



## Clinical trial results:

### A Multi-center, Exploratory Study to Assess Dupilumab Effect on Pruritus Neuro-mechanisms in Patients With Atopic Dermatitis

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2020-003542-36 |
| Trial protocol           | DE             |
| Global end of trial date | 30 August 2022 |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 24 August 2023 |
| First version publication date | 24 August 2023 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | LPS16763 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT04823130     |
| WHO universal trial number (UTN)   | U1111-1251-5658 |

Notes:

#### Sponsors

|                              |                                                                                          |
|------------------------------|------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Sanofi aventis recherche & développement                                                 |
| Sponsor organisation address | 1 Avenue Pierre Brossolette, Chilly-Mazarin Cedex, France, 91380                         |
| Public contact               | Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com |
| Scientific contact           | Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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                       | 10 October 2022 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 30 August 2022  |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

Assess change in neuronal architecture following long term treatment with dupilumab in skin biopsies from atopic dermatitis (AD) subjects with chronic pruritus.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 22 April 2021 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 23 |
| Country: Number of subjects enrolled | Germany: 31       |
| Worldwide total number of subjects   | 54                |
| EEA total number of subjects         | 31                |

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)                      | 46 |

|                     |   |
|---------------------|---|
| From 65 to 84 years | 8 |
| 85 years and over   | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 3 active sites in the United States and Germany. A total of 54 subjects were enrolled between 22 April 2021 to 30 March 2022 under the dupilumab or the healthy subjects arm groups.

### Pre-assignment

Screening details:

Healthy subjects were considered as a reference comparator group and received no treatment. Healthy subjects underwent a 7-day observational period following collection of the skin biopsy on Day 1. Only safety data was collected for the healthy subjects and no other endpoints were assessed.

### Period 1

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

### Arms

|                              |                           |
|------------------------------|---------------------------|
| Are arms mutually exclusive? | Yes                       |
| <b>Arm title</b>             | Healthy Subjects: Control |

Arm description:

Healthy subjects with site, age, gender, race, location of targeted lesional and non-lesional skin area matched to selected AD subjects, received no treatment, and were considered as a control group.

|                                                           |                             |
|-----------------------------------------------------------|-----------------------------|
| Arm type                                                  | No intervention             |
| No investigational medicinal product assigned in this arm |                             |
| <b>Arm title</b>                                          | Subjects With AD: Dupilumab |

Arm description:

Subjects with moderate to severe AD received dupilumab 600 milligrams (mg) subcutaneous (SC) injection on Day 1, followed by dupilumab 300 mg SC injection every 2 weeks (Q2W) from Week 3 to Week 15.

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

Dosage and administration details:

Dupilumab 600 mg SC injection on Day 1 followed by dupilumab 300 mg SC injection Q2W.

| <b>Number of subjects in period 1</b> | Healthy Subjects:<br>Control | Subjects With AD:<br>Dupilumab |
|---------------------------------------|------------------------------|--------------------------------|
| Started                               | 19                           | 35                             |
| Safety Population                     | 13                           | 31                             |
| Completed                             | 10                           | 28                             |
| Not completed                         | 9                            | 7                              |
| Failure to meet inclusion criteria    | 6                            | 4                              |
| Other-unspecified                     | 1                            | -                              |

|                       |   |   |
|-----------------------|---|---|
| Withdrawal by Subject | 2 | 3 |
|-----------------------|---|---|

## Baseline characteristics

### Reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Healthy Subjects: Control |
|-----------------------|---------------------------|

Reporting group description:

Healthy subjects with site, age, gender, race, location of targeted lesional and non-lesional skin area matched to selected AD subjects, received no treatment, and were considered as a control group.

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Subjects With AD: Dupilumab |
|-----------------------|-----------------------------|

Reporting group description:

Subjects with moderate to severe AD received dupilumab 600 milligrams (mg) subcutaneous (SC) injection on Day 1, followed by dupilumab 300 mg SC injection every 2 weeks (Q2W) from Week 3 to Week 15.

| Reporting group values             | Healthy Subjects:<br>Control | Subjects With AD:<br>Dupilumab | Total |
|------------------------------------|------------------------------|--------------------------------|-------|
| Number of subjects                 | 19                           | 35                             | 54    |
| Age categorical<br>Units: Subjects |                              |                                |       |

|                                                                         |                |                |    |
|-------------------------------------------------------------------------|----------------|----------------|----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 41.3<br>± 14.1 | 41.2<br>± 18.1 | -  |
| Gender categorical<br>Units: Subjects                                   |                |                |    |
| Female                                                                  | 13             | 19             | 32 |
| Male                                                                    | 6              | 16             | 22 |
| Race<br>Units: Subjects                                                 |                |                |    |
| American Indian or Alaska Native                                        | 0              | 0              | 0  |
| Asian                                                                   | 0              | 1              | 1  |
| Native Hawaiian or Other Pacific Islander                               | 0              | 0              | 0  |
| Black or African American                                               | 0              | 0              | 0  |
| White                                                                   | 19             | 33             | 52 |
| More than one race                                                      | 0              | 1              | 1  |
| Unknown or Not Reported                                                 | 0              | 0              | 0  |

## End points

### End points reporting groups

|                                                                                                                                                                                                         |                             |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Reporting group title                                                                                                                                                                                   | Healthy Subjects: Control   |
| Reporting group description:                                                                                                                                                                            |                             |
| Healthy subjects with site, age, gender, race, location of targeted lesional and non-lesional skin area matched to selected AD subjects, received no treatment, and were considered as a control group. |                             |
| Reporting group title                                                                                                                                                                                   | Subjects With AD: Dupilumab |
| Reporting group description:                                                                                                                                                                            |                             |
| Subjects with moderate to severe AD received dupilumab 600 milligrams (mg) subcutaneous (SC) injection on Day 1, followed by dupilumab 300 mg SC injection every 2 weeks (Q2W) from Week 3 to Week 15.  |                             |

### Primary: Change From Baseline in Intraepidermal Nerve Fiber Density on Lesional Skin at Week 17

|                 |                                                                                                          |
|-----------------|----------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Intraepidermal Nerve Fiber Density on Lesional Skin at Week 17 <sup>[1][2]</sup> |
|-----------------|----------------------------------------------------------------------------------------------------------|

#### End point description:

Skin biopsies were used to analyse the epidermal nerve fiber density. Nerve fibers were visualised by staining consecutive sections for the pan-axonal marker protein gene product 9.5 (PGP9.5); and the basement membrane was visualised by staining for collagen type 4. Quantification of intraepidermal nerve fiber density was calculated by assessing nerve fibers crossing the basement membrane per square millimetre (F/mm<sup>2</sup>). Analysis was performed on modified intent-to-treat (mITT) population which included all AD subjects who received at least 1 dose of investigational medicinal product (IMP) who had at least 1 skin biopsy performed, irrespective of compliance with study protocol and procedures, and who did not use prohibited therapies for AD from screening to end of study. Here, 'number of subjects analysed' = subjects with available data for this endpoint and 'n' = subjects with available data for each specified category.

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

#### End point timeframe:

Baseline, Week 17

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the endpoint was descriptive in nature, no statistical analyses was reported.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was not planned to be collected and analysed for 'healthy subjects' arm.

| End point values                     | Subjects With AD: Dupilumab |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 27                          |  |  |  |
| Units: F/mm <sup>2</sup>             |                             |  |  |  |
| arithmetic mean (standard deviation) |                             |  |  |  |
| Baseline (n=27)                      | 8.4567 (± 7.2502)           |  |  |  |
| Change at Week 17 (n=20)             | 4.2618 (± 6.7538)           |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects With Change From Baseline in Nerve Fiber Branching on Lesional Skin at Week 17

|                 |                                                                                                                                     |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects With Change From Baseline in Nerve Fiber Branching on Lesional Skin at Week 17 <sup>[3]</sup> <sup>[4]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Skin biopsies were used to analyse the epidermal nerve fiber branching. Nerve fibers were visualised by staining consecutive sections for the pan-axonal marker PGP9.5; and the basement membrane was visualised by staining for collagen type 4. Branching of epidermal nerve fibers was assessed semi-quantitatively by classifying subjects into 4 groups depending on the predominant intraepidermal nerve fiber branching pattern as follows: only linear (100% linear), mainly linear (>60% linear), mainly branched (>60% branched), only branched (100% branched). Percentage of subjects with change in nerve fiber branching status from baseline on lesional skin at Week 17 are reported in this endpoint. Analysis was performed on mITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

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

End point timeframe:

Baseline, Week 17

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the endpoint was descriptive in nature, no statistical analyses was reported.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was not planned to be collected and analysed for 'healthy subjects' arm.

| End point values              | Subjects With AD: Dupilumab |  |  |  |
|-------------------------------|-----------------------------|--|--|--|
| Subject group type            | Reporting group             |  |  |  |
| Number of subjects analysed   | 15                          |  |  |  |
| Units: percentage of subjects |                             |  |  |  |
| number (not applicable)       |                             |  |  |  |
| Only linear                   | 0                           |  |  |  |
| Mainly linear                 | 60.0                        |  |  |  |
| Mainly branched               | 40.0                        |  |  |  |
| Branched fibers               | 0                           |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Intraepidermal Nerve Fiber Density on Lesional Skin at Weeks 3 and 21

|                 |                                                                                                              |
|-----------------|--------------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Intraepidermal Nerve Fiber Density on Lesional Skin at Weeks 3 and 21 <sup>[5]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------------|

End point description:

Skin biopsies were used to analyse the epidermal nerve fiber density. Nerve fibers were visualised by staining consecutive sections for the pan-axonal marker PGP9.5; and the basement membrane was visualised by staining for collagen type 4. Quantification of intraepidermal nerve fiber density was calculated by assessing nerve fibers crossing the basement membrane per square millimetre (F/mm<sup>2</sup>).

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

End point timeframe:

Baseline, Weeks 3 and 21

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data for this endpoint was not planned to be collected and analysed for 'healthy subjects' arm.

| End point values                     | Subjects With AD: Dupilumab |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 0 <sup>[6]</sup>            |  |  |  |
| Units: F/mm <sup>2</sup>             |                             |  |  |  |
| arithmetic mean (standard deviation) | ( )                         |  |  |  |

Notes:

[6] - Data was not collected and analysed for this endpoint as no optional biopsies done at Week 3 and 21.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Nerve Fiber Branching on Lesional Skin at Weeks 3 and 21

|                 |                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Nerve Fiber Branching on Lesional Skin at Weeks 3 and 21 <sup>[7]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------|

End point description:

Skin biopsies were used to analyse the epidermal nerve fiber branching. Nerve fibers were visualised by staining consecutive sections for the pan-axonal marker PGP9.5, and the basement membrane was visualised by staining for collagen type 4. Branching of epidermal nerve fibers was assessed semi-quantitatively by classifying subjects into 4 groups depending on the predominant intraepidermal nerve fiber branching pattern as follows: only linear (100% linear), mainly linear (>60% linear), mainly branched (>60% branched), only branched (100% branched).

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

End point timeframe:

Baseline, Weeks 3 and 21

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data for this endpoint was not planned to be collected and analysed for 'healthy subjects' arm.

| End point values            | Subjects With AD: Dupilumab |  |  |  |
|-----------------------------|-----------------------------|--|--|--|
| Subject group type          | Reporting group             |  |  |  |
| Number of subjects analysed | 0 <sup>[8]</sup>            |  |  |  |
| Units: percent branching    |                             |  |  |  |
| number (not applicable)     |                             |  |  |  |

Notes:

[8] - Data was not collected and analysed for this endpoint as no optional biopsies done at Week 3 and 21.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Peak Pruritus Assessed by Numeric Rating

## Scale (NRS) at Weeks 17 and 21

|                 |                                                                                                                |
|-----------------|----------------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Peak Pruritus Assessed by Numeric Rating Scale (NRS) at Weeks 17 and 21 <sup>[9]</sup> |
|-----------------|----------------------------------------------------------------------------------------------------------------|

### End point description:

Peak Pruritus NRS was an assessment tool used to report the intensity of subject's pruritus (itch) during a daily recall period. Subjects were asked to rate their worst itch on a 0 ("No itch") to 10 ("Worst itch imaginable") NRS by answering the following question: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?". Higher scores indicated greater severity. Analysis was performed on mITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

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

### End point timeframe:

Baseline, Weeks 17 and 21

### Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data for this endpoint was not planned to be collected and analysed for 'healthy subjects' arm.

|                                      |                             |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| <b>End point values</b>              | Subjects With AD: Dupilumab |  |  |  |
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 7                           |  |  |  |
| Units: score on a scale              |                             |  |  |  |
| arithmetic mean (standard deviation) |                             |  |  |  |
| Week 17                              | -6.6 (± 3.6)                |  |  |  |
| Week 21                              | -7.4 (± 1.4)                |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Eczema and Severity Index (EASI) Total Score at Weeks 17 and 21

|                 |                                                                                                         |
|-----------------|---------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Eczema and Severity Index (EASI) Total Score at Weeks 17 and 21 <sup>[10]</sup> |
|-----------------|---------------------------------------------------------------------------------------------------------|

### End point description:

EASI was a validated measure used to assess the severity and extent of AD. Four AD disease characteristics (erythema, thickness [induration, papulation, and edema], scratching [excoriation], and lichenification) were each assessed for severity by the Investigator on a scale of "0" (absent) through "3" (severe). EASI area score was based upon percent (%) body surface area (BSA) with AD in each body region: 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), and 6 (90% to 100%). Total EASI score was derived as the sum of the 4 region scores and ranged from 0 (minimum) to 72 (maximum). Higher scores indicated greater severity of AD. Analysis was performed on mITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint and 'n' = subjects with available data for each specified category.

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

### End point timeframe:

Baseline, Weeks 17 and 21

### Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was not planned to be collected and analysed for 'healthy subjects' arm.

|                                      |                             |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| <b>End point values</b>              | Subjects With AD: Dupilumab |  |  |  |
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 12                          |  |  |  |
| Units: score on a scale              |                             |  |  |  |
| arithmetic mean (standard deviation) |                             |  |  |  |
| Week 17 (n=12)                       | -18.9 (± 6.4)               |  |  |  |
| Week 21 (n=10)                       | -19.5 (± 6.4)               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Scoring Atopic Dermatitis (SCORAD) Total Score at Weeks 17 and 21

|                 |                                                                                                           |
|-----------------|-----------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Scoring Atopic Dermatitis (SCORAD) Total Score at Weeks 17 and 21 <sup>[11]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------|

End point description:

SCORAD: standardise extent & severity of AD consists of 3 components i.e., A =extent or affected BSA assessed as % of each defined body area and reported as sum of all areas, with maximum score of 100%. B=severity of 6 specific symptoms of AD (redness, swelling, oozing/crusting, excoriation, skin thickening/lichenification, dryness) assessed using following scale: none(0), mild(1), moderate(2), or severe(3) (for maximum of 18 total points) & C=subjective symptoms scored by subjects on VAS, where "0"=no itch (or no sleeplessness) & "10"=worst imaginable itch (or sleeplessness) with maximum score of 20. SCORAD total score was calculated using these 3 aspects: extent (A: 0-100), severity (B: 0-18), & subjective symptoms (C: 0-20) using formula:  $A/5 + 7*B/2 + C$ . SCORAD total score ranged from 0 to 103, where 0 = no disease to 103 = severe disease. Higher values of SCORAD represent worse outcome. mITT. 'Number of subjects analysed' = subjects with available data for this endpoint.

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

End point timeframe:

Baseline, Weeks 17 and 21

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was not planned to be collected and analysed for 'healthy subjects' arm.

|                                      |                             |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| <b>End point values</b>              | Subjects With AD: Dupilumab |  |  |  |
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 19 <sup>[12]</sup>          |  |  |  |
| Units: score on a scale              |                             |  |  |  |
| arithmetic mean (standard deviation) |                             |  |  |  |
| Week 17 (n=19)                       | -77.2 (± 32.3)              |  |  |  |
| Week 21 (n=15)                       | -81.3 (± 35.0)              |  |  |  |

Notes:

[12] - Here, 'n' = subjects with available data for each specified category.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Patient-Reported Outcomes Measurement Information (PROMIS-itch) Total Score at Weeks 17 and 21

|                 |                                                                                                                                        |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Patient-Reported Outcomes Measurement Information (PROMIS-itch) Total Score at Weeks 17 and 21 <sup>[13]</sup> |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------|

### End point description:

PROMIS-itch represents a novel suite of participant-reported outcome (PRO) measures for the itch. The PROMIS-Itch severity score consists of 7 questions: 4 questions scored on a scale of 1 to 5: 1) How intense was your itch at its worst; 2) How intense was your itch in general; 3) What is your level of itch right now; 4) How often did you feel the itch; and rest 3 questions (same questions as 1 to 3 mentioned before but scaled on a scale of 0 to 10) were scored on a scale of 0 to 10. Higher scores for each question indicated worse outcome. The total PROMIS-itch score was calculated as the sum of the 7 questions and ranged from 4 (better outcome) to 50 (worse outcome), where a higher score indicated worse condition. Analysis was performed on mITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

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

### End point timeframe:

Baseline, Weeks 17 and 21

### Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was not planned to be collected and analysed for 'healthy subjects' arm.

| End point values                     | Subjects With AD: Dupilumab |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 13                          |  |  |  |
| Units: score on a scale              |                             |  |  |  |
| arithmetic mean (standard deviation) |                             |  |  |  |
| Week 17                              | -30.8 (± 9.0)               |  |  |  |
| Week 21                              | -28.8 (± 11.5)              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Patient Oriented Eczema Measure (POEM) Total Score at Weeks 17 and 21

|                 |                                                                                                               |
|-----------------|---------------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Patient Oriented Eczema Measure (POEM) Total Score at Weeks 17 and 21 <sup>[14]</sup> |
|-----------------|---------------------------------------------------------------------------------------------------------------|

### End point description:

The POEM was a 7-item, validated questionnaire used in clinical practice and clinical trials to assess disease symptoms in children and adults with AD. The format is subject response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on symptom frequency during the past week (i.e., 0 = 'no days', 1 = '1 to 2 days', 2 = '3 to 4 days', 3 = '5 to 6' days, and 4 = 'every day'). The sum of the 7 items gives the total POEM score of 0 (absent disease) to 28 (severe disease). Higher scores indicated more severe disease and poor quality of life. Analysis was performed on mITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint and 'n' = subjects with available data for each specified category.

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

### End point timeframe:

Baseline, Weeks 17 and 21

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was not planned to be collected and analysed for 'healthy subjects' arm.

| End point values                     | Subjects With AD: Dupilumab |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 14                          |  |  |  |
| Units: score on a scale              |                             |  |  |  |
| arithmetic mean (standard deviation) |                             |  |  |  |
| Week 17 (n=14)                       | -17.2 (± 5.3)               |  |  |  |
| Week 21 (n=13)                       | -16.1 (± 5.9)               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Dermatology Life Quality Index (DLQI) Total Score at Weeks 17 and 21

|                 |                                                                                                              |
|-----------------|--------------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Dermatology Life Quality Index (DLQI) Total Score at Weeks 17 and 21 <sup>[15]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------------|

End point description:

DLQI was a 10-item PRO questionnaire that measured the impact of AD disease symptoms and treatment on quality of life. Each question was evaluated on a 4-point scale ranged from 0 to 3 where, 0 = not at all, 1= a little, 2= a lot, 3= very much, where higher scores indicated more impact on quality of life. Scores from all 10 questions were added up to give DLQI total score that ranged from 0 (not at all) to 30 (very much). Higher scores indicated more impact on quality of life of subjects. Analysis was performed on mITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint and 'n' = subjects with available data for each specified category.

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

End point timeframe:

Baseline, Weeks 17 and 21

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was not planned to be collected and analysed for 'healthy subjects' arm.

| End point values                     | Subjects With AD: Dupilumab |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 17                          |  |  |  |
| Units: score on a scale              |                             |  |  |  |
| arithmetic mean (standard deviation) |                             |  |  |  |
| Week 17 (n=17)                       | -16.1 (± 7.4)               |  |  |  |
| Week 21 (n=16)                       | -14.8 (± 8.1)               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Atopic Dermatitis Control Tool (ADCT) Total Score at Weeks 17 and 21

|                 |                                                                                                              |
|-----------------|--------------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Atopic Dermatitis Control Tool (ADCT) Total Score at Weeks 17 and 21 <sup>[16]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------------|

End point description:

ADCT was a PRO questionnaire designed to assess subject-self-perceived control of their eczema. ADCT contained 6 items allowing a comprehensive coverage of the dimensions defining AD control, i.e., overall severity of AD symptoms, frequency of intense episodes of itching, extent of AD related bother, impact on sleep, impact on daily activities, impact on mood or emotions. Each item of the ADCT is rated from 0 (no problem) to 4 (worst) Likert scale and is equally weighted. The sum of the 6 items gives the total score that ranged from 0 (best disease control) to 24 (worst disease control). Higher scores indicate lower AD control. Analysis was performed on mITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

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

End point timeframe:

Baseline, Weeks 17 and 21

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was not planned to be collected and analysed for 'healthy subjects' arm.

| End point values                     | Subjects With AD: Dupilumab |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 14                          |  |  |  |
| Units: score on a scale              |                             |  |  |  |
| arithmetic mean (standard deviation) |                             |  |  |  |
| Week 17                              | -17.9 (± 4.1)               |  |  |  |
| Week 21                              | -15.9 (± 6.2)               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Sleep Quality Numerical Rating Scale at Weeks 17 and 21

|                 |                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Sleep Quality Numerical Rating Scale at Weeks 17 and 21 <sup>[17]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------|

End point description:

Sleep quality NRS was used to assess the quality of the subject's previous night's sleep using a 0 ("Worst possible sleep") to 10 ("Best possible sleep") NRS. Subjects were asked to complete the following question upon awakening: "Select the number (0 to 10) that best describes the quality of your sleep last night". Higher score indicated better outcome. Analysis was performed on mITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint and 'n' = subjects with available data for each specified category.

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

End point timeframe:

Baseline, Weeks 17 and 21

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was not planned to be collected and analysed for 'healthy subjects' arm.

| End point values                     | Subjects With AD: Dupilumab |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 5                           |  |  |  |
| Units: score on a scale              |                             |  |  |  |
| arithmetic mean (standard deviation) |                             |  |  |  |
| Week 17 (n=3)                        | 0.7 (± 5.0)                 |  |  |  |
| Week 21 (n=5)                        | 3.0 (± 5.4)                 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Skin Pain Numerical Rating Scale at Weeks 17 and 21

|                 |                                                                                             |
|-----------------|---------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Skin Pain Numerical Rating Scale at Weeks 17 and 21 <sup>[18]</sup> |
|-----------------|---------------------------------------------------------------------------------------------|

End point description:

Skin pain NRS was used to assess subject's skin pain at its worst in the past 24 hours using a 0 ("Not at all") to 10 ("Very much") NRS. Subjects were asked the following question: "Think about all the areas of your skin with eczema. How much did your skin burn at its worst in the past 24 hours?" Lower score indicated better outcome. Analysis was performed on mITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint and 'n' = subjects with available data for each specified category.

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

End point timeframe:

Baseline, Weeks 17 and 21

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was not planned to be collected and analysed for 'healthy subjects' arm.

| End point values                     | Subjects With AD: Dupilumab |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 4                           |  |  |  |
| Units: score on a scale              |                             |  |  |  |
| arithmetic mean (standard deviation) |                             |  |  |  |
| Week 17 (n=3)                        | -5.3 (± 2.9)                |  |  |  |
| Week 21 (n=4)                        | -5.3 (± 2.2)                |  |  |  |

## Statistical analyses

**Secondary: Change From Baseline in Skin Sensitivity Numerical Rating Scale at Weeks 17 and 21**

|                 |                                                                                                    |
|-----------------|----------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Skin Sensitivity Numerical Rating Scale at Weeks 17 and 21 <sup>[19]</sup> |
|-----------------|----------------------------------------------------------------------------------------------------|

## End point description:

Skin sensitivity NRS was a 1 item PRO measure asking the subjects to rate their skin sensitivity to touch using a 0 ("Normal") to 10 ("Extremely sensitive") NRS. Subjects were asked the following question: "Think about all the areas of your skin with eczema. How sensitive was your skin at its worst in the past 24 hours?" Lower score indicated better outcome. Analysis was performed on mITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint and 'n' = subjects with available data for each specified category.

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

## End point timeframe:

Baseline, Weeks 17 and 21

## Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was not planned to be collected and analysed for 'healthy subjects' arm.

| End point values                     | Subjects With AD: Dupilumab |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 4                           |  |  |  |
| Units: score on a scale              |                             |  |  |  |
| arithmetic mean (standard deviation) |                             |  |  |  |
| Week 17 (n=3)                        | -7.7 (± 1.5)                |  |  |  |
| Week 21 (n=4)                        | -7.3 (± 2.2)                |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change From Baseline in Skin Burning Numerical Rating Scale at Weeks 17 and 21**

|                 |                                                                                                |
|-----------------|------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Skin Burning Numerical Rating Scale at Weeks 17 and 21 <sup>[20]</sup> |
|-----------------|------------------------------------------------------------------------------------------------|

## End point description:

Skin burning NRS was a 1-item PRO measure asking subjects to rate the burning sensation of their skin in the past 24 hours using a 0 ("Not at all") to 10 ("Very much") NRS. Subjects were asked the following question: "Think about all the areas of your skin with eczema. How much did your skin burn at its worst in the past 24 hours?" Lower score indicated better outcome. Analysis was performed on mITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint and 'n' = subjects with available data for each specified category.

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

## End point timeframe:

Baseline, Weeks 17 and 21

## Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was not planned to be collected and analysed for 'healthy subjects' arm.

arm.

| End point values                     | Subjects With AD: Dupilumab |  |  |  |
|--------------------------------------|-----------------------------|--|--|--|
| Subject group type                   | Reporting group             |  |  |  |
| Number of subjects analysed          | 4                           |  |  |  |
| Units: score on a scale              |                             |  |  |  |
| arithmetic mean (standard deviation) |                             |  |  |  |
| Week 17 (n=3)                        | -4.3 (± 1.5)                |  |  |  |
| Week 21 (n=4)                        | -5.5 (± 2.9)                |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Change of Greater Than or Equal to ( $\geq 4$ ) Point in Pruritus Numerical Rating Scale From Baseline at Weeks 17 and 21

|                 |                                                                                                                                                                       |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects With Change of Greater Than or Equal to ( $\geq 4$ ) Point in Pruritus Numerical Rating Scale From Baseline at Weeks 17 and 21 <sup>[21]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Pruritus NRS was an assessment tool used to report the intensity of subject's pruritus (itch) during a daily recall period. Subjects were asked to rate their worst itch on a 0 ("No itch") to 10 ("Worst itch imaginable") NRS by answering the following question: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?". Higher scores indicated greater severity. Percentage of subjects with change of  $\geq 4$  point in pruritus NRS scale from baseline at Weeks 17 and 21 are reported in this endpoint. Analysis was performed on mITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

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

End point timeframe:

Baseline, Weeks 17 and 21

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was not planned to be collected and analysed for 'healthy subjects' arm.

| End point values              | Subjects With AD: Dupilumab |  |  |  |
|-------------------------------|-----------------------------|--|--|--|
| Subject group type            | Reporting group             |  |  |  |
| Number of subjects analysed   | 7                           |  |  |  |
| Units: percentage of subjects |                             |  |  |  |
| number (not applicable)       |                             |  |  |  |
| Week 17                       | 0                           |  |  |  |
| Week 21                       | 0                           |  |  |  |

## Statistical analyses



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

For Dupilumab group subjects: from first dose (i.e., Day 1) of IMP administration up to end of study visit (i.e., up to Week 21). For healthy participants: from Baseline up to end of study for healthy subjects group (i.e., at Day 8)

Adverse event reporting additional description:

Analysis was performed on safety population.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Healthy Subjects |
|-----------------------|------------------|

Reporting group description:

Healthy subjects with site, age, gender, race, location of targeted lesional and non-lesional skin area matched to selected AD subjects, received no treatment, and were considered as a control group.

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Subjects With AD: Dupilumab |
|-----------------------|-----------------------------|

Reporting group description:

Subjects with moderate to severe AD received dupilumab 600 mg SC injection on Day 1, followed by dupilumab 300 mg SC injection Q2W from Week 3 to Week 15.

| Serious adverse events                            | Healthy Subjects | Subjects With AD: Dupilumab |  |
|---------------------------------------------------|------------------|-----------------------------|--|
| Total subjects affected by serious adverse events |                  |                             |  |
| subjects affected / exposed                       | 0 / 13 (0.00%)   | 1 / 31 (3.23%)              |  |
| number of deaths (all causes)                     | 0                | 0                           |  |
| number of deaths resulting from adverse events    |                  |                             |  |
| Respiratory, thoracic and mediastinal disorders   |                  |                             |  |
| Pulmonary Embolism                                |                  |                             |  |
| subjects affected / exposed                       | 0 / 13 (0.00%)   | 1 / 31 (3.23%)              |  |
| occurrences causally related to treatment / all   | 0 / 0            | 0 / 1                       |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0                       |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events                            | Healthy Subjects | Subjects With AD: Dupilumab |  |
|-------------------------------------------------------|------------------|-----------------------------|--|
| Total subjects affected by non-serious adverse events |                  |                             |  |
| subjects affected / exposed                           | 0 / 13 (0.00%)   | 24 / 31 (77.42%)            |  |

|                                                                                                                                                                                                                                        |                                                                           |                                                                            |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------|--|
| Injury, poisoning and procedural complications<br>Accidental Overdose<br>subjects affected / exposed<br>occurrences (all)                                                                                                              | 0 / 13 (0.00%)<br>0                                                       | 1 / 31 (3.23%)<br>1                                                        |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypoaesthesia<br>subjects affected / exposed<br>occurrences (all) | 0 / 13 (0.00%)<br>0<br><br>0 / 13 (0.00%)<br>0<br><br>0 / 13 (0.00%)<br>0 | 1 / 31 (3.23%)<br>1<br><br>7 / 31 (22.58%)<br>9<br><br>1 / 31 (3.23%)<br>2 |  |
| General disorders and administration site conditions<br>Injection Site Mass<br>subjects affected / exposed<br>occurrences (all)<br><br>Injection Site Swelling<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 13 (0.00%)<br>0<br><br>0 / 13 (0.00%)<br>0                            | 1 / 31 (3.23%)<br>1<br><br>1 / 31 (3.23%)<br>1                             |  |
| Eye disorders<br>Conjunctivitis Allergic<br>subjects affected / exposed<br>occurrences (all)<br><br>Eye Pruritus<br>subjects affected / exposed<br>occurrences (all)                                                                   | 0 / 13 (0.00%)<br>0<br><br>0 / 13 (0.00%)<br>0                            | 1 / 31 (3.23%)<br>1<br><br>2 / 31 (6.45%)<br>2                             |  |
| Gastrointestinal disorders<br>Abdominal Pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Abdominal Pain Upper<br>subjects affected / exposed<br>occurrences (all)<br><br>Food Poisoning                                 | 0 / 13 (0.00%)<br>0<br><br>0 / 13 (0.00%)<br>0                            | 1 / 31 (3.23%)<br>1<br><br>1 / 31 (3.23%)<br>1                             |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Nausea                                          |                |                |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 2 / 31 (6.45%) |  |
| occurrences (all)                               | 0              | 3              |  |
| Toothache                                       |                |                |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Skin and subcutaneous tissue disorders          |                |                |  |
| Alopecia                                        |                |                |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Dermatitis Atopic                               |                |                |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 3 / 31 (9.68%) |  |
| occurrences (all)                               | 0              | 3              |  |
| Eczema                                          |                |                |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Neurodermatitis                                 |                |                |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Pain Of Skin                                    |                |                |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Pruritus                                        |                |                |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Psoriasis                                       |                |                |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Rash                                            |                |                |  |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Musculoskeletal and connective tissue disorders |                |                |  |

|                             |                |                |  |
|-----------------------------|----------------|----------------|--|
| Back Pain                   |                |                |  |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)           | 0              | 1              |  |
| Bursitis                    |                |                |  |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)           | 0              | 1              |  |
| Infections and infestations |                |                |  |
| Asymptomatic Covid-19       |                |                |  |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)           | 0              | 1              |  |
| Bronchitis                  |                |                |  |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)           | 0              | 1              |  |
| Conjunctivitis              |                |                |  |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 31 (6.45%) |  |
| occurrences (all)           | 0              | 2              |  |
| Cystitis                    |                |                |  |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)           | 0              | 1              |  |
| Impetigo                    |                |                |  |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)           | 0              | 1              |  |
| Nasopharyngitis             |                |                |  |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)           | 0              | 1              |  |
| Oral Herpes                 |                |                |  |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)           | 0              | 1              |  |
| Rhinitis                    |                |                |  |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)           | 0              | 1              |  |
| Sinusitis                   |                |                |  |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)           | 0              | 1              |  |
| Suspected Covid-19          |                |                |  |

|                             |                |                |  |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)           | 0              | 1              |  |
| Tinea Infection             |                |                |  |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)           | 0              | 1              |  |
| Urinary Tract Infection     |                |                |  |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)           | 0              | 1              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported