry and reported as the number of cells per square millimeter. Analysis was performed on PD population. Here, number of subjects analysed = subjects with available data for this endpoint.

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

End point timeframe:

Baseline, Week 12

| End point values | Placebo | Dupilumab | | |
|--------------------------------------|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 17 | | |
| Units: cells/mm ² | | | | |
| arithmetic mean (standard deviation) | 2.37 (± 90.20) | -20.89 (± 59.09) | | |

Statistical analyses

| | |
|----------------------------|-----------------------|
| Statistical analysis title | Dupilumab vs. Placebo |
|----------------------------|-----------------------|

Statistical analysis description:

Analysis was performed using a linear fixed-effect model with treatment, region and ICS dose level as fixed effects, and the baseline value as continuous covariate.

| | |
|---|---------------------------|
| Comparison groups | Dupilumab v Placebo |
| Number of subjects included in analysis | 38 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4494 [3] |
| Method | Linear fixed-effect model |
| Parameter estimate | LS mean difference |
| Point estimate | -18.98 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -60.92 |
| upper limit | 22.97 |

Notes:

[3] - Threshold for significance at 0.05 level.

Primary: Change From Baseline in T-Lymphocytes Count in the Bronchial Submucosa at Week 12

| | |
|--|---|
| End point title | Change From Baseline in T-Lymphocytes Count in the Bronchial Submucosa at Week 12 |
| End point description: T-Lymphocytes i.e. CD3 positive cells were counted in the bronchial submucosa of biopsy thin sections using quantitative immunohistochemistry and reported as the number of cells per square millimeter. Analysis was performed on PD population. Here, number of subjects analysed = subjects with available data for this outcome measure. | |
| End point type | Primary |
| End point timeframe: Baseline, Week 12 | |

| End point values | Placebo | Dupilumab | | |
|---------------------------------------|----------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 16 | | |
| Units: cells/mm ² | | | | |
| median (inter-quartile range (Q1-Q3)) | -36.70 (-200.25 to 267.51) | 34.21 (-95.08 to 232.99) | | |

Statistical analyses

| | |
|--|-------------------------|
| Statistical analysis title | Dupilumab vs. Placebo |
| Statistical analysis description: Analysis was performed using a rank ANCOVA model stratified by ICS dose level and region. | |
| Comparison groups | Placebo v Dupilumab |
| Number of subjects included in analysis | 36 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6865 ^[4] |
| Method | Rank Ancova |

Notes:

[4] - Threshold for significance at 0.05 level.

Primary: Change From Baseline in T-Helper Lymphocytes Count in the Bronchial Submucosa at Week 12

| | |
|--|--|
| End point title | Change From Baseline in T-Helper Lymphocytes Count in the Bronchial Submucosa at Week 12 |
| End point description: T-helper i.e. CD4 positive lymphocytes were counted in the bronchial submucosa of biopsy thin sections using quantitative immunohistochemistry and reported as the number of cells per square millimeter. Analysis was performed on PD population. Here, number of subjects analysed = subjects with available data for this endpoint. | |
| End point type | Primary |
| End point timeframe: Baseline, Week 12 | |

| End point values | Placebo | Dupilumab | | |
|---------------------------------------|--------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 16 | | |
| Units: cells/mm ² | | | | |
| median (inter-quartile range (Q1-Q3)) | 7.26 (-179.43 to 224.96) | 62.34 (-100.62 to 159.09) | | |

Statistical analyses

| Statistical analysis title | Dupilumab vs. Placebo |
|---|-------------------------|
| Statistical analysis description: | |
| Analysis was performed using a rank ANCOVA model stratified by ICS dose level and region. | |
| Comparison groups | Dupilumab v Placebo |
| Number of subjects included in analysis | 36 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7588 ^[5] |
| Method | Rank ANCOVA |

Notes:

[5] - Threshold for significance at 0.05 level.

Primary: Change From Baseline in Mucin-Stained Area in the Bronchial Submucosa at Week 12

| | |
|-----------------|--|
| End point title | Change From Baseline in Mucin-Stained Area in the Bronchial Submucosa at Week 12 |
|-----------------|--|

End point description:

Mucin was identified by staining with Alcian-blue periodic acid-Schiff and/or immunostaining for MUC5AC and then the mucin-positive area was measured and expressed per square millimeter. Analysis was performed on PD population. Here, number of subjects analysed = subjects with available data for this outcome measure.

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

End point timeframe:

Baseline, Week 12

| End point values | Placebo | Dupilumab | | |
|--------------------------------------|------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 16 | | |
| Units: cells/mm ² | | | | |
| arithmetic mean (standard deviation) | 64.09 (± 391.96) | -142.74 (± 477.89) | | |

Statistical analyses

| Statistical analysis title | Dupilumab vs. Placebo |
|----------------------------|-----------------------|
|----------------------------|-----------------------|

Statistical analysis description:

Analysis was performed using linear fixed-effect model on log-transformed data, with treatment, region and ICS dose level as fixed effects, and the baseline value as continuous covariate.

| | |
|---|---------------------------|
| Comparison groups | Placebo v Dupilumab |
| Number of subjects included in analysis | 36 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0336 ^[6] |
| Method | Linear fixed-effect model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -235.02 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -414.19 |
| upper limit | -55.84 |

Notes:

[6] - Threshold for significance at 0.05 level.

Secondary: Change From Baseline in Fractional Exhaled Nitric Oxide (FeNO) at Week 12

| | |
|-----------------|---|
| End point title | Change From Baseline in Fractional Exhaled Nitric Oxide (FeNO) at Week 12 |
|-----------------|---|

End point description:

FeNO is a surrogate marker for airway inflammation. FeNO was analysed using a NIOX instrument or similar analyzer using a flow rate of 50 mL/second, and reported in ppb. Analysis was performed on secondary PD population which consisted of all randomized and treated subjects. Here, number of subjects analysed = subjects with available data for this endpoint.

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

End point timeframe:

Baseline, Week 12

| End point values | Placebo | Dupilumab | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 18 | | |
| Units: ppb | | | | |
| arithmetic mean (standard deviation) | 3.9 (± 22.8) | -15.1 (± 18.3) | | |

Statistical analyses

| | |
|-----------------------------------|-----------------------|
| Statistical analysis title | Dupilumab vs. Placebo |
|-----------------------------------|-----------------------|

Statistical analysis description:

Analysis was performed using a Mixed-effect Model with Repeated Measures (MMRM) with treatment, treatment-by-visit interaction, region, and ICS dose level as fixed effects, and baseline biomarker-by-visit interaction as fixed covariate, and assuming an unstructured covariance structure separately by treatment group.

| | |
|-------------------|---------------------|
| Comparison groups | Dupilumab v Placebo |
|-------------------|---------------------|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 39 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0012 ^[7] |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -22.4 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -32.9 |
| upper limit | -11.9 |

Notes:

[7] - Threshold for significance at 0.05 level.

Secondary: Average Change in Fractional Exhaled Nitric Oxide (FeNO) From Baseline to Week 6 Through Week 12

| | |
|-----------------|--|
| End point title | Average Change in Fractional Exhaled Nitric Oxide (FeNO) From Baseline to Week 6 Through Week 12 |
|-----------------|--|

End point description:

FeNO is a surrogate marker for airway inflammation. FeNO was analyzed using a NIOX instrument or similar analyzer using a flow rate of 50 mL/s, and reported in ppb. The average change in FeNO from baseline to Week 6 through Week 12 was calculated as follows: For each participant the change in FeNO from Baseline to Week 6, Week 8, Week 10 and Week 12 was calculated (value at Week X - value at baseline). Subsequently the weekly mean of these 4 "change from baseline" values was determined (Weeks 6, 8, 10 and 12). Using these weekly mean values the overall arithmetic mean and standard deviation of the average change in FeNO from baseline to Week 6 through Week 12 was calculated.

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

End point timeframe:

From Baseline to Week 6 through Week 12

| End point values | Placebo | Dupilumab | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 20 | | |
| Units: ppb | | | | |
| arithmetic mean (standard deviation) | 3.5 (± 18) | -16 (± 18) | | |

Statistical analyses

| | |
|----------------------------|-----------------------|
| Statistical analysis title | Dupilumab vs. Placebo |
|----------------------------|-----------------------|

Statistical analysis description:

Analysis was performed using a Mixed-effect model with Repeated Measures with treatment (MRMM) with treatment, treatment-by-visit interaction, region, and ICS dose level as fixed effects, and baseline biomarker-by-visit interaction as fixed covariate, and assuming an unstructured covariance structure separately by treatment group.

| | |
|-------------------|---------------------|
| Comparison groups | Dupilumab v Placebo |
|-------------------|---------------------|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 42 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0005 ^[8] |
| Method | MMRM |
| Parameter estimate | LS mean difference |
| Point estimate | -22 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -31.3 |
| upper limit | -12.8 |

Notes:

[8] - Threshold for significance at 0.05 level.

Secondary: Number of Subjects With Antidrug Antibodies (ADA)

| | |
|------------------------|--|
| End point title | Number of Subjects With Antidrug Antibodies (ADA) |
| End point description: | Anti-drug antibodies were detected using a validated immunoassay. Incidence of ADA were classified as following: 1) Pre-existing immunoreactivity - an ADA positive response in the assay at baseline with all post treatment ADA results negative or an ADA positive response at baseline with all post treatment ADA responses less than 4-fold over baseline titer levels. 2) Treatment-emergent ADA: an ADA positive response in the assay post first dose, when baseline results were negative or missing. 3) Treatment-boosted ADA: an ADA positive response in the assay post first dose that was greater-than or equal to 4-fold over baseline titer levels, when baseline results were positive. Analysis was performed on ADA population which consisted of all subjects with at least one qualified ADA result in the ADA assay following the first dose of the study medication. |
| End point type | Secondary |
| End point timeframe: | From Baseline up to 24 weeks |

| End point values | Placebo | Dupilumab | | |
|------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 19 | | |
| Units: subjects | | | | |
| number (not applicable) | | | | |
| With pre-existing immunoreactivity | 1 | 0 | | |
| With treatment-emergent ADA | 0 | 1 | | |
| With treatment-boosted ADA | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) Assessment: Serum Functional Dupilumab Concentration

| | |
|-----------------|---|
| End point title | Pharmacokinetics (PK) Assessment: Serum Functional Dupilumab Concentration ^[9] |
|-----------------|---|

End point description:

Serum functional dupilumab concentrations were determined using an enzyme-linked immunosorbent assay (ELISA) method. Analysis was performed on PK population which consisted of all subjects with at least one non-missing and eligible post-baseline dupilumab serum concentration data. Here, "n" represents number of subjects with available data for specified time points.

Data for this endpoint were not planned to be analysed for placebo arm.

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

End point timeframe:

Week 0, Week 2, 6, 8, 12, 18, End of study (Week 24)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint were not planned to be analysed for placebo arm.

| End point values | Dupilumab | | | |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 20 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 0 (n= 20) | 0.00 (± 0.00) | | | |
| Week 2 (n= 20) | 52675.00 (± 23107.55) | | | |
| Week 6 (n= 20) | 59969.00 (± 27422.27) | | | |
| Week 8 (n= 20) | 61097.95 (± 29775.23) | | | |
| Week 12 (n= 20) | 67387.00 (± 32800.44) | | | |
| Week 18 (n= 6) | 20728.17 (± 17718.93) | | | |
| Week 24 (n= 5) | 1851.20 (± 2796.78) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs)

| | |
|-----------------|---|
| End point title | Number of Subjects With Treatment Emergent Adverse Events (TEAEs) |
|-----------------|---|

End point description:

Adverse event (AE) was defined as any untoward medical occurrence in a subject who received investigational medicinal product (IMP) without regard to possibility of causal relationship with this treatment. TEAEs: AEs that developed or worsened or became serious during the interval between the first administration of study medication and the end of the 12 week Post-treatment Period. Serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. Any TEAE included both serious and non-serious AEs. Analysis was performed on safety population which consisted of all subjects randomized and exposed to study medication, regardless of the amount of treatment administered.

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

End point timeframe:

Baseline up to Week 24

| End point values | Placebo | Dupilumab | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 20 | | |
| Units: subjects | | | | |
| number (not applicable) | | | | |
| Any TEAE | 17 | 15 | | |
| Any treatment emergent SAE | 0 | 1 | | |
| Any TEAE leading to death | 0 | 0 | | |
| Any TEAE leading to permanent discontinuation | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from signature of the informed consent form up to the end of study (i.e. up to the end of Post-treatment period [Week 24]) regardless of seriousness or relationship to investigational medicinal product (IMP).

Adverse event reporting additional description:

Reported AEs and deaths are treatment emergent AEs that developed/worsened and deaths that occurred during 'treatment-emergent period' (from first dose of investigational product injection up to the end of Post-treatment period [Week 24]). Analysis was performed on safety population.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

Reporting groups

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

Reporting group description:

Placebo (for dupilumab), 2 subcutaneous injections on Day 1 (Week 1) as a loading dose followed by a single injection q2w from Week 2 to Week 14 added to stable ICS/LABA therapy. Salbutamol/albuterol or Levosalbutamol/levalbuterol was given as reliever medication.

| | |
|-----------------------|-----------|
| Reporting group title | Dupilumab |
|-----------------------|-----------|

Reporting group description:

Dupilumab, 2 subcutaneous injections on Day 1 as a loading dose for a total of 600 mg, followed by a single 300 mg injection q2w from Week 2 to Week 14 added to stable ICS/LABA therapy. Salbutamol/albuterol or Levosalbutamol/levalbuterol was given as reliever medication.

| Serious adverse events | Placebo | Dupilumab | |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 20 (5.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 20 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo | Dupilumab | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 11 / 22 (50.00%) | 14 / 20 (70.00%) | |
| Injury, poisoning and procedural complications | | | |
| Road Traffic Accident | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 2 / 20 (10.00%) | |
| occurrences (all) | 0 | 2 | |
| Accidental Overdose | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 2 / 20 (10.00%) | |
| occurrences (all) | 1 | 3 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 1 / 20 (5.00%) | |
| occurrences (all) | 3 | 1 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 22 (13.64%) | 5 / 20 (25.00%) | |
| occurrences (all) | 9 | 11 | |
| General disorders and administration site conditions | | | |
| Injection Site Erythema | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 3 / 20 (15.00%) | |
| occurrences (all) | 8 | 8 | |
| Injection Site Inflammation | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 1 / 20 (5.00%) | |
| occurrences (all) | 3 | 3 | |
| Injection Site Pruritus | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 2 / 20 (10.00%) | |
| occurrences (all) | 1 | 3 | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 2 / 20 (10.00%) | |
| occurrences (all) | 0 | 2 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 3 / 20 (15.00%) | |
| occurrences (all) | 1 | 3 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--|-----------------|-----------------|--|
| Asthma subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) | 2 / 20 (10.00%) | |
| | 1 | 2 | |
| | | | |
| Cough subjects affected / exposed occurrences (all) | 2 / 22 (9.09%) | 1 / 20 (5.00%) | |
| | 2 | 1 | |
| | | | |
| Wheezing subjects affected / exposed occurrences (all) | 2 / 22 (9.09%) | 0 / 20 (0.00%) | |
| | 2 | 0 | |
| | | | |
| Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) | 3 / 20 (15.00%) | |
| | 0 | 3 | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 4 / 22 (18.18%) | 2 / 20 (10.00%) | |
| | 6 | 2 | |
| | | | |
| Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) | 3 / 20 (15.00%) | |
| | 1 | 3 | |
| | | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 18 February 2016 | Following changes were made: <ul style="list-style-type: none">- Virus serology and anti-drug antibody sampling times moved for subjects entering the long-term extension study- Chest imaging added for subjects entering the long-term extension study- Virus serology testing modified to align with exclusion criteria for the other dupilumab clinical trials in asthma and allow more low risk subjects to be enrolled- Peak Expiratory Flow measurements operational requirements clarified- Prednisolone added as an equivalent alternative treatment to prednisone after the bronchoscopy procedure- Anti-drug antibody sampling times, follow-up and terminology modified for harmonization across the clinical program- Previous local protocol amendments for Germany and UK incorporated to simplify documentation for these countries- Exclusion criterion related to infections simplified to allow inclusion of low risk subjects with common non-threatening conditions |
| 23 November 2016 | Following changes were made: <ul style="list-style-type: none">- Clinical Study Director changed- Non-investigational product list updated- Clarified the screening period extension as a one-time window- Clarified the timing of performing spirometry during all visits- Language regarding steering committee removed- Changes made to inclusion/exclusion criteria- Permanent discontinuation criteria clarified- List of exploratory biomarkers modified- Anti-drug antibody sampling time modified to detect early ADA responses |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported