Clinical trial results:
A Phase 4, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Study of the Effect of Dupilumab on Sleep Disturbance in Patients with Uncontrolled Persistent Asthma (Dupilumab Asthma Sleep Study MORPHEO)

Summary

EudraCT number	2020-001217-20
Trial protocol	DE GB NL PT IT
Global end of trial date	10 November 2023

Results information

Result version number	v1 (current)
This version publication date	23 November 2024
First version publication date	23 November 2024

Trial information

Trial identification

Sponsor protocol code	LPS16677

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04502862
WHO universal trial number (UTN)	U1111-1249-6054

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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 November 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 November 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 sleep.

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 trial, participants were provided with individual participant cards indicating the nature of the trial the participant is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 August 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 27
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Portugal: 8
Country: Number of subjects enrolled	Russian Federation: 29
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Ukraine: 37
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	United States: 52
Worldwide total number of subjects	202
EEA total number of subjects	44

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)	196
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 52 centers in 11 countries. A total of 397 participants were screened between 10 August 2020 to 30 May 2023, of which 195 participants were screen failures. Screen failures were mainly due to not meeting the eligibility criteria.

Pre-assignment

Screening details:

A total of 202 participants were randomized in a ratio of 1:1 to receive dupilumab or matching placebo every 2 weeks (Q2W) for 12 weeks.

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 200 mg Q2W

Arm description:

Participants received a loading dose of 400 milligrams (mg) of dupilumab (2 injections × 200 mg) subcutaneous (SC) on Day 1, followed by 200 mg Q2W for 12 weeks.

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

Dosage and administration details:

Dupilumab 200 mg was provided as a 175 mg/mL
dupilumab solution in a prefilled syringe
to deliver 200 mg in 1.14 milliliter (mL). It was administered as SC injection with initial loading dose of 400 mg of dupilumab (2 injections × 200 mg) on Day1, followed by 200 mg Q2W for 12 weeks.

Arm title	Placebo

Arm description:

Participants received an initial loading dose of matching placebo (2 injections of placebo) SC on Day 1, followed by 1 injection of placebo Q2W for 12 weeks.

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

Dosage and administration details:

Placebo matching dupilumab 200 mg was supplied as an identical formulation to the active 200 mg formulation without dupilumab, in a prefilled syringe to deliver placebo in 1.14 mL. It was administered as SC injection with an initial loading dose of matching placebo (2 injections of placebo) on Day 1, followed by 1 injection of placebo Q2W for 12 weeks.

Number of subjects in period 1	Dupilumab 200 mg Q2W	Placebo
Started	101	101
Randomized and treated	100	101
Completed	95	94
Not completed	6	7
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	1
Not Related to COVID-19 pandemic	4	6

Baseline characteristics

Reporting groups	
Reporting group title	Dupilumab 200 mg Q2W
Reporting group description:	
Participants received a loading dose of 400 milligrams (mg) of dupilumab (2 injections × 200 mg) subcutaneous (SC) on Day 1, followed by 200 mg Q2W for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received an initial loading dose of matching placebo (2 injections of placebo) SC on Day 1, followed by 1 injection of placebo Q2W for 12 weeks.	

Reporting group values	Dupilumab 200 mg Q2W	Placebo	Total
Number of subjects	101	101	202
Age categorical			
Units:			
Adults (18-64 years)	97	99	196
From 65-84 years	4	2	6
Age Continuous			
Units: Years			
arithmetic mean	46.9	46.6	
standard deviation	± 12.63	± 12.71	-
Sex: Female, Male			
Units: Participants			
Female	68	76	144
Male	33	25	58
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	4	3	7
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	4	4	8
White	92	92	184
More than one race	1	0	1
Unknown or Not Reported	0	1	1
Sleep Disturbance Score			
Sleep disturbance score was assessed by ASDQ. Participants recorded severity of disturbance of sleep due to asthma as: 0 = slept through night, no asthma symptoms; 1 = slept well, no night time awakenings because of asthma, but some asthma symptoms in the morning; 2 = woke up once because of asthma; 3 = woke up several times because of asthma and 4 = bad night, awake most of the night because of asthma. Total scores range:0 (no impact of asthma on sleep) and 4 (higher impact of asthma on sleep). Higher scores=worse outcomes.Only those participants with data available at baseline are reported.			
Units: Score on a scale			
arithmetic mean	1.89	1.83	
standard deviation	± 0.769	± 0.754	-

End points

End points reporting groups

Reporting group title	Dupilumab 200 mg Q2W
Reporting group description:	
Participants received a loading dose of 400 milligrams (mg) of dupilumab (2 injections × 200 mg) subcutaneous (SC) on Day 1, followed by 200 mg Q2W for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received an initial loading dose of matching placebo (2 injections of placebo) SC on Day 1, followed by 1 injection of placebo Q2W for 12 weeks.	
Subject analysis set title	Dupilumab 200 mg Q2W (ITT for primary endpoint [ITTp])
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants received a loading dose of 400 mg of dupilumab (2 injections × 200 mg) SC on Day 1, followed by 200 mg Q2W for 12 weeks.	
Subject analysis set title	Placebo (ITTp)
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants received an initial loading dose of matching placebo (2 injections of placebo) SC on Day 1, followed by 1 injection of placebo Q2W for 12 weeks.	

Primary: Change From Baseline to Week 12 in Sleep Disturbance Score Using the Asthma Sleep Disturbance Questionnaire (ASDQ)

End point title	Change From Baseline to Week 12 in Sleep Disturbance Score Using the Asthma Sleep Disturbance Questionnaire (ASDQ)
End point description:	
ASDQ is participant-reported outcome (PRO) measure where participants recorded severity of disturbance of sleep due to asthma in an electronic diary, once a day upon awakening,as:0=slept through the night,no asthma symptoms;1=slept well,no night time awakenings because of asthma,but some asthma symptoms in morning;2= woke up once because of asthma (may/may not include early awakening);3=woke up several times because of asthma (may or may not include early awakening) and 4=bad night, awake most of the night because of asthma.Total scores=0(no impact of asthma on sleep) to 4 (higher impact of asthma on sleep). Higher scores=worse outcomes.Baseline=averaging data collected/recorded from Day -6 to Day 1. ITTp analysis set=all ITT participants excluding those who used original version of sleep disturbance questionnaire at baseline and/or post-baseline included in MMRM model. Only those participants with data collected at baseline and at least one post-baseline until Week 12 are reported.	
End point type	Primary
End point timeframe:	
Baseline (Day -6 to Day 1) up to Week 12	

End point values	Dupilumab 200 mg Q2W (ITT for primary endpoint [ITTp])	Placebo (ITTp)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	93		
Units: Score on a scale				
least squares mean (standard error)	-0.88 (± 0.077)	-0.81 (± 0.077)		

Statistical analyses

Statistical analysis title	Dupilumab 200 mg Q2W (ITTp) versus Placebo (ITTp)

Statistical analysis description:

The MMRM model included study intervention, age, body mass index (BMI), region (Eastern Europe, rest of world [ROW]), inhaled corticosteroids [ICS] dose level at baseline (ICS dose level medium, ICS dose level high), visit (up to Week 12), study intervention-by-visit interaction, baseline asthma control questionnaire (ACQ-5), baseline sleep disturbance score and baseline-by-visit interaction as covariates.

Comparison groups	Dupilumab 200 mg Q2W (ITT for primary endpoint [ITTp]) v Placebo (ITTp)
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.512 [1]
Method	MMRM
Parameter estimate	Least square mean difference
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.14
Variability estimate	Standard error of the mean
Dispersion value	0.107

Notes:

[1] - A hierarchical testing procedure was used to control type I error and handle primary and first 2 secondary endpoints (reported sequentially) analyses at a 2-sided significance level of 0.05.

Secondary: Change From Baseline to Week 12 on the Number of Nocturnal Awakenings (Sleep Diary)

End point title	Change From Baseline to Week 12 on the Number of Nocturnal Awakenings (Sleep Diary)

End point description:

Sleep diary is used to assess adult sleep disturbance due to asthma. Number of nocturnal awakenings was determined based on answer on question from sleep diary: "Approximately how many times did you wake up last night (not including when you woke up for the day today)?" Baseline was calculated by averaging the data collected/recorded from Day -6 to Day 1. The ITT analysis set consisted of all randomized participants included in the MMRM model. Only those participants with data collected at baseline and at least one post-baseline until Week 12 are reported.

End point type	Secondary

End point timeframe:

Baseline (Day -6 to Day 1) up to Week 12

End point values	Dupilumab 200 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: Number of nocturnal awakenings				
least squares mean (standard error)	-0.71 (± 0.080)	-0.71 (± 0.080)		

Statistical analyses

Statistical analysis title	Dupilumab 200 mg Q2W versus Placebo

Statistical analysis description:

The MMRM model included study intervention, age, BMI, region (Eastern Europe, ROW), ICS dose level at baseline (ICS dose level medium, ICS dose level high), visit (up to Week 12), study intervention-by-visit interaction, baseline ACQ-5, baseline number of nocturnal awakenings and baseline-by-visit interaction as covariates.

Comparison groups	Dupilumab 200 mg Q2W v Placebo
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.967 [2]
Method	MMRM
Parameter estimate	Least square mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.22
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[2] - A hierarchical testing procedure was used to control type I error and handle primary and first 2 secondary endpoints (reported sequentially) analyses at a 2-sided significance level of 0.05.

Secondary: Change From Baseline to Week 12 in Restorative Sleep (Sleep Diary)

End point title	Change From Baseline to Week 12 in Restorative Sleep (Sleep Diary)

End point description:

Sleep Diary is used to assess adult sleep disturbance due to asthma. Question about restorative sleep asks participants to recall "when they got up for the day today". Restorative sleep was assessed on a 11-point scale which ranged from 0 (worst possible sleep) to 10 (best possible sleep); higher scores indicated better outcomes. Baseline was calculated by averaging the data collected/recorded from Day -6 to Day 1. The ITT analysis set consisted of all randomized participants included in the MMRM model. Only those participants with data collected at baseline and at least one post-baseline until Week 12 are reported.

End point type	Secondary

End point timeframe:

Baseline (Day -6 to Day 1) up to Week 12

End point values	Dupilumab 200 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: Score on a scale				
least squares mean (standard error)	1.15 (± 0.152)	1.02 (± 0.152)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 12 in Sleep Quality (Sleep Diary)

End point title	Change From Baseline to Week 12 in Sleep Quality (Sleep Diary)

End point description:

Sleep diary is used to assess adult sleep disturbance due to asthma. Sleep quality was assessed on a 11-point scale which ranged from 0 (worst possible sleep) to 10 (best possible sleep); higher scores indicated better outcomes. Baseline was calculated by averaging the data collected/recorded from Day -6 to Day 1. The ITT analysis set consisted of all randomized participants included in the MMRM model. Only those participants with data collected at baseline and at least one post-baseline until Week 12 are reported.

End point type	Secondary

End point timeframe:

Baseline (Day -6 to Day 1) up to Week 12

End point values	Dupilumab 200 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: Score on a scale				
least squares mean (standard error)	1.14 (± 0.151)	0.97 (± 0.152)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 12 in Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep-Related Impairment 8a Scale

End point title	Change From Baseline to Week 12 in Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep-Related Impairment 8a Scale

End point description:

PROMIS sleep-related impairment eight-term 8a scale questionnaire focuses on self-reported perceptions of alertness,sleepiness,tiredness during usual waking hours,perceived functional impairments during wakefulness associated with sleep problems or impaired alertness.It assesses sleep-related impairment over past 7 days.Each item rated on 5-point scale(1=not at all;2=a little bit;3=somewhat;4=quite a bit;5=very much)with a raw score=8 to 40;higher scores=greater sleep impairment.PROMIS T-score is presented;rescales raw score into standardized score with mean:50 and standard deviation:10.Possible range for T-score=30 to 80;higher scores=greater severity of sleep

impairment.Baseline=last available valid(non-missing)value upto and including day of first dose of investigational medicinal product(IMP).ITT analysis set=all randomized participants included in MMRM model. Only those participants with data collected at baseline and at least one post-baseline until Week 12 are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) up to Week 12

End point values	Dupilumab 200 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	96		
Units: T-score				
least squares mean (standard error)	-7.20 (± 0.624)	-6.51 (± 0.626)		

Statistical analyses

Statistical analysis title	Dupilumab 200 mg Q2W versus Placebo

Statistical analysis description:

The MMRM model included study intervention, age, BMI, region (Eastern Europe, ROW), ICS dose level at baseline (ICS dose level medium, ICS dose level high), visit (up to Week 12), study intervention-by-visit interaction, baseline ACQ-5, baseline PROMIS total score and baseline-by-visit interaction as covariates.

Comparison groups	Dupilumab 200 mg Q2W v Placebo
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.422 [3]
Method	MMRM
Parameter estimate	Least square mean difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	1.01
Variability estimate	Standard error of the mean
Dispersion value	0.865

Notes:

[3] - A hierarchical testing procedure was used to control type I error and handle primary and first 2 secondary endpoints (reported sequentially) analyses at a 2-sided significance level of 0.05.

Secondary: Change From Baseline to Week 12 in Wake After Sleep Onset (WASO) (Sleep Diary)

End point title	Change From Baseline to Week 12 in Wake After Sleep Onset (WASO) (Sleep Diary)

End point description:

Sleep Diary is used to assess adult sleep disturbance due to asthma. WASO was calculated as time awake after initial sleep onset but before the final awakening. Baseline was calculated by averaging the

data collected/recorded from Day -6 to Day 1. The ITT analysis set consisted of all randomized participants included in the MMRM model. Only those participants with data collected at baseline and at least one post-baseline until Week 12 are reported.

End point type	Secondary

End point timeframe:

Baseline (Day -6 to Day 1) up to Week 12

End point values	Dupilumab 200 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: Minutes				
least squares mean (standard error)	-30.58 (± 3.945)	-26.48 (± 3.962)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 12 in WASO Based on Actigraphy Data

End point title	Change From Baseline to Week 12 in WASO Based on Actigraphy Data

End point description:

Wrist actigraphy is a procedure that records and integrates occurrence and degree of limb movement activity over an extended recording period. The signals generated by wrist movement are sensed by a tiny microcomputer contained within watch and translated into activity counts. Algorithms have been developed to translate these activity counts or "epochs" (or "periods") that correspond to times when a person is likely to be asleep or wake. Actigraph was worn on wrist of non-dominant hand to provide estimates of duration, timing and patterns of sleep in study participants. After watch data were scored by selected expert center, a number of summary measurements were generated, including WASO. Baseline was calculated by averaging the data collected/recorded from Day -6 to Day 1. The ITT analysis set consisted of all randomized participants included in the MMRM model. Only those participants with data collected at baseline and at least one post-baseline until Week 12 are reported.

End point type	Secondary

End point timeframe:

Baseline (Day -6 to Day 1) up to Week 12

End point values	Dupilumab 200 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	92		
Units: Minutes				
least squares mean (standard error)	-1.64 (± 2.286)	-1.17 (± 2.215)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 12 in Asthma Daytime Symptom Diary (ADSD)

End point title	Change From Baseline to Week 12 in Asthma Daytime Symptom Diary (ADSD)

End point description:

ADSD is a PRO measure designed to measure asthma symptoms in adult and adolescent (12 years of age and older) participants diagnosed with mild to severe asthma. ADSD assesses asthma severity based on participant self-report of asthma core symptoms, i.e., difficulty breathing, wheezing, shortness of breath, chest tightness, chest pain, and cough. Participants were asked to complete the ADSD every night before they go to bed, thinking about their asthma symptoms today, from when they got up this morning until now. ADSD is composed of 6 items rated using an 11-point NRS that ranges from 0 = None to 10 = as bad as you can imagine. Total score was calculated by averaging all 6 items and therefore the score ranged from 0 to 10. Higher scores=worse outcomes. Baseline=average of the data from Day -7 to Day -1. ITT analysis set=all randomized participants included in MMRM model. Only those participants with data collected at baseline and at least one post-baseline until Week 12 are reported.

End point type	Secondary

End point timeframe:

Baseline (Day -7 to Day -1) up to Week 12

End point values	Dupilumab 200 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	70		
Units: Score on a scale				
least squares mean (standard error)	-1.78 (± 0.192)	-1.56 (± 0.193)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 12 in Asthma Nighttime Symptom Diary (ANSD)

End point title	Change From Baseline to Week 12 in Asthma Nighttime Symptom Diary (ANSD)

End point description:

ANSD is a PRO measure designed to measure asthma symptoms in adult and adolescent (12 years of age and older) participants diagnosed with mild to severe asthma. ANSD assesses asthma severity based on participant self-report of asthma core symptoms, i.e., difficulty breathing, wheezing, shortness of breath, chest tightness, chest pain, and cough. Participants were asked to complete the ANSD when getting up, thinking about their asthma symptoms last night from when they went to bed until now. ANSD is composed of 6 items rated using an 11-point NRS that ranges from 0 = None to 10 = as bad as you can imagine. Higher scores indicated worse outcomes. Total score was calculated by averaging all 6 items and therefore the score ranged from 0 to 10. Baseline=average of the data from Day -6 to Day -1. ITT analysis set=all randomized participants included in the MMRM model. Only those participants with data collected at baseline and at least one post-baseline until Week 12 are reported.

End point type	Secondary

End point timeframe:

Baseline (Day -6 to Day -1) up to Week 12

End point values	Dupilumab 200 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	85		
Units: Score on a scale				
least squares mean (standard error)	-1.58 (± 0.178)	-1.36 (± 0.178)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 12 in Pre-Bronchodilator Forced Expiratory Volume (pre-BD FEV1)

End point title	Change From Baseline to Week 12 in Pre-Bronchodilator Forced Expiratory Volume (pre-BD FEV1)

End point description:

FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer. For pre-BD FEV1, spirometry was performed before IMP administration and after withholding the standard of care asthma treatment which was verified before performing the measurements. 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 all randomized participants included in the MMRM model. Only those participants with data collected at baseline and at least one post-baseline until Week 12 are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) up to Week 12

End point values	Dupilumab 200 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	99		
Units: Liter				
least squares mean (standard error)	0.49 (± 0.044)	0.27 (± 0.047)		

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 Treatment-

Emergent Adverse Events Of Special Interest (TEAESIs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs), Treatment-Emergent Serious Adverse Events (TESAEs), and Treatment-Emergent Adverse Events Of Special Interest (TEAESIs)

End point description:

AE:untoward medical occurrence in participant or 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 to last administration of IMP+98 days or until participant switches to commercialized dupilumab or other biologics. SAE: untoward medical occurrence 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 a congenital anomaly/birth defect,was a medically important event. AESI:AE scientific and medical concern specific to Sponsor's product or program, for which ongoing monitoring and immediate notification by Investigator to Sponsor is required. Safety analysis set=all randomized participants who took at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

From first dose of study drug (Day 1) up to 12 weeks after last dose of study drug, approximately 30 weeks

End point values	Dupilumab 200 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	101		
Units: Participants				
Any TEAE	48	46		
Any TESAE	3	3		
Any TEAESI	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Potentially Clinically Significant Abnormalities (PCSA) in Vital Signs

End point title	Number of Participants With Potentially Clinically Significant Abnormalities (PCSA) in Vital Signs

End point description:

Vital signs included systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) and weight. Criteria for PCSA: SBP: ≤95 millimeters of mercury (mmHg) and decrease from baseline ≥20 mmHg, ≥160 mmHg and increase from baseline ≥20 mmHg; DBP: ≤45 mmHg and decrease from baseline ≥10 mmHg, ≥110 mmHg and increase from baseline ≥10 mmHg; HR: ≤50 beats per minute (bpm) and decrease from baseline ≥20 bpm, ≥120 bpm and increase from baseline ≥20 bpm; Weight: ≥5% increase from baseline, ≥5% decrease from baseline. Safety analysis set included all randomized participants who took at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

From first dose of study drug (Day 1) up to 12 weeks after last dose of study drug, approximately 30 weeks

End point values	Dupilumab 200 mg Q2W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	101		
Units: Participants				
SBP:≤95 mmHg, decrease from baseline ≥20 mmHg	0	1		
SBP: ≥160 mmHg and increase from baseline ≥20 mmHg	1	2		
DBP:≤45 mmHg and decrease from baseline ≥10 mmHg	0	0		
DBP: ≥110 mmHg and increase from baseline ≥10mmHg	0	0		
HR: ≤50 bpm and decrease from baseline ≥20 bpm	0	0		
HR: ≥120 bpm and increase from baseline ≥20 bpm	0	0		
Weight: ≥5% increase from baseline	3	6		
Weight: ≥5% decrease from baseline	5	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAEs were collected from first dose of study drug (Day 1) up to 12 weeks after last dose of study drug, approximately 30 weeks. All-cause mortality (deaths) were collected from first dose of study drug (Day 1) up to end of study, approximately 39 months.

Adverse event reporting additional description:

Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received an initial loading dose of matching placebo (2 injections of placebo) SC on Day 1, followed by 1 injection of placebo Q2W for 12 weeks.

Reporting group title	Dupilumab 200 mg Q2W

Reporting group description:

Participants received a loading dose of 400 mg of dupilumab (2 injections × 200 mg) SC on Day 1, followed by 200mg Q2W for 12 weeks.

Serious adverse events	Placebo	Dupilumab 200 mg Q2W	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 101 (2.97%)	3 / 100 (3.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia Fracture			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis Acute			

subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression Suicidal			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide Attempt			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urosepsis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19 Pneumonia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (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 200 mg Q2W	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 101 (17.82%)	13 / 100 (13.00%)	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	14 / 101 (13.86%)	9 / 100 (9.00%)	
occurrences (all)	17	11	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 101 (6.93%)	4 / 100 (4.00%)	
occurrences (all)	7	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 September 2020	Decision to perform the polysomnography (PSG) assessments in the substudy at participant’s home using Type II PSG devices instead of on-site overnight assessments as initially planned. This decision was taken considering that the participants' safety was of outmost importance in the context of the Coronavirus Disease-2019 (COVID-19) pandemic with unpredictable evolution. In addition, an updated version of the sleep disturbance questionnaire had been implemented based on participant feedback to improve its understanding. Further updates had been done in AESI listing and Benefit/Risk assessment chapter based on the new SAR231893 Investigator's Brochure dated 19-Jun-2020.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported