Clinical trial results:
A Randomized Double-blind Placebo Controlled Study Evaluating the Effect of Dupilumab on Sleep in Adult Patients With Moderate to Severe Atopic Dermatitis

Summary

EudraCT number	2018-004705-26
Trial protocol	GB DE FR IT
Global end of trial date	06 October 2021

Results information

Result version number	v1 (current)
This version publication date	21 October 2022
First version publication date	21 October 2022

Trial information

Trial identification

Sponsor protocol code	LPS15497

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04033367
WHO universal trial number (UTN)	U1111-1223-4147

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin Cedex, France, 91385
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 October 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of dupilumab on sleep quality in adult subjects with moderate to severe atopic dermatitis (AD).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 August 2019
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	Spain: 16
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 24
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	Australia: 38
Country: Number of subjects enrolled	Israel: 10
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	United Arab Emirates: 10
Country: Number of subjects enrolled	United States: 43
Worldwide total number of subjects	188
EEA total number of subjects	75

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)	174
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 46 centres in 10 countries. A total of 267 subjects were screened between 22 August 2019 and 13 April 2021, of which 188 subjects were enrolled and randomised. A total of 79 subjects failed screening mainly due to not meeting eligibility criteria.

Pre-assignment

Screening details:

Subjects were randomly assigned to receive either dupilumab or placebo in a 2:1 ratio via interactive voice response system.

Period 1

Period 1 title	Double-blind Period (Up to Week 12)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Dupilumab

Arm description:

Subjects received dupilumab 600 milligrams (mg) (loading dose) injection subcutaneously (SC) on Day 1 followed by dupilumab 300 mg injection SC every 2 weeks (q2w) up to Week 10 in the double-blind (DB) period of 12 weeks.

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

Dosage and administration details:

Subjects received dupilumab 600 mg (loading dose) injection SC on Day 1 followed by dupilumab 300 mg injection SC q2w up to Week 10.

Arm title	Placebo

Arm description:

Subjects received placebo matching to dupilumab injection SC on day 1 then followed by placebo injection SC q2w up to Week 10 in the DB period of 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received placebo matching to dupilumab injection SC on day 1 then followed by placebo injection SC q2w up to Week 10.

Number of subjects in period 1	Dupilumab	Placebo
Started	127	61
Completed	122	60
Not completed	5	1
Adverse event	1	1
Withdrawal by Subject	4	-

Period 2

Period 2 title	OLE Period (Week 12 to Week 24)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dupilumab/Dupilumab

Arm description:

Subjects previously treated with dupilumab during the DB period, entered in the OLE period and continued to receive dupilumab 300 mg injection SC q2w from Week 12 up to Week 22 in the OLE period.

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

Dosage and administration details:

Subjects received dupilumab 300 mg injection SC q2w from Week 12 to Week 22.

Arm title	Placebo/Dupilumab

Arm description:

Subjects previously treated with placebo during the DB period, entered in the OLE period and received dupilumab 600 mg (loading dose) at Week 12 followed by dupilumab 300 mg injection SC q2w up to Week 22 in the OLE period.

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

Dosage and administration details:

Subjects received dupilumab 600 mg (loading dose) at Week 12 and then dupilumab 300 mg injection SC q2w up to Week 22.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection

Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received placebo matched to dupilumab q2w during the DB period.

Number of subjects in period 2	Dupilumab/Dupilumab	Placebo/Dupilumab
Started	122	60
Completed	117	59
Not completed	5	1
Withdrawal by Subject	4	1
Other-Unspecified	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Dupilumab
Reporting group description:	
Subjects received dupilumab 600 milligrams (mg) (loading dose) injection subcutaneously (SC) on Day 1 followed by dupilumab 300 mg injection SC every 2 weeks (q2w) up to Week 10 in the double-blind (DB) period of 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matching to dupilumab injection SC on day 1 then followed by placebo injection SC q2w up to Week 10 in the DB period of 12 weeks.	

Reporting group values	Dupilumab	Placebo	Total
Number of subjects	127	61	188
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	36.2	34.5	
standard deviation	± 14.68	± 15.36	-
Gender categorical			
Units: Subjects			
Female	66	31	97
Male	61	30	91
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	13	11	24
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	6	1	7
White	103	46	149
More than one race	2	0	2
Unknown or Not Reported	3	3	6

End points

End points reporting groups

Reporting group title	Dupilumab
Reporting group description:	
Subjects received dupilumab 600 milligrams (mg) (loading dose) injection subcutaneously (SC) on Day 1 followed by dupilumab 300 mg injection SC every 2 weeks (q2w) up to Week 10 in the double-blind (DB) period of 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matching to dupilumab injection SC on day 1 then followed by placebo injection SC q2w up to Week 10 in the DB period of 12 weeks.	
Reporting group title	Dupilumab/Dupilumab
Reporting group description:	
Subjects previously treated with dupilumab during the DB period, entered in the OLE period and continued to receive dupilumab 300 mg injection SC q2w from Week 12 up to Week 22 in the OLE period.	
Reporting group title	Placebo/Dupilumab
Reporting group description:	
Subjects previously treated with placebo during the DB period, entered in the OLE period and received dupilumab 600 mg (loading dose) at Week 12 followed by dupilumab 300 mg injection SC q2w up to Week 22 in the OLE period.	

Primary: DB Period: Percent Change From Baseline in Sleep Quality Numerical Rating Scale (NRS) at Week 12

End point title	DB Period: Percent Change From Baseline in Sleep Quality Numerical Rating Scale (NRS) at Week 12
End point description:	
Sleep quality NRS was used to assess the quality of the subject's previous night's sleep. It was collected on an 11-point scale ranged from 0 (worst possible sleep) to 10 (best possible sleep), where higher score indicated better outcome. Percent change from Baseline in sleep quality NRS at Week 12 was reported in this endpoint. Analysis was performed on modified intent-to-treat (mITT) analysis set which included all randomised subjects with a treatment kit number allocated and recorded in the interactive response technology database, regardless of whether the treatment kit was used or not, who had a Baseline and at least one post-baseline measurement. Here, 'number of subjects analysed' = subjects with available data for this endpoint.	
End point type	Primary
End point timeframe:	
Baseline, Week 12	

End point values	Dupilumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	60		
Units: percent change				
arithmetic mean (standard deviation)	-47.71 (± 27.240)	-32.98 (± 29.536)		

Statistical analyses

Statistical analysis title	Dupilumab versus Placebo

Statistical analysis description:

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 primary endpoint was statistically significant at two-sided 0.05 level.

Comparison groups	Placebo v Dupilumab
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Mixed models analysis
Parameter estimate	Least square mean difference
Point estimate	-15.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.13
upper limit	-6.9

Notes:

[1] - Threshold of significance at 0.05.

Secondary: DB Period: Percent Change From Baseline in Peak Pruritus NRS at Week 12

End point title	DB Period: Percent Change From Baseline in Peak Pruritus NRS at Week 12

End point description:

Peak Pruritus NRS was an assessment tool that was used by subjects to report the intensity of their pruritus (itch) during a 24-hour recall period. Subjects were asked the following question: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?". Subjects answered the question at the specified time point (for the last 24 hours) on the scale of 0 (no itch) to 10 (worst itch imaginable), where higher scores indicated greater severity. Analysis was performed on mITT set. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Dupilumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	48		
Units: percent change				
arithmetic mean (standard deviation)	-52.45 (± 30.614)	-23.29 (± 30.075)		

Statistical analyses

Statistical analysis title	Dupilumab versus Placebo

Statistical analysis description:

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 endpoints was statistically significant at two-sided 0.05 level.

Comparison groups	Dupilumab v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	Mixed models analysis
Parameter estimate	Least square mean difference
Point estimate	-27.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.96
upper limit	-17.78

Notes:

[2] - Threshold of significance at 0.05.

Secondary: DB Period: Change From Baseline in SCORing Atopic Dermatitis (SCORAD) Total Score at Week 12

End point title	DB Period: Change From Baseline in SCORing Atopic Dermatitis (SCORAD) Total Score at Week 12

End point description:

SCORAD a validated scoring index for AD, consists of 3 components i.e., A =extent or affected body surface area (BSA) assessed as percentage of each defined body area and reported as sum of all areas, with maximum score of 100%. B=severity of 6 specific symptoms of AD (redness, swelling, oozing/crusting, excoriation, skin thickening/lichenification, dryness) assessed using following scale: none(0), mild(1), moderate(2), or severe(3)(for maximum of 18 total points) and C=subjective assessment of itch and sleep loss on VAS where 0 = no itching or no trouble sleeping and 10 = unbearable itching or a lot of trouble sleeping with maximum score of 20 . These 3 aspects: extent (A: 0-100), severity (B: 0-18), and subjective symptoms (C: 0-20) combined using A/5 + 7*B/2+ C to give maximum possible total score of 103, where 0 = no disease and 103 = severe disease. Higher values of SCORAD = worse outcome. mITT set. 'Number of subjects analyzed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Dupilumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	48		
Units: score on a scale				
arithmetic mean (standard deviation)	-37.78 (± 17.743)	-20.55 (± 17.944)		

Statistical analyses

Statistical analysis title	Dupilumab versus Placebo

Statistical analysis description:

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 level.

Comparison groups	Dupilumab v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [3]
Method	Mixed models analysis
Parameter estimate	Least square mean difference
Point estimate	-15.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.56
upper limit	-9.56

Notes:

[3] - Threshold of significance at 0.05.

Secondary: DB Period: Change From Baseline in SCORAD Sleep Visual Analog Scale (VAS) at Week 12

End point title	DB Period: Change From Baseline in SCORAD Sleep Visual Analog Scale (VAS) at Week 12

End point description:

SCORAD is a validated scoring index for AD, which combines extent (A, 0-100), severity (B, 0-18), and subjective symptoms (C, 0-20) based on itch and sleeplessness, each scored (0-10). The SCORAD for an individual was calculated by the formula: A/5 + 7B/2 + C (can range from 0 to 103). Subjective symptoms (i.e., itch and sleeplessness/sleep loss) were each scored by the subject using a VAS ranging from 0 to 10, where “0” is no itch (or no sleep loss) and “10” is the worst imaginable itch (or sleeplessness). Change from Baseline in SCORAD sleeplessness/sleep loss VAS score is reported in this endpoint. Analysis was performed on mITT set. Here, 'number of subjets analyzed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Dupilumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	47		
Units: score on a scale				
arithmetic mean (standard deviation)	-4.85 (± 2.953)	-2.31 (± 3.024)		

Statistical analyses

Statistical analysis title	Dupilumab versus Placebo

Statistical analysis description:

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 level.

Comparison groups	Dupilumab v Placebo
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [4]
Method	Mixed models analysis
Parameter estimate	Least square mean difference
Point estimate	-2.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.97
upper limit	-1.18

Notes:

[4] - Threshold of significance at 0.05.

Secondary: DB Period: Change From Baseline in Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Related Impairment Short Form 8a (SF8a) Total T-Score at Week 12

End point title	DB Period: Change From Baseline in Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Related Impairment Short Form 8a (SF8a) Total T-Score at Week 12

End point description:

PROMIS is a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), Level 2, sleep disturbance measure. In this study, 8- item PROMIS Sleep Related Impairment SF8a that assesses the domain of sleep related impairment in the past 7 days in individuals aged 18 and older, was used. Each item asks the subject to rate the severity of the subject's sleep related impairment during the past 7 days (at each specified visit) on a 5-point scale (1 = not at all; 2 = a little bit; 3 = somewhat; 4 = quite a bit; and 5 = very much) with raw score ranging from 8 to 40; higher scores indicating greater severity of sleep impairment. PROMIS T-score rescales the raw score into a standardised score with a mean of 50 and a standard deviation of 10. Possible range for T-score is 30 to 80, with higher scores indicating greater severity of sleep impairment. Analysis was performed on mITT set. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Dupilumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	54		
Units: T-score				
arithmetic mean (standard deviation)	-11.42 (± 6.710)	-7.77 (± 7.240)		

Statistical analyses

Statistical analysis title	Dupilumab versus Placebo

Statistical analysis description:

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 level.

Comparison groups	Dupilumab v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [5]
Method	Mixed models analysis
Parameter estimate	Least square mean difference
Point estimate	-3.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.68
upper limit	-1.53

Notes:

[5] - Threshold of significance at 0.05.

Secondary: DB Period: Change From Baseline in Total Sleep Time (TST) at Week 12

End point title	DB Period: Change From Baseline in Total Sleep Time (TST) at Week 12

End point description:

A sleep diary was designed to gather information about subject's daily sleep pattern. It measured night-time sleep assessments. TST (in minutes) was calculated using the formula: Time of waking up for the day minus time of falling sleep minus Wake After Sleep Onset (WASO), where WASO = time awake after initial sleep onset but before the final awakening for the day. Data for WASO was collected from Question 3 of the Sleep Diary: "Considering all the times you woke up last night, how much time were you awake in total?". Baseline and Post-baseline weekly average data were calculated based on the mean of the data over the 7 days prior to and including the day at the Baseline or at the end of the corresponding week. In this endpoint, change from Baseline in TST at Week 12 is reported. Analysis was performed on mITT set. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Dupilumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	47		
Units: minutes				
arithmetic mean (standard deviation)	9.00 (± 70.987)	-6.36 (± 55.620)		

Statistical analyses

Statistical analysis title	Dupilumab versus Placebo

Statistical analysis description:

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 level.

Comparison groups	Dupilumab v Placebo
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.297 [6]
Method	Mixed models analysis
Parameter estimate	Least square mean difference
Point estimate	9.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.86
upper limit	28.79

Notes:

[6] - Threshold of significance at 0.05.

Secondary: DB Period: Change From Baseline in Weekly Average Sleep Efficiency (SE) at Week 12

End point title	DB Period: Change From Baseline in Weekly Average Sleep Efficiency (SE) at Week 12

End point description:

A sleep diary was designed to gather information about subject's daily sleep pattern. It measured night-time sleep assessments. SE was calculated using the formula: (TST divided by [Time of waking up for the day − Time of trying to fall sleep]) multiplied by 100 percent (%). TST (in minutes) was calculated using the formula: Time of waking up for the day minus time of falling sleep minus Wake After Sleep Onset (WASO), where WASO = time awake after initial sleep onset but before the final awakening for the day. Baseline and Post-baseline weekly average data were calculated based on the mean of the data over the 7 days prior to and including the day at the Baseline or at the end of the corresponding week. In this endpoint, change from Baseline in SE at Week 12 is reported. Analysis was performed on mITT set. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Dupilumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	47		
Units: percentage of time in bed spent asleep				
arithmetic mean (standard deviation)	1.81 (± 6.593)	1.53 (± 6.018)		

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Change From Baseline in Weekly Average Wake After Sleep Onset (WASO) at Week 12

End point title	DB Period: Change From Baseline in Weekly Average Wake After Sleep Onset (WASO) at Week 12

End point description:

A sleep diary was designed to gather information about subject's daily sleep pattern. It measured night-time sleep assessments. WASO = time awake (in minutes) after initial sleep onset but before the final awakening for the day. Data for WASO was collected from Question 3 of the Sleep Diary: "Considering all the times you woke up last night, how much time were you awake in total?". Baseline and Post-baseline weekly average data were calculated based on the mean of the data over the 7 days prior to and including the day at the Baseline or at the end of the corresponding week. In this endpoint, change from Baseline in WASO at Week 12 is reported. Analysis was performed on mITT set. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Dupilumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	47		
Units: minutes				
arithmetic mean (standard deviation)	-6.79 (± 22.786)	-9.19 (± 24.661)		

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Change From Baseline in Weekly Average Sleep Onset Latency (SOL) at Week 12

End point title	DB Period: Change From Baseline in Weekly Average Sleep Onset Latency (SOL) at Week 12

End point description:

A sleep diary was designed to gather information about subject's daily sleep pattern. It measured night-time sleep assessments. SOL (in minutes) was calculated using the formula: Time of falling sleep – Time of trying to fall sleep. Baseline and Post-baseline weekly average data were calculated based on the mean of the data over the 7 days prior to and including the day at the Baseline or at the end of the corresponding week. In this endpoint, change from Baseline in SOL at Week 12 is reported. Analysis was performed on mITT set. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Dupilumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	47		
Units: minutes				
arithmetic mean (standard deviation)	-1.44 (± 19.983)	-3.37 (± 21.477)		

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percentage of Subjects With Eczema Area Severity Index-50 (EASI-50) (Greater Than or Equal to [>=] 50% Improvement From Baseline) at Week 12

End point title	DB Period: Percentage of Subjects With Eczema Area Severity Index-50 (EASI-50) (Greater Than or Equal to [>=] 50% Improvement From Baseline) at Week 12

End point description:

EASI evaluates severity of subjects with AD (excluded scalp, palms, soles) based on severity of AD clinical signs and % BSA affected. Severity of clinical signs of AD (erythema, induration/papulation, excoriation and lichenification) scored separately for each of 4 body regions (head and neck, upper limbs, trunk [including axillae and groin] and lower limbs [including buttocks]) on 4-point scale: 0= absent; 1= mild; 2= moderate; 3= severe. EASI area score was based upon % BSA with AD in each body region: 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), and 6 (90% to 100%). Total EASI score ranged from 0.0 to 72.0, higher scores = greater severity of AD. Percentage of subjects with EASI-50 (>=50% improvement from Baseline) at Week 12 is reported in this endpoint. Analysis was performed on mITT set. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Week 12

End point values	Dupilumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	48		
Units: percentage of subjects				
number (not applicable)	89.0	58.3		

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Percentage of Subjects With Eczema Area Severity Index-75 (EASI-75) (>= 75% Improvement From Baseline) at Week 12

End point title	DB Period: Percentage of Subjects With Eczema Area Severity Index-75 (EASI-75) (>= 75% Improvement From Baseline) at Week 12

End point description:

EASI evaluates severity of subjects with AD (excluded scalp, palms, soles) based on severity of AD clinical signs and % BSA affected. Severity of clinical signs of AD (erythema, induration/papulation, excoriation and lichenification) scored separately for each of 4 body regions (head and neck, upper limbs, trunk [including axillae and groin] and lower limbs [including buttocks]) on 4-point scale: 0= absent; 1= mild; 2= moderate; 3= severe. EASI area score was based upon % BSA with AD in each body region: 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), and 6 (90% to 100%). Total EASI score ranged from 0.0 to 72.0, higher scores = greater severity of AD. Percentage of subjects with EASI-75 (>=75% improvement from Baseline) at Week 12 is reported in this endpoint. Analysis was performed on mITT set. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Week 12

End point values	Dupilumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	48		
Units: percentage of subjects				
number (not applicable)	60.6	29.2		

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Change From Baseline in Patient Oriented Eczema Measure (POEM) Total Score at Week 12

End point title	DB Period: Change From Baseline in Patient Oriented Eczema Measure (POEM) Total Score at Week 12

End point description:

The POEM is a 7-item, validated questionnaire used in clinical practice and clinical trials to assess disease symptoms in children and adults with AD. The format is subject response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on symptom frequency during the past week (i.e., 0 = 'no days', 1 = '1 to 2 days', 2 = '3 to 4 days', 3 = '5 to 6' days, and 4 = 'every day'). The sum of the 7 items gives the total POEM score of 0 (absent disease) to 28 (severe disease). Higher scores indicated more severe disease and poor quality of life. Analysis was performed on mITT set. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Dupilumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	39		
Units: score on a scale				
arithmetic mean (standard deviation)	-13.63 (± 7.496)	-4.44 (± 6.824)		

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Change From Baseline in Dermatology Life Quality Index (DLQI) Total Score at Week 12

End point title	DB Period: Change From Baseline in Dermatology Life Quality Index (DLQI) Total Score at Week 12

End point description:

DLQI was a 10-item questionnaire that measures the impact of skin disease. Each question was evaluated on a 4-point scale ranged 0 to 3 where, 0 = not at all, 1= a little, 2= a lot, 3= very much, where higher scores indicated more impact on quality of life. Scores from all 10 questions were added up to give DLQI total score range from 0 (not at all) to 30 (very much). Higher scores indicated more impact on quality of life of subjects. Analysis was performed on mITT set. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Dupilumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	39		
Units: score on a scale				
arithmetic mean (standard deviation)	-11.82 (± 6.503)	-7.54 (± 6.801)		

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point title	DB Period: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point description:

An Adverse Event (AE) was defined as any untoward medical occurrence in a subject who received study drug and did not necessarily have to have a causal relationship with the treatment. Serious adverse events (SAEs) were defined as any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, was a medically important event. TEAEs were defined as AEs that developed, worsened or became serious during the TEAE period (from the first investigational medicinal product [IMP] administration to the last IMP administration + 14 days) in DB period. Analysis was performed on safety analysis set (SAS) which included all randomised subjects who received at least 1 dose or partial dose of the IMP, analysed

according to the treatment actually received.

End point type	Secondary

End point timeframe:

Baseline up to up to 14 days after last IMP administration (i.e., up to Week 12)

End point values	Dupilumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	61		
Units: subjects				
Any TEAEs	72	41		
Any TESAEs	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Entire Study Duration: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Entire Study Duration: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point description:

An AE was defined as any untoward medical occurrence in a subject who received study drug and did not necessarily have to have a causal relationship with the treatment. SAEs were defined as any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, was a medically important event. TEAEs were defined as AEs that developed, worsened or became serious during the TEAE period (from the first IMP administration to the last IMP administration + 14 days).

End point type	Secondary

End point timeframe:

Baseline up to up to 14 days after last IMP administration (i.e., up to Week 24)

End point values	Dupilumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	61		
Units: subjects				
Any TEAEs	89	46		
Any TESAEs	3	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first IMP administration up to Week 12 (for DB period arms) and from first IMP administration in OLE period up to Week 24 (for OLE period arms)

Adverse event reporting additional description:

Reported AEs were TEAEs that occurred/worsened in grade or became serious during TEAE period (defined as the time from the first IMP administration in DB period to the last IMP administration in OLE period + 14 days). Analysis was performed on SAS.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	DB period: Placebo

Reporting group description:

Subjects received placebo matching to dupilumab injection SC on day 1 then followed by placebo injection SC q2w up to Week 10 in the DB period of 12 weeks.

Reporting group title	DB period: Dupilumab

Reporting group description:

Subjects received dupilumab 600 mg (loading dose) injection SC on Day 1 followed by dupilumab 300 mg injection SC q2w up to Week 10 in the DB period of 12 weeks.

Reporting group title	OLE period: Placebo/Dupilumab

Reporting group description:

Subjects received placebo matching to dupilumab injection SC on Day 1 then followed by placebo injection SC q2w up to Week 10 in the DB period of 12 weeks. After completion of DB period, subjects entered in the OLE period (Week 12 to 24) and received dupilumab 600 mg (loading dose) at Week 12 followed by dupilumab 300 mg SC q2w up to Week 22.

Reporting group title	OLE period: Dupilumab/Dupilumab

Reporting group description:

Subjects received dupilumab 600 mg (loading dose) injection SC on Day 1 followed by dupilumab 300 mg injection SC q2w up to Week 10 in the DB period of 12 weeks. After completion of DB period, subjects entered in the OLE period (Week 12 to 24) and continued to receive dupilumab 300 mg SC q2w from Week 12 up to Week 22.

Serious adverse events	DB period: Placebo	DB period: Dupilumab	OLE period: Placebo/Dupilumab
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 61 (1.64%)	2 / 127 (1.57%)	0 / 60 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder Transitional Cell Carcinoma			
subjects affected / exposed	1 / 61 (1.64%)	0 / 127 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 61 (0.00%)	0 / 127 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Fractures			
subjects affected / exposed	0 / 61 (0.00%)	0 / 127 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	0 / 61 (0.00%)	1 / 127 (0.79%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Polyarthritis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 127 (0.79%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	OLE period: Dupilumab/Dupilumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 122 (0.82%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder Transitional Cell Carcinoma			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			

subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple Fractures			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Polyarthritis			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	DB period: Placebo	DB period: Dupilumab	OLE period: Placebo/Dupilumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 61 (29.51%)	26 / 127 (20.47%)	17 / 60 (28.33%)
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	0 / 61 (0.00%)	1 / 127 (0.79%)	6 / 60 (10.00%)
occurrences (all)	0	1	6
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 61 (8.20%)	9 / 127 (7.09%)	3 / 60 (5.00%)
occurrences (all)	5	10	3
Skin and subcutaneous tissue disorders			
Dermatitis Atopic			
subjects affected / exposed	8 / 61 (13.11%)	4 / 127 (3.15%)	1 / 60 (1.67%)
occurrences (all)	10	6	1

Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 3 / 61 (4.92%) 3 3 / 61 (4.92%) 3	 12 / 127 (9.45%) 12 2 / 127 (1.57%) 2	 7 / 60 (11.67%) 7 4 / 60 (6.67%) 4

Non-serious adverse events	OLE period: Dupilumab/Dupilumab		
Total subjects affected by non-serious adverse events subjects affected / exposed	 24 / 122 (19.67%)		
Injury, poisoning and procedural complications Accidental Overdose subjects affected / exposed occurrences (all)	 15 / 122 (12.30%) 15		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 2 / 122 (1.64%) 2		
Skin and subcutaneous tissue disorders Dermatitis Atopic subjects affected / exposed occurrences (all)	 3 / 122 (2.46%) 4		
Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 3 / 122 (2.46%) 3 2 / 122 (1.64%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 April 2020	Following changes were done: • For subjects in the polysomnography (PSG) sub-study, the sleep quality NRS and the peak pruritus NRS were to be completed for 5 days prior to Baseline. Inclusion criteria was updated accordingly. • Inclusion criterion updated to reduce the period of AD diagnosis to 2 years before the screening instead of 3 years. • Inclusion criterion was updated to allow an EASI score >= 12 instead of >= 16 at screening and Baseline to enter the study. • Exclusion criterion 14 was updated to allow subjects taking sedative anxiolytic or hypnotic treatments other than melatonin within 3 months before randomisation, to be included in the study if this intake was occasional (i.e., no more than twice a week) except within 2 weeks before randomisation. • Previous scale was replaced by the one actually used in the study in the section of Appendix 9 clinician-reported outcome-EASI.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported