Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Dupilumab in Patients With Severe Steroid Dependent Asthma

Summary

EudraCT number	2015-001573-40
Trial protocol	NL ES BE PL HU IT
Global end of trial date	13 November 2017

Results information

Result version number	v1
This version publication date	18 May 2018
First version publication date	28 May 2018

Trial information

Trial identification

Sponsor protocol code	EFC13691

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02528214
WHO universal trial number (UTN)	U1111-1170-7152
Other trial identifiers	Study Name: LIBERTY ASTHMA VENTURE

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of dupilumab, compared with placebo, for reducing the use of maintenance oral corticosteroids (OCS) in subjects with severe steroid-dependent asthma.

Protection of trial subjects:

Paediatric Subjects: The study was conducted by investigators experienced in the treatment of paediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anaesthesia may have been used to minimize distress and discomfort. Adult 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. The following applies to both Paediatric and Adult Subjects: 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:

Oral corticosteroids (OCS [(prednisone or prednisolone]) therapy and stable high dose of inhaled corticosteroid (ICS) in combination with a second or third controller medication for at least 1 month prior to screening and continued throughout the study. Albuterol/salbutamol or levalbuterol/levosalbutamol was given as reliever medication.

Evidence for comparator: -

Actual start date of recruitment	15 October 2015
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: 5
Country: Number of subjects enrolled	Poland: 41
Country: Number of subjects enrolled	Romania: 12
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Argentina: 17
Country: Number of subjects enrolled	Brazil: 6

Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Chile: 17
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Mexico: 17
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Ukraine: 19
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	210
EEA total number of subjects	92

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)	3
Adults (18-64 years)	179
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 68 centers in 17 countries. A total of 390 subjects were screened between October 2015 & April 2017, of which, 210 subjects were randomized & treated. 180 subjects were screen failure mainly due to exclusion criteria met & inclusion criteria not met. Assignment was done by Interactive Voice/Web Response System(IVRS/IWRS).

Pre-assignment

Screening details:

The screening period included an OCS optimization phase(up to 10 weeks)where subjects using OCS other than prednisone/prednisolone switched to these OCS. At the end of period, subjects were randomized in 1:1 ratio for dupilumab & placebo. Randomization was stratified by optimized OCS dose(=<10mg/day & >10mg/day) at randomization visit & by 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, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo q2w

Arm description:

2 subcutaneous injections of Placebo (for Dupilumab) as a loading dose on Day 1, followed by a single injection every 2 weeks (q2w) for 24 weeks in combination with OCS - (prednisone or prednisolone) and stable ICS. OCS dose was reduced according to a predetermined titration schedule every 4 weeks until week 20.

Arm type	Experimental
Investigational medicinal product name	Placebo (for Dupilumab)
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 the abdomen or upper thigh or upper arm.

Arm title	Dupilumab 300 mg q2w

Arm description:

2 subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a single 300 mg injection q2w for 24 weeks in combination with OCS - (prednisone or prednisolone) and stable ICS. OCS dose was reduced according to a predetermined titration schedule every 4 weeks until week 20.

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

Dosage and administration details:

Subcutaneous injection (300 mg/2 ml) in the abdomen, upper thigh or upper arm.

Number of subjects in period 1	Placebo q2w	Dupilumab 300 mg q2w
Started	107	103
Treated	107	103
Completed	102	101
Not completed	5	2
Other than specified above	1	1
Adverse event	4	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo q2w
Reporting group description:	
2 subcutaneous injections of Placebo (for Dupilumab) as a loading dose on Day 1, followed by a single injection every 2 weeks (q2w) for 24 weeks in combination with OCS - (prednisone or prednisolone) and stable ICS. OCS dose was reduced according to a predetermined titration schedule every 4 weeks until week 20.	
Reporting group title	Dupilumab 300 mg q2w
Reporting group description:	
2 subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a single 300 mg injection q2w for 24 weeks in combination with OCS - (prednisone or prednisolone) and stable ICS. OCS dose was reduced according to a predetermined titration schedule every 4 weeks until week 20.	

Reporting group values	Placebo q2w	Dupilumab 300 mg q2w	Total
Number of subjects	107	103	210
Age categorical Units: Subjects			
Adolescents (12-17 years)	2	1	3
Adults (18-64 years)	88	91	179
From 65-84 years	17	11	28
Age continuous Units: years			
arithmetic mean	50.7	51.9	
standard deviation	± 12.8	± 12.5	-
Gender categorical Units: Subjects			
Female	65	62	127
Male	42	41	83
Race Units: Subjects			
Caucasian/White	100	97	197
Black/of African descent	1	4	5
Asian/Oriental	2	0	2
American Indian or Alaska Native	2	0	2
Native Hawaiian or Other Pacific Islander	0	1	1
Other	2	1	3
Ethnicity Units: Subjects			
Hispanic	22	23	45
Not Hispanic	85	80	165
Baseline Blood Eosinophil Count Units: Subjects			
<0.15 Giga/L	38	22	60
>=0.15 - <0.3 Giga/L	28	33	61
>=0.3 Giga/L	41	48	89

Baseline Optimized Daily OCS Dose			
During screening period and before randomization, dose of OCS was adjusted in each subject to achieve the lowest OCS dose, also known as the optimized dose, required for management of the subject's asthma. Subjects using OCS medications other than prednisone or prednisolone were switched to either of these corticosteroids at a dose clinically comparable to their current stable OCS dose. To optimize the OCS dose, investigators were instructed to adjust the OCS dose weekly according to a pre-specified titration schedule, based on changes in subject's asthma control, and their clinical judgment.			
Units: mg/day			
arithmetic mean	11.75	10.75	
standard deviation	± 6.31	± 5.90	-
Daily OCS Dose at Visit 1 (i.e. preoptimization)			
Units: mg/day			
arithmetic mean	11.83	11.79	
standard deviation	± 6.02	± 6.40	-

End points

End points reporting groups

Reporting group title	Placebo q2w

Reporting group description:

2 subcutaneous injections of Placebo (for Dupilumab) as a loading dose on Day 1, followed by a single injection every 2 weeks (q2w) for 24 weeks in combination with OCS - (prednisone or prednisolone) and stable ICS. OCS dose was reduced according to a predetermined titration schedule every 4 weeks until week 20.

Reporting group title	Dupilumab 300 mg q2w

Reporting group description:

2 subcutaneous injections of Dupilumab 300 mg (for a total of 600 mg) as a loading dose on Day 1, followed by a single 300 mg injection q2w for 24 weeks in combination with OCS - (prednisone or prednisolone) and stable ICS. OCS dose was reduced according to a predetermined titration schedule every 4 weeks until week 20.

Primary: Percentage Reduction From Baseline in Oral Corticosteroids (OCS) Dose at Week 24 While Maintaining Asthma Control

End point title	Percentage Reduction From Baseline in Oral Corticosteroids (OCS) Dose at Week 24 While Maintaining Asthma Control

End point description:

Percentage reduction of OCS dose was calculated from observed data as (optimized OCS dose at baseline - final OCS dose at Week 24)/optimized OCS dose at baseline x 100. Analysis was performed on intent-to- treat (ITT) population which included randomized population analyzed according to the treatment group allocated by randomization regardless of whether the treatment kit was used or not. Here "n" = subjects with available data for specified categories.

End point type	Primary

End point timeframe:

Baseline, Week 24

End point values	Placebo q2w	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	103		
Units: mg/day				
arithmetic mean (standard deviation)				
Baseline (n= 107, 103)	11.75 (± 6.31)	10.75 (± 5.90)		
Week 24 (n= 106, 101)	6.32 (± 6.75)	3.13 (± 5.44)		
Percent reduction at Week 24 (n= 106, 101)	45.28 (± 50.73)	73.85 (± 39.78)		

Statistical analyses

Statistical analysis title	Dupilumab vs. Placebo

Statistical analysis description:

The endpoint was analyzed using analysis of covariance (ANCOVA) model which included percentage reduction of OCS dose at Week 24 as the response variable, and treatment group, baseline eosinophil level, optimized OCS dose at baseline, region as covariates. Missing data was imputed using a pattern

mixture model by multiple imputation approach.

Comparison groups	Dupilumab 300 mg q2w v Placebo q2w
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001 [2]
Method	ANCOVA
Parameter estimate	Least square (LS) mean difference
Point estimate	28.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.81
upper limit	40.67

Notes:

[1] - A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the endpoints are reported and continued when previous endpoint was statistically significant at two-sided 0.05. Only the primary and the first 4 secondary endpoints were included in the procedure.
[2] - Threshold for significance at two-sided 0.05 level. LS mean difference represents reduction difference i.e. dupilumab - placebo.

Secondary: Percentage of Subjects Achieving >= 50% Reduction in Oral Corticosteroids dose at Week 24 While Maintaining Asthma Control

End point title	Percentage of Subjects Achieving >= 50% Reduction in Oral Corticosteroids dose at Week 24 While Maintaining Asthma Control

End point description:

Subjects were classified according to the binary status of whether or not the 50% OCS dose reduction criterion was achieved at week 24. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo q2w	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	103		
Units: percentage of subjects				
number (not applicable)	53.3	79.6		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs. Placebo q2w

Statistical analysis description:

The endpoint was analyzed using a logistic regression model. The model included the binary status of whether or not a subject achieved the 50% OCS dose reduction criterion as the response variable, and treatment groups, optimized OCS dose at baseline, regions, and baseline eosinophil level subgroups as covariates. Missing data was imputed by using a pattern mixture model by multiple imputation approach.

Comparison groups	Dupilumab 300 mg q2w v Placebo q2w

Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001 [4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.06
upper limit	7.67

Notes:

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

Secondary: Percentage of Subjects Achieving a Reduction in Oral Corticosteroids dose to <5 mg/day at Week 24 While Maintaining Asthma Control

End point title	Percentage of Subjects Achieving a Reduction in Oral Corticosteroids dose to <5 mg/day at Week 24 While Maintaining Asthma Control

End point description:

Subjects were classified according to the binary status of whether or not the reduction of OCS dose to <5 mg/day was achieved at week 24. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo q2w	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	103		
Units: percentage of subjects				
number (not applicable)	37.4	71.8		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs. Placebo q2w

Statistical analysis description:

The endpoint was analyzed using a logistic regression model. The model included the binary status of whether or not a subject achieved a reduction of OCS dose to <5 mg/day at Week 24 as the response variable, treatment groups, optimized OCS dose at baseline, regions, and baseline eosinophil level subgroups as covariates. Missing data was imputed by using a pattern mixture model by multiple imputation approach.

Comparison groups	Dupilumab 300 mg q2w v Placebo q2w

Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001 [6]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.39
upper limit	8.39

Notes:

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

Secondary: Percentage of Subjects Achieving Maximum Possible Reduction in Oral Corticosteroids Dose Per Protocol at Week 24 While Maintaining Asthma Control

End point title	Percentage of Subjects Achieving Maximum Possible Reduction in Oral Corticosteroids Dose Per Protocol at Week 24 While Maintaining Asthma Control

End point description:

For all subjects except those with baseline OCS dose at 35 mg/day, the maximum possible reduction corresponds to reduction to 0 mg/day (no longer requiring OCS). For subjects starting with 35 mg/day at baseline, the maximum possible reduction is 32.5 mg/day (i.e., minimum dose per protocol is 2.5 mg). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo q2w	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	103		
Units: percentage of subjects				
number (not applicable)	29.9	52.4		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs. Placebo q2w

Statistical analysis description:

The endpoint was analyzed using a logistic regression model. The model included binary status of whether or not a subject achieved their maximum possible reduction of OCS dose per protocol at Week 24 as the response variable, treatment groups, optimized OCS dose at baseline, regions, and baseline eosinophil level subgroups as covariates. Missing data was imputed by using a pattern mixture model by multiple imputation approach.

Comparison groups	Dupilumab 300 mg q2w v Placebo q2w

Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.0024 [8]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	4.73

Notes:

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

Secondary: Percentage of Subjects Who No Longer Require Oral Corticosteroids Dose at Week 24 While Maintaining Asthma Control

End point title	Percentage of Subjects Who No Longer Require Oral Corticosteroids Dose at Week 24 While Maintaining Asthma Control

End point description:

Subjects were classified according to the binary status of whether or not the subject still requires OCS at week 24 while maintaining asthma control. Analysis was performed on ITT population with baseline OCS dose less than or equal to 30 mg/day. Here, Number of subjects analyzed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo q2w	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	103		
Units: percentage of subjects				
number (not applicable)	29.2	52.4		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg q2w vs. Placebo q2w

Statistical analysis description:

The endpoint was analyzed using a logistic regression model. The model included the binary status of whether or not a subject no longer required OCS at Week 24 as the response variable, and treatment groups, optimized OCS dose at baseline, regions, and baseline eosinophil level subgroups as covariates. Missing data was imputed using a pattern mixture model by multiple imputation approach.

Comparison groups	Dupilumab 300 mg q2w v Placebo q2w

Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.0015 [10]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.47
upper limit	5.1

Notes:

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

Secondary: Absolute Reduction From Baseline in Oral Corticosteroids Dose at Week 24 While Maintaining Asthma Control

End point title	Absolute Reduction From Baseline in Oral Corticosteroids Dose at Week 24 While Maintaining Asthma Control

End point description:

Analysis was performed on ITT population but not included in the hierarchical testing procedure. Here, "n"= subjects with available data for specified categories.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo q2w	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	103		
Units: mg/day				
arithmetic mean (standard deviation)				
Baseline (n= 107, 103)	11.75 (± 6.31)	10.75 (± 5.90)		
Week 24 (n= 106, 101)	6.32 (± 6.75)	3.13 (± 5.44)		
Absolute reduction at Week 24 (n= 106, 101)	5.45 (± 6.80)	7.66 (± 6.10)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Asthma Control Questionnaire 5-Question Version (ACQ-5) Score at Weeks 2, 4, 8, 12, 16, 20, and 24

End point title	Change From Baseline in Asthma Control Questionnaire 5-Question Version (ACQ-5) Score at Weeks 2, 4, 8, 12, 16, 20, and 24

End point description:

The ACQ-5 has 5 questions, reflecting top-scoring 5 asthma symptoms: woken at night by symptoms, wake in mornings with symptoms, limitation of daily activities, shortness of breath and wheeze. Subjects were asked to recall how their asthma had been during previous week and to respond to each of 5 symptom questions on a 7-point scale ranged from 0 (no impairment) to 6 (maximum impairment). ACQ-5 total score was mean of scores of all 5 questions and, therefore, ranged from 0 (totally controlled) to 6 (severely uncontrolled). Higher score indicated lower asthma control. Analysis was performed on ITT population. Here, n= subjects with available data for specified categories.

End point type	Other pre-specified

End point timeframe:

Baseline and at Weeks 2, 4, 8, 12, 16, 20, and 24

End point values	Placebo q2w	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	103		
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Week 2 (n= 102, 95)	-0.18 (± 0.67)	-0.49 (± 0.86)		
Change at Week 4 (n= 103, 93)	-0.36 (± 0.81)	-0.61 (± 1.01)		
Change at Week 8 (n= 104, 96)	-0.39 (± 1.13)	-0.68 (± 1.06)		
Change at Week 12 (n= 101, 96)	-0.54 (± 1.17)	-0.92 (± 1.09)		
Change at Week 16 (n= 104, 95)	-0.57 (± 1.05)	-0.87 (± 1.18)		
Change at Week 20 (n= 102, 97)	-0.53 (± 1.09)	-0.83 (± 1.19)		
Change at Week 24 (n= 99, 96)	-0.57 (± 1.19)	-0.94 (± 1.22)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Asthma Quality of Life Questionnaire (AQLQ) Global Score at Week 12 and Week 24

End point title	Change From Baseline in Asthma Quality of Life Questionnaire (AQLQ) Global Score at Week 12 and Week 24

End point description:

AQLQ is a disease-specific, self-administered quality of life questionnaire designed to measure functional impairments that were most important to subjects with asthma. AQLQ comprised of 32 items in 4 domains: symptoms (12 items), activity limitation (11 items), emotional function (5 items), environmental stimuli (4 items). Each item was scored on a 7-point likert scale (1=maximal impairment, 7=no impairment). The 32 items of the questionnaire were averaged to produce one overall quality of life score ranging from 1 (severely impaired) to 7 (not impaired at all). Higher scores indicate better quality of life. Analysis was performed on ITT population. Here, n= subjects with available data for specified categories.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 12 and Week 24

End point values	Placebo q2w	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	103		
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Week 12 (105, 98)	0.56 (± 1.08)	0.78 (± 1.09)		
Change at Week 24 (100, 98)	0.56 (± 0.97)	0.94 (± 1.17)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L) Scores at Week 12 and Week 24

End point title	Change From Baseline in European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L) Scores at Week 12 and Week 24

End point description:

EQ-5D-5L is a standardized health-related quality of life questionnaire developed by EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. EQ-5D consists of EQ-5D descriptive system and EQ visual analogue scale (VAS). EQ-5D descriptive system comprises of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The 5D-5L systems are converted into a single index utility score between 0 to 1, where higher score indicates a better health state. EQ-5D-5L-VAS records subject's self-rated health on a vertical VAS that allows them to indicate their health state that can range from 0 (worst imaginable) to 100 (best imaginable). Analysis was performed on ITT population. Here, "n"=subjects with available data for specified categories.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 12 and Week 24

End point values	Placebo q2w	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	103		
Units: score on a scale				
arithmetic mean (standard deviation)				
Single Index: Change at Week 12 (n= 105, 98)	0.04 (± 0.20)	0.03 (± 0.17)		
Single Index: Change at Week 24 (n= 100, 98)	0.05 (± 0.18)	0.05 (± 0.18)		
VAS Score: Change at Week 12 (n=105,98)	5.99 (± 16.85)	9.34 (± 18.20)		
VAS Score: Change at Week 24 (n=100,98)	4.16 (± 16.74)	11.06 (± 17.60)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Hospital Anxiety and Depression Scale (HADS) Total Score at Week 12 and Week 24

End point title	Change From Baseline in Hospital Anxiety and Depression Scale (HADS) Total Score at Week 12 and Week 24

End point description:

The HADS is a general scale to detect states of anxiety and depression already used and validated in asthma, which includes HADS-A and HADS-D subscales. The instrument is comprised of 14 items: 7 related to anxiety (HADS-A) and 7 to depression (HADS-D). Each item on the questionnaire is scored from 0-3. And, the total score is the sum of the scores of the 14 items ranging from 0 (no symptoms) to 42 (severe symptoms), with higher scores indicating higher anxiety/depression complains. Analysis was performed on ITT population. Here "n" signifies number of subjects with available data for specified categories.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 12 and Week 24

End point values	Placebo q2w	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	103		
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Week 12 (n=105, 98)	-0.75 (± 5.50)	-2.13 (± 5.32)		
Change at Week 24 (n= 100, 98)	-0.99 (± 5.36)	-2.53 (± 5.98)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Sino Nasal Outcome Test-22 (SNOT-22) Global Score at Week 12 and Week 24

End point title	Change From Baseline in Sino Nasal Outcome Test-22 (SNOT-22) Global Score at Week 12 and Week 24

End point description:

The SNOT-22 is a validated measure of health related quality of life in sino nasal disease. It is a 22 item questionnaire with each item assigned a score ranging from 0-5. The total score may range from 0 (no disease) -110 (worst disease), lower scores represent better health related quality of life. Analysis was performed on ITT population with bilateral nasal polyposis/chronic rhinosinusitis. Here "n" = subjects with available data for specified categories.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 12 and Week 24

End point values	Placebo q2w	Dupilumab 300 mg q2w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	31		
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Week 12 (n= 38, 29)	-3.79 (± 21.34)	-12.45 (± 17.10)		
Change at Week 24 (n= 37, 27)	-2.46 (± 19.11)	-14.56 (± 15.89)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Week 36) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs were treatment emergent AEs developed/worsened occurred during 'treatment-emergent period'(from first dose of study drug injection up to end of 12 weeks post-treatment period) or entry in the LTS12551 study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Placebo q2w

Reporting group description:

Subjects who received Placebo (for Dupilumab) in combination with OCS and stable ICS (mean exposure of 24 weeks).

Reporting group title	Dupilumab 300mg q2w

Reporting group description:

Subjects who received Dupilumab 300 mg q2w in combination with OCS and stable ICS (mean exposure of 24 weeks).

Serious adverse events	Placebo q2w	Dupilumab 300mg q2w	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 107 (5.61%)	9 / 103 (8.74%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastrointestinal Stromal Tumour			
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Acetabulum Fracture			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign Body Aspiration			

subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 107 (0.00%)	2 / 103 (1.94%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	3 / 107 (2.80%)	3 / 103 (2.91%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthmatic Crisis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chylothorax			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Aspiration			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Mass			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	0 / 107 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 2 Diabetes Mellitus			
subjects affected / exposed	1 / 107 (0.93%)	0 / 103 (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 q2w	Dupilumab 300mg q2w	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 107 (28.04%)	29 / 103 (28.16%)	
Investigations			
Eosinophil Count Increased			
subjects affected / exposed	0 / 107 (0.00%)	7 / 103 (6.80%)	
occurrences (all)	0	7	
Infections and infestations			
Bronchitis			
subjects affected / exposed	6 / 107 (5.61%)	7 / 103 (6.80%)	
occurrences (all)	7	7	
Influenza			
subjects affected / exposed	6 / 107 (5.61%)	3 / 103 (2.91%)	
occurrences (all)	6	3	
Sinusitis			
subjects affected / exposed	4 / 107 (3.74%)	7 / 103 (6.80%)	
occurrences (all)	5	9	
Viral Upper Respiratory Tract Infection			

subjects affected / exposed occurrences (all)	19 / 107 (17.76%) 23	9 / 103 (8.74%) 12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 July 2016	Following changes were made: - Added instructions to allow the investigator to stop the downward titration of OCS in case of a safety concern; - Modified the forced expiratory volume in 1 second (FEV1) inclusion criteria for screening period and prior to randomization; - Deleted the exclusion criteria on birth control for male subjects with a female partner of childbearing potential; - Modification of the definition of the adverse events of special interest (AESIs) for infections, opportunistic infections, and the reporting requirements for systemic allergic reactions related to IMP and requiring treatment; - Updated the list of controller medications; - Modified the criteria for temporary treatment discontinuation to include infection and infestation that do not respond to medical treatment and updated the list of criteria for permanent treatment discontinuation to be consistent with changes to AESI criteria; - Provided clarification of hepatitis serology testing and interpretation of the results in context of eligibility criteria; - Added chest X-Ray or magnetic resonance imaging (MRI) at Visit 10 for subjects who planned to roll over into a long term study.
25 January 2017	Following changes were made: Increased the number of subjects to be enrolled from 150 to 180.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported