Clinical trial results:
Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of Dupilumab on Airway Inflammation Through Assessments of Lung Function, Mucus Plugging and Other Lung Imaging Parameters in Patients with Asthma

Summary

EudraCT number	2019-004647-74
Trial protocol	GB DK SE PT ES BG FR IT RO
Global end of trial date	21 August 2023

Results information

Result version number	v1 (current)
This version publication date	28 July 2024
First version publication date	28 July 2024

Trial information

Trial identification

Sponsor protocol code	LPS15834

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04400318
WHO universal trial number (UTN)	U1111-1238-4679

Notes:

Sponsors

Sponsor organisation name	Sanofi SAG
Sponsor organisation address	54-56 Rue la Boétie, Paris, France, 75008
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	12 September 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of dupilumab on lung inflammation and related changes in airway volumes detectable by functional respiratory imaging.

Protection of trial subjects:

Participants were fully informed of all pertinent aspects of clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the participant and considering the local culture. During the course of the trail, participants were provided with individual participant cards indicating the nature of the trial the participant is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 June 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 36
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Romania: 11
Country: Number of subjects enrolled	Saudi Arabia: 4
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	Ukraine: 23
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 11
Worldwide total number of subjects	109
EEA total number of subjects	64

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)	96
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 317 participants were screened from 20 Jun 2020 to 06 Jan 2023 at 72 study sites in 14 countries of which 208 participants were screen failures. Screen failures were mainly due to not meeting the eligibility criteria.

Pre-assignment

Screening details:

A total of 109 participants were randomized in a ratio of 2:1 to receive dupilumab 300 milligrams (mg) or matching placebo every 2 weeks (Q2W) for 24 weeks. Randomization was stratified by inhaled corticosteroids (ICS) dose level (medium/high no less than 40% in 'high ICS' stratum) and region (Eastern Europe/Rest of the World [ROW]).

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	Dupilumab 300 mg Q2W

Arm description:

Participants received a loading dose of dupilumab 600 mg as 2 subcutaneous (SC) injections on Day 1, followed by a single dupilumab 300 mg SC injection Q2W for 24 weeks along with a stable dose of medium to high ICS dose in combination with a second controller medication +/- a third controller.

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

Dosage and administration details:

Dupilumab was supplied as a 150 milligram per milliliter (mg/mL) solution in prefilled glass syringe to deliver 300 mg in a 2 mL injection. SC injection sites were alternated between the upper thighs, 4 quadrants of the abdomen or the upper arms, so that the same site was not injected twice during consecutive administrations.

Arm title	Placebo

Arm description:

Participants received placebo matched to dupilumab as 2 x 2 milliliter (mL) SC injections on Day 1, followed by a single SC injection Q2W for 24 weeks along with a stable dose of medium to high ICS dose in combination with a second controller medication +/- a third controller.

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

Dosage and administration details:

Matching placebo was supplied as an identical formulation to the active formulation without dupilumab, in a prefilled syringe to deliver placebo in a 2 mL injection. SC injection sites were alternated between the upper thighs, 4 quadrants of the abdomen or the upper arms, so that the same site was not injected twice during consecutive administrations.

Number of subjects in period 1	Dupilumab 300 mg Q2W	Placebo
Started	72	37
Completed	70	33
Not completed	2	4
Consent withdrawn by subject	1	1
Not Related to Coronavirus Disease 2019 Pandemic	-	3
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Dupilumab 300 mg Q2W
Reporting group description:	
Participants received a loading dose of dupilumab 600 mg as 2 subcutaneous (SC) injections on Day 1, followed by a single dupilumab 300 mg SC injection Q2W for 24 weeks along with a stable dose of medium to high ICS dose in combination with a second controller medication +/- a third controller.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to dupilumab as 2 x 2 milliliter (mL) SC injections on Day 1, followed by a single SC injection Q2W for 24 weeks along with a stable dose of medium to high ICS dose in combination with a second controller medication +/- a third controller.	

Reporting group values	Dupilumab 300 mg Q2W	Placebo	Total
Number of subjects	72	37	109
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	51.0	49.4	
standard deviation	± 12.81	± 12.33	-
Sex: Female, Male Units: participants			
Female	46	22	68
Male	26	15	41
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	8	2	10
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	1
White	64	34	98
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Untrimmed Distal Specific Airway Volumes ([s]iVaw) at Total Lung Capacity (TLC)			
Only those participants with data available at baseline are reported.			
Units: milliliter (mL)			
arithmetic mean	1.90526	1.90562	
standard deviation	± 0.954024	± 1.161739	-

End points

End points reporting groups

Reporting group title	Dupilumab 300 mg Q2W
Reporting group description:	
Participants received a loading dose of dupilumab 600 mg as 2 subcutaneous (SC) injections on Day 1, followed by a single dupilumab 300 mg SC injection Q2W for 24 weeks along with a stable dose of medium to high ICS dose in combination with a second controller medication +/- a third controller.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to dupilumab as 2 x 2 milliliter (mL) SC injections on Day 1, followed by a single SC injection Q2W for 24 weeks along with a stable dose of medium to high ICS dose in combination with a second controller medication +/- a third controller.	

Primary: Percentage of Participants who Achieved Fractional Exhaled Nitric Oxide (FeNO) Less Than (<) 25 Parts Per Billion (ppb) at Week 24

End point title	Percentage of Participants who Achieved Fractional Exhaled Nitric Oxide (FeNO) Less Than (<) 25 Parts Per Billion (ppb) at Week 24
End point description:	
FeNO was analyzed using a NIOX instrument using a flow rate of 50 milliliters per second (mL/s). This assessment was conducted prior to spirometry and following a fast of greater than or equal to (≥1) hour. The test was performed after a wash out period of bronchodilators. The ITT analysis set consisted of randomized participants (participants with a study intervention kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the study intervention kit was used or not).	
End point type	Primary
End point timeframe:	
Week 24	

End point values	Dupilumab 300 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	37		
Units: percentage of participants				
number (not applicable)	56.9	10.8		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q2W versus Placebo
Statistical analysis description:	
Odds Ratio, 95% confidence interval (CI) of the odds ratio and p-value between the dupilumab and placebo group based on the Cochran-Mantel-Haenszel (CMH) test adjusted by ICS dose level (medium/high) and region (Eastern Europe/ROW).	
Comparison groups	Dupilumab 300 mg Q2W v Placebo

Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	9.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.13
upper limit	30.82

Primary: Percent Change From Baseline to Week 24 in Untrimmed Distal Specific Airway Volumes ([s]iVaw) at Total Lung Capacity (TLC)

End point title	Percent Change From Baseline to Week 24 in Untrimmed Distal Specific Airway Volumes ([s]iVaw) at Total Lung Capacity (TLC)

End point description:

Specific airway volume [(s)iVaw] is the change of volume of the airways (in mL), taking into account the lung volume changes (in liter [L]) as well. It corresponds to the ratio between the airway volume (iVaw) and the lobar volume. This way the airway volumes are normalized across participants and become specific. Untrimmed distal [s]iVaw at TLC was assessed based on 3-dimensional (D) rendering of high-resolution computed tomography (HRCT) scans. Baseline was defined as the last available valid (non-missing) value up to and including the day of first dose of investigational medicinal product (IMP). The ITT analysis set consisted of randomized participants (participants with a study intervention kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the study intervention kit was used or not). Only participants with data collected at Week 24 are reported.

End point type	Primary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Dupilumab 300 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	34		
Units: percent change				
least squares mean (standard error)	19.73 (± 8.102)	-2.04 (± 11.538)		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q2W versus Placebo

Statistical analysis description:

The mixed model for repeated measures (MMRM) included study intervention, baseline value, region, ICS dose level, visits, study intervention by visit interaction, and baseline by visit interaction terms all as fixed effects. Region, ICS, study intervention and visits were considered as categorical parameters.

Comparison groups	Dupilumab 300 mg Q2W v Placebo

Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.138
Method	MMRM
Parameter estimate	Least square mean difference
Point estimate	21.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.73
upper limit	51.25
Variability estimate	Standard error of the mean
Dispersion value	14.022

Secondary: Change From Baseline to Week 24 in Global Lung Mucus Score (University of California, San Francisco [UCSF] Mucus Scoring)

End point title	Change From Baseline to Week 24 in Global Lung Mucus Score (University of California, San Francisco [UCSF] Mucus Scoring)

End point description:

The mucus scoring system was derived, with very minor differences, from UCSF mucus score. The mucus score was calculated by counting the number of bronchopulmonary segments which contained 1 or more mucus plug, up to a maximum score of 18 corresponding to the 18 bronchopulmonary segments present in most people. In this system, a mucus plug is defined as a complete occlusion of the airway visible at TLC. Each bronchopulmonary segment is given a score of 1 (mucus plug[s] present) or 0 (mucus plug[s] absent). The segment scores of each lobe are summed to generate a total mucus score for both lungs, yielding a mucus score ranging from 0-18. Higher scores indicate worse outcome. Baseline was defined as the last available valid (non-missing) value up to and including the date of first dose of IMP. Results are based on the ITT analysis set. Only participants with data collected at Week 24 are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Dupilumab 300 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	34		
Units: score on a scale				
least squares mean (standard error)	-3.48 (± 0.463)	1.44 (± 0.656)		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q2W versus Placebo

Statistical analysis description:

MMRM model included study intervention (dupilumab, placebo), baseline value of global lung UCSF mucus scoring, region (Eastern Europe/ROW), ICS dose level (medium/high), visit (up to Week 24),

study intervention-by-visit interaction and baseline-by-visit interaction as covariates.

Comparison groups	Dupilumab 300 mg Q2W v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001
Method	MMRM
Parameter estimate	Least square mean difference
Point estimate	-4.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	-3.34
Variability estimate	Standard error of the mean
Dispersion value	0.798

Notes:

[1] - A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the endpoint is reported and continued when previous endpoint was statistically significant at two-sided 0.05. Only 2 endpoints measures (#4 and #5) were included in this procedure.

Secondary: Percent Change From Baseline to Week 24 in Trimmed Distal Specific Airway Resistance ([s]iRaw) at TLC

End point title	Percent Change From Baseline to Week 24 in Trimmed Distal Specific Airway Resistance ([s]iRaw) at TLC

End point description:

iRaw is defined as the total pressure drop over an airway, divided by the flow rate through that airway. The specific airway resistance (s)iRaw is derived from iRaw by multiplying the airway resistance with the lobar volume. This way the airway resistances are normalized across participants and become specific. Trimmed distal ([s]iRaw) at TLC was assessed using HRCT scan. Baseline was defined as the last available valid (non-missing) value up to and including the day of first dose of IMP. The ITT analysis set consisted of randomized participants (participants with a study intervention kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the study intervention kit was used or not). Only participants with data collected at Week 24 are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Dupilumab 300 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	34		
Units: percent change				
least squares mean (standard error)	36.85 (± 22.562)	90.30 (± 32.541)		

Statistical analyses

Statistical analysis title	Dupilumab 300 mg Q2W versus Placebo

Statistical analysis description:

MMRM model included study intervention (dupilumab, placebo), baseline value of trimmed distal [s]iRaw at TLC, region (Eastern Europe/ROW), ICS dose level (medium/high), visit (up to Week 24), study intervention-by-visit interaction, and baseline-by-visit interaction as covariates.

Comparison groups	Dupilumab 300 mg Q2W v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.18
Method	MMRM
Parameter estimate	Least square mean difference
Point estimate	-53.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-132.09
upper limit	25.19
Variability estimate	Standard error of the mean
Dispersion value	39.562

Notes:

[2] - A hierarchical testing procedure was used to control the overall type I error. Testing was then performed sequentially in order the endpoint is reported and continued when previous endpoint was statistically significant at two-sided 0.05. Only 2 secondary endpoints (#4 and #5) were included in this procedure.

Secondary: Percent Change From Baseline to Week 24 in Untrimmed Distal Specific Airway Volumes ([s]iVaw) at Functional Residual Capacity (FRC)

End point title	Percent Change From Baseline to Week 24 in Untrimmed Distal Specific Airway Volumes ([s]iVaw) at Functional Residual Capacity (FRC)

End point description:

(s)iVaw is the change of volume of the airways (mL), taking into account the lung volume changes (in L) as well. It corresponds to the ratio between the airway volume (iVaw) and the lobar volume. Untrimmed distal [s]iVaw at FRC was assessed based on 3D rendering of HRCT scans. Baseline was defined as the last available valid (non-missing) value up to and including the day of first dose of IMP. The ITT analysis set consisted of randomized participants (participants with a study intervention kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the study intervention kit was used or not). Only participants with data collected at Week 24 are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Dupilumab 300 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	35		
Units: percent change				
least squares mean (standard error)	225.91 (± 92.250)	-17.07 (± 129.384)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline to Week 24 in Global Lung Lobar Volumes (iVlobes) at TLC

End point title	Percent Change From Baseline to Week 24 in Global Lung Lobar Volumes (iVlobes) at TLC

End point description:

The lung volume was determined from the HRCT scan at TLC, by identifying and grouping the voxels that represent the air in the lungs. The total lung volume along with the volume of each lobe individually was determined which allowed to pick up substantial regional physiological changes of the airways and the lobe volumes. Baseline was defined as the last available valid (non-missing) value up to and including the day of first dose of IMP. The ITT analysis set consisted of randomized participants (participants with a study intervention kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the study intervention kit was used or not). Only participants with data collected at Week 24 are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Dupilumab 300 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	34		
Units: percent change				
least squares mean (standard error)	-0.98 (± 1.691)	-3.74 (± 2.401)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 24 in HRCT-Based Internal Airflow Distribution (IAD) for Each Lung Zone

End point title	Change From Baseline to Week 24 in HRCT-Based Internal Airflow Distribution (IAD) for Each Lung Zone

End point description:

The IAD was assessed in the upper and lower lung using HRCT scan. By segmenting the lobes at FRC and TLC for each participant, the participant-specific airflow distribution can be established by assessing lobar and volume expansion. Baseline was defined as the last available valid (non-missing) value up to and including the date of the first dose of IMP. The ITT analysis set consisted of randomized participants (participants with a study intervention kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the study intervention kit was used or not). Only participants with data collected at Week 24 are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Dupilumab 300 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	34		
Units: percentage of IAD				
least squares mean (standard error)				
Upper Lung	-0.61 (± 0.803)	-0.11 (± 1.133)		
Lower Lung	0.61 (± 0.803)	0.11 (± 1.133)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline to Week 24 in Trimmed Distal Specific Airway Resistance ([s]iRaw) at FRC

End point title	Percent Change From Baseline to Week 24 in Trimmed Distal Specific Airway Resistance ([s]iRaw) at FRC

End point description:

iRaw is defined as the total pressure drop over an airway, divided by the flow rate through that airway. The specific airway resistance (s)iRaw is derived from iRaw by multiplying the airway resistance with the lobar volume. This way, the airway resistances are normalized across participants and become specific. Trimmed distal [s]iRaw at FRC was assessed using HRCT scan. Baseline was defined as the last available valid (non-missing) value up to and including the day of the first dose of IMP. The ITT analysis set consisted of randomized participants (participants with a study intervention kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the study intervention kit was used or not). Only participants with data collected at Week 24 are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Dupilumab 300 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	35		
Units: percent change				
least squares mean (standard error)	98.73 (± 70.143)	207.87 (± 98.445)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 24 in Image-Based Ventilation/Perfusion (iV/Q) at TLC for Each Lung Zone

End point title	Change From Baseline to Week 24 in Image-Based Ventilation/Perfusion (iV/Q) at TLC for Each Lung Zone

End point description:

Blood vessel density can be considered a surrogate for perfusion, hence image-based perfusion (IQ) is calculated by blood vessel density at TLC multiplied by image-based volume at TLC. Image-based ventilation (IV) is calculated by the imaged volume at TLC subtracted from the image-based volume at FRC. The ventilation/perfusion ratio IV/Q is then the ratio IV/IQ. The iV/Q was assessed in the upper and lower lung using HRCT scan at TLC. Baseline was defined as the last available valid (non-missing) value up to and including the day of the first dose of IMP. The ITT analysis set consisted of randomized participants (participants with a study intervention kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the study intervention kit was used or not). Only participants with data collected at Week 24 are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Dupilumab 300 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	34		
Units: Ratio				
least squares mean (standard error)				
Upper Lung	1.42 (± 0.538)	-0.45 (± 0.758)		
Lower Lung	1.75 (± 0.579)	-0.91 (± 0.817)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 24 in FeNO

End point title	Change From Baseline to Week 24 in FeNO

End point description:

FeNO was analyzed using a NIOX instrument using a flow rate of 50 mL/s. This assessment was conducted prior to spirometry and following a fast of ≥1 hour. The test was performed after a wash out period of bronchodilators. Baseline was defined as the last available valid (non-missing) value up to and including the day of the first dose of IMP. The ITT analysis set consisted of randomized participants (participants with a study intervention kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the study intervention kit was used or not).

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Dupilumab 300 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	37		
Units: parts per billion				
least squares mean (standard error)	-35.49 (± 2.440)	-12.56 (± 3.444)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 24 in Pre-Bronchodilator and Post-Bronchodilator Forced Expiratory Volume in 1 Second (FEV1)

End point title	Change From Baseline to Week 24 in Pre-Bronchodilator and Post-Bronchodilator Forced Expiratory Volume in 1 Second (FEV1)

End point description:

FEV1 was the volume of air exhaled in the first second of a forced expiration. Lung function parameters: pre- and post-bronchodilator FEV1 were measured by spirometry before IMP administration. Spirometry was performed after a wash out period of bronchodilators. Post-BD FEV1 was measured within 30 minutes after short-acting beta-2 agonists (2 to up to 4 puffs of albuterol/salbutamol) administration. Baseline was defined as the last available valid (non-missing) value up to and including the date of the first dose of IMP. The ITT analysis set consisted of randomized participants (participants with a study intervention kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the study intervention kit was used or not).

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Dupilumab 300 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	37		
Units: liter				
least squares mean (standard error)				
Pre-Bronchodilator FEV1	0.655 (± 0.0637)	0.274 (± 0.0885)		
Post-Bronchodilator FEV1	0.468 (± 0.0661)	0.151 (± 0.0928)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Adverse Events (TEAEs), Treatment-emergent Serious Adverse Events (TESAEs), and Adverse Events of Special Interest (AESIs)

End point title	Number of Participants With Treatment-emergent Adverse

	Events (TEAEs), Treatment-emergent Serious Adverse Events (TESAEs), and Adverse Events of Special Interest (AESIs)

End point description:

AE:any untoward medical occurrence in participant/clinical study participant, temporally associated with use of study intervention, whether or not considered related to study intervention. TEAEs:AEs that developed or worsened or became serious during TEAE period, defined as time from first administration of IMP (Day 1) to last administration of IMP+98 days and up to end of study follow-up. Serious adverse events(SAE):AE that at any dose: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was congenital anomaly/birth defect, was medically important event. AESI:AE (serious or nonserious) of scientific and medical concern specific to Sponsor's product or program, for which ongoing monitoring and immediate notification by Investigator to Sponsor is required. The safety analysis set included all randomized participants who received at least 1 injection of IMP.

End point type	Secondary

End point timeframe:

From first dose of study drug (Day 1) up to end of study (up to 36 weeks)

End point values	Dupilumab 300 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	37		
Units: participants				
Any TEAE	31	21		
Any TESAE	3	1		
Any AESI	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 24 in 7 Item Asthma Control Questionnaire (ACQ-7)

End point title	Change From Baseline to Week 24 in 7 Item Asthma Control Questionnaire (ACQ-7)

End point description:

The ACQ-7 comprises of 7 items: first 5 items assess most common asthma symptoms:1.frequency in past week awoken by asthma during night;2.severity of asthma symptoms in morning; 3.limitation of daily activities due to asthma; 4.shortness of breath due to asthma;5.wheeze; plus questions 6.short-acting bronchodilator use; and 7.FEV1 (pre-bronchodilator use, % and % predicted use).Participants are asked to recall how their asthma has been during previous week,to respond to symptom questions on a 7-point scale (0=no impairment,6=maximum impairment).Clinic staff scores the FEV1% predicted on a 7-point scale.A global score is calculated:questions are equally weighted;overall ACQ-7 score is mean of 7 questions, between 0 (totally controlled) and 6 (severely uncontrolled).Higher score indicates lower asthma control.Baseline=last available valid (non-missing) value up to and including day of first dose of IMP. ITT analysis set.Only participants with data collected at Week 24 are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Dupilumab 300 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	36		
Units: score on a scale				
least squares mean (standard error)	-1.36 (± 0.101)	-0.62 (± 0.143)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug (Day 1) up to end of study (up to 36 weeks)	
Adverse event reporting additional description:	
Analysis was performed on safety analysis set.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups	
Reporting group title	Dupilumab 300 mg Q2W
Reporting group description:	
Participants received a loading dose of dupilumab 600 mg as 2 SC injections on Day 1, followed by a single dupilumab 300 mg SC injection Q2W for 24 weeks along with a stable dose of medium to high ICS dose in combination with a second controller medication +/- a third controller.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to dupilumab as 2 x 2 mL SC injections on Day 1, followed by a single SC injection Q2W for 24 weeks along with a stable dose of medium to high ICS dose in combination with a second controller medication +/- a third controller.	

Serious adverse events	Dupilumab 300 mg Q2W	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 72 (4.17%)	1 / 37 (2.70%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Facial Bones Fracture			
subjects affected / exposed	1 / 72 (1.39%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft Tissue Injury			
subjects affected / exposed	1 / 72 (1.39%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Eosinophilia			

subjects affected / exposed	1 / 72 (1.39%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Eosinophilic Granulomatosis With Polyangiitis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 72 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Dupilumab 300 mg Q2W	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 72 (25.00%)	15 / 37 (40.54%)	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 72 (6.94%)	3 / 37 (8.11%)	
occurrences (all)	6	3	
General disorders and administration site conditions			
Injection Site Reaction			
subjects affected / exposed	4 / 72 (5.56%)	1 / 37 (2.70%)	
occurrences (all)	10	2	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 72 (0.00%)	2 / 37 (5.41%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Sleep Apnoea Syndrome			

subjects affected / exposed	0 / 72 (0.00%)	2 / 37 (5.41%)	
occurrences (all)	0	2	
Asthma			
subjects affected / exposed	4 / 72 (5.56%)	9 / 37 (24.32%)	
occurrences (all)	4	11	
Rhinorrhoea			
subjects affected / exposed	1 / 72 (1.39%)	2 / 37 (5.41%)	
occurrences (all)	1	2	
Infections and infestations			
Covid-19			
subjects affected / exposed	7 / 72 (9.72%)	3 / 37 (8.11%)	
occurrences (all)	7	3	
Pneumonia			
subjects affected / exposed	0 / 72 (0.00%)	2 / 37 (5.41%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2020	The main reason for this amendment was to meet requirements for Regulatory Agency.
15 March 2021	The main reasons for this amendment were to introduce some clarifications in the eligibility criteria, to decrease the participant burden and to allow more flexibility for some of the study procedures (e.g., FeNO assessment, complete clinical examination, the sequence of the study procedures). The safety reporting (AESI) were aligned with the updated Investigator's brochure and contingency measures were incorporated in case of a regional or national emergency. The stratification factor related to regions was changed to Eastern Europe/ROW. In total, no more than 40% participants should be in "Eastern Europe" strata.
13 April 2023	The main reason for this amendment was evolving interest to evaluate FeNO as an airway inflammatory biomarker related to structural lung changes. Therefore, the primary endpoint FEV1 was proposed to be replaced with the secondary endpoint of FeNO, leading to an overall reduction in sample size. Objectives and Endpoints section was updated. Updates were made to the sample size calculation and hypotheses reflecting the change to the primary endpoint. The efficacy analyses were updated based on changes to the endpoints. Minor grammatical, editorial, and/or administrative changes were made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported