Clinical trial results:
A Randomized, Double-blind, Placebo-controlled, Multi-center, Parallel-group Study of Dupilumab in Patients With Chronic Inducible Cold Urticaria who Remain Symptomatic Despite the use of H1-antihistamine Treatment

Summary

EudraCT number	2020-003756-33
Trial protocol	DE
Global end of trial date	20 April 2023

Results information

Result version number	v1 (current)
This version publication date	02 November 2023
First version publication date	02 November 2023

Trial information

Trial identification

Sponsor protocol code	EFC16720

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04681729
WHO universal trial number (UTN)	U1111-1246-6913
Other trial identifiers	IND: 105379

Notes:

Sponsors

Sponsor organisation name	Sanofi Aventis Recherche & Développement
Sponsor organisation address	1 Avenue Pierre Brossolette, Chilly-Mazarin, 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)	Yes
EMA paediatric investigation plan number(s)	EMEA-001501-PIP09-21
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 May 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of dupilumab in adult and adolescent subjects with primary acquired chronic inducible cold urticaria (ColdU) who remained symptomatic despite the use of an H1-antihistamine treatment.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of adolescent and adult subjects. The parent(s) or guardian(s), as well as the adult 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. In addition to the consent form for the parent(s)/guardian(s), an assent form in age-appropriate language was provided and explained to the subject. Repeated invasive procedures were minimised. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimise distress and discomfort. 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:

Long acting non-sedating H1-antihistamine as standard of care background and rescue therapy at their recommended dose during the study were: Cetirizine 10 milligrams (mg) once daily (QD), Levocetirizine dihydrochloride 5 mg QD, Ebastine 10 mg QD, Fexofenadine 60 mg twice per day or 180 mg QD, Loratadine 10 mg QD, Desloratadine 5 mg QD, Bilastine 20 mg QD, Rupatadine 10 mg QD and other H1-antihistamine.

Evidence for comparator: -

Actual start date of recruitment	10 December 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: 20
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Japan: 10
Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	82
EEA total number of subjects	18

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)	8
Adults (18-64 years)	71
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 32 active sites in 5 countries. A total of 123 subjects were screened between 10 December 2020 and 22 June 2022, of which 41 were screen failures. Screen failures were mainly due to not meeting eligibility criteria.

Pre-assignment

Screening details:

A total of 82 subjects were randomised in 1:1 ratio to receive the study treatment with dupilumab or placebo. Randomisation was stratified by age (adults versus adolescents with body weight greater than [>=] 60 kilograms [kg] or >=30 kg and less than [<] 60 kg), country and background H1-antihistamine regular/daily use (Yes/No).

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, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects based on their BW >=60 kg or BW >=30 kg and <60 kg received loading dose of placebo (matched to dupilumab 600 mg or 400 mg) subcutaneous (SC) injection on Day 1, respectively, followed by placebo (matched to dupilumab 300 mg or 200 mg) SC injection every 2 weeks (q2w) up to Week 22 along with their established standard of care background therapy with a long-acting non-sedating H1-antihistamine.

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:

Based on BW (>=60 kg or >=30 kg and <60 kg), placebo matched to dupilumab loading dose (600 mg or 400 mg) SC injection on Day 1, respectively, followed by placebo matched to dupilumab (300 mg or 200 mg) SC injection q2w up to Week 22.

Arm title	Dupilumab

Arm description:

Subjects based on their BW >=60 kg or >=30 kg and <60 kg received loading dose of dupilumab 600 mg or 400 mg SC injection on Day 1, respectively, followed by dupilumab 300 mg or 200 mg SC injection q2w up to Week 22 along with their established standard of care background therapy with a long-acting non-sedating H1-antihistamine.

Arm type	Experimental
Investigational medicinal product name	Dupilumab
Investigational medicinal product code	SAR231893/REGN668
Other name	Dupixent®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Based on BW (>=60 kg or >=30 kg and <60 kg), dupilumab loading dose (600 mg [2 injections of 300 mg] or 400 mg [2 injections of 200 mg]) SC injection on Day 1, respectively, followed by dupilumab

(300 mg or 200 mg) SC injection q2w up to Week 22.

Number of subjects in period 1	Placebo	Dupilumab
Started	40	42
Completed	30	31
Not completed	10	11
Lack of efficacy	2	2
Withdrawal by subject	8	9

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects based on their BW >=60 kg or BW >=30 kg and <60 kg received loading dose of placebo (matched to dupilumab 600 mg or 400 mg) subcutaneous (SC) injection on Day 1, respectively, followed by placebo (matched to dupilumab 300 mg or 200 mg) SC injection every 2 weeks (q2w) up to Week 22 along with their established standard of care background therapy with a long-acting non-sedating H1-antihistamine.	
Reporting group title	Dupilumab
Reporting group description:	
Subjects based on their BW >=60 kg or >=30 kg and <60 kg received loading dose of dupilumab 600 mg or 400 mg SC injection on Day 1, respectively, followed by dupilumab 300 mg or 200 mg SC injection q2w up to Week 22 along with their established standard of care background therapy with a long-acting non-sedating H1-antihistamine.	

Reporting group values	Placebo	Dupilumab	Total
Number of subjects	40	42	82
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	37.9	33.0	
standard deviation	± 16.3	± 13.1	-
Gender categorical Units: Subjects			
Female	30	33	63
Male	10	9	19
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	4	6	10
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	35	35	70
More than one race	0	1	1
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects based on their BW >=60 kg or BW >=30 kg and <60 kg received loading dose of placebo (matched to dupilumab 600 mg or 400 mg) subcutaneous (SC) injection on Day 1, respectively, followed by placebo (matched to dupilumab 300 mg or 200 mg) SC injection every 2 weeks (q2w) up to Week 22 along with their established standard of care background therapy with a long-acting non-sedating H1-antihistamine.

Reporting group title	Dupilumab

Reporting group description:

Subjects based on their BW >=60 kg or >=30 kg and <60 kg received loading dose of dupilumab 600 mg or 400 mg SC injection on Day 1, respectively, followed by dupilumab 300 mg or 200 mg SC injection q2w up to Week 22 along with their established standard of care background therapy with a long-acting non-sedating H1-antihistamine.

Subject analysis set title	Dupilumab
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects based on their BW >= 60 kg or >=30 kg and < 60 kg received loading dose of dupilumab 600 mg or 400 mg SC injection on Day 1, respectively, followed by dupilumab 300 mg or 200 mg SC injection q2w up to Week 22 along with their established standard of care background therapy with a long-acting non-sedating H1-antihistamine.

Primary: Percentage of Subjects With Negative Ice Cube Provocation Test at Week 24

End point title	Percentage of Subjects With Negative Ice Cube Provocation Test at Week 24

End point description:

The ice cube provocation test is the most frequently used provocation method for cold urticaria (ColdU). A negative ice cube provocation test was defined as the absence of confluent hives/wheal at the entire skin site of exposure after ice cube provocation test. Ice cube was applied on forearm skin for 5 minutes. Provocation test reading time was 10 minutes after removal of ice cube. Analysis was performed on intent-to-treat (ITT) population which included all randomised subjects who had been allocated to a randomised intervention by Interactive response technology (IRT) regardless of whether the treatment kit was used or not and were analysed according to the intervention group allocated by randomisation. Percentage of subjects with negative ice cube provocation test at Week 24 are reported in this endpoint.

End point type	Primary

End point timeframe:

Week 24

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	42		
Units: percentage of subjects				
number (not applicable)	37.5	40.5		

Statistical analyses

Statistical analysis title	Dupilumab versus Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control the family-wise type-I error. Testing was then performed sequentially in order the endpoints were reported and continued when primary endpoint was statistically significant at two-sided 0.01.

Comparison groups	Placebo v Dupilumab
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9492 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	2.56

Notes:

[1] - Cochran-Mantel-Haenszel test was performed on the association between the ice cube provocation test result and intervention group, stratified by region and background H1-antihistamine regular/daily use (Yes or No). Threshold of significance at 0.01.

Secondary: Change From Baseline in Urticaria Control Test (UCT) Scale Scores at Week 24

End point title	Change From Baseline in Urticaria Control Test (UCT) Scale Scores at Week 24

End point description:

UCT is validated patient reported outcome (PRO) questionnaire used for assessing urticaria control. UCT has been developed and validated with subjects with Chronic Spontaneous Urticaria (CSU) and Chronic inducible urticaria (CIndU). It comprised of 4 items: severity of physical symptoms of urticaria (itch, hives and/or swelling); quality of life (QoL) impairment; frequency of treatment being not sufficient to control urticaria; overall urticarial control. Each item was rated on a 5-point Likert scale ranged from 0 (high disease activity) to 4 (low disease activity). The UCT total score was calculated as sum of all 4 individual item scores, ranged from 0 to 16. Higher scores indicated low disease activity and complete disease control, and vice-versa. LS mean and SE were analysed using Analysis of covariance (ANCOVA) model with corresponding Baseline value, intervention group, region and background H1-antihistamine regular/daily use (Yes or No) as covariates. Analysed on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[2]	32[3]		
Units: score on a scale				
least squares mean (standard error)	3.75 (± 0.89)	4.36 (± 0.80)		

Notes:

[2] - Here, 'number of subjects analysed' = subjects with available data for this endpoint.

[3] - Here, 'number of subjects analysed' = subjects with available data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Urticaria Control Test (UCT) Score >=12 at Week 24

End point title	Percentage of Subjects With Urticaria Control Test (UCT) Score >=12 at Week 24

End point description:

The UCT is a validated PRO questionnaire used for assessing urticaria control. The questionnaire has been developed and validated with subjects with CSU and CIndU. It comprised of 4 items: severity of physical symptoms of urticaria (itch, hives and/or swelling); QoL impairment; frequency of treatment being not sufficient to control urticaria; overall urticarial control. Each item was rated on a 5-point Likert scale ranging from 0 to 4, with low score indicating high disease activity and low disease control, and vice-versa. The UCT total score was calculated as sum of all 4 individual item scores, which ranged from 0 to 16. Higher scores indicated low disease activity and complete disease control, and vice-versa. A score of >=12 on the scale indicates well-controlled urticaria. Analysis was performed on ITT population. Percentage of subjects with UCT score >=12 (i.e., well controlled urticaria) at Week 24 are reported in this endpoint.

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	42		
Units: percentage of subjects				
number (not applicable)	27.5	33.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with an Improvement of >=3 points From Baseline in Urticaria Control Test Score at Week 24

End point title	Percentage of Subjects with an Improvement of >=3 points From Baseline in Urticaria Control Test Score at Week 24

End point description:

The UCT is a validated PRO questionnaire used for assessing urticaria control. The questionnaire has been developed and validated with subjects with CSU and CIndU. It comprised of 4 items: severity of physical symptoms of urticaria (itch, hives and/or swelling); QoL impairment; frequency of treatment being not sufficient to control urticaria; overall urticarial control. Each item was rated on a 5-point Likert scale ranging from 0 (high disease activity) to 4 (low disease activity), with low score indicating high disease activity and low disease control, and vice-versa. The UCT total score was calculated as sum of all 4 individual item scores, which ranged from 0 to 16. Higher scores indicated low disease activity and complete disease control, and vice-versa. Analysis was performed on ITT population. Percentage of subjects with an improvement of >=3 points from Baseline in UCT score at Week 24 are reported in this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	42		
Units: percentage of subjects				
number (not applicable)	30.0	45.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Local Wheal Intensity Scale Score at Week 12 and 24

End point title	Change From Baseline in Local Wheal Intensity Scale Score at Week 12 and 24

End point description:

Wheal intensity Likert scale (ranging from 0 to 5) is a clinician-reported endpoint completed at the study visit, 10 minutes after removal of the ice cube from the subject's arm. The scale comprised of a single item assessing the intensity of subjects' cutaneous reaction rated as follows: 0 = no wheals; 1 = numerous small, non-coalescent wheals; 2 = a large, regular, slightly edematous, coalescent wheal; 3 = a large and moderately edematous wheal; 4 = a large, regular, and significantly edematous wheal without pseudopodia; and 5 = a large, very edematous wheal with pseudopodia. Higher score indicated greater severity. LS mean and SE were analysed using ANCOVA model with the corresponding Baseline value, intervention group, region and background H1-antihistamine regular/daily use (Yes or No) as covariates. Analysis was performed on ITT population. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and 24

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	42		
Units: score on a scale				
least squares mean (standard error)				
Week 12 (n=38,39)	-1.49 (± 0.23)	-1.19 (± 0.23)		
Week 24 (n=32,33)	-1.52 (± 0.28)	-1.55 (± 0.27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Local Itch Severity Scale Score at Week 12 and

24

End point title	Change From Baseline in Local Itch Severity Scale Score at Week 12 and 24

End point description:

Local itch (pruritus) severity was assessed using the peak pruritus numerical rating scale (NRS). Peak pruritus NRS is a PRO comprised of a single item rated on a scale ranged from 0 (“No itch”) to 10 (“Worst itch imaginable”), where higher scores indicated worse itch. Subjects were asked to rate the intensity of their worst local site itch (pruritus) 10 minutes after removal of the ice cube. LS mean and SE were analysed using ANCOVA model with the corresponding Baseline value, intervention group, region and background H1-antihistamine regular/daily use (Yes or No) as covariates. Analysis was performed on ITT population. Here, 'n' = subjects with available data for each specified category. Change from Baseline in local itch severity score at the provocation site at Week 12 and 24 is reported in this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and 24

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	42		
Units: score on a scale				
least squares mean (standard error)				
Week 12 (n=35, 34)	-2.12 (± 0.58)	-2.52 (± 0.59)		
Week 24 (n=30,29)	-2.18 (± 0.63)	-2.43 (± 0.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Local Skin Burning Sensation Scale Score at Week 12 and 24

End point title	Change from Baseline in Local Skin Burning Sensation Scale Score at Week 12 and 24

End point description:

Local skin burning sensation was assessed using peak burning sensation NRS which is a PRO comprised of a single item rated on a scale ranged from 0 (“No burning sensation”) to 10 (“Worst imaginable burning sensation”). Higher score indicated worst burning sensation. Subjects were asked to rate the intensity of the worst local site burning sensation of their skin 10 minutes after the removal of the ice cube. LS mean and SE were analysed using ANCOVA model with the corresponding Baseline value, intervention group, region and background H1-antihistamine regular/daily use (Yes or No) as covariates. Analysis was performed on ITT population. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and 24

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	42		
Units: score on a scale				
least squares mean (standard error)				
Week 12 (n=35,34)	-1.60 (± 0.60)	-2.43 (± 0.61)		
Week 24 (n=30,29)	-1.76 (± 0.69)	-2.04 (± 0.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Local Pain Severity Scale Score at Week 12 and 24

End point title	Change From Baseline in Local Pain Severity Scale Score at Week 12 and 24

End point description:

Local pain severity was assessed using peak pain NRS. The peak pain NRS is a PRO comprised of a single item rated on a scale ranged from 0 (“No pain”) to 10 (“Worst imaginable pain”). Higher score indicated worst pain. Subjects were asked to rate the intensity of their worst local site pain 10 minutes after removal of the ice cube. LS mean and SE was analysed using ANCOVA model with the corresponding Baseline value, intervention group, region and background H1-antihistamine regular/daily use (Yes or No) as covariates. Analysis was performed on ITT population. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and 24

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	42		
Units: score on a scale				
least squares mean (standard error)				
Week 12 (n=35,34)	-1.82 (± 0.54)	-2.14 (± 0.55)		
Week 24 (n=30,29)	-1.60 (± 0.58)	-2.28 (± 0.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Negative Ice Cube Provocation Test at Week 12

End point title	Percentage of Subjects With Negative Ice Cube Provocation Test at Week 12

End point description:

The ice cube provocation test is the most frequently used provocation method for ColdU. A negative ice

cube provocation test was defined as the absence of confluent hives/wheal at the entire skin site of exposure after ice cube provocation test. Ice cube was applied on forearm skin for 5 minutes. Provocation test reading time was 10 minutes after removal of ice cube. Analysis was performed on ITT population. Percentage of subjects with negative ice cube provocation test at Week 12 are reported in this endpoint.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	42		
Units: percentage of subjects				
number (not applicable)	35.0	31.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Cold Urticaria Signs and Symptoms Severity Scale Score at Week 24

End point title	Change From Baseline in Cold Urticaria Signs and Symptoms Severity Scale Score at Week 24

End point description:

Cold Urticaria Activity Score (ColdUAS) is disease-specific PRO questionnaire designed to determine cold urticaria disease activity. Intended for subjects with cold urticaria aged 12 years old and above; developed and comprehensively tested with adults and adolescent subjects with cold urticaria. Disease activity assessment was based on daily documentation of cold-induced skin reactions (wheals and swelling), skin sensations (itching, burning, pain or feeling hot), avoidance behavior and trigger exposure, and overall symptoms severity. Skin reaction, skin sensations, exposition to cold temperatures that usually cause ColdU symptoms and overall symptom severity were rated on a 4-point scale ranged from 0 (less severe) to 4 (more severe), where higher score indicated more signs and symptoms. LS mean and SE were analysed using ANCOVA model with corresponding Baseline value, intervention group, region and background H1-antihistamine regular/daily use (Yes/No) as covariates. ITT.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[4]	24[5]		
Units: score on a scale				
least squares mean (standard error)	-1.04 (± 0.23)	-1.28 (± 0.22)		

Notes:

[4] - Here, 'number of subjects analysed' = subjects with available data for this endpoint.

[5] - Here, 'number of subjects analysed' = subjects with available data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Percentage of Cold Urticaria Sign and Symptom-Free Days at Week 24

End point title	Change From Baseline in Percentage of Cold Urticaria Sign and Symptom-Free Days at Week 24

End point description:

ColdUAS: disease-specific PRO questionnaire to determine cold urticaria disease activity in adults and adolescents with cold urticaria. For change from Baseline in percentage of cold urticaria sign and symptom-free days, responses to ColdUAS question (Q) 1 (rating severity of signs: wheals and swelling) and ColdUAS, Q2 (rating severity of symptoms: itch, burning, pain, or feeling hot) on days exposed to cold (ColdUAS Q3 responded Yes) were used. Within 14-day interval before each visit the number of sign and symptom-free days (ColdUAS Q1=0 and Q2=0) on days exposed to cold (ColdUAS Q3 greater than >0) was counted and divided by total number of days exposed to cold in this interval. Percentage of cold urticaria sign and symptom free days = sign and symptom free days/cold exposure days in 14 days window*100. LS mean and SE by ANCOVA model with the corresponding Baseline value, intervention group, region and background H1-antihistamines regular/daily use (Yes/No) as covariates. ITT.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[6]	24[7]		
Units: percentage of days				
least squares mean (standard error)	15.66 (± 7.49)	27.82 (± 7.26)		

Notes:

[6] - Here, 'number of subjects analysed' = subjects with available data for this endpoint.

[7] - Here, 'number of subjects analysed' = subjects with available data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health-related Quality-of-life (HRQoL) as Measured by Dermatology Life Quality Index (DLQI) Scale Scores at Week 24

End point title	Change From Baseline in Health-related Quality-of-life (HRQoL) as Measured by Dermatology Life Quality Index (DLQI) Scale Scores at Week 24

End point description:

DLQI is a PRO developed to measure dermatology-specific HRQoL in adults. It comprises 10 items assessing the impact of skin disease on subject's HRQoL over the previous week. The items cover symptoms, leisure activities, work/school or holiday time, personal relationships including intimate, side effects of treatment, and emotional reactions to having a skin disease. It is a validated questionnaire

used in clinical practice and clinical trials. For 9-items; response scale was a 4-point Likert scale ranging from 0 = "Not at all" to 3 = "Very much", where higher score=more impact of QoL, and vice-versa. The remaining 1 item about work/studying was rated on a 3-point Likert scale ranged from 0="Not at all" to 2="A lot". DLQI total score was the sum of score of all the items and ranged from 0 to 30, with a high score indicated poor HRQoL, and vice-versa. LS mean and SE from ANCOVA model. ITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	29		
Units: score on a scale				
least squares mean (standard error)	-4.70 (± 1.08)	-4.32 (± 1.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Cold Urticaria Quality of Life (ColdU-QoL) Scale Score at Week 24

End point title	Change From Baseline in Cold Urticaria Quality of Life (ColdU-QoL) Scale Score at Week 24

End point description:

The ColdU-QoL questionnaire is a disease-specific PRO questionnaire designed to assess the impact of cold urticaria on subjects' HRQoL. It has been developed and comprehensively tested with adults and adolescent subjects with cold urticaria. The questionnaire contains 19 items, each rated using a 5-point Likert scale ranged from 0 (Not at all / Never) to 4 (Very much / Very often). The total raw score of the ColdU-QoL was transformed to a 0 to 100 score for analysis using the formula: ColdU-QoL total score = Sum of the score of all completed items/Maximum possible sum of the
score of all completed items*100. Higher scores indicated higher ColdU-related QoL impairment, and vice-versa. LS mean and SE were analysed from ANCOVA model with the corresponding Baseline value, intervention group, region and background H1-antihistamine regular/daily use (Yes or No) as covariates. ITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: score on a scale				
least squares mean (standard error)	-20.12 (± 3.81)	-20.07 (± 3.65)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Receiving Rescue Therapy for Primary Acquired Chronic Inducible Cold Urticaria

End point title	Percentage of Subjects Receiving Rescue Therapy for Primary Acquired Chronic Inducible Cold Urticaria

End point description:

Rescue therapy included additional doses of H1-antihistamines and short course of oral corticosteroids (OCS). Analysis was performed ITT population.

End point type	Secondary

End point timeframe:

From first IMP administration (Day 1) up to Week 24

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	42		
Units: percentage of subjects				
number (not applicable)				
H1-antihistamines	32.5	45.2		
OCS	2.5	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Cold Exposure Triggered Urticaria That Required Hospitalisation/Emergency Medical Care Visit or Treatment With Epinephrine

End point title	Percentage of Subjects With Cold Exposure Triggered Urticaria That Required Hospitalisation/Emergency Medical Care Visit or Treatment With Epinephrine

End point description:

Percentage of subjects with cold exposure triggered urticaria that required hospitalisation/emergency medical care visit or treatment with epinephrine are reported in this endpoint. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From first IMP administration (Day 1) up to 14 weeks after last IMP administration (i.e., up to Week 36)

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	42		
Units: percentage of subjects				
number (not applicable)				
Hospitalisation/emergency medical care visit	0	0		
Epinephrine treatment	0	0		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)[8]

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) was 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, or was a medically important event. TEAEs were defined as AEs that developed, worsened or became serious during the treatment-emergent period (from the first investigational medicinal product [IMP] administration to the last IMP administration + 14 weeks). Analysis was performed on safety population which included all subjects who were randomised and received at least 1 dose of study intervention and were analysed according to the intervention actually received.

End point type	Secondary

End point timeframe:

From first IMP administration (Day 1) up to 14 weeks after last IMP administration (i.e., up to Week 36)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data was reported for the arms applicable for the endpoint.

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	39	43		
Units: subjects				
TEAEs	27	23		
TESAEs	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Antidrug Antibodies (ADA) Response

End point title	Number of Subjects With Treatment-emergent Antidrug Antibodies (ADA) Response

End point description:

ADA response was categorised as: Treatment-emergent and Treatment-boosted. Treatment-emergent ADAs were defined as a positive response in the ADA assay post-first dose, when baseline results were negative or missing. Treatment-boosted ADAs: defined as an ADA positive response in the assay post first dose that was >=4-fold over baseline titer levels, when Baseline results were positive. Titer values were defined as low titer (< 1,000); moderate (1,000 less than or equal to [<=] titer <=10,000) and high titer (> 10,000). Analysis was performed on ADA population which included all subjects who were randomised and received at least one dose of the study intervention and had at least one non-missing ADA result after first dose of study intervention. Subjects were analysed according to the intervention actually received.

End point type	Secondary

End point timeframe:

From first IMP administration (Day 1) up to 14 weeks after last IMP administration (i.e., up to Week 36)

End point values	Placebo	Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	38		
Units: subjects				
Treatment-emergent ADAs	0	4		
Treatment-boosted ADAs	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first IMP administration (Day 1) up to 14 weeks after last IMP administration (i.e., up to Week 36)

Adverse event reporting additional description:

Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Dupilumab

Reporting group description:

Subjects based on their BW >=60 kg or >=30 kg and <60 kg received loading dose of dupilumab 600 mg or 400 mg SC injection on Day 1, respectively, followed by dupilumab 300 mg or 200 mg SC injection q2w up to Week 22 along with their established standard of care background therapy with a long-acting non-sedating H1-antihistamine.

Reporting group title	Placebo

Reporting group description:

Subjects based on their BW >=60 kg or BW >=30 kg and <60 kg received loading dose of placebo (matched to dupilumab 600 mg or 400 mg) SC injection on Day 1, respectively, followed by placebo (matched to dupilumab 300 mg or 200 mg) SC injection q2w up to Week 22 along with their established standard of care background therapy with a long-acting non-sedating H1-antihistamine.

Serious adverse events	Dupilumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 43 (2.33%)	0 / 39 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Psychiatric disorders			
Bipolar Disorder			
subjects affected / exposed	1 / 43 (2.33%)	0 / 39 (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	Dupilumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 43 (32.56%)	16 / 39 (41.03%)	
Injury, poisoning and procedural complications			

Accidental Overdose			
subjects affected / exposed	1 / 43 (2.33%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 43 (2.33%)	2 / 39 (5.13%)	
occurrences (all)	1	3	
General disorders and administration site conditions			
Injection Site Erythema			
subjects affected / exposed	3 / 43 (6.98%)	0 / 39 (0.00%)	
occurrences (all)	4	0	
Injection Site Pain			
subjects affected / exposed	4 / 43 (9.30%)	1 / 39 (2.56%)	
occurrences (all)	8	1	
Injection Site Reaction			
subjects affected / exposed	6 / 43 (13.95%)	1 / 39 (2.56%)	
occurrences (all)	26	1	
Pyrexia			
subjects affected / exposed	0 / 43 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Eczema Asteatotic			
subjects affected / exposed	0 / 43 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	3	
Infections and infestations			
Suspected Covid-19			
subjects affected / exposed	2 / 43 (4.65%)	3 / 39 (7.69%)	
occurrences (all)	2	3	
Covid-19			
subjects affected / exposed	5 / 43 (11.63%)	8 / 39 (20.51%)	
occurrences (all)	5	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 September 2022	Following changes were made: - Newly proposed secondary endpoints were considered sensitive to detect a shift in cold urticaria signs and symptoms severity, either via reduction in signs/symptoms severity score or change in proportion of symptom-free days. Symptom-free days were considered clinically meaningful for assessment of treatment benefit. An exploratory endpoint evaluating avoidance to cold had close relation to quality of life that was severely impacted in cold urticaria subjects, mainly because of avoidance to cold. The proposed modifications affected the ColdUAS data analysis. - Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) scales were used in the study as a benchmark/anchor instrument for the analysis of the other PROs. Therefore, they were considered exploratory endpoints rather than secondary ones. - The following endpoint was removed: Time to first rescue therapy for primary acquired chronic induced ColdU during the planned treatment period compared with placebo. - ColdUAS7 scoring was not validated by the scale developer and therefore the endpoints evaluating change in ColdUAS7 score were removed. - Handling of missing data after taking highly influential prohibited medications and/or highly influential rescue medications or after withdrawal of study intervention were modified to include each subject's own worst data in order to better reflect the clinical scenario of treatment failure. - Clarified that the responsibility to unblind treatment assignment in emergency situations resided solely with the investigator as per the European Medicines Agency (EMA) Good Clinical Practice Inspectors Working Group (GCP IWG) and the Clinical Trial Facilitation Group (CTFG). Consequently, the Sponsor cannot require or insist on being involved in the decision to unblind, stall or delay in any way the unblinding of trial subject treatment in emergency situations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported