



Clinical trial results:

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

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2017-001262-25 |
| Trial protocol | DE |
| Global end of trial date | 28 February 2023 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 31 October 2024 |
| First version publication date | 17 March 2024 |
| Version creation reason | <ul style="list-style-type: none">• New data added to full data set update primary and secondary endpoints |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | D-001-02 |
|-----------------------|----------|

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. Dr. Marcus Maurer, Charité - Universitätsmedizin Berlin; Campus Benjamin Franklin Institute for Allergology, 0049 030450518043, marcus.maurer@charite.de |
| Scientific contact | Prof. Dr. Marcus Maurer, Charité - Universitätsmedizin Berlin; Campus Benjamin Franklin Institute for Allergology, 0049 030450518043, 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 | 09 November 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 February 2023 |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 February 2023 |
| 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 as loading dose and/or Dupilumab 300 mg and/or placebo in patients with ChIU regarding the difference in the change of ChIUAS7 (Itch 7) from baseline to week 16 in adult patients with H1-antihistamine resistant ChIU.

Urticaria activity score over 7 days (UAS7) [Time Frame: Change from 7 days prior to baseline (V1) to 7 days prior to week 16 (V9)]

0-42 Points total range over 7 days, higher values equal more disease activity

Protection of trial subjects:

The conduct of this study met all legal and regulatory requirements and in accordance with ethical principles of the Declaration of Helsinki.

Background therapy:

Dupilumab is a novel monoclonal antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling and was previously found to be effective in atopic dermatitis and asthma. Considering that CSU and atopic diseases share many common features (e.g. key pathogenic role of mast cells and immunoglobulin E (IgE), itch is a dominant symptom, Th2 dominance), it is reasonable to expect that Dupilumab is beneficial in CSU.

These results suggest that Dupilumab may provide an effective treatment option for patients with insufficient treatment responses to H1-antihistamines exhibiting wheal and flare type skin reactions.

The gold standard treatment of CSU consists of administration of antihistamines. In more than 50% of the patients, symptoms persist with standard dosing of antihistamines. In antihistamine-refractory patients with chronic spontaneous urticaria, the currently only licensed treatment is omalizumab, a monoclonal anti-IgE antibody. In 2014, omalizumab has been licensed for add-on therapy in CSU patients who still have symptoms despite standard-dosed antihistamine treatment. There is, however, still a great medical need for additional treatment options, as 20-40% of patients are still without effective therapy. These patients have no other licensed treatment option and can only be treated off-label with therapeutics with several known safety risks such as Cyclosporine A.

Dupilumab has excellent potential to provide symptom control in CSU. This study will provide additional valuable insights into the therapeutic potential of Dupilumab in improving quality of life in these patients, in addition to managing CSU symptoms.

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 12 November 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: 48 |
| Worldwide total number of subjects | 48 |
| EEA total number of subjects | 48 |

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) | 47 |
| From 65 to 84 years | 1 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 6 study centers in Germany, between 28/10/2018 and 07/07/2021.

Pre-assignment

Screening details:

A total of 61 subjects entered the screening period (up to 2 weeks). The remaining 48 subjects were randomized.

Period 1

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

Arms

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

| | |
|------------------|-------|
| Arm title | Verum |
|------------------|-------|

Arm description: -

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Dupilumab (anti-IL4Ra) |
| 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 as loading dose and Dupilumab 300 mg

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

Dosage and administration details:

Dupilumab 600 mg as loading dose and Placebo

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description: -

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

Dosage and administration details:

Dupilumab 600 mg as loading dose and Placebo

| Number of subjects in period 1 | Verum | Placebo |
|---------------------------------------|-------|---------|
| Started | 30 | 18 |
| Completed | 22 | 10 |
| Not completed | 8 | 8 |
| Consent withdrawn by subject | 7 | 6 |
| Lost to follow-up | 1 | 1 |
| Protocol deviation | - | 1 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---------|
| Reporting group title | Verum |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

| Reporting group values | Verum | Placebo | Total |
|---|---------|---------|-------|
| Number of subjects | 30 | 18 | 48 |
| 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) | 30 | 17 | 47 |
| From 65-84 years | 0 | 1 | 1 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 34.33 | 31.61 | |
| standard deviation | ± 11.79 | ± 13.09 | - |
| Gender categorical Units: Subjects | | | |
| Female | 12 | 5 | 17 |
| Male | 18 | 13 | 31 |

End points

End points reporting groups

| | |
|--------------------------------|---------|
| Reporting group title | Verum |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

Primary: change in CholUAS7 (Itch 7)

| | |
|--------------------------|-----------------------------|
| End point title | change in CholUAS7 (Itch 7) |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| from baseline to week 16 | |

| End point values | Verum | Placebo | | |
|---|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 10 | | |
| Units: score | | | | |
| arithmetic mean (confidence interval 95%) | 0.574 (-0.003 to 1.150) | 0.205 (-0.544 to 0.954) | | |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | secondary endpoints-resulzs/secondary endpoints_CHED.pdf |
|-----------------------------------|--|

Statistical analyses

| | |
|--|----------------------------|
| Statistical analysis title | Mean Difference CholUAS7 |
| Statistical analysis description: | |
| The primary endpoint will be tested for treatment differences using the non-parametric Wilcoxon Rank Sum Test and with an (unadjusted) analysis of variance (ANOVA) model as sensitivity analyses. | |
| Comparison groups | Verum v Placebo |
| Number of subjects included in analysis | 32 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | = 0.442 |
| Method | ANOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.368 |

| | |
|----------------------|--------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.324 |
| upper limit | 0.587 |
| Variability estimate | Standard deviation |

Notes:

[1] - The primary outcome was defined as the difference in the change in cholinergic urticaria activity score 7 (CholUAS7) from baseline to week 16 (with negative values indicating an improvement). Treatment with Dupilumab did not show a relevant difference compared to placebo.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

overall trial

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 20 |
|--------------------|----|

Reporting groups

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

Reporting group description: -

| | |
|-----------------------|-------|
| Reporting group title | Verum |
|-----------------------|-------|

Reporting group description: -

| Serious adverse events | Placebo | Verum | |
|---|----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 3 / 30 (10.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Fracture | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| surgical removal ovarian cyst | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| surgical Intervention, Metall explantation | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Nail bed infection | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 30 (3.33%) | |
| 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: 5 %

| Non-serious adverse events | Placebo | Verum | |
|---|--|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 15 / 18 (83.33%) | 30 / 30 (100.00%) | |
| Investigations | | | |
| TSH increased | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 2 | |
| Alanine transaminase (ALT) increased | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| ph value in Vagina changed | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Surgical and medical procedures | | | |
| Tooth extraction | Additional description: Dental and gingival therapeutic procedures | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 30 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 6 / 18 (33.33%) | 13 / 30 (43.33%) | |
| occurrences (all) | 18 | 18 | |
| General disorders and administration site conditions | | | |
| Injection site reaction | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 1 / 30 (3.33%) | |
| occurrences (all) | 2 | 5 | |
| Urticarias worsening (Disease progression) | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 2 / 30 (6.67%) | |
| occurrences (all) | 1 | 2 | |
| Vaccination related complications | Additional description: CoV-19 Vaccination - Fever/arm pain/headache | | |

| | | | |
|--|--|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 2 / 30 (6.67%) 5 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 2 | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 2 / 30 (6.67%) | |
| occurrences (all) | 1 | 2 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 2 / 30 (6.67%) | |
| occurrences (all) | 8 | 3 | |
| Gastroesophageal reflux | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Pain of skin | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 3 | |
| Exanthema/ Eczema | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 2 | |
| Erythema | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 6 | |
| Sweat gland disorder | Additional description: Apocrine and eccrine gland disorders/ sweat feet | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 30 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 4 | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 2 / 30 (6.67%) | |
| occurrences (all) | 1 | 2 | |
| Pain in extremity | | | |

| | | | |
|--|---|---------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 18 (11.11%) 2 | 0 / 30 (0.00%) 0 | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 4 / 30 (13.33%) | |
| occurrences (all) | 1 | 4 | |
| COVID-19 infection | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | 2 / 30 (6.67%) | |
| occurrences (all) | 3 | 2 | |
| Vaginal infection | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 30 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 8 / 18 (44.44%) | 11 / 30 (36.67%) | |
| occurrences (all) | 13 | 16 | |
| infections- other | Additional description: gastrointestinal / conjunctivitis/ subcutaneous abscess/ Helminthic infections | | |
| subjects affected / exposed | 2 / 18 (11.11%) | 2 / 30 (6.67%) | |
| occurrences (all) | 2 | 2 | |
| Herpes simplex reactivation | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 08 April 2018 | update Protocol Version 2.0 - changed wording or added some Exclusion criteria; -replaces " Treatment with omalizumab within 3 months prior to screening"/ added CholUSI as secondary objective / · Change of address of laboratory for BHRA analysis / · Safety supervision prolonged to 120 min for the first 3 visits with IMP administration/ · Prohibit treatment table concretized ... |
| 24 March 2020 | update Protocol Version 3.0 - Changes related to COVID-19:· Training of study subjects in self-application of IMP · Possibility for self-application of IMP at home in combination with telephone based visits · Adjustment of table of assessments · Adjustment of rules for rescreening of patients |
| 29 May 2020 | update Protocol Version 3.1 : Early study termination: added the following points -if the regular study specific risk assessment evolves in a negative way and it is not possible to adjust the insurance rate to the new risk assessment -if the approval of the Competent Authority or the Ethics Committee is withdrawn |
| 16 December 2020 | update Protocol Version 4.0: · Timelines were updated/ · number of centers was changed to approx. 8 centers/ Clinical chemistry was corrected/ Urinalysis was elaborated / · "short physical exam" was replaced by "symptom focused physical examination" |
| 06 April 2021 | update Protocol Version 5.0: Changes related to COVID-19: In/Exclusion criteria: Patients with active confirmed SARS -CoV2 infection are to be excluded - Before each visit, all patients to be tested negative for SARS-CoV-2 by a rapid test result not older than 24h. Exceptions: fully vaccinated or recently recovered up to 6 months after infection/ remote visits due to pandemic situation · New Chapter 12: regarding mitigation measures due to COVID-19 Pandemic including: Patient visits by phone call, self-application of IMP, central laboratory analyses, central ECG reading, monitoring activities, reduction of recruitment/temporary halt of recruitment |
| 03 September 2021 | update Protocol Version 6.0: Study duration extension |
| 21 December 2021 | update Protocol Version 7.0 -Assessment schedule changed: Urinalysis added |
| 15 August 2022 | update Protocol Version 8.0 : Recruitment proved to be more difficult than expected and was stopped early after 3.7 years with a total final patient number N (total) = 48 included into the trial. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported