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