Clinical trial results:
A Phase 3b/4 Randomized, Open-label, Efficacy Assessor Blinded Study, Comparing the Safety and Assessor Blinded Efficacy of Upadacitinib to Dupilumab in Subjects With Moderate to Severe Atopic Dermatitis (Level-Up)

Summary

EudraCT number	2022-002482-15
Trial protocol	ES HU SK SE FR PL IT PT DK NL GR BE BG HR
Global end of trial date	08 August 2024

Results information

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

Trial information

Trial identification

Sponsor protocol code	M23-696

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05601882
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 8006339110, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 August 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 August 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Atopic dermatitis (AD) is a skin condition that may cause a rash and itching due to inflammation of the skin. This study compares upadacitinib to dupilumab in adolescent and adult subjects with moderate to severe AD and inadequate response to systemic therapies. Adverse events and change in disease activity will be assessed.

The study is comprised of a 35-day Screening Period, a 16-week treatment Period 1 and a 16-week treatment Period 2. Subjects are randomly assigned to receive upadacitinib Dose A or dupilumab in Period 1. There is a 30-day or 12-week follow-up visit for those on upadacitinib or dupilumab respectively, who won't enter Period 2. In Period 2, subjects will receive upadacitinib Dose A or Dose B for 16 weeks, followed by a 30-day follow-up visit. Approximately 880 adolescent and adult subjects ages 12 to 64 with moderate to severe AD who are candidates for systemic therapy will be enrolled at up to 330 sites worldwide.

Protection of trial subjects:

Adult subjects ≥18 years of age at Screening Visit or their legally authorized representative must voluntarily sign and date an informed consent, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures and comply with the requirements of this study protocol.

For subjects ≥12 and < 18 years of age at Screening Visit: Parent or legal guardian, as required, has voluntarily signed and dated an informed consent form, approved by an IEC, after the nature of the study has been explained and the subject's parent or legal guardian has had the opportunity to ask questions. Subjects will be included in all discussions in order to obtain verbal/and or written assent. Parent/legal guardian and subject must comply with the requirements of this study protocol. If a subject becomes of legal age during the course of the study, that subject will need to be consented using the approved informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 November 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 22
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Bulgaria: 34
Country: Number of subjects enrolled	Canada: 67
Country: Number of subjects enrolled	China: 66

Country: Number of subjects enrolled	Croatia: 34
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 86
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Hungary: 51
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	Japan: 27
Country: Number of subjects enrolled	Korea, Republic of: 58
Country: Number of subjects enrolled	Mexico: 14
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 111
Country: Number of subjects enrolled	Portugal: 57
Country: Number of subjects enrolled	Puerto Rico: 15
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Slovakia: 16
Country: Number of subjects enrolled	South Africa: 23
Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	Taiwan: 40
Country: Number of subjects enrolled	Türkiye: 8
Country: Number of subjects enrolled	United States: 111
Worldwide total number of subjects	920
EEA total number of subjects	465

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)	117
Adults (18-64 years)	803
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Eligible subjects were randomized in a 1:1 ratio to receive either upadacitinib (Upa) 15 mg QD or dupilumab (Dup) in Period 1. At Week 16, those with a < EASI 75 response entered Period 2; those from the Dup arm were offered the option to receive Upa 15 mg QD while those from the Upa arm either continued or escalated to Upa 30 mg QD until Week 32.

Period 1

Period 1 title	Period 1 (Baseline – Week 16)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dupilumab (Period 1)

Arm description:

Adult participants received a loading dose of 600 mg dupilumab by subcutaneous (SC) injection at the Baseline visit followed by 300 mg dupilumab SC every other week (EOW) until Week 16.

Adolescents (12 to 17 years of age and weighing at least 40 kg) received treatment according to their body weight. Participants weighing 40 to < 60 kg received a loading dose of 400 mg dupilumab SC at the Baseline visit followed by 200 mg SC EOW until Week 16. Those weighing 60 kg or more received a loading dose of 600 mg dupilumab SC at the Baseline visit followed by 300 mg dupilumab SC EOW until Week 16.

Arm type	Experimental
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:

Dupilumab is administered as a subcutaneous (SC) injection.

Arm title	Upadacitinib (Period 1)

Arm description:

Participants received 15 mg upadacitinib orally once a day (QD) up to Week 16. Starting at Week 4, participants had their dose increased to 30 mg QD if they had a < 50% reduction from Baseline in Eczema Area and Severity Index (EASI 50) response or a < 4-point improvement from Baseline in Worst Pruritus Numerical Rating Scale (WP-NRS; weekly average). Starting at Week 8, participants had their dose increased to 30 mg QD if they had a < EASI 75 response.

Arm type	Experimental
Investigational medicinal product name	Upadacitinib
Investigational medicinal product code	
Other name	ABT-494, RINVOQ
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Extended-release tablet

Number of subjects in period 1	Dupilumab (Period 1)	Upadacitinib (Period 1)
Started	462	458
Completed	423	418
Not completed	39	40
Other, not specified	16	16
Lost to follow-up	2	-
Withdrawal by subject	21	24

Period 2

Period 2 title	Period 2 (Week 16 - Week 32)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dupilumab -> Upadacitinib (Period 2)

Arm description:

At Week 16, participants receiving dupilumab as per its label in Period 1 were reassigned based on their Eczema Area and Severity Index (EASI) response. Those with < EASI 75 were offered the option to receive oral doses of upadacitinib 15 mg QD in Period 2 up to Week 32. Those with ≥ EASI 75 completed the end of study procedures. Starting at Week 20, participants with < EASI 75 or a < 4-point improvement from Baseline in Worst Pruritus Numerical Rating Scale (WP-NRS; weekly average) had their dose increased to 30 mg QD up to Week 32.

Arm type	Experimental
Investigational medicinal product name	Upadacitinib
Investigational medicinal product code	
Other name	ABT-494, RINVOQ
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Extended-release tablet

Arm title	Upadacitinib -> Upadacitinib 30 mg (Period 2)

Arm description:

At Week 16, participants receiving upadacitinib in Period 1 were reassigned based on their Eczema Area and Severity Index (EASI) response. Those with < EASI 75 were allocated or continued to receive upadacitinib 30 mg QD in Period 2. Those with ≥ EASI 75 completed the end of study procedures.

Arm type	Experimental
Investigational medicinal product name	Upadacitinib
Investigational medicinal product code	
Other name	ABT-494, RINVOQ
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Extended-release tablet

Number of subjects in period 2[1]	Dupilumab -> Upadacitinib (Period 2)	Upadacitinib -> Upadacitinib 30 mg (Period 2)
Started	208	147
Completed	198	131
Not completed	10	16
Other, not specified	4	11
Lost to follow-up	3	1
Withdrawal by subject	3	4

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: At Week 16, subjects from both treatment arms in Period 1 with a < EASI 75 response entered Period 2; subjects from the dupilumab arm were offered the option to receive upadacitinib 15 mg QD while subjects from the upadacitinib arm either continued (if already receiving 30 mg) or escalated to upadacitinib 30 mg QD (if receiving 15 mg QD) until Week 32. Those with ≥ EASI 75 completed the end of study procedures.

Baseline characteristics

Reporting groups

Reporting group title	Dupilumab (Period 1)

Reporting group description:

Adult participants received a loading dose of 600 mg dupilumab by subcutaneous (SC) injection at the Baseline visit followed by 300 mg dupilumab SC every other week (EOW) until Week 16.

Adolescents (12 to 17 years of age and weighing at least 40 kg) received treatment according to their body weight. Participants weighing 40 to < 60 kg received a loading dose of 400 mg dupilumab SC at the Baseline visit followed by 200 mg SC EOW until Week 16. Those weighing 60 kg or more received a loading dose of 600 mg dupilumab SC at the Baseline visit followed by 300 mg dupilumab SC EOW until Week 16.

Reporting group title	Upadacitinib (Period 1)

Reporting group description:

Participants received 15 mg upadacitinib orally once a day (QD) up to Week 16. Starting at Week 4, participants had their dose increased to 30 mg QD if they had a < 50% reduction from Baseline in Eczema Area and Severity Index (EASI 50) response or a < 4-point improvement from Baseline in Worst Pruritus Numerical Rating Scale (WP-NRS; weekly average). Starting at Week 8, participants had their dose increased to 30 mg QD if they had a < EASI 75 response.

Reporting group values	Dupilumab (Period 1)	Upadacitinib (Period 1)	Total
Number of subjects	462	458	920
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	30.9	31.0	
standard deviation	± 12.79	± 12.71	-
Gender categorical Units: Subjects			
Female	217	195	412
Male	245	263	508
Ethnicity Units: Subjects			
Hispanic or Latino	41	44	85
Not Hispanic or Latino	421	414	835
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	2	2	4
Asian	137	122	259
Native Hawaiian or Other Pacific Islander	1	3	4
Black or African American	19	20	39
White	296	303	599
More than one race	5	6	11
Unknown or Not Reported	2	2	4

End points

End points reporting groups

Reporting group title	Dupilumab (Period 1)

Reporting group description:

Adult participants received a loading dose of 600 mg dupilumab by subcutaneous (SC) injection at the Baseline visit followed by 300 mg dupilumab SC every other week (EOW) until Week 16.

Adolescents (12 to 17 years of age and weighing at least 40 kg) received treatment according to their body weight. Participants weighing 40 to < 60 kg received a loading dose of 400 mg dupilumab SC at the Baseline visit followed by 200 mg SC EOW until Week 16. Those weighing 60 kg or more received a loading dose of 600 mg dupilumab SC at the Baseline visit followed by 300 mg dupilumab SC EOW until Week 16.

Reporting group title	Upadacitinib (Period 1)

Reporting group description:

Participants received 15 mg upadacitinib orally once a day (QD) up to Week 16. Starting at Week 4, participants had their dose increased to 30 mg QD if they had a < 50% reduction from Baseline in Eczema Area and Severity Index (EASI 50) response or a < 4-point improvement from Baseline in Worst Pruritus Numerical Rating Scale (WP-NRS; weekly average). Starting at Week 8, participants had their dose increased to 30 mg QD if they had a < EASI 75 response.

Reporting group title	Dupilumab -> Upadacitinib (Period 2)

Reporting group description:

At Week 16, participants receiving dupilumab as per its label in Period 1 were reassigned based on their Eczema Area and Severity Index (EASI) response. Those with < EASI 75 were offered the option to receive oral doses of upadacitinib 15 mg QD in Period 2 up to Week 32. Those with ≥ EASI 75 completed the end of study procedures. Starting at Week 20, participants with < EASI 75 or a < 4-point improvement from Baseline in Worst Pruritus Numerical Rating Scale (WP-NRS; weekly average) had their dose increased to 30 mg QD up to Week 32.

Reporting group title	Upadacitinib -> Upadacitinib 30 mg (Period 2)

Reporting group description:

At Week 16, participants receiving upadacitinib in Period 1 were reassigned based on their Eczema Area and Severity Index (EASI) response. Those with < EASI 75 were allocated or continued to receive upadacitinib 30 mg QD in Period 2. Those with ≥ EASI 75 completed the end of study procedures.

Primary: Percentage of Participants Achieving a ≥ 90% Reduction From Baseline in Eczema Area and Severity Index Score (EASI 90) and Worst Pruritus Numerical Rating Scale of 0 or 1 (WP-NRS 0/1) at Week 16

End point title	Percentage of Participants Achieving a ≥ 90% Reduction From Baseline in Eczema Area and Severity Index Score (EASI 90) and Worst Pruritus Numerical Rating Scale of 0 or 1 (WP-NRS 0/1) at Week 16

End point description:

The EASI is a composite index with scores ranging from 0 to 72. Four AD disease characteristics are assessed for severity on a scale of "0" (absent) through "3" (severe), and area of AD involvement is assessed as a percentage by body area of head, trunk, upper extremities, and lower extremities and converted to a score of 0 to 6. In each body region, the area is expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%).

The Worst Pruritus NRS was used to report intensity of pruritus during a 24- hour recall period using an electronic hand-held device. Subjects rated itch (pruritus) intensity at its worst on an 11-point scale from 0 (no itch) to 10 (worst imaginable itch).

Analysis population: subjects randomized at Baseline; non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or any other missing data that can be reasonably assumed to be Missing at Random (NRI-MI) was used.

End point type	Primary

End point timeframe:

Baseline and Week 16

End point values	Dupilumab (Period 1)	Upadacitinib (Period 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	458		
Units: percentage of participants				
number (confidence interval 95%)	8.9 (6.3 to 11.5)	19.9 (16.2 to 23.5)		

Statistical analyses

Statistical analysis title	Upadacitinib (Per. 1) vs Dupilumab (Per. 1)

Statistical analysis description:

Analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by Validated Investigator's Global Assessment for Atopic Dermatitis categories [(vIGA-AD (moderate [3] versus severe [4])] and age (12 to < 18; 18 to < 40; ≥40 to < 64 years)

Response rate difference = Upadacitinib (Period 1) - Dupilumab (Period 1)

Comparison groups	Dupilumab (Period 1) v Upadacitinib (Period 1)
Number of subjects included in analysis	920
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	11
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.6
upper limit	15.5

Secondary: Percentage of Participants Achieving a ≥ 90% Reduction From Baseline in Eczema Area and Severity Index Score (EASI 90) at Week 16

End point title	Percentage of Participants Achieving a ≥ 90% Reduction From Baseline in Eczema Area and Severity Index Score (EASI 90) at Week 16

End point description:

The EASI is a composite index with scores ranging from 0 to 72. Four AD disease characteristics (erythema, thickness [induration, papulation, edema], scratching [excoriation], and lichenification) assessed for severity on a scale of "0" (absent) through "3" (severe). In addition, the area of AD involvement is assessed as a percentage by body area of head, trunk (including the genital area), upper extremities, and lower extremities (including the buttocks), and converted to a score of 0 to 6. In each body region, the area is expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%).

Analysis population: subjects randomized at Baseline; non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or any other missing data that can be reasonably assumed to be Missing at Random (NRI-MI) was used.

End point type	Secondary
End point timeframe:	
Baseline and Week 16	

End point values	Dupilumab (Period 1)	Upadacitinib (Period 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	458		
Units: percentage of participants				
number (confidence interval 95%)	22.5 (18.7 to 26.3)	40.8 (36.3 to 45.3)		

Statistical analyses

Statistical analysis title	Upadacitinib (Per. 1) vs Dupilumab (Per. 1)

Statistical analysis description:

Analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by Validated Investigator's Global Assessment for Atopic Dermatitis categories [(vIGA-AD (moderate [3] versus severe [4])] and age (12 to < 18; 18 to < 40; ≥40 to < 64 years)

Response rate difference = Upadacitinib (Period 1) - Dupilumab (Period 1)

Comparison groups	Dupilumab (Period 1) v Upadacitinib (Period 1)
Number of subjects included in analysis	920
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	18.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.5
upper limit	24.2

Secondary: Percentage of Participants Achieving a Worst Pruritus Numerical Rating Scale of 0 or 1 (WP-NRS 0/1) at Week 16 Among Participants With Baseline WP-NRS > 1

End point title	Percentage of Participants Achieving a Worst Pruritus Numerical Rating Scale of 0 or 1 (WP-NRS 0/1) at Week 16 Among Participants With Baseline WP-NRS > 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 rated 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).

Analysis population: subjects randomized at Baseline; non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or any other missing data that can be reasonably assumed to be Missing at Random (NRI-MI) was used.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Dupilumab (Period 1)	Upadacitinib (Period 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	459	454		
Units: percentage of participants				
number (confidence interval 95%)	15.5 (12.2 to 18.8)	30.2 (26.0 to 34.4)		

Statistical analyses

Statistical analysis title	Upadacitinib (Per. 1) vs Dupilumab (Per. 1)

Statistical analysis description:

Analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by Validated Investigator's Global Assessment for Atopic Dermatitis categories [(vIGA-AD (moderate [3] versus severe [4])] and age (12 to < 18; 18 to < 40; ≥40 to < 64 years)

Response rate difference = Upadacitinib (Period 1) - Dupilumab (Period 1)

Comparison groups	Dupilumab (Period 1) v Upadacitinib (Period 1)
Number of subjects included in analysis	913
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	14.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.4
upper limit	20

Secondary: Percentage of Participants Achieving an Improvement (Reduction) in Worst Pruritus Numerical Rating Scale (WP-NRS) ≥4 at Week 16 Among Those With

Baseline WP-NRS ≥4

End point title	Percentage of Participants Achieving an Improvement (Reduction) in Worst Pruritus Numerical Rating Scale (WP-NRS) ≥4 at Week 16 Among Those With Baseline WP-NRS ≥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 rated 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).

Analysis population: subjects randomized at Baseline; non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or any other missing data that can be reasonably assumed to be Missing at Random (NRI-MI) was used.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Dupilumab (Period 1)	Upadacitinib (Period 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	457	448		
Units: percentage of participants				
number (confidence interval 95%)	38.1 (33.6 to 42.5)	54.7 (50.1 to 59.3)		

Statistical analyses

Statistical analysis title	Upadacitinib (Per. 1) vs Dupilumab (Per. 1)

Statistical analysis description:

Analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by Validated Investigator's Global Assessment for Atopic Dermatitis categories [(vIGA-AD (moderate [3] versus severe [4])] and age (12 to < 18; 18 to < 40; ≥40 to < 64 years)

Response rate difference = Upadacitinib (Period 1) - Dupilumab (Period 1)

Comparison groups	Dupilumab (Period 1) v Upadacitinib (Period 1)
Number of subjects included in analysis	905
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	16.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.2
upper limit	23

Secondary: Percentage of Participants Achieving a Worst Pruritus Numerical Rating Scale of 0 or 1 (WP-NRS 0/1) at Week 4 Among Participants With Baseline WP-NRS > 1

End point title	Percentage of Participants Achieving a Worst Pruritus Numerical Rating Scale of 0 or 1 (WP-NRS 0/1) at Week 4 Among Participants With Baseline WP-NRS > 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 rated 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).

Analysis population: subjects randomized at Baseline; non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or any other missing data that can be reasonably assumed to be Missing at Random (NRI-MI) was used.

End point type	Secondary

End point timeframe:

Baseline and Week 4

End point values	Dupilumab (Period 1)	Upadacitinib (Period 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	459	454		
Units: percentage of participants				
number (confidence interval 95%)	2.8 (1.3 to 4.3)	16.1 (12.7 to 19.5)		

Statistical analyses

Statistical analysis title	Upadacitinib (Per. 1) vs Dupilumab (Per. 1)

Statistical analysis description:

Analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by Validated Investigator's Global Assessment for Atopic Dermatitis categories [(vIGA-AD (moderate [3] versus severe [4])] and age (12 to < 18; 18 to < 40; ≥40 to < 64 years)

Response rate difference = Upadacitinib (Period 1) - Dupilumab (Period 1)

Comparison groups	Dupilumab (Period 1) v Upadacitinib (Period 1)
Number of subjects included in analysis	913
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	13.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	9.6
upper limit	16.9

Secondary: Percentage of Participants Achieving a Worst Pruritus Numerical Rating Scale of 0 or 1 (WP-NRS 0/1) at Week 2 among Participants with Baseline WP-NRS > 1

End point title	Percentage of Participants Achieving a Worst Pruritus Numerical Rating Scale of 0 or 1 (WP-NRS 0/1) at Week 2 among Participants with Baseline WP-NRS > 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 rated 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).

Analysis population: subjects randomized at Baseline; non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or any other missing data that can be reasonably assumed to be Missing at Random (NRI-MI) was used.

End point type	Secondary

End point timeframe:

Baseline and Week 2

End point values	Dupilumab (Period 1)	Upadacitinib (Period 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	459	454		
Units: percentage of participants				
number (confidence interval 95%)	1.3 (0.3 to 2.3)	7.7 (5.3 to 10.2)		

Statistical analyses

Statistical analysis title	Upadacitinib (Per. 1) vs Dupilumab (Per. 1)

Statistical analysis description:

Analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by Validated Investigator's Global Assessment for Atopic Dermatitis categories [(vIGA-AD (moderate [3] versus severe [4])] and age (12 to < 18; 18 to < 40; ≥40 to < 64 years)

Response rate difference = Upadacitinib (Period 1) - Dupilumab (Period 1)

Comparison groups	Dupilumab (Period 1) v Upadacitinib (Period 1)

Number of subjects included in analysis	913
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	6.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.8
upper limit	9.1

Secondary: Percentage of Participants Achieving a ≥ 90% Reduction From Baseline in Eczema Area and Severity Index Score (EASI 90) at Week 4

End point title	Percentage of Participants Achieving a ≥ 90% Reduction From Baseline in Eczema Area and Severity Index Score (EASI 90) at Week 4

End point description:

The EASI is a composite index with scores ranging from 0 to 72. Four AD disease characteristics (erythema, thickness [induration, papulation, edema], scratching [excoriation], and lichenification) assessed for severity on a scale of "0" (absent) through "3" (severe). In addition, the area of AD involvement is assessed as a percentage by body area of head, trunk (including the genital area), upper extremities, and lower extremities (including the buttocks), and converted to a score of 0 to 6. In each body region, the area is expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%).

Analysis population: subjects randomized at Baseline; non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or any other missing data that can be reasonably assumed to be Missing at Random (NRI-MI) was used.

End point type	Secondary

End point timeframe:

Baseline and Week 4

End point values	Dupilumab (Period 1)	Upadacitinib (Period 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	458		
Units: percentage of participants				
number (confidence interval 95%)	9.7 (7.0 to 12.4)	23.8 (19.9 to 27.7)		

Statistical analyses

Statistical analysis title	Upadacitinib (Per. 1) vs Dupilumab (Per. 1)

Statistical analysis description:

Analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by Validated Investigator's Global Assessment for Atopic Dermatitis categories [(vIGA-AD (moderate [3] versus severe [4])] and age (12

to < 18; 18 to < 40; ≥40 to < 64 years)

Response rate difference = Upadacitinib (Period 1) - Dupilumab (Period 1)

Comparison groups	Dupilumab (Period 1) v Upadacitinib (Period 1)
Number of subjects included in analysis	920
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	14.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.4
upper limit	18.8

Secondary: Percentage of Participants Achieving a ≥ 75% Reduction From Baseline in Eczema Area and Severity Index Score (EASI 75) at Week 2

End point title	Percentage of Participants Achieving a ≥ 75% Reduction From Baseline in Eczema Area and Severity Index Score (EASI 75) at Week 2

End point description:

The EASI is a composite index with scores ranging from 0 to 72. Four AD disease characteristics (erythema, thickness [induration, papulation, edema], scratching [excoriation], and lichenification) assessed for severity on a scale of "0" (absent) through "3" (severe). In addition, the area of AD involvement is assessed as a percentage by body area of head, trunk (including the genital area), upper extremities, and lower extremities (including the buttocks), and converted to a score of 0 to 6. In each body region, the area is expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%).

Analysis population: subjects randomized at Baseline; non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or any other missing data that can be reasonably assumed to be Missing at Random (NRI-MI) was used.

End point type	Secondary
End point timeframe:	
Baseline and Week 2	

End point values	Dupilumab (Period 1)	Upadacitinib (Period 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	458		
Units: percentage of participants				
number (confidence interval 95%)	8.2 (5.7 to 10.7)	26.7 (22.7 to 30.8)		

Statistical analyses

Statistical analysis title	Upadacitinib (Per. 1) vs Dupilumab (Per. 1)

Statistical analysis description:

Analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by Validated Investigator's Global Assessment for Atopic Dermatitis categories [(vIGA-AD (moderate [3] versus severe [4])] and age (12 to < 18; 18 to < 40; ≥40 to < 64 years)

Response rate difference = Upadacitinib (Period 1) - Dupilumab (Period 1)

Comparison groups	Dupilumab (Period 1) v Upadacitinib (Period 1)
Number of subjects included in analysis	920
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	18.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.9
upper limit	23.3

Secondary: Percentage of Participants Achieving a 100% Reduction From Baseline in Eczema Area and Severity Index Score (EASI 100) at Week 16

End point title	Percentage of Participants Achieving a 100% Reduction From Baseline in Eczema Area and Severity Index Score (EASI 100) at Week 16

End point description:

The EASI is a composite index with scores ranging from 0 to 72. Four AD disease characteristics (erythema, thickness [induration, papulation, edema], scratching [excoriation], and lichenification) assessed for severity on a scale of "0" (absent) through "3" (severe). In addition, the area of AD involvement is assessed as a percentage by body area of head, trunk (including the genital area), upper extremities, and lower extremities (including the buttocks), and converted to a score of 0 to 6. In each body region, the area is expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%).

Analysis population: subjects randomized at Baseline; non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or any other missing data that can be reasonably assumed to be Missing at Random (NRI-MI) was used.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Dupilumab (Period 1)	Upadacitinib (Period 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	458		
Units: percentage of participants				
number (confidence interval 95%)	5.6 (3.5 to 7.7)	14.8 (11.6 to 18.1)		

Statistical analyses

Statistical analysis title	Upadacitinib (Per. 1) vs Dupilumab (Per. 1)

Statistical analysis description:

Analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by Validated Investigator's Global Assessment for Atopic Dermatitis categories [(vIGA-AD (moderate [3] versus severe [4])] and age (12 to < 18; 18 to < 40; ≥40 to < 64 years)

Response rate difference = Upadacitinib (Period 1) - Dupilumab (Period 1)

Comparison groups	Dupilumab (Period 1) v Upadacitinib (Period 1)
Number of subjects included in analysis	920
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	9.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.4
upper limit	13.1

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality and adverse events were collected from the time informed consent was signed through the end of the study.

Adverse event reporting additional description:

Median time on follow-up was for 113 days for the Dupilumab (Period 1) group; 114 days for the Upadacitinib (Period 1) group; 225 days for the Dupilumab -> Upadacitinib (Period 2) group; and 224 days for the Upadacitinib -> Upadacitinib 30 mg (Period 2) group.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Dupilumab (Period 1)

Reporting group description:

Adult participants received a loading dose of 600 mg dupilumab by subcutaneous (SC) injection at the Baseline visit followed by 300 mg dupilumab SC every other week (EOW) until Week 16.

Adolescents (12 to 17 years of age and weighing at least 40 kg) received treatment according to their body weight. Participants weighing 40 to < 60 kg received a loading dose of 400 mg dupilumab SC at the Baseline visit followed by 200 mg SC EOW until Week 16. Those weighing 60 kg or more received a loading dose of 600 mg dupilumab SC at the Baseline visit followed by 300 mg dupilumab SC EOW until Week 16.

Reporting group title	Upadacitinib -> Upadacitinib 30 mg (Period 2)

Reporting group description:

At Week 16, participants receiving upadacitinib in Period 1 were reassigned based on their Eczema Area and Severity Index (EASI) response. Those with < EASI 75 were allocated or continued to receive upadacitinib 30 mg QD in Period 2. Those with ≥ EASI 75 completed the end of study procedures.

Reporting group title	Dupilumab -> Upadacitinib (Period 2)

Reporting group description:

At Week 16, participants receiving dupilumab as per its label in Period 1 were reassigned based on their Eczema Area and Severity Index (EASI) response. Those with < EASI 75 were offered the option to receive oral doses of upadacitinib 15 mg QD in Period 2 up to Week 32. Those with ≥ EASI 75 completed the end of study procedures. Starting at Week 20, participants with < EASI 75 or a < 4-point improvement from Baseline in Worst Pruritus Numerical Rating Scale (WP-NRS; weekly average) had their dose increased to 30 mg QD up to Week 32.

Reporting group title	Upadacitinib (Period 1)

Reporting group description:

Participants received 15 mg upadacitinib orally once a day (QD) up to Week 16. Starting at Week 4, participants had their dose increased to 30 mg QD if they had a < 50% reduction from Baseline in Eczema Area and Severity Index (EASI 50) response or a < 4-point improvement from Baseline in Worst Pruritus Numerical Rating Scale (WP-NRS; weekly average). Starting at Week 8, participants had their dose increased to 30 mg QD if they had a < EASI 75 response.

Serious adverse events	Dupilumab (Period 1)	Upadacitinib -> Upadacitinib 30 mg (Period 2)	Dupilumab -> Upadacitinib (Period 2)
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 462 (1.08%)	4 / 147 (2.72%)	0 / 208 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Vascular disorders			
PERIPHERAL ARTERY OCCLUSION			
subjects affected / exposed	0 / 462 (0.00%)	0 / 147 (0.00%)	0 / 208 (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
Nervous system disorders			
MIGRAINE WITHOUT AURA			
subjects affected / exposed	0 / 462 (0.00%)	1 / 147 (0.68%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EPILEPSY			
subjects affected / exposed	0 / 462 (0.00%)	1 / 147 (0.68%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
ANAPHYLACTIC REACTION			
subjects affected / exposed	0 / 462 (0.00%)	0 / 147 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
DRUG-INDUCED LIVER INJURY			
subjects affected / exposed	1 / 462 (0.22%)	0 / 147 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
DERMATITIS ATOPIC			
subjects affected / exposed	1 / 462 (0.22%)	1 / 147 (0.68%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
SUICIDAL IDEATION			
subjects affected / exposed	0 / 462 (0.00%)	0 / 147 (0.00%)	0 / 208 (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
MAJOR DEPRESSION			

subjects affected / exposed	0 / 462 (0.00%)	0 / 147 (0.00%)	0 / 208 (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
DEPRESSION			
subjects affected / exposed	1 / 462 (0.22%)	0 / 147 (0.00%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
JUVENILE IDIOPATHIC ARTHRITIS			
subjects affected / exposed	1 / 462 (0.22%)	0 / 147 (0.00%)	0 / 208 (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
Infections and infestations			
SEPSIS			
subjects affected / exposed	1 / 462 (0.22%)	0 / 147 (0.00%)	0 / 208 (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
PNEUMONIA			
subjects affected / exposed	1 / 462 (0.22%)	1 / 147 (0.68%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Upadacitinib (Period 1)		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 458 (0.87%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
PERIPHERAL ARTERY OCCLUSION			
subjects affected / exposed	1 / 458 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
MIGRAINE WITHOUT AURA			

subjects affected / exposed	0 / 458 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
EPILEPSY			
subjects affected / exposed	0 / 458 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
ANAPHYLACTIC REACTION			
subjects affected / exposed	1 / 458 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
DRUG-INDUCED LIVER INJURY			
subjects affected / exposed	0 / 458 (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 / 458 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
SUICIDAL IDEATION			
subjects affected / exposed	1 / 458 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
MAJOR DEPRESSION			
subjects affected / exposed	1 / 458 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
DEPRESSION			

subjects affected / exposed	0 / 458 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
JUVENILE IDIOPATHIC ARTHRITIS			
subjects affected / exposed	0 / 458 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
SEPSIS			
subjects affected / exposed	0 / 458 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA			
subjects affected / exposed	0 / 458 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Dupilumab (Period 1)	Upadacitinib -> Upadacitinib 30 mg (Period 2)	Dupilumab -> Upadacitinib (Period 2)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	87 / 462 (18.83%)	30 / 147 (20.41%)	57 / 208 (27.40%)
Nervous system disorders			
HEADACHE			
subjects affected / exposed	16 / 462 (3.46%)	1 / 147 (0.68%)	5 / 208 (2.40%)
occurrences (all)	20	1	5
Skin and subcutaneous tissue disorders			
DERMATITIS ATOPIC			
subjects affected / exposed	15 / 462 (3.25%)	9 / 147 (6.12%)	12 / 208 (5.77%)
occurrences (all)	17	10	12
ACNE			
subjects affected / exposed	7 / 462 (1.52%)	5 / 147 (3.40%)	14 / 208 (6.73%)
occurrences (all)	7	5	14
Infections and infestations			

NASOPHARYNGITIS			
subjects affected / exposed	35 / 462 (7.58%)	12 / 147 (8.16%)	18 / 208 (8.65%)
occurrences (all)	43	13	20
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	22 / 462 (4.76%)	7 / 147 (4.76%)	12 / 208 (5.77%)
occurrences (all)	28	9	12

Non-serious adverse events	Upadacitinib (Period 1)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	156 / 458 (34.06%)		
Nervous system disorders			
HEADACHE			
subjects affected / exposed	27 / 458 (5.90%)		
occurrences (all)	32		
Skin and subcutaneous tissue disorders			
DERMATITIS ATOPIC			
subjects affected / exposed	23 / 458 (5.02%)		
occurrences (all)	24		
ACNE			
subjects affected / exposed	55 / 458 (12.01%)		
occurrences (all)	56		
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	58 / 458 (12.66%)		
occurrences (all)	74		
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	27 / 458 (5.90%)		
occurrences (all)	33		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 May 2023	Version 2.0/Amendment 1 clarified the following points: ● Estimand definition and the handling rule of the intercurrent events ● Clarified the primary endpoint ● Added additional details for safety assessments, and Tanner Stage assessments included for adolescent subjects required by regulatory agencies ● Included that the permanent discontinuation from the study will be mandatory in any subject who has been treated for at least 8 weeks with upadacitinib 30 mg QD and has not achieved an EASI 50 response from Baseline after rescue with TCS for at least 1 week per FDA request ● Clarified the eligibility criteria language to enroll subjects < 64 to ensure no subject 65 or older is enrolled and for laboratory values specific to pediatric studies

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported