Clinical trial results:
A Randomized, 24-Week Treatment, Double-blind, Placebo-controlled Efficacy and Safety Study of Dupilumab 300 mg Every Other Week, in Patients With Bilateral Nasal Polyposis on a Background Therapy With Intranasal Corticosteroids

Summary

EudraCT number	2015-003101-42
Trial protocol	GB HU DE NL CZ FR PL BG IT
Global end of trial date	05 July 2018

Results information

Result version number	v1 (current)
This version publication date	20 July 2019
First version publication date	20 July 2019

Trial information

Trial identification

Sponsor protocol code	EFC14146

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02912468
WHO universal trial number (UTN)	U1111-1178-5390

Notes:

Sponsors

Sponsor organisation name	Sanofi
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 July 2018
Global end of trial reached?	Yes
Global end of trial date	05 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of dupilumab 300 mg every 2 weeks (q2w) compared to placebo on a background of mometasone furoate nasal spray (MFNS) in reducing nasal congestion (NC)/obstruction severity and endoscopic nasal polyp score (NPS) in subjects with bilateral nasal polyposis (NP).

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 was 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	05 December 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	Netherlands: 3
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	Bulgaria: 11
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Hungary: 34
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	Romania: 39
Country: Number of subjects enrolled	Russian Federation: 20
Country: Number of subjects enrolled	Ukraine: 45
Country: Number of subjects enrolled	United States: 34
Worldwide total number of subjects	276
EEA total number of subjects	177

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	233
From 65 to 84 years	42
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Study subjects were involved in the study from 05 December 2016 to 05 July 2018 at 67 active centres in 13 countries. A total of 506 subjects were screened, of which 276 subjects were enrolled and randomised to receive dupilumab 300 mg or placebo. A total of 230 subjects failed screening mainly due to failure to meet inclusion criteria.

Pre-assignment

Screening details:

Randomisation was stratified by the presence of comorbid asthma and/or non-steroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD), prior NP surgery (yes or no), and country.

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), 1 subcutaneous (SC) injection every 2 weeks (q2w) from Day 1 of Week 0 up to Week 24 added to background therapy of intranasal MFNS at stable dose.

Arm type	Placebo
Investigational medicinal product name	Placebo (matched to dupilumab 300 mg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

2 millilitre (mL), SC injection once q2w using a prefilled syringe for 24 weeks.

Arm title	Dupilumab 300 mg

Arm description:

Dupilumab 300 mg SC injection q2w from Day 1 of Week 0 up to Week 24 added to background therapy of intranasal MFNS at stable dose.

Arm type	Experimental
Investigational medicinal product name	Dupilumab 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

2 mL, SC injection once q2w using a prefilled syringe for 24 weeks.

Number of subjects in period 1	Placebo	Dupilumab 300 mg
Started	133	143
Treated	133	142
Safety Population	132	143
Completed	124	138
Not completed	9	5
Randomised and not treated	-	1
Consent withdrawn by subject	6	2
Adverse Event	3	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo (for dupilumab), 1 subcutaneous (SC) injection every 2 weeks (q2w) from Day 1 of Week 0 up to Week 24 added to background therapy of intranasal MFNS at stable dose.	
Reporting group title	Dupilumab 300 mg
Reporting group description:	
Dupilumab 300 mg SC injection q2w from Day 1 of Week 0 up to Week 24 added to background therapy of intranasal MFNS at stable dose.	

Reporting group values	Placebo	Dupilumab 300 mg	Total
Number of subjects	133	143	276
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	50.83	50.17	
standard deviation	± 13.21	± 13.59	-
Gender categorical Units: Subjects			
Female	63	55	118
Male	70	88	158
Ethnicity			
In the placebo arm, 131 subjects were only involved in the evaluation of the specified baseline measure.			
Units: Subjects			
Hispanic or Latino	1	5	6
Not Hispanic or Latino	130	138	268
Unknown	2	0	2
Race Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	0	1	1
Black or African American	7	2	9
White	126	138	264
Unknown or Not Reported	0	1	1
Nasal Congestion/Obstruction Symptom Severity Score			
NC symptom severity was assessed by the subjects on a scale of 0 to 3, where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms, with higher scores indicated more severity.			
Units: score on a scale			
arithmetic mean	2.45	2.26	
standard deviation	± 0.55	± 0.57	-
Nasal Polyp Score			
NPS was the sum of right and left nostril scores, as evaluated by means of nasal endoscopy. For each nostril, NPS was graded based on polyp size from 0 to 4 (0 = no polyps to 4 = large polyps causing complete obstruction of the inferior nasal cavity), with a lower score indicating smaller-sized polyps. Total NPS was the sum of right and left nostril scores and ranges from 0 (no polyps) to 8 (large polyps),			

with higher score representing more severe disease. In the placebo arm, 132 subjects were only involved in the evaluation of the specified baseline measure.			
Units: score on a scale			
arithmetic mean	5.86	5.64	
standard deviation	± 1.31	± 1.23	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo (for dupilumab), 1 subcutaneous (SC) injection every 2 weeks (q2w) from Day 1 of Week 0 up to Week 24 added to background therapy of intranasal MFNS at stable dose.	
Reporting group title	Dupilumab 300 mg
Reporting group description:	
Dupilumab 300 mg SC injection q2w from Day 1 of Week 0 up to Week 24 added to background therapy of intranasal MFNS at stable dose.	

Primary: Change From Baseline at Week 24 in Nasal Congestion/Obstruction Symptom Severity Score

End point title	Change From Baseline at Week 24 in Nasal Congestion/Obstruction Symptom Severity Score
End point description:	
NC symptom severity was assessed by the subjects on a daily basis from Visit 1 and throughout the study using an e-diary on a scale of 0 to 3, where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms, with higher scores indicated more severity. Least squares (LS) means and standard error (SE) were obtained from Analysis of covariance (ANCOVA) model described in Statistical Analysis Overview. The analysis was performed on intent-to-treat (ITT) population which included all randomised subjects who were analysed according to the treatment group allocated by randomisation.	
End point type	Primary
End point timeframe:	
Baseline, Week 24	

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	143		
Units: score on a scale				
least squares mean (standard error)	-0.45 (± 0.07)	-1.34 (± 0.07)		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg versus Placebo
Statistical analysis description:	
Data were analysed using a hybrid method of the worst-observation carried forward (WOCF) and multiple imputation (MI). The imputed completed data were analysed by fitting ANCOVA model with corresponding baseline, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates. Statistical inference obtained from all imputed data was combined using Rubin’s rule.	
Comparison groups	Dupilumab 300 mg v Placebo

Number of subjects included in analysis	276
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	-1.07
upper limit	-0.71

Primary: Change From Baseline at Week 24 in Nasal Polyp Score

End point title	Change From Baseline at Week 24 in Nasal Polyp Score

End point description:

NPS: sum of right, left nostril scores, evaluated by nasal endoscopy. For each nostril, NPS was graded based on polyp size from 0=no polyps to 4=large polyps causing complete obstruction of inferior nasal cavity; lower score=smaller sized polyps. Total NPS: sum of right and left nostril scores; ranges from 0 (no polyps) to 8 (large polyps), higher score =more severe disease. NPS was assessed by centralised, blinded, independent review of the nasal endoscopy video recordings. LS means and SE were obtained from ANCOVA model described in Statistical Analysis Overview. The analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects evaluable for this end point.

End point type	Primary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	143		
Units: score on a scale				
least squares mean (standard error)	0.17 (± 0.15)	-1.89 (± 0.14)		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg versus Palcebo

Statistical analysis description:

Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting an ANCOVA model with corresponding baseline, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates. Statistical inference obtained from all imputed data was combined using Rubin's rule.

Comparison groups	Dupilumab 300 mg v Placebo

Number of subjects included in analysis	275
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-2.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.43
upper limit	-1.69

Secondary: Change From Baseline at Week 24 in Opacification of Sinuses Measured by Lund-Mackay Score

End point title	Change From Baseline at Week 24 in Opacification of Sinuses Measured by Lund-Mackay Score

End point description:

The LMK scoring system rated each of both the left and right frontal, maxillary, sphenoid, ostiomeatal complex, anterior ethmoid and posterior ethmoid sinuses using following grading: 0 = normal, 1 = partial opacification, 2 = total opacification. The total score was the sum of scores from each side and ranges from 0 (normal) to 24 (more opacified); higher score indicated more severe disease. LS means and SE were obtained from ANCOVA model described in Statistical Analysis Overview. NOTE: For Japan regulatory submission only, this end point is not included as a secondary outcome measure and is instead one of the co-primary outcome measures. The analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	141		
Units: score on a scale				
least squares mean (standard error)	-0.74 (± 0.37)	-8.18 (± 0.34)		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg versus Placebo

Statistical analysis description:

Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting an ANCOVA model with corresponding baseline, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates. Statistical inference obtained from all imputed data was combined using Rubin's rule.

Comparison groups	Dupilumab 300 mg v Placebo

Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001 [2]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-7.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.35
upper limit	-6.53

Notes:

[1] - Hierarchical testing procedure was used to control type I error. For regions outside of Japan, this first secondary endpoint was not tested unless both co-primary endpoints were significant at the 0.05 level. Hierarchical testing continued only when previous endpoint was statistically significant. For Japan submission, LMK was instead a co-primary endpoint which also had to be met before secondary endpoints were tested in the hierarchy. Last endpoint in hierarchy is Week 24 SNOT-22.
[2] - Threshold for significance at 0.05 level.

Secondary: Change From Baseline at Week 24 in Total Symptom Score (TSS)

End point title	Change From Baseline at Week 24 in Total Symptom Score (TSS)

End point description:

The TSS was the sum of subject-assessed nasal symptom scores for NC/obstruction, decreased/loss of sense of smell, and rhinorrhea (anterior/posterior nasal discharge), each accessed on 0 to 3 categorical scale (where 0
= no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms). Total score ranged from 0 (no symptoms) to 9 (severe symptoms). Higher score indicated more severe symptoms. LS means and SE were obtained from ANCOVA model described in Statistical Analysis Overview. The analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	143		
Units: score on a scale				
least squares mean (standard error)	-1.17 (± 0.17)	-3.77 (± 0.16)		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg versus Placebo

Statistical analysis description:

Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting an ANCOVA model with corresponding baseline, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates. Statistical inference obtained from all imputed data was combined using Rubin’s rule.

Comparison groups	Dupilumab 300 mg v Placebo

Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001 [4]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-2.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.04
upper limit	-2.17

Notes:

[3] - Testing according to the hierarchical testing procedure (only performed if previous end points were statistically significant).
[4] - Threshold for significance at 0.05 level.

Secondary: Change From Baseline at Week 24 in the University of Pennsylvania Smell Identification Test (UPSIT) Score

End point title	Change From Baseline at Week 24 in the University of Pennsylvania Smell Identification Test (UPSIT) Score

End point description:

The UPSIT was a 40-item test to measure the individual's ability to detect odours. Total score ranges from 0 (anosmia) to 40 (normal sense of smell), lower score indicated severe smell loss. LS means and SE were obtained from ANCOVA model described in Statistical Analysis Overview. The analysis was performed on ITT. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	140		
Units: score on a scale				
least squares mean (standard error)	0.70 (± 0.71)	11.26 (± 0.67)		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg versus Placebo

Statistical analysis description:

Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting an ANCOVA model with corresponding baseline, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates. Statistical inference obtained from all imputed data was combined using Rubin's rule.

Comparison groups	Dupilumab 300 mg v Placebo

Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001 [6]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	10.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.79
upper limit	12.34

Notes:

[5] - Testing according to the hierarchical testing procedure (only performed if previous end points were statistically significant).
[6] - Threshold for significance at 0.05 level.

Secondary: Change From Baseline at Week 24 in Severity of Decreased/Loss of Smell as Assessed by Subject Daily

End point title	Change From Baseline at Week 24 in Severity of Decreased/Loss of Smell as Assessed by Subject Daily

End point description:

The severity of decreased/loss of sense of smell was reported by the subjects using a 0 to 3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms), higher score indicated more severe symptoms. LS means and SE were obtained from ANCOVA model described in Statistical Analysis Overview. The analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	143		
Units: score on a scale				
least squares mean (standard error)	-0.29 (± 0.07)	-1.41 (± 0.07)		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg versus Placebo

Statistical analysis description:

Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting an ANCOVA model with corresponding baseline, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates. Statistical inference obtained from all imputed data was combined using Rubin's rule.

Comparison groups	Dupilumab 300 mg v Placebo

Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.0001 [8]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.31
upper limit	-0.93

Notes:

[7] - Testing according to the hierarchical testing procedure (only performed if previous end points were statistically significant).
[8] - Threshold for significance at 0.05 level.

Secondary: Change From Baseline at Week 24 in 22-item Sino-nasal Outcome Test (SNOT-22) Scores

End point title	Change From Baseline at Week 24 in 22-item Sino-nasal Outcome Test (SNOT-22) Scores

End point description:

The SNOT-22 is a validated questionnaire that was used to assess the impact of chronic rhinosinusitis phenotype with nasal polyps (CRSwNP) on health-related quality of life (HRQoL). It is a 22 item questionnaire with each item assigned a score ranging from 0 (no problem) to 5 (problem as bad as it can be). The total score may range from 0 (no disease) to 110 (worst disease), lower scores representing better health related quality of life. LS means and SE were obtained from ANCOVA model described in Statistical Analysis Overview. The analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	137		
Units: score on a scale				
least squares mean (standard error)	-9.31 (± 1.62)	-30.43 (± 1.54)		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg versus Placebo

Statistical analysis description:

Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting an ANCOVA model with corresponding baseline, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates. Statistical inference obtained from all imputed data was combined using Rubin's rule.

Comparison groups	Dupilumab 300 mg v Placebo
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.0001 [10]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-21.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.17
upper limit	-17.06

Notes:

[9] - Testing according to the hierarchical testing procedure (only performed if previous end points were statistically significant).
[10] - Threshold for significance at 0.05 level.

Secondary: Rescue Treatment Use: Estimate of Percentage of Subjects With >=1 Event by Week 24 Obtained Using Kaplan-Meier Method

End point title	Rescue Treatment Use: Estimate of Percentage of Subjects With >=1 Event by Week 24 Obtained Using Kaplan-Meier Method

End point description:

Rescue treatment was defined as usage of systemic corticosteroids (SCS) or NP surgery (actual or planned) during the treatment period. Rescue treatment included:
- SCS: Betamethasone, dexamethasone, dexamethasone sodium phosphate, hydrocortisone sodium succinate, methylprednisolone, prednisolone, prednisolone metasulfobenzoate sodium, prednisone, and triamcinolone.
- Sino-nasal surgery for NP when there was worsening of signs and/or symptoms during the study.

Estimate of percentage of subjects with event by Week 24 was obtained using Kaplan-Meier method. The analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	143		
Units: percentage of subjects with event				
number (confidence interval 95%)				
SCS treatment	18.9 (12.7 to 26.0)	6.5 (3.2 to 11.5)		
NP surgery	7.5 (3.7 to 13.2)	2.1 (0.6 to 5.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 24 in Visual Analogue Scale (VAS) for Rhinosinusitis

End point title	Change From Baseline at Week 24 in Visual Analogue Scale (VAS) for Rhinosinusitis

End point description:

The VAS for rhinosinusitis was used to evaluate the total disease severity. Subjects were asked to indicate on a 10 centimetres (cm) VAS the answer to the question, "How troublesome are your symptoms of your rhinosinusitis?" The range of the VAS was from 0 (not troublesome) to 10 (worse thinkable troublesome), where higher score indicated worse thinkable troublesome. Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting an ANCOVA model with corresponding baseline, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates. The analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	136		
Units: centimetres				
least squares mean (standard error)	-1.34 (± 0.24)	-4.54 (± 0.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 24 in Nasal Peak Inspiratory Flow (NPIF)

End point title	Change From Baseline at Week 24 in Nasal Peak Inspiratory Flow (NPIF)

End point description:

NPIF evaluation represented a physiologic measure of the air flow through both nasal cavities during forced inspiration expressed in litres per minute. Higher NPIF values are indicative of better nasal air flow. Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting an ANCOVA model with corresponding baseline, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates. The analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	143		
Units: litres per minute				
least squares mean (standard error)	14.09 (± 3.97)	54.50 (± 3.73)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 24 in Rhinorrhea Daily Symptom Score

End point title	Change From Baseline at Week 24 in Rhinorrhea Daily Symptom Score

End point description:

Rhinorrhea was reported by the subjects using a 0 to 3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms), where higher scores indicated more severe symptoms. Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting an ANCOVA model with corresponding baseline, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates. The analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	143		
Units: score on a scale				
least squares mean (standard error)	-0.42 (± 0.06)	-1.04 (± 0.06)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 24 in Forced Expiratory Volume in 1 Second (FEV1) for Subjects With Asthma

End point title	Change From Baseline at Week 24 in Forced Expiratory Volume in 1 Second (FEV1) for Subjects With Asthma

End point description:

FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer. Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting an ANCOVA model with corresponding baseline, treatment group, prior surgery history, and regions as covariates. Analysis was performed on a subset of subjects which included all randomised subjects with asthma.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	82		
Units: litres				
least squares mean (standard error)	-0.06 (± 0.05)	0.15 (± 0.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 24 in Asthma Control Questionnaire-6 (ACQ-6) Scores for Subjects With Asthma

End point title	Change From Baseline at Week 24 in Asthma Control Questionnaire-6 (ACQ-6) Scores for Subjects With Asthma

End point description:

ACQ-6 had 6 questions which assessed the most common asthma symptoms (woken by asthma, symptoms on waking, activity limitation, shortness of breath, wheezing, puffs/inhalations use). Subjects were asked to recall how their asthma had been during the previous week and to respond to the symptom questions on a 7-point scale ranged from 0 = no impairment to 6 = maximum impairment. The ACQ-6 score was the mean of the scores of all 6 questions and therefore, ranged from 0 (totally controlled) to 6 (severely uncontrolled), with higher scores indicated lower asthma control. Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting an ANCOVA model with the corresponding baseline value, treatment group, prior surgery, and regions as covariates. Analysis was performed on a subset of subjects which included all randomised subjects with asthma and had available data for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	75		
Units: score on a scale				
least squares mean (standard error)	-0.24 (± 0.10)	-1.00 (± 0.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Weeks 28, 32, 36, 40, 44 and 48 in Nasal

Congestion Symptom Severity Score (Assessments Performed 4-24 Weeks After End of Treatment)

End point title	Change From Baseline at Weeks 28, 32, 36, 40, 44 and 48 in Nasal Congestion Symptom Severity Score (Assessments Performed 4-24 Weeks After End of Treatment)

End point description:

NC symptom severity was assessed by the subjects on a daily basis from Visit 1 and throughout the study using an e-diary on a scale of 0 to 3, where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms, with higher scores indicated more severity. Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting ANCOVA model with corresponding baseline, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates. The analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48 (Post-baseline assessments performed 4-24 weeks after end of treatment)

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	143		
Units: score on a scale				
least squares mean (standard error)				
Week 28	-0.48 (± 0.07)	-1.36 (± 0.07)		
Week 32	-0.50 (± 0.07)	-1.33 (± 0.07)		
Week 36	-0.53 (± 0.07)	-1.05 (± 0.07)		
Week 40	-0.51 (± 0.08)	-0.83 (± 0.07)		
Week 44	-0.49 (± 0.08)	-0.77 (± 0.07)		
Week 48	-0.52 (± 0.08)	-0.77 (± 0.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Weeks 36 and 48 in Nasal Polyp Score (Assessments Performed 12 and 24 Weeks After End of Treatment)

End point title	Change From Baseline at Weeks 36 and 48 in Nasal Polyp Score (Assessments Performed 12 and 24 Weeks After End of Treatment)

End point description:

NPS: sum of right and left nostril scores, as evaluated by means of nasal endoscopy. For each nostril, NPS was graded based on polyp size from 0 to 4 (0 = no polyps to 4 = large polyps causing complete obstruction of inferior nasal cavity), with a lower score indicating smaller-sized polyps. Total NPS: sum of right and left nostril scores and ranges from 0 (no polyp) to 8 (large polyp), with highest score representing more severe disease. NPS was assessed by centralised, blinded independent review of the nasal endoscopy video recordings. Data were analysed using a hybrid method of the WOCF and MI. LS means and SE were obtained from ANCOVA model. The analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 36, Week 48 (post-baseline assessments performed 12 and 24 weeks after end of treatment)

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	143		
Units: score on a scale				
least squares mean (standard error)				
Week 36	-0.06 (± 0.14)	-0.99 (± 0.13)		
Week 48	0.14 (± 0.13)	-0.66 (± 0.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 48 in Opacification of Sinuses Measured by Lund-Mackay Score (Assessment Performed 24 Weeks After End of Treatment)

End point title	Change From Baseline at Week 48 in Opacification of Sinuses Measured by Lund-Mackay Score (Assessment Performed 24 Weeks After End of Treatment)

End point description:

The LMK scoring system rated each of both the left and right frontal, maxillary, sphenoid, ostiomeatal complex, anterior ethmoid and posterior ethmoid sinuses using following grading: 0 = normal, 1 = partial opacification, 2 = total opacification. The total score was the sum of scores from each side and ranges from 0 (normal) to 24 (more opacified); higher score indicated more severe disease. Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting an ANCOVA model with corresponding baseline, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates. The analysis was performed on ITT population. Here, `number of subjects analysed = subjects evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 48 (Post-baseline assessment performed 24 weeks after end of treatment)

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	141		
Units: score on a scale				
least squares mean (standard error)	-0.82 (± 0.38)	-2.62 (± 0.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Weeks 28, 32, 36, 40, 44 and 48 in Total

Symptom Score (Assessments Performed 4-24 Weeks After End of Treatment)

End point title	Change From Baseline at Weeks 28, 32, 36, 40, 44 and 48 in Total Symptom Score (Assessments Performed 4-24 Weeks After End of Treatment)

End point description:

The TSS was the sum of subject-assessed nasal symptom scores for NC/obstruction, decreased/loss of sense of smell, and rhinorrhea (anterior/posterior nasal discharge), each accessed on 0-3 categorical scale (where
0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms). Total score ranged from 0 (no symptoms) to 9 (severe symptoms). Higher score indicated more severe symptoms. Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting an ANCOVA model with corresponding baseline, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates. The analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48 (Post-baseline assessments performed 4-24 weeks after end of treatment)

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	143		
Units: score on a scale				
least squares mean (standard error)				
Week 28	-1.18 (± 0.17)	-3.84 (± 0.16)		
Week 32	-1.25 (± 0.17)	-3.64 (± 0.17)		
Week 36	-1.31 (± 0.18)	-2.91 (± 0.17)		
Week 40	-1.27 (± 0.18)	-2.28 (± 0.17)		
Week 44	-1.20 (± 0.18)	-2.09 (± 0.17)		
Week 48	-1.28 (± 0.19)	-2.05 (± 0.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 48 in University of Pennsylvania Smell Identification Test (Assessment Performed 24 Weeks After End of Treatment)

End point title	Change From Baseline at Week 48 in University of Pennsylvania Smell Identification Test (Assessment Performed 24 Weeks After End of Treatment)

End point description:

The UPSIT was a 40-item test to measure the individual’s ability to detect odours. Total score ranges from 0 (anosmia) to 40 (normal sense of smell), lower score indicated severe smell loss. Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting an ANCOVA model with corresponding baseline, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates. The analysis was performed on ITT population. Here, ‘number of subjects analysed’ = subjects evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 48 (Post-baseline assessment performed 24 weeks after end of treatment)

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	140		
Units: score on a scale				
least squares mean (standard error)	0.21 (± 0.77)	4.20 (± 0.73)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Weeks 28, 32, 36, 40, 44 and 48 in Severity of Decreased/Loss of Smell as Assessed by Participant Daily (Assessments Performed 4-24 Weeks After End of Treatment)

End point title	Change From Baseline at Weeks 28, 32, 36, 40, 44 and 48 in Severity of Decreased/Loss of Smell as Assessed by Participant Daily (Assessments Performed 4-24 Weeks After End of Treatment)

End point description:

The severity of decreased/loss of sense of smell was reported by the subjects using a 0 to 3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms), higher score indicated more severe symptoms. Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting an ANCOVA model with corresponding baseline, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates. The analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48 (Post-baseline assessments performed 4-24 weeks after end of treatment)

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	143		
Units: score on a scale				
least squares mean (standard error)				
Week 28	-0.28 (± 0.08)	-1.45 (± 0.07)		
Week 32	-0.31 (± 0.08)	-1.36 (± 0.07)		
Week 36	-0.33 (± 0.08)	-1.07 (± 0.07)		
Week 40	-0.30 (± 0.07)	-0.83 (± 0.07)		
Week 44	-0.28 (± 0.07)	-0.74 (± 0.07)		
Week 48	-0.30 (± 0.07)	-0.71 (± 0.06)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Weeks 36 and 48 in 22-item Sino-nasal Outcome Test Scores (Assessments Performed 12 and 24 Weeks After End of Treatment)

End point title	Change From Baseline at Weeks 36 and 48 in 22-item Sino-nasal Outcome Test Scores (Assessments Performed 12 and 24 Weeks After End of Treatment)

End point description:

The SNOT-22 is a validated questionnaire that was used to assess the impact of CRSwNP on HRQoL. It is a 22 item questionnaire with each item assigned a score ranging from 0 (no problem) to 5 (problem as bad as it can be). The total score may range from 0 (no disease) to 110 (worst disease), lower scores representing better health related quality of life. Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting an ANCOVA model with corresponding baseline, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates. The analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 36 and Week 48 (Post-baseline assessments performed 12 and 24 weeks after end of treatment)

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	137		
Units: score on scale				
least squares mean (standard error)				
Week 36	-8.31 (± 1.75)	-20.87 (± 1.67)		
Week 48	-8.36 (± 1.88)	-17.66 (± 1.80)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rescue Treatment Use: Estimate of Percentage of Subjects With >=1 Event by Week 48 Obtained Using Kaplan-Meier Method

End point title	Rescue Treatment Use: Estimate of Percentage of Subjects With >=1 Event by Week 48 Obtained Using Kaplan-Meier Method

End point description:

Rescue treatment was defined as usage of SCS or NP surgery (actual or planned) during the study. Rescue treatment included:

- SCS: Betamethasone, dexamethasone, dexamethasone sodium phosphate, hydrocortisone sodium succinate, methylprednisolone, prednisolone, prednisolone metasulfobenzoate sodium, prednisone, and triamcinolone.
- Sino-nasal surgery for nasal polyps when there was worsening of signs and/or symptoms during the study.

Estimate of percentage of subjects with event by Week 48 was obtained using Kaplan-Meier method. The analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline up to Week 48

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	143		
Units: percentage of subjects with event				
number (confidence interval 95%)				
SCS treatment	28.8 (21.4 to 36.7)	21.4 (15.0 to 28.5)		
NP surgery	12.5 (7.5 to 18.9)	6.3 (2.9 to 11.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Weeks 36 and 48 in Visual Analog Scale for Rhinosinusitis (Assessments Performed 12 and 24 Weeks After End of Treatment)

End point title	Change From Baseline at Weeks 36 and 48 in Visual Analog Scale for Rhinosinusitis (Assessments Performed 12 and 24 Weeks After End of Treatment)

End point description:

The VAS for rhinosinusitis was used to evaluate the total disease severity. The subjects were asked to indicate on a 10 cm VAS the answer to the question, "How troublesome are your symptoms of your rhinosinusitis?" The range of the VAS was from 0 (not troublesome) to 10 (worse thinkable troublesome), where higher score indicated worse thinkable troublesome. Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting an ANCOVA model with corresponding baseline, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates. The analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 36 and Week 48 (Post-baseline assessments performed 12 and 24 weeks after end of treatment)

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	136		
Units: centimetres				
least squares mean (standard error)				
Week 36	-1.36 (± 0.26)	-3.02 (± 0.25)		
Week 48	-1.17 (± 0.25)	-2.42 (± 0.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Weeks 28, 32, 36, 40, 44 and 48 in Rhinorrhea Daily Symptom Score (Assessments Performed 4-24 Weeks After End of Treatment)

End point title	Change From Baseline at Weeks 28, 32, 36, 40, 44 and 48 in Rhinorrhea Daily Symptom Score (Assessments Performed 4-24 Weeks After End of Treatment)

End point description:

Rhinorrhea was reported by subjects using a 0 to 3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms), where higher scores indicated more severe symptoms. Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting an ANCOVA model with corresponding baseline, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates. The analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48 (Post-baseline assessments performed 4-24 weeks after end of treatment)

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	143		
Units: score on a scale				
least squares mean (standard error)				
Week 28	-0.42 (± 0.06)	-1.04 (± 0.06)		
Week 32	-0.43 (± 0.06)	-0.97 (± 0.06)		
Week 36	-0.44 (± 0.07)	-0.80 (± 0.06)		
Week 40	-0.44 (± 0.07)	-0.63 (± 0.06)		
Week 44	-0.41 (± 0.07)	-0.58 (± 0.06)		
Week 48	-0.45 (± 0.07)	-0.58 (± 0.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 48 in Forced Expiratory Volume in 1 Second for Subjects With Asthma (Assessment Performed 24 Weeks After End of Treatment)

End point title	Change From Baseline at Week 48 in Forced Expiratory Volume in 1 Second for Subjects With Asthma (Assessment Performed

	24 Weeks After End of Treatment)

End point description:

FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer. Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting an ANCOVA model with corresponding baseline, treatment group, prior surgery history, and regions as covariates. Analysis was performed on a subset of subjects which included all randomised subjects with asthma.

End point type	Secondary

End point timeframe:

Baseline, Week 48 (Post-baseline assessment performed 24 weeks after end of treatment)

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	82		
Units: litres				
least squares mean (standard error)	-0.11 (± 0.05)	-0.05 (± 0.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 48 in Asthma Control Questionnaire-6 Scores for Subjects With Asthma (Assessment Performed 24 Weeks After End of Treatment)

End point title	Change From Baseline at Week 48 in Asthma Control Questionnaire-6 Scores for Subjects With Asthma (Assessment Performed 24 Weeks After End of Treatment)

End point description:

ACQ-6 had 6 questions which assessed the most common asthma symptoms (woken by asthma, symptoms on waking, activity limitation, shortness of breath, wheezing, puffs/inhalations use). Subjects were asked to recall how their asthma had been during the previous week and to respond to the symptom questions on a 7-point scale ranged from 0 = no impairment to 6 = maximum impairment. The ACQ-6 score was the mean of the scores of all 6 questions and therefore, ranged from 0 (totally controlled) to 6 (severely uncontrolled), with higher scores indicated lower asthma control. Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting an ANCOVA model with the corresponding baseline value, treatment group, prior surgery, and regions as covariates. Analysis was performed on a subset of subjects which included all randomised subjects with asthma and had available data for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 48 (Post-baseline assessment performed 24 weeks after end of treatment)

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	75		
Units: score on a scale				
least squares mean (standard error)	-0.09 (± 0.11)	-0.55 (± 0.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs) and TEAEs Leading to Treatment Discontinuation

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs) and TEAEs Leading to Treatment Discontinuation

End point description:

Adverse Event (AE), any untoward medical occurrence that did not necessarily have to have a causal relationship with study treatment. TEAEs were defined as AEs that developed or worsened in grade or became
serious during TEAE period which was defined as the period from the time of first dose of study drug until 98 days following the last administration of study drug. Serious adverse event (SAE) was defined as any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is a medically important event.. The analysis was performed on safety population which included all subjects who received at least 1 dose or part of a dose of the study drug, analysed according to the treatment actually received.

End point type	Secondary

End point timeframe:

Baseline up to 98 days following the last administration of study drug (up to 36 weeks)

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	143		
Units: subjects				
number (not applicable)				
Any TEAE	93	93		
Any treatment emergent SAE	19	6		
TEAE leading to treatment discontinuation	3	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Dupilumab Concentration in Serum

End point title	Functional Dupilumab Concentration in Serum[11]

End point description:

Analysis performed on pharmacokinetic population included all subjects who received at least 1 dose of study drug with at least 1 evaluable functional dupilumab concentration result. Here, 'number analysed' = number of subjects with available data for each specified category. Data for this end point was not planned to be collected and analysed for placebo.

End point type	Secondary

End point timeframe:

Baseline, Week 4, 8, 16, 24, 36, End of study (Week 48)

Notes:

[11] - 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: The end point was planned to be analysed for Dupilumab arm only.

End point values	Dupilumab 300 mg			
Subject group type	Reporting group			
Number of subjects analysed	142			
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline (n=139)	0.00 (± 0.00)			
Week 4 (n=138)	31267.18 (± 13008.16)			
Week 8 (n=141)	48306.73 (± 20621.18)			
Week 16 (n=138)	63958.12 (± 29822.30)			
Week 24 (n=136)	69224.11 (± 36933.70)			
Week 36 (n=136)	356.53 (± 1501.69)			
Week 48 (n=138)	39.00 (± 0.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent And Treatment-Boosted Antidrug Antibodies (ADA) Response

End point title	Number of Subjects With Treatment-Emergent And Treatment-Boosted Antidrug Antibodies (ADA) Response

End point description:

ADA response was categorised as: treatment emergent and treatment boosted response. 1) Treatment emergent was defined as a positive response in the ADA assay post first dose, when baseline results are negative or missing. 2) Treatment boosted was defined as: An ADA positive response in the assay post first dose that is greater-than or equal to 4-fold over baseline titer levels, when baseline results are positive. The analysis was performed on ADA population which included subjects who received at least 1 dose of study drug with at least one non-missing ADA assay result following the first dose of the study medication.

End point type	Secondary

End point timeframe:

Baseline to End of study (Week 48)

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	143		
Units: subjects				
With treatment-emergent ADA	7	22		
With treatment-boosted ADA	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Total SCS Rescue Dose Prescribed During Treatment Period

End point title	Mean Total SCS Rescue Dose Prescribed During Treatment Period

End point description:

SCS included: Betamethasone, dexamethasone, dexamethasone sodium phosphate, hydrocortisone sodium succinate, methylprednisolone, prednisolone, prednisolone metasulfobenzoate sodium, prednisone, and triamcinolone. For every subject, total dose was calculated as (prescribed total daily dose*duration of SCS use). Then, mean of the total dose of 25 subjects (placebo group) and 9 subjects (Dupilumab group) was derived. The analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	9		
Units: milligrams				
arithmetic mean (standard deviation)	366.07 (± 247.07)	686.65 (± 1575.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Systemic Corticosteroids Rescue Intake Duration: Average Duration per Subject

End point title	Total Systemic Corticosteroids Rescue Intake Duration: Average Duration per Subject

End point description:

Rescue treatment was defined as usage of SCS or NP surgery (actual or planned) during the treatment period. SCS rescue intake duration was defined as the duration (in days) from start of SCS rescue medication till the end of SCS rescue treatment. The analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	9		
Units: days				
arithmetic mean (standard deviation)	11.04 (± 6.79)	23.33 (± 50.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 24 in European Quality of Life 5 Dimension (EQ-5D) Visual Analog Scale Score

End point title	Change From Baseline at Week 24 in European Quality of Life 5 Dimension (EQ-5D) Visual Analog Scale Score

End point description:

The EQ-5D was a standardized HRQoL questionnaire consisting of EQ-5D descriptive system and EQ VAS. EQ-5D descriptive system comprised of 5 dimensions: mobility, selfcare, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. EQ-VAS recorded the subject's self-rated health on a vertical VAS that allowed them to indicate their health state that can range from 0 (worst imaginable) to 100 (best imaginable). The analysis was performed on ITT population. Here, 'number of subjects analyzed' = subjects evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	136		
Units: score on a scale				
least squares mean (standard error)	1.74 (± 1.54)	12.00 (± 1.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 24 in Nasal Congestion Symptom Severity Score: Subgroup of Subjects With Asthma

End point title	Change From Baseline at Week 24 in Nasal Congestion Symptom Severity Score: Subgroup of Subjects With Asthma

End point description:

NC symptom severity was assessed by the subjects on a daily basis from Visit 1 and throughout the study using an e-diary on a scale of 0 to 3, where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms, with higher scores indicated more severity. Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting ANCOVA model with corresponding baseline, treatment group, prior surgery history, and regions as covariates. Analysis was performed on a subset of subjects, which included all randomised subjects with asthma.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	82		
Units: score on a scale				
least squares mean (standard error)	-0.36 (± 0.09)	-1.48 (± 0.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 24 in Nasal Congestion Symptom Severity Score: Subgroup of Subjects With Prior Nasal Polyp Surgery

End point title	Change From Baseline at Week 24 in Nasal Congestion Symptom Severity Score: Subgroup of Subjects With Prior Nasal Polyp Surgery

End point description:

NC symptom severity was assessed by the subjects on a daily basis from Visit 1 and throughout the study using an e-diary on a scale of 0 to 3, where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms, with higher scores indicated more severity. Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting ANCOVA model with corresponding baseline, treatment group, asthma/NSAID-ERD status, and regions as covariates. Analysis was performed on a subset of subjects, which included all randomised subjects with prior NP surgery history.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	99		
Units: score on a scale				
least squares mean (standard error)	-0.52 (± 0.09)	-1.41 (± 0.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 24 in Nasal Polyp Score: Subgroup of Subjects With Asthma

End point title	Change From Baseline at Week 24 in Nasal Polyp Score: Subgroup of Subjects With Asthma

End point description:

NPS was the sum of right and left nostril scores, as evaluated by means of nasal endoscopy. For each nostril, NPS was graded based on polyp size from 0 to 4 (0 = no polyps to 4 = large polyps causing complete obstruction of the inferior nasal cavity), with a lower score indicating smaller-sized polyps. Total NPS was the sum of right and left nostril scores and ranges from 0 (no polyp) to 8 (large polyp), with highest score representing more severe disease. NPS was assessed by centralised, blinded, independent review of the nasal endoscopy video recordings. Data were analysed using a hybrid method of the WOCF and MI. LS mean and SE were obtained from ANCOVA model. Analysis was performed on a subset of subjects, which included all randomised subjects with asthma and had available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	82		
Units: score on a scale				
least squares mean (standard error)	0.27 (± 0.20)	-1.89 (± 0.20)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 24 in Nasal Polyp Score: Subgroup of Subjects With Prior Nasal Polyp Surgery

End point title	Change From Baseline at Week 24 in Nasal Polyp Score: Subgroup of Subjects With Prior Nasal Polyp Surgery

End point description:

NPS was the sum of right and left nostril scores, as evaluated by means of nasal endoscopy. For each nostril, NPS was graded based on polyp size from 0 to 4 (0 = no polyps to 4 = large polyps causing complete obstruction of the inferior nasal cavity), with a lower score indicating smaller-sized polyps.

Total NPS was the sum of right and left nostril scores and ranges from 0 (no polyp) to 8 (large polyp), with highest score representing more severe disease. NPS assessed by centralised scoring of nasal endoscopy video recordings. NPS was assessed by centralised, blinded, independent review of the nasal endoscopy video recordings. Data were analysed using a hybrid method of the WOCF and MI. LS mean and SE were obtained from ANCOVA model. Analysis was performed on a subset of subjects, which included all randomised subjects with prior NP surgery history and had available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	99		
Units: score on a scale				
least squares mean (standard error)	0.14 (± 0.18)	-1.86 (± 0.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 24 in Opacification of Sinuses Measured by Lund Mackay Score: Subgroup of Subjects With Asthma

End point title	Change From Baseline at Week 24 in Opacification of Sinuses Measured by Lund Mackay Score: Subgroup of Subjects With Asthma

End point description:

The LMK scoring system rated each of both the left and right frontal, maxillary, sphenoid, ostiomeatal complex, anterior ethmoid and posterior ethmoid sinuses using following grading: 0 = normal, 1 = partial opacification, 2 = total opacification. The total score was the sum of scores from each side and ranges from 0 (normal) to 24 (more opacified); higher score indicated more severe disease. Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting an ANCOVA model with corresponding baseline, treatment group, prior surgery history, and regions as covariates. Analysis was performed on a subset of subjects, which included all randomised subjects with asthma and had available data for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	81		
Units: score on a scale				
least squares mean (standard error)	-0.15 (± 0.47)	-7.97 (± 0.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 24 in Opacification of Sinuses Measured by Lund Mackay Score: Subgroup of Subjects With Prior Nasal Polyp Surgery

End point title	Change From Baseline at Week 24 in Opacification of Sinuses Measured by Lund Mackay Score: Subgroup of Subjects With Prior Nasal Polyp Surgery

End point description:

The LMK scoring system rated each of both the left and right frontal, maxillary, sphenoid, ostiomeatal complex, anterior ethmoid and posterior ethmoid sinuses using following grading: 0 = normal, 1 = partial opacification, 2 = total opacification. The total score was the sum of scores from each side and ranges from 0 (normal) to 24 (more opacified); higher score indicated more severe disease. Data were analysed using a hybrid method of the WOCF and MI. The imputed completed data were analysed by fitting an ANCOVA model with corresponding baseline, treatment group, asthma/NSAID-ERD status, and regions as covariates. Analysis was performed on a subset of subjects, which included all randomised subjects with prior NP surgery history and had available data for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	98		
Units: score on a scale				
least squares mean (standard error)	-0.39 (± 0.42)	-7.60 (± 0.41)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to end of study regardless of seriousness or relationship to investigational product. Time frame for reporting of TEAE was up to 36 weeks.

Adverse event reporting additional description:

Reported AEs are treatment emergent AEs that developed/worsened during the 'on treatment period' (from the first IMP administration to the last study drug administration + 98 days). Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo (for dupilumab), 1 SC injection q2w from Day 1 of Week 0 up to Week 24 added to background therapy of intranasal MFNS at stable dose.

Reporting group title	Dupilumab 300 mg

Reporting group description:

Dupilumab 300 mg SC injection q2w from Day 1 of Week 0 up to Week 24 added to background therapy of intranasal MFNS at stable dose.

Serious adverse events	Placebo	Dupilumab 300 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 132 (14.39%)	6 / 143 (4.20%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anal Cancer			
subjects affected / exposed	1 / 132 (0.76%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Clavicle Fracture			
subjects affected / exposed	1 / 132 (0.76%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Acute Myocardial Infarction			
subjects affected / exposed	0 / 132 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic Valve Stenosis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carpal Tunnel Syndrome			
subjects affected / exposed	0 / 132 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar Radiculopathy			
subjects affected / exposed	1 / 132 (0.76%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Eosinophilic Granulomatosis With Polyangiitis			
subjects affected / exposed	1 / 132 (0.76%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vitreous Haemorrhage			
subjects affected / exposed	1 / 132 (0.76%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine Polyp			
subjects affected / exposed	0 / 132 (0.00%)	1 / 143 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Asthma			
subjects affected / exposed	2 / 132 (1.52%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Rhinosinusitis With Nasal Polyps			
subjects affected / exposed	1 / 132 (0.76%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal Polyps			
subjects affected / exposed	7 / 132 (5.30%)	2 / 143 (1.40%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Foot Deformity			
subjects affected / exposed	1 / 132 (0.76%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute Sinusitis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 132 (0.76%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 132 (0.76%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Dupilumab 300 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 132 (46.21%)	55 / 143 (38.46%)	
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 132 (8.33%)	7 / 143 (4.90%)	
occurrences (all)	13	7	
General disorders and administration site conditions			
Injection Site Erythema			
subjects affected / exposed	12 / 132 (9.09%)	8 / 143 (5.59%)	
occurrences (all)	30	25	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	8 / 132 (6.06%)	3 / 143 (2.10%)	
occurrences (all)	11	3	
Cough			
subjects affected / exposed	7 / 132 (5.30%)	4 / 143 (2.80%)	
occurrences (all)	9	4	
Epistaxis			
subjects affected / exposed	4 / 132 (3.03%)	11 / 143 (7.69%)	
occurrences (all)	7	13	
Nasal Polyps			
subjects affected / exposed	17 / 132 (12.88%)	16 / 143 (11.19%)	
occurrences (all)	26	17	
Infections and infestations			
Bronchitis			
subjects affected / exposed	8 / 132 (6.06%)	0 / 143 (0.00%)	
occurrences (all)	8	0	
Nasopharyngitis			
subjects affected / exposed	20 / 132 (15.15%)	19 / 143 (13.29%)	
occurrences (all)	25	25	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 May 2017	Following amendment changes were made Clarification of early treatment discontinuation language, restesting of dynamic laboratory values during screening, analysis changed to systemic corticosteroids from oral corticosteroids, EQ-5D elevated from exploratory endpoint to secondary endpoint, clarified CT scan administration to be mandatory unless not approved by local ethics committee or institutional review board, intranasal decongestants added to list of prohibited medications except as needed for nasal endoscopy procedure, study procedures could be performed over 3 days if necessary as long as the visit window was respected, updated safety language throughout the protocol to be consistent with most current safety information per latest investigators brochure: male birth control no longer required, clarified that rescue therapy prescribed by the investigator will not be provided by the Sponsor.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: