



## Clinical trial results:

**A multicenter, randomized, double-blind, placebo-controlled, phase 2, 16-week treatment study with a 16 week follow-up period to assess the efficacy and safety of Dupilumab (anti-IL4Ra) in adult patients with chronic spontaneous urticaria despite H1-antihistamine treatment.**

### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2017-004458-41  |
| Trial protocol           | DE              |
| Global end of trial date | 01 October 2021 |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 19 May 2023  |
| First version publication date | 19 May 2023  |

### Trial information

#### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | D-001-01 |
|-----------------------|----------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03749135 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Charité - Universitätsmedizin Berlin   |
| Sponsor organisation address | Charitéplatz 1, Berlin, Germany, 10117   |
| Public contact               | Prof. Marcus Maurer , Charité - Universitätsmedizin Berlin,<br>Institute of Allergology,<br>Hindenburgdamm 30,<br>12203 Berlin, marcus.maurer@charite.de |
| Scientific contact           | Prof. Marcus Maurer , Charité - Universitätsmedizin Berlin,<br>Institute of Allergology,<br>Hindenburgdamm 30,<br>12203 Berlin, marcus.maurer@charite.de |

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                       | 28 February 2022 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 07 July 2021     |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 01 October 2021  |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is the evaluation of Dupilumab (600 mg loading dose and subsequent 300 mg regular long term dose) being superior to placebo regarding be the difference in the change in urticaria activity score 7 (UAS7) from baseline to week 16 in adult patients with moderate to severe CSU and with H1-antihistamine resistant alone or in combination with LTRA.

Protection of trial subjects:

Safety assessment included adverse event reporting and routine clinical and laboratory assessments. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy:

Dupilumab is a human monoclonal antibody that inhibits IL-4 and IL-13 signaling by binding to the IL-4Rα. Dupilumab was previously found to be effective in atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis, prurigo nodularis, and eosinophilic esophagitis. Considering that CSU and atopic diseases share many common features (e.g. key pathogenic role of mast cells and IgE, itch is a dominant symptom, Th2 dominance), it was reasonable to expect that Dupilumab is beneficial in CSU.

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 04 October 2018 |
| 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 | Germany: 73 |
| Worldwide total number of subjects   | 73          |
| EEA total number of subjects         | 73          |

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)      | 66 |
| From 65 to 84 years       | 7  |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 6 study centers in Germany, between 04/10/2018 and 07/07/2021.

### Pre-assignment

Screening details:

92 patients were assessed for eligibility, 73 patients were randomised. All patients included in this study will be subjected at the screening visit, V0 (day -14) to physical examination, vital signs & weight assessment, electrocardiogram, serum pregnancy test and basic laboratory control (hematology panel, clinical chemistry panel, urinalysis).

### Period 1

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

### Arms

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

Arm description:

Patients received Dupilumab 600 mg (2 injections) initially, followed by Dupilumab 300 mg (1 injection) administered subcutaneously every two weeks.

|  |  |
|--|--|
| Arm type                               | Experimental                                 |
| Investigational medicinal product name | Dupilumab                                    |
| Investigational medicinal product code | SAR231893                                    |
| Other name                             | Dupixent                                     |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Dupilumab 600 mg s.c. loading dose followed by 300 mg every two weeks

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

Arm description:

patients received two injections placebo (2 injections of 2 ml) on randomization visit and afterwards one injection every two weeks (injections of 2 mL).

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

Dosage and administration details:

Placebo s.c. loading dose followed by Placebo injection s.c. biweekly for 14 weeks

| <b>Number of subjects in period 1</b> | Dupilumab | Placebo |
|---------------------------------------|-----------|---------|
| Started                               | 48        | 25      |
| Completed                             | 36        | 22      |
| Not completed                         | 12        | 3       |
| Consent withdrawn by subject          | 7         | 2       |
| Adverse event, non-fatal              | 1         | -       |
| Pregnancy                             | -         | 1       |
| Lost to follow-up                     | 4         | -       |

## Baseline characteristics

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Dupilumab |
|-----------------------|-----------|

Reporting group description:

Patients received Dupilumab 600 mg (2 injections) initially, followed by Dupilumab 300 mg (1 injection) administered subcutaneously every two weeks.

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

patients received two injections placebo (2 injections of 2 ml) on randomization visit and afterwards one injection every two weeks (injections of 2 mL).

| Reporting group values                             | Dupilumab | Placebo | Total |
|--|-----------|---------|-------|
| Number of subjects                                 | 48        | 25      | 73    |
| Age categorical                                    |           |         |       |
| Units: Subjects                                    |           |         |       |
| In utero   | 0         | 0       | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0         | 0       | 0     |
| Newborns (0-27 days)                               | 0         | 0       | 0     |
| Infants and toddlers (28 days-23 months)           | 0         | 0       | 0     |
| Children (2-11 years)                              | 0         | 0       | 0     |
| Adolescents (12-17 years)                          | 0         | 0       | 0     |
| Adults (18-64 years)                               | 46        | 20      | 66    |
| From 65-84 years                                   | 2         | 5       | 7     |
| 85 years and over                                  | 0         | 0       | 0     |
| Age continuous                                     |           |         |       |
| Units: years                                       |           |         |       |
| arithmetic mean                                    | 40        | 45.3    |       |
| standard deviation                                 | ± 14.5    | ± 6.3   | -     |
| Gender categorical                                 |           |         |       |
| Units: Subjects                                    |           |         |       |
| Female   | 28        | 16      | 44    |
| Male   | 20        | 9       | 29    |
| Skin type (Fitzpatrick)                            |           |         |       |
| Units: Subjects                                    |           |         |       |
| Typ I  | 1         | 1       | 2     |
| Typ II   | 36        | 17      | 53    |
| Typ III  | 10        | 5       | 15    |
| Typ IV   | 1         | 2       | 3     |
| IgE subgroups                                      |           |         |       |
| Units: Subjects                                    |           |         |       |
| <100 kU/l  | 21        | 15      | 36    |
| ≥100 kU/l  | 27        | 10      | 37    |
| UAS7 subgroups                                     |           |         |       |
| Units: Subjects                                    |           |         |       |
| UAS7 < 28  | 27        | 10      | 37    |
| UAS7 ≥ 28  | 21        | 15      | 36    |
| CSU duration                                       |           |         |       |

|  |         |        |    |
|--|---------|--------|----|
| Units: Subjects  |         |        |    |
| >10 years  | 16      | 10     | 26 |
| 2-10 years   | 27      | 9      | 36 |
| <2 years   | 5       | 6      | 11 |
| Total IgE  |         |        |    |
| Units: IU/ml   |         |        |    |
| arithmetic mean  | 199.2   | 90.6   |    |
| standard deviation   | ± 223.8 | ± 70.6 | -  |
| UAS7 score   |         |        |    |
| urticaria activity score 7, UAS7, also used clinically, is the sum of UAS scores over 7 consecutive days.  |         |        |    |
| Units: Score   |         |        |    |
| arithmetic mean  | 25.9    | 26.8   |    |
| standard deviation   | ± 7.9   | ± 8.9  | -  |
| HSS7 score   |         |        |    |
| The weekly Hives Severity Score  |         |        |    |
| Units: Score   |         |        |    |
| arithmetic mean  | 12.6    | 13.3   |    |
| standard deviation   | ± 5.2   | ± 5.1  | -  |
| ISS7 score   |         |        |    |
| Weekly Itch Severity Score (ISS7)  |         |        |    |
| Units: Score   |         |        |    |
| arithmetic mean  | 13.4    | 13.5   |    |
| standard deviation   | ± 4.2   | ± 4.7  | -  |
| AAS7   |         |        |    |
| Weekly Angioedema Activity Score (AAS7)  |         |        |    |
| Units: Score   |         |        |    |
| arithmetic mean  | 33.5    | 32.3   |    |
| standard deviation   | ± 22.1  | ± 19.0 | -  |
| UCT  |         |        |    |
| Urticaria Control Test   |         |        |    |
| Units: Score   |         |        |    |
| arithmetic mean  | 5.3     | 4.9    |    |
| standard deviation   | ± 2.9   | ± 3.2  | -  |
| DLQI   |         |        |    |
| The Dermatology life Quality Index (DLQI) is a ten-question questionnaire used to measure the impact of skin disease on the quality of life of an affected person. It is designed for people aged 16 years and above |         |        |    |
| Units: score   |         |        |    |
| arithmetic mean  | 11.4    | 12.4   |    |
| standard deviation   | ± 6.5   | ± 7.6  | -  |
| CU-Q2oL  |         |        |    |
| Chronic Urticaria Quality of Life questionnaire (CU-Q2oL)  |         |        |    |
| Units: Score   |         |        |    |
| arithmetic mean  | 44.1    | 45.1   |    |
| standard deviation   | ± 17.7  | ± 16.5 | -  |

## End points

### End points reporting groups

|   |           |
|---|-----------|
| Reporting group title   | Dupilumab |
| Reporting group description:<br>Patients received Dupilumab 600 mg (2 injections) initially, followed by Dupilumab 300 mg (1 injection) administered subcutaneously every two weeks.      |           |
| Reporting group title   | Placebo   |
| Reporting group description:<br>patients received two injections placebo (2 injections of 2 ml) on randomization visit and afterwards one injection every two weeks (injections of 2 mL). |           |

### Primary: change in urticaria activity score 7 (UAS7)

|   |   |
|---|---|
| End point title   | change in urticaria activity score 7 (UAS7) |
| End point description:<br>The primary analysis of the primary endpoint (change of the UAS7 from baseline to week 16, with lower values indicating an improvement) was performed on the ITT-population comparing treatments (Dupilumab vs. placebo) in an analysis of covariance (ANCOVA) model with the fixed factors treatment and study sites (sites with 10 or less patients were pooled together for this analysis), and with baseline UAS7 score (visit 1) as a covariate. The adjusted (least square, LS) group means for each treatment group was presented with their respective 95% confidence interval and an exploratory p-value for the group difference.<br>The primary endpoint was tested for treatment differences using the non-parametric Wilcoxon Rank Sum Test and with an (unadjusted) analysis of variance (ANOVA) model as sensitivity analyses. In addition, the primary analysis was repeated for the per-protocol-population and for the full analysis set (FAS). |   |
| End point type  | Primary                                     |
| End point timeframe:<br>from baseline to week 16  |   |

| End point values                      | Dupilumab          | Placebo            |  |  |
|---------------------------------------|--------------------|--------------------|--|--|
| Subject group type                    | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed           | 36                 | 22                 |  |  |
| Units: score                          |                    |                    |  |  |
| median (inter-quartile range (Q1-Q3)) | 16.0 (8.5 to 25.0) | 15.0 (1.0 to 28.0) |  |  |

|                            |   |
|----------------------------|---|
| Attachments (see zip file) | results_secondary-endpoints/primary and secondary |
|----------------------------|---|

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title  | change in UAS7 from baseline to week 16 |
| Statistical analysis description:<br>The secondary analysis of the primary outcome was performed for treatment differences using the non-parametric Wilcoxon Rank Sum Test (Table 5-6) and with an (unadjusted) analysis of variance (ANOVA) model (Table 5-7) as sensitivity analyses. |   |
| Comparison groups   | Dupilumab v Placebo                     |



|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 58                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[1]</sup> |
| P-value                                 | = 0.307                    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | Mean difference (net)      |
| Point estimate                          | -3.1                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -9.2                       |
| upper limit                             | 3                          |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 3.04                       |

Notes:

[1] - The primary analysis of the primary endpoint (change of the UAS7 from baseline to week 16, with lower values indicating an improvement) was performed on the ITT-population comparing treatments (Dupilumab vs. placebo) in an analysis of covariance (ANCOVA) model with the fixed factors treatment and study sites (sites with 10 or less patients were pooled together for this analysis), and with baseline UAS7 score (visit 1) as a covariate. The adjusted (least square, LS) group means for each treatment

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

overall time

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

### Dictionary used

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

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

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Dupilumab |
|-----------------------|-----------|

Reporting group description: -

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events                                  | Dupilumab      | Placebo        |  |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events       |                |                |  |
| subjects affected / exposed                             | 2 / 48 (4.17%) | 1 / 25 (4.00%) |  |
| number of deaths (all causes)                           | 0              | 0              |  |
| number of deaths resulting from adverse events          | 0              | 0              |  |
| General disorders and administration site conditions    |                |                |  |
| Cellulitis right upper arm at site of reaction, hospit. |                |                |  |
| subjects affected / exposed                             | 1 / 48 (2.08%) | 0 / 25 (0.00%) |  |
| occurrences causally related to treatment / all         | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all              | 0 / 0          | 0 / 0          |  |
| Skin and subcutaneous tissue disorders                  |                |                |  |
| severe urticaria with hospitalisation                   |                |                |  |
| subjects affected / exposed                             | 0 / 48 (0.00%) | 1 / 25 (4.00%) |  |
| occurrences causally related to treatment / all         | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all              | 0 / 0          | 0 / 0          |  |
| Infections and infestations                             |                |                |  |
| Appendicitis  |                |                |  |
| subjects affected / exposed                             | 1 / 48 (2.08%) | 0 / 25 (0.00%) |  |
| occurrences causally related to treatment / all         | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all              | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | Dupilumab        | Placebo          |  |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 38 / 48 (79.17%) | 20 / 25 (80.00%) |  |
| Nervous system disorders                              |                  |                  |  |
| Headache  |                  |                  |  |
| subjects affected / exposed                           | 6 / 48 (12.50%)  | 3 / 25 (12.00%)  |  |
| occurrences (all)                                     | 10               | 5                |  |
| General disorders and administration site conditions  |                  |                  |  |
| Reaction at injection side/local site reaction        |                  |                  |  |
| subjects affected / exposed                           | 3 / 48 (6.25%)   | 1 / 25 (4.00%)   |  |
| occurrences (all)                                     | 12               | 1                |  |
| Fever   |                  |                  |  |
| subjects affected / exposed                           | 2 / 48 (4.17%)   | 0 / 25 (0.00%)   |  |
| occurrences (all)                                     | 3                | 0                |  |
| Nausea and Vomitting                                  |                  |                  |  |
| subjects affected / exposed                           | 4 / 48 (8.33%)   | 1 / 25 (4.00%)   |  |
| occurrences (all)                                     | 7                | 2                |  |
| Fatigue   |                  |                  |  |
| subjects affected / exposed                           | 1 / 48 (2.08%)   | 3 / 25 (12.00%)  |  |
| occurrences (all)                                     | 1                | 3                |  |
| Immune system disorders                               |                  |                  |  |
| Insect sting with swelling/hurting                    |                  |                  |  |
| subjects affected / exposed                           | 6 / 48 (12.50%)  | 1 / 25 (4.00%)   |  |
| occurrences (all)                                     | 6                | 1                |  |
| Eye disorders   |                  |                  |  |
| Dry eyes  |                  |                  |  |
| subjects affected / exposed                           | 3 / 48 (6.25%)   | 1 / 25 (4.00%)   |  |
| occurrences (all)                                     | 3                | 1                |  |
| Gastrointestinal disorders                            |                  |                  |  |
| Gastritis, Stomach pain                               |                  |                  |  |
| subjects affected / exposed                           | 2 / 48 (4.17%)   | 2 / 25 (8.00%)   |  |
| occurrences (all)                                     | 2                | 3                |  |
| Diarrhea, Adominal pain                               |                  |                  |  |

|  |   |   |  |
|--|---|---|--|
| subjects affected / exposed<br>occurrences (all)   | 5 / 48 (10.42%)<br>5  | 5 / 25 (20.00%)<br>5  |  |
| Respiratory, thoracic and mediastinal disorders<br>Sore throat<br>subjects affected / exposed<br>occurrences (all)   | 0 / 48 (0.00%)<br>0   | 1 / 25 (4.00%)<br>3   |  |
| Skin and subcutaneous tissue disorders<br>Scabies<br>subjects affected / exposed<br>occurrences (all)<br><br>Urticaria exacerbation/ worsening CSU<br>subjects affected / exposed<br>occurrences (all)   | 0 / 48 (0.00%)<br>0<br><br>4 / 48 (8.33%)<br>22                               | 1 / 25 (4.00%)<br>2<br><br>3 / 25 (12.00%)<br>3                               |  |
| Psychiatric disorders<br>Restless/ unrest<br>subjects affected / exposed<br>occurrences (all)  | 0 / 48 (0.00%)<br>0   | 2 / 25 (8.00%)<br>2   |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all)   | 2 / 48 (4.17%)<br>3   | 2 / 25 (8.00%)<br>2   |  |
| Infections and infestations<br>Upper respiratory tract infections<br>subjects affected / exposed<br>occurrences (all)<br><br>Herpes labialis reactivation<br>subjects affected / exposed<br>occurrences (all)<br><br>Urinary tract<br>Infection/Cystitis/Hämaturie<br>subjects affected / exposed<br>occurrences (all) | 14 / 48 (29.17%)<br>18<br><br>2 / 48 (4.17%)<br>3<br><br>5 / 48 (10.42%)<br>5 | 10 / 25 (40.00%)<br>19<br><br>1 / 25 (4.00%)<br>1<br><br>5 / 25 (20.00%)<br>6 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 08 May 2019      | new protocol version 2.0: change of exclusion criteria, Assessment schedule and of adress of laboratory for BHRA analysis   |
| 18 December 2019 | new protocol version 3.0: change then umber of participating centers: "aproximately 6 study centers" replaces "3 study centers", - study duration prolonged to "Last subject last visit": Q2 2021   |
| 13 May 2020      | new protocol version 4.0: Changes related to COVID-19: <ul style="list-style-type: none"><li>- Training of of study subjects in selfapplication of IMP</li><li>- Possibility for self-application of IMP at home in combination with telephone based visits</li><li>- Adjustment of table of assessments</li><li>- Adjustment of rules for rescreening of patients adjustment of table of assessments</li><li>- Adjustments of rules for rescreening of patient</li></ul> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported