Clinical trial results:
A Phase 2/3 Study Investigating the Pharmacokinetics, Safety, and Efficacy of Dupilumab in Patients Aged 6 Months to < 6 Years with Moderate-to-Severe Atopic Dermatitis

Summary

EudraCT number	2016-000955-28
Trial protocol	DE GB PL
Global end of trial date	08 July 2021

Results information

Result version number	v1 (current)
This version publication date	22 January 2022
First version publication date	22 January 2022

Trial information

Trial identification

Sponsor protocol code	R668-AD-1539

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03346434
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Rd., Tarrytown, NY, United States, 10591
Public contact	Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com
Scientific contact	Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001501-PIP01-13
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of Part A of this study was to characterize the safety and pharmacokinetics (PK) of dupilumab administered as a single dose in pediatric subjects, greater than or equal to (≥) 6 months to less than (<) 6 years of age with severe atopic dermatitis (AD). The main objective of Part B of this study was to demonstrate the efficacy of multiple doses of dupilumab over 16 weeks of treatment when administered concomitantly with topical corticosteroids (TCS) in pediatric subjects, greater than or equal to (≥) 6 months to less than (<) 6 years of age, with moderate-to-severe AD.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 41
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	United States: 138
Worldwide total number of subjects	202
EEA total number of subjects	49

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)	31
Children (2-11 years)	171

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

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 2 parts: Part A and Part B. Part A enrolled subjects in the United States, Germany, and the United Kingdom. Part B enrolled subjects in the United States, Germany, Poland, and the United Kingdom. Subjects who enrolled in Part A of study were not eligible to participate in Part B.

Pre-assignment

Screening details:

Subjects in Part A enrolled in 2 sequential age cohorts: Cohort 1 (≥2 to <6 yrs) and Cohort 2 (≥6 months to <2 yrs). Each age cohort received dupilumab in 1 of 2 doses: 3 milligrams per kilogram (mg/kg) or 6 mg/kg. Subjects in Part B were randomized to 1 of 2 treatment groups: placebo + TCS or dupilumab 200/300 mg every four weeks (Q4W) + TCS.

Period 1

Period 1 title	Part A and Part B (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Part A was an open-label, single ascending dose, sequential cohort study and Part B was a randomized, double-blind, placebo-controlled study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 3 mg/kg

Arm description:

Subjects received a single subcutaneous (SC) injection of dupilumab at a dose of 3 mg/kg at Day 1. At week 4, subjects could roll over into an open-label extension (OLE) study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 4 weeks for safety.

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

Dosage and administration details:

Subjects received SC injection of dupilumab on different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms.

Arm title	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 6 mg/kg

Arm description:

Subjects received a single SC injection of dupilumab at a dose of 6 mg/kg at Day 1. At week 4, subjects could roll over into an OLE study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 4 weeks for safety.

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

Dosage and administration details:

Subjects received SC injection of dupilumab on different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms.

Arm title	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 3 mg/kg

Arm description:

Subjects received a single SC injection of dupilumab at a dose of 3 mg/kg at Day 1. At week 4, subjects could roll over into an OLE study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 4 weeks for safety.

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

Dosage and administration details:

Subjects received SC injection of dupilumab on different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms.

Arm title	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 6 mg/kg

Arm description:

Subjects received a single SC injection of dupilumab at a dose of 6 mg/kg at Day 1. At week 4, subjects could roll over into an OLE study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 4 weeks for safety.

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

Dosage and administration details:

Subjects received SC injection of dupilumab on different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms.

Arm title	Part B: Placebo + TCS

Arm description:

Subjects received SC injection of placebo matched to dupilumab Q4W along with low potency TCS on areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy) for 16 weeks. At week 16, subjects could roll over into an OLE study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).

Arm type	Experimental
Investigational medicinal product name	TCS
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

Subjects applied low potency TCS once daily to areas with active lesions.

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

Dosage and administration details:

Subjects received SC injection placebo matched to dupilumab on different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms.

Arm title	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS

Arm description:

Subjects with baseline weight of ≥ 5 to < 15 kilogram (kg) received SC injections of 200 mg or subjects

with baseline weight ≥ 15 to < 30 kg received SC injections of 300 mg of dupilumab at Day 1 and Q4W from Week 4 to Week 12. Subjects applied daily low potency TCS on areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy) for 16 weeks. At week 16, subjects could roll over into an OLE study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, EOS period].

Arm type	Experimental
Investigational medicinal product name	TCS
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

Subjects applied low potency TCS once daily to areas with active lesions.

Investigational medicinal product name	Dupilumab
Investigational medicinal product code	REGN668
Other name	DUPIXENT®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received SC injection of dupilumab on different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms

Number of subjects in period 1	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 3 mg/kg	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 6 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 3 mg/kg
Started	10	10	10
Completed Part A	10	10	9
Completed Part B	0 [1]	0 [2]	0 [3]
Completed	10	10	9
Not completed	0	0	1
Consent withdrawn by subject	-	-	1
Subject randomised in error	-	-	-
Subjects transitioned to OLE study	-	-	-
Lost to follow-up	-	-	-

Number of subjects in period 1	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 6 mg/kg	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS
Started	10	79	83
Completed Part A	10	0 [4]	0 [5]
Completed Part B	0 [6]	1	1
Completed	10	1	1
Not completed	0	78	82
Consent withdrawn by subject	-	1	-
Subject randomised in error	-	1	-
Subjects transitioned to OLE study	-	75	81

Lost to follow-up	-	1	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: 10 subjects completed Part A of the study and all subjects transitioned to OLE study at Week 4.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: 10 subjects completed Part A of the study and all subjects transitioned to OLE study at Week 4.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: 10 subjects completed Part A of the study, out of which 9 subjects transitioned to OLE study at Week 4.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects who completed Part B, thus not entering OLE period were reported in this milestone for more clarity of study design.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects who completed Part B, thus not entering OLE period were reported in this milestone for more clarity of study design.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: 10 subjects completed Part A of the study and all subjects transitioned to OLE study at Week 4.

Baseline characteristics

Reporting groups

Reporting group title	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 3 mg/kg

Reporting group description:

Subjects received a single subcutaneous (SC) injection of dupilumab at a dose of 3 mg/kg at Day 1. At week 4, subjects could roll over into an open-label extension (OLE) study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 4 weeks for safety.

Reporting group title	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 6 mg/kg

Reporting group description:

Subjects received a single SC injection of dupilumab at a dose of 6 mg/kg at Day 1. At week 4, subjects could roll over into an OLE study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 4 weeks for safety.

Reporting group title	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 3 mg/kg

Reporting group description:

Subjects received a single SC injection of dupilumab at a dose of 3 mg/kg at Day 1. At week 4, subjects could roll over into an OLE study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 4 weeks for safety.

Reporting group title	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 6 mg/kg

Reporting group description:

Subjects received a single SC injection of dupilumab at a dose of 6 mg/kg at Day 1. At week 4, subjects could roll over into an OLE study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 4 weeks for safety.

Reporting group title	Part B: Placebo + TCS

Reporting group description:

Subjects received SC injection of placebo matched to dupilumab Q4W along with low potency TCS on areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy) for 16 weeks. At week 16, subjects could roll over into an OLE study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).

Reporting group title	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS

Reporting group description:

Subjects with baseline weight of ≥ 5 to < 15 kilogram (kg) received SC injections of 200 mg or subjects with baseline weight ≥ 15 to < 30 kg received SC injections of 300 mg of dupilumab at Day 1 and Q4W from Week 4 to Week 12. Subjects applied daily low potency TCS on areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy) for 16 weeks. At week 16, subjects could roll over into an OLE study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, EOS period].

Reporting group values	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 3 mg/kg	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 6 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 3 mg/kg
Number of subjects	10	10	10
Age categorical Units: Subjects			
6 months - <2 years	0	0	10
≥2 years and <6 years	10	10	0
Gender categorical Units: Subjects			
Female	4	3	1
Male	6	7	9

Eczema Area and Severity Index (EASI)			
EASI score is used to measure severity and extent of AD and measured erythema, infiltration, excoriation and lichenification on 4 anatomic regions of body: head, trunk, upper and lower extremities. Total EASI score ranges from 0 (minimum) to 72 (maximum) points, with higher scores indicating worse severity of AD. Part A: Safety analysis set (SAF) included all subjects who received any study drug and were analysed based on actual treatment received. Part B: Full analysis set (FAS) included all randomised subjects and analyses were based on treatment allocated at randomisation (as randomised).			
Units: Score on a Scale			
arithmetic mean	35.2	40.2	34.4
standard deviation	± 9.21	± 11.81	± 14.25

Reporting group values	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 6 mg/kg	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS
Number of subjects	10	79	83
Age categorical			
Units: Subjects			
6 months - <2 years	10	5	6
≥2 years and <6 years	0	74	77
Gender categorical			
Units: Subjects			
Female	2	24	39
Male	8	55	44
Eczema Area and Severity Index (EASI)			
EASI score is used to measure severity and extent of AD and measured erythema, infiltration, excoriation and lichenification on 4 anatomic regions of body: head, trunk, upper and lower extremities. Total EASI score ranges from 0 (minimum) to 72 (maximum) points, with higher scores indicating worse severity of AD. Part A: Safety analysis set (SAF) included all subjects who received any study drug and were analysed based on actual treatment received. Part B: Full analysis set (FAS) included all randomised subjects and analyses were based on treatment allocated at randomisation (as randomised).			
Units: Score on a Scale			
arithmetic mean	36.1	33.1	35.1
standard deviation	± 12.94	± 12.18	± 13.88

Reporting group values	Total		
Number of subjects	202		
Age categorical			
Units: Subjects			
6 months - <2 years	31		
≥2 years and <6 years	171		
Gender categorical			
Units: Subjects			
Female	73		
Male	129		
Eczema Area and Severity Index (EASI)			
EASI score is used to measure severity and extent of AD and measured erythema, infiltration, excoriation and lichenification on 4 anatomic regions of body: head, trunk, upper and lower extremities. Total EASI score ranges from 0 (minimum) to 72 (maximum) points, with higher scores indicating worse severity of AD. Part A: Safety analysis set (SAF) included all subjects who received any study drug and were analysed based on actual treatment received. Part B: Full analysis set (FAS) included all randomised subjects and analyses were based on treatment allocated at randomisation (as randomised).			
Units: Score on a Scale			
arithmetic mean			

standard deviation	-		

End points

End points reporting groups

Reporting group title	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 3 mg/kg

Reporting group description:

Subjects received a single subcutaneous (SC) injection of dupilumab at a dose of 3 mg/kg at Day 1. At week 4, subjects could roll over into an open-label extension (OLE) study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 4 weeks for safety.

Reporting group title	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 6 mg/kg

Reporting group description:

Subjects received a single SC injection of dupilumab at a dose of 6 mg/kg at Day 1. At week 4, subjects could roll over into an OLE study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 4 weeks for safety.

Reporting group title	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 3 mg/kg

Reporting group description:

Subjects received a single SC injection of dupilumab at a dose of 3 mg/kg at Day 1. At week 4, subjects could roll over into an OLE study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 4 weeks for safety.

Reporting group title	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 6 mg/kg

Reporting group description:

Subjects received a single SC injection of dupilumab at a dose of 6 mg/kg at Day 1. At week 4, subjects could roll over into an OLE study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 4 weeks for safety.

Reporting group title	Part B: Placebo + TCS

Reporting group description:

Subjects received SC injection of placebo matched to dupilumab Q4W along with low potency TCS on areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy) for 16 weeks. At week 16, subjects could roll over into an OLE study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]).

Reporting group title	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS

Reporting group description:

Subjects with baseline weight of ≥ 5 to < 15 kilogram (kg) received SC injections of 200 mg or subjects with baseline weight ≥ 15 to < 30 kg received SC injections of 300 mg of dupilumab at Day 1 and Q4W from Week 4 to Week 12. Subjects applied daily low potency TCS on areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy) for 16 weeks. At week 16, subjects could roll over into an OLE study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, EOS period].

Primary: Part A: Maximum Observed Serum Concentration (Cmax) of Functional Dupilumab

End point title	Part A: Maximum Observed Serum Concentration (Cmax) of Functional Dupilumab[1][2]

End point description:

Serum concentration of functional dupilumab was reported. The Pharmacokinetic Analysis Set (PKAS) included all treated subjects who received any study drug (safety analysis set) and who had at least 1 non-missing functional dupilumab measurement following the administration of the first dose of study drug.

End point type	Primary

End point timeframe:

Post-dose on Days 1, 3, 8, 18, and 29

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Data for this endpoint was planned to be reported for Part A arms only.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part A arms only.

End point values	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 3 mg/kg	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 6 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 3 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	10	10	10
Units: Milligrams per Liter (mg/L)				
arithmetic mean (standard deviation)	25.2 (± 7.44)	49.8 (± 11.3)	20.1 (± 6.81)	46.1 (± 11.1)

Statistical analyses

No statistical analyses for this end point

Primary: Part A: Dose Normalized Maximum Observed Serum Concentration (Cmax/Dose) of Dupilumab

End point title	Part A: Dose Normalized Maximum Observed Serum Concentration (Cmax/Dose) of Dupilumab[3][4]

End point description:

Dose normalized was calculated as Cmax obtained directly from the concentration versus time curve divided by dose. PKAS included all treated subjects who received any study drug (safety analysis set) and who had at least 1 non-missing functional dupilumab measurement following the administration of the first dose of study drug. Cmax/dose was measured in Milligrams per Liter/Milligrams per Kilogram ([mg/L]/[mg/kg]).

End point type	Primary

End point timeframe:

Post-dose on Days 1, 3, 8, 18, and 29

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Data for this endpoint was planned to be reported for Part A arms only.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part A arms only.

End point values	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 3 mg/kg	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 6 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 3 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	10	10	10
Units: [mg/L]/[mg/kg]				
arithmetic mean (standard deviation)	8.39 (± 2.48)	8.30 (± 1.89)	6.70 (± 2.27)	7.68 (± 1.86)

Statistical analyses

No statistical analyses for this end point

Primary: Part A: Time to Reach the Maximum Serum Concentration (tmax) of Dupilumab

End point title	Part A: Time to Reach the Maximum Serum Concentration (tmax) of Dupilumab[5][6]

End point description:

Tmax was obtained directly from the concentration versus time curve. PKAS included all treated subjects who received any study drug (safety analysis set) and who had at least 1 non-missing functional dupilumab measurement following the administration of the first dose of study drug.

End point type	Primary

End point timeframe:

Post-dose on Days 1, 3, 8, 18, and 29

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Data for this endpoint was planned to be reported for Part A arms only.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part A arms only.

End point values	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 3 mg/kg	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 6 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 3 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	10	10	10
Units: Days				
median (full range (min-max))	1.92 (1.72 to 3.02)	1.97 (1.87 to 7.82)	1.95 (1.75 to 3.08)	2.10 (1.80 to 7.99)

Statistical analyses

No statistical analyses for this end point

Primary: Part A: Last Quantifiable Serum Concentration (Clast) of Dupilumab

End point title	Part A: Last Quantifiable Serum Concentration (Clast) of Dupilumab[7][8]

End point description:

Clast is the last measurable serum concentration of dupilumab. PKAS included all treated subjects who received any study drug (safety analysis set) and who had at least 1 non-missing functional dupilumab measurement following the administration of the first dose of study drug.

End point type	Primary

End point timeframe:

Post-dose on Days 1, 3, 8, 18, and 29

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Data for this endpoint was planned to be reported for Part A arms only.

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

End point values	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 3 mg/kg	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 6 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 3 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	10	10	10
Units: mg/L				
arithmetic mean (standard deviation)	6.64 (± 6.16)	6.14 (± 4.69)	5.64 (± 4.52)	15.1 (± 9.48)

Statistical analyses

No statistical analyses for this end point

Primary: Part A: Time of the Last Quantifiable Serum Concentration (tlast) of Dupilumab

End point title	Part A: Time of the Last Quantifiable Serum Concentration (tlast) of Dupilumab[9][10]

End point description:

Tlast was defined as the last time point with a measurable serum concentration of dupilumab. PKAS included all treated subjects who received any study drug (safety analysis set) and who had at least 1 non-missing functional dupilumab measurement following the administration of the first dose of study drug.

End point type	Primary

End point timeframe:

Post-dose on Days 1, 3, 8, 18, and 29

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Data for this endpoint was planned to be reported for Part A arms only.

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part A arms only.

End point values	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 3 mg/kg	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 6 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 3 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	10	10	10
Units: Days				
median (full range (min-max))	14.8 (6.79 to 28.0)	26.5 (15.0 to 32.0)	8.56 (6.88 to 16.9)	16.0 (6.95 to 28.0)

Statistical analyses

No statistical analyses for this end point

Primary: Part A: Area Under the Serum Concentration-Time Curve from Time Zero to the Time of the Last Measurable Concentration (AUClast) of Dupilumab

End point title	Part A: Area Under the Serum Concentration-Time Curve from Time Zero to the Time of the Last Measurable Concentration (AUClast) of Dupilumab[11][12]

End point description:

AUClast was defined as area under the serum concentration time-curve from zero to the last measured concentration. PKAS included all treated subjects who received any study drug (safety analysis set) and who had at least 1 non-missing functional dupilumab measurement following the administration of the first dose of study drug.

End point type	Primary

End point timeframe:

Post-dose on Days 1, 3, 8, 18, and 29

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Data for this endpoint was planned to be reported for Part A arms only.

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part A arms only.

End point values	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 3 mg/kg	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 6 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 3 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	10	10	10
Units: Days*Milligrams per Liter (day*mg/L)				
arithmetic mean (standard deviation)	198 (± 125)	622 (± 184)	123 (± 86.0)	493 (± 294)

Statistical analyses

No statistical analyses for this end point

Primary: Part A: Dose Normalized Area Under the Serum Concentration-Time Curve from Time Zero to the Time of the Last Measurable Concentration (AUClast/Dose) of Dupilumab

End point title	Part A: Dose Normalized Area Under the Serum Concentration-Time Curve from Time Zero to the Time of the Last Measurable Concentration (AUClast/Dose) of Dupilumab[13][14]

End point description:

Dose normalized AUClast was calculated by AUClast/dose. PKAS included all treated subjects who received any study drug (safety analysis set) and who had at least 1 non-missing functional dupilumab measurement following the administration of the first dose of study drug.

End point type	Primary

End point timeframe:

Post-dose on Days 1, 3, 8, 18, and 29

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was reported for this endpoint

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part A arms only.

End point values	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 3 mg/kg	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 6 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 3 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	10	10	10
Units: [day*mg/L]/[mg/kg]				
arithmetic mean (standard deviation)	66.0 (± 41.6)	104 (± 30.6)	41.0 (± 28.7)	82.1 (± 48.9)

Statistical analyses

No statistical analyses for this end point

Primary: Part A: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs)

End point title	Part A: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs)[15][16]

End point description:

Adverse Event (AE) was defined as any untoward medical occurrence in a subject administered a study drug which may/may not have a causal relationship with study drug. Serious AE (SAE) was defined as any untoward medical occurrence that resulted in any of following outcomes: death, life-threatening, required initial/prolonged in-participant hospitalization, persistent/significant disability/incapacity, congenital anomaly/birth defect/considered as medically important event. TEAE was defined as AE starting/worsening after first intake of study drug. TEAEs included subjects with both SAEs and non-SAEs. Number of subjects with TEAEs were reported. The safety analysis set (SAF) included all subjects who received any study drug and were analysed based on the actual treatment received.

End point type	Primary

End point timeframe:

Baseline up to Week 4

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was reported for this endpoint

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part A arms only.

End point values	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 3 mg/kg	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 6 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 3 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: Subjects	3	2	7	7

Statistical analyses

No statistical analyses for this end point

Primary: Part A: Number of Subjects with TEAEs by Severity According to Qualitative Toxicity Scale

End point title	Part A: Number of Subjects with TEAEs by Severity According to Qualitative Toxicity Scale[17][18]

End point description:

Severity of TEAEs were graded using Qualitative Toxicity Scale, as follows: Mild: Subject is aware of the event or symptom, but the event or symptom is easily tolerated; Moderate: Subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity; Severe: Significant impairment of functioning: the Subject is unable to carry out his or her usual activities. Number of subjects with TEAEs by severity were reported. The SAF included all subjects who received any study drug and were analysed based on the actual treatment received.

End point type	Primary

End point timeframe:

Baseline up to Week 4

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was reported for this endpoint

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part A arms only.

End point values	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 3 mg/kg	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 6 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 3 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: Subjects				
Mild	1	2	4	5
Moderate	2	0	2	2
Severe	0	0	1	0

Statistical analyses

No statistical analyses for this end point

Primary: Part B: Percentage of Subjects With Investigator's Global Assessment (IGA) Score 0 or 1 at Week 16

End point title	Part B: Percentage of Subjects With Investigator's Global Assessment (IGA) Score 0 or 1 at Week 16[19]

End point description:

The IGA is an assessment scale used in clinical studies to rate the severity of AD globally, based on a 5-point scale ranging from 0 to 4 where 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe. A negative change from baseline indicated improvement. Percentage of subjects with IGA score of '0' or '1' is reported. The FAS included all randomised subjects. Efficacy analyses were based on the treatment allocated at randomisation (as randomised). Missing data due to withdrawn consent, adverse event (AE), lack of efficacy were imputed as non responder. Missing data due to any other reason including COVID-19 were imputed using multiple imputation (MI). Subjects were considered as non-responders after initiation of rescue treatment.

End point type	Primary

End point timeframe:

Week 16

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part B arms only.

End point values	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	83		
Units: Percentage of Subjects				
number (confidence interval 95%)	3.9 (-0.42 to 8.21)	27.7 (18.45 to 38.62)		

Statistical analyses

Statistical analysis title	Placebo + TCS vs Dupilumab 200/300 mg Q4W
Comparison groups	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS v Part B: Placebo + TCS
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	23.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.27
upper limit	34.37

Notes:

[20] - Threshold for significance at 0.05 level.

Primary: Part B: Percentage of Subjects with Eczema Area and Severity Index (EASI) -75 (EASI-75) (≥75% Improvement from Baseline) at Week 16

End point title	Part B: Percentage of Subjects with Eczema Area and Severity Index (EASI) -75 (EASI-75) (≥75% Improvement from Baseline) at Week 16[21]

End point description:

The EASI score is used to measure the severity and extent of AD and measured erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper, and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores indicating the worse severity of AD. EASI-75 responders were the subjects who achieved ≥75% overall improvement in EASI score from baseline at Week 16. The FAS included all randomised subjects. Efficacy analyses were based on the treatment allocated at randomisation (as randomised). Missing data due to withdrawn consent, AE, lack of efficacy were imputed as non responder. Missing data due to any other reason including COVID-19 were imputed using MI. Subjects were considered as non-responders after initiation of rescue treatment.

End point type	Primary

End point timeframe:

Week 16

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part B arms only.

End point values	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	83		
Units: Percentage of Subjects				
number (confidence interval 95%)	10.7 (3.65 to 17.74)	53.0 (41.74 to 64.07)		

Statistical analyses

Statistical analysis title	Placebo + TCS vs Dupilumab 200/300 mg Q4W
Comparison groups	Part B: Placebo + TCS v Part B: Dupilumab 200 mg or 300 mg Q4W + TCS
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [22]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	42.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	29.47
upper limit	55.16

Notes:

[22] - Threshold for significance at 0.05 level.

Secondary: Part A: Number of Subjects with Serious TEAEs and Severe TEAEs

End point title	Part A: Number of Subjects with Serious TEAEs and Severe TEAEs[23]

End point description:

Adverse Event (AE) was defined as any untoward medical occurrence in a subject administered a study drug which may/may not have a causal relationship with study drug. A serious TEAE was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect. Severe TEAE: significant impairment of functioning the subject is unable to carry out his or her usual activities. The SAF included all subjects who received any study drug and were analysed based on the actual treatment received.

End point type	Secondary

End point timeframe:

Baseline up to Week 4

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part A arms only.

End point values	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 3 mg/kg	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 6 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 3 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: Subjects				
Subjects with serious TEAEs	1	0	1	0
Subjects with severe TEAEs	0	0	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Percent Change From Baseline in EASI Score at Week 4

End point title	Part A: Percent Change From Baseline in EASI Score at Week

End point description:

The EASI score is used to measure the severity and extent of AD and measured erythema, infiltration, excoriation, and lichenification on 4 anatomic regions of the body: head, trunk, upper, and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores indicated the worse severity of AD. A negative change from baseline indicated improvement. The SAF included all subjects who received any study drug and was analysed based on the actual treatment received.

End point type	Secondary

End point timeframe:

Week 4

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part A arms only.

End point values	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 3 mg/kg	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 6 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 3 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: Percent Change				
arithmetic mean (standard deviation)	-26.6 (± 47.37)	-48.7 (± 28.89)	-22.4 (± 42.52)	-43.2 (± 35.55)

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Percent Change From Baseline in SCORing Atopic Dermatitis (SCORAD) Score at Week 4

End point title	Part A: Percent Change From Baseline in SCORing Atopic Dermatitis (SCORAD) Score at Week 4[25]

End point description:

SCORAD was used to assess the extent and severity of AD. Extent and severity of eczema as well as subjective symptoms (insomnia, etc) were assessed and scored. SCORAD total score ranges from 0 (absent disease) to 103 (severe disease). A negative change from baseline indicated improvement. SAF included all subjects who received any study drug and was analysed based on the actual treatment received.

End point type	Secondary

End point timeframe:

Week 4

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part A arms only.

End point values	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 3 mg/kg	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 6 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 3 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: Percent Change				
arithmetic mean (standard deviation)	-18.6 (± 26.18)	-31.9 (± 17.45)	-22.4 (± 26.44)	-28.1 (± 27.84)

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Percentage of Subjects with IGA Score 0 or 1 at Week 4

End point title	Part A: Percentage of Subjects with IGA Score 0 or 1 at Week

End point description:

The IGA is an assessment scale used in clinical studies to rate the severity of AD globally, based on a 5-point scale ranging from 0 to 4 where 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe. Percentage of subjects with IGA score of '0' or '1' were reported. SAF included all subjects who received any study drug and was analysed based on the actual treatment received.

End point type	Secondary

End point timeframe:

Week 4

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part A arms only.

End point values	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 3 mg/kg	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 6 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 3 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: Percentage of Subjects				
number (confidence interval 95%)	10.0 (0.25 to 44.50)	0.0 (0.00 to 30.85)	10.0 (0.25 to 44.50)	10.0 (0.25 to 44.50)

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Number of Subjects with At least One Positive Treatment-Emergent Anti-Drug Antibodies (ADA)

End point title	Part A: Number of Subjects with At least One Positive Treatment-Emergent Anti-Drug Antibodies (ADA)[27]

End point description:

Treatment boosted (TB) Response: Any post-dose positive result at least 9-fold over the baseline level when baseline is positive; Treatment emergent (TE) Response: Post-dose positive result when baseline results were negative. The ADA Analysis Set (AAS) included all treated subjects who received any study drug and who had at least 1 non-missing ADA result following the first dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to Day 57

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part A arms only.

End point values	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 3 mg/kg	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 6 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 3 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 6 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	10
Units: Subjects				
TB Response	0	0	1	0
TE Response	5	4	5	5

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Subjects with Serious TEAEs and Skin Infection TEAEs (Excluding Herpetic Infections) Through Week 16

End point title	Part B: Number of Subjects with Serious TEAEs and Skin Infection TEAEs (Excluding Herpetic Infections) Through Week 16[28]

End point description:

Adverse Event (AE) was defined as any untoward medical occurrence in a subject administered a study drug which may/may not have a causal relationship with study drug. A serious TEAE was defined as any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. Skin infection TEAEs were identified based on blinded adjudication of all reported TEAEs under the 2 primary System Organ Classes (SOC): SOC = 'Infection and Infestations' or SOC = 'Skin and Subcutaneous Tissue Disorders.' SAF included all randomized subjects who received at least one dose of study drug and was analysed as treated.

End point type	Secondary

End point timeframe:

Baseline through Week 16

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part B arms only.

End point values	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	83		
Units: Subjects				
Subjects with serious TEAEs	4	0		
Subjects with skin infection TEAEs	19	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Subjects with At least One Positive Treatment-Emergent ADA

End point title	Part B: Number of Subjects with At least One Positive Treatment-Emergent ADA[29]

End point description:

Treatment emergent (TE): Post-dose positive result when baseline results were negative. AAS included all subjects who received any study drug and who had at least one non-missing ADA result after the first dose of the study drug.

End point type	Secondary

End point timeframe:

Baseline up to Day 197

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part B arms only.

End point values	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	74		
Units: Subjects	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Percent Change From Baseline in EASI Score at Week 16

End point title	Part B: Percent Change From Baseline in EASI Score at Week 16[30]

End point description:

The EASI score is used to measure the severity and extent of AD and measures erythema, infiltration, excoriation, and lichenification on 4 anatomic regions of the body: head, trunk, upper, and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores indicating the worse severity of AD. A negative change from baseline indicated improvement. FAS included all randomised subjects. Efficacy analyses were based on the treatment allocated at randomisation (as randomised). Missing data due to withdrawn consent, AE, or lack of efficacy and data after rescue were imputed by post baseline worst observation carried forward (WOCF). If there was no post baseline assessment, the baseline value was used. Missing values due to other reasons including COVID-19 were imputed by MI approach.

End point type	Secondary

End point timeframe:

Week 16

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part B arms only.

End point values	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	83		
Units: Percent Change				
least squares mean (standard error)	-19.6 (± 5.13)	-70.0 (± 4.85)		

Statistical analyses

Statistical analysis title	Placebo + TCS vs Dupilumab 200/300 mg Q4W
Comparison groups	Part B: Placebo + TCS v Part B: Dupilumab 200 mg or 300 mg Q4W + TCS
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [31]
Method	ANCOVA
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-50.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-62.38
upper limit	-38.4

Notes:

[31] - Threshold for significance at 0.05 level.

Secondary: Part B: Percent Change From Baseline in Weekly Average of Daily Worst Scratch/Itch/Numerical Rating Scale (NRS) at Week 16

End point title	Part B: Percent Change From Baseline in Weekly Average of Daily Worst Scratch/Itch/Numerical Rating Scale (NRS) at Week 16[32]

End point description:

Pruritus NRS is an assessment tool used to report intensity of subject's pruritus (itch), both average & maximum intensity, during 24-hr recall period. Subjects were asked two questions: 1) For average itch intensity: how would you rate your itch overall (on average) during the previous 24 hrs; 2) For maximum itch intensity: How would you rate your itch at the worst moment during the previous 24 hrs? Both questions were rated on a scale: 0-10 with 0=no itch & 10=worst itch imaginable. A negative change from baseline indicated improvement. The FAS included all randomised subjects. Efficacy analyses were based on the treatment allocated at randomisation (as randomised). Missing data due to withdrawn consent, AE, or lack of efficacy and data after rescue were imputed by post baseline WOCF. If there was no post baseline assessment, the baseline value was used. Missing values due to other reasons including COVID-19 were imputed by MI approach.

End point type	Secondary

End point timeframe:

Week 16

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part B arms only.

End point values	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	83		
Units: Percent Change				
least squares mean (standard error)	-2.2 (± 5.22)	-49.4 (± 5.03)		

Statistical analyses

Statistical analysis title	Placebo + TCS vs Dupilumab 200/300 mg Q4W
Comparison groups	Part B: Placebo + TCS v Part B: Dupilumab 200 mg or 300 mg Q4W + TCS
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [33]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-47.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-59.47
upper limit	-34.79

Notes:

[33] - Threshold for significance at 0.05 level.

Secondary: Part B: Percentage of Subjects with Improvement (Reduction From Baseline) of Weekly Average of Daily Worst Scratch/Itch/NRS ≥4 Points at Week 16

End point title	Part B: Percentage of Subjects with Improvement (Reduction From Baseline) of Weekly Average of Daily Worst Scratch/Itch/NRS ≥4 Points at Week 16[34]

End point description:

Pruritus NRS is an assessment tool used to report intensity of subject's pruritus (itch), both average & maximum intensity, during 24-hr recall period. Subjects were asked two questions: 1) For average itch intensity: how would you rate your itch overall (on average) during the previous 24 hrs; & 2) For maximum itch intensity: How would you rate your itch at the worst moment during the previous 24 hrs? Both questions were rated on a scale: 0-10 with 0=no itch & 10=worst itch imaginable. The FAS included all randomised subjects. Efficacy analyses were based on the treatment allocated at randomisation (as randomised). Missing data due to withdrawn consent, AE, lack of efficacy were imputed as non responder. Missing data due to any other reason including COVID-19 were imputed using MI. Subjects were considered as non-responders after initiation of rescue treatment.

End point type	Secondary

End point timeframe:

Week 16

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part B arms only.

End point values	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	83		
Units: Percentage of Subjects				
number (confidence interval 95%)	8.9 (2.25 to 15.51)	48.1 (37.05 to 59.15)		

Statistical analyses

Statistical analysis title	Placebo + TCS vs Dupilumab 200/300 mg Q4W
Comparison groups	Part B: Placebo + TCS v Part B: Dupilumab 200 mg or 300 mg Q4W + TCS
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [35]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	39.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	26.18
upper limit	52.27

Notes:

[35] - Threshold for significance at 0.05 level.

Secondary: Part B: Percentage of Subjects with Improvement (Reduction From Baseline) of Weekly Average of Daily Worst Scratch/Itch/NRS ≥3 Points at Week 16

End point title	Part B: Percentage of Subjects with Improvement (Reduction From Baseline) of Weekly Average of Daily Worst Scratch/Itch/NRS ≥3 Points at Week 16[36]

End point description:

Pruritus NRS is an assessment tool used to report intensity of subject's pruritus (itch), both average & maximum intensity, during 24-hr recall period. Subjects were asked two questions: 1) For average itch intensity: how would you rate your itch overall (on average) during the previous 24 hrs; & 2) For maximum itch intensity: How would you rate your itch at the worst moment during the previous 24 hrs? Both questions were rated on a scale: 0-10 with 0=no itch & 10=worst itch imaginable. The FAS included all randomised subjects. Efficacy analyses were based on the treatment allocated at randomisation (as randomised). Missing data due to withdrawn consent, AE, lack of efficacy were imputed as non responder. Missing data due to any other reason including COVID-19 were imputed using MI. Subjects were considered as non-responders after initiation of rescue treatment.

End point type	Secondary

End point timeframe:

Week 16

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part B arms only.

End point values	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	83		
Units: Percentage of Subjects				
number (confidence interval 95%)	9.9 (2.59 to 17.22)	53.3 (42.29 to 64.22)		

Statistical analyses

Statistical analysis title	Placebo + TCS vs Dupilumab 200/300 mg Q4W
Comparison groups	Part B: Placebo + TCS v Part B: Dupilumab 200 mg or 300 mg Q4W + TCS
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [37]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	43.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	30.03
upper limit	56.67

Notes:

[37] - Threshold for significance at 0.05 level.

Secondary: Part B: Percentage of Subjects Who Achieved EASI-50 (≥50% Improvement From Baseline) at Week 16

End point title	Part B: Percentage of Subjects Who Achieved EASI-50 (≥50% Improvement From Baseline) at Week 16[38]

End point description:

The EASI score is used to measure the severity and extent of AD and measured erythema, infiltration, excoriation, and lichenification on 4 anatomic regions of the body: head, trunk, upper, and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores indicating the worse severity of AD. EASI-50 responders were the subjects who achieved ≥50% overall improvement in EASI score from baseline at Week 16. The FAS included all randomised subjects. Efficacy analyses were based on the treatment allocated at randomisation (as randomised). Missing data due to withdrawn consent, AE, lack of efficacy were imputed as non responder. Missing data due to any other reason including COVID-19 were imputed using MI. Subjects were considered as non-responders after initiation of rescue treatment.

End point type	Secondary

End point timeframe:

Week 16

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part B arms only.

End point values	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	83		
Units: Percentage of Subjects				
number (confidence interval 95%)	20.2 (11.09 to 29.23)	68.7 (57.56 to 78.41)		

Statistical analyses

Statistical analysis title	Placebo + TCS vs Dupilumab 200/300 mg Q4W
Comparison groups	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS v Part B: Placebo + TCS
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [39]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	48.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	35.03
upper limit	62

Notes:

[39] - Threshold for significance at 0.05 level.

Secondary: Part B: Percentage of Subjects Who Achieved EASI-90 (≥90% Improvement From Baseline) at Week 16

End point title	Part B: Percentage of Subjects Who Achieved EASI-90 (≥90% Improvement From Baseline) at Week 16[40]

End point description:

The EASI score is used to measure the severity and extent of AD and measured erythema, infiltration, excoriation, and lichenification on 4 anatomic regions of the body: head, trunk, upper, and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores indicating the worse severity of AD. EASI-90 responders were the subjects who achieved ≥90% overall improvement in EASI score from baseline at Week 16. The FAS included all randomised subjects. Efficacy analyses were based on the treatment allocated at randomisation (as randomised). Missing data due to withdrawn consent, AE, lack of efficacy were imputed as non responder. Missing data due to any other reason including COVID-19 were imputed using MI. Subjects were considered as non-responders after initiation of rescue treatment.

End point type	Secondary

End point timeframe:

Week 16

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part B arms only.

End point values	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	83		
Units: Percentage of Subjects				
number (confidence interval 95%)	2.8 (-1.02 to 6.66)	25.3 (16.39 to 36.04)		

Statistical analyses

Statistical analysis title	Placebo + TCS vs Dupilumab 200/300 mg Q4W
Comparison groups	Part B: Placebo + TCS v Part B: Dupilumab 200 mg or 300 mg Q4W + TCS
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [41]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference
Point estimate	22.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.37
upper limit	32.6

Notes:

[41] - Threshold for significance at 0.05 level.

Secondary: Part B: Change From Baseline in Percent Body Surface Area (BSA) Affected by Atopic Dermatitis (AD) at Week 16

End point title	Part B: Change From Baseline in Percent Body Surface Area (BSA) Affected by Atopic Dermatitis (AD) at Week 16[42]

End point description:

BSA affected by AD was assessed for each section of the body (the possible highest score for each region was: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]). It was reported as a percentage of all major body sections combined. A negative change from baseline indicated improvement. The FAS included all randomised subjects. Efficacy analyses were based on the treatment allocated at randomisation (as randomised). Missing data due to withdrawn consent, AE, or lack of efficacy and data after rescue were imputed by post baseline WOCF. If there was no post baseline assessment, the baseline value was used. Missing values due to other reasons including COVID-19 were imputed by MI approach.

End point type	Secondary

End point timeframe:

Week 16

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part B arms only.

End point values	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	83		
Units: Percent of BSA				
least squares mean (standard error)	-10.74 (± 2.926)	-35.00 (± 2.815)		

Statistical analyses

Statistical analysis title	Placebo + TCS vs Dupilumab 200/300 mg Q4W
Comparison groups	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS v Part B: Placebo + TCS
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [43]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-24.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.204
upper limit	-17.329

Notes:

[43] - Threshold for significance at 0.05 level.

Secondary: Part B: Change From Baseline in Patient Oriented Eczema Measure (POEM) at Week 16

End point title	Part B: Change From Baseline in Patient Oriented Eczema Measure (POEM) at Week 16[44]

End point description:

The POEM is a 7-item questionnaire that assesses disease symptoms (dryness, itching, flaking, cracking, sleep loss, bleeding and weeping) with a scoring system of 0 (absent disease) to 28 (severe disease) (high score indicative of poor quality of life [QOL]). A negative change from baseline indicated improvement. The FAS included all randomised subjects. Efficacy analyses were based on the treatment allocated at randomisation (as randomised). Missing data due to withdrawn consent, AE, or lack of efficacy and data after rescue were imputed by post baseline WOCF. If there was no post baseline assessment, the baseline value was used. Missing values due to other reasons including COVID-19 were imputed by MI approach.

End point type	Secondary

End point timeframe:

Week 16

Notes:

[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part B arms only.

End point values	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	83		
Units: Score on a Scale				
least squares mean (standard error)	-3.8 (± 0.92)	-12.9 (± 0.89)		

Statistical analyses

Statistical analysis title	Placebo + TCS vs Dupilumab 200/300 mg Q4W
Comparison groups	Part B: Placebo + TCS v Part B: Dupilumab 200 mg or 300 mg Q4W + TCS
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [45]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-9.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.26
upper limit	-6.89

Notes:

[45] - Threshold for significance at 0.05 level.

Secondary: Part B: Percent Change From Baseline in SCORing Atopic Dermatitis (SCORAD) at Week 16

End point title	Part B: Percent Change From Baseline in SCORing Atopic Dermatitis (SCORAD) at Week 16[46]

End point description:

The SCORAD index is a clinical tool for assessing the severity of atopic dermatitis (AD). Extent and intensity of eczema as well as subjective signs (insomnia, etc.) are assessed and scored. Total score ranges from 0 (absent disease) to 103 (severe disease). A negative change from baseline indicated improvement. The FAS included all randomised subjects. Efficacy analyses were based on the treatment allocated at randomisation (as randomised). Missing data due to withdrawn consent, AE, or lack of efficacy and data after rescue were imputed by post baseline WOCF. If there was no post baseline assessment, the baseline value was used. Missing values due to other reasons including COVID-19 were imputed by MI approach.

End point type	Secondary

End point timeframe:

Week 16

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part B arms only.

End point values	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	83		
Units: Percent Change				
least squares mean (standard error)	-16.2 (± 3.54)	-54.7 (± 3.39)		

Statistical analyses

Statistical analysis title	Placebo + TCS vs Dupilumab 200/300 mg Q4W
Comparison groups	Part B: Placebo + TCS v Part B: Dupilumab 200 mg or 300 mg Q4W + TCS
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [47]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-38.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-46.65
upper limit	-30.21

Notes:

[47] - Threshold for significance at 0.05 level.

Secondary: Part B: Change from Baseline in Subject's Sleep Quality NRS at Week 16

End point title	Part B: Change from Baseline in Subject's Sleep Quality NRS at Week 16[48]

End point description:

A sleep diary was completed by the parent/caregiver, included 2 questions assessing the caregiver's sleep, and 6 questions assessing the child's sleep based on caregiver observation. Sleep diary items, either alone or in combination served as subjective measures of sleep quality, difficulty falling asleep, nighttime awakenings, and sleep duration. Sleep quality was measured using an 11-point NRS (0 to 10) in which 0 indicated worst possible sleep while 10 indicated best possible sleep. The FAS included all randomised subjects. Efficacy analyses were based on the treatment allocated at randomisation (as randomised). Missing data due to withdrawn consent, AE, or lack of efficacy and data after rescue were imputed by post baseline WOCF. If there was no post baseline assessment, the baseline value was used. Missing values due to other reasons including COVID-19 were imputed by MI approach.

End point type	Secondary

End point timeframe:

Week 16

Notes:

[48] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part B arms only.

End point values	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	83		
Units: Score on a Scale				
least squares mean (standard error)	0.34 (± 0.256)	2.04 (± 0.251)		

Statistical analyses

Statistical analysis title	Placebo + TCS vs Dupilumab 200/300 mg Q4W
Comparison groups	Part B: Placebo + TCS v Part B: Dupilumab 200 mg or 300 mg Q4W + TCS
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [49]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.093
upper limit	2.317

Notes:

[49] - Threshold significance was at 0.05 level.

Secondary: Part B: Change from Baseline in Subject's Skin Pain NRS at Week 16

End point title	Part B: Change from Baseline in Subject's Skin Pain NRS at Week 16[50]

End point description:

Skin pain was assessed by the parent/caregiver and measured using a 11-point scale (0 to 10) in which 0 indicated no pain while 10 indicated worst pain possible. A negative change from baseline indicated improvement. The FAS included all randomised subjects. Efficacy analyses were based on the treatment allocated at randomisation (as randomised). Missing data due to withdrawn consent, AE, or lack of efficacy and data after rescue were imputed by post baseline WOCF. If there was no post baseline assessment, the baseline value was used. Missing values due to other reasons including COVID-19 were imputed by MI approach.

End point type	Secondary

End point timeframe:

Week 16

Notes:

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was planned to be reported for Part B arms only.

End point values	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	83		
Units: Score on a Scale				
least squares mean (standard error)	-0.62 (± 0.302)	-3.93 (± 0.295)		

Statistical analyses

Statistical analysis title	Placebo + TCS vs Dupilumab 200/300 mg Q4W
Comparison groups	Part B: Placebo + TCS v Part B: Dupilumab 200 mg or 300 mg Q4W + TCS
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [51]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-3.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.029
upper limit	-2.6

Notes:

[51] - Threshold significance at 0.05 level.

Secondary: Part B: Change From Baseline in Dermatitis Family Index (DFI) at Week 16

End point title	Part B: Change From Baseline in Dermatitis Family Index (DFI) at Week 16[52]

End point description:

DFI is a 10-item questionnaire with items inquiring about housework, food preparation, sleep, family leisure activity, shopping, expenditure, tiredness, emotional distress, relationships, and impact of helping with treatment on the primary caregiver's life. DFI questions were scored on a four-point Likert scale ranging from 0 to 3, so that the total DFI score ranges from 0 to 30. Timeframe of reference was the past week. A higher DFI score indicated greater impairment in family Quality of life (QOL) as affected by atopic dermatitis. A negative change from baseline indicated improvement. FAS included all randomised subjects. Efficacy analyses were based on the treatment allocated at randomisation (as randomised). Missing data due to withdrawn consent, AE, or lack of efficacy and data after rescue were imputed by post baseline WOCF. If there was no post baseline assessment, the baseline value was used. Missing values due to other reasons including COVID-19 were imputed by MI approach.

End point type	Secondary

End point timeframe:

Week 16

Notes:

[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part B arms only.

End point values	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	83		
Units: Score on a Scale				
least squares mean (standard error)	-2.68 (± 0.839)	-10.48 (± 0.806)		

Statistical analyses

Statistical analysis title	Placebo + TCS vs Dupilumab 200/300 mg Q4W
Comparison groups	Part B: Placebo + TCS v Part B: Dupilumab 200 mg or 300 mg Q4W + TCS
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [53]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-7.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.789
upper limit	-5.814

Notes:

[53] - Threshold significance at 0.05 level.

Secondary: Part B: Change From Baseline in Children's Dermatology Life Quality Index (CDLQI) at Week 16

End point title	Part B: Change From Baseline in Children's Dermatology Life Quality Index (CDLQI) at Week 16[54]

End point description:

CDLQI is a validated 10 question tool to measure impact of skin disease on QOL in children by assessing how much the skin problem has affected the subjects over past week. Nine questions were scored as follows: Very much = 3, Quite a lot = 2, Only a little = 1, Not at all or unanswered = 0. Question 7 has an added possible response, which was scored as 3. CDLQI equals the sum of the score of each question (max. = 30, min. = 0). Higher the score, the greater the impact on QOL. A negative change from baseline indicated improvement. FAS included all randomised subjects. Efficacy analyses were based on the treatment allocated at randomisation (as randomised). Subjects ≥4 years of age were evaluated for this endpoint. Missing data due to withdrawn consent, AE, or lack of efficacy and data after rescue were imputed by post baseline WOCF. If there was no post baseline assessment, the baseline value was used. Missing values due to other reasons including COVID-19 were imputed by MI approach.

End point type	Secondary

End point timeframe:

Week 16

Notes:

[54] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part B arms only.

End point values	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	47		
Units: Score on a Scale				
least squares mean (standard error)	-2.5 (± 1.66)	-10.0 (± 1.56)		

Statistical analyses

Statistical analysis title	Placebo + TCS vs Dupilumab 200/300 mg Q4W
Comparison groups	Part B: Placebo + TCS v Part B: Dupilumab 200 mg or 300 mg Q4W + TCS
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [55]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-7.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.29
upper limit	-4.75

Notes:

[55] - Threshold significance at 0.05 level.

Secondary: Part B: Change from Baseline in Infants' Dermatology Quality of Life Index (IDQOL) at Week 16

End point title	Part B: Change from Baseline in Infants' Dermatology Quality of Life Index (IDQOL) at Week 16[56]

End point description:

Infants' Dermatitis Quality of Life Index (IDQOL) were used to evaluate quality of life for subjects of age less than 4 years. IDQOL questionnaires were designed for infants (below the age of 4 years) with atopic dermatitis. The IDQOL was calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score in each questionnaire, the more quality of life is impaired. A negative change from baseline indicated improvement. The FAS included all randomised subjects. Efficacy analyses were based on the treatment allocated at randomisation (as randomised). Missing data due to withdrawn consent, AE, or lack of efficacy and data after rescue were imputed by post baseline WOCF. If there was no post baseline assessment, the baseline value was used. Missing values due to other reasons including COVID-19 were imputed by MI approach.

End point type	Secondary

End point timeframe:

Week 16

Notes:

[56] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part B arms only.

End point values	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	36		
Units: Score on a Scale				
least squares mean (standard error)	-1.95 (± 1.078)	-10.91 (± 1.159)		

Statistical analyses

Statistical analysis title	Placebo + TCS vs Dupilumab 200/300 mg Q4W
Comparison groups	Part B: Placebo + TCS v Part B: Dupilumab 200 mg or 300 mg Q4W + TCS
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [57]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-8.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.711
upper limit	-6.202

Notes:

[57] - Threshold significance at 0.05 level.

Secondary: Part B: Percentage of Topical Corticosteroid (TCS) Medication-free Days From Baseline to Week 16

End point title	Part B: Percentage of Topical Corticosteroid (TCS) Medication-free Days From Baseline to Week 16[58]

End point description:

Percentage of TCS medication-free days was calculated as the number of days that a subject used neither TCS/TCI nor system rescue therapy divided by the study days. The FAS included all randomised subjects. Efficacy analyses were based on the treatment allocated at randomisation (as randomised).

End point type	Secondary

End point timeframe:

Baseline up to Week 16

Notes:

[58] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part B arms only.

End point values	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	82		
Units: Percentage of Days				
median (full range (min-max))	0.04 (0.0 to 0.9)	0.21 (0.0 to 1.0)		

Statistical analyses

Statistical analysis title	Placebo + TCS vs Dupilumab 200/300 mg Q4W
Comparison groups	Part B: Placebo + TCS v Part B: Dupilumab 200 mg or 300 mg Q4W + TCS
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0015 [59]
Method	ANCOVA

Notes:

[59] - Threshold significance is at 0.05 level.

Secondary: Part B: Mean Weekly Dose of Low Potency TCS in Grams From Baseline to Week 16

End point title	Part B: Mean Weekly Dose of Low Potency TCS in Grams From Baseline to Week 16[60]

End point description:

Mean weekly dose of TCS in grams/week for low potency TCS from baseline to Week 16 were reported. The FAS included all randomised subjects. Efficacy analyses were based on the treatment allocated at randomisation (as randomised).

End point type	Secondary

End point timeframe:

Baseline up to Week 16

Notes:

[60] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part B arms only.

End point values	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	81		
Units: Grams per Week				
least squares mean (standard error)	13.4 (± 1.44)	10.5 (± 1.39)		

Statistical analyses

Statistical analysis title	Placebo + TCS vs Dupilumab 200/300 mg Q4W
Comparison groups	Part B: Placebo + TCS v Part B: Dupilumab 200 mg or 300 mg Q4W + TCS
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0997 [61]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.35
upper limit	0.56

Notes:

[61] - Threshold significance at 0.05 level.

Secondary: Part B: Mean Weekly Dose of TCS in Grams for Medium or High Potency TCS From Baseline to Week 16

End point title	Part B: Mean Weekly Dose of TCS in Grams for Medium or High Potency TCS From Baseline to Week 16[62]

End point description:

Mean weekly dose of TCS in grams/week for medium or high potency TCS from baseline to Week 16 were reported. The FAS included all randomised subjects. Efficacy analyses were based on the treatment allocated at randomisation (as randomised).

End point type	Secondary

End point timeframe:

Baseline up to Week 16

Notes:

[62] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part B arms only.

End point values	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	24		
Units: Grams per Week				
least squares mean (standard error)	6.1 (± 1.70)	3.0 (± 1.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Mean of Caregiver Missed Work Days Through Week 16

End point title	Part B: Mean of Caregiver Missed Work Days Through Week

End point description:

Mean of caregiver missed work days through Week 16 was reported. The FAS included all randomised subjects. Efficacy analyses were based on the treatment allocated at randomisation (as randomised).

End point type	Secondary

End point timeframe:

Baseline through Week 16

Notes:

[63] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was planned to be reported for Part B arms only.

End point values	Part B: Placebo + TCS	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: Days				
arithmetic mean (standard deviation)	5.05 (± 8.975)	2.49 (± 5.524)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From day of first treatment until the end of study

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1, 23.1

Reporting groups

Reporting group title	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 3 mg/kg

Reporting group description:

Subjects received a single subcutaneous (SC) injection of dupilumab at a dose of 3 mg/kg at Day 1. At week 4, subjects could roll over into an open-label extension (OLE) study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 4 weeks for safety.
(Part A: MedDRA version 21.1)

Reporting group title	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS

Reporting group description:

Subjects with baseline weight of ≥ 5 to < 15 kilogram (kg) received SC injections of 200 mg or subjects with baseline weight ≥ 15 to < 30 kg received SC injections of 300 mg of dupilumab at Day 1 and Q4W from Week 4 to Week 12. Subjects applied daily low potency TCS on areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy) for 16 weeks. At week 16, subjects could roll over into an OLE study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, EOS period]. (Part B: MedDRA version 23.1)

Reporting group title	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 6 mg/kg

Reporting group description:

Subjects received a single SC injection of dupilumab at a dose of 6 mg/kg at Day 1. At week 4, subjects could roll over into an OLE study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 4 weeks for safety. (Part A: MedDRA version 21.1)

Reporting group title	Part B: Placebo + TCS

Reporting group description:

Subjects received SC injection of placebo matched to dupilumab Q4W along with low potency TCS on areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy) for 16 weeks. At week 16, subjects could roll over into an OLE study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 12 weeks for safety ([Week 28, end of study (EOS) period]). (Part B: MedDRA version 23.1)

Reporting group title	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 6 mg/kg

Reporting group description:

Subjects received a single SC injection of dupilumab at a dose of 6 mg/kg at Day 1. At week 4, subjects could roll over into an OLE study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 4 weeks for safety. (Part A: MedDRA version 21.1)

Reporting group title	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 3 mg/kg

Reporting group description:

Subjects received a single SC injection of dupilumab at a dose of 3 mg/kg at Day 1. At week 4, subjects could roll over into an OLE study (R668-AD-1434), if considered eligible. Subjects who did not enter the OLE study were followed for up to an additional 4 weeks for safety. (Part A: MedDRA version 21.1)

Serious adverse events	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 3 mg/kg	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 6 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)	0 / 83 (0.00%)	0 / 10 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 83 (0.00%)	0 / 10 (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
Hypersensitivity			
subjects affected / exposed	0 / 10 (0.00%)	0 / 83 (0.00%)	0 / 10 (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			
Dermatitis atopic			
subjects affected / exposed	0 / 10 (0.00%)	0 / 83 (0.00%)	0 / 10 (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			
Cellulitis staphylococcal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 83 (0.00%)	0 / 10 (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 infected			
subjects affected / exposed	0 / 10 (0.00%)	0 / 83 (0.00%)	0 / 10 (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
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 83 (0.00%)	0 / 10 (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

Serious adverse events	Part B: Placebo + TCS	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 6 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 3

			mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 78 (5.13%)	0 / 10 (0.00%)	1 / 10 (10.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 78 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	1 / 78 (1.28%)	0 / 10 (0.00%)	0 / 10 (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
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	1 / 78 (1.28%)	0 / 10 (0.00%)	0 / 10 (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
Infections and infestations			
Cellulitis staphylococcal			
subjects affected / exposed	1 / 78 (1.28%)	0 / 10 (0.00%)	0 / 10 (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 infected			
subjects affected / exposed	1 / 78 (1.28%)	0 / 10 (0.00%)	0 / 10 (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
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 10 (0.00%)	0 / 10 (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

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

Non-serious adverse events	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 3 mg/kg	Part B: Dupilumab 200 mg or 300 mg Q4W + TCS	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 6 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 10 (70.00%)	29 / 83 (34.94%)	2 / 10 (20.00%)
Injury, poisoning and procedural complications			
Skin abrasion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 83 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 10 (0.00%)	3 / 83 (3.61%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Thrombocytosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 83 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 83 (1.20%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	2 / 10 (20.00%)	1 / 83 (1.20%)	0 / 10 (0.00%)
occurrences (all)	2	1	0
Eye disorders			
Lacrimation increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 83 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 10 (10.00%)	2 / 83 (2.41%)	0 / 10 (0.00%)
occurrences (all)	1	3	0
Diarrhoea			
subjects affected / exposed	1 / 10 (10.00%)	1 / 83 (1.20%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Teething			
subjects affected / exposed	1 / 10 (10.00%)	0 / 83 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal			

disorders			
Asthma			
subjects affected / exposed	0 / 10 (0.00%)	3 / 83 (3.61%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Cough			
subjects affected / exposed	1 / 10 (10.00%)	0 / 83 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	0 / 10 (0.00%)	12 / 83 (14.46%)	0 / 10 (0.00%)
occurrences (all)	0	17	0
Urticaria			
subjects affected / exposed	1 / 10 (10.00%)	1 / 83 (1.20%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	1 / 10 (10.00%)	0 / 83 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 10 (10.00%)	7 / 83 (8.43%)	1 / 10 (10.00%)
occurrences (all)	1	8	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 10 (10.00%)	5 / 83 (6.02%)	0 / 10 (0.00%)
occurrences (all)	1	5	0
Impetigo			
subjects affected / exposed	1 / 10 (10.00%)	3 / 83 (3.61%)	0 / 10 (0.00%)
occurrences (all)	1	3	0
Folliculitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 83 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Part B: Placebo + TCS	Part A: Cohort 1 (≥2 to <6 years old): Dupilumab 6 mg/kg	Part A: Cohort 2 (≥6 months to <2 years): Dupilumab 3 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 78 (57.69%)	7 / 10 (70.00%)	3 / 10 (30.00%)

Injury, poisoning and procedural complications			
Skin abrasion			
subjects affected / exposed	0 / 78 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	6 / 78 (7.69%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	9	0	0
Thrombocytosis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 78 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	7 / 78 (8.97%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	9	0	1
Eye disorders			
Lacrimation increased			
subjects affected / exposed	0 / 78 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 78 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	2 / 78 (2.56%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	2	1	0
Teething			
subjects affected / exposed	0 / 78 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	5 / 78 (6.41%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	8	0	0

Cough			
subjects affected / exposed	5 / 78 (6.41%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	6	1	0
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	24 / 78 (30.77%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	46	1	1
Urticaria			
subjects affected / exposed	4 / 78 (5.13%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	4	1	0
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	0 / 78 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 78 (8.97%)	2 / 10 (20.00%)	1 / 10 (10.00%)
occurrences (all)	8	2	1
Upper respiratory tract infection			
subjects affected / exposed	7 / 78 (8.97%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	9	1	0
Impetigo			
subjects affected / exposed	6 / 78 (7.69%)	1 / 10 (10.00%)	1 / 10 (10.00%)
occurrences (all)	7	1	1
Folliculitis			
subjects affected / exposed	0 / 78 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 July 2017	The purpose of amendment 2 was to harmonize the protocol across regions and to simplify regulatory submissions.
22 November 2019	The purpose of amendment 3 was to seek approval of the dose regimens for part B of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported