



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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

10 mg Rupadatine on demand

Reporting group title	Rupatadine 10-20mg continuously
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Reporting group description: -

Serious adverse events	Placebo	Rupatadine 10-20mg continuously	
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 continuously	
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 occurrences (all)	1 / 21 (4.76%) 1	0 / 42 (0.00%) 0	
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 42 (2.38%) 1	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2	7 / 42 (16.67%) 11	
General disorders and administration site conditions tiredness subjects affected / exposed occurrences (all) fever subjects affected / exposed occurrences (all) swelling of cheek /Edema face subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 2 0 / 21 (0.00%) 0 0 / 21 (0.00%) 0	0 / 42 (0.00%) 0 1 / 42 (2.38%) 1 1 / 42 (2.38%) 1	
Gastrointestinal disorders Epigastric pain/Diarrhea subjects affected / exposed occurrences (all) dental root infection subjects affected / exposed occurrences (all) increased stool volume subjects affected / exposed occurrences (all) heartburn subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1 1 / 21 (4.76%) 1 0 / 21 (0.00%) 0 0 / 21 (0.00%) 0	2 / 42 (4.76%) 2 0 / 42 (0.00%) 0 1 / 42 (2.38%) 1 1 / 42 (2.38%) 3	
Respiratory, thoracic and mediastinal disorders			

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