Clinical trial results:
A multi-center, randomized, double blind, dose escalating phase III study on the efficacy, safety and long term outcome of continuous vs. on demand treatment of chronic spontaneous urticaria with rupatadine

Summary

EudraCT number	2013-003542-17
Trial protocol	DE ES
Global end of trial date	20 November 2020

Results information

Result version number	v1 (current)
This version publication date	25 May 2023
First version publication date	25 May 2023

Trial information

Trial identification

Sponsor protocol code	CU-LATER

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Charité- Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Allergie-Centrum-Charité Department, Charité Universitätsmedizin Berlin, 49 30450 518043, marcus.maurer@charite.de
Scientific contact	Allergie-Centrum-Charité Department, Charité Universitätsmedizin Berlin, 49 30450 518043, 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 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 November 2020
Global end of trial reached?	Yes
Global end of trial date	20 November 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare CSU disease activity at the end of the follow up phase between patients that had been treated daily continuously vs. on-demand in the treatment phase.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2014
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	Spain: 16
Country: Number of subjects enrolled	Germany: 47
Worldwide total number of subjects	63
EEA total number of subjects	63

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)	57
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 5 study centers in Germany 4 in Spain, first patient in was on 10/02/2015.

Pre-assignment

Screening details:

A total of 77 number subjects entered the screening period (up to 2 weeks), of whom 14 patients excluded before randomization. The remaining number of 63 subjects were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo-Group

Arm description:

Patients received on demand tablet of rupatadine 10 mg x 14 ± 2 days (intake only if needed). The following ingredients are used to manufacture the placebo: pregelatinised maize-starch, microcrystalline cellulose, red iron oxide (E-172), yellow iron oxide (E-172), lactose monohydrate, magnesium stearate. The proportions of these ingredients are similar to those used in the rupatadine active product.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received two weeks one tablets of placebo daily x 14 ± 2 days (1-0-0) from Visit 3 to Visit 4, than up dosing to the end of treatment phase --> Group A2 received two tablets of placebo daily (morning and evening intake, 1-0-1) / one on demand tablet of rupatadine 10 mg x 14 ± 2 days (intake only if needed).

Arm title	Rupatadine 10-20mg daily continuous

Arm description:

Patients received two weeks one tablets of rupatadine (10 mg) daily x 14 ± 2 days (1-0-0) from Visit 2 to Visit 3, than up dosing to 20 mg twice daily (1-0-1) from Visit 3 to Visit 4.

Arm type	Experimental
Investigational medicinal product name	Rupadatine
Investigational medicinal product code	182349-12-8
Other name	Urtimed
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Group B1 received 10 mg rupatadine continuously: one tablet of rupatadine 10 mg once daily (1-0-0

two weeks), than dosing up to 20 mg daily, Group B2: intake twice daily 10mg rupatadine, 1-0-1 / one on-demand tablet of placebo x 14 ± 2 days (intake only if needed).

Number of subjects in period 1	Placebo-Group	Rupatadine 10-20mg daily continuous
Started	21	42
Completed	19	38
Not completed	2	4
Consent withdrawn by subject	-	1
lost of contact	2	2
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo-Group

Reporting group description:

Patients received on demand tablet of rupatadine 10 mg x 14 ± 2 days (intake only if needed).
The following ingredients are used to manufacture the placebo: pregelatinised maize-starch, microcrystalline cellulose, red iron oxide (E-172), yellow iron oxide (E-172), lactose monohydrate, magnesium stearate. The proportions of these ingredients are similar to those used in the rupatadine active product.

Reporting group title	Rupatadine 10-20mg daily continuous

Reporting group description:

Patients received two weeks one tablets of rupatadine (10 mg) daily x 14 ± 2 days (1-0-0) from Visit 2 to Visit 3, than up dosing to 20 mg twice daily (1-0-1) from Visit 3 to Visit 4.

Reporting group values	Placebo-Group	Rupatadine 10-20mg daily continuous	Total
Number of subjects	21	42	63
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)	11	21	32
From 65-84 years	1	3	4
85 years and over	0	0	0
not recorded	9	18	27
Age continuous Units: years			
arithmetic mean	42	43	
full range (min-max)	21 to 72	19 to 69	-
Gender categorical Units: Subjects			
Female	12	32	44
Male	9	10	19
UAS-7 Units: Score			
arithmetic mean	18.62	18.78	
full range (min-max)	13.65 to 23.58	15.98 to 21.57	-

End points

End points reporting groups

Reporting group title	Placebo-Group

Reporting group description:

Patients received on demand tablet of rupatadine 10 mg x 14 ± 2 days (intake only if needed).
The following ingredients are used to manufacture the placebo: pregelatinised maize-starch, microcrystalline cellulose, red iron oxide (E-172), yellow iron oxide (E-172), lactose monohydrate, magnesium stearate. The proportions of these ingredients are similar to those used in the rupatadine active product.

Reporting group title	Rupatadine 10-20mg daily continuous

Reporting group description:

Patients received two weeks one tablets of rupatadine (10 mg) daily x 14 ± 2 days (1-0-0) from Visit 2 to Visit 3, than up dosing to 20 mg twice daily (1-0-1) from Visit 3 to Visit 4.

Primary: change in UAS-7

End point title	change in UAS-7

End point description:

Full analysis set: Based on Generalised Estimating Equations (GEE) to account for centre heterogeneity with adjusted for baseline UAS-7 and based on multiple imputation to account for missing values (10 imputed datasets), # Rupatadine 10 mg (n=3) and 20 mg (n=36) in daily continuously group.

End point type	Primary

End point timeframe:

from baseline to visit 5 (week 16)

End point values	Placebo-Group	Rupatadine 10-20mg daily continuous		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	38		
Units: Score				
arithmetic mean (full range (min-max))	-3.0 (-8.0 to 1.9)	-6.4 (-9.5 to -3.3)		

Attachments (see zip file)	secondary_endpoints/Analyses of secondary outcomes.pdf

Statistical analyses

Statistical analysis title	group difference UAS-7 from baseline to Visit 5
Comparison groups	Placebo-Group v Rupatadine 10-20mg daily continuous

Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	other[1]
Method	GEEs
Parameter estimate	Mean difference (final values)
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.9
upper limit	0.9
Variability estimate	Standard error of the mean
Dispersion value	2.24

Notes:

[1] - Primary outcome (UAS-7 change from baseline to visit 5) was analysed by using Generalized Estimating Equations (GEEs) with Gaussian family, identity link function and exchangeable correlation structure to account for centre heterogeneity and adjusted for baseline UAS-7.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From Baseline (visit2) up to the end of study	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18
Reporting groups	
Reporting group title	Placebo
Reporting group description: 10 mg Rupadatine on demand	
Reporting group title	Rupatadine 10-20mg continuoisly
Reporting group description: -	

Serious adverse events	Placebo	Rupatadine 10-20mg continuoisly	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	0 / 42 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo	Rupatadine 10-20mg continuoisly	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 21 (57.14%)	24 / 42 (57.14%)	
Investigations			
CK-elevation			
subjects affected / exposed	0 / 21 (0.00%)	1 / 42 (2.38%)	
occurrences (all)	0	1	
side effects due to single use of symbioflor1 (higher heartrate, dry mouth)			
subjects affected / exposed	0 / 21 (0.00%)	1 / 42 (2.38%)	
occurrences (all)	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

lump in right mamma			
subjects affected / exposed	1 / 21 (4.76%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 21 (0.00%)	1 / 42 (2.38%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 21 (9.52%)	7 / 42 (16.67%)	
occurrences (all)	2	11	
General disorders and administration site conditions			
tiredness			
subjects affected / exposed	1 / 21 (4.76%)	0 / 42 (0.00%)	
occurrences (all)	2	0	
fever			
subjects affected / exposed	0 / 21 (0.00%)	1 / 42 (2.38%)	
occurrences (all)	0	1	
swelling of cheek /Edema face			
subjects affected / exposed	0 / 21 (0.00%)	1 / 42 (2.38%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Epigastric pain/Diarrhea			
subjects affected / exposed	1 / 21 (4.76%)	2 / 42 (4.76%)	
occurrences (all)	1	2	
dental root infection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
increased stool volume			
subjects affected / exposed	0 / 21 (0.00%)	1 / 42 (2.38%)	
occurrences (all)	0	1	
heartburn			
subjects affected / exposed	0 / 21 (0.00%)	1 / 42 (2.38%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal disorders			

Dyspnoea	Additional description: with known allergic asthma		
subjects affected / exposed	0 / 21 (0.00%)	1 / 42 (2.38%)	
occurrences (all)	0	2	
sore throat			
subjects affected / exposed	1 / 21 (4.76%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
eczema of the foot/hands			
subjects affected / exposed	0 / 21 (0.00%)	2 / 42 (4.76%)	
occurrences (all)	0	2	
Xerosis cutis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 21 (4.76%)	2 / 42 (4.76%)	
occurrences (all)	2	2	
Muscle pain			
subjects affected / exposed	1 / 21 (4.76%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
pain knee			
subjects affected / exposed	1 / 21 (4.76%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	1 / 21 (4.76%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
common cold/ upper resp. Infection			
subjects affected / exposed	5 / 21 (23.81%)	14 / 42 (33.33%)	
occurrences (all)	5	14	
otitis externa			
subjects affected / exposed	0 / 21 (0.00%)	2 / 42 (4.76%)	
occurrences (all)	0	2	
folliculitis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 42 (0.00%)	
occurrences (all)	0	0	

cystitis			
subjects affected / exposed	0 / 21 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Herpes simplex reactivation			
subjects affected / exposed	0 / 21 (0.00%)	1 / 42 (2.38%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 42 (2.38%)	
occurrences (all)	0	1	
Paronychia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 42 (2.38%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hyperkalaemia	Additional description: (5.7 mmol/l)		
subjects affected / exposed	1 / 21 (4.76%)	0 / 42 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 June 2014	change of the trial protocol
28 October 2016	request for prolongation of recruitment period

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported