Clinical trial results:
A Phase 2A Study Investigating the Safety, Pharmacokinetics, Immunogenicity, and Exploratory Efficacy of Dupilumab in Patients Aged 6 to <18 Years With Atopic Dermatitis

Summary

EudraCT number	2014-003263-37
Trial protocol	HU DE CZ PL GB Outside EU/EEA
Global end of trial date	13 March 2016

Results information

Result version number	v2 (current)
This version publication date	31 October 2020
First version publication date	30 March 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	R668-AD-1412

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02407756
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Rd., Tarrytown, United States, 10591
Public contact	Clinical Trial Administrator, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com
Scientific contact	Clinical Trial 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To characterize the safety and pharmacokinetics (PK) of Dupilumab in pediatric subjects with moderate-to-severe atopic dermatitis (AD) (for adolescents ≥12 to <18 years of age) or severe AD (for children ≥6 to <12 years of age).

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	16 March 2015
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: 25
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Czech Republic: 3
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Canada: 12
Worldwide total number of subjects	78
EEA total number of subjects	66

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	38

Adolescents (12-17 years)	40
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 25 sites in 6 countries. A total of 88 subjects were screened between 17 Mar 2015 & 25 Sep 2015 of whom 78 subjects were randomized and 77 were treated. Ten subjects were screen failures as 5 were due to exclusion criteria met & inclusion criteria not met, 4 subjects withdrew consent and 1 subject was lost to follow-up.

Pre-assignment

Screening details:

A total of 40 adolescents (aged ≥12 to <18 years) and 38 children (aged ≥6 to <12 years) were enrolled and randomized to 2 sequential ascending dose cohorts: Cohort 1 (2 mg/kg) and Cohort 2 (4 mg/kg). Dosing started with cohort 1. Proceeding to the next cohort occurred once all initial 8 patients enrolled had been observed for at least 2 weeks.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dupilumab 2mg/kg: Adolescents

Arm description:

Dupilumab 2 mg/kg as a single dose on Day 1 followed by 8-week PK sampling period then 4 repeated doses weekly in subjects aged between ≥12 to <18 years.

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

Dosage and administration details:

Subcutaneous injection in the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs and upper arms.

Arm title	Dupilumab 2mg/kg: Children

Arm description:

Dupilumab 2 mg/kg as a single dose on Day 1 followed by 8-week PK sampling period then 4 repeated doses weekly in subjects aged between ≥6 to <12 years.

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

Dosage and administration details:

Subcutaneous injection in the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs and upper arms.

Arm title	Dupilumab 4mg/kg: Adolescents

Arm description:

Dupilumab 4 mg/kg as a single dose on Day 1 followed by 8-week PK sampling period then 4 repeated doses weekly in subjects aged between ≥12 to <18 years.

Arm type	Experimental

Investigational medicinal product name	Dupilumab
Investigational medicinal product code	REGN668, SAR231893
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection in the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs and upper arms.

Arm title	Dupilumab 4mg/kg: Children

Arm description:

Dupilumab 4 mg/kg as a single dose on Day 1 followed by 8-week PK sampling period then 4 repeated doses weekly in subjects aged between ≥6 to <12 years.

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

Dosage and administration details:

Subcutaneous injection in the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs and upper arms.

Number of subjects in period 1[1]	Dupilumab 2mg/kg: Adolescents	Dupilumab 2mg/kg: Children	Dupilumab 4mg/kg: Adolescents
Started	20	18	20
Treated	20	18	20
Completed	20	18	20

Number of subjects in period 1[1]	Dupilumab 4mg/kg: Children
Started	19
Treated	19
Completed	19

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One subject in the 4 mg/kg (Cohort 2b) arm did not receive study drug and was withdrawn from the study on study day 1 during Part A period due to withdrawal of consent (fear of study drug injection) and was not included in the analysis. Analysis was performed on safety analysis set (SAF) that included all subjects who received any study drug.

Baseline characteristics

Reporting groups	
Reporting group title	Dupilumab 2mg/kg: Adolescents
Reporting group description:	
Dupilumab 2 mg/kg as a single dose on Day 1 followed by 8-week PK sampling period then 4 repeated doses weekly in subjects aged between ≥12 to <18 years.	
Reporting group title	Dupilumab 2mg/kg: Children
Reporting group description:	
Dupilumab 2 mg/kg as a single dose on Day 1 followed by 8-week PK sampling period then 4 repeated doses weekly in subjects aged between ≥6 to <12 years.	
Reporting group title	Dupilumab 4mg/kg: Adolescents
Reporting group description:	
Dupilumab 4 mg/kg as a single dose on Day 1 followed by 8-week PK sampling period then 4 repeated doses weekly in subjects aged between ≥12 to <18 years.	
Reporting group title	Dupilumab 4mg/kg: Children
Reporting group description:	
Dupilumab 4 mg/kg as a single dose on Day 1 followed by 8-week PK sampling period then 4 repeated doses weekly in subjects aged between ≥6 to <12 years.	

Reporting group values	Dupilumab 2mg/kg: Adolescents	Dupilumab 2mg/kg: Children	Dupilumab 4mg/kg: Adolescents
Number of subjects	20	18	20
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	14.7	8.2	14.3
standard deviation	± 2.01	± 1.62	± 1.66
Gender categorical			
Units: Subjects			
Female	11	9	11
Male	9	9	9
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	20	18	20
Race			
Units: Subjects			
White	17	17	15
Black or African American	0	0	1
Asian	2	0	3
Other	1	1	1
Number of Subjects with Investigator Global Assessment (IGA) score of 3 or 4			
IGA is an assessment scale used to determine severity of AD and clinical response to treatment on a 5-point scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe) based on erythema and papulation/ infiltration. Therapeutic response is an IGA score of 0 (clear) or 1 (almost clear). Analysis was performed on SAF.			
Units: Subjects			
IGA score of 3	8	1	11

IGA score of 4	12	17	9

Eczema Area and Severity Index (EASI) score			
The EASI score was used to measure the severity and extent of atopic dermatitis (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 to 72 points, with the higher scores reflecting the worse severity of AD. Analysis was performed on Safety Analysis set (SAF).			
Units: Score on a scale			
arithmetic mean	34.8	32.9	28.6
standard deviation	± 17	± 15.53	± 14.7
Pruritus Numerical Rating Scale (NRS)			
Pruritus NRS scale is an assessment tool that is used to report the intensity of subject's pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). Weekly average obtained in the 7-day period prior to the baseline visit. Analysis was performed on SAF.			
Units: Score on a scale			
arithmetic mean	6.1	6.4	6.9
standard deviation	± 2.47	± 2.23	± 2.21
Body Surface Area (BSA) Involvement with Atopic Dermatitis (AD)			
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. Analysis was performed on SAF.			
Units: Percentage of body surface area			
arithmetic mean	52.2	59	45.9
standard deviation	± 24.78	± 22.49	± 25.34
SCORing Atopic Dermatitis (SCORAD) Score			
SCORAD is a clinical tool for assessing the severity of atopic dermatitis developed by the European Task Force on Atopic Dermatitis ("Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis". Dermatology (Basel) 186 (1): 23–31. 1993). 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]). Analysis was performed on SAF.			
Units: Score on a scale			
arithmetic mean	68	66.4	63
standard deviation	± 13.19	± 13.06	± 14.43

Reporting group values	Dupilumab 4mg/kg: Children	Total	
Number of subjects	19	77	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	8.2		
standard deviation	± 1.99	-	
Gender categorical			
Units: Subjects			
Female	8	39	
Male	11	38	

Ethnicity Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	18	76	
Race Units: Subjects			
White	18	67	
Black or African American	1	2	
Asian	0	5	
Other	0	3	
Number of Subjects with Investigator Global Assessment (IGA) score of 3 or 4			
IGA is an assessment scale used to determine severity of AD and clinical response to treatment on a 5-point scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe) based on erythema and papulation/ infiltration. Therapeutic response is an IGA score of 0 (clear) or 1 (almost clear). Analysis was performed on SAF.			
Units: Subjects			
IGA score of 3	0	20	
IGA score of 4	19	57	
Eczema Area and Severity Index (EASI) score			
The EASI score was used to measure the severity and extent of atopic dermatitis (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 to 72 points, with the higher scores reflecting the worse severity of AD. Analysis was performed on Safety Analysis set (SAF).			
Units: Score on a scale			
arithmetic mean	38.8		
standard deviation	± 18.64	-	
Pruritus Numerical Rating Scale (NRS)			
Pruritus NRS scale is an assessment tool that is used to report the intensity of subject’s pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). Weekly average obtained in the 7-day period prior to the baseline visit. Analysis was performed on SAF.			
Units: Score on a scale			
arithmetic mean	6.7		
standard deviation	± 2.35	-	
Body Surface Area (BSA) Involvement with Atopic Dermatitis (AD)			
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. Analysis was performed on SAF.			
Units: Percentage of body surface area			
arithmetic mean	62.3		
standard deviation	± 30.34	-	
SCORing Atopic Dermatitis (SCORAD) Score			
SCORAD is a clinical tool for assessing the severity of atopic dermatitis developed by the European Task Force on Atopic Dermatitis ("Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis". Dermatology (Basel) 186 (1): 23–31. 1993). 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]). Analysis was performed on SAF.			
Units: Score on a scale			
arithmetic mean	72.7		
standard deviation	± 12.96	-	

End points

End points reporting groups

Reporting group title	Dupilumab 2mg/kg: Adolescents
Reporting group description:	
Dupilumab 2 mg/kg as a single dose on Day 1 followed by 8-week PK sampling period then 4 repeated doses weekly in subjects aged between ≥12 to <18 years.	
Reporting group title	Dupilumab 2mg/kg: Children
Reporting group description:	
Dupilumab 2 mg/kg as a single dose on Day 1 followed by 8-week PK sampling period then 4 repeated doses weekly in subjects aged between ≥6 to <12 years.	
Reporting group title	Dupilumab 4mg/kg: Adolescents
Reporting group description:	
Dupilumab 4 mg/kg as a single dose on Day 1 followed by 8-week PK sampling period then 4 repeated doses weekly in subjects aged between ≥12 to <18 years.	
Reporting group title	Dupilumab 4mg/kg: Children
Reporting group description:	
Dupilumab 4 mg/kg as a single dose on Day 1 followed by 8-week PK sampling period then 4 repeated doses weekly in subjects aged between ≥6 to <12 years.	

Primary: Pharmacokinetics (PK) of dupilumab: Maximum plasma concentration observed (Cmax) after single administration

End point title	Pharmacokinetics (PK) of dupilumab: Maximum plasma concentration observed (Cmax) after single administration[1]
End point description:	
Peak dupilumab concentration in serum following single dose administration. Analysis was performed on PK analysis set that included all treated subjects who received the study medication and had at least 1 quantified (non-missing) result for dupilumab concentration following the first dose of the study drug.	
End point type	Primary
End point timeframe:	
Day 2, 4, 8, 15, 22, 29, 36, 43, and 50	

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: Statistical analysis is descriptive only. No formal statistical comparison was performed.

End point values	Dupilumab 2mg/kg: Adolescents	Dupilumab 2mg/kg: Children	Dupilumab 4mg/kg: Adolescents	Dupilumab 4mg/kg: Children
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	18	20	19
Units: mg/L				
arithmetic mean (standard deviation)	9.91 (± 2.15)	14.3 (± 5.9)	23.1 (± 8.71)	32.4 (± 7.04)

Statistical analyses

No statistical analyses for this end point

Primary: PK of dupilumab: Area under the plasma concentration versus time curve

(AUClast) after single administration

End point title	PK of dupilumab: Area under the plasma concentration versus time curve (AUClast) after single administration[2]

End point description:

Mean AUC estimates were calculated using mean concentration data at each time point, using a non-compartmental approach (NCA). Calculated AUClast (computed from time zero to the time of the last positive concentration) are presented. Analysis was performed on PK analysis set that included all treated subjects who received the study medication and had at least 1 quantified (non-missing) result for dupilumab concentration following the first dose of the study drug.

End point type	Primary

End point timeframe:

Day 2, 4, 8, 15, 22, 29, 36, 43, and 50

Notes:

[2] - 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: Statistical analysis is descriptive only. No formal statistical comparison was performed.

End point values	Dupilumab 2mg/kg: Adolescents	Dupilumab 2mg/kg: Children	Dupilumab 4mg/kg: Adolescents	Dupilumab 4mg/kg: Children
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20[3]	18[4]	20[5]	19[6]
Units: Day*mg/L				
arithmetic mean (standard deviation)	104 (± 99999)	160 (± 99999)	362 (± 99999)	330 (± 99999)

Notes:

[3] - Standard deviation was not calculated

[4] - Standard deviation was not calculated

[5] - Standard deviation was not calculated

[6] - Standard deviation was not calculated

Statistical analyses

No statistical analyses for this end point

Primary: PK of dupilumab: Trough dupilumab concentration in serum (Ctrough) before 3rd and 4th repeated dose

End point title	PK of dupilumab: Trough dupilumab concentration in serum (Ctrough) before 3rd and 4th repeated dose[7]

End point description:

Analysis was performed on PK analysis set that included all treated subjects who received the study medication and had at least 1 quantified (non-missing) result for dupilumab concentration following the first dose of study drug.

End point type	Primary

End point timeframe:

Pre-dose on Day 71 and Day 85

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: Statistical analysis is descriptive only. No formal statistical comparison was performed.

End point values	Dupilumab 2mg/kg: Adolescents	Dupilumab 2mg/kg: Children	Dupilumab 4mg/kg: Adolescents	Dupilumab 4mg/kg: Children
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	18	20	19
Units: mg/L				
arithmetic mean (standard deviation)				
Day 71	10.4 (± 7.16)	17.2 (± 8.44)	32.8 (± 18.9)	42.1 (± 19.4)
Day 85	18.5 (± 12.4)	28 (± 12.9)	58.5 (± 24.4)	60.3 (± 36.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent reduction from baseline in Eczema Area and Severity Index (EASI) at Week 12

End point title	Percent reduction from baseline in Eczema Area and Severity Index (EASI) at Week 12

End point description:

The EASI score was used to measure the severity and extent of atopic dermatitis (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 to 72 points, with the higher scores reflecting the worse severity of AD. Analysis was performed on safety analysis set (SAF) that included all subjects who received any study drug. Data after rescue treatment use during the Part B period were set to missing, then missing values were imputed by last observation carried forward (LOCF).

End point type	Secondary

End point timeframe:

Baseline to Week 12 (one week after last dose)

End point values	Dupilumab 2mg/kg: Adolescents	Dupilumab 2mg/kg: Children	Dupilumab 4mg/kg: Adolescents	Dupilumab 4mg/kg: Children
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	18	20	19
Units: percent change				
arithmetic mean (standard deviation)	-66.4 (± 29.25)	-76.2 (± 25.48)	-69.7 (± 24.48)	-63.4 (± 25.37)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent reduction from baseline in SCORing Atopic Dermatitis (SCORAD) Score at Week 12

End point title	Percent reduction from baseline in SCORing Atopic Dermatitis (SCORAD) Score at Week 12

End point description:

SCORAD is a clinical tool for assessing the severity of atopic dermatitis developed by the European Task

Force on Atopic Dermatitis ("Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis". Dermatology (Basel) 186 (1): 23–31. 1993). 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]). Analysis was performed on SAF. Data after rescue treatment use during the Part B period were set to missing, then missing values were imputed by LOCF.

End point type	Secondary

End point timeframe:

Baseline to Week 12 (one week after last dose)

End point values	Dupilumab 2mg/kg: Adolescents	Dupilumab 2mg/kg: Children	Dupilumab 4mg/kg: Adolescents	Dupilumab 4mg/kg: Children
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	18	20	19
Units: percent change				
arithmetic mean (standard deviation)	-47.7 (± 27.27)	-57.5 (± 23.1)	-43.4 (± 25.38)	-46.9 (± 24.31)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent reduction from baseline in Pruritus Numerical Rating Scale (NRS) at Week 12

End point title	Percent reduction from baseline in Pruritus Numerical Rating Scale (NRS) at Week 12

End point description:

Pruritus NRS scale is an assessment tool that is used to report the intensity of subject’s pruritus (itch), both maximum and average intensity, during a 24-hour recall period. Subjects were asked the following question: how would a subject rate his itch at the worst moment during the previous 24 hours (for maximum itch intensity on a scale of 0 – 10 [0 = no itch; 10 = worst itch imaginable]). Analysis was performed on SAF. Data after rescue treatment use during the Part B period were set to missing, then missing values were imputed by LOCF.

End point type	Secondary

End point timeframe:

Baseline to Week 12 (one week after last dose)

End point values	Dupilumab 2mg/kg: Adolescents	Dupilumab 2mg/kg: Children	Dupilumab 4mg/kg: Adolescents	Dupilumab 4mg/kg: Children
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	18	20	19
Units: Percent change				
arithmetic mean (standard deviation)	-30.8 (± 68.35)	-41.6 (± 35.32)	-37.6 (± 34.42)	-39.6 (± 40.88)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with Investigator Global Assessment (IGA) score of "0" or "1" (clear or almost clear) at Week 12

End point title	Percentage of subjects with Investigator Global Assessment (IGA) score of "0" or "1" (clear or almost clear) at Week 12

End point description:

IGA is an assessment scale used to determine severity of AD and clinical response to treatment on a 5-point scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe) based on erythema and papulation/infiltration. Therapeutic response is an IGA score of 0 (clear) or 1 (almost clear). Analysis was performed on SAF. Subjects with rescue treatment usage during the Part B period were specified as non-responders from the time the rescue was used.

End point type	Secondary

End point timeframe:

Week 12

End point values	Dupilumab 2mg/kg: Adolescents	Dupilumab 2mg/kg: Children	Dupilumab 4mg/kg: Adolescents	Dupilumab 4mg/kg: Children
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	18	20	19
Units: Percentage of subjects				
number (not applicable)	10	16.7	35	21.1

Statistical analyses

No statistical analyses for this end point

Secondary: Percent reduction from baseline in Body Surface Area (BSA) at week 12

End point title	Percent reduction from baseline in Body Surface Area (BSA) at week 12

End point description:

Body surface area 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. Analysis was performed on SAF. Here "Number of subjects analyzed" = number of subjects who were evaluated for this specific endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Dupilumab 2mg/kg: Adolescents	Dupilumab 2mg/kg: Children	Dupilumab 4mg/kg: Adolescents	Dupilumab 4mg/kg: Children
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	16	19	19
Units: Percentage of body surface area				
arithmetic mean (standard deviation)	-61 (± 31.08)	-70 (± 31.93)	-60.4 (± 34.04)	-50 (± 30.8)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to the final visit (Week 20) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Treatment Emergent Adverse Events (TEAEs) that developed/ worsened during the treatment and follow-up period (time period from the administration of first dose of study drug to End of Study (EOS) visit [8 weeks after the last dose). Analysis was performed on SAF.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Dupilumab 2mg/kg: Adolescents

Reporting group description:

Dupilumab 2 mg/kg as a single dose on Day 1 followed by 8-week PK sampling period, then 4 repeated doses weekly in subjects aged between ≥12 to <18 years.

Reporting group title	Dupilumab 2mg/kg: Children

Reporting group description:

Dupilumab 2 mg/kg as a single dose on Day 1 followed by 8-week PK sampling period, then 4 repeated doses weekly in subjects aged between ≥6 to <12 years.

Reporting group title	Dupilumab 4 mg/kg: Adolescents

Reporting group description:

Dupilumab 4 mg/kg as a single dose on Day 1 followed by 8-week PK sampling period, then 4 repeated doses weekly in subjects aged between ≥12 to <18 years.

Reporting group title	Dupilumab 4 mg/kg: Children

Reporting group description:

Dupilumab 4 mg/kg as a single dose on Day 1 followed by 8-week PK sampling period), then 4 repeated doses weekly in subjects aged between ≥6 to <12 years.

Serious adverse events	Dupilumab 2mg/kg: Adolescents	Dupilumab 2mg/kg: Children	Dupilumab 4 mg/kg: Adolescents
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	1 / 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	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (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			
Staphylococcal skin infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (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	1 / 20 (5.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Dupilumab 4 mg/kg: Children		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 19 (10.53%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Staphylococcal skin infection			

subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arthritis bacterial			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dermatitis infected			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Dupilumab 2mg/kg: Adolescents	Dupilumab 2mg/kg: Children	Dupilumab 4 mg/kg: Adolescents
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 20 (55.00%)	11 / 18 (61.11%)	16 / 20 (80.00%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	2
Chills			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	2 / 20 (10.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	4	0	0
Injection site urticaria			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Injection site swelling			

subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Injection site irritation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Injection site erythema			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Feeling of body temperature change			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Hypersensitivity			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Allergic oedema			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Asthma			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	1 / 20 (5.00%)
occurrences (all)	0	2	2
Dyspnoea			

subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	2
Rhinitis allergic			
subjects affected / exposed	2 / 20 (10.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Nasal disorder			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Anxiety			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Investigations			
Protein urine present			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Ligament sprain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Contusion			

subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Hand fracture			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Bone contusion			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Muscle strain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Post procedural inflammation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Congenital, familial and genetic disorders			
Dermoid cyst			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Cardiac disorders			
Cyanosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Akathisia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	2
Headache			
subjects affected / exposed	1 / 20 (5.00%)	1 / 18 (5.56%)	1 / 20 (5.00%)
occurrences (all)	2	1	1
Lethargy			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Syncope			

subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Eosinophilia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Aphthous stomatitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Cheilitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Vomiting			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	2 / 20 (10.00%)
occurrences (all)	1	0	2
Mouth ulceration			

subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Dermatitis contact			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Alopecia areata			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Dermatitis atopic			
subjects affected / exposed	2 / 20 (10.00%)	5 / 18 (27.78%)	3 / 20 (15.00%)
occurrences (all)	2	11	6
Alopecia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	2
Erythema			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Skin erosion			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Psoriasis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0

Pain of skin			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Solar dermatitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Vitiligo			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Haematuria			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Arthralgia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Bone pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Epiphysiolysis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

Bacterial disease carrier			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Acute tonsillitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Croup infectious			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Dermatitis infected			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	2 / 20 (10.00%)
occurrences (all)	0	1	4
Ear infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Folliculitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Gingivitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Herpes simplex			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	3
Molluscum contagiosum			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	2 / 20 (10.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0

Laryngitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Herpes virus infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	2 / 20 (10.00%)	5 / 18 (27.78%)	8 / 20 (40.00%)
occurrences (all)	3	9	11
Oral herpes			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Pharyngitis bacterial			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Paronychia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Skin bacterial infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Skin candida			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	2 / 20 (10.00%)	1 / 18 (5.56%)	1 / 20 (5.00%)
occurrences (all)	2	1	1

Tonsillitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1

Non-serious adverse events	Dupilumab 4 mg/kg: Children		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 19 (94.74%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Injection site urticaria			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	3		
Injection site swelling			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Injection site irritation			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		

Injection site erythema			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Feeling of body temperature change			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Food allergy			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hypersensitivity			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Allergic oedema			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Asthma			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	8		
Dyspnoea			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		

Rhinitis allergic subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Nasal disorder subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0 1 / 19 (5.26%) 2 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1		
Psychiatric disorders Depressed mood subjects affected / exposed occurrences (all) Anxiety subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0 0 / 19 (0.00%) 0		
Investigations Protein urine present subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0		
Injury, poisoning and procedural complications Animal bite subjects affected / exposed occurrences (all) Ligament sprain subjects affected / exposed occurrences (all) Contusion subjects affected / exposed occurrences (all) Hand fracture subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0 1 / 19 (5.26%) 1 0 / 19 (0.00%) 0 0 / 19 (0.00%) 0		

Bone contusion subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Muscle strain subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0		
Post procedural inflammation subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0		
Congenital, familial and genetic disorders Dermoid cyst subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0		
Cardiac disorders Cyanosis subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 3		
Akathisia subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0		
Headache subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 3		
Lethargy subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Syncope subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0		
Paraesthesia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		

Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Eosinophilia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	3		
Gastrointestinal disorders			
Aphthous stomatitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Cheilitis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			

Acne				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Dermatitis contact				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Alopecia areata				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Dermatitis atopic				
subjects affected / exposed	5 / 19 (26.32%)			
occurrences (all)	10			
Alopecia				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Dry skin				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Erythema				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Skin erosion				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Psoriasis				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Rash				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Pain of skin				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Solar dermatitis				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			

Vitiligo subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all)	 0 / 19 (0.00%) 0 1 / 19 (5.26%) 2		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) Haematuria subjects affected / exposed occurrences (all)	 0 / 19 (0.00%) 0 0 / 19 (0.00%) 0		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Bone pain subjects affected / exposed occurrences (all) Epiphysiolysis subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 0 / 19 (0.00%) 0 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1 0 / 19 (0.00%) 0 1 / 19 (5.26%) 1		
Infections and infestations Bacterial disease carrier subjects affected / exposed occurrences (all) Acute tonsillitis subjects affected / exposed occurrences (all)	 0 / 19 (0.00%) 0 1 / 19 (5.26%) 2		

Gastrointestinal infection				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Conjunctivitis				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	2			
Croup infectious				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Dermatitis infected				
subjects affected / exposed	2 / 19 (10.53%)			
occurrences (all)	5			
Ear infection				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Folliculitis				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Gingivitis				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Herpes simplex				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Molluscum contagiosum				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Influenza				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Laryngitis				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Herpes virus infection				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			

Nasopharyngitis				
subjects affected / exposed	10 / 19 (52.63%)			
occurrences (all)	11			
Oral herpes				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Rhinitis				
subjects affected / exposed	2 / 19 (10.53%)			
occurrences (all)	2			
Pharyngitis bacterial				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Pharyngitis streptococcal				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Paronychia				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Skin bacterial infection				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	2			
Skin candida				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Urinary tract infection				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Upper respiratory tract infection				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Tonsillitis				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Viral upper respiratory tract infection				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			

Metabolism and nutrition disorders Increased appetite subjects affected / exposed occurrences (all)	 0 / 19 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 June 2015	Following changes were made: •Changes were made regarding the use of topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) were permitted during the study to avoid subjects being unnecessarily deprived of topical medication. •Clarified the use of prescription moisturizers started prior to the study were permitted to continue during the study, but initiation of prescription moisturizers during the study was not allowed. •Clarified the definition of "childbearing potential" for the purpose of the study, and added a note regarding additional requirement for adequate contraceptive methods in certain countries to avoid ambiguity in the interpretation of the relevant exclusion criterion. •Added assessment of body surface area (BSA) affected by AD, at the same time points other efficacy assessments were being performed; added BSA related secondary endpoint. •Clarified that only subjects with a history of active infection with hepatitis B or C or evidence of active disease at screening were excluded from the study. •Clarified the duration of close monitoring required after study drug administration and assessments performed during the monitoring period. • Added text regarding opportunity for subjects who completed the study to enroll into an open-label extension study to continue Dupilumab treatment. •Reduced the amount of information gathered from subjects on pruritus based on NRS. •Clarified cheek swab sample taken for DNA extraction (removed the options of taking whole blood or saliva sample).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31595499