



## 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"><li>• New data added to full data set update primary and secondary endpoints</li></ul>

### Trial information

#### Trial identification

Sponsor protocol code	D-001-02
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#### 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:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	Germany: 48
Worldwide total number of subjects	48
EEA total number of subjects	48

Notes:

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**Subjects enrolled per age group**

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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
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<b>Arm title</b>	Verum
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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

<b>Arm title</b>	Placebo
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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

<b>Number of subjects in period 1</b>	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)		

<b>Attachments (see zip file)</b>	secondary endpoints-resulzs/secondary endpoints_CHED.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	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 <sup>[1]</sup>
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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	20
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### Reporting groups

Reporting group title	Placebo
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Reporting group description: -

Reporting group title	Verum
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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 %

<b>Non-serious adverse events</b>	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:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported