Clinical trial results:
A Phase 3b Multicenter, Randomized, Double-Blind, Double-Dummy, Active Controlled Study Comparing the Safety and Efficacy of Upadacitinib to Dupilumab in Adult Subjects With Moderate to Severe Atopic Dermatitis

Summary

EudraCT number	2018-002264-57
Trial protocol	DE FI GB NL SE FR HU NO ES HR IT
Global end of trial date	09 December 2020

Results information

Result version number	v2 (current)
This version publication date	12 July 2024
First version publication date	18 December 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	M16-046

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03738397
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	Global Medical Services, AbbVie, 001 800-633-9110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 800-633-9110, abbvieclinicaltrials@abbvie.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 December 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to evaluate the efficacy and safety of upadacitinib versus dupilumab for the treatment of adult subjects with moderate to severe atopic dermatitis (AD) who are candidates for systemic therapy.

Protection of trial subjects:

Subject read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 February 2019
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	Australia: 68
Country: Number of subjects enrolled	Canada: 73
Country: Number of subjects enrolled	Croatia: 5
Country: Number of subjects enrolled	Czechia: 19
Country: Number of subjects enrolled	Finland: 19
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Ireland: 5
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Malaysia: 28
Country: Number of subjects enrolled	Netherlands: 15
Country: Number of subjects enrolled	New Zealand: 27
Country: Number of subjects enrolled	Norway: 10
Country: Number of subjects enrolled	Poland: 35
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	Taiwan: 37
Country: Number of subjects enrolled	Ukraine: 9
Country: Number of subjects enrolled	United Kingdom: 12

Country: Number of subjects enrolled	United States: 179
Worldwide total number of subjects	673
EEA total number of subjects	230

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	643
From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were randomized at 128 sites located in 22 countries (Australia, Canada, Croatia, Czechia, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Malaysia, Netherlands, New Zealand, Norway, Poland, Singapore, Spain, Taiwan, Ukraine, United Kingdom, and the United States).

Pre-assignment

Screening details:

Participants were randomly assigned in a 1:1 ratio to receive upadacitinib or dupilumab. Randomization was stratified by disease severity (Validated Investigator Global Assessment Scale for Atopic Dermatitis [vIGA-AD] moderate [3] vs severe [4]) and age (<40, ≥ 40 to < 65, ≥ 65 years).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Dupilumab 300 mg EOW

Arm description:

Participants received a loading dose of 600 mg dupilumab by subcutaneous (SC) injection on Day 1 followed by 300 mg dupilumab SC every other week (EOW) until Week 22 and placebo to upadacitinib orally once a day (QD) up to Week 24.

Arm type	Active comparator
Investigational medicinal product name	Placebo to upadacitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Administered orally once a day.

Investigational medicinal product name	Dupilumab
Investigational medicinal product code	
Other name	Dupixent®
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered as a subcutaneous injection every 2 weeks after a loading dose of 600 mg, starting at week 2 until Week 22.

Arm title	Upadacitinib 30 mg QD

Arm description:

Participants received 30 mg upadacitinib orally once a day up to Week 24 and placebo to dupilumab SC EOW up to Week 22.

Arm type	Experimental
Investigational medicinal product name	Placebo to dupilumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details: Administered as a subcutaneous injection every 2 weeks until Week 22.	
Investigational medicinal product name	Upadacitinib
Investigational medicinal product code	ABT-494
Other name	RINVOQ®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: Administered orally once a day	

Number of subjects in period 1	Dupilumab 300 mg EOW	Upadacitinib 30 mg QD
Started	331	342
Completed	308	312
Not completed	23	30
Consent withdrawn by subject	8	11
Adverse event, non-fatal	3	7
Other	4	6
COVID-19 logistical restrictions	1	1
Lost to follow-up	7	5

Baseline characteristics

Reporting groups	
Reporting group title	Dupilumab 300 mg EOW
Reporting group description:	
Participants received a loading dose of 600 mg dupilumab by subcutaneous (SC) injection on Day 1 followed by 300 mg dupilumab SC every other week (EOW) until Week 22 and placebo to upadacitinib orally once a day (QD) up to Week 24.	
Reporting group title	Upadacitinib 30 mg QD
Reporting group description:	
Participants received 30 mg upadacitinib orally once a day up to Week 24 and placebo to dupilumab SC EOW up to Week 22.	

Reporting group values	Dupilumab 300 mg EOW	Upadacitinib 30 mg QD	Total
Number of subjects	331	342	673
Age categorical Units: Subjects			
< 40 years	223	228	451
≥ 40 to < 65 years	94	98	192
≥ 65 years	14	16	30
Age continuous Units: years			
arithmetic mean	36.3	36.2	
standard deviation	± 13.81	± 14.42	-
Gender categorical Units: Subjects			
Female	139	159	298
Male	192	183	375
Ethnicity Units: Subjects			
Hispanic or Latino	31	25	56
Not Hispanic or Latino	300	317	617
Race Units: Subjects			
White	231	229	460
Black or African American	15	25	40
Asian	78	77	155
American Indian/Alaska Native	1	2	3
Native Hawaiian or Other Pacific Islander	1	3	4
Multiple	5	6	11
Disease Severity			
Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD) was used to assess the severity of AD based on lesion appearance on the following scale: •0-Clear: No signs of AD; •1-Almost clear: Barely perceptible erythema, induration/papulation and/or lichenification; •2-Mild: Slight but definite erythema, induration/papulation and/or minimal lichenification. No oozing or crusting; •3-Moderate: Clearly perceptible erythema, induration/papulation and/or lichenification, possible oozing or crusting; •4-Severe: Marked erythema, induration/papulation and/or lichenification.			
Units: Subjects			

3 (Moderate)	159	169	328
4 (Severe)	172	173	345

Eczema Area and Severity Index (EASI) Score			
EASI is a tool to measure the extent and severity of atopic eczema based on assessments of the head/neck, trunk, upper limbs and lower limbs. For each region the percentage of skin affected, and the severity of eczema (scored as none [0], mild [1], moderate [2], or severe [3]) for redness, thickness, scratching, and lichenification are assessed. The EASI score is the sum of the scores for each region and ranges from 0 to 72, where higher scores represent worse disease.			
Units: score on a scale			
arithmetic mean	29.21	30.96	
standard deviation	± 11.551	± 12.550	-
Duration Since AD Diagnosis			
Units: years			
arithmetic mean	25.474	23.608	
standard deviation	± 14.8251	± 14.7697	-

End points

End points reporting groups

Reporting group title	Dupilumab 300 mg EOW
Reporting group description:	
Participants received a loading dose of 600 mg dupilumab by subcutaneous (SC) injection on Day 1 followed by 300 mg dupilumab SC every other week (EOW) until Week 22 and placebo to upadacitinib orally once a day (QD) up to Week 24.	
Reporting group title	Upadacitinib 30 mg QD
Reporting group description:	
Participants received 30 mg upadacitinib orally once a day up to Week 24 and placebo to dupilumab SC EOW up to Week 22.	

Primary: Percentage of Participants Achieving a 75% Reduction From Baseline in Eczema Area and Severity Index (EASI 75) at Week 16

End point title	Percentage of Participants Achieving a 75% Reduction From Baseline in Eczema Area and Severity Index (EASI 75) at Week 16
End point description:	
EASI is a tool used to measure the extent (area) and severity of atopic eczema based on assessments of the head/neck, trunk, upper limbs and lower limbs. For each region the area score is recorded as the percentage of skin affected and the severity score is calculated as the sum of the intensity scores (scored as none [0], mild [1], moderate [2], or severe [3]) for redness (erythema, inflammation), thickness (induration, papulation, swelling - acute eczema), scratching (excoriation), and lichenification (lined skin, prurigo nodules - chronic eczema). The total EASI score for each region is calculated by multiplying the severity score by the area score, adjusting for the proportion of the body region to the whole body. The final EASI score is the sum of the 4 region scores and ranges from 0 to 72 where higher scores represent worse disease. Non-responder imputation incorporating multiple imputation (MI) to handle missing data due to COVID-19 (NRI-C) was used in the analysis.	
End point type	Primary
End point timeframe:	
Baseline and Week 16	

End point values	Dupilumab 300 mg EOW	Upadacitinib 30 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331[1]	342		
Units: percentage of participants				
number (confidence interval 95%)	62.6 (57.4 to 67.8)	72.4 (67.6 to 77.2)		

Notes:

[1] - Intent-to-treat (ITT) population (all randomized participants)

Statistical analyses

Statistical analysis title	Analysis of EASI 75 Response at Week 16
Comparison groups	Dupilumab 300 mg EOW v Upadacitinib 30 mg QD

Number of subjects included in analysis	673
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.007 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	9.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.6
upper limit	16.7

Notes:

[2] - A multiple testing procedure was used to provide a strong control of the type I error rate at alpha = 0.05 (2-sided) across analyses comparing upadacitinib versus dupilumab with respect to the primary and ranked secondary endpoints.

[3] - Cochran-Mantel-Haenszel test adjusted for vIGA-AD categories (moderate [3] versus severe [4]).

Secondary: Percent Change From Baseline in Worst Pruritus Numerical Rating Scale (NRS) Score at Week 16

End point title	Percent Change From Baseline in Worst Pruritus Numerical Rating Scale (NRS) Score at Week 16

End point description:

The Worst Pruritus NRS is an assessment tool that participants used to report the intensity of their pruritus during a 24-hour recall period using an electronic hand-held device. Participants were asked to rate itch (pruritus) intensity at its worst during the past 24 hours on an 11-point scale from 0 (no itch) to 10 (worst imaginable itch).
The percent change from Baseline was calculated from a rolling weekly average; a negative change from Baseline indicates improvement.
The intent-to-treat population with non-missing Baseline and at least one post-baseline value was used in the analysis; missing data were handled using a mixed-effect model with repeated measurements (MMRM) including observed measurements at all visits, except that measurements after any rescue medication were excluded.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Dupilumab 300 mg EOW	Upadacitinib 30 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239[4]	252[5]		
Units: percent change				
least squares mean (standard error)	-49.58 (± 1.986)	-67.78 (± 1.906)		

Notes:

[4] - ITT population with non-missing percent change from Baseline values

[5] - ITT population with non-missing percent change from Baseline values

Statistical analyses

Statistical analysis title	Analysis of Change in Pruritus NRS at Week 16
Comparison groups	Dupilumab 300 mg EOW v Upadacitinib 30 mg QD

Number of subjects included in analysis	491
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.001 [7]
Method	Mixed Effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-18.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.61
upper limit	-12.8
Variability estimate	Standard error of the mean
Dispersion value	2.753

Notes:

[6] - A multiple testing procedure was used to provide a strong control of the type I error rate at alpha = 0.05 (2-sided) across analyses comparing upadacitinib versus dupilumab with respect to the primary and ranked secondary endpoints.

[7] - Mixed-effect model repeat measurement with Baseline, treatment, visit, treatment by visit interaction, and Baseline vIGA-AD categories in the model.

Secondary: Percentage of Participants Who Achieved a 100% Reduction From Baseline in EASI Score (EASI 100) at Week 16

End point title	Percentage of Participants Who Achieved a 100% Reduction From Baseline in EASI Score (EASI 100) at Week 16

End point description:

EASI is a tool used to measure the extent (area) and severity of atopic eczema based on assessments of the head/neck, trunk, upper limbs and lower limbs. For each region the area score is recorded as the percentage of skin affected and the severity score is calculated as the sum of the intensity scores (scored as none [0], mild [1], moderate [2], or severe [3]) for redness (erythema, inflammation), thickness (induration, papulation, swelling - acute eczema), scratching (excoriation), and lichenification (lined skin, prurigo nodules - chronic eczema). The total EASI score for each region is calculated by multiplying the severity score by the area score, adjusting for the proportion of the body region to the whole body. The final EASI score is the sum of the 4 region scores and ranges from 0 to 72 where higher scores represent worse disease.
Non-responder imputation incorporating multiple imputation (MI) to handle missing data due to COVID-19 (NRI-C) was used in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Dupilumab 300 mg EOW	Upadacitinib 30 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	342		
Units: percentage of participants				
number (confidence interval 95%)	7.9 (5.0 to 10.8)	28.4 (23.6 to 33.2)		

Statistical analyses

Statistical analysis title	Analysis of EASI 100 Response at Week 16
Comparison groups	Upadacitinib 30 mg QD v Dupilumab 300 mg EOW
Number of subjects included in analysis	673
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	< 0.001 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	20.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.8
upper limit	26

Notes:

[8] - A multiple testing procedure was used to provide a strong control of the type I error rate at alpha = 0.05 (2-sided) across analyses comparing upadacitinib versus dupilumab with respect to the primary and ranked secondary endpoints.
[9] - Cochran-Mantel-Haenszel test adjusted for vIGA-AD categories (moderate [3] versus severe [4]).

Secondary: Percent Change From Baseline in Worst Pruritus Numerical Rating Scale (NRS) Score at Week 4

End point title	Percent Change From Baseline in Worst Pruritus Numerical Rating Scale (NRS) Score at Week 4

End point description:

The Worst Pruritus NRS is an assessment tool that participants used to report the intensity of their pruritus during a 24-hour recall period using an electronic hand-held device. Participants were asked to rate itch (pruritus) intensity at its worst during the past 24 hours on an 11-point scale from 0 (no itch) to 10 (worst imaginable itch).
The percent change from Baseline was calculated from a rolling weekly average; a negative change from Baseline indicates improvement.
The intent-to-treat population with non-missing Baseline and at least one post-baseline value was used in the analysis; missing data were handled using a mixed-effect model with repeated measurements (MMRM) including observed measurements at all visits, except that measurements after any rescue medication were excluded.

End point type	Secondary

End point timeframe:

Baseline and Week 4

End point values	Dupilumab 300 mg EOW	Upadacitinib 30 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297[10]	327[11]		
Units: percent change				
least squares mean (standard error)	-32.39 (± 2.288)	-60.41 (± 2.204)		

Notes:

[10] - ITT population with non-missing percent change from Baseline values

[11] - ITT population with non-missing percent change from Baseline values

Statistical analyses

Statistical analysis title	Analysis of Change in Pruritus NRS at Week 4
Comparison groups	Dupilumab 300 mg EOW v Upadacitinib 30 mg QD
Number of subjects included in analysis	624
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	< 0.001 [13]
Method	Mixed Effect Model Repeated Measurement
Parameter estimate	LS Mean Difference
Point estimate	-28.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.25
upper limit	-21.78
Variability estimate	Standard error of the mean
Dispersion value	3.177

Notes:

[12] - A multiple testing procedure was used to provide a strong control of the type I error rate at alpha = 0.05 (2-sided) across analyses comparing upadacitinib versus dupilumab with respect to the primary and ranked secondary endpoints.
[13] - Mixed-effect model repeat measurement with Baseline, treatment, visit, treatment by visit interaction, and Baseline vIGA-AD categories in the model.

Secondary: Percentage of Participants Achieving a 75% Reduction From Baseline in EASI Score at Week 2

End point title	Percentage of Participants Achieving a 75% Reduction From Baseline in EASI Score at Week 2

End point description:

EASI is a tool used to measure the extent (area) and severity of atopic eczema based on assessments of the head/neck, trunk, upper limbs and lower limbs. For each region the area score is recorded as the percentage of skin affected and the severity score is calculated as the sum of the intensity scores (scored as none [0], mild [1], moderate [2], or severe [3]) for redness (erythema, inflammation), thickness (induration, papulation, swelling - acute eczema), scratching (excoriation), and lichenification (lined skin, prurigo nodules - chronic eczema). The total EASI score for each region is calculated by multiplying the severity score by the area score, adjusting for the proportion of the body region to the whole body. The final EASI score is the sum of the 4 region scores and ranges from 0 to 72 where higher scores represent worse disease.
Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C) was used in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 2

End point values	Dupilumab 300 mg EOW	Upadacitinib 30 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	342		
Units: percentage of participants				
number (confidence interval 95%)	18.2 (14.0 to 22.4)	44.3 (39.1 to 49.6)		

Statistical analyses

Statistical analysis title	Analysis of EASI 75 Response at Week 2
Comparison groups	Dupilumab 300 mg EOW v Upadacitinib 30 mg QD
Number of subjects included in analysis	673
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	< 0.001 [15]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	26
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.3
upper limit	32.7

Notes:

[14] - A multiple testing procedure was used to provide a strong control of the type I error rate at alpha = 0.05 (2-sided) across analyses comparing upadacitinib versus dupilumab with respect to the primary and ranked secondary endpoints.
[15] - Cochran-Mantel-Haenszel test adjusted for vIGA-AD categories (moderate [3] versus severe [4]).

Secondary: Percentage of Participants Achieving a 90% Reduction from Baseline in EASI Score (EASI 90) at Week 16

End point title	Percentage of Participants Achieving a 90% Reduction from Baseline in EASI Score (EASI 90) at Week 16

End point description:

EASI is a tool used to measure the extent (area) and severity of atopic eczema based on assessments of the head/neck, trunk, upper limbs and lower limbs. For each region the area score is recorded as the percentage of skin affected and the severity score is calculated as the sum of the intensity scores (scored as none [0], mild [1], moderate [2], or severe [3]) for redness (erythema, inflammation), thickness (induration, papulation, swelling - acute eczema), scratching (excoriation), and lichenification (lined skin, prurigo nodules - chronic eczema). The total EASI score for each region is calculated by multiplying the severity score by the area score, adjusting for the proportion of the body region to the whole body. The final EASI score is the sum of the 4 region scores and ranges from 0 to 72 where higher scores represent worse disease.
Non-responder imputation incorporating multiple imputation (MI) to handle missing data due to COVID-19 (NRI-C) was used in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Dupilumab 300 mg EOW	Upadacitinib 30 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	342		
Units: percentage of participants				
number (confidence interval 95%)	40.3 (35.0 to 45.6)	61.6 (56.4 to 66.8)		

Statistical analyses

Statistical analysis title	Analysis of EASI 90 Response at Week 16
Comparison groups	Dupilumab 300 mg EOW v Upadacitinib 30 mg QD
Number of subjects included in analysis	673
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	< 0.001 [17]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	21.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.8
upper limit	28.6

Notes:

[16] - A multiple testing procedure was used to provide a strong control of the type I error rate at alpha = 0.05 (2-sided) across analyses comparing upadacitinib versus dupilumab with respect to the primary and ranked secondary endpoints.
[17] - Cochran-Mantel-Haenszel test adjusted for vIGA-AD categories (moderate [3] versus severe [4]).

Secondary: Percent Change From Baseline in Worst Pruritus Numerical Rating Scale (NRS) Score at Week 1

End point title	Percent Change From Baseline in Worst Pruritus Numerical Rating Scale (NRS) Score at Week 1

End point description:

The Worst Pruritus NRS is an assessment tool that participants used to report the intensity of their pruritus during a 24-hour recall period using an electronic hand-held device. Participants were asked to rate itch (pruritus) intensity at its worst during the past 24 hours on an 11-point scale from 0 (no itch) to 10 (worst imaginable itch).
The percent change from Baseline was calculated from a rolling weekly average; a negative change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline and Week 1

End point values	Dupilumab 300 mg EOW	Upadacitinib 30 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314[18]	331[19]		
Units: percent change				
least squares mean (standard error)	-8.94 (± 1.831)	-31.96 (± 1.772)		

Notes:

[18] - ITT population with non-missing percent change from Baseline values

[19] - ITT population with non-missing percent change from Baseline values

Statistical analyses

Statistical analysis title	Analysis of Change in Pruritus NRS at Week 1
Comparison groups	Dupilumab 300 mg EOW v Upadacitinib 30 mg QD

Number of subjects included in analysis	645
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	< 0.001 [21]
Method	Mixed Effect Model Repeated Measurement
Parameter estimate	LS Mean Difference
Point estimate	-23.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.03
upper limit	-18.02
Variability estimate	Standard error of the mean
Dispersion value	2.548

Notes:

[20] - A multiple testing procedure was used to provide a strong control of the type I error rate at alpha = 0.05 (2-sided) across analyses comparing upadacitinib versus dupilumab with respect to the primary and ranked secondary endpoints.

[21] - Mixed-effect model repeat measurement with Baseline, treatment, visit, treatment by visit interaction, and Baseline vIGA-AD categories in the model.

Secondary: Percentage of Participants Achieving a Reduction of ≥ 4 Points From Baseline in Worst Pruritus NRS at Week 16

End point title	Percentage of Participants Achieving a Reduction of ≥ 4 Points From Baseline in Worst Pruritus NRS at Week 16

End point description:

The Worst Pruritus NRS is an assessment tool that participants used to report the intensity of their pruritus during a 24-hour recall period using an electronic hand-held device. Participants were asked to rate itch (pruritus) intensity at its worst during the past 24 hours on an 11-point scale from 0 (no itch) to 10 (worst imaginable itch).

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Dupilumab 300 mg EOW	Upadacitinib 30 mg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323[22]	334[23]		
Units: percentage of participants				
number (confidence interval 95%)	36.4 (31.1 to 41.6)	56.1 (50.8 to 61.5)		

Notes:

[22] - Intent-to-treat population with Baseline worst pruritus NRS score ≥ 4

[23] - Intent-to-treat population with Baseline worst pruritus NRS score ≥ 4

Statistical analyses

Statistical analysis title	Analysis of Worst Pruritus NRS Response
Comparison groups	Dupilumab 300 mg EOW v Upadacitinib 30 mg QD

Number of subjects included in analysis	657
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	< 0.001 [25]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	19.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.4
upper limit	27.3

Notes:

[24] - A multiple testing procedure was used to provide a strong control of the type I error rate at alpha = 0.05 (2-sided) across analyses comparing upadacitinib versus dupilumab with respect to the primary and ranked secondary endpoints.

[25] - Cochran-Mantel-Haenszel test adjusted for vIGA-AD categories (moderate [3] versus severe [4]).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Deaths: from Day 1 to 12 weeks after last dose of study drug (34 weeks).
Adverse events: From first dose of upadacitinib/dupilumab through 30 days following the last dose of upadacitinib or 84 days following the last dose of dupilumab (up to 34 weeks).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Upadacitinib 30 mg QD

Reporting group description:

Participants received 30 mg upadacitinib orally once a day up to Week 24 and placebo to dupilumab SC EOW up to Week 22.

Reporting group title	Dupilumab 300 mg EOW

Reporting group description:

Participants received a loading dose of 600 mg dupilumab by SC injection on Day 1 followed by 300 mg dupilumab SC EOW until Week 22 and placebo to upadacitinib orally QD up to Week 24.

Serious adverse events	Upadacitinib 30 mg QD	Dupilumab 300 mg EOW	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 342 (4.09%)	7 / 331 (2.11%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
INVASIVE DUCTAL BREAST CARCINOMA			
subjects affected / exposed	1 / 342 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARATHYROID TUMOUR BENIGN			
subjects affected / exposed	1 / 342 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
ABORTION INDUCED			

subjects affected / exposed	1 / 342 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
TYPE I HYPERSENSITIVITY			
subjects affected / exposed	0 / 342 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FOOD ALLERGY			
subjects affected / exposed	1 / 342 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ASTHMA			
subjects affected / exposed	0 / 342 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
INTENTIONAL SELF-INJURY			
subjects affected / exposed	1 / 342 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	0 / 342 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
PELVIC FRACTURE			
subjects affected / exposed	0 / 342 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
JOINT INJURY			

subjects affected / exposed	1 / 342 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
LYMPHOPENIA			
subjects affected / exposed	1 / 342 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	1 / 342 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
GLAUCOMA			
subjects affected / exposed	1 / 342 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
INCARCERATED UMBILICAL HERNIA			
subjects affected / exposed	0 / 342 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
ECZEMA			
subjects affected / exposed	1 / 342 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DERMATITIS ATOPIC			
subjects affected / exposed	1 / 342 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			

subjects affected / exposed	1 / 342 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
BURSITIS			
subjects affected / exposed	0 / 342 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 342 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	1 / 342 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
SEPSIS			
subjects affected / exposed	1 / 342 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	1 / 342 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
PELVIC ABSCESS			
subjects affected / exposed	1 / 342 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
subjects affected / exposed	1 / 342 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

HERPES SIMPLEX			
subjects affected / exposed	1 / 342 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			
subjects affected / exposed	0 / 342 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed	0 / 342 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BETA HAEMOLYTIC STREPTOCOCCAL INFECTION			
subjects affected / exposed	1 / 342 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Metabolism and nutrition disorders			
HYPERGLYCAEMIA			
subjects affected / exposed	1 / 342 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Upadacitinib 30 mg QD	Dupilumab 300 mg EOW	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	167 / 342 (48.83%)	134 / 331 (40.48%)	
Investigations			
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	26 / 342 (7.60%)	10 / 331 (3.02%)	
occurrences (all)	27	12	
Nervous system disorders			
HEADACHE			

subjects affected / exposed	17 / 342 (4.97%)	24 / 331 (7.25%)	
occurrences (all)	22	32	
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	64 / 342 (18.71%)	11 / 331 (3.32%)	
occurrences (all)	72	12	
DERMATITIS ATOPIC			
subjects affected / exposed	36 / 342 (10.53%)	32 / 331 (9.67%)	
occurrences (all)	52	51	
Infections and infestations			
CONJUNCTIVITIS			
subjects affected / exposed	5 / 342 (1.46%)	35 / 331 (10.57%)	
occurrences (all)	6	36	
FOLLICULITIS			
subjects affected / exposed	22 / 342 (6.43%)	4 / 331 (1.21%)	
occurrences (all)	22	4	
NASOPHARYNGITIS			
subjects affected / exposed	23 / 342 (6.73%)	27 / 331 (8.16%)	
occurrences (all)	33	31	
ORAL HERPES			
subjects affected / exposed	17 / 342 (4.97%)	9 / 331 (2.72%)	
occurrences (all)	21	10	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	26 / 342 (7.60%)	17 / 331 (5.14%)	
occurrences (all)	26	20	
URINARY TRACT INFECTION			
subjects affected / exposed	18 / 342 (5.26%)	15 / 331 (4.53%)	
occurrences (all)	19	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 March 2020	Version 2, Global amendment added ranked secondary endpoints (Percent change from Baseline to Week 4 in Worst Pruritus NRS; Proportion of subjects achieving EASI 75 at Week 2; and Percent change from Baseline to Week 1 in Worst Pruritus NRS) to align with endpoints in other upadacitinib AD studies. To reflect the most recent updates to AESIs and toxicity management guidance in the Investigator Brochure, CTCAE v4.03 was retained for AE reporting in this global protocol amendment. An option to enroll in a separate open-label extension study of oral upadacitinib 30 mg in which they were to be treated for an additional 52 weeks was added for all countries.
28 October 2020	Version 3, Global Amendment updated the secondary endpoint to include Worst Pruritus NRS ≥ 4 at Week 16 (from an additional endpoint) and added the additional endpoint of daily Worst Pruritus NRS ≥ 4 up to Day 28 to harmonize with protocol Version 2.2.1. Modifications to the statistical analyses due to the COVID-19 pandemic were added.
10 November 2020	Version 4, Global Amendment clarified that the primary analysis was performed on the data from Week 24 database lock.

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/34347860