# Clinical trial results:
# A randomized double-blind placebo-controlled parallel group study assessing the efficacy and safety of dupilumab in patients with Allergic Fungal Rhinosinusitis (AFRS)

## Summary

| | |
|---|---|
| EudraCT number | 2020-002999-12 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 07 March 2025 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 23 October 2025 |
| First version publication date | 23 October 2025 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | EFC16724 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04684524 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Sanofi aventis recherche & développement |
| Sponsor organisation address | 82 Avenue Raspail, Gentilly, France, 94250 |
| Public contact | Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com |
| Scientific contact | Trial Transparency Team, Sanofi aventis recherche & développement, 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? | Yes |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 16 April 2025 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 07 March 2025 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of treatment with dupilumab to reduce sinus opacification in a population with allergic fungal rhinosinusitis (AFRS)

Protection of trial subjects:

For pediatrics: The study was conducted by investigators experienced in the treatment of pediatric participants. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia might have been used to minimize distress and discomfort.
For adults: Participants 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 participant and considering the local culture. During the course of the trial, participants were provided with individual participant cards indicating the nature of the trial the participant 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 | 01 December 2020 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Argentina: 17 |
| Country: Number of subjects enrolled | Canada: 2 |
| Country: Number of subjects enrolled | China: 16 |
| Country: Number of subjects enrolled | India: 4 |
| Country: Number of subjects enrolled | Japan: 4 |
| Country: Number of subjects enrolled | Saudi Arabia: 2 |
| Country: Number of subjects enrolled | Türkiye: 4 |
| Country: Number of subjects enrolled | United States: 13 |
| Worldwide total number of subjects | 62 |
| 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) | 1 |
| Adolescents (12-17 years) | 5 |
| Adults (18-64 years) | 51 |
| From 65 to 84 years | 5 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at 45 centers in 9 countries. A total of 152 participants were screened from 01-Dec-2020 to 28-Nov-2023 of which 90 were screen failures. Screen failures were mainly due to not meeting eligibility criteria.

### Pre-assignment

Screening details:

A total of 62 participants were randomized in a 1:1 ratio to receive either dupilumab or matching placebo in this study. Reasons for study discontinuation are presented.

### 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, Monitor, Carer |

### Arms

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

Arm description:

Participants received placebo matched to dupilumab via subcutaneous (SC) injection for 52 weeks.

| | |
|---|---|
| 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:

Placebo matched to dupilumab was administered via SC injection for 52 weeks.

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

Arm description:

Participants received dupilumab depending on the weight at screening via SC injection for 52 weeks as follows: • 300 milligrams (mg) every 2 weeks (q2w) for all adults and adolescents/children weighing >=60 kilograms (kg) • 200 mg q2w for adolescents/children weighing >=30 kg and <60 kg • 300 mg every 4 weeks (q4w) for adolescents/children weighing >=15 kg and <30 kg.

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

Dosage and administration details:

Dupilumab was administered for 52 weeks as specified in the protocol.

| **Number of subjects in period 1** | Placebo | Dupilumab |
|---|---|---|
| Started | 29 | 33 |
| Randomized and treated | 28 | 33 |
| Completed | 21 | 29 |
| Not completed | 8 | 4 |
| Consent withdrawn by subject | 5 | 3 |
| Adverse event, non-fatal | 1 | 1 |
| Unspecified | 2 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received placebo matched to dupilumab via subcutaneous (SC) injection for 52 weeks. | |
| Reporting group title | Dupilumab |
| Reporting group description: | |
| Participants received dupilumab depending on the weight at screening via SC injection for 52 weeks as follows: • 300 milligrams (mg) every 2 weeks (q2w) for all adults and adolescents/children weighing >=60 kilograms (kg) • 200 mg q2w for adolescents/children weighing >=30 kg and <60 kg • 300 mg every 4 weeks (q4w) for adolescents/children weighing >=15 kg and <30 kg. | |

| Reporting group values | Placebo | Dupilumab | Total |
|---|---|---|---|
| Number of subjects | 29 | 33 | 62 |
| Age categorical<br>Units: Subjects | | | |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 37.4 | 41.9 | |
| standard deviation | ± 14.0 | ± 17.5 | - |
| Sex: Female, Male<br>Units: participants | | | |
| Female | 4 | 13 | 17 |
| Male | 25 | 20 | 45 |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 13 | 12 | 25 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 3 | 5 | 8 |
| White | 12 | 15 | 27 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 1 | 1 | 2 |
| Lund Mackay (LMK) score | | | |
| The LMK total score is based on assessment of the computerized tomography (CT) scan findings for each sinus area (maxillary, anterior ethmoid, posterior ethmoid, sphenoid, and frontal sinus on each side). The extent of mucosal opacification is rated on a 3-point scale ranging from 0 = normal to 2 = total opacification. In addition, the ostiomeatal complex is graded as 0 = not occluded or 2 = occluded. The maximum score is 12 per side; total score ranges from 0 (normal) to 24 (more opacified) corresponding to the sum of all sinuses and the ostiomeatal unit. Higher score indicated worse outcome. | | | |
| Units: score on a scale | | | |
| arithmetic mean | 18.4 | 17.5 | |
| standard deviation | ± 3.4 | ± 3.8 | - |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received placebo matched to dupilumab via subcutaneous (SC) injection for 52 weeks. | |
| Reporting group title | Dupilumab |
| Reporting group description: | |
| Participants received dupilumab depending on the weight at screening via SC injection for 52 weeks as follows: • 300 milligrams (mg) every 2 weeks (q2w) for all adults and adolescents/children weighing >=60 kilograms (kg) • 200 mg q2w for adolescents/children weighing >=30 kg and <60 kg • 300 mg every 4 weeks (q4w) for adolescents/children weighing >=15 kg and <30 kg. | |

### Primary: Change From Baseline to Week 52 in Opacification of Sinuses Assessed by CT Scan Using the LMK Score

| | |
|---|---|
| End point title | Change From Baseline to Week 52 in Opacification of Sinuses Assessed by CT Scan Using the LMK Score |
| End point description: | |
| The LMK score is used to quantify the degree of opacification of each sinus on CT scan. The CT scan LMK staging system represents the most widely established method of sinus CT scoring. The LMK total score is based on assessment of the CT scan findings for each sinus area (maxillary, anterior ethmoid, posterior ethmoid, sphenoid, and frontal sinus on each side). The extent of mucosal opacification is rated on a 3-point scale ranging from 0 = normal to 2 = total opacification. In addition, the ostiomeatal complex is graded as 0 = not occluded or 2 = occluded. The maximum score is 12 per side; total score ranges from 0 (normal) to 24 (more opacified) corresponding to the sum of all sinuses and the ostiomeatal unit. Higher scores indicate worse outcome; a negative change from baseline indicate improvement. Baseline was defined as the last available value before the first dose of study drug. The intent-to-treat (ITT) population included all randomized participants. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline (Day 1) and Week 52 | |

| **End point values** | Placebo | Dupilumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 33 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.81 (± 0.81) | -9.17 (± 0.74) | | |

### Statistical analyses

| **Statistical analysis title** | Week 52: Change From Baseline in LMK score |
|---|---|
| Statistical analysis description: | |
| Each of the imputed complete data were analyzed by fitting an analysis of covariance (ANCOVA) model with the corresponding baseline value, intervention group, time from last surgery (<=2 years, >2 years), and region (Americas and Asia) as covariates. | |
| Comparison groups | Placebo v Dupilumab |

| | |
|---|---|
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Least squares (LS) Mean Difference |
| Point estimate | -7.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.38 |
| upper limit | -5.35 |

## Secondary: Change From Baseline to Week 24 in Monthly Average Nasal Congestion/Obstruction Score From the Nasal Symptom Diary

| | |
|---|---|
| End point title | Change From Baseline to Week 24 in Monthly Average Nasal Congestion/Obstruction Score From the Nasal Symptom Diary |

End point description:

The nasal symptom diary is designed to assess the severity of chronic rhinosinusitis (CRS) nasal symptoms on daily basis. Score range: 0 = no symptoms, 1 = mild symptoms (symptoms clearly present, but minimal awareness and easily tolerated), 2= moderate symptoms (definite awareness of symptoms that is bothersome but tolerable) and 3 = severe symptoms (symptoms that are hard to tolerate, cause interference with activities or daily living). Higher scores denote greater symptom severity; a negative change from baseline indicate improvement. Baseline was defined as the average of the scores in the 7 days prior to the first dose of study drug. The ITT population included all randomized participants.

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

End point timeframe:

Baseline (Day -7 to Day -1) and Week 24

| End point values | Placebo | Dupilumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 33 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -0.43 (± 0.13) | -1.30 (± 0.11) | | |

## Statistical analyses

| Statistical analysis title | Week 24:Nasal Congestion/Obstruction Score |
|---|---|

Statistical analysis description:

Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, time from last surgery (<=2 years, >2 years), and region (Americas and Asia) as covariates.

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

| | |
|---|---|
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.18 |
| upper limit | -0.56 |

## Secondary: Change From Baseline to Week 24 in Endoscopy Nasal Polyp Score (NPS)

| | |
|---|---|
| End point title | Change From Baseline to Week 24 in Endoscopy Nasal Polyp Score (NPS) |

End point description:

The bilateral endoscopy NPS is determined by the clinician who assesses nasal polyp formation. Polyps on each side of the nose are graded based on polyp size; scores: 0 = no polyps; 1 = small polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2 = polyps reaching below the lower border of the middle turbinate; 3 = large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate and 4 = large polyps causing complete obstruction. The total score is the sum of the right and left nostrils, ranging from 0 (no obstruction) to 8 (complete obstruction); higher score indicating worse outcome; a negative change from baseline indicate improvement. Baseline was defined as the last available value before the first dose of study drug. The ITT population included all randomized participants.

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

End point timeframe:

Baseline (Day 1) and Week 24

| End point values | Placebo | Dupilumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 33 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -0.80 (± 0.38) | -3.16 (± 0.34) | | |

### Statistical analyses

| Statistical analysis title | Change From Baseline to Week 24 in Endoscopy NPS |
|---|---|

Statistical analysis description:

Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, time from last surgery (<=2 years, >2 years), and region (Americas and Asia) as covariates.

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

| | |
|---|---|
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.31 |
| upper limit | -1.41 |

## Secondary: Change From Baseline to Week 24 in Opacification of Sinuses Assessed by CT Scan Using the LMK Score

| | |
|---|---|
| End point title | Change From Baseline to Week 24 in Opacification of Sinuses Assessed by CT Scan Using the LMK Score |

End point description:

The LMK score is used to quantify the degree of opacification of each sinus on CT scan. The CT scan LMK staging system represents the most widely established method of sinus CT scoring. The LMK total score is based on assessment of the CT scan findings for each sinus area (maxillary, anterior ethmoid, posterior ethmoid, sphenoid, and frontal sinus on each side). The extent of mucosal opacification is rated on a 3-point scale ranging from 0 = normal to 2 = total opacification. In addition, the ostiomeatal complex is graded as 0 = not occluded or 2 = occluded. The maximum score is 12 per side; total score ranges from 0 (normal) to 24 (more opacified) corresponding to the sum of all sinuses and the ostiomeatal unit. Higher scores indicate worse outcome; a negative change from baseline indicate improvement. Baseline was defined as the last available value before the first dose of study drug. The ITT population included all randomized participants.

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

End point timeframe:

Baseline (Day 1) and Week 24

| **End point values** | Placebo | Dupilumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 33 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.93 (± 0.82) | -7.38 (± 0.80) | | |

### Statistical analyses

| **Statistical analysis title** | Week 24: Change From Baseline in LMK Score |
|---|---|

Statistical analysis description:

Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, time from last surgery (<=2 years, >2 years), and region (Americas and Asia) as covariates.

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

| | |
|---|---|
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -5.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.48 |
| upper limit | -3.43 |

## Secondary: Change From Baseline to Week 24 in Monthly Average Total Symptom Score (TSS) Derived From the Nasal Symptom Diary

| | |
|---|---|
| End point title | Change From Baseline to Week 24 in Monthly Average Total Symptom Score (TSS) Derived From the Nasal Symptom Diary |

End point description:

The nasal symptom diary is designed to assess the severity of CRS nasal symptoms on daily basis The TSS is a composite score consisting of the sum of the following symptoms assessed daily in the morning: nasal congestion/obstruction, decreased/loss of sense of smell, rhinorrhea (average of anterior/posterior nasal discharge). Each of the individual items were scored from 0 = no symptoms to 3 = severe symptoms. TSS is the sum of individual items and ranges between 0 = no symptoms and 9 = severe symptoms. Higher scores on the TSS indicate greater symptom severity; a negative change from baseline indicate improvement. Baseline was defined as the average of the scores in the 7 days prior to the first dose of study drug. The ITT population included all randomized participants.

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

End point timeframe:

Baseline (Day -7 to Day -1) and Week 24

| **End point values** | Placebo | Dupilumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 33 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.26 (± 0.35) | -3.45 (± 0.31) | | |

### Statistical analyses

| **Statistical analysis title** | Change From Baseline to Week 24 in TSS |
|---|---|

Statistical analysis description:

Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, time from last surgery (<=2 years, >2 years), and region (Americas and Asia) as covariates.

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

| | |
|---|---|
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.04 |
| upper limit | -1.32 |

## Secondary: Change From Baseline to Week 24 in University of Pennsylvania Smell Identification Test (UPSIT)

| | |
|---|---|
| End point title | Change From Baseline to Week 24 in University of Pennsylvania Smell Identification Test (UPSIT) |

End point description:

The UPSIT (UPSIT 40 odorant test) is a rapid and easy-to-administer method to quantitatively assess human olfactory function. The test consists of 4 booklets, each containing 10 odorants with 1 odorant per page. Above each odorant strip is a multiple-choice question with 4 alternative words to describe the odor and the participant is asked to indicate which word best describes the odor. Each smell has a possible of 4 answers with one being correct, therefore the potential total scores can range from 0 (worst possible score) to 40 (best possible score), with 1 point being awarded for each correctly identified odor, higher scores indicating better olfactory function; i.e. better sense of smell. Baseline was defined as the last available value before the first dose of study drug. The ITT population included all randomized participants.

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

End point timeframe:

Baseline (Day 1) and Week 24

| End point values | Placebo | Dupilumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 33 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | 4.41 (± 1.71) | 8.87 (± 1.60) | | |

## Statistical analyses

| Statistical analysis title | Change From Baseline to Week 24 in UPSIT |
|---|---|

Statistical analysis description:

Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, time from last surgery (<=2 years, >2 years), and region (Americas and Asia) as covariates.

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

| | |
|---|---|
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0392 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 4.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.22 |
| upper limit | 8.71 |

## Secondary: Change From Baseline to Week 24 in Monthly Average Decreased/Loss of Smell Using the Nasal Symptom Diary

| | |
|---|---|
| End point title | Change From Baseline to Week 24 in Monthly Average Decreased/Loss of Smell Using the Nasal Symptom Diary |

End point description:

The nasal symptom diary is designed to assess the severity of CRS nasal symptoms on daily basis. Each of the individual items of the diary are scored as: 0 = no symptoms, 1 = mild symptoms (symptoms clearly present, but minimal awareness and easily tolerated), 2= moderate symptoms (definite awareness of symptoms that is bothersome but tolerable) and 3 = severe symptoms (symptoms that are hard to tolerate, cause interference with activities or daily living). Higher scores denote greater symptom severity; a negative change from baseline indicate improvement. Baseline was defined as the average of the scores in the 7 days prior to the first dose of study drug. The ITT population included all randomized participants.

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

End point timeframe:

Baseline (Day -7 to Day -1) and Week 24

| **End point values** | Placebo | Dupilumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 33 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -0.39 (± 0.16) | -1.28 (± 0.15) | | |

## Statistical analyses

| **Statistical analysis title** | Week 24: Decreased/Loss of Smell |
|---|---|

Statistical analysis description:

Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, time from last surgery (<=2 years, >2 years), and region (Americas and Asia) as covariates.

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

| | |
|---|---|
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.29 |
| upper limit | -0.49 |

## Secondary: Change From Baseline to Week 52 in Endoscopy NPS

| | |
|---|---|
| End point title | Change From Baseline to Week 52 in Endoscopy NPS |

End point description:

The bilateral endoscopy NPS is determined by the clinician who assesses nasal polyp formation. Polyps on each side of the nose are graded based on polyp size; scores: 0 = no polyps; 1 = small polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2 = polyps reaching below the lower border of the middle turbinate; 3 = large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate and 4 = large polyps causing complete obstruction. The total score is the sum of the right and left nostrils, ranging from 0 (no obstruction) to 8 (complete obstruction); higher score indicating worse outcome; a negative change from baseline indicate improvement. Baseline was defined as the last available value before the first dose of study drug. The ITT population included all randomized participants.

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

End point timeframe:

Baseline (Day 1) and Week 52

| **End point values** | Placebo | Dupilumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 33 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -0.55 (± 0.43) | -3.32 (± 0.39) | | |

## Statistical analyses

| **Statistical analysis title** | Change From Baseline to Week 52 in Endoscopy NPS |
|---|---|

Statistical analysis description:

Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, time from last surgery (<=2 years, >2 years), and region (Americas and Asia) as covariates.

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

| | |
|---|---|
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.82 |
| upper limit | -1.72 |

## Secondary: Change From Baseline to Week 52 in Monthly Average Nasal Congestion/Obstruction Score From the Nasal Symptom Diary

| | |
|---|---|
| End point title | Change From Baseline to Week 52 in Monthly Average Nasal Congestion/Obstruction Score From the Nasal Symptom Diary |

End point description:

The nasal symptom diary is designed to assess the severity of CRS nasal symptoms on daily basis. Score range: 0 = no symptoms, 1 = mild symptoms (symptoms clearly present, but minimal awareness and easily tolerated), 2= moderate symptoms (definite awareness of symptoms that is bothersome but tolerable) and 3 = severe symptoms (symptoms that are hard to tolerate, cause interference with activities or daily living). Higher scores denote greater symptom severity; a negative change from baseline indicate improvement. Baseline was defined as the average of the scores in the 7 days prior to the first dose of study drug. The ITT population included all randomized participants.

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

End point timeframe:

Baseline (Day -7 to Day -1) and Week 52

| **End point values** | Placebo | Dupilumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 33 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -0.17 (± 0.15) | -1.57 (± 0.14) | | |

## Statistical analyses

| **Statistical analysis title** | Week 52: Nasal Congestion/Obstruction Score |
|---|---|

Statistical analysis description:

Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, time from last surgery (<=2 years, >2 years), and region (Americas and Asia) as covariates.

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

| | |
|---|---|
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.77 |
| upper limit | -1.02 |

## Secondary: Change From Baseline to Week 52 in 22-item Sino-Nasal Outcome Test (SNOT-22) Total Score

| | |
|---|---|
| End point title | Change From Baseline to Week 52 in 22-item Sino-Nasal Outcome Test (SNOT-22) Total Score |

End point description:

The SNOT-22 is a validated questionnaire designed to assess the impact of CRS on participants health-related quality of life (HRQoL) and has 22 items covering symptoms, social/emotional impact, productivity, and sleep consequences of CRS. The recall period is past 2 weeks. Each item is rated on a 6-point Likert scale; response options ranging from 0 = no problem to 5 = problem as bad as it can be. A global score ranging from 0 (no impact) to 110 (severe impact) is calculated by summing the responses to all items; higher score indicates greater rhinosinusitis-related health burden; a negative change from baseline indicate improvement. Baseline was defined as the last available value before the first dose of study drug. The ITT population included all randomized participants. Only those participants with data collected is presented.

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

End point timeframe:

Baseline (Day 1) and Week 52

| **End point values** | Placebo | Dupilumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 33 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -12.64 (± 4.06) | -29.94 (± 3.75) | | |

## Statistical analyses

| **Statistical analysis title** | Week 52: SNOT-22 Total Score |
|---|---|

Statistical analysis description:

Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, time from last surgery (<=2 years, >2 years), and region (Americas and Asia) as covariates.

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

| | |
|---|---|
| Number of subjects included in analysis | 61 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0004 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -17.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -26.86 |
| upper limit | -7.74 |

## Secondary: Change From Baseline to Week 52 in Three-dimensional CT Total Volume Occupied by Disease in all Sinuses

| | |
|---|---|
| End point title | Change From Baseline to Week 52 in Three-dimensional CT Total Volume Occupied by Disease in all Sinuses |

End point description:

This method is used to calculate the percent occupied by disease. It is performed at locations including ethmoid sinus, frontal sinus, maxillary sinus, and sphenoid sinus. The total volume occupied by disease in all sinuses is reported here. For the analysis, central reading at baseline was used for comparison with Week 52 reading; a negative change from baseline indicated improvement. Baseline was defined as the last available value before the first dose of study drug. The ITT population included all randomized participants.

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

End point timeframe:

Baseline (Day 1) and Week 52

| End point values | Placebo | Dupilumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 33 | | |
| Units: percent | | | | |
| least squares mean (standard error) | -5.73 (± 3.91) | -42.04 (± 3.47) | | |

### Statistical analyses

| Statistical analysis title | Week 52:Three-dimensional CT Total Volume |
|---|---|

Statistical analysis description:

Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, time from last surgery (<=2 years, >2 years), and region (Americas and Asia) as covariates.

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

| | |
|---|---|
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -36.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -45.59 |
| upper limit | -27.03 |

## Secondary: Percentage of Participants who Received Systemic Corticosteroids (SCS) and/or Underwent or Planned to Undergo Surgery for AFRS at Week 52

| | |
|---|---|
| End point title | Percentage of Participants who Received Systemic Corticosteroids (SCS) and/or Underwent or Planned to Undergo Surgery for AFRS at Week 52 |

End point description:

SCS use was defined as the use of SCS for rescue treatment of AFRS or for another reason and was captured by the Investigator (or designee) in electronic case report form (eCRF). Participants who underwent or planned to undergo surgery for AFRS were also recorded in eCRF. The ITT population included all randomized participants.

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

End point timeframe:

Week 52

| **End point values** | Placebo | Dupilumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 33 | | |
| Units: percentage of particpants | | | | |
| number (not applicable) | 31.0 | 3.0 | | |

### Statistical analyses

| **Statistical analysis title** | SCS and/or Surgery for AFRS |
|---|---|

Statistical analysis description:

Risk difference was estimated using Mantel-Haenszel estimate and confidence limits, with Mantel-Haenszel stratum weights for time from last surgery (<=2 years, >2 years) and region (Americas and Asia) and the Sato variance estimator.

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

| | |
|---|---|
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 |
| Method | Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -29.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -46.42 |
| upper limit | -11.79 |

## Secondary: Change From Baseline to Week 24 in SNOT-22 Total Score

| | |
|---|---|
| End point title | Change From Baseline to Week 24 in SNOT-22 Total Score |

End point description:

The SNOT-22 is a validated questionnaire designed to assess the impact of CRS on participants HRQoL and has 22 items covering symptoms, social/emotional impact, productivity, and sleep consequences of CRS. The recall period is past 2 weeks. Each item is rated on a 6-point Likert scale; response options ranging from 0 = no problem to 5 = problem as bad as it can be. A global score ranging from 0 (no impact) to 110 (severe impact) is calculated by summing the responses to all items; higher score indicates greater rhinosinusitis-related health burden; a negative change from baseline indicate improvement. Baseline was defined as the last available value before the first dose of study drug. The ITT population included all randomized participants. Only those participants with data collected is presented.

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

End point timeframe:

Baseline (Day 1) and Week 24

| End point values | Placebo | Dupilumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 33 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -11.63 (± 4.02) | -26.74 (± 3.81) | | |

### Statistical analyses

| Statistical analysis title | Week 24: SNOT-22 Total Score |
|---|---|

Statistical analysis description:

Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, time from last surgery (<=2 years, >2 years), and region (Americas and Asia) as covariates.

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

| | |
|---|---|
| Number of subjects included in analysis | 61 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0032 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -15.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -25.15 |
| upper limit | -5.07 |

## Secondary: Percent Change From Baseline in Serum Total Immunoglobulin-E (IgE) to Week 52

| | |
|---|---|
| End point title | Percent Change From Baseline in Serum Total Immunoglobulin-E (IgE) to Week 52 |

End point description:

Blood samples were collected at specified timepoints for the assessment of IgE. Total IgE was measured with a quantitative method approved for diagnostic testing; a negative change from baseline indicated improvement. Baseline was defined as the last available value before the first dose of study drug. The safety population included all randomized participants who took at least 1 dose of study drug, regardless of the amount of treatment administered.

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

End point timeframe:

Baseline (Day 1) and Week 52

| **End point values** | Placebo | Dupilumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 33 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | 6.91 (± 10.86) | -73.81 (± 11.40) | | |

## Statistical analyses

| **Statistical analysis title** | Week 52: Serum Total IgE |
|---|---|

Statistical analysis description:

Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, time from last surgery (<=2 years, >2 years), and region (Americas and Asia) as covariates.

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

| | |
|---|---|
| Number of subjects included in analysis | 61 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -80.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -112.82 |
| upper limit | -48.61 |

## Secondary: Change From Baseline to Weeks 24 and 52 in the Monthly Average Rhinorrhea Score From the Nasal Symptom Diary

| | |
|---|---|
| End point title | Change From Baseline to Weeks 24 and 52 in the Monthly Average Rhinorrhea Score From the Nasal Symptom Diary |

End point description:

The nasal symptom diary is designed to assess the severity of CRS nasal symptoms on daily basis. Score range: 0 = no symptoms, 1 = mild symptoms (symptoms clearly present, but minimal awareness and easily tolerated), 2= moderate symptoms (definite awareness of symptoms that is bothersome but tolerable) and 3 = severe symptoms (symptoms that are hard to tolerate, cause interference with activities, or daily living). Higher scores denote greater symptom severity; a negative change from baseline indicate improvement. Severity of rhinorrhea (average of anterior [runny nose]/posterior nasal discharge [post-nasal drip]) is presented here. Baseline was defined as the average of the scores in the 7 days prior to the first dose of study drug. The ITT population included all randomized participants.

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

End point timeframe:

Baseline (Day -7 to Day -1) and Weeks 24 and 52

| End point values | Placebo | Dupilumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 33 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 24 | -0.44 (± 0.13) | -0.92 (± 0.12) | | |
| Week 52 | -0.33 (± 0.15) | -1.09 (± 0.13) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline to Week 52 in Monthly Average TSS Derived From the Nasal Symptom Diary

| | |
|---|---|
| End point title | Change From Baseline to Week 52 in Monthly Average TSS Derived From the Nasal Symptom Diary |

End point description:

The nasal symptom diary is designed to assess the severity of CRS nasal symptoms on daily basis. The TSS is a composite score consisting of the sum of the following symptoms assessed daily in the morning: nasal congestion/obstruction, decreased/loss of sense of smell, rhinorrhea (average of anterior/posterior nasal discharge). Each of the individual items were scored from 0 = no symptoms to 3 = severe symptoms. TSS is the sum of individual items and ranges between 0 = no symptoms and 9 = severe symptoms. Higher scores on the TSS indicate greater symptom severity; a negative change from baseline indicate improvement. Baseline was defined as the average of the scores in the 7 days prior to the first dose of study drug. The ITT population included all randomized participants.

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

End point timeframe:

Baseline (Day -7 to Day -1) and Week 52

| **End point values** | Placebo | Dupilumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 33 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -0.71 (± 0.39) | -4.10 (± 0.35) | | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change From Baseline to Weeks 24 and 52 in Visual Analog Scale (VAS) Rhinosinusitis**

| End point title | Change From Baseline to Weeks 24 and 52 in Visual Analog Scale (VAS) Rhinosinusitis |
|---|---|

End point description:

The rhinosinusitis VAS is used to evaluate the overall severity of the rhinosinusitis. It is a recommended scale to determine the participant's disease severity and to guide the treatment for CRS. The participant is asked to answer the following question: "How troublesome are your symptoms of your rhinosinusitis" on a 10-centimeter VAS from 0 = not troublesome to 10 = worst thinkable troublesome. Based on their score on the VAS, the severity of rhinosinusitis is divided into 3 categories as follows: mild = VAS 0 to 3, moderate = VAS >3 to 7 and severe = VAS >7 to 10; higher score indicating worse outcome; a negative change from baseline indicate improvement. Baseline was defined as the last available value before the first dose of study drug. The ITT population included all randomized participants. Only those participants with data collected is presented.

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

End point timeframe:

Baseline (Day 1) and Weeks 24 and 52

| **End point values** | Placebo | Dupilumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 33 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 24 | -1.29 (± 0.61) | -4.30 (± 0.58) | | |

| | | | | |
|---|---|---|---|---|
| Week 52 | -1.20 (± 0.57) | -5.52 (± 0.54) | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline to Week 52 in UPSIT

| End point title | Change From Baseline to Week 52 in UPSIT |
|---|---|

End point description:

The UPSIT (UPSIT 40 odorant test) is a rapid and easy-to-administer method to quantitatively assess human olfactory function. The test consists of 4 booklets, each containing 10 odorants with 1 odorant per page. Above each odorant strip is a multiple-choice question with 4 alternative words to describe the odor and the participant is asked to indicate which word best describes the odor. Each smell has a possible of 4 answers with one being correct, therefore the potential total scores can range from 0 (worst possible score) to 40 (best possible score), with 1 point being awarded for each correctly identified odor, higher scores indicating better olfactory function, i.e. better sense of smell. Baseline was defined as the last available value before the first dose of study drug. The ITT population included all randomized participants.

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

End point timeframe:

Baseline (Day 1) and Week 52

| End point values | Placebo | Dupilumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 33 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | 2.12 (± 1.73) | 9.45 (± 1.57) | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline to Week 52 in Monthly Average Decreased/Loss of Smell Using the Nasal Symptom Diary

| End point title | Change From Baseline to Week 52 in Monthly Average Decreased/Loss of Smell Using the Nasal Symptom Diary |
|---|---|

End point description:

The nasal symptom diary is designed to assess the severity of CRS nasal symptoms on daily basis. Each of the individual items of the diary are scored as: 0 = no symptoms, 1 = mild symptoms (symptoms clearly present, but minimal awareness and easily tolerated), 2= moderate symptoms (definite awareness of symptoms that is bothersome but tolerable) and 3 = severe symptoms (symptoms that are hard to tolerate, cause interference with activities or daily living). Higher scores denote greater symptom severity; a negative change from baseline indicate improvement. Baseline was defined as the average of the scores in the 7 days prior to the first dose of study drug. The ITT population included all randomized participants.

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

End point timeframe:

Baseline (Day -7 to Day -1) and Week 52

| End point values | Placebo | Dupilumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 33 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -0.24 (± 0.17) | -1.41 (± 0.16) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

| End point title | Number of Participants with Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs) |
|---|---|

End point description:

An AE was any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study drug, whether or not considered related to the study drug. A SAE was defined as any untoward medical occurrence that, at any dose: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent disability/incapacity, was a congenital anomaly/birth defect or was a medically important event. TEAEs were AEs that developed, worsened or became serious during the treatment-emergent period. The safety population included all randomized participants who took at least 1 dose of study drug, regardless of the amount of treatment administered.

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

End point timeframe:

From first dose of study drug (Day 1) up to end of follow-up per participant, up to approximately 64 weeks

| End point values | Placebo | Dupilumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 33 | | |
| Units: participants | | | | |
| TEAEs | 22 | 23 | | |
| TESAEs | 3 | 0 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Serum Concentration of Dupilumab Over Time

| End point title | Serum Concentration of Dupilumab Over Time[1] |
|---|---|

End point description:

Blood samples were collected at the specified timepoints to obtain serum concentration of dupilumab. The pharmacokinetic (PK) population included all participants in the safety population with at least 1 post-baseline PK result. Here, n= only those participants with data collected at specified timepoints.

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

End point timeframe:

Baseline (Day 1) and Weeks 12, 24 and 52

Notes:

[1] - 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: Only participants in Dupilumab arm were assessed for this endpoint.

| **End point values** | Dupilumab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 19 | | | |
| Units: nanogram/milliliter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 (n=13) | 0.00 (± 0.00) | | | |
| Week 12 (n=14) | 47750.00 (± 17828.70) | | | |
| Week 24 (n=18) | 49597.78 (± 26542.80) | | | |
| Week 52 (n=19) | 57284.21 (± 27401.32) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change from Baseline in Fungal-specific IgE at Week 52

| End point title | Percent Change from Baseline in Fungal-specific IgE at Week 52 |
|---|---|

End point description:

Blood samples were collected at specified timepoints for the assessment of fungal-specific IgE which was measured with a quantitative method approved for diagnostic testing; a negative change from baseline indicated improvement. Baseline was defined as the last available value before the first dose of study drug. The safety population included all randomized participants who took at least 1 dose of study intervention, regardless of the amount of treatment administered. Here n= only those participants with data collected for each specified category and 99999=Standard deviation cannot be calculated for 1 participant.

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

End point timeframe:

Baseline (Day 1) and Week 52

| End point values | Placebo | Dupilumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 13 | | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | | | | |
| A. fumigatus Antigen IgE Antibody (AB) (n=1,3) | -65.79 (± 99999) | -77.20 (± 9.00) | | |
| F. proliferatum Antigen IgE AB (n=11,10) | -20.18 (± 38.03) | -66.09 (± 16.88) | | |
| C. lunata Antigen IgE AB (n=12,10) | 1.56 (± 29.80) | -74.82 (± 12.34) | | |
| S. rostrata Antigen IgE AB (n=12,10) | 28.89 (± 52.58) | -61.77 (± 14.37) | | |
| C. albicans Antigen IgE AB (n=14,13) | 15.69 (± 33.17) | -63.60 (± 17.06) | | |
| B. spicifera Antigen IgE AB (n=12,10) | 19.12 (± 52.10) | -56.26 (± 22.36) | | |
| A. niger Antigen IgE AB (n=8,8) | 2.46 (± 55.43) | -67.48 (± 13.72) | | |
| A. flavus Antigen IgE AB (n=11,9) | 0.75 (± 44.77) | -52.94 (± 19.62) | | |
| A. tenuis alternata Antigen IgE AB (n=15,11) | 16.06 (± 47.96) | -56.07 (± 21.78) | | |
| Mould Mix 2 IgE (n=5,8) | -17.50 (± 29.93) | -66.81 (± 20.86) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Treatment-emergent Anti-drug Antibodies (ADA) to Dupilumab

| End point title | Number of Participants With Treatment-emergent Anti-drug Antibodies (ADA) to Dupilumab |
|---|---|

End point description:

Plasma samples were collected to evaluate antibodies to dupilumab. Treatment-emergent ADA responses were defined as a positive response in the ADA assay post first dose, when baseline results were negative or missing. The ADA population included all participants from the safety population with at least 1 post-baseline ADA result (positive, negative or inconclusive).

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

End point timeframe:

From first dose of study drug (Day 1) up to end of follow-up per participant, up to approximately 64 weeks

| End point values | Placebo | Dupilumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 19 | 22 | | |
| Units: participants | 0 | 1 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events and deaths were assessed from first dose of study drug (Day 1) up to end of follow-up per participant, up to approximately 64 weeks

Adverse event reporting additional description:

Analysis was performed on the safety population.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 27.1 |

### Reporting groups

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

Reporting group description:

Participants received dupilumab depending on the weight at screening via SC injection for 52 weeks as follows:
• 300 mg q2wfor all adults and adolescents/children weighing >=60 kg
• 200 mg q2w for adolescents/children weighing >=30 kg and <60 kg
•300 mg q4w for adolescents/children weighing >=15 kg and <30 kg.

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

Reporting group description:

Participants received placebo matched to dupilumab via SC injection for 52 weeks.

| Serious adverse events | Dupilumab | Placebo | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 3 / 28 (10.71%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Allergic Fungal Rhinosinusitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 28 (7.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Ureterolithiasis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 28 (3.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 28 (3.57%) | |
| 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** | Dupilumab | Placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 16 / 33 (48.48%) | 15 / 28 (53.57%) | |
| Investigations | | | |
| Alanine Aminotransferase Increased | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 1 / 28 (3.57%) | |
| occurrences (all) | 2 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Accidental Overdose | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 4 / 28 (14.29%) | |
| occurrences (all) | 3 | 5 | |
| Thermal Burn | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 28 (7.14%) | |
| occurrences (all) | 0 | 2 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 0 / 28 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Gastrointestinal disorders | | | |
| Abdominal Pain | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 0 / 28 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 0 / 28 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Allergic Fungal Rhinosinusitis | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 6 / 28 (21.43%) | |
| occurrences (all) | 1 | 7 | |
| Asthma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 28 (7.14%) | |
| occurrences (all) | 0 | 4 | |
| Epistaxis | | | |
| subjects affected / exposed | 4 / 33 (12.12%) | 1 / 28 (3.57%) | |
| occurrences (all) | 4 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain In Extremity | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 28 (7.14%) | |
| occurrences (all) | 0 | 2 | |
| Infections and infestations | | | |
| Covid-19 | | | |
| subjects affected / exposed | 5 / 33 (15.15%) | 4 / 28 (14.29%) | |
| occurrences (all) | 5 | 4 | |
| Suspected Covid-19 | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 0 / 28 (0.00%) | |
| occurrences (all) | 2 | 0 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 30 March 2021 | This amendment instituted changes in response to Health Authorities feedback following review of the protocol and the overall pediatric development plan. The enrolment of study participants was extended to children aged >=6 years old. The study assessments and the drug were adapted to this population and were reflected in this amendment. The inclusion criteria were modified to allow more suitable criteria for participant enrolment, while maintaining the necessary inclusion/exclusion criteria to achieve the scientific aims of the study and maintain participant safety. |
| 23 November 2021 | The primary purpose of the amendment was to address recruitment challenges, while maintaining the necessary inclusion/exclusion criteria to achieve the scientific aims of the study and maintain participant safety. Inclusion/exclusion criteria were modified in order to be more in line with the current clinical practice of Investigators in terms of diagnosis and management of participants with AFRS. Additional changes included statistical analysis of the secondary endpoints. The Sponsor changed the handling of surgery for AFRS or starting prohibited biologics from worst possible score to worst observation carried forward to better reflect the clinical scenario of treatment failure. |
| 01 March 2023 | Due to severe recruitment challenges attributed to the Coronavirus-Disease 2019 (COVID-19) pandemic, the Sponsor reduced the sample size of the study from 120 participants to 62 participants and updated the primary endpoint from the proportion of participants who undergo or plan to receive rescue therapy (SCS and/or surgery) to an objective endpoint that was not impacted by the pandemic dynamics and was clinically relevant, namely change from baseline in sinus opacifications assessed by CT scans using the LMK score at Week 52. In addition, the alpha level of 0.01 was changed to 0.05, and the study was to be considered positive when the primary endpoint achieved statistical significance with 2-sided significance level of 0.05. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported