



## Clinical trial results:

### A Phase 2b Multicenter, Randomized, Placebo-Controlled, Double-Blind Dose-Ranging Study to Evaluate ABT-494 (Upadacitinib) in Adult Subjects with Moderate to Severe Atopic Dermatitis

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2016-002451-21  |
| Trial protocol           | NL FI IE BE ES  |
| Global end of trial date | 31 January 2019 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1               |
| This version publication date  | 08 February 2020 |
| First version publication date | 08 February 2020 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | M16-048 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02925117 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Abbvie Deutschland GmbH & Co.KG   |
| Sponsor organisation address | AbbVie House, Vanwall Business Park, Maidenhead, Berkshire, United Kingdom, SL6-4UB |
| Public contact               | Global Medical Services, AbbVie, 011 800-633-9110,                                  |
| Scientific contact           | Alvina Chu, MD, AbbVie, alvina.chu@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                       | 31 January 2019 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 31 January 2019 |
| 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 safety and efficacy of multiple doses of upadacitinib monotherapy versus placebo in the treatment of adults with moderate to severe atopic dermatitis (AD).

Protection of trial subjects:

All subjects entering the study had to sign an informed consent that was explained to them and questions encouraged.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 25 October 2016 |
| 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: 17     |
| Country: Number of subjects enrolled | Canada: 41        |
| Country: Number of subjects enrolled | Finland: 3        |
| Country: Number of subjects enrolled | Germany: 3        |
| Country: Number of subjects enrolled | Japan: 10         |
| Country: Number of subjects enrolled | Netherlands: 17   |
| Country: Number of subjects enrolled | Spain: 1          |
| Country: Number of subjects enrolled | United States: 75 |
| Worldwide total number of subjects   | 167               |
| EEA total number of subjects         | 24                |

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)      | 152 |
| From 65 to 84 years       | 15  |
| 85 years and over         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled at 36 sites in 8 countries (Australia, Canada, Finland, Germany, Japan, Netherlands, Spain, and the United States [US]).

The study included a 16-week double-blind treatment period (period 1) followed by a 72-week double-blind treatment period (Period 2) for a total of 88 weeks of treatment.

### Pre-assignment

Screening details:

Participants were randomized in a 1:1:1:1 ratio, stratified by geographic region (US and Canada; European Union and Australia; and Japan). Participants who completed Period 1 were re-randomized at Week 16 within their original treatment group assignments to either upadacitinib or placebo in a 1:1 ratio. Rescue therapy was provided from Week 20.

### Period 1

|                              |                         |
|------------------------------|-------------------------|
| Period 1 title               | Period 1                |
| Is this the baseline period? | Yes                     |
| Allocation method            | Randomised - controlled |
| Blinding used                | Double blind            |
| Roles blinded                | Subject, Investigator   |

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

Participants randomized to receive placebo once daily (QD) for 16 weeks in Period 1.

|  |          |
|--|----------|
| Arm type                               | Placebo  |
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Administered orally once a day

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | Upadacitinib 7.5 mg |
|------------------|---------------------|

Arm description:

Participants randomized to receive upadacitinib 7.5 mg once daily for 16 weeks in Period 1.

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

Dosage and administration details:

Administered orally once a day

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Upadacitinib 15 mg |
|------------------|--------------------|

Arm description:

Participants randomized to receive upadacitinib 15 mg once daily for 16 weeks in Period 1.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                    |
|--|--------------------|
| Investigational medicinal product name | Upadacitinib       |
| Investigational medicinal product code | ABT-494            |
| Other name                             | RINVOQ™            |
| Pharmaceutical forms                   | Tablet             |
| Routes of administration               | Oral use           |
| Dosage and administration details:     |                    |
| Administered orally once a day         |                    |
| <b>Arm title</b>                       | Upadacitinib 30 mg |

Arm description:

Participants randomized to receive upadacitinib 30 mg once daily for 16 weeks in Period 1.

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

Dosage and administration details:

Administered orally once a day

| <b>Number of subjects in period 1</b> | Placebo | Upadacitinib 7.5 mg | Upadacitinib 15 mg |
|---------------------------------------|---------|---------------------|--------------------|
| Started                               | 41      | 42                  | 42                 |
| Received Treatment                    | 40      | 42                  | 42                 |
| Completed                             | 23      | 31                  | 37                 |
| Not completed                         | 18      | 11                  | 5                  |
| Consent withdrawn by subject          | 10      | 3                   | 3                  |
| Adverse event, non-fatal              | 1       | 3                   | 1                  |
| Other                                 | 5       | 4                   | 1                  |
| Lost to follow-up                     | 2       | 1                   | -                  |

| <b>Number of subjects in period 1</b> | Upadacitinib 30 mg |
|---------------------------------------|--------------------|
| Started                               | 42                 |
| Received Treatment                    | 42                 |
| Completed                             | 39                 |
| Not completed                         | 3                  |
| Consent withdrawn by subject          | -                  |
| Adverse event, non-fatal              | 2                  |
| Other                                 | 1                  |
| Lost to follow-up                     | -                  |

**Period 2**

|                              |                         |
|------------------------------|-------------------------|
| Period 2 title               | Period 2                |
| Is this the baseline period? | No                      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Double blind            |
| Roles blinded                | Subject, Investigator   |

**Arms**

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Placebo / Placebo |
|------------------|-------------------|

## Arm description:

Participants originally randomized to placebo were re-randomized at Week 16 to receive placebo tablets once a day for 72 weeks in Period 2.

|  |          |
|--|----------|
| Arm type                               | Placebo  |
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

## Dosage and administration details:

Administered orally once a day

|                  |                              |
|------------------|------------------------------|
| <b>Arm title</b> | Placebo / Upadacitinib 30 mg |
|------------------|------------------------------|

## Arm description:

Participants originally randomized to placebo were re-randomized at Week 16 to receive 30 mg upadacitinib once a day for 72 weeks in Period 2.

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

## Dosage and administration details:

Administered orally once a day

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | Upadacitinib 7.5 mg / Placebo |
|------------------|-------------------------------|

## Arm description:

Participants originally randomized to 7.5 mg upadacitinib were re-randomized at Week 16 to receive placebo tablets once a day for 72 weeks in Period 2.

|  |          |
|--|----------|
| Arm type                               | Placebo  |
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

## Dosage and administration details:

Administered orally once a day

|                  |   |
|------------------|---|
| <b>Arm title</b> | Upadacitinib 7.5 mg / Upadacitinib 7.5 mg |
|------------------|---|

## Arm description:

Participants originally randomized to 7.5 mg upadacitinib were re-randomized at Week 16 to receive 7.5 mg upadacitinib once a day for 72 weeks in Period 2.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|   |   |
|---|---|
| Investigational medicinal product name  | Upadacitinib                            |
| Investigational medicinal product code  | ABT-494                                 |
| Other name  | RINVOQ™                                 |
| Pharmaceutical forms  | Tablet                                  |
| Routes of administration  | Oral use                                |
| Dosage and administration details:  |   |
| Administered orally once a day  |   |
| <b>Arm title</b>  | Upadacitinib 15 mg / Placebo            |
| Arm description:  |   |
| Participants originally randomized to 15 mg upadacitinib were re-randomized at Week 16 to receive placebo tablets once a day for 72 weeks in Period 2.    |   |
| Arm type  | Placebo                                 |
| Investigational medicinal product name  | Placebo                                 |
| Investigational medicinal product code  |   |
| Other name  |   |
| Pharmaceutical forms  | Tablet                                  |
| Routes of administration  | Oral use                                |
| Dosage and administration details:  |   |
| Administered orally once a day  |   |
| <b>Arm title</b>  | Upadacitinib 15 mg / Upadacitinib 15 mg |
| Arm description:  |   |
| Participants originally randomized to 15 mg upadacitinib were re-randomized at Week 16 to receive 15 mg upadacitinib once a day for 72 weeks in Period 2. |   |
| Arm type  | Experimental                            |
| Investigational medicinal product name  | Upadacitinib                            |
| Investigational medicinal product code  | ABT-494                                 |
| Other name  | RINVOQ™                                 |
| Pharmaceutical forms  | Tablet                                  |
| Routes of administration  | Oral use                                |
| Dosage and administration details:  |   |
| Administered orally once a day  |   |
| <b>Arm title</b>  | Upadacitinib 30 mg / Placebo            |
| Arm description:  |   |
| Participants originally randomized to 30 mg upadacitinib were re-randomized at Week 16 to receive placebo tablets once a day for 72 weeks in Period 2.    |   |
| Arm type  | Placebo                                 |
| Investigational medicinal product name  | Placebo                                 |
| Investigational medicinal product code  |   |
| Other name  |   |
| Pharmaceutical forms  | Tablet                                  |
| Routes of administration  | Oral use                                |
| Dosage and administration details:  |   |
| Administered orally once a day  |   |
| <b>Arm title</b>  | Upadacitinib 30 mg / Upadacitinib 30 mg |
| Arm description:  |   |
| Participants originally randomized to 30 mg upadacitinib were re-randomized at Week 16 to receive 30 mg upadacitinib once a day for 72 weeks in Period 2. |   |
| Arm type  | Experimental                            |

|  |              |
|--|--------------|
| Investigational medicinal product name | Upadacitinib |
| Investigational medicinal product code | ABT-494      |
| Other name                             | RINVOQ™      |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Administered orally once a day

| <b>Number of subjects in period 2<sup>[1]</sup></b> | Placebo / Placebo | Placebo / Upadacitinib 30 mg | Upadacitinib 7.5 mg / Placebo |
|---|-------------------|------------------------------|-------------------------------|
| Started   | 10                | 10                           | 15                            |
| Received Treatment                                  | 10                | 10                           | 15                            |
| Rescued by Upadacitinib 30 mg                       | 8                 | 1 <sup>[2]</sup>             | 13                            |
| Completed   | 8                 | 5                            | 9                             |
| Not completed                                       | 2                 | 5                            | 6                             |
| Consent withdrawn by subject                        | -                 | 1                            | 4                             |
| Adverse event, non-fatal                            | -                 | 1                            | -                             |
| Other   | 1                 | 1                            | 1                             |
| Lost to follow-up                                   | 1                 | 2                            | 1                             |

| <b>Number of subjects in period 2<sup>[1]</sup></b> | Upadacitinib 7.5 mg / Upadacitinib 7.5 mg | Upadacitinib 15 mg / Placebo | Upadacitinib 15 mg / Upadacitinib 15 mg |
|---|---|------------------------------|---|
| Started   | 16  | 19                           | 18                                      |
| Received Treatment                                  | 16  | 19                           | 18                                      |
| Rescued by Upadacitinib 30 mg                       | 12  | 17                           | 12                                      |
| Completed   | 11  | 13                           | 12                                      |
| Not completed                                       | 5   | 6                            | 6                                       |
| Consent withdrawn by subject                        | 3   | 2                            | 2                                       |
| Adverse event, non-fatal                            | -   | -                            | -                                       |
| Other   | 1   | 3                            | 4                                       |
| Lost to follow-up                                   | 1   | 1                            | -                                       |

| <b>Number of subjects in period 2<sup>[1]</sup></b> | Upadacitinib 30 mg / Placebo | Upadacitinib 30 mg / Upadacitinib 30 mg |
|---|------------------------------|---|
| Started   | 19                           | 19                                      |
| Received Treatment                                  | 19                           | 19                                      |
| Rescued by Upadacitinib 30 mg                       | 14                           | 4 <sup>[3]</sup>                        |
| Completed   | 11                           | 14                                      |
| Not completed                                       | 8                            | 5                                       |
| Consent withdrawn by subject                        | 2                            | 2                                       |
| Adverse event, non-fatal                            | 3                            | 2                                       |
| Other   | 3                            | -                                       |

|                   |   |   |
|-------------------|---|---|
| Lost to follow-up | - | 1 |
|-------------------|---|---|

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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: Four participants completed Week 16 but were not re-randomized into Period 2.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One participant re-randomized to 30 mg upadacitinib was rescued during Period 2; 5 participants completed Period 2.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Four participants re-randomized to 30 mg upadacitinib were rescued during Period 2; 14 participants completed Period 2.

## Baseline characteristics

### Reporting groups

|   |                     |
|---|---------------------|
| Reporting group title   | Placebo             |
| Reporting group description:  |                     |
| Participants randomized to receive placebo once daily (QD) for 16 weeks in Period 1.        |                     |
| Reporting group title   | Upadacitinib 7.5 mg |
| Reporting group description:  |                     |
| Participants randomized to receive upadacitinib 7.5 mg once daily for 16 weeks in Period 1. |                     |
| Reporting group title   | Upadacitinib 15 mg  |
| Reporting group description:  |                     |
| Participants randomized to receive upadacitinib 15 mg once daily for 16 weeks in Period 1.  |                     |
| Reporting group title   | Upadacitinib 30 mg  |
| Reporting group description:  |                     |
| Participants randomized to receive upadacitinib 30 mg once daily for 16 weeks in Period 1.  |                     |

| Reporting group values                    | Placebo | Upadacitinib 7.5 mg | Upadacitinib 15 mg |
|---|---------|---------------------|--------------------|
| Number of subjects                        | 41      | 42                  | 42                 |
| Age categorical<br>Units: Subjects        |         |                     |                    |
| < 40 years                                | 25      | 22                  | 25                 |
| 40 - 64 years                             | 11      | 16                  | 14                 |
| ≥ 65 years                                | 5       | 4                   | 3                  |
| Age continuous<br>Units: years            |         |                     |                    |
| arithmetic mean                           | 39.9    | 41.5                | 38.5               |
| standard deviation                        | ± 17.52 | ± 15.36             | ± 15.24            |
| Gender categorical<br>Units: Subjects     |         |                     |                    |
| Female                                    | 17      | 14                  | 12                 |
| Male                                      | 24      | 28                  | 30                 |
| Race<br>Units: Subjects                   |         |                     |                    |
| White                                     | 28      | 24                  | 21                 |
| Black or African American                 | 6       | 7                   | 10                 |
| Asian                                     | 7       | 9                   | 9                  |
| American Indian/Alaska Native             | 0       | 0                   | 1                  |
| Native Hawaiian or Other Pacific Islander | 0       | 2                   | 1                  |
| Ethnicity<br>Units: Subjects              |         |                     |                    |
| Hispanic or Latino                        | 0       | 2                   | 2                  |
| Not Hispanic or Latino                    | 41      | 40                  | 40                 |
| Geographic Region<br>Units: Subjects      |         |                     |                    |
| US/Canada                                 | 29      | 29                  | 29                 |
| EU/Australia                              | 10      | 11                  | 10                 |
| Japan                                     | 2       | 2                   | 3                  |

|   |         |         |         |
|---|---------|---------|---------|
| Duration of Atopic Dermatitis Diagnosis   |         |         |         |
| n = 40 in the placebo group   |         |         |         |
| Units: years  |         |         |         |
| arithmetic mean   | 26.84   | 30.44   | 22.59   |
| standard deviation  | ± 18.76 | ± 18.07 | ± 15.78 |
| Eczema Area and Severity Index (EASI)   |         |         |         |
| 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: scores on a scale  |         |         |         |
| arithmetic mean   | 32.62   | 31.42   | 31.40   |
| standard deviation  | ± 14.49 | ± 15.76 | ± 12.26 |

| Reporting group values                    | Upadacitinib 30 mg | Total |  |
|---|--------------------|-------|--|
| Number of subjects                        | 42                 | 167   |  |
| Age categorical                           |                    |       |  |
| Units: Subjects                           |                    |       |  |
| < 40 years                                | 22                 | 94    |  |
| 40 - 64 years                             | 17                 | 58    |  |
| ≥ 65 years                                | 3                  | 15    |  |
| Age continuous                            |                    |       |  |
| Units: years                              |                    |       |  |
| arithmetic mean                           | 39.9               | -     |  |
| standard deviation                        | ± 15.30            |       |  |
| Gender categorical                        |                    |       |  |
| Units: Subjects                           |                    |       |  |
| Female                                    | 20                 | 63    |  |
| Male                                      | 22                 | 104   |  |
| Race                                      |                    |       |  |
| Units: Subjects                           |                    |       |  |
| White                                     | 23                 | 96    |  |
| Black or African American                 | 6                  | 29    |  |
| Asian                                     | 13                 | 38    |  |
| American Indian/Alaska Native             | 0                  | 1     |  |
| Native Hawaiian or Other Pacific Islander | 0                  | 3     |  |
| Ethnicity                                 |                    |       |  |
| Units: Subjects                           |                    |       |  |
| Hispanic or Latino                        | 1                  | 5     |  |
| Not Hispanic or Latino                    | 41                 | 162   |  |
| Geographic Region                         |                    |       |  |
| Units: Subjects                           |                    |       |  |
| US/Canada                                 | 29                 | 116   |  |
| EU/Australia                              | 10                 | 41    |  |
| Japan                                     | 3                  | 10    |  |
| Duration of Atopic Dermatitis Diagnosis   |                    |       |  |
| n = 40 in the placebo group               |                    |       |  |
| Units: years                              |                    |       |  |
| arithmetic mean                           | 24.24              | -     |  |
| standard deviation                        | ± 13.58            |       |  |
| Eczema Area and Severity Index (EASI)     |                    |       |  |

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: scores on a scale |         |   |  |
| arithmetic mean          | 28.15   |   |  |
| standard deviation       | ± 11.62 | - |  |

## End points

### End points reporting groups

|   |   |
|---|---|
| Reporting group title   | Placebo                                   |
| Reporting group description:<br>Participants randomized to receive placebo once daily (QD) for 16 weeks in Period 1.  |   |
| Reporting group title   | Upadacitinib 7.5 mg                       |
| Reporting group description:<br>Participants randomized to receive upadacitinib 7.5 mg once daily for 16 weeks in Period 1.   |   |
| Reporting group title   | Upadacitinib 15 mg                        |
| Reporting group description:<br>Participants randomized to receive upadacitinib 15 mg once daily for 16 weeks in Period 1.  |   |
| Reporting group title   | Upadacitinib 30 mg                        |
| Reporting group description:<br>Participants randomized to receive upadacitinib 30 mg once daily for 16 weeks in Period 1.  |   |
| Reporting group title   | Placebo / Placebo                         |
| Reporting group description:<br>Participants originally randomized to placebo were re-randomized at Week 16 to receive placebo tablets once a day for 72 weeks in Period 2.                 |   |
| Reporting group title   | Placebo / Upadacitinib 30 mg              |
| Reporting group description:<br>Participants originally randomized to placebo were re-randomized at Week 16 to receive 30 mg upadacitinib once a day for 72 weeks in Period 2.              |   |
| Reporting group title   | Upadacitinib 7.5 mg / Placebo             |
| Reporting group description:<br>Participants originally randomized to 7.5 mg upadacitinib were re-randomized at Week 16 to receive placebo tablets once a day for 72 weeks in Period 2.     |   |
| Reporting group title   | Upadacitinib 7.5 mg / Upadacitinib 7.5 mg |
| Reporting group description:<br>Participants originally randomized to 7.5 mg upadacitinib were re-randomized at Week 16 to receive 7.5 mg upadacitinib once a day for 72 weeks in Period 2. |   |
| Reporting group title   | Upadacitinib 15 mg / Placebo              |
| Reporting group description:<br>Participants originally randomized to 15 mg upadacitinib were re-randomized at Week 16 to receive placebo tablets once a day for 72 weeks in Period 2.      |   |
| Reporting group title   | Upadacitinib 15 mg / Upadacitinib 15 mg   |
| Reporting group description:<br>Participants originally randomized to 15 mg upadacitinib were re-randomized at Week 16 to receive 15 mg upadacitinib once a day for 72 weeks in Period 2.   |   |
| Reporting group title   | Upadacitinib 30 mg / Placebo              |
| Reporting group description:<br>Participants originally randomized to 30 mg upadacitinib were re-randomized at Week 16 to receive placebo tablets once a day for 72 weeks in Period 2.      |   |
| Reporting group title   | Upadacitinib 30 mg / Upadacitinib 30 mg   |
| Reporting group description:<br>Participants originally randomized to 30 mg upadacitinib were re-randomized at Week 16 to receive 30 mg upadacitinib once a day for 72 weeks in Period 2.   |   |

## Primary: Percent Change from Baseline in Eczema Area and Severity Index (EASI) Score at Week 16

|                 |  |
|-----------------|--|
| End point title | Percent Change from Baseline in Eczema Area and Severity Index (EASI) Score 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 by eczema. For each region, 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, with adjustment 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; a negative change from baseline indicates improvement. Last observation carried forward (LOCF) imputation was used.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline and Week 16

| End point values                    | Placebo           | Upadacitinib 7.5 mg | Upadacitinib 15 mg | Upadacitinib 30 mg |
|-------------------------------------|-------------------|---------------------|--------------------|--------------------|
| Subject group type                  | Reporting group   | Reporting group     | Reporting group    | Reporting group    |
| Number of subjects analysed         | 39 <sup>[1]</sup> | 42                  | 42                 | 42                 |
| Units: percent change               |                   |                     |                    |                    |
| least squares mean (standard error) | -23.0 (± 6.42)    | -39.4 (± 6.24)      | -61.7 (± 6.12)     | -74.4 (± 6.13)     |

Notes:

[1] - Randomized participants with at least one post-baseline assessment

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Analysis of % Change From Baseline in EASI |
| Comparison groups                       | Upadacitinib 30 mg v Placebo               |
| Number of subjects included in analysis | 81   |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority                                |
| P-value                                 | < 0.001 <sup>[2]</sup>                     |
| Method                                  | ANCOVA                                     |
| Parameter estimate                      | LS Mean Difference                         |
| Point estimate                          | -51.4                                      |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | -66.5                                      |
| upper limit                             | -36.3                                      |
| Variability estimate                    | Standard error of the mean                 |
| Dispersion value                        | 7.65                                       |

Notes:

[2] - Analysis of covariance (ANCOVA) with stratum (geographic region), baseline value, and treatment in the model.

|                            |  |
|----------------------------|--|
| Statistical analysis title | Analysis of % Change From Baseline in EASI |
|----------------------------|--|

|   |                              |
|---|------------------------------|
| Comparison groups                       | Placebo v Upadacitinib 15 mg |
| Number of subjects included in analysis | 81                           |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | < 0.001 <sup>[3]</sup>       |
| Method                                  | ANCOVA                       |
| Parameter estimate                      | LS Mean Difference           |
| Point estimate                          | -38.7                        |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | -53.7                        |
| upper limit                             | -23.6                        |
| Variability estimate                    | Standard error of the mean   |
| Dispersion value                        | 7.61                         |

Notes:

[3] - Analysis of covariance (ANCOVA) with stratum (geographic region), baseline value, and treatment in the model.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of % Change From Baseline in EASI |
| Comparison groups                       | Placebo v Upadacitinib 7.5 mg              |
| Number of subjects included in analysis | 81   |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority                                |
| P-value                                 | = 0.032 <sup>[4]</sup>                     |
| Method                                  | ANCOVA                                     |
| Parameter estimate                      | LS Mean Difference                         |
| Point estimate                          | -16.4                                      |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | -31.4                                      |
| upper limit                             | -1.4                                       |
| Variability estimate                    | Standard error of the mean                 |
| Dispersion value                        | 7.61                                       |

Notes:

[4] - Analysis of covariance (ANCOVA) with stratum (geographic region), baseline value, and treatment in the model.

### **Secondary: Percentage of Participants who Achieved a 75% Reduction in EASI Score (EASI 75) at Week 16**

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants who Achieved a 75% Reduction in EASI Score (EASI 75) at Week 16 |
|-----------------|--|

End point description:

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.

An EASI 75 response is defined as at least a 75% reduction (improvement) in EASI score relative to the Baseline value.

Participants with missing values at Week 16 were counted as non-responders in this analysis (non-responder imputation).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:  
Baseline and Week 16

| End point values                  | Placebo         | Upadacitinib 7.5 mg | Upadacitinib 15 mg | Upadacitinib 30 mg |
|-----------------------------------|-----------------|---------------------|--------------------|--------------------|
| Subject group type                | Reporting group | Reporting group     | Reporting group    | Reporting group    |
| Number of subjects analysed       | 41              | 42                  | 42                 | 42                 |
| Units: percentage of participants |                 |                     |                    |                    |
| number (not applicable)           | 9.8             | 28.6                | 52.4               | 69.0               |

## Statistical analyses

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Analysis of EASI 75 at Week 16 |
| Comparison groups                       | Placebo v Upadacitinib 30 mg   |
| Number of subjects included in analysis | 83                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | < 0.001 <sup>[5]</sup>         |
| Method                                  | Cochran-Mantel-Haenszel        |
| Parameter estimate                      | Adjusted Difference            |
| Point estimate                          | 58.7                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 42.5                           |
| upper limit                             | 74.8                           |

Notes:

[5] - Cochran-Mantel-Haenszel test, adjusted for stratum (geographic region).

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Analysis of EASI 75 at Week 16 |
| Comparison groups                       | Placebo v Upadacitinib 15 mg   |
| Number of subjects included in analysis | 83                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | < 0.001 <sup>[6]</sup>         |
| Method                                  | Cochran-Mantel-Haenszel        |
| Parameter estimate                      | Adjusted Difference            |
| Point estimate                          | 42.5                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 25.5                           |
| upper limit                             | 59.6                           |

Notes:

[6] - Cochran-Mantel-Haenszel test, adjusted for stratum (geographic region).

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Analysis of EASI 75 at Week 16 |
| Comparison groups                       | Placebo v Upadacitinib 7.5 mg  |
| Number of subjects included in analysis | 83                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.022 <sup>[7]</sup>         |
| Method                                  | Cochran-Mantel-Haenszel        |
| Parameter estimate                      | Adjusted Difference            |
| Point estimate                          | 18.7                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 2.7                            |
| upper limit                             | 34.7                           |

Notes:

[7] - Cochran-Mantel-Haenszel test, adjusted for stratum (geographic region).

### Secondary: Percentage of Participants Achieving an Investigator Global Assessment (IGA) of "0" or "1" at Week 16

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants Achieving an Investigator Global Assessment (IGA) of "0" or "1" at Week 16 |
|-----------------|---|

End point description:

Investigator's Global Assessment for Atopic Dermatitis (IGA) was scored on the following scale:

0: Clear (No inflammatory signs of atopic dermatitis)

1: Almost Clear (Just perceptible erythema and just perceptible papulation/infiltration)

2: Mild (Mild erythema and mild papulation/infiltration)

3: Moderate (Moderate erythema and moderate papulation/infiltration)

4: Severe (Severe erythema and severe papulation/infiltration with or without oozing/crusting)

The percentage of participants with a score of 0 or 1 at Week 16 is reported.

Non-responder imputation was used.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 16

| End point values                  | Placebo         | Upadacitinib 7.5 mg | Upadacitinib 15 mg | Upadacitinib 30 mg |
|-----------------------------------|-----------------|---------------------|--------------------|--------------------|
| Subject group type                | Reporting group | Reporting group     | Reporting group    | Reporting group    |
| Number of subjects analysed       | 41              | 42                  | 42                 | 42                 |
| Units: percentage of participants |                 |                     |                    |                    |
| number (not applicable)           | 2.4             | 14.3                | 31.0               | 50.0               |

### Statistical analyses

|                                   |                                     |
|-----------------------------------|-------------------------------------|
| <b>Statistical analysis title</b> | Analysis of IGA Response at Week 16 |
| Comparison groups                 | Placebo v Upadacitinib 30 mg        |

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 83                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | < 0.001 <sup>[8]</sup>  |
| Method                                  | Cochran-Mantel-Haenszel |
| Parameter estimate                      | Adjusted Difference     |
| Point estimate                          | 46.9                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 31.1                    |
| upper limit                             | 62.7                    |

Notes:

[8] - Cochran-Mantel-Haenszel test, adjusted for stratum (geographic region).

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | Analysis of IGA Response at Week 16 |
| Comparison groups                       | Placebo v Upadacitinib 15 mg        |
| Number of subjects included in analysis | 83                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | < 0.001 <sup>[9]</sup>              |
| Method                                  | Cochran-Mantel-Haenszel             |
| Parameter estimate                      | Adjusted Difference                 |
| Point estimate                          | 28.6                                |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | 13.8                                |
| upper limit                             | 43.4                                |

Notes:

[9] - Cochran-Mantel-Haenszel test, adjusted for stratum (geographic region).

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | Analysis of IGA Response at Week 16 |
| Comparison groups                       | Placebo v Upadacitinib 7.5 mg       |
| Number of subjects included in analysis | 83                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.044 <sup>[10]</sup>             |
| Method                                  | Cochran-Mantel-Haenszel             |
| Parameter estimate                      | Adjusted Difference                 |
| Point estimate                          | 11.9                                |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | 0.3                                 |
| upper limit                             | 23.5                                |

Notes:

[10] - Cochran-Mantel-Haenszel test, adjusted for stratum (geographic region).

## Secondary: Percent Change from Baseline to Weeks 2, 8, and 16 in Pruritus

## Numerical Rating Scale (NRS)

|                 |   |
|-----------------|---|
| End point title | Percent Change from Baseline to Weeks 2, 8, and 16 in Pruritus Numerical Rating Scale (NRS) |
|-----------------|---|

End point description:

Participants were asked to rate itch in the past 24 hours on a daily basis using a scale from 0 to 10, with 0 being no itch and 10 being the worst imaginable itch. The percent change from Baseline at each week was calculated from a rolling weekly average.

Last observation carried forward (LOCF) imputation was used.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Weeks 2, 8, and 16

| End point values                    | Placebo            | Upadacitinib 7.5 mg | Upadacitinib 15 mg | Upadacitinib 30 mg |
|-------------------------------------|--------------------|---------------------|--------------------|--------------------|
| Subject group type                  | Reporting group    | Reporting group     | Reporting group    | Reporting group    |
| Number of subjects analysed         | 37 <sup>[11]</sup> | 40                  | 37                 | 42                 |
| Units: units on a scale             |                    |                     |                    |                    |
| least squares mean (standard error) |                    |                     |                    |                    |
| Week 2 (n = 37, 39, 37, 42)         | 1.7 (± 5.59)       | -29.3 (± 5.45)      | -46.0 (± 5.44)     | -57.6 (± 5.24)     |
| Week 8 (n = 37, 40, 37, 42)         | -6.7 (± 7.51)      | -35.5 (± 7.28)      | -45.1 (± 7.32)     | -73.1 (± 7.05)     |
| Week 16 (n = 37, 40, 37, 42)        | -9.7 (± 8.30)      | -39.6 (± 8.04)      | -48.0 (± 8.08)     | -68.9 (± 7.79)     |

Notes:

[11] - Participants with at least one post-baseline measurement

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Analysis of % Change in Pruritus NRS at Week 2 |
| Comparison groups                       | Placebo v Upadacitinib 30 mg                   |
| Number of subjects included in analysis | 79   |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | superiority                                    |
| P-value                                 | < 0.001 <sup>[12]</sup>                        |
| Method                                  | ANCOVA   |
| Parameter estimate                      | LS Mean Difference                             |
| Point estimate                          | -59.3  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -72.3  |
| upper limit                             | -46.3  |
| Variability estimate                    | Standard error of the mean                     |
| Dispersion value                        | 6.58   |

Notes:

[12] - ANCOVA with stratum (geographic region), baseline value, and treatment in the model.

|                            |  |
|----------------------------|--|
| Statistical analysis title | Analysis of % Change in Pruritus NRS at Week 2 |
| Comparison groups          | Placebo v Upadacitinib 15 mg                   |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 74                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | < 0.001 <sup>[13]</sup>    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LS Mean Difference         |
| Point estimate                          | -47.7                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -61.1                      |
| upper limit                             | -34.3                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 6.78                       |

Notes:

[13] - ANCOVA with stratum (geographic region), baseline value, and treatment in the model.

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Analysis of % Change in Pruritus NRS at Week 2 |
| Statistical analysis description:   |  |
| The number of subjects included in the analysis of the comparison of Placebo vs Upadacitinib 7.5 mg at Week 2 is 76 subjects, rather than 77 subjects, since 1 subject in the Upadacitinib 7.5 mg had missing data at Week 2. |  |
| Comparison groups   | Placebo v Upadacitinib 7.5 mg                  |
| Number of subjects included in analysis   | 77   |
| Analysis specification  | Pre-specified                                  |
| Analysis type   | superiority                                    |
| P-value   | < 0.001 <sup>[14]</sup>                        |
| Method  | ANCOVA   |
| Parameter estimate  | LS Mean Difference                             |
| Point estimate  | -31.1  |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | -44.3  |
| upper limit   | -17.8  |
| Variability estimate  | Standard error of the mean                     |
| Dispersion value  | 6.7  |

Notes:

[14] - ANCOVA with stratum (geographic region), baseline value, and treatment in the model.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of % Change in Pruritus NRS at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 30 mg                   |
| Number of subjects included in analysis | 79   |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | superiority                                    |
| P-value                                 | < 0.001 <sup>[15]</sup>                        |
| Method                                  | ANCOVA   |
| Parameter estimate                      | LS Mean Difference                             |
| Point estimate                          | -66.4  |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -83.9                      |
| upper limit          | -48.9                      |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 8.85                       |

Notes:

[15] - ANCOVA with stratum (geographic region), baseline value, and treatment in the model.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of % Change in Pruritus NRS at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 15 mg                   |
| Number of subjects included in analysis | 74   |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | superiority                                    |
| P-value                                 | < 0.001 <sup>[16]</sup>                        |
| Method                                  | ANCOVA   |
| Parameter estimate                      | LS Mean Difference                             |
| Point estimate                          | -38.4  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -56.4  |
| upper limit                             | -20.4  |
| Variability estimate                    | Standard error of the mean                     |
| Dispersion value                        | 9.13   |

Notes:

[16] - ANCOVA with stratum (geographic region), baseline value, and treatment in the model.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of % Change in Pruritus NRS at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 7.5 mg                  |
| Number of subjects included in analysis | 77   |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | superiority                                    |
| P-value                                 | = 0.002 <sup>[17]</sup>                        |
| Method                                  | ANCOVA   |
| Parameter estimate                      | LS Mean Difference                             |
| Point estimate                          | -28.9  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -46.6  |
| upper limit                             | -11.2  |
| Variability estimate                    | Standard error of the mean                     |
| Dispersion value                        | 8.96   |

Notes:

[17] - ANCOVA with stratum (geographic region), baseline value, and treatment in the model.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Analysis of % Change in Pruritus NRS at Week 16 |
| Comparison groups                 | Placebo v Upadacitinib 30 mg                    |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 79                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | < 0.001 <sup>[18]</sup>    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LS Mean Difference         |
| Point estimate                          | -59.2                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -78.6                      |
| upper limit                             | -39.9                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 9.78                       |

Notes:

[18] - ANCOVA with stratum (geographic region), baseline value, and treatment in the model.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of % Change in Pruritus NRS at Week 16 |
| Comparison groups                       | Placebo v Upadacitinib 15 mg                    |
| Number of subjects included in analysis | 74  |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | superiority                                     |
| P-value                                 | < 0.001 <sup>[19]</sup>                         |
| Method                                  | ANCOVA  |
| Parameter estimate                      | LS Mean Difference                              |
| Point estimate                          | -38.3   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -58.3   |
| upper limit                             | -18.4   |
| Variability estimate                    | Standard error of the mean                      |
| Dispersion value                        | 10.08   |

Notes:

[19] - ANCOVA with stratum (geographic region), baseline value, and treatment in the model.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of % Change in Pruritus NRS at Week 16 |
| Comparison groups                       | Placebo v Upadacitinib 7.5 mg                   |
| Number of subjects included in analysis | 77  |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | superiority                                     |
| P-value                                 | = 0.003 <sup>[20]</sup>                         |
| Method                                  | ANCOVA  |
| Parameter estimate                      | LS Mean Difference                              |
| Point estimate                          | -29.9   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -49.4   |
| upper limit                             | -10.3   |

|                      |                            |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value     | 9.9                        |

Notes:

[20] - ANCOVA with stratum (geographic region), baseline value, and treatment in the model.

## Secondary: Percent Change from Baseline in EASI Score at Week 8

|                 |  |
|-----------------|--|
| End point title | Percent Change from Baseline in EASI Score at Week 8 |
|-----------------|--|

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 by eczema. For each region, 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, with adjustment 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; a negative change from baseline indicates improvement. Last observation carried forward (LOCF) imputation was used.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 8

| End point values                    | Placebo            | Upadacitinib 7.5 mg | Upadacitinib 15 mg | Upadacitinib 30 mg |
|-------------------------------------|--------------------|---------------------|--------------------|--------------------|
| Subject group type                  | Reporting group    | Reporting group     | Reporting group    | Reporting group    |
| Number of subjects analysed         | 39 <sup>[21]</sup> | 42                  | 42                 | 42                 |
| Units: percent change               |                    |                     |                    |                    |
| least squares mean (standard error) | -17.5 (± 6.27)     | -43.7 (± 6.09)      | -65.4 (± 5.97)     | -82.8 (± 5.98)     |

Notes:

[21] - Participants with at least one post-baseline measurement

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of % Change in EASI at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 30 mg           |
| Number of subjects included in analysis | 81                                     |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[22]</sup>                |
| Method                                  | ANCOVA                                 |
| Parameter estimate                      | LS Mean Difference                     |
| Point estimate                          | -65.3                                  |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -80                                    |
| upper limit                             | -50.5                                  |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 7.46                                   |

Notes:

[22] - ANCOVA with stratum (geographic region), baseline value, and treatment in the model.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of % Change in EASI at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 15 mg           |
| Number of subjects included in analysis | 81                                     |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[23]</sup>                |
| Method                                  | ANCOVA                                 |
| Parameter estimate                      | LS Mean Difference                     |
| Point estimate                          | -47.9                                  |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -62.6                                  |
| upper limit                             | -33.3                                  |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 7.42                                   |

Notes:

[23] - ANCOVA with stratum (geographic region), baseline value, and treatment in the model.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of % Change in EASI at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 7.5 mg          |
| Number of subjects included in analysis | 81                                     |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[24]</sup>                |
| Method                                  | ANCOVA                                 |
| Parameter estimate                      | LS Mean Difference                     |
| Point estimate                          | -26.2                                  |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -40.8                                  |
| upper limit                             | -11.5                                  |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 7.42                                   |

Notes:

[24] - ANCOVA with stratum (geographic region), baseline value, and treatment in the model.

## **Secondary: Percent Change from Baseline in SCORing Atopic Dermatitis (SCORAD) Score at Weeks 8 and 16**

|                 |  |
|-----------------|--|
| End point title | Percent Change from Baseline in SCORing Atopic Dermatitis (SCORAD) Score at Weeks 8 and 16 |
|-----------------|--|

End point description:

SCORAD is a clinical tool used to assess the extent and severity of eczema (SCORing Atopic Dermatitis). The extent is assessed using the rule of 9 to calculate the affected area (A) as a percentage of the whole body (0-100%). The intensity part of the SCORAD (B) consists of 6 items: erythema, oedema/papulation, excoriations, lichenification, oozing/crusts and dryness, each graded on a scale from 0 (none) to 3 (severe), for a total score of 0 to 18. Subjective items (C) include daily pruritus and sleeplessness, each scored on a visual analogue scale (VAS) from 0 to 10 (total score 0-20). SCORAD is

calculated as  $A/5 + 7B/2 + C$ , and ranges from 0 to 103 (worst). A negative change from Baseline indicates improvement.

Last observation carried forward imputation was used.

|                             |           |
|-----------------------------|-----------|
| End point type              | Secondary |
| End point timeframe:        |           |
| Baseline and Weeks 8 and 16 |           |

| End point values                    | Placebo            | Upadacitinib 7.5 mg | Upadacitinib 15 mg | Upadacitinib 30 mg |
|-------------------------------------|--------------------|---------------------|--------------------|--------------------|
| Subject group type                  | Reporting group    | Reporting group     | Reporting group    | Reporting group    |
| Number of subjects analysed         | 33 <sup>[25]</sup> | 39                  | 36                 | 40                 |
| Units: percent change               |                    |                     |                    |                    |
| least squares mean (standard error) |                    |                     |                    |                    |
| Week 8                              | -7.0 (± 5.84)      | -35.4 (± 5.53)      | -44.1 (± 5.69)     | -65.3 (± 5.52)     |
| Week 16                             | -12.4 (± 5.97)     | -32.5 (± 5.66)      | -46.9 (± 5.82)     | -60.4 (± 5.65)     |

Notes:

[25] - Participants with Baseline and at least one post-baseline measurement

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of % Change in SCORAD at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 30 mg             |
| Number of subjects included in analysis | 73                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | < 0.001 <sup>[26]</sup>                  |
| Method                                  | ANCOVA                                   |
| Parameter estimate                      | LS Mean Difference                       |
| Point estimate                          | -58.3                                    |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -71.7                                    |
| upper limit                             | -44.9                                    |
| Variability estimate                    | Standard error of the mean               |
| Dispersion value                        | 6.78                                     |

Notes:

[26] - ANCOVA with stratum (geographic region), baseline value, and treatment in the model.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of % Change in SCORAD at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 15 mg             |
| Number of subjects included in analysis | 69                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | < 0.001 <sup>[27]</sup>                  |
| Method                                  | ANCOVA                                   |
| Parameter estimate                      | LS Mean Difference                       |
| Point estimate                          | -37.1                                    |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -50.8                      |
| upper limit          | -23.4                      |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 6.94                       |

Notes:

[27] - ANCOVA with stratum (geographic region), baseline value, and treatment in the model.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of % Change in SCORAD at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 7.5 mg            |
| Number of subjects included in analysis | 72                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | < 0.001 <sup>[28]</sup>                  |
| Method                                  | ANCOVA                                   |
| Parameter estimate                      | LS Mean Difference                       |
| Point estimate                          | -28.4                                    |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -41.9                                    |
| upper limit                             | -15                                      |
| Variability estimate                    | Standard error of the mean               |
| Dispersion value                        | 6.81                                     |

Notes:

[28] - ANCOVA with stratum (geographic region), baseline value, and treatment in the model.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of % Change in SCORAD at Week 16 |
| Comparison groups                       | Placebo v Upadacitinib 30 mg              |
| Number of subjects included in analysis | 73  |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | superiority                               |
| P-value                                 | < 0.001 <sup>[29]</sup>                   |
| Method                                  | ANCOVA                                    |
| Parameter estimate                      | LS Mean Difference                        |
| Point estimate                          | -48                                       |
| Confidence interval                     |   |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | -61.7                                     |
| upper limit                             | -34.3                                     |
| Variability estimate                    | Standard error of the mean                |
| Dispersion value                        | 6.93                                      |

Notes:

[29] - ANCOVA with stratum (geographic region), baseline value, and treatment in the model.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Analysis of % Change in SCORAD at Week 16 |
| Comparison groups                 | Placebo v Upadacitinib 15 mg              |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 69                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | < 0.001 <sup>[30]</sup>    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LS Mean Difference         |
| Point estimate                          | -34.5                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -48.5                      |
| upper limit                             | -20.5                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 7.1                        |

Notes:

[30] - ANCOVA with stratum (geographic region), baseline value, and treatment in the model.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of % Change in SCORAD at Week 16 |
| Comparison groups                       | Placebo v Upadacitinib 7.5 mg             |
| Number of subjects included in analysis | 72  |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | superiority                               |
| P-value                                 | = 0.004 <sup>[31]</sup>                   |
| Method                                  | ANCOVA                                    |
| Parameter estimate                      | LS Mean Difference                        |
| Point estimate                          | -20.2                                     |
| Confidence interval                     |   |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | -33.9                                     |
| upper limit                             | -6.4                                      |
| Variability estimate                    | Standard error of the mean                |
| Dispersion value                        | 6.96                                      |

Notes:

[31] - ANCOVA with stratum (geographic region), baseline value, and treatment in the model.

## Secondary: Percentage of Participants who Achieved an EASI 75 Response at Week 8

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants who Achieved an EASI 75 Response at Week 8 |
|-----------------|---|

End point description:

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.

An EASI 75 response is defined as at least a 75% reduction (improvement) in EASI score relative to the Baseline value.

Participants with missing values at Week 8 were counted as non-responders in this analysis (non-responder imputation).

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline and Week 8  |           |

| <b>End point values</b>           | Placebo         | Upadacitinib 7.5 mg | Upadacitinib 15 mg | Upadacitinib 30 mg |
|-----------------------------------|-----------------|---------------------|--------------------|--------------------|
| Subject group type                | Reporting group | Reporting group     | Reporting group    | Reporting group    |
| Number of subjects analysed       | 41              | 42                  | 42                 | 42                 |
| Units: percentage of participants |                 |                     |                    |                    |
| number (not applicable)           | 7.3             | 31.0                | 52.4               | 81.0               |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of EASI 75 Response at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 30 mg           |
| Number of subjects included in analysis | 83                                     |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[32]</sup>                |
| Method                                  | Cochran-Mantel-Haenszel                |
| Parameter estimate                      | Adjusted Difference                    |
| Point estimate                          | 72.7                                   |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | 58.3                                   |
| upper limit                             | 87.1                                   |

Notes:

[32] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of EASI 75 Response at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 15 mg           |
| Number of subjects included in analysis | 83                                     |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[33]</sup>                |
| Method                                  | Cochran-Mantel-Haenszel                |
| Parameter estimate                      | Adjusted Difference                    |
| Point estimate                          | 44.9                                   |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | 27.9                                   |
| upper limit                             | 61.9                                   |

Notes:

[33] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Analysis of EASI 75 Response at Week 8 |
| Comparison groups                 | Placebo v Upadacitinib 7.5 mg          |

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 83                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.004 <sup>[34]</sup> |
| Method                                  | Cochran-Mantel-Haenszel |
| Parameter estimate                      | Adjusted Difference     |
| Point estimate                          | 23.4                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 7.5                     |
| upper limit                             | 39.4                    |

Notes:

[34] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

## Secondary: Percentage of Participants who Achieved an EASI 50 Response at Weeks 8 and 16

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants who Achieved an EASI 50 Response at Weeks 8 and 16 |
|-----------------|---|

End point description:

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.

An EASI 50 response is defined as at least a 50% reduction (improvement) in EASI score relative to the Baseline value.

Participants with missing values at each time point were counted as non-responders in this analysis (non-responder imputation).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Weeks 8 and 16

| End point values                  | Placebo         | Upadacitinib 7.5 mg | Upadacitinib 15 mg | Upadacitinib 30 mg |
|-----------------------------------|-----------------|---------------------|--------------------|--------------------|
| Subject group type                | Reporting group | Reporting group     | Reporting group    | Reporting group    |
| Number of subjects analysed       | 41              | 42                  | 42                 | 42                 |
| Units: percentage of participants |                 |                     |                    |                    |
| number (not applicable)           |                 |                     |                    |                    |
| Week 8                            | 22.0            | 54.8                | 71.4               | 92.9               |
| Week 16                           | 22.0            | 50.0                | 71.4               | 83.3               |

## Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Analysis of EASI 50 Response at Week 8 |
| Comparison groups          | Upadacitinib 30 mg v Placebo           |

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 83                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | < 0.001 <sup>[35]</sup> |
| Method                                  | Cochran-Mantel-Haenszel |
| Parameter estimate                      | Adjusted Difference     |
| Point estimate                          | 70.7                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 56.2                    |
| upper limit                             | 85.2                    |

Notes:

[35] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of EASI 50 Response at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 15 mg           |
| Number of subjects included in analysis | 83                                     |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[36]</sup>                |
| Method                                  | Cochran-Mantel-Haenszel                |
| Parameter estimate                      | Adjusted Difference                    |
| Point estimate                          | 49                                     |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | 30.8                                   |
| upper limit                             | 67.3                                   |

Notes:

[36] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of EASI 50 Response at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 7.5 mg          |
| Number of subjects included in analysis | 83                                     |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[37]</sup>                |
| Method                                  | Cochran-Mantel-Haenszel                |
| Parameter estimate                      | Adjusted Difference                    |
| Point estimate                          | 32.8                                   |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | 13.4                                   |
| upper limit                             | 52.2                                   |

Notes:

[37] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Analysis of EASI 50 Response at Week 16 |
|-----------------------------------|---|

|   |                              |
|---|------------------------------|
| Comparison groups                       | Placebo v Upadacitinib 30 mg |
| Number of subjects included in analysis | 83                           |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | < 0.001 <sup>[38]</sup>      |
| Method                                  | Cochran-Mantel-Haenszel      |
| Parameter estimate                      | Adjusted Difference          |
| Point estimate                          | 60.6                         |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 45.3                         |
| upper limit                             | 75.9                         |

Notes:

[38] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of EASI 50 Response at Week 16 |
| Comparison groups                       | Placebo v Upadacitinib 15 mg            |
| Number of subjects included in analysis | 83                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | < 0.001 <sup>[39]</sup>                 |
| Method                                  | Cochran-Mantel-Haenszel                 |
| Parameter estimate                      | Adjusted Difference                     |
| Point estimate                          | 48.6                                    |
| Confidence interval                     |   |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | 31.3                                    |
| upper limit                             | 65.9                                    |

Notes:

[39] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of EASI 50 Response at Week 16 |
| Comparison groups                       | Placebo v Upadacitinib 7.5 mg           |
| Number of subjects included in analysis | 83                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.003 <sup>[40]</sup>                 |
| Method                                  | Cochran-Mantel-Haenszel                 |
| Parameter estimate                      | Adjusted Difference                     |
| Point estimate                          | 28.2                                    |
| Confidence interval                     |   |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | 9.8                                     |
| upper limit                             | 46.6                                    |

Notes:

[40] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

## Secondary: Percentage of Participants who Achieved an EASI 90 Response at Weeks 8 and 16

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants who Achieved an EASI 90 Response at Weeks 8 and 16 |
|-----------------|---|

End point description:

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.

An EASI 90 response is defined as at least a 90% reduction (improvement) in EASI score relative to the Baseline value.

Participants with missing values at Week 16 were counted as non-responders in this analysis (non-responder imputation).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Weeks 8 and 16

| End point values                  | Placebo         | Upadacitinib 7.5 mg | Upadacitinib 15 mg | Upadacitinib 30 mg |
|-----------------------------------|-----------------|---------------------|--------------------|--------------------|
| Subject group type                | Reporting group | Reporting group     | Reporting group    | Reporting group    |
| Number of subjects analysed       | 41              | 42                  | 42                 | 42                 |
| Units: percentage of participants |                 |                     |                    |                    |
| number (not applicable)           |                 |                     |                    |                    |
| Week 8                            | 0.0             | 9.5                 | 26.2               | 45.2               |
| Week 16                           | 2.4             | 14.3                | 26.2               | 50.0               |

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Analysis of EASI 90 Response at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 30 mg           |
| Number of subjects included in analysis | 83                                     |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[41]</sup>                |
| Method                                  | Cochran-Mantel-Haenszel                |
| Parameter estimate                      | Adjusted Difference                    |
| Point estimate                          | 43.8                                   |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | 29.1                                   |
| upper limit                             | 58.5                                   |

Notes:

[41] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|                            |  |
|----------------------------|--|
| Statistical analysis title | Analysis of EASI 90 Response at Week 8 |
| Comparison groups          | Placebo v Upadacitinib 15 mg           |

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 83                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | < 0.001 <sup>[42]</sup> |
| Method                                  | Cochran-Mantel-Haenszel |
| Parameter estimate                      | Adjusted Difference     |
| Point estimate                          | 26.1                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 12.6                    |
| upper limit                             | 39.6                    |

Notes:

[42] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of EASI 90 Response at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 7.5 mg          |
| Number of subjects included in analysis | 83                                     |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | = 0.051 <sup>[43]</sup>                |
| Method                                  | Cochran-Mantel-Haenszel                |
| Parameter estimate                      | Adjusted Difference                    |
| Point estimate                          | 9.4                                    |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | 0                                      |
| upper limit                             | 18.8                                   |

Notes:

[43] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of EASI 90 Response at Week 16 |
| Comparison groups                       | Placebo v Upadacitinib 30 mg            |
| Number of subjects included in analysis | 83                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | < 0.001 <sup>[44]</sup>                 |
| Method                                  | Cochran-Mantel-Haenszel                 |
| Parameter estimate                      | Adjusted Difference                     |
| Point estimate                          | 46.9                                    |
| Confidence interval                     |   |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | 31.3                                    |
| upper limit                             | 62.4                                    |

Notes:

[44] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Analysis of EASI 90 Response at Week 16 |
|-----------------------------------|---|

|   |                              |
|---|------------------------------|
| Comparison groups                       | Placebo v Upadacitinib 15 mg |
| Number of subjects included in analysis | 83                           |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | = 0.001 <sup>[45]</sup>      |
| Method                                  | Cochran-Mantel-Haenszel      |
| Parameter estimate                      | Adjusted Difference          |
| Point estimate                          | 23.8                         |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 9.6                          |
| upper limit                             | 38.1                         |

Notes:

[45] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of EASI 90 Response at Week 16 |
| Comparison groups                       | Placebo v Upadacitinib 7.5 mg           |
| Number of subjects included in analysis | 83                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.049 <sup>[46]</sup>                 |
| Method                                  | Cochran-Mantel-Haenszel                 |
| Parameter estimate                      | Adjusted Difference                     |
| Point estimate                          | 11.8                                    |
| Confidence interval                     |   |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | 0.1                                     |
| upper limit                             | 23.6                                    |

Notes:

[46] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

## Secondary: Percentage of Participants who Achieved a SCORAD 50 Response at Weeks 8 and 16

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants who Achieved a SCORAD 50 Response at Weeks 8 and 16 |
|-----------------|--|

End point description:

A SCORAD 50 response is defined as at least a 50% reduction (improvement) in SCORAD score relative to the Baseline value.

SCORAD is a clinical tool used to assess the extent and severity of eczema (SCORing Atopic Dermatitis). The extent is assessed using the rule of 9 to calculate the affected area (A) as a percentage of the whole body (0-100%). The intensity part of the SCORAD (B) consists of 6 items: erythema, oedema/papulation, excoriations, lichenification, oozing/crusts and dryness, each graded on a scale from 0 (none) to 3 (severe), for a total score of 0 to 18. Subjective items (C) include daily pruritus and sleeplessness, each scored on a visual analogue scale (VAS) from 0 to 10 (total score 0-20). SCORAD is calculated as  $A/5 + 7B/2 + C$ , and ranges from 0 to 103 (worst).

Non-responder imputation was used.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Weeks 8 and 16

| <b>End point values</b>           | Placebo         | Upadacitinib 7.5 mg | Upadacitinib 15 mg | Upadacitinib 30 mg |
|-----------------------------------|-----------------|---------------------|--------------------|--------------------|
| Subject group type                | Reporting group | Reporting group     | Reporting group    | Reporting group    |
| Number of subjects analysed       | 41              | 42                  | 42                 | 42                 |
| Units: percentage of participants |                 |                     |                    |                    |
| number (not applicable)           |                 |                     |                    |                    |
| Week 8                            | 7.3             | 33.3                | 42.9               | 76.2               |
| Week 16                           | 7.3             | 28.6                | 42.9               | 61.9               |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of SCORAD 50 Response at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 30 mg             |
| Number of subjects included in analysis | 83                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | < 0.001 <sup>[47]</sup>                  |
| Method                                  | Cochran-Mantel-Haenszel                  |
| Parameter estimate                      | Adjusted Difference                      |
| Point estimate                          | 68.4                                     |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | 54                                       |
| upper limit                             | 82.8                                     |

Notes:

[47] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of SCORAD 50 Response at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 15 mg             |
| Number of subjects included in analysis | 83                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | < 0.001 <sup>[48]</sup>                  |
| Method                                  | Cochran-Mantel-Haenszel                  |
| Parameter estimate                      | Adjusted Difference                      |
| Point estimate                          | 35.3                                     |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | 18.5                                     |
| upper limit                             | 52.2                                     |

Notes:

[48] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of SCORAD 50 Response at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 7.5 mg            |
| Number of subjects included in analysis | 83                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.002 <sup>[49]</sup>                  |
| Method                                  | Cochran-Mantel-Haenszel                  |
| Parameter estimate                      | Adjusted Difference                      |
| Point estimate                          | 25.7                                     |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | 9.6                                      |
| upper limit                             | 41.7                                     |

Notes:

[49] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of SCORAD 50 Response at Week 16 |
| Comparison groups                       | Placebo v Upadacitinib 30 mg              |
| Number of subjects included in analysis | 83  |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | superiority                               |
| P-value                                 | < 0.001 <sup>[50]</sup>                   |
| Method                                  | Cochran-Mantel-Haenszel                   |
| Parameter estimate                      | Adjusted Difference                       |
| Point estimate                          | 54.5                                      |
| Confidence interval                     |   |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | 39  |
| upper limit                             | 69.9                                      |

Notes:

[50] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of SCORAD 50 Response at Week 16 |
| Comparison groups                       | Placebo v Upadacitinib 15 mg              |
| Number of subjects included in analysis | 83  |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | superiority                               |
| P-value                                 | < 0.001 <sup>[51]</sup>                   |
| Method                                  | Cochran-Mantel-Haenszel                   |
| Parameter estimate                      | Adjusted Difference                       |
| Point estimate                          | 35.8                                      |
| Confidence interval                     |   |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | 19.1                                      |
| upper limit                             | 52.5                                      |

Notes:

[51] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of SCORAD 50 Response at Week 16 |
| Comparison groups                       | Placebo v Upadacitinib 7.5 mg             |
| Number of subjects included in analysis | 83  |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | superiority                               |
| P-value                                 | = 0.008 <sup>[52]</sup>                   |
| Method                                  | Cochran-Mantel-Haenszel                   |
| Parameter estimate                      | Adjusted Difference                       |
| Point estimate                          | 21.2                                      |
| Confidence interval                     |   |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | 5.7                                       |
| upper limit                             | 36.8                                      |

Notes:

[52] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

### Secondary: Percentage of Participants who Achieved a SCORAD 75 Response at Weeks 8 and 16

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants who Achieved a SCORAD 75 Response at Weeks 8 and 16 |
|-----------------|--|

End point description:

A SCORAD 75 response is defined as at least a 75% reduction (improvement) in SCORAD score relative to the Baseline value.

SCORAD is a clinical tool used to assess the extent and severity of eczema (SCORing Atopic Dermatitis). The extent is assessed using the rule of 9 to calculate the affected area (A) as a percentage of the whole body (0-100%). The intensity part of the SCORAD (B) consists of 6 items: erythema, oedema/papulation, excoriations, lichenification, oozing/crusts and dryness, each graded on a scale from 0 (none) to 3 (severe), for a total score of 0 to 18. Subjective items (C) include daily pruritus and sleeplessness, each scored on a visual analogue scale (VAS) from 0 to 10 (total score 0-20). SCORAD is calculated as  $A/5 + 7B/2 + C$ , and ranges from 0 to 103 (worst).

Non-responder imputation was used.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Weeks 8 and 16

| End point values                  | Placebo         | Upadacitinib 7.5 mg | Upadacitinib 15 mg | Upadacitinib 30 mg |
|-----------------------------------|-----------------|---------------------|--------------------|--------------------|
| Subject group type                | Reporting group | Reporting group     | Reporting group    | Reporting group    |
| Number of subjects analysed       | 41              | 42                  | 42                 | 42                 |
| Units: percentage of participants |                 |                     |                    |                    |
| number (not applicable)           |                 |                     |                    |                    |
| Week 8                            | 0.0             | 9.5                 | 9.5                | 31.0               |
| Week 16                           | 2.4             | 4.8                 | 21.4               | 40.5               |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of SCORAD 75 Response at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 30 mg             |
| Number of subjects included in analysis | 83                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | < 0.001 <sup>[53]</sup>                  |
| Method                                  | Cochran-Mantel-Haenszel                  |
| Parameter estimate                      | Adjusted Difference                      |
| Point estimate                          | 30.4                                     |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | 16.2                                     |
| upper limit                             | 44.6                                     |

Notes:

[53] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of SCORAD 75 Response at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 15 mg             |
| Number of subjects included in analysis | 83                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.052 <sup>[54]</sup>                  |
| Method                                  | Cochran-Mantel-Haenszel                  |
| Parameter estimate                      | Adjusted Difference                      |
| Point estimate                          | 9.4                                      |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -0.1                                     |
| upper limit                             | 18.9                                     |

Notes:

[54] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of SCORAD 75 Response at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 7.5 mg            |
| Number of subjects included in analysis | 83                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.048 <sup>[55]</sup>                  |
| Method                                  | Cochran-Mantel-Haenszel                  |
| Parameter estimate                      | Adjusted Difference                      |
| Point estimate                          | 9.3                                      |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | 0.1                                      |
| upper limit                             | 18.5                                     |

Notes:

[55] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of SCORAD 75 Response at Week 16 |
| Comparison groups                       | Placebo v Upadacitinib 30 mg              |
| Number of subjects included in analysis | 83  |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | superiority                               |
| P-value                                 | < 0.001 <sup>[56]</sup>                   |
| Method                                  | Cochran-Mantel-Haenszel                   |
| Parameter estimate                      | Adjusted Difference                       |
| Point estimate                          | 37.7                                      |
| Confidence interval                     |   |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | 22.2                                      |
| upper limit                             | 53.3                                      |

Notes:

[56] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of SCORAD 75 Response at Week 16 |
| Comparison groups                       | Placebo v Upadacitinib 15 mg              |
| Number of subjects included in analysis | 83  |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | superiority                               |
| P-value                                 | = 0.006 <sup>[57]</sup>                   |
| Method                                  | Cochran-Mantel-Haenszel                   |
| Parameter estimate                      | Adjusted Difference                       |
| Point estimate                          | 19  |
| Confidence interval                     |   |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | 5.6                                       |
| upper limit                             | 32.5                                      |

Notes:

[57] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of SCORAD 75 Response at Week 16 |
| Comparison groups                       | Upadacitinib 7.5 mg v Placebo             |
| Number of subjects included in analysis | 83  |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | superiority                               |
| P-value                                 | = 0.581 <sup>[58]</sup>                   |
| Method                                  | Cochran-Mantel-Haenszel                   |
| Parameter estimate                      | Adjusted Difference                       |
| Point estimate                          | 2.4                                       |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -6      |
| upper limit         | 10.8    |

Notes:

[58] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

## Secondary: Percentage of Participants who Achieved a SCORAD 90 Response at Weeks 8 and 16

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants who Achieved a SCORAD 90 Response at Weeks 8 and 16 |
|-----------------|--|

End point description:

A SCORAD 90 response is defined as at least a 90% reduction (improvement) in SCORAD score relative to the Baseline value.

SCORAD is a clinical tool used to assess the extent and severity of eczema (SCORing Atopic Dermatitis). The extent is assessed using the rule of 9 to calculate the affected area (A) as a percentage of the whole body (0-100%). The intensity part of the SCORAD (B) consists of 6 items: erythema, oedema/papulation, excoriations, lichenification, oozing/crusts and dryness, each graded on a scale from 0 (none) to 3 (severe), for a total score of 0 to 18. Subjective items (C) include daily pruritus and sleeplessness, each scored on a visual analogue scale (VAS) from 0 to 10 (total score 0-20). SCORAD is calculated as  $A/5 + 7B/2 + C$ , and ranges from 0 to 103 (worst).

Non-responder imputation was used.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Weeks 8 and 16

| End point values                  | Placebo         | Upadacitinib 7.5 mg | Upadacitinib 15 mg | Upadacitinib 30 mg |
|-----------------------------------|-----------------|---------------------|--------------------|--------------------|
| Subject group type                | Reporting group | Reporting group     | Reporting group    | Reporting group    |
| Number of subjects analysed       | 41              | 42                  | 42                 | 42                 |
| Units: percentage of participants |                 |                     |                    |                    |
| number (not applicable)           |                 |                     |                    |                    |
| Week 8                            | 0.0             | 4.8                 | 2.4                | 14.3               |
| Week 16                           | 0.0             | 2.4                 | 9.5                | 23.8               |

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Analysis of SCORAD 90 Response at Week 8 |
| Comparison groups                       | Upadacitinib 30 mg v Placebo             |
| Number of subjects included in analysis | 83                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.012 <sup>[59]</sup>                  |
| Method                                  | Cochran-Mantel-Haenszel                  |
| Parameter estimate                      | Adjusted Difference                      |
| Point estimate                          | 14.2                                     |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 3.2     |
| upper limit         | 25.2    |

Notes:

[59] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of SCORAD 90 Response at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 15 mg             |
| Number of subjects included in analysis | 83                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.428 <sup>[60]</sup>                  |
| Method                                  | Cochran-Mantel-Haenszel                  |
| Parameter estimate                      | Adjusted Difference                      |
| Point estimate                          | 2.3                                      |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -3.4                                     |
| upper limit                             | 8  |

Notes:

[60] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of SCORAD 90 Response at Week 8 |
| Comparison groups                       | Placebo v Upadacitinib 7.5 mg            |
| Number of subjects included in analysis | 83                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.206 <sup>[61]</sup>                  |
| Method                                  | Cochran-Mantel-Haenszel                  |
| Parameter estimate                      | Adjusted Difference                      |
| Point estimate                          | 4.6                                      |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -2.5                                     |
| upper limit                             | 11.8                                     |

Notes:

[61] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Analysis of SCORAD 90 Response at Week 16 |
| Comparison groups                 | Placebo v Upadacitinib 30 mg              |

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 83                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | < 0.001 <sup>[62]</sup> |
| Method                                  | Cochran-Mantel-Haenszel |
| Parameter estimate                      | Adjusted Difference     |
| Point estimate                          | 23.3                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 10.4                    |
| upper limit                             | 36.2                    |

Notes:

[62] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of SCORAD 90 Response at Week 16 |
| Comparison groups                       | Placebo v Upadacitinib 15 mg              |
| Number of subjects included in analysis | 83  |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | superiority                               |
| P-value                                 | = 0.048 <sup>[63]</sup>                   |
| Method                                  | Cochran-Mantel-Haenszel                   |
| Parameter estimate                      | Adjusted Difference                       |
| Point estimate                          | 9.4                                       |
| Confidence interval                     |   |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | 0.1                                       |
| upper limit                             | 18.8                                      |

Notes:

[63] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of SCORAD 90 Response at Week 16 |
| Comparison groups                       | Placebo v Upadacitinib 7.5 mg             |
| Number of subjects included in analysis | 83  |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | superiority                               |
| P-value                                 | = 0.426 <sup>[64]</sup>                   |
| Method                                  | Cochran-Mantel-Haenszel                   |
| Parameter estimate                      | Adjusted Difference                       |
| Point estimate                          | 2.4                                       |
| Confidence interval                     |   |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | -3.4                                      |
| upper limit                             | 8.1                                       |

Notes:

[64] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

## Secondary: Change from Baseline in Percentage of Body Surface Area (BSA)

## Affected by Atopic Dermatitis at Week 16

|  |  |
|--|--|
| End point title  | Change from Baseline in Percentage of Body Surface Area (BSA) Affected by Atopic Dermatitis at Week 16 |
| End point description:<br>Body surface area (BSA) affected by atopic dermatitis was assessed by the physician and is expressed as a percentage of the total BSA. For purposes of the estimation, the total surface of the participant's palm plus five digits was assumed to be approximately equivalent to 1% BSA.<br>Last observation carried forward imputation was used. |  |
| End point type   | Secondary  |
| End point timeframe:<br>Baseline and Week 16   |  |

| End point values                       | Placebo            | Upadacitinib 7.5 mg | Upadacitinib 15 mg | Upadacitinib 30 mg |
|--|--------------------|---------------------|--------------------|--------------------|
| Subject group type                     | Reporting group    | Reporting group     | Reporting group    | Reporting group    |
| Number of subjects analysed            | 39 <sup>[65]</sup> | 42                  | 42                 | 42                 |
| Units: percentage of body surface area |                    |                     |                    |                    |
| least squares mean (standard error)    | -4.1 (± 3.58)      | -11.7 (± 3.48)      | -27.1 (± 3.43)     | -30.7 (± 3.43)     |

Notes:

[65] - Participants with at least one post-baseline measurement

## Statistical analyses

|   |                                      |
|---|--------------------------------------|
| Statistical analysis title              | Analysis of Change in BSA at Week 16 |
| Comparison groups                       | Upadacitinib 30 mg v Placebo         |
| Number of subjects included in analysis | 81                                   |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | superiority                          |
| P-value                                 | < 0.001 <sup>[66]</sup>              |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | -26.5                                |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -34.9                                |
| upper limit                             | -18.1                                |
| Variability estimate                    | Standard error of the mean           |
| Dispersion value                        | 4.25                                 |

Notes:

[66] - ANCOVA with stratum (geographic region), baseline value, and treatment in the model.

|                            |                                      |
|----------------------------|--------------------------------------|
| Statistical analysis title | Analysis of Change in BSA at Week 16 |
| Comparison groups          | Placebo v Upadacitinib 15 mg         |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 81                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | < 0.001 <sup>[67]</sup>    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LS Mean Difference         |
| Point estimate                          | -23                        |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -31.4                      |
| upper limit                             | -14.6                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 4.27                       |

Notes:

[67] - ANCOVA with stratum (geographic region), baseline value, and treatment in the model.

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>       | Analysis of Change in BSA at Week 16 |
| Comparison groups                       | Placebo v Upadacitinib 7.5 mg        |
| Number of subjects included in analysis | 81                                   |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | superiority                          |
| P-value                                 | = 0.075 <sup>[68]</sup>              |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | -7.6                                 |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -16                                  |
| upper limit                             | 0.8                                  |
| Variability estimate                    | Standard error of the mean           |
| Dispersion value                        | 4.25                                 |

Notes:

[68] - ANCOVA with stratum (geographic region), baseline value, and treatment in the model.

### **Secondary: Percentage of Participants with Reduction of $\geq 4$ Points from Baseline in Pruritus NRS at Week 16**

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants with Reduction of $\geq 4$ Points from Baseline in Pruritus NRS at Week 16 |
|-----------------|---|

End point description:

Participants were asked to rate itch in the past 24 hours on a daily basis using a scale from 0 to 10, with 0 being no itch and 10 being the worst imaginable itch. The percentage of participants with reduction of  $\geq 4$  points from Baseline in pruritus NRS was assessed in participants with a baseline pruritus NRS of  $\geq 4$ . Non-responder imputation was used.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 16

| End point values                  | Placebo            | Upadacitinib 7.5 mg | Upadacitinib 15 mg | Upadacitinib 30 mg |
|-----------------------------------|--------------------|---------------------|--------------------|--------------------|
| Subject group type                | Reporting group    | Reporting group     | Reporting group    | Reporting group    |
| Number of subjects analysed       | 35 <sup>[69]</sup> | 37                  | 32                 | 36                 |
| Units: percentage of participants |                    |                     |                    |                    |
| number (not applicable)           | 5.7                | 24.3                | 59.4               | 52.8               |

Notes:

[69] - Participants with Baseline pruritus NRS of  $\geq 4$

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of Reduction in Pruritus NRS $\geq 4$ Points |
| Comparison groups                       | Placebo v Upadacitinib 30 mg                          |
| Number of subjects included in analysis | 71  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | $< 0.001$ <sup>[70]</sup>                             |
| Method                                  | Cochran-Mantel-Haenszel                               |
| Parameter estimate                      | Adjusted Difference                                   |
| Point estimate                          | 47.4  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 29.6  |
| upper limit                             | 65.2  |

Notes:

[70] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of Reduction in Pruritus NRS $\geq 4$ Points |
| Comparison groups                       | Placebo v Upadacitinib 15 mg                          |
| Number of subjects included in analysis | 67  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | $< 0.001$ <sup>[71]</sup>                             |
| Method                                  | Cochran-Mantel-Haenszel                               |
| Parameter estimate                      | Adjusted Difference                                   |
| Point estimate                          | 53.4  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 35.5  |
| upper limit                             | 71.3  |

Notes:

[71] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Analysis of Reduction in Pruritus NRS $\geq 4$ Points |
| Comparison groups                 | Placebo v Upadacitinib 7.5 mg                         |

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 72                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.021 <sup>[72]</sup> |
| Method                                  | Cochran-Mantel-Haenszel |
| Parameter estimate                      | Adjusted Difference     |
| Point estimate                          | 18.6                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 2.8                     |
| upper limit                             | 34.3                    |

Notes:

[72] - Cochran-Mantel-Haenszel test adjusted for stratum (geographic region).

## Secondary: Percent Change from Re-randomization (Week 16) in EASI Score in Period 2

|                 |  |
|-----------------|--|
| End point title | Percent Change from Re-randomization (Week 16) in EASI Score in Period 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 by eczema. For each region, 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, with adjustment 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; a negative change from baseline indicates improvement. Last observation carried forward imputation was used.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Re-randomization (Week 16) and Weeks 20, 24, 32, 40, 52, 64, 76, and 88

| End point values                    | Placebo /<br>Placebo | Placebo /<br>Upadacitinib 30<br>mg | Upadacitinib<br>7.5 mg /<br>Placebo | Upadacitinib<br>7.5 mg /<br>Upadacitinib<br>7.5 mg |
|-------------------------------------|----------------------|------------------------------------|-------------------------------------|--|
| Subject group type                  | Reporting group      | Reporting group                    | Reporting group                     | Reporting group                                    |
| Number of subjects analysed         | 10                   | 10                                 | 15                                  | 15   |
| Units: percent change               |                      |                                    |                                     |  |
| least squares mean (standard error) |                      |                                    |                                     |  |
| Week 20                             | 50.7 (± 33.50)       | 11.8 (± 30.59)                     | 186.0 (± 46.53)                     | 79.1 (± 48.42)                                     |
| Week 24                             | 13.5 (± 17.13)       | -67.5 (± 15.64)                    | 189.6 (± 44.17)                     | 59.0 (± 45.97)                                     |
| Week 32                             | -2.3 (± 15.15)       | -83.1 (± 13.83)                    | 181.5 (± 44.74)                     | 63.5 (± 46.56)                                     |
| Week 40                             | -31.2 (± 18.16)      | -92.0 (± 16.58)                    | 200.9 (± 41.58)                     | 77.6 (± 43.27)                                     |
| Week 52                             | -29.8 (± 17.74)      | -90.1 (± 16.20)                    | 189.1 (± 43.65)                     | 74.4 (± 45.42)                                     |
| Week 64                             | -35.8 (± 17.34)      | -91.4 (± 15.83)                    | 179.9 (± 44.91)                     | 71.8 (± 46.74)                                     |

|         |                 |                 |                 |                |
|---------|-----------------|-----------------|-----------------|----------------|
| Week 76 | -37.3 (± 19.09) | -90.3 (± 17.43) | 201.4 (± 41.89) | 77.7 (± 43.60) |
| Week 88 | -37.7 (± 19.18) | -84.6 (± 17.51) | 170.7 (± 46.87) | 69.1 (± 48.78) |

| End point values                    | Upadacitinib 15 mg / Placebo | Upadacitinib 15 mg / Upadacitinib 15 mg | Upadacitinib 30 mg / Placebo | Upadacitinib 30 mg / Upadacitinib 30 mg |
|-------------------------------------|------------------------------|---|------------------------------|---|
| Subject group type                  | Reporting group              | Reporting group                         | Reporting group              | Reporting group                         |
| Number of subjects analysed         | 17                           | 18 <sup>[73]</sup>                      | 14 <sup>[74]</sup>           | 19 <sup>[75]</sup>                      |
| Units: percent change               |                              |   |                              |   |
| least squares mean (standard error) |                              |   |                              |   |
| Week 20                             | 582.3 (± 172.19)             | 65.7 (± 178.24)                         | 791.5 (± 262.34)             | -73.8 (± 215.54)                        |
| Week 24                             | 607.3 (± 169.49)             | 72.6 (± 175.44)                         | 898.5 (± 248.78)             | -69.6 (± 200.01)                        |
| Week 32                             | 613.3 (± 169.63)             | 151.7 (± 175.59)                        | 771.5 (± 252.90)             | -28.8 (± 210.78)                        |
| Week 40                             | 608.8 (± 169.95)             | 154.1 (± 175.92)                        | 778.9 (± 344.45)             | 140.6 (± 293.17)                        |
| Week 52                             | 613.8 (± 166.85)             | 104.1 (± 164.05)                        | 799.5 (± 254.30)             | -13.3 (± 216.44)                        |
| Week 64                             | 614.6 (± 166.57)             | 104.1 (± 163.78)                        | 802.1 (± 278.76)             | 63.6 (± 237.26)                         |
| Week 76                             | 614.0 (± 168.03)             | 130.2 (± 169.29)                        | 787.8 (± 262.89)             | 24.4 (± 219.11)                         |
| Week 88                             | 617.5 (± 165.84)             | 99.3 (± 163.06)                         | 769.7 (± 265.64)             | 39.0 (± 226.10)                         |

Notes:

[73] - n = 16 at Weeks 20, 24, 32, and 40; n = 17 at Week 76

[74] - n = 13 at Weeks 20, 24

[75] - n = 18 at Weeks 20, 40, 52, 64, and 88

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with an EASI 75 Response in Period 2 in Participants who were Re-randomized as EASI 75 Non-responders at Week 16

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants with an EASI 75 Response in Period 2 in Participants who were Re-randomized as EASI 75 Non-responders at Week 16 |
|-----------------|---|

End point description:

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.

An EASI 75 response is defined as at least a 75% reduction (improvement) in EASI score relative to the Baseline value, and was analyzed in participants who were re-randomized at Week 16 and were EASI 75 non-responders at Week 16.

|  |           |
|--|-----------|
| End point type                           | Secondary |
| End point timeframe:                     |           |
| Weeks 20, 24, 32, 40, 52, 64, 76, and 88 |           |

| End point values                       | Placebo / Placebo | Placebo / Upadacitinib 30 mg | Upadacitinib 7.5 mg / Placebo | Upadacitinib 7.5 mg / Upadacitinib 7.5 mg |
|--|-------------------|------------------------------|-------------------------------|---|
| Subject group type                     | Reporting group   | Reporting group              | Reporting group               | Reporting group                           |
| Number of subjects analysed            | 9                 | 8                            | 10                            | 11  |
| Units: percentage of participants      |                   |                              |                               |   |
| number (not applicable)                |                   |                              |                               |   |
| Week 20 (n = 9, 8, 10, 11, 7, 8, 5, 4) | 11.1              | 12.5                         | 0                             | 9.1                                       |
| Week 24 (n = 1, 7, 0, 3, 1, 2, 3, 3)   | 100               | 85.7                         | 0                             | 33.3                                      |
| Week 32 (n = 1, 6, 0, 2, 1, 2, 2, 2)   | 100               | 100                          | 0                             | 0   |
| Week 40 (n = 1, 6, 0, 0, 1, 1, 1, 2)   | 100               | 66.7                         | 0                             | 0   |
| Week 52 (n = 1, 6, 0, 0, 1, 1, 0, 2)   | 100               | 66.7                         | 0                             | 0   |
| Week 64 (n = 1, 5, 0, 0, 1, 1, 0, 1)   | 100               | 80.0                         | 0                             | 0   |
| Week 76 (n = 1, 3, 0, 0, 1, 1, 0, 1)   | 100               | 100                          | 0                             | 0   |
| Week 88 (n = 1, 2, 0, 0, 1, 1, 0, 1)   | 100               | 100                          | 0                             | 0   |

| End point values                       | Upadacitinib 15 mg / Placebo | Upadacitinib 15 mg / Upadacitinib 15 mg | Upadacitinib 30 mg / Placebo | Upadacitinib 30 mg / Upadacitinib 30 mg |
|--|------------------------------|---|------------------------------|---|
| Subject group type                     | Reporting group              | Reporting group                         | Reporting group              | Reporting group                         |
| Number of subjects analysed            | 7                            | 8                                       | 5                            | 4                                       |
| Units: percentage of participants      |                              |   |                              |   |
| number (not applicable)                |                              |   |                              |   |
| Week 20 (n = 9, 8, 10, 11, 7, 8, 5, 4) | 0                            | 12.5                                    | 20.0                         | 25.0                                    |
| Week 24 (n = 1, 7, 0, 3, 1, 2, 3, 3)   | 0                            | 0                                       | 33.3                         | 33.3                                    |
| Week 32 (n = 1, 6, 0, 2, 1, 2, 2, 2)   | 0                            | 50.0                                    | 50.0                         | 50.0                                    |
| Week 40 (n = 1, 6, 0, 0, 1, 1, 1, 2)   | 0                            | 100                                     | 0                            | 50.0                                    |
| Week 52 (n = 1, 6, 0, 0, 1, 1, 0, 2)   | 0                            | 100                                     | 0                            | 50.0                                    |
| Week 64 (n = 1, 5, 0, 0, 1, 1, 0, 1)   | 0                            | 100                                     | 0                            | 100                                     |
| Week 76 (n = 1, 3, 0, 0, 1, 1, 0, 1)   | 0                            | 100                                     | 0                            | 100                                     |
| Week 88 (n = 1, 2, 0, 0, 1, 1, 0, 1)   | 0                            | 100                                     | 0                            | 100                                     |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants who Achieved a Dermatology Life Quality Index (DLQI) = "0" or "1" at Weeks 8 and 16

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants who Achieved a Dermatology Life Quality Index (DLQI) = "0" or "1" at Weeks 8 and 16 |
|-----------------|--|

End point description:

The DLQI is a 10-item questionnaire that asks participants to evaluate the degree that psoriasis has affected their quality of life in the last week in the following 6 aspects: symptoms and feelings, daily activities, leisure, work or school activities, personal relationships and treatment related feelings.

Participants answer the 10 questions on a scale from 0 (not at all) to 3 (very much). The DLQI is calculated by summing the scores of the 10 questions, resulting in a maximum of 30 and a minimum of 0 with higher scores indicating more impaired quality of life. A score of 0 or 1 means that the disease has no effect at all.

Dermatology Life Quality Index outcomes were defined but are not reported because of an error in the programming of the electronic device used to administer the questionnaire that precluded determination of these outcomes.

|                             |           |
|-----------------------------|-----------|
| End point type              | Secondary |
| End point timeframe:        |           |
| Baseline and Weeks 8 and 16 |           |

| End point values                  | Placebo           | Upadacitinib 7.5 mg | Upadacitinib 15 mg | Upadacitinib 30 mg |
|-----------------------------------|-------------------|---------------------|--------------------|--------------------|
| Subject group type                | Reporting group   | Reporting group     | Reporting group    | Reporting group    |
| Number of subjects analysed       | 0 <sup>[76]</sup> | 0 <sup>[77]</sup>   | 0 <sup>[78]</sup>  | 0 <sup>[79]</sup>  |
| Units: percentage of participants |                   |                     |                    |                    |
| number (not applicable)           |                   |                     |                    |                    |

Notes:

[76] - Not reported due to an error in the electronic device used to administer the questionnaire

[77] - Not reported due to an error in the electronic device used to administer the questionnaire

[78] - Not reported due to an error in the electronic device used to administer the questionnaire

[79] - Not reported due to an error in the electronic device used to administer the questionnaire

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in DLQI at Weeks 8 and 16

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in DLQI at Weeks 8 and 16 |
|-----------------|--|

End point description:

The DLQI is a 10-item questionnaire that asks participants to evaluate the degree that psoriasis has affected their quality of life in the last week in the following 6 aspects: symptoms and feelings, daily activities, leisure, work or school activities, personal relationships and treatment related feelings. Participants answer the 10 questions on a scale from 0 (not at all) to 3 (very much). The DLQI is calculated by summing the scores of the 10 questions, resulting in a maximum of 30 and a minimum of 0 with higher scores indicating more impaired quality of life. A negative change from Baseline indicates improvement.

Dermatology Life Quality Index outcomes were defined but are not reported because of an error in the programming of the electronic device used to administer the questionnaire that precluded determination of these outcomes.

|                             |           |
|-----------------------------|-----------|
| End point type              | Secondary |
| End point timeframe:        |           |
| Baseline and Weeks 8 and 16 |           |

| End point values                    | Placebo           | Upadacitinib 7.5 mg | Upadacitinib 15 mg | Upadacitinib 30 mg |
|-------------------------------------|-------------------|---------------------|--------------------|--------------------|
| Subject group type                  | Reporting group   | Reporting group     | Reporting group    | Reporting group    |
| Number of subjects analysed         | 0 <sup>[80]</sup> | 0 <sup>[81]</sup>   | 0 <sup>[82]</sup>  | 0 <sup>[83]</sup>  |
| Units: scores on a scale            |                   |                     |                    |                    |
| least squares mean (standard error) | ()                | ()                  | ()                 | ()                 |

Notes:

[80] - Not reported due to an error in the electronic device used to administer the questionnaire

[81] - Not reported due to an error in the electronic device used to administer the questionnaire

[82] - Not reported due to an error in the electronic device used to administer the questionnaire

[83] - Not reported due to an error in the electronic device used to administer the questionnaire

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Loss of EASI 50 Response Relative to Baseline Among Participants Re-randomized as EASI 75 Responders at Week 16

|                 |   |
|-----------------|---|
| End point title | Time to Loss of EASI 50 Response Relative to Baseline Among Participants Re-randomized as EASI 75 Responders at Week 16 |
|-----------------|---|

End point description:

Time to loss of EASI 50 response in Period 2 relative to Baseline among those who were re-randomized as EASI 75 responders at Week 16.

Time to loss of EASI 50 response was measured from Week 16 to the date of the first assessment in Period 2 where a participant's EASI score was higher than 50% of their Baseline score.

Participants with no loss of response were censored at their last treatment visit or the start of rescue treatment, whichever occurred first. "99999" indicates data that could not be estimated due to a low number of events.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From re-randomization at Week 16 until Week 88

| End point values                 | Placebo / Placebo      | Placebo / Upadacitinib 30 mg | Upadacitinib 7.5 mg / Placebo | Upadacitinib 7.5 mg / Upadacitinib 7.5 mg |
|----------------------------------|------------------------|------------------------------|-------------------------------|---|
| Subject group type               | Reporting group        | Reporting group              | Reporting group               | Reporting group                           |
| Number of subjects analysed      | 1                      | 2                            | 5                             | 5   |
| Units: days                      |                        |                              |                               |   |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (99999 to 99999)       | 29 (27 to 99999)              | 99999 (29 to 99999)                       |

| End point values                 | Upadacitinib 15 mg / Placebo | Upadacitinib 15 mg / Upadacitinib 15 mg | Upadacitinib 30 mg / Placebo | Upadacitinib 30 mg / Upadacitinib 30 mg |
|----------------------------------|------------------------------|---|------------------------------|---|
| Subject group type               | Reporting group              | Reporting group                         | Reporting group              | Reporting group                         |
| Number of subjects analysed      | 12                           | 10                                      | 14                           | 15                                      |
| Units: days                      |                              |   |                              |   |
| median (confidence interval 95%) | 30 (17 to 55)                | 114 (29 to 99999)                       | 28 (25 to 36)                | 99999 (99999 to 99999)                  |

## **Statistical analyses**

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug up to 30 days after last dose. Period 1: 16 weeks, Period 2: 72 weeks.

Adverse event reporting additional description:

Any adverse event that occurred on or after the first dose of upadacitinib 30 mg rescue therapy is counted in the upadacitinib 30 mg group. Participants receiving rescue therapy after upadacitinib 7.5 mg or 15 mg treatment are counted in the denominators of both 7.5 mg/15 mg and 30 mg dose groups.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Period 1: Placebo |
|-----------------------|-------------------|

Reporting group description:

Participants received placebo once daily (QD) for 16 weeks in Period 1.

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Period 1: Upadacitinib 7.5 mg |
|-----------------------|-------------------------------|

Reporting group description:

Participants received upadacitinib 7.5 mg once daily for 16 weeks in Period 1.

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Period 1: Upadacitinib 15 mg |
|-----------------------|------------------------------|

Reporting group description:

Participants received upadacitinib 15 mg once daily for 16 weeks in Period 1.

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Period 1: Upadacitinib 30 mg |
|-----------------------|------------------------------|

Reporting group description:

Participants received upadacitinib 30 mg once daily for 16 weeks in Period 1.

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Period 1+2: Upadacitinib 7.5 mg |
|-----------------------|---------------------------------|

Reporting group description:

Participants originally randomized to upadacitinib 7.5 mg received upadacitinib 7.5 mg once daily for 16 weeks in Period 1; Participants re-randomized to upadacitinib 7.5 mg in Period 2 continued to receive upadacitinib 7.5 mg for 72 weeks in Period 2 or until rescue.

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Period 1+2: Upadacitinib 15 mg |
|-----------------------|--------------------------------|

Reporting group description:

Participants originally randomized to upadacitinib 15 mg received upadacitinib 15 mg once daily for 16 weeks in Period 1; Participants re-randomized to upadacitinib 15 mg in Period 2 continued to receive upadacitinib 15 mg for 72 weeks in Period 2 or until rescue.

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Period 1+2: Upadacitinib 30 mg |
|-----------------------|--------------------------------|

Reporting group description:

Participants originally randomized to upadacitinib 30 mg received upadacitinib 30 mg once daily for 16 weeks in Period 1. Participants re-randomized to upadacitinib 30 mg in Period 2 continued to receive upadacitinib 30 mg for 72 weeks in Period 2. Participants originally randomized to placebo and re-randomized to upadacitinib 30 mg at Week 16 received upadacitinib 30 mg from Week 16 to Week 88. Participants re-randomized to upadacitinib 7.5 mg or 15 mg at Week 16 who were rescued starting at Week 20 or later received upadacitinib 30 mg until Week 88.

| Serious adverse events                            | Period 1: Placebo | Period 1:<br>Upadacitinib 7.5 mg | Period 1:<br>Upadacitinib 15 mg |
|---|-------------------|----------------------------------|---------------------------------|
| Total subjects affected by serious adverse events |                   |                                  |                                 |
| subjects affected / exposed                       | 1 / 40 (2.50%)    | 2 / 42 (4.76%)                   | 1 / 42 (2.38%)                  |
| number of deaths (all causes)                     | 0                 | 0                                | 0                               |

|  |                |                |                |
|--|----------------|----------------|----------------|
| number of deaths resulting from adverse events   | 0              | 0              | 0              |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)<br>SQUAMOUS CELL CARCINOMA OF SKIN |                |                |                |
| subjects affected / exposed  | 0 / 40 (0.00%) | 0 / 42 (0.00%) | 0 / 42 (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          |
| Cardiac disorders<br>ATRIAL FIBRILLATION   |                |                |                |
| subjects affected / exposed  | 1 / 40 (2.50%) | 0 / 42 (0.00%) | 0 / 42 (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          |
| CARDIO-RESPIRATORY ARREST  |                |                |                |
| subjects affected / exposed  | 0 / 40 (0.00%) | 0 / 42 (0.00%) | 0 / 42 (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          |
| PERICARDITIS   |                |                |                |
| subjects affected / exposed  | 0 / 40 (0.00%) | 0 / 42 (0.00%) | 0 / 42 (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          |
| Gastrointestinal disorders<br>OESOPHAGEAL FISTULA  |                |                |                |
| subjects affected / exposed  | 0 / 40 (0.00%) | 0 / 42 (0.00%) | 0 / 42 (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          |
| Respiratory, thoracic and mediastinal disorders<br>PULMONARY EMBOLISM                                  |                |                |                |
| subjects affected / exposed  | 0 / 40 (0.00%) | 0 / 42 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all  | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all   | 0 / 0          | 0 / 0          | 0 / 0          |
| Skin and subcutaneous tissue disorders<br>DERMATITIS ATOPIC  |                |                |                |
| subjects affected / exposed  | 0 / 40 (0.00%) | 1 / 42 (2.38%) | 0 / 42 (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          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Renal and urinary disorders                     |                |                |                |
| URETEROLITHIASIS                                |                |                |                |
| subjects affected / exposed                     | 0 / 40 (0.00%) | 0 / 42 (0.00%) | 0 / 42 (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          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| OSTEOARTHRITIS                                  |                |                |                |
| subjects affected / exposed                     | 0 / 40 (0.00%) | 0 / 42 (0.00%) | 0 / 42 (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          |
| ROTATOR CUFF SYNDROME                           |                |                |                |
| subjects affected / exposed                     | 0 / 40 (0.00%) | 0 / 42 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| APPENDICITIS                                    |                |                |                |
| subjects affected / exposed                     | 0 / 40 (0.00%) | 0 / 42 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| PERICORONITIS                                   |                |                |                |
| subjects affected / exposed                     | 0 / 40 (0.00%) | 1 / 42 (2.38%) | 0 / 42 (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          |
| SEPSIS  |                |                |                |
| subjects affected / exposed                     | 0 / 40 (0.00%) | 0 / 42 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| SKIN INFECTION                                  |                |                |                |
| subjects affected / exposed                     | 0 / 40 (0.00%) | 1 / 42 (2.38%) | 0 / 42 (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          |

| Serious adverse events                            | Period 1:<br>Upadacitinib 30 mg | Period 1+2:<br>Upadacitinib 7.5 mg | Period 1+2:<br>Upadacitinib 15 mg |
|---|---------------------------------|------------------------------------|-----------------------------------|
| Total subjects affected by serious adverse events |                                 |                                    |                                   |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed  | 0 / 42 (0.00%) | 2 / 42 (4.76%) | 1 / 42 (2.38%) |
| number of deaths (all causes)  | 0              | 0              | 0              |
| number of deaths resulting from adverse events   | 0              | 0              | 0              |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)<br>SQUAMOUS CELL CARCINOMA OF SKIN |                |                |                |
| subjects affected / exposed  | 0 / 42 (0.00%) | 0 / 42 (0.00%) | 0 / 42 (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          |
| Cardiac disorders<br>ATRIAL FIBRILLATION   |                |                |                |
| subjects affected / exposed  | 0 / 42 (0.00%) | 0 / 42 (0.00%) | 0 / 42 (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          |
| CARDIO-RESPIRATORY ARREST  |                |                |                |
| subjects affected / exposed  | 0 / 42 (0.00%) | 0 / 42 (0.00%) | 0 / 42 (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          |
| PERICARDITIS   |                |                |                |
| subjects affected / exposed  | 0 / 42 (0.00%) | 0 / 42 (0.00%) | 0 / 42 (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          |
| Gastrointestinal disorders<br>OESOPHAGEAL FISTULA  |                |                |                |
| subjects affected / exposed  | 0 / 42 (0.00%) | 0 / 42 (0.00%) | 0 / 42 (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          |
| Respiratory, thoracic and mediastinal disorders<br>PULMONARY EMBOLISM                                  |                |                |                |
| subjects affected / exposed  | 0 / 42 (0.00%) | 0 / 42 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all  | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all   | 0 / 0          | 0 / 0          | 0 / 0          |
| Skin and subcutaneous tissue disorders<br>DERMATITIS ATOPIC  |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 42 (2.38%) | 0 / 42 (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          |
| Renal and urinary disorders                     |                |                |                |
| URETEROLITHIASIS                                |                |                |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 42 (0.00%) | 0 / 42 (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          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| OSTEOARTHRITIS                                  |                |                |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 42 (0.00%) | 0 / 42 (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          |
| ROTATOR CUFF SYNDROME                           |                |                |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 42 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| APPENDICITIS                                    |                |                |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 42 (0.00%) | 1 / 42 (2.38%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| PERICORONITIS                                   |                |                |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 42 (2.38%) | 0 / 42 (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          |
| SEPSIS  |                |                |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 0 / 42 (0.00%) | 0 / 42 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| SKIN INFECTION                                  |                |                |                |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 42 (2.38%) | 0 / 42 (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          |

| <b>Serious adverse events</b>                                       | Period 1+2:<br>Upadacitinib 30 mg |  |  |
|---|-----------------------------------|--|--|
| Total subjects affected by serious adverse events                   |                                   |  |  |
| subjects affected / exposed   | 7 / 114 (6.14%)                   |  |  |
| number of deaths (all causes)                                       | 2                                 |  |  |
| number of deaths resulting from adverse events                      | 2                                 |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                   |  |  |
| SQUAMOUS CELL CARCINOMA OF SKIN                                     |                                   |  |  |
| subjects affected / exposed   | 1 / 114 (0.88%)                   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                             |  |  |
| deaths causally related to treatment / all                          | 0 / 0                             |  |  |
| Cardiac disorders   |                                   |  |  |
| ATRIAL FIBRILLATION   |                                   |  |  |
| subjects affected / exposed   | 0 / 114 (0.00%)                   |  |  |
| occurrences causally related to treatment / all                     | 0 / 0                             |  |  |
| deaths causally related to treatment / all                          | 0 / 0                             |  |  |
| CARDIO-RESPIRATORY ARREST   |                                   |  |  |
| subjects affected / exposed   | 1 / 114 (0.88%)                   |  |  |
| occurrences causally related to treatment / all                     | 1 / 1                             |  |  |
| deaths causally related to treatment / all                          | 1 / 1                             |  |  |
| PERICARDITIS  |                                   |  |  |
| subjects affected / exposed   | 1 / 114 (0.88%)                   |  |  |
| occurrences causally related to treatment / all                     | 1 / 1                             |  |  |
| deaths causally related to treatment / all                          | 1 / 1                             |  |  |
| Gastrointestinal disorders  |                                   |  |  |
| OESOPHAGEAL FISTULA   |                                   |  |  |
| subjects affected / exposed   | 1 / 114 (0.88%)                   |  |  |
| occurrences causally related to treatment / all                     | 1 / 1                             |  |  |
| deaths causally related to treatment / all                          | 1 / 1                             |  |  |
| Respiratory, thoracic and mediastinal disorders                     |                                   |  |  |
| PULMONARY EMBOLISM  |                                   |  |  |
| subjects affected / exposed   | 1 / 114 (0.88%)                   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                             |  |  |
| deaths causally related to treatment / all                          | 0 / 0                             |  |  |
| Skin and subcutaneous tissue disorders                              |                                   |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| DERMATITIS ATOPIC                               |                 |  |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal and urinary disorders                     |                 |  |  |
| URETEROLITHIASIS                                |                 |  |  |
| subjects affected / exposed                     | 1 / 114 (0.88%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| OSTEOARTHRITIS                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 114 (0.88%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| ROTATOR CUFF SYNDROME                           |                 |  |  |
| subjects affected / exposed                     | 1 / 114 (0.88%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| APPENDICITIS                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| PERICORONITIS                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| SEPSIS  |                 |  |  |
| subjects affected / exposed                     | 1 / 114 (0.88%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 1 / 1           |  |  |
| SKIN INFECTION                                  |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 114 (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 %

| <b>Non-serious adverse events</b>                     | Period 1: Placebo | Period 1:<br>Upadacitinib 7.5 mg | Period 1:<br>Upadacitinib 15 mg |
|---|-------------------|----------------------------------|---------------------------------|
| Total subjects affected by non-serious adverse events |                   |                                  |                                 |
| subjects affected / exposed                           | 15 / 40 (37.50%)  | 21 / 42 (50.00%)                 | 17 / 42 (40.48%)                |
| Investigations  |                   |                                  |                                 |
| BLOOD CREATINE PHOSPHOKINASE INCREASED                |                   |                                  |                                 |
| subjects affected / exposed                           | 2 / 40 (5.00%)    | 0 / 42 (0.00%)                   | 3 / 42 (7.14%)                  |
| occurrences (all)                                     | 2                 | 0                                | 3                               |
| Injury, poisoning and procedural complications        |                   |                                  |                                 |
| LIGAMENT SPRAIN                                       |                   |                                  |                                 |
| subjects affected / exposed                           | 2 / 40 (5.00%)    | 0 / 42 (0.00%)                   | 0 / 42 (0.00%)                  |
| occurrences (all)                                     | 2                 | 0                                | 0                               |
| Nervous system disorders                              |                   |                                  |                                 |
| HEADACHE  |                   |                                  |                                 |
| subjects affected / exposed                           | 1 / 40 (2.50%)    | 3 / 42 (7.14%)                   | 3 / 42 (7.14%)                  |
| occurrences (all)                                     | 1                 | 3                                | 3                               |
| Gastrointestinal disorders                            |                   |                                  |                                 |
| DIARRHOEA   |                   |                                  |                                 |
| subjects affected / exposed                           | 2 / 40 (5.00%)    | 2 / 42 (4.76%)                   | 2 / 42 (4.76%)                  |
| occurrences (all)                                     | 2                 | 2                                | 4                               |
| NAUSEA  |                   |                                  |                                 |
| subjects affected / exposed                           | 1 / 40 (2.50%)    | 3 / 42 (7.14%)                   | 1 / 42 (2.38%)                  |
| occurrences (all)                                     | 1                 | 3                                | 1                               |
| Respiratory, thoracic and mediastinal disorders       |                   |                                  |                                 |
| OROPHARYNGEAL PAIN                                    |                   |                                  |                                 |
| subjects affected / exposed                           | 0 / 40 (0.00%)    | 3 / 42 (7.14%)                   | 0 / 42 (0.00%)                  |
| occurrences (all)                                     | 0                 | 3                                | 0                               |
| Skin and subcutaneous tissue disorders                |                   |                                  |                                 |
| ACNE  |                   |                                  |                                 |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)   | 1 / 40 (2.50%)<br>1  | 4 / 42 (9.52%)<br>6  | 2 / 42 (4.76%)<br>2  |
| DERMATITIS ATOPIC<br>subjects affected / exposed<br>occurrences (all)                            | 2 / 40 (5.00%)<br>2  | 5 / 42 (11.90%)<br>6 | 2 / 42 (4.76%)<br>2  |
| DERMATITIS CONTACT<br>subjects affected / exposed<br>occurrences (all)                           | 2 / 40 (5.00%)<br>2  | 0 / 42 (0.00%)<br>0  | 1 / 42 (2.38%)<br>1  |
| Renal and urinary disorders<br>HAEMATURIA<br>subjects affected / exposed<br>occurrences (all)    | 2 / 40 (5.00%)<br>2  | 0 / 42 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0  |
| PROTEINURIA<br>subjects affected / exposed<br>occurrences (all)                                  | 2 / 40 (5.00%)<br>2  | 0 / 42 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0  |
| Infections and infestations<br>HERPES ZOSTER<br>subjects affected / exposed<br>occurrences (all) | 0 / 40 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0  |
| IMPETIGO<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 40 (0.00%)<br>0  | 1 / 42 (2.38%)<br>1  | 0 / 42 (0.00%)<br>0  |
| INFLUENZA<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 40 (0.00%)<br>0  | 3 / 42 (7.14%)<br>3  | 0 / 42 (0.00%)<br>0  |
| NASOPHARYNGITIS<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 40 (2.50%)<br>1  | 2 / 42 (4.76%)<br>2  | 4 / 42 (9.52%)<br>5  |
| UPPER RESPIRATORY TRACT<br>INFECTION<br>subjects affected / exposed<br>occurrences (all)         | 4 / 40 (10.00%)<br>4 | 7 / 42 (16.67%)<br>7 | 5 / 42 (11.90%)<br>5 |
| URINARY TRACT INFECTION<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 40 (0.00%)<br>0  | 2 / 42 (4.76%)<br>2  | 2 / 42 (4.76%)<br>2  |

|                                   |                                 |                                    |                                   |
|-----------------------------------|---------------------------------|------------------------------------|-----------------------------------|
| <b>Non-serious adverse events</b> | Period 1:<br>Upadacitinib 30 mg | Period 1+2:<br>Upadacitinib 7.5 mg | Period 1+2:<br>Upadacitinib 15 mg |
|-----------------------------------|---------------------------------|------------------------------------|-----------------------------------|

|   |  |  |  |
|---|--|--|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed  | 21 / 42 (50.00%)   | 23 / 42 (54.76%)   | 22 / 42 (52.38%)   |
| Investigations<br>BLOOD CREATINE PHOSPHOKINASE INCREASED<br>subjects affected / exposed<br>occurrences (all)  | 4 / 42 (9.52%)<br>4  | 0 / 42 (0.00%)<br>0  | 3 / 42 (7.14%)<br>3  |
| Injury, poisoning and procedural complications<br>LIGAMENT SPRAIN<br>subjects affected / exposed<br>occurrences (all)   | 0 / 42 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0  | 0 / 42 (0.00%)<br>0  |
| Nervous system disorders<br>HEADACHE<br>subjects affected / exposed<br>occurrences (all)  | 4 / 42 (9.52%)<br>4  | 3 / 42 (7.14%)<br>3  | 3 / 42 (7.14%)<br>3  |
| Gastrointestinal disorders<br>DIARRHOEA<br>subjects affected / exposed<br>occurrences (all)<br><br>NAUSEA<br>subjects affected / exposed<br>occurrences (all)   | 0 / 42 (0.00%)<br>0<br><br>3 / 42 (7.14%)<br>3                             | 2 / 42 (4.76%)<br>2<br><br>3 / 42 (7.14%)<br>3                             | 2 / 42 (4.76%)<br>5<br><br>1 / 42 (2.38%)<br>1                             |
| Respiratory, thoracic and mediastinal disorders<br>OROPHARYNGEAL PAIN<br>subjects affected / exposed<br>occurrences (all)   | 0 / 42 (0.00%)<br>0  | 3 / 42 (7.14%)<br>3  | 0 / 42 (0.00%)<br>0  |
| Skin and subcutaneous tissue disorders<br>ACNE<br>subjects affected / exposed<br>occurrences (all)<br><br>DERMATITIS ATOPIC<br>subjects affected / exposed<br>occurrences (all)<br><br>DERMATITIS CONTACT<br>subjects affected / exposed<br>occurrences (all) | 6 / 42 (14.29%)<br>7<br><br>4 / 42 (9.52%)<br>5<br><br>1 / 42 (2.38%)<br>1 | 4 / 42 (9.52%)<br>6<br><br>6 / 42 (14.29%)<br>7<br><br>0 / 42 (0.00%)<br>0 | 2 / 42 (4.76%)<br>2<br><br>5 / 42 (11.90%)<br>5<br><br>1 / 42 (2.38%)<br>1 |
| Renal and urinary disorders   |  |  |  |

|                                   |                 |                 |                 |
|-----------------------------------|-----------------|-----------------|-----------------|
| HAEMATURIA                        |                 |                 |                 |
| subjects affected / exposed       | 0 / 42 (0.00%)  | 0 / 42 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)                 | 0               | 0               | 0               |
| PROTEINURIA                       |                 |                 |                 |
| subjects affected / exposed       | 0 / 42 (0.00%)  | 0 / 42 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)                 | 0               | 0               | 0               |
| Infections and infestations       |                 |                 |                 |
| HERPES ZOSTER                     |                 |                 |                 |
| subjects affected / exposed       | 0 / 42 (0.00%)  | 0 / 42 (0.00%)  | 0 / 42 (0.00%)  |
| occurrences (all)                 | 0               | 0               | 0               |
| IMPETIGO                          |                 |                 |                 |
| subjects affected / exposed       | 2 / 42 (4.76%)  | 1 / 42 (2.38%)  | 0 / 42 (0.00%)  |
| occurrences (all)                 | 2               | 1               | 0               |
| INFLUENZA                         |                 |                 |                 |
| subjects affected / exposed       | 0 / 42 (0.00%)  | 3 / 42 (7.14%)  | 0 / 42 (0.00%)  |
| occurrences (all)                 | 0               | 3               | 0               |
| NASOPHARYNGITIS                   |                 |                 |                 |
| subjects affected / exposed       | 3 / 42 (7.14%)  | 3 / 42 (7.14%)  | 5 / 42 (11.90%) |
| occurrences (all)                 | 3               | 3               | 6               |
| UPPER RESPIRATORY TRACT INFECTION |                 |                 |                 |
| subjects affected / exposed       | 5 / 42 (11.90%) | 7 / 42 (16.67%) | 7 / 42 (16.67%) |
| occurrences (all)                 | 9               | 7               | 7               |
| URINARY TRACT INFECTION           |                 |                 |                 |
| subjects affected / exposed       | 1 / 42 (2.38%)  | 2 / 42 (4.76%)  | 2 / 42 (4.76%)  |
| occurrences (all)                 | 1               | 2               | 2               |

|   |                                   |  |  |
|---|-----------------------------------|--|--|
| <b>Non-serious adverse events</b>                     | Period 1+2:<br>Upadacitinib 30 mg |  |  |
| Total subjects affected by non-serious adverse events |                                   |  |  |
| subjects affected / exposed                           | 68 / 114 (59.65%)                 |  |  |
| Investigations  |                                   |  |  |
| BLOOD CREATINE PHOSPHOKINASE INCREASED                |                                   |  |  |
| subjects affected / exposed                           | 7 / 114 (6.14%)                   |  |  |
| occurrences (all)                                     | 8                                 |  |  |
| Injury, poisoning and procedural complications        |                                   |  |  |

|   |  |  |  |
|---|--|--|--|
| LIGAMENT SPRAIN<br>subjects affected / exposed<br>occurrences (all)   | 1 / 114 (0.88%)<br>1   |  |  |
| Nervous system disorders<br>HEADACHE<br>subjects affected / exposed<br>occurrences (all)  | 7 / 114 (6.14%)<br>7   |  |  |
| Gastrointestinal disorders<br>DIARRHOEA<br>subjects affected / exposed<br>occurrences (all)<br><br>NAUSEA<br>subjects affected / exposed<br>occurrences (all)   | 2 / 114 (1.75%)<br>2<br><br>6 / 114 (5.26%)<br>8                                   |  |  |
| Respiratory, thoracic and mediastinal disorders<br>OROPHARYNGEAL PAIN<br>subjects affected / exposed<br>occurrences (all)   | 0 / 114 (0.00%)<br>0   |  |  |
| Skin and subcutaneous tissue disorders<br>ACNE<br>subjects affected / exposed<br>occurrences (all)<br><br>DERMATITIS ATOPIC<br>subjects affected / exposed<br>occurrences (all)<br><br>DERMATITIS CONTACT<br>subjects affected / exposed<br>occurrences (all) | 13 / 114 (11.40%)<br>14<br><br>22 / 114 (19.30%)<br>25<br><br>2 / 114 (1.75%)<br>2 |  |  |
| Renal and urinary disorders<br>HAEMATURIA<br>subjects affected / exposed<br>occurrences (all)<br><br>PROTEINURIA<br>subjects affected / exposed<br>occurrences (all)  | 1 / 114 (0.88%)<br>1<br><br>1 / 114 (0.88%)<br>1                                   |  |  |
| Infections and infestations   |  |  |  |

|                                      |                   |  |  |
|--------------------------------------|-------------------|--|--|
| HERPES ZOSTER                        |                   |  |  |
| subjects affected / exposed          | 10 / 114 (8.77%)  |  |  |
| occurrences (all)                    | 10                |  |  |
| IMPETIGO                             |                   |  |  |
| subjects affected / exposed          | 8 / 114 (7.02%)   |  |  |
| occurrences (all)                    | 8                 |  |  |
| INFLUENZA                            |                   |  |  |
| subjects affected / exposed          | 3 / 114 (2.63%)   |  |  |
| occurrences (all)                    | 4                 |  |  |
| NASOPHARYNGITIS                      |                   |  |  |
| subjects affected / exposed          | 11 / 114 (9.65%)  |  |  |
| occurrences (all)                    | 16                |  |  |
| UPPER RESPIRATORY TRACT<br>INFECTION |                   |  |  |
| subjects affected / exposed          | 26 / 114 (22.81%) |  |  |
| occurrences (all)                    | 47                |  |  |
| URINARY TRACT INFECTION              |                   |  |  |
| subjects affected / exposed          | 6 / 114 (5.26%)   |  |  |
| occurrences (all)                    | 8                 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 25 July 2016     | <ul style="list-style-type: none"><li>- Updated contraception timeline requirements for females and clarified consent requirements in Japan.</li><li>- Updated Exclusion Criteria for topical treatment criteria.</li><li>- Updated list of prohibited therapies to remove non-atopic dermatitis related treatments. Updated tanning booth and extended sun exposure criteria.</li><li>- Updated live vaccine timeline requirements for Japan.</li><li>- Updated requirements for allowed topical corticosteroids for rescue therapy.</li></ul>   |
| 18 October 2016  | <ul style="list-style-type: none"><li>- Updated details regarding upadacitinib pharmacokinetic data.</li><li>- Added discontinuation criteria during Period 1 and Period 2.</li><li>- Added secondary endpoints for Period 2.</li></ul>   |
| 16 December 2016 | <ul style="list-style-type: none"><li>- Updated rescue therapy and Premature Discontinuation Visits for subjects who prematurely discontinue from study drug to improve readability and provide clarity.</li><li>- Updated Inclusion Criteria to clarify diagnosis, pregnancy testing, and contraception requirements.</li><li>- Updated Exclusion Criteria</li><li>- Updated text to clarify administration criteria for vaccines for Prior and Concomitant Therapy</li><li>- Updated Prohibited Therapy to clarify exceptions for administering live vaccines.</li><li>- Updated contraception requirements.</li><li>- Added three new PRO questionnaires.</li><li>- Added a Week 16 primary endpoint analysis.</li></ul>   |
| 07 June 2017     | <ul style="list-style-type: none"><li>- Extended the study from 40 weeks to 88 weeks of treatment. Added visits every 12 weeks post Week 40 (Week 52, Week 64, Week 76, and Week 88). Removed optional visits at Week 28 and Week 36 and added optional Visit 4 weeks post topical rescue therapy.</li><li>- Updated list of examples of biologic therapies for Prohibited Therapy.</li><li>- Updated language to require a Visit 4 weeks after receiving topical rescue therapy instead of at Week 28 or Week 36.</li><li>- Updated blood samples collection schedule to reduce patient burden.</li><li>- Updated list of AEs of special interest to be consistent with the product safety statistical analysis plan.</li><li>- Removed Week 8 interim analysis language that is no longer planned.</li><li>- Added Week 32 interim analysis language.</li></ul> |
| 30 August 2017   | <ul style="list-style-type: none"><li>- Updated list of AEs of special interest to be consistent with the current AbbVie list of AEs of special interest.</li></ul>   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported