



Clinical trial results:

Master protocol of three randomized, double-blind, placebo-controlled, multi-center, parallel-group studies of dupilumab in patients with chronic spontaneous urticaria (CSU) who remain symptomatic despite the use of H1 antihistamine treatment in patients naïve to omalizumab and in patients who are intolerant or incomplete responders to omalizumab

Summary

EudraCT number	2019-003775-19
Trial protocol	DE FR HU GB ES Outside EU/EEA
Global end of trial date	25 October 2024

Results information

Result version number	v1 (current)
This version publication date	09 May 2025
First version publication date	09 May 2025

Trial information

Trial identification

Sponsor protocol code	EFC16461
-----------------------	----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04180488
WHO universal trial number (UTN)	U1111-1241-8208

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	82 Avenue Raspail, Gentilly, France, 94250
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	20 August 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	25 October 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of dupilumab in study participants with chronic spontaneous urticaria (CSU) who remain symptomatic despite the use of H1 antihistamine (Study A and Study C: omalizumab naïve; Study B: omalizumab intolerant or incomplete responders).

Protection of trial subjects:

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

For adults: Participants 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 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	11 December 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	Argentina: 41
Country: Number of subjects enrolled	Canada: 99
Country: Number of subjects enrolled	China: 44
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Japan: 52
Country: Number of subjects enrolled	Russian Federation: 40
Country: Number of subjects enrolled	Spain: 33
Country: Number of subjects enrolled	United States: 45

Worldwide total number of subjects	397
EEA total number of subjects	76

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)	5
Adolescents (12-17 years)	12
Adults (18-64 years)	329
From 65 to 84 years	51
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study comprised of 3 randomized studies of similar design: 2 studies were conducted in participants who were omalizumab naïve (Study A [55 centers in 9 countries] and Study C [50 centers in 9 countries]) and 1 study was conducted in participants who were omalizumab intolerant or incomplete responders (Study B [61 centers in 11 countries]).

Pre-assignment

Screening details:

Total 138 participants in Study A, 108 participants in Study B and 151 participants in Study C were randomized in a 1:1 ratio to receive either weight-tiered dupilumab or matching placebo in respective studies. As pre-specified in the protocol and statistical analysis plan (SAP), the results are presented by study and treatment group/intervention.

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, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Study A: Placebo

Arm description:

Participants who were omalizumab naïve received placebo matched to dupilumab as subcutaneous (SC) injection including loading dose from Day 1 up to 24 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 matched to dupilumab was administered from Day 1 up to 24 weeks.

Arm title	Study A: Dupilumab
------------------	--------------------

Arm description:

Participants who were omalizumab naïve received dupilumab for 24 weeks as follows:

- 300 milligrams (mg) SC injection every 2 weeks (q2w) for adults and those adolescents who weighed ≥ 60 kilograms (kg) at screening starting from Week 2 following a loading dose of 600 mg (2×300 mg injections) on Day 1,
- 200 mg SC injection q2w for adolescents who weighed < 60 kg and children (≥ 6 to < 12 years of age) who weighed ≥ 30 kg at screening starting from Week 2 following a loading dose of 400 mg (2×200 mg injections) on Day 1 and
- 300 mg SC injection every 4 weeks (q4w) for children (≥ 6 to < 12 years of age) who weighed < 30 kg and ≥ 15 kg at screening starting from Week 4 following a loading dose of 600 mg (2×300 mg injections) on Day 1.

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

Dosage and administration details:

Dupilumab was administered for 24 weeks as specified in the protocol.

Arm title	Study B: Placebo
------------------	------------------

Arm description:

Participants who were intolerant or incomplete responders to omalizumab received placebo matched to dupilumab as SC injection including loading dose from Day 1 up to 24 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 matched to dupilumab was administered from Day 1 up to 24 weeks.

Arm title	Study B: Dupilumab
------------------	--------------------

Arm description:

Participants who were intolerant or incomplete responders to omalizumab received dupilumab for 24 weeks as follows:

- 300 mg SC injection q2w for adults and those adolescents weighing ≥ 60 kg at screening starting from Week 2 following a loading dose of 600 mg (2×300 mg injections) on Day 1 or
- 200 mg SC injection q2w for adolescents weighing < 60 kg at screening starting from Week 2 following a loading dose of 400 mg (2×200 mg injections) on Day 1.

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

Dosage and administration details:

Dupilumab was administered for 24 weeks as specified in the protocol.

Arm title	Study C: Placebo
------------------	------------------

Arm description:

Participants who were omalizumab naïve received placebo matched to dupilumab as SC injection including loading dose from Day 1 up to 24 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 matched to dupilumab was administered from Day 1 up to 24 weeks.

Arm title	Study C: Dupilumab
------------------	--------------------

Arm description:

Participants who were omalizumab naïve received dupilumab for 24 weeks as follows:

- 300 mg SC injection q2w for adults and those adolescents who weighed ≥ 60 kg at screening starting from Week 2 following a loading dose of 600 mg (2×300 mg injections) on Day 1,
- 200 mg SC injection q2w for adolescents who weighed < 60 kg and children (≥ 6 to < 12 years of age) who weighed ≥ 30 kg at screening starting from Week 2 following a loading dose of 400 mg (2×200 mg injections) on Day 1 and
- 300 mg SC injection q4w for children (≥ 6 to < 12 years of age) who weighed < 30 kg and ≥ 15 kg at

screening starting from Week 4 following a loading dose of 600 mg (2×300 mg injections) on Day 1.

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

Dosage and administration details:

Dupilumab was administered for 24 weeks as specified in the protocol.

Number of subjects in period 1	Study A: Placebo	Study A: Dupilumab	Study B: Placebo
Started	68	70	54
Completed	55	63	47
Not completed	13	7	7
Consent withdrawn by subject	8	4	5
Adverse event, non-fatal	3	2	-
Not related to Coronavirus Disease-2019 (COVID-19)	2	1	1
Poor compliance to protocol	-	-	1

Number of subjects in period 1	Study B: Dupilumab	Study C: Placebo	Study C: Dupilumab
Started	54	77	74
Completed	49	67	66
Not completed	5	10	8
Consent withdrawn by subject	2	8	6
Adverse event, non-fatal	-	-	-
Not related to Coronavirus Disease-2019 (COVID-19)	3	2	2
Poor compliance to protocol	-	-	-

Baseline characteristics

Reporting groups

Reporting group title	Study A: Placebo
-----------------------	------------------

Reporting group description:

Participants who were omalizumab naïve received placebo matched to dupilumab as subcutaneous (SC) injection including loading dose from Day 1 up to 24 weeks.

Reporting group title	Study A: Dupilumab
-----------------------	--------------------

Reporting group description:

Participants who were omalizumab naïve received dupilumab for 24 weeks as follows:

- 300 milligrams (mg) SC injection every 2 weeks (q2w) for adults and those adolescents who weighed ≥ 60 kilograms (kg) at screening starting from Week 2 following a loading dose of 600 mg (2×300 mg injections) on Day 1,
- 200 mg SC injection q2w for adolescents who weighed < 60 kg and children (≥ 6 to < 12 years of age) who weighed ≥ 30 kg at screening starting from Week 2 following a loading dose of 400 mg (2×200 mg injections) on Day 1 and
- 300 mg SC injection every 4 weeks (q4w) for children (≥ 6 to < 12 years of age) who weighed < 30 kg and ≥ 15 kg at screening starting from Week 4 following a loading dose of 600 mg (2×300 mg injections) on Day 1.

Reporting group title	Study B: Placebo
-----------------------	------------------

Reporting group description:

Participants who were intolerant or incomplete responders to omalizumab received placebo matched to dupilumab as SC injection including loading dose from Day 1 up to 24 weeks.

Reporting group title	Study B: Dupilumab
-----------------------	--------------------

Reporting group description:

Participants who were intolerant or incomplete responders to omalizumab received dupilumab for 24 weeks as follows:

- 300 mg SC injection q2w for adults and those adolescents weighing ≥ 60 kg at screening starting from Week 2 following a loading dose of 600 mg (2×300 mg injections) on Day 1 or
- 200 mg SC injection q2w for adolescents weighing < 60 kg at screening starting from Week 2 following a loading dose of 400 mg (2×200 mg injections) on Day 1.

Reporting group title	Study C: Placebo
-----------------------	------------------

Reporting group description:

Participants who were omalizumab naïve received placebo matched to dupilumab as SC injection including loading dose from Day 1 up to 24 weeks.

Reporting group title	Study C: Dupilumab
-----------------------	--------------------

Reporting group description:

Participants who were omalizumab naïve received dupilumab for 24 weeks as follows:

- 300 mg SC injection q2w for adults and those adolescents who weighed ≥ 60 kg at screening starting from Week 2 following a loading dose of 600 mg (2×300 mg injections) on Day 1,
- 200 mg SC injection q2w for adolescents who weighed < 60 kg and children (≥ 6 to < 12 years of age) who weighed ≥ 30 kg at screening starting from Week 2 following a loading dose of 400 mg (2×200 mg injections) on Day 1 and
- 300 mg SC injection q4w for children (≥ 6 to < 12 years of age) who weighed < 30 kg and ≥ 15 kg at screening starting from Week 4 following a loading dose of 600 mg (2×300 mg injections) on Day 1.

Reporting group values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo
Number of subjects	68	70	54
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean	41.9	40.7	46.8
standard deviation	± 14.8	± 16.2	± 16.3

Sex: Female, Male			
Units: participants			
Female	50	41	41
Male	18	29	13
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	1	0
Asian	16	19	11
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	1	2
White	48	47	41
More than one race	1	1	0
Unknown or Not Reported	1	1	0
Weekly Urticaria Activity (UAS7) Score			
Once daily UAS is sum of daily hive severity score (HSS) and daily itch severity score (ISS) recorded in electronic (e)-diary. Daily HSS assesses number of wheals; range 0 (none) to 3 (more than 50 hives) whereas daily ISS assesses itch intensity; range 0 (none) to 3 (intense). Daily UAS scores range from 0 to 6 point/day. Once daily UAS scores are summed over 7-day period to create UAS7 with an overall scale of 0 (no urticaria) to 42 (severe urticaria). Higher scores=greater severity of urticaria symptoms. Baseline=sum of daily scores for the 7 days prior to the day of randomization.			
Units: score on a scale			
arithmetic mean	30.8	31.9	31.9
standard deviation	± 8.2	± 7.2	± 8.1

Reporting group values	Study B: Dupilumab	Study C: Placebo	Study C: Dupilumab
Number of subjects	54	77	74
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean	48.6	44.0	45.6
standard deviation	± 15.6	± 16.7	± 17.1
Sex: Female, Male			
Units: participants			
Female	37	59	47
Male	17	18	27
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	1
Asian	6	29	33
Native Hawaiian or Other Pacific Islander	1	0	0
Black or African American	3	2	0
White	43	38	32
More than one race	0	2	1
Unknown or Not Reported	1	6	7
Weekly Urticaria Activity (UAS7) Score			
Once daily UAS is sum of daily hive severity score (HSS) and daily itch severity score (ISS) recorded in electronic (e)-diary. Daily HSS assesses number of wheals; range 0 (none) to 3 (more than 50 hives) whereas daily ISS assesses itch intensity; range 0 (none) to 3 (intense). Daily UAS scores range from 0 to 6 point/day. Once daily UAS scores are summed over 7-day period to create UAS7 with an overall scale of 0 (no urticaria) to 42 (severe urticaria). Higher scores=greater severity of urticaria symptoms. Baseline=sum of daily scores for the 7 days prior to the day of randomization.			

Units: score on a scale			
arithmetic mean	31.0	28.1	28.6
standard deviation	± 7.9	± 7.9	± 7.1

Reporting group values	Total		
Number of subjects	397		
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: participants			
Female	275		
Male	122		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	2		
Asian	114		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	10		
White	249		
More than one race	5		
Unknown or Not Reported	16		
Weekly Urticaria Activity (UAS7) Score			
Once daily UAS is sum of daily hive severity score (HSS) and daily itch severity score (ISS) recorded in electronic (e)-diary. Daily HSS assesses number of wheals; range 0 (none) to 3 (more than 50 hives) whereas daily ISS assesses itch intensity; range 0 (none) to 3 (intense). Daily UAS scores range from 0 to 6 point/day. Once daily UAS scores are summed over 7-day period to create UAS7 with an overall scale of 0 (no urticaria) to 42 (severe urticaria). Higher scores=greater severity of urticaria symptoms. Baseline=sum of daily scores for the 7 days prior to the day of randomization.			
Units: score on a scale			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Study A: Placebo
Reporting group description: Participants who were omalizumab naïve received placebo matched to dupilumab as subcutaneous (SC) injection including loading dose from Day 1 up to 24 weeks.	
Reporting group title	Study A: Dupilumab
Reporting group description: Participants who were omalizumab naïve received dupilumab for 24 weeks as follows: <ul style="list-style-type: none">- 300 milligrams (mg) SC injection every 2 weeks (q2w) for adults and those adolescents who weighed ≥ 60 kilograms (kg) at screening starting from Week 2 following a loading dose of 600 mg (2×300 mg injections) on Day 1,- 200 mg SC injection q2w for adolescents who weighed < 60 kg and children (≥ 6 to < 12 years of age) who weighed ≥ 30 kg at screening starting from Week 2 following a loading dose of 400 mg (2×200 mg injections) on Day 1 and- 300 mg SC injection every 4 weeks (q4w) for children (≥ 6 to < 12 years of age) who weighed < 30 kg and ≥ 15 kg at screening starting from Week 4 following a loading dose of 600 mg (2×300 mg injections) on Day 1.	
Reporting group title	Study B: Placebo
Reporting group description: Participants who were intolerant or incomplete responders to omalizumab received placebo matched to dupilumab as SC injection including loading dose from Day 1 up to 24 weeks.	
Reporting group title	Study B: Dupilumab
Reporting group description: Participants who were intolerant or incomplete responders to omalizumab received dupilumab for 24 weeks as follows: <ul style="list-style-type: none">- 300 mg SC injection q2w for adults and those adolescents weighing ≥ 60 kg at screening starting from Week 2 following a loading dose of 600 mg (2×300 mg injections) on Day 1 or- 200 mg SC injection q2w for adolescents weighing < 60 kg at screening starting from Week 2 following a loading dose of 400 mg (2×200 mg injections) on Day 1.	
Reporting group title	Study C: Placebo
Reporting group description: Participants who were omalizumab naïve received placebo matched to dupilumab as SC injection including loading dose from Day 1 up to 24 weeks.	
Reporting group title	Study C: Dupilumab
Reporting group description: Participants who were omalizumab naïve received dupilumab for 24 weeks as follows: <ul style="list-style-type: none">- 300 mg SC injection q2w for adults and those adolescents who weighed ≥ 60 kg at screening starting from Week 2 following a loading dose of 600 mg (2×300 mg injections) on Day 1,- 200 mg SC injection q2w for adolescents who weighed < 60 kg and children (≥ 6 to < 12 years of age) who weighed ≥ 30 kg at screening starting from Week 2 following a loading dose of 400 mg (2×200 mg injections) on Day 1 and- 300 mg SC injection q4w for children (≥ 6 to < 12 years of age) who weighed < 30 kg and ≥ 15 kg at screening starting from Week 4 following a loading dose of 600 mg (2×300 mg injections) on Day 1.	

Primary: Change From Baseline in Weekly Urticaria Activity Score at Week 24

End point title	Change From Baseline in Weekly Urticaria Activity Score at Week 24
End point description: UAS is a validated composite patient-reported outcome (PRO) measure for assessing CSU. The once daily UAS is the sum of the daily HSS and daily ISS recorded in e-diary. Daily HSS assesses number of wheals and range from 0 (none) to 3 (more than 50 hives) whereas daily ISS assesses itch intensity and range from 0 (none) to 3 (intense). The daily UAS scores range from 0 to 6 point/day. Once daily UAS scores are summed over 7-day period to create the UAS7 with an overall scale of 0 (no urticaria) to 42 (severe urticaria). Higher scores indicate greater severity of urticaria symptoms. Least squares (LS) mean is presented. Baseline was defined as the sum of the daily scores for the 7 days prior to the day of	

randomization. The intent-to-treat (ITT) population included all randomized participants analyzed according to the intervention group allocated by randomization.

End point type	Primary
End point timeframe:	
Baseline (Day 1) and Week 24	

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	70	54	54
Units: score on a scale				
least squares mean (standard error)	-12.00 (\pm 1.81)	-20.53 (\pm 1.76)	-8.54 (\pm 2.14)	-14.37 (\pm 2.16)

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	74		
Units: score on a scale				
least squares mean (standard error)	-11.21 (\pm 2.65)	-15.86 (\pm 2.66)		

Statistical analyses

Statistical analysis title	Change From Baseline in UAS7 at Week 24
-----------------------------------	---

Statistical analysis description:

Analyzed by fitting an analysis of covariance (ANCOVA) model with the corresponding baseline value, intervention group, presence of angioedema at baseline, and regions as covariates.

Comparison groups	Study A: Placebo v Study A: Dupilumab
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.0003 ^[2]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-8.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.16
upper limit	-3.9

Notes:

[1] - A hierarchical testing procedure was used to control the overall type I error.

[2] - Threshold for significance at 2-sided 0.05 level.

Statistical analysis title	Change From Baseline in UAS7 at Week 24
-----------------------------------	---

Statistical analysis description:

Analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, presence of angioedema at baseline, and regions as covariates.

Comparison groups	Study C: Placebo v Study C: Dupilumab
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.0226 ^[4]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-4.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.65
upper limit	-0.65

Notes:

[3] - A hierarchical testing procedure was used to control the overall type I error.

[4] - Threshold for significance at 2-sided 0.05 level.

Statistical analysis title	Change From Baseline in UAS7 at Week 24
-----------------------------------	---

Statistical analysis description:

Analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, presence of angioedema at baseline, and regions as covariates.

Comparison groups	Study B: Placebo v Study B: Dupilumab
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.039 ^[6]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-5.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.37
upper limit	-0.3

Notes:

[5] - A hierarchical testing procedure was used to control the overall type I error.

[6] - Threshold for significance at 2-sided 0.043 level.

Secondary: Change From Baseline in Weekly Itch Severity Score at Week 24

End point title	Change From Baseline in Weekly Itch Severity Score at Week 24
-----------------	---

End point description:

ISS was recorded in e-diary. The ISS represents severity of itch on a scale ranging from 0 (none) to 3 (intense). The ISS7 score was the sum of daily ISS scores recorded by a participant at the same time each day over 7 days with an overall scale of 0 (no impact) to 21 (severe impact). Higher scores indicated greater intensity of itch. LS mean is presented. Baseline was defined as the sum of daily scores obtained for 7 days prior to randomization. The ITT population included all randomized participants analyzed according to the intervention group allocated by randomization.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) and Week 24

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	70	54	54
Units: score on a scale				
least squares mean (standard error)	-6.01 (\pm 0.94)	-10.24 (\pm 0.91)	-4.81 (\pm 1.08)	-7.68 (\pm 1.10)

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	74		
Units: score on a scale				
least squares mean (standard error)	-6.10 (\pm 1.40)	-8.64 (\pm 1.41)		

Statistical analyses

Statistical analysis title	Change From Baseline in ISS7 at Week 24
Statistical analysis description:	
Analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, presence of angioedema at baseline, and regions as covariates.	
Comparison groups	Study A: Placebo v Study A: Dupilumab
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	= 0.0005 ^[8]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-4.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.63
upper limit	-1.84

Notes:

[7] - A hierarchical testing procedure was used to control the overall type I error.

[8] - Threshold for significance at 2-sided 0.05 level.

Statistical analysis title	Change From Baseline in ISS7 at Week 24
Statistical analysis description:	
Analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, presence of angioedema at baseline, and regions as covariates.	
Comparison groups	Study C: Placebo v Study C: Dupilumab

Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.0184 ^[10]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.65
upper limit	-0.43

Notes:

[9] - A hierarchical testing procedure was used to control the overall type I error.

[10] - Threshold for significance at 2-sided 0.05 level.

Statistical analysis title	Change From Baseline in ISS7 at Week 24
-----------------------------------	---

Statistical analysis description:

Analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, presence of angioedema at baseline, and regions as covariates.

Comparison groups	Study B: Placebo v Study B: Dupilumab
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	= 0.0449 ^[12]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.68
upper limit	-0.07

Notes:

[11] - A hierarchical testing procedure was used to control the overall type I error.

[12] - Threshold for significance at 2-sided 0.043 level.

Secondary: Change From Baseline in Weekly Hives Severity Score at Week 24

End point title	Change From Baseline in Weekly Hives Severity Score at Week 24
-----------------	--

End point description:

Daily HSS was recorded in e-diary. The HSS7 score is the sum of daily HSS ranging from 0 (none) to 3 (more than 50 hives) recorded by a participant at the same time of each day over 7 days with an overall scale of 0 (no hives) to 21 (severe hives). Higher scores indicate greater intensity of hives. LS mean is presented. Baseline was defined as the sum of the daily scores for the 7 days prior to the day of randomization. The ITT population included all randomized participants analyzed according to the intervention group allocated by randomization.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) and Week 24

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	70	54	54
Units: score on a scale				
least squares mean (standard error)	-5.90 (\pm 0.93)	-10.28 (\pm 0.91)	-3.63 (\pm 1.11)	-6.64 (\pm 1.11)

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	74		
Units: score on a scale				
least squares mean (standard error)	-5.11 (\pm 1.31)	-7.27 (\pm 1.32)		

Statistical analyses

Statistical analysis title	Change From Baseline in HSS7 at Week 24
Statistical analysis description:	
Analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, presence of angioedema at baseline, and regions as covariates.	
Comparison groups	Study A: Placebo v Study A: Dupilumab
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority ^[13]
P-value	= 0.0003 ^[14]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-4.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.78
upper limit	-1.98

Notes:

[13] - A hierarchical testing procedure was used to control the overall type I error.

[14] - Threshold for significance at 2-sided 0.05 level.

Statistical analysis title	Change From Baseline in HSS7 at Week 24
Statistical analysis description:	
Analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, presence of angioedema at baseline, and regions as covariates.	
Comparison groups	Study C: Placebo v Study C: Dupilumab

Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority ^[15]
P-value	= 0.0316 ^[16]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.15
upper limit	-0.19

Notes:

[15] - A hierarchical testing procedure was used to control the overall type I error.

[16] - Threshold for significance at 2- sided 0.05 level.

Secondary: Percentage of Responders for Weekly Itch Severity Score Minimally Important Difference (MID) at Week 24

End point title	Percentage of Responders for Weekly Itch Severity Score Minimally Important Difference (MID) at Week 24
-----------------	---

End point description:

The ISS represents severity of itch on a scale ranging from 0 (none) to 3 (intense). The ISS7 score was the sum of daily ISS scores recorded by a participant at the same time each day over 7 days with an overall scale of 0 (no impact) to 21 (severe impact). Higher scores indicated greater intensity of itch. An ISS7 MID response was defined as ≥ 5 points decrease from baseline after study intervention. The ITT population included all randomized participants analyzed according to the intervention group allocated by randomization.

End point type	Secondary
----------------	-----------

End point timeframe:

Week 24

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	70	54	54
Units: percentage of participants				
number (not applicable)	42.6	72.9	38.9	59.3

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	74		
Units: percentage of participants				
number (not applicable)	51.9	70.3		

Statistical analyses

Statistical analysis title	Percentage of Responders for ISS7 MID at Week 24
Statistical analysis description:	
CMH test was performed on the association between the responder status and intervention group, adjusted by baseline disease severity (UAS7 <28, >=28), presence of angioedema at baseline, and region.	
Comparison groups	Study C: Placebo v Study C: Dupilumab
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority ^[17]
P-value	= 0.0109 ^[18]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.507
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.231
upper limit	5.107

Notes:

[17] - A hierarchical testing procedure was used to control the overall type I error.

[18] - Threshold for significance at 2-sided 0.05 level.

Statistical analysis title	Percentage of Responders for ISS7 MID at Week 24
Statistical analysis description:	
Cochran-Mantel-Haenszel (CMH) test performed on association between responder status and intervention group, adjusted by baseline disease severity (UAS7<28,>=28), presence of angioedema at baseline and region.	
Comparison groups	Study A: Placebo v Study A: Dupilumab
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority ^[19]
P-value	= 0.0014 ^[20]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.413
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.596
upper limit	7.299

Notes:

[19] - A hierarchical testing procedure was used to control the overall type I error.

[20] - Threshold for significance at 2-sided 0.05 level.

Secondary: Percentage of Participants With Weekly Urticaria Activity Score <=6 at Week 24

End point title	Percentage of Participants With Weekly Urticaria Activity Score <=6 at Week 24
-----------------	--

End point description:

UAS is a validated composite PRO measure for assessing CSU activity. The once daily UAS is the sum of the daily HSS and daily ISS recorded in e-diary. Daily HSS assesses number of wheals and range from 0 (none) to 3 (more than 50 hives) whereas daily ISS assesses itch intensity and range from 0 (none) to 3 (intense). The daily UAS scores range from 0 to 6 point/day. Once daily UAS scores are summed over 7-

day period to create the UAS7 with an overall scale of 0 (no urticaria) to 42 (severe urticaria). Higher scores indicate greater severity of urticaria symptoms. In evaluating urticaria control using UAS7, an UAS7 score of ≤ 6 indicated a well-controlled urticaria. The ITT population included all randomized participants analyzed according to the intervention group allocated by randomization.

End point type	Secondary
End point timeframe:	
Week 24	

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	70	54	54
Units: percentage of participants				
number (not applicable)	23.5	45.7	18.5	24.1

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	74		
Units: percentage of participants				
number (not applicable)	23.4	40.5		

Statistical analyses

Statistical analysis title	Percentage of Participants With UAS7 ≤ 6 at Week 24
-----------------------------------	--

Statistical analysis description:

CMH test was performed on the association between the responder status and intervention group, adjusted by baseline disease severity (UAS7 < 28 , ≥ 28), presence of angioedema at baseline, and region.

Comparison groups	Study C: Placebo v Study C: Dupilumab
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority ^[21]
P-value	= 0.0045 ^[22]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.137
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.371
upper limit	7.176

Notes:

[21] - A hierarchical testing procedure was used to control the overall type I error.

[22] - Threshold for significance at 2- sided 0.05 level.

Statistical analysis title	Percentage of Participants With UAS7 ≤ 6 at Week 24
Statistical analysis description:	
CMH test was performed on the association between the responder status and intervention group, adjusted by baseline disease severity (UAS7 <28, ≥28), presence of angioedema at baseline, and region.	
Comparison groups	Study A: Placebo v Study A: Dupilumab
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority ^[23]
P-value	= 0.0075 ^[24]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.848
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.301
upper limit	6.234

Notes:

[23] - A hierarchical testing procedure was used to control the overall type I error

[24] - Threshold for significance at 2-sided 0.05 level.

Secondary: Percentage of Participants With Weekly Urticaria Activity Score =0 at Week 24

End point title	Percentage of Participants With Weekly Urticaria Activity Score =0 at Week 24
-----------------	---

End point description:

UAS is a validated composite PRO measure for assessing CSU activity. The once daily UAS is the sum of the daily HSS and daily ISS recorded in e-diary. Daily HSS assesses number of wheals and range from 0 (none) to 3 (more than 50 hives) whereas daily ISS assesses itch intensity and range from 0 (none) to 3 (intense). The daily UAS scores range from 0 to 6 point/day. Once daily UAS scores are summed over 7-day period to create the UAS7 with an overall scale of 0 (no urticaria) to 42 (severe urticaria). Higher scores indicate greater severity of urticaria symptoms. In evaluating urticaria control using UAS7, an UAS7 score of 0 indicated an absence of both itch and hives and a complete resolution of CSU symptoms. The ITT population included all randomized participants analyzed according to the intervention group allocated by randomization.

End point type	Secondary
End point timeframe:	
Week 24	

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	70	54	54
Units: percentage of participants				
number (not applicable)	13.2	31.4	9.3	13.0

End point values	Study C: Placebo	Study C: Dupilumab		
------------------	------------------	--------------------	--	--

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	74		
Units: percentage of participants				
number (not applicable)	18.2	29.7		

Statistical analyses

Statistical analysis title	UAS7=0 at Week 24
Statistical analysis description:	
CMH test was performed on the association between the responder status and intervention group, adjusted by baseline disease severity (UAS7 <28, >=28), presence of angioedema at baseline, and region.	
Comparison groups	Study C: Placebo v Study C: Dupilumab
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority ^[25]
P-value	= 0.0187 ^[26]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.677
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.127
upper limit	6.359

Notes:

[25] - A hierarchical testing procedure was used to control the overall type I error.

[26] - Threshold for significance at 2-sided 0.05 level.

Statistical analysis title	UAS7=0 at Week 24
Statistical analysis description:	
CMH test was performed on the association between the responder status and intervention group, adjusted by baseline disease severity (UAS7 <28, >=28), presence of angioedema at baseline, and region.	
Comparison groups	Study A: Placebo v Study A: Dupilumab
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority ^[27]
P-value	= 0.0199 ^[28]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.908
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.173
upper limit	7.209

Notes:

[27] - A hierarchical testing procedure was used to control the overall type I error.

[28] - Threshold for significance at 2- sided 0.05 level.

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

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

End point description:

The UCT assessed urticaria control based on 4 items (severity of pruritus and wheals urticaria symptoms; frequency of treatment being not sufficient; quality-of-life [QoL] impairment; overall urticarial control). Each item was rated on a 5-point Likert-type scale from 0 (no control) to 4 (maximum control). The overall UCT score was the sum of all 4 individual item scores with a range of 0 (no disease control) to 16 (complete disease control). Higher scores indicated greater disease control. LS mean is presented. Baseline was defined as the last available value up to randomization date and prior to the first dose of study intervention. The ITT population included all randomized participants analyzed according to the intervention group allocated by randomization.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) and Week 24

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	70	54	54
Units: score on a scale				
least squares mean (standard error)	4.88 (± 0.61)	7.71 (± 0.59)	3.38 (± 0.74)	5.33 (± 0.77)

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	74		
Units: score on a scale				
least squares mean (standard error)	4.16 (± 0.94)	5.09 (± 0.95)		

Statistical analyses

Statistical analysis title	Change From Baseline in UCT at Week 24
----------------------------	--

Statistical analysis description:

Analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, presence of angioedema at baseline, and regions as covariates.

Comparison groups	Study C: Placebo v Study C: Dupilumab
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority ^[29]
P-value	= 0.194 ^[30]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.93

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	2.34

Notes:

[29] - A hierarchical testing procedure was used to control the overall type I error.

[30] - Threshold for significance at 2-sided 0.05 level.

Secondary: Change From Baseline in Weekly Itch Severity Score at Week 12

End point title	Change From Baseline in Weekly Itch Severity Score at Week 12
-----------------	---

End point description:

ISS was recorded in e-diary. The ISS represents severity of itch on a scale ranging from 0 (none) to 3 (intense). The ISS7 score was the sum of daily ISS scores recorded by a participant at the same time each day over 7 days with an overall scale of 0 (no impact) to 21 (severe impact). Higher scores indicated greater intensity of itch. LS mean is presented. Baseline was defined as the sum of daily scores obtained for 7 days prior to randomization. The ITT population included all randomized participants analyzed according to the intervention group allocated by randomization.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) and Week 12

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	70	54	54
Units: score on a scale				
least squares mean (standard error)	-6.01 (± 0.85)	-8.37 (± 0.84)	-4.52 (± 0.95)	-7.37 (± 0.97)

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	74		
Units: score on a scale				
least squares mean (standard error)	-5.31 (± 1.32)	-7.15 (± 1.32)		

Statistical analyses

Statistical analysis title	Change From Baseline in ISS7 at Week 12
----------------------------	---

Statistical analysis description:

Analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, presence of angioedema at baseline, and regions as covariates.

Comparison groups	Study A: Placebo v Study A: Dupilumab
-------------------	---------------------------------------

Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority ^[31]
P-value	= 0.0377 ^[32]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	-0.13

Notes:

[31] - A hierarchical testing procedure was used to control the overall type I error.

[32] - Threshold for significance at 2-sided 0.05 level.

Secondary: Change From Baseline in Weekly Urticaria Activity Score at Week 12

End point title	Change From Baseline in Weekly Urticaria Activity Score at Week 12
-----------------	--

End point description:

UAS is a validated composite PRO measure for assessing CSU activity. The once daily UAS is the sum of the daily HSS and daily ISS recorded in e-diary. Daily HSS assesses number of wheals and range from 0 (none) to 3 (more than 50 hives) whereas daily ISS assesses itch intensity and range from 0 (none) to 3 (intense). The daily UAS scores range from 0 to 6 point/day. Once daily UAS scores are summed over 7-day period to create the UAS7 with an overall scale of 0 (no urticaria) to 42 (severe urticaria). Higher scores indicate greater severity of urticaria symptoms. LS mean is presented. Baseline was defined as the sum of the daily scores for the 7 days prior to the day of randomization. The ITT population included all randomized participants analyzed according to the intervention group allocated by randomization.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) and Week 12

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	70	54	54
Units: score on a scale				
least squares mean (standard error)	-11.79 (± 1.64)	-16.81 (± 1.62)	-8.22 (± 1.91)	-13.33 (± 1.94)

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	74		
Units: score on a scale				
least squares mean (standard error)	-9.51 (± 2.54)	-12.87 (± 2.54)		

Statistical analyses

Statistical analysis title	Change From Baseline in UAS7 at Week 12
Statistical analysis description:	
Analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, presence of angioedema at baseline, and regions as covariates.	
Comparison groups	Study A: Placebo v Study A: Dupilumab
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority ^[33]
P-value	= 0.0223 ^[34]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-5.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.32
upper limit	-0.72

Notes:

[33] - A hierarchical testing procedure was used to control the overall type I error.

[34] - Threshold for significance at 2-sided 0.05 level.

Secondary: Percentage of Participants With Weekly Urticaria Activity Score ≤6 and =0 at Week 12

End point title	Percentage of Participants With Weekly Urticaria Activity Score ≤6 and =0 at Week 12
End point description:	
UAS is a validated composite PRO measure for assessing CSU activity. The once daily UAS is the sum of the daily HSS and daily ISS recorded in e-diary. Daily HSS assesses number of wheals and range from 0 (none) to 3 (more than 50 hives) whereas daily ISS assesses itch intensity and range from 0 (none) to 3 (intense). The daily UAS scores range from 0 to 6 point/day. Once daily UAS scores are summed over 7-day period to create the UAS7 with an overall scale of 0 (no urticaria) to 42 (severe urticaria). Higher scores indicate greater severity of urticaria symptoms. In evaluating urticaria control using UAS7, an UAS7 score of ≤6 indicated a well-controlled urticaria and an UAS7 score of 0 indicated an absence of both itch and hives and a complete resolution of CSU symptoms. The ITT population included all randomized participants analyzed according to the intervention group allocated by randomization.	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	70	54	54
Units: percentage of participants				
number (not applicable)				
UAS7 ≤6	17.6	34.3	9.3	24.1
UAS7=0	8.8	15.7	1.9	13.0

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	74		
Units: percentage of participants				
number (not applicable)				
UAS7 ≤6	16.9	31.1		
UAS7=0	11.7	17.6		

Statistical analyses

Statistical analysis title	UAS7 ≤6 at Week 12
Statistical analysis description:	
CMH test was performed on the association between the responder status and intervention group, adjusted by baseline disease severity (UAS7 <28, ≥28), presence of angioedema at baseline, and region.	
Comparison groups	Study A: Placebo v Study A: Dupilumab
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority ^[35]
P-value	= 0.0215 ^[36]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.645
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.154
upper limit	6.061

Notes:

[35] - A hierarchical testing procedure was used to control the overall type I error.

[36] - Threshold for significance at 2-sided 0.05 level.

Secondary: Percentage of Responders for Weekly Itch Severity Score Minimally Important Difference at Week 12

End point title	Percentage of Responders for Weekly Itch Severity Score Minimally Important Difference at Week 12
-----------------	---

End point description:

The ISS represents severity of itch on a scale ranging from 0 (none) to 3 (intense). The ISS7 score was the sum of daily ISS scores recorded by a participant at the same time each day over 7 days with an

overall scale of 0 (no impact) to 21 (severe impact). Higher scores indicated greater intensity of itch. An ISS7 MID response was defined as ≥ 5 points decrease from baseline after study intervention. The ITT population included all randomized participants analyzed according to the intervention group allocated by randomization.

End point type	Secondary
End point timeframe:	
Week 12	

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	70	54	54
Units: percentage of participants				
number (not applicable)	52.9	70.0	46.3	64.8

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	74		
Units: percentage of participants				
number (not applicable)	51.9	58.1		

Statistical analyses

Statistical analysis title	MID at Week 12
Statistical analysis description:	
	CMH test was performed on the association between the responder status and intervention group, adjusted by baseline disease severity (UAS7 <28, ≥ 28), presence of angioedema at baseline, and region.
Comparison groups	Study A: Placebo v Study A: Dupilumab
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority ^[37]
P-value	= 0.0971 ^[38]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.872
Confidence interval	
level	Other: 85 %
sides	2-sided
lower limit	0.893
upper limit	3.923

Notes:

[37] - A hierarchical testing procedure was used to control the overall type I error.

[38] - Threshold for significance at 2-sided 0.05 level.

Secondary: Change From Baseline in Weekly Hives Severity Score at Week 12

End point title	Change From Baseline in Weekly Hives Severity Score at Week 12
-----------------	--

End point description:

Daily HSS was recorded in e-diary. The HSS7 score is the sum of daily HSS ranging from 0 (none) to 3 (more than 50 hives) recorded by a participant at the same time of each day over 7 days with an overall scale of 0 (no hives) to 21 (severe hives). Higher scores indicate greater intensity of hives. LS mean is presented. Baseline was defined as the sum of the daily scores for the 7 days prior to the day of randomization. The ITT population included all randomized participants analyzed according to the intervention group allocated by randomization.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) and Week 12

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	70	54	54
Units: score on a scale				
least squares mean (standard error)	-5.69 (± 0.83)	-8.39 (± 0.83)	-3.71 (± 1.01)	-5.97 (± 1.02)

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	74		
Units: score on a scale				
least squares mean (standard error)	-4.22 (± 1.28)	-5.75 (± 1.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Urticaria Control Test at Week 12

End point title	Change From Baseline in Urticaria Control Test at Week 12
-----------------	---

End point description:

The UCT assessed urticaria control based on 4 items (severity of pruritus and wheals urticaria symptoms; frequency of treatment being not sufficient; QoL impairment; overall urticarial control). Each item was rated on a 5-point Likert-type scale from 0 (no control) to 4 (maximum control). The overall UCT score was the sum of all 4 individual item scores with a range of 0 (no disease control) to 16 (complete disease control). Higher scores indicated greater disease control. LS mean is presented. Baseline was defined as the last available value up to randomization date and prior to the first dose of study intervention. The ITT population included all randomized participants analyzed according to the intervention group allocated by randomization.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) and Week 12

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	70	54	54
Units: score on a scale				
least squares mean (standard error)	4.62 (\pm 0.57)	6.48 (\pm 0.57)	3.11 (\pm 0.65)	5.48 (\pm 0.67)

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	74		
Units: score on a scale				
least squares mean (standard error)	3.26 (\pm 0.88)	4.61 (\pm 0.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Weekly Itch Severity Score at Weeks 4, 8, 16 and 20

End point title	Change From Baseline in Weekly Itch Severity Score at Weeks 4, 8, 16 and 20
-----------------	---

End point description:

ISS was recorded in e-diary. The ISS represents severity of itch on a scale ranging from 0 (none) to 3 (intense). The ISS7 score was the sum of daily ISS scores recorded by a participant at the same time each day over 7 days with an overall scale of 0 (no impact) to 21 (severe impact). Higher scores indicated greater intensity of itch. Mean is presented. Baseline was defined as the sum of daily scores obtained for 7 days prior to randomization. The ITT population included all randomized participants analyzed according to the intervention group allocated by randomization. Only those participants with data collected at specified timepoints are reported. Here, n=participants analyzed for specified category.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) and Weeks 4, 8, 16 and 20

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	70	54	54
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=65,70,54,54,72,69)	-3.30 (\pm 6.54)	-4.96 (\pm 5.49)	-4.12 (\pm 6.28)	-5.51 (\pm 5.64)
Week 8 (n=62,68,50,52,70,69)	-4.98 (\pm 7.49)	-6.99 (\pm 6.78)	-4.27 (\pm 5.92)	-7.25 (\pm 6.29)
Week 16 (n=58,66,50,51,68,70)	-5.61 (\pm 7.45)	-9.43 (\pm 6.86)	-4.52 (\pm 6.68)	-8.05 (\pm 7.43)

Week 20 (n=57,64,49,50,67,66)	-6.40 (± 7.82)	-10.04 (± 7.22)	-5.35 (± 7.17)	-7.54 (± 7.94)
-------------------------------	----------------	-----------------	----------------	----------------

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	70		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=65,70,54,54,72,69)	-3.78 (± 4.73)	-5.26 (± 5.16)		
Week 8 (n=62,68,50,52,70,69)	-4.92 (± 5.67)	-7.83 (± 6.02)		
Week 16 (n=58,66,50,51,68,70)	-6.22 (± 5.78)	-8.24 (± 7.37)		
Week 20 (n=57,64,49,50,67,66)	-6.64 (± 6.43)	-9.27 (± 6.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Weekly Itch Severity Score Minimally Important Difference Response During the 24-Week Treatment Period

End point title	Time to First Weekly Itch Severity Score Minimally Important Difference Response During the 24-Week Treatment Period
-----------------	--

End point description:

The ISS represents severity of itch on a scale ranging from 0 (none) to 3 (intense). The ISS7 score was the sum of daily ISS scores recorded by a participant at the same time each day over 7 days with an overall scale of 0 (no impact) to 21 (severe impact). Higher scores indicated greater intensity of itch. The MID for ISS7 was a change of 5.0 points. Time to first ISS7 MID response (ISS7 ≥ 5) was defined as time to reduction from baseline of 5 points or more. Kaplan-Meier estimate is presented. Baseline was defined as the sum of daily scores obtained for 7 days prior to randomization. The ITT population included all randomized participants analyzed according to the intervention group allocated by randomization.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) up to Week 24

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	70	54	54
Units: weeks				
median (confidence interval 95%)	4.0 (2.0 to 8.0)	3.0 (2.0 to 5.0)	4.0 (2.0 to 7.0)	3.0 (2.0 to 4.0)

End point values	Study C: Placebo	Study C: Dupilumab		
------------------	------------------	--------------------	--	--

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	74		
Units: weeks				
median (confidence interval 95%)	5.0 (3.0 to 7.0)	3.5 (3.0 to 5.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Angioedema Activity Score Over 7 Days (AAS7) at Weeks 12 and 24

End point title	Change From Baseline in Angioedema Activity Score Over 7 Days (AAS7) at Weeks 12 and 24
-----------------	---

End point description:

AAS is a diary in which participants document on daily basis presence or absence of angioedema during past 24hours. If angioedema is present, participants answer 5 additional questions about time of day swelling episode occurred and severity and impact on daily functioning and appearance this swelling episode has had. Each AAS item is scored between 0 (minimum) and 3 (maximum). Daily AASs range from (no episodes) to 15 (severe episodes) points. AAS7 score is sum of daily AAS scores reported by participant at same time of each day over 7 days, with range of 0 (no angioedema episodes) to 105 (highest angioedema severity). Higher scores indicate greater angioedema activity. Mean is presented. Baseline: sum of the daily scores for the 7 days prior to the day of randomization. Analysis was performed on ITT population. Only those participants with angioedema at baseline and with data collected at specified timepoints are reported. Here, n=participants analyzed for specified category.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) and Weeks 12 and 24

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	27	32	20
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 12 (n=31,27,32,19,18,11)	-23.46 (± 21.76)	-19.14 (± 18.89)	-16.74 (± 21.74)	-19.41 (± 34.44)
Week 24 (n=29,26,28,20,21,12)	-23.56 (± 23.04)	-18.76 (± 22.85)	-15.83 (± 25.73)	-13.95 (± 37.22)

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	12		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 12 (n=31,27,32,19,18,11)	-32.14 (± 32.15)	-34.33 (± 36.19)		
Week 24 (n=29,26,28,20,21,12)	-31.00 (± 36.38)	-36.28 (± 27.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Well-controlled Participants (Urticaria Control Test ≥ 12) at Weeks 12 and 24

End point title	Percentage of Well-controlled Participants (Urticaria Control Test ≥ 12) at Weeks 12 and 24
-----------------	---

End point description:

The UCT assessed urticaria control based on 4 items (severity of pruritus and wheals urticaria symptoms; frequency of treatment being not sufficient; QoL impairment; overall urticarial control). Each item was rated on a 5-point Likert-type scale from 0 (no control) to 4 (maximum control). The overall UCT score was the sum of all 4 individual item scores with a range of 0 (no disease control) to 16 (complete disease control). Higher scores indicated greater disease control. An UCT score of ≥ 12 (out of maximum 16) indicated a well-controlled urticaria disease status. The ITT population included all randomized participants analyzed according to the intervention group allocated by randomization.

End point type	Secondary
----------------	-----------

End point timeframe:

Weeks 12 and 24

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	70	54	54
Units: percentage of participants				
number (not applicable)				
Week 12	27.9	44.3	18.5	51.9
Week 24	30.9	48.6	20.4	44.4

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	74		
Units: percentage of participants				
number (not applicable)				
Week 12	22.1	37.8		
Week 24	39.0	50.0		

Statistical analyses

Secondary: Change From Baseline in Health-related Quality-of-life as Measured by Children's Dermatology Life Quality Index (CDLQI) in Participants ≥ 6 to <16 Years old at Weeks 12 and 24

End point title	Change From Baseline in Health-related Quality-of-life as Measured by Children's Dermatology Life Quality Index (CDLQI) in Participants ≥ 6 to <16 Years old at Weeks 12 and 24
-----------------	--

End point description:

CDLQI measures impact of skin disease on children's HRQoL; contains 10 questions (symptoms feelings associated with disease, impact of disease on leisure, school or holidays, personal relationships, sleep & side effects of treatment for skin disease); recall period of 7 days. 9 of 10 questions scored on 4-point Likert scale from 0 (not at all/question unanswered) to 3 (very much). Question 7 has additional possible response (prevented school) and assigned score of 3 (0 [not at all] to 3 [definitely]). Total CDLQI score = sum of score of each question ranging 0 (no impact) to 30 (severe impact). Higher score = greater impact on child's HRQoL. Mean is presented. Baseline: last available value up to randomization date and prior to first dose of study intervention. ITT population. Only those participants ≥ 6 and <16 years with data collected at specified timepoints are reported. n = participants analyzed for specified category. 99999 = number analyzed was 0; 9999 = standard deviation not calculated for 1 participant.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) and Weeks 12 and 24

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	2	0 ^[39]	1
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 12 (n=1,2,0,1,5,2)	-5.00 (\pm 9999)	-8.00 (\pm 5.66)	()	-7 (\pm 9999)
Week 24 (0,2,0,1,5,2)	99999 (\pm 99999)	-12.50 (\pm 12.02)	()	-7 (\pm 9999)

Notes:

[39] - No participants were analyzed.

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	2		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 12 (n=1,2,0,1,5,2)	-4.60 (\pm 10.04)	-9.00 (\pm 2.83)		
Week 24 (0,2,0,1,5,2)	-5.60 (\pm 7.83)	-4.50 (\pm 7.78)		

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) in Participants ≥ 16 Years old at Weeks 12 and 24

End point title	Change From Baseline in Health-related Quality-of-life (HRQoL) as Measured by Dermatology Life Quality Index (DLQI) in Participants ≥ 16 Years old at Weeks 12 and 24
-----------------	--

End point description:

DLQI assesses impact of skin disease on participants' HRQoL over previous week; contains 10 questions related to symptoms, leisure activities, work/school or holiday time, personal relationships including intimate, side effects of treatment, and emotional reactions to having a skin disease. Questions (except question 7) scored on 4-point Likert scale: 0 (not at all), 1 (a little), 2 (a lot), 3 (very much). Question 7 about work/studying asked whether work/study was prevented; then (if "No") to what degree the skin condition has been a problem at work/study; item again rated on 3-point Likert scale: 0 (not at all) to 3 (a lot). Total DLQI = summing score of each question; ranged from 0 (no impact) to 30 (severe impact). Higher scores indicated poor HRQoL. Baseline: last available value up to randomization date and prior to first dose of study intervention. ITT population. Only those participants ≥ 16 years with data collected at specified timepoints are reported. n = participants analyzed for specified category.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) and Weeks 12 and 24

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	65	51	47
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 12 (n=65,65,51,47,67,70)	-7.55 (\pm 7.47)	-8.55 (\pm 6.27)	-4.53 (\pm 6.28)	-6.77 (\pm 6.92)
Week 24 (n=61,64,49,45,63,67)	-7.56 (\pm 8.13)	-9.50 (\pm 5.92)	-4.96 (\pm 6.87)	-6.91 (\pm 7.51)

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	70		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 12 (n=65,65,51,47,67,70)	-5.01 (\pm 6.25)	-6.61 (\pm 7.04)		
Week 24 (n=61,64,49,45,63,67)	-6.81 (\pm 6.54)	-8.09 (\pm 7.66)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression of Change (PGIC) of Chronic Spontaneous Urticaria at Weeks 12 and 24

End point title	Patient Global Impression of Change (PGIC) of Chronic Spontaneous Urticaria at Weeks 12 and 24
-----------------	--

End point description:

The PGIC is a 1-item questionnaire that asks the participant to provide the overall self-assessment of change in their CSU on a 7-point scale compared to just before participant started taking the study intervention. Response choices are: 0 (very much better), 1 (moderately better), 2 (a little better), 3 (no change), 4 (a little worse), 5 (moderately worse), 6 (very much worse). Higher score indicate worsening. The ITT population included all randomized participants analyzed according to the intervention group allocated by randomization. Only those participants with data collected at Weeks 12 and 24 are reported. Here, n=participants analyzed for specified category.

End point type	Secondary
----------------	-----------

End point timeframe:

Weeks 12 and 24

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	69	54	52
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 12 (n=66,69,54,52,73,73)	1.68 (± 1.43)	1.10 (± 1.24)	2.06 (± 1.29)	1.62 (± 1.46)
Week 24 (n=61,68,50,50,68,70)	1.70 (± 1.50)	1.04 (± 1.51)	1.90 (± 1.64)	1.44 (± 1.55)

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	73		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 12 (n=66,69,54,52,73,73)	1.59 (± 1.23)	1.27 (± 1.44)		
Week 24 (n=61,68,50,50,68,70)	1.18 (± 1.36)	1.01 (± 1.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient Global Impression of Severity (PGIS) of Chronic Spontaneous Urticaria at Weeks 12 and 24

End point title	Change From Baseline in Patient Global Impression of Severity (PGIS) of Chronic Spontaneous Urticaria at Weeks 12 and 24
-----------------	--

End point description:

The PGIS is a 1-item questionnaire that asks participants to provide the overall self-assessment of their disease severity on a 4-point scale for the past week. Response choices are: 1 (none), 2 (mild), 3 (moderate), 4 (severe). Higher score indicate more severity. Baseline was defined as the last available value up to randomization date and prior to the first dose of study intervention. The ITT population included all randomized participants analyzed according to the intervention group allocated by randomization. Only those participants with data collected at specified timepoints are reported. Here, n=participants analyzed for a specified category.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) and Weeks 12 and 24

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	69	54	52
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 12 (n=66,69,54,52,73,73)	-0.89 (± 0.98)	-1.23 (± 0.93)	-0.46 (± 0.93)	-1.15 (± 1.04)
Week 24 (n=61,68,50,50,68,70)	-0.97 (± 1.18)	-1.44 (± 0.92)	-0.54 (± 1.16)	-0.96 (± 1.05)

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	73		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 12 (n=66,69,54,52,73,73)	-0.82 (± 0.98)	-0.95 (± 0.97)		
Week 24 (n=61,68,50,50,68,70)	-1.03 (± 1.09)	-1.33 (± 1.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Oral Corticosteroid (OCS) use for Chronic Spontaneous Urticaria During the 24-week Treatment Period

End point title	Time to First Oral Corticosteroid (OCS) use for Chronic Spontaneous Urticaria During the 24-week Treatment Period
-----------------	---

End point description:

Participants receiving OCS as rescue medications for CSU were recorded by the Investigator in e-case report form (eCRF) during the 24-week treatment period. Kaplan-Meier estimate for time to first OCS use is presented. The ITT population included all randomized participants analyzed according to the intervention group allocated by randomization.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) up to Week 24

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	70	54	54
Units: weeks				
median (confidence interval 95%)	0.110 (0.048 to 0.200)	0.087 (0.035 to 0.168)	0.158 (0.074 to 0.271)	0.116 (0.047 to 0.220)

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	74		
Units: weeks				
median (confidence interval 95%)	0.067 (0.025 to 0.138)	0.014 (0.001 to 0.068)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Receiving Oral Corticosteroid for Chronic Spontaneous Urticaria During the 24-week Treatment Period

End point title	Percentage of Participants Receiving Oral Corticosteroid for Chronic Spontaneous Urticaria During the 24-week Treatment Period
-----------------	--

End point description:

Percentage of participants receiving OCS as rescue medications for CSU were recorded by the Investigator in eCRF during the 24-week treatment period. The ITT population included all randomized participants analyzed according to the intervention group allocated by randomization.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) up to Week 24

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	70	54	54
Units: percentage of participants				
number (not applicable)	10.3	8.6	14.8	11.1

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	74		

Units: percentage of participants				
number (not applicable)	6.5	1.4		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)
-----------------	--

End point description:

An AE was any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. SAE was any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent disability/incapacity, was a congenital anomaly/birth defect or was an important medical event. TEAEs were defined as AEs that developed, worsened or became serious during the TE period. The safety population included all participants randomly assigned to study intervention and who took at least 1 dose of study intervention. As pre-specified in the protocol and SAP, the results are presented by study and treatment group/intervention.

End point type	Secondary
----------------	-----------

End point timeframe:

From first dose of study intervention (Day 1) up to end of follow-up, approximately 36 weeks each for Study A, B and C

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	70	54	54
Units: participants				
TEAEs	40	38	29	33
TESAEs	5	2	2	3

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	74		
Units: participants				
TEAEs	41	40		
TESAEs	1	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Anti-drug Antibodies (ADA) Against Dupilumab

End point title	Number of Participants With Treatment-emergent Anti-drug Antibodies (ADA) Against Dupilumab
-----------------	---

End point description:

Blood samples were collected at specified timepoints and ADA samples were assayed using validated methods. Treatment-emergent ADA response was defined as a positive response in the ADA assay post first dose when baseline results were negative or missing. Number of participants with treatment-emergent ADA response is presented. The ADA population included all participants in the safety population who had at least 1 non-missing ADA result after first dose of the study intervention.

End point type	Secondary
----------------	-----------

End point timeframe:

Up to Week 24

End point values	Study A: Placebo	Study A: Dupilumab	Study B: Placebo	Study B: Dupilumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	69	53	52
Units: participants	1	9	2	10

End point values	Study C: Placebo	Study C: Dupilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	72		
Units: participants	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study intervention (Day 1) up to end of follow-up, approximately 36 weeks each for Study A, B and C

Adverse event reporting additional description:

Analysis was performed on the safety population. As pre-specified in the protocol and SAP, the results are presented by study and treatment group/intervention.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	27.0
--------------------	------

Reporting groups

Reporting group title	Study A: Placebo
-----------------------	------------------

Reporting group description:

Participants who were omalizumab naïve received placebo matched to dupilumab as SC injection including loading dose from Day 1 up to 24 weeks.

Reporting group title	Study C: Dupilumab
-----------------------	--------------------

Reporting group description:

Participants who were omalizumab naïve received dupilumab for 24 weeks as follows:

- 300 mg SC injection q2w for adults and those adolescents who weighed ≥ 60 kg at screening starting from Week 2 following a loading dose of 600 mg (2×300 mg injections) on Day 1,
- 200 mg SC injection q2w for adolescents who weighed < 60 kg and children (≥ 6 to < 12 years of age) who weighed ≥ 30 kg at screening starting from Week 2 following a loading dose of 400 mg (2×200 mg injections) on Day 1 and
- 300 mg SC injection q4w for children (≥ 6 to < 12 years of age) who weighed < 30 kg and ≥ 15 kg at screening starting from Week 4 following a loading dose of 600 mg (2×300 mg injections) on Day 1.

Reporting group title	Study B: Dupilumab
-----------------------	--------------------

Reporting group description:

Participants who were intolerant or incomplete responders to omalizumab received dupilumab for 24 weeks as follows:

- 300 mg SC injection q2w for adults and those adolescents weighing ≥ 60 kg at screening starting from Week 2 following a loading dose of 600 mg (2×300 mg injections) on Day 1 or
- 200 mg SC injection q2w for adolescents weighing < 60 kg at screening starting from Week 2 following a loading dose of 400 mg (2×200 mg injections) on Day 1.

Reporting group title	Study C: Placebo
-----------------------	------------------

Reporting group description:

Participants who were omalizumab naïve received placebo matched to dupilumab as SC injection including loading dose from Day 1 up to 24 weeks.

Reporting group title	Study A: Dupilumab
-----------------------	--------------------

Reporting group description:

Participants who were omalizumab naïve received dupilumab for 24 weeks as follows:

- 300 mg SC injection q2w for adults and those adolescents who weighed ≥ 60 kg at screening starting from Week 2 following a loading dose of 600 mg (2×300 mg injections) on Day 1,
- 200 mg SC injection q2w for adolescents who weighed < 60 kg and children (≥ 6 to < 12 years of age) who weighed ≥ 30 kg at screening starting from Week 2 following a loading dose of 400 mg (2×200 mg injections) on Day 1 and
- 300 mg SC injection q4w for children (≥ 6 to < 12 years of age) who weighed < 30 kg and ≥ 15 kg at screening starting from Week 4 following a loading dose of 600 mg (2×300 mg injections) on Day 1.

Reporting group title	Study B: Placebo
-----------------------	------------------

Reporting group description:

Participants who were intolerant or incomplete responders to omalizumab received placebo matched to dupilumab as SC injection including loading dose from Day 1 up to 24 weeks.

Serious adverse events	Study A: Placebo	Study C: Dupilumab	Study B: Dupilumab
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 68 (7.35%)	5 / 74 (6.76%)	3 / 54 (5.56%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colorectal Adenocarcinoma			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	0 / 54 (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
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	0 / 54 (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
Cardiac disorders			
Angina Unstable			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	0 / 54 (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
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	0 / 54 (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
Haemorrhoids			
subjects affected / exposed	0 / 68 (0.00%)	0 / 74 (0.00%)	0 / 54 (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
Intestinal Obstruction			
subjects affected / exposed	0 / 68 (0.00%)	0 / 74 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	0 / 54 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	0 / 54 (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
Asthma			
subjects affected / exposed	0 / 68 (0.00%)	0 / 74 (0.00%)	0 / 54 (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
Hepatobiliary disorders			
Hepatic Steatosis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	0 / 54 (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
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	0 / 54 (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
Dermatitis Atopic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	0 / 54 (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
Chronic Spontaneous Urticaria			
subjects affected / exposed	0 / 68 (0.00%)	0 / 74 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Idiopathic Angioedema			
subjects affected / exposed	0 / 68 (0.00%)	0 / 74 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 68 (0.00%)	0 / 74 (0.00%)	0 / 54 (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
Completed Suicide			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pain In Extremity			
subjects affected / exposed	0 / 68 (0.00%)	0 / 74 (0.00%)	0 / 54 (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
Osteoarthritis			
subjects affected / exposed	0 / 68 (0.00%)	0 / 74 (0.00%)	0 / 54 (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
Infections and infestations			
Pneumonia Bacterial			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	0 / 54 (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
Covid-19 Pneumonia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	0 / 54 (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

Serious adverse events	Study C: Placebo	Study A: Dupilumab	Study B: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 77 (1.30%)	2 / 70 (2.86%)	2 / 54 (3.70%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colorectal Adenocarcinoma			

subjects affected / exposed	0 / 77 (0.00%)	0 / 70 (0.00%)	0 / 54 (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
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 77 (0.00%)	0 / 70 (0.00%)	0 / 54 (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
Cardiac disorders			
Angina Unstable			
subjects affected / exposed	0 / 77 (0.00%)	0 / 70 (0.00%)	0 / 54 (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
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	0 / 77 (0.00%)	0 / 70 (0.00%)	0 / 54 (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
Haemorrhoids			
subjects affected / exposed	0 / 77 (0.00%)	1 / 70 (1.43%)	0 / 54 (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
Intestinal Obstruction			
subjects affected / exposed	0 / 77 (0.00%)	0 / 70 (0.00%)	0 / 54 (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
Nausea			
subjects affected / exposed	0 / 77 (0.00%)	0 / 70 (0.00%)	0 / 54 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	0 / 77 (0.00%)	0 / 70 (0.00%)	0 / 54 (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
Asthma			
subjects affected / exposed	1 / 77 (1.30%)	0 / 70 (0.00%)	0 / 54 (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
Hepatobiliary disorders			
Hepatic Steatosis			
subjects affected / exposed	0 / 77 (0.00%)	0 / 70 (0.00%)	0 / 54 (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
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 77 (0.00%)	0 / 70 (0.00%)	0 / 54 (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
Dermatitis Atopic			
subjects affected / exposed	0 / 77 (0.00%)	0 / 70 (0.00%)	0 / 54 (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
Chronic Spontaneous Urticaria			
subjects affected / exposed	0 / 77 (0.00%)	0 / 70 (0.00%)	0 / 54 (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
Idiopathic Angioedema			
subjects affected / exposed	0 / 77 (0.00%)	0 / 70 (0.00%)	0 / 54 (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
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 77 (0.00%)	1 / 70 (1.43%)	0 / 54 (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

Completed Suicide			
subjects affected / exposed	0 / 77 (0.00%)	0 / 70 (0.00%)	0 / 54 (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
Musculoskeletal and connective tissue disorders			
Pain In Extremity			
subjects affected / exposed	0 / 77 (0.00%)	0 / 70 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 77 (0.00%)	0 / 70 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia Bacterial			
subjects affected / exposed	0 / 77 (0.00%)	0 / 70 (0.00%)	0 / 54 (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
Covid-19 Pneumonia			
subjects affected / exposed	0 / 77 (0.00%)	0 / 70 (0.00%)	0 / 54 (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

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

Non-serious adverse events	Study A: Placebo	Study C: Dupilumab	Study B: Dupilumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 68 (27.94%)	20 / 74 (27.03%)	17 / 54 (31.48%)
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	0 / 68 (0.00%)	5 / 74 (6.76%)	3 / 54 (5.56%)
occurrences (all)	0	5	3
Vascular disorders			

Hypertension subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	0 / 74 (0.00%) 0	3 / 54 (5.56%) 3
General disorders and administration site conditions Injection Site Erythema subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 9	4 / 74 (5.41%) 10	0 / 54 (0.00%) 0
Injection Site Reaction subjects affected / exposed occurrences (all)	2 / 68 (2.94%) 10	3 / 74 (4.05%) 8	1 / 54 (1.85%) 1
Skin and subcutaneous tissue disorders Chronic Spontaneous Urticaria subjects affected / exposed occurrences (all)	6 / 68 (8.82%) 6	2 / 74 (2.70%) 2	6 / 54 (11.11%) 8
Angioedema subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 4	3 / 74 (4.05%) 3	2 / 54 (3.70%) 2
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 68 (4.41%) 3	4 / 74 (5.41%) 4	1 / 54 (1.85%) 1
Covid-19 subjects affected / exposed occurrences (all)	2 / 68 (2.94%) 2	6 / 74 (8.11%) 6	5 / 54 (9.26%) 5

Non-serious adverse events	Study C: Placebo	Study A: Dupilumab	Study B: Placebo
Total subjects affected by non-serious adverse events subjects affected / exposed	15 / 77 (19.48%)	12 / 70 (17.14%)	15 / 54 (27.78%)
Injury, poisoning and procedural complications Accidental Overdose subjects affected / exposed occurrences (all)	2 / 77 (2.60%) 2	1 / 70 (1.43%) 1	2 / 54 (3.70%) 2
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	0 / 70 (0.00%) 0	1 / 54 (1.85%) 1
General disorders and administration site conditions			

Injection Site Erythema subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	3 / 70 (4.29%) 13	3 / 54 (5.56%) 4
Injection Site Reaction subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	4 / 70 (5.71%) 9	1 / 54 (1.85%) 2
Skin and subcutaneous tissue disorders			
Chronic Spontaneous Urticaria subjects affected / exposed occurrences (all)	3 / 77 (3.90%) 4	3 / 70 (4.29%) 4	3 / 54 (5.56%) 4
Angioedema subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	1 / 70 (1.43%) 1	0 / 54 (0.00%) 0
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 77 (7.79%) 6	1 / 70 (1.43%) 1	4 / 54 (7.41%) 5
Covid-19 subjects affected / exposed occurrences (all)	4 / 77 (5.19%) 4	1 / 70 (1.43%) 1	4 / 54 (7.41%) 4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 April 2020	The primary purpose of this amendment was to increase the sample size of Study A (omalizumab naïve population) based on recommendation from Food and Drug Administration to power the studies using conservative assumptions with regards to intervention effect and variability and to include children aged ≥ 6 to < 12 years (for Study A only), and to switch the primary and the key secondary endpoints to establish UAS7 as the primary endpoint for European Union (EU) and EU reference countries based on recommendations from European Medicines Agency.
29 April 2021	The primary purpose of this amendment was to plan for an interim analysis for Study B when 80 randomized participants would have completed their 24-week intervention period.
17 March 2022	The primary purpose of this amendment was to conduct a Study C with a study population and design similar to the completed Study A to meet Health Authority requirements to provide data from 2 adequate and well-controlled clinical trials to support filing of a marketing application. In addition, key Study A results and information on the Study B prespecified interim analysis outcome were added to this amended protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported