# 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:<br>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:<br>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<br>Units: Subjects | | | |
| < 40 years | 223 | 228 | 451 |
| ≥ 40 to < 65 years | 94 | 98 | 192 |
| ≥ 65 years | 14 | 16 | 30 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 36.3 | 36.2 | |
| standard deviation | ± 13.81 | ± 14.42 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 139 | 159 | 298 |
| Male | 192 | 183 | 375 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 31 | 25 | 56 |
| Not Hispanic or Latino | 300 | 317 | 617 |
| Race<br>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:<br>•0-Clear: No signs of AD;<br>•1-Almost clear: Barely perceptible erythema, induration/papulation and/or lichenification;<br>•2-Mild: Slight but definite erythema, induration/papulation and/or minimal lichenification. No oozing or crusting;<br>•3-Moderate: Clearly perceptible erythema, induration/papulation and/or lichenification, possible oozing or crusting;<br>•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.<br>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