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, Institute of Allergology, Hindenburgdamm 30, 12203 Berlin, marcus.maurer@charite.de
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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
Arm title	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

Arm title	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

Number of subjects in period 1	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 abov			
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:	
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).	

Primary: change in urticaria activity score 7 (UAS7)

End point title	change in urticaria activity score 7 (UAS7)
End point description:	
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. 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:	
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 secundary

Statistical analyses

Statistical analysis title	change in UAS7 from baseline to week 16
Statistical analysis description:	
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[1]
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			
servere 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 %

Non-serious adverse events	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	5 / 48 (10.42%)	5 / 25 (20.00%)	
occurrences (all)	5	5	
Respiratory, thoracic and mediastinal disorders			
Sore throat			
subjects affected / exposed	0 / 48 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			
Scabies			
subjects affected / exposed	0 / 48 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	2	
Urticaria excerbation/ worsening CSU			
subjects affected / exposed	4 / 48 (8.33%)	3 / 25 (12.00%)	
occurrences (all)	22	3	
Psychiatric disorders			
Restless/ unrest			
subjects affected / exposed	0 / 48 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 48 (4.17%)	2 / 25 (8.00%)	
occurrences (all)	3	2	
Infections and infestations			
Upper respiratory tract infections			
subjects affected / exposed	14 / 48 (29.17%)	10 / 25 (40.00%)	
occurrences (all)	18	19	
Herpes labialis reactivation			
subjects affected / exposed	2 / 48 (4.17%)	1 / 25 (4.00%)	
occurrences (all)	3	1	
Urinary tract Infection/Cystitis/Hämaturie			
subjects affected / exposed	5 / 48 (10.42%)	5 / 25 (20.00%)	
occurrences (all)	5	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: - Training of of study subjects in selfapplication 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 adjustment of table of assessments - Adjustments of rules for rescreening of patient

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported