Clinical trial results:
A multi-center, double-blind placebo-controlled parallel group phase II study of the efficacy and safety of rilonacept in subjects with cold contact urticaria (CCU)

Summary

EudraCT number	2012-005726-30
Trial protocol	DE
Global end of trial date	14 March 2018

Results information

Result version number	v2 (current)
This version publication date	03 July 2022
First version publication date	02 June 2022
Version creation reason	• Correction of full data set correction secondaryl endpoints

Trial information

Trial identification

Sponsor protocol code	CURES-IL1T-OT-1236

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Charitè- Universitätsmedizin Berlin
Sponsor organisation address	Chariteplatz 1, Berlin, Germany, 10117
Public contact	Allergie-Centrum-Charité, Charité - Universitätsmedizin , +49 30 450 518342, Karoline.Krause@charite.de
Scientific contact	Allergie-Centrum-Charité, Charité - Universitätsmedizin , +49 30 450 518342, Karoline.Krause@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 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 March 2018
Global end of trial reached?	Yes
Global end of trial date	14 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of rilonacept on the clinical signs and symptoms of cold contact urticaria

Protection of trial subjects:

Safety of patients treated with rilonacept 160mg and 320mg: This includes physical examination, routine safety laboratory assessments, vital signs and adverse event reporting. Furthermore, the patients were monitored for spontaneous complaints after treatments.
Safety analysis will include examination of treatment-emergent adverse events (TEAE) and changes in vital signs and laboratory tests.

Background therapy:

Rilonacept is a dimeric glycoprotein with a total molecular weight of ~251 kDa, of which 80% is protein (201 kDa), and 20% is carbohydrate (50 kDa). The dimer is covalently linked by disulfide bonds in the Fc region. Rilonacept is expressed recombinantly in Chinese hamster ovary (CHO) cells and is purified with a series of chromatographic and filtration techniques. Rilonacept is similar to etanercept (Enbrel), the TNF antagonist approved for rheumatoid arthritis (RA), in that it is a fusion protein consisting of human cytokine receptor extracellular domains and the Fc portion of human IgG1.
Human experience with rilonacept includes 21 clinical studies. In total 2026 patients and 91 healthy volunteers have been exposed to rilonacept. Overall, rilonacept was administered to 383 patients with rheumatoid arthritis, 1511 with gout arthritis, 38 with osteoarthritis, 113 with cryopyrin associated periodic syndromes (CAPS), like familial cold autoinflammatory syndrome (FCAS) and Muckle-wells syndrome(MWS), 15 with systemic juvenile arthritis, 6 with end stage renal disease, 26 with coronary artery disease and 6 with rheumatic polymyalgia. Another pilot, open-label study (investigator-initiated trial) was performed in 2 patients with MWS and 8 patients with Schnitzler syndrome at the Dept. of Dermatology and Allergy, Charité-Universitätsmedizin Berlin to assess the the safety and tolerability and efficacy of rilonacept in these patients.

Evidence for comparator: -

Actual start date of recruitment	03 June 2013
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: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	20
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 2 study centers in Germany, between 02/19/2015 (first patient first visit) and 03/14/2018 (last patient last visit).

Pre-assignment

Screening details:

All patients included in this study will be subjected at the screening visit, V1 (d-14) to physical examination, vital signs assessment, electrocardiogram, QuantiFERON TB test, serum pregnancy test and basic laboratory control (hematology panel, chemistry panel, CRP and urinalysis).

Period 1

Period 1 title	Overall trial
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Rilonacept 160mg

Arm description:

Rilonacept s.c every 7 days

Arm type	Experimental
Investigational medicinal product name	Rilonacept
Investigational medicinal product code	
Other name	Arcalyst
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

160 mg per week and from day 0 to day 42

Arm title	Placebo

Arm description:

Placebo s.c every 7 days

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

same as in the Rilonacept arm

Number of subjects in period 1	Rilonacept 160mg	Placebo
Started	11	9
Completed	10	9
Not completed	1	0
unknown	1	-

Period 2

Period 2 title	Open label phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:
no blinding during open label study

Arms

Are arms mutually exclusive?	No
Arm title	Rilonacept 160mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Rilonacept
Investigational medicinal product code	
Other name	Arcalyst
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:
160 mg per week and from day 0 to day 42

Arm title	Rilonacept 320mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Rilonacept 320mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:
Rilonacept 320mg injection (s.c.)

Number of subjects in period 2	Rilonacept 160mg	Rilonacept 320mg
Started	9	3
Completed	8	3
Not completed	1	0
unknown	1	-

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	20	20	
Age categorical			
Adult (18 years of age)			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	45.55		
inter-quartile range (Q1-Q3)	33 to 58	-	
Gender categorical			
Units: Subjects			
Female	7	7	
Male	13	13	
CTT			
Critical temperature threshold			
Units: celsius temperature			
arithmetic mean	19.5		
standard deviation	± 5.2	-	
Duration of cold urticaria			
Units: Months			
arithmetic mean	156		
standard deviation	± 167.9	-	
BMI			
Units: kg/m²			
arithmetic mean	27.54		
standard deviation	± 4.9	-	

Subject analysis sets

Subject analysis set title	Rilonacept 320mg (open label)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

3 Patients were accepted from the double blind study phase

Reporting group values	Rilonacept 320mg (open label)		
Number of subjects	2		
Age categorical			
Adult (18 years of age)			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	59		
inter-quartile range (Q1-Q3)	49 to 72		
Gender categorical			
Units: Subjects			
Female	1		
Male	2		
CTT			
Critical temperature threshold			
Units: celsius temperature			
arithmetic mean	17		
standard deviation	± 12.73		
Duration of cold urticaria			
Units: Months			
arithmetic mean	200		
standard deviation	± 100.6		
BMI			
Units: kg/m²			
arithmetic mean	25		
standard deviation	± 4.5		

End points

End points reporting groups

Reporting group title	Rilonacept 160mg
Reporting group description: Rilonacept s.c every 7 days	
Reporting group title	Placebo
Reporting group description: Placebo s.c every 7 days	
Reporting group title	Rilonacept 160mg
Reporting group description: -	
Reporting group title	Rilonacept 320mg
Reporting group description: -	
Subject analysis set title	Rilonacept 320mg (open label)
Subject analysis set type	Sub-group analysis
Subject analysis set description: 3 Patients were accepted from the double blind study phase	

Primary: change in critical temperature thresholds (CTT)

End point title	change in critical temperature thresholds (CTT)
End point description:	
End point type	Primary
End point timeframe: from baseline to day 42	

End point values	Rilonacept 160mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	9		
Units: °C				
arithmetic mean (standard deviation)	0.89 (± 4.6)	-0.44 (± 3.43)		

Statistical analyses

Statistical analysis title	Test of critical temperature thresholds
Comparison groups	Rilonacept 160mg v Placebo
Number of subjects included in analysis	19
Analysis specification	Post-hoc
Analysis type	superiority
P-value	≤ 0.05
Method	t-test, 2-sided

Primary: change in critical temperature thresholds (CTT) (open label)	
End point title	change in critical temperature thresholds (CTT) (open label)
End point description:	

End point type	Primary
End point timeframe:	
from baseline to day 42	

End point values	Rilonacept 160mg	Rilonacept 320mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	2		
Units: °C				
arithmetic mean (standard deviation)	-1 (± 4.03)	2 (± 5.7)		

Statistical analyses

Statistical analysis title	CTT (open label)
Comparison groups	Rilonacept 320mg v Rilonacept 160mg
Number of subjects included in analysis	11
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Secondary: Dermatology Life Quality Index	
End point title	Dermatology Life Quality Index
End point description:	

End point type	Secondary
End point timeframe:	
from baseline to day 42	

End point values	Rilonacept 160mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	9		
Units: total scores				
arithmetic mean (standard deviation)	-3.8 (± 2.7)	0.0 (± 3.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: disease intensity

End point title	disease intensity

End point description:

End point type	Secondary

End point timeframe:
from baseline to day 42

End point values	Rilonacept 160mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	9		
Units: scores				
arithmetic mean (standard deviation)	1.1 (± 4.1)	1.78 (± 6.2)		

Statistical analyses

Statistical analysis title	disease intensity
Comparison groups	Rilonacept 160mg v Placebo
Number of subjects included in analysis	19
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.05
Method	t-test, 2-sided

Secondary: Dermatology Life Quality Index (open label)

End point title	Dermatology Life Quality Index (open label)

End point description:

End point type	Secondary

End point timeframe: from baseline to day 42

End point values	Rilonacept 160mg	Rilonacept 320mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	2		
Units: total scores				
arithmetic mean (standard deviation)	-0.36 (± 4.8)	-4.5 (± 2.12)		

Statistical analyses

Statistical analysis title	DLQI (open label)
Comparison groups	Rilonacept 320mg v Rilonacept 160mg
Number of subjects included in analysis	11
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Secondary: disease intensity (open label)	
End point title	disease intensity (open label)
End point description:	
End point type	Secondary
End point timeframe: from baseline to day 42	

End point values	Rilonacept 160mg	Rilonacept 320mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	2		
Units: scores				
arithmetic mean (standard deviation)	0.27 (± 2.28)	1.5 (± 2.12)		

Statistical analyses

Statistical analysis title	ACUSI open label
Comparison groups	Rilonacept 320mg v Rilonacept 160mg
Number of subjects included in analysis	11
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Secondary: Mast cell mediator release in blood of CCU

End point title	Mast cell mediator release in blood of CCU

End point description:

During the course of the study, mast cell mediators were determined by cold water provocation at the end of the double-blind study phase and at the end of the study at V8. The mediators IL-1ra, IL-6, IL-18 and HSP70 were determined before the provocation with 4°C cold water as after the 5-minute provocation time and subsequently after 10 and 20 minutes.

The IL1 receptor antibody could not be analyzed because the levels were below the detection level.

End point type	Secondary

End point timeframe:

From V2-V5 plus open label V8
12 Weeks

End point values	Rilonacept 160mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	9		
Units: Subjects	11	9		

Attachments (see zip file)	mastcell mediators.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: overall treatment period	
Assessment type	Systematic
Dictionary used	
Dictionary name	own
Dictionary version	1
Reporting groups	
Reporting group title	Rilonacept 160mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Rilonacept 160mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (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: 5 %

Non-serious adverse events	Rilonacept 160mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 11 (90.91%)	5 / 9 (55.56%)	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 11 (36.36%)	3 / 9 (33.33%)	
occurrences (all)	4	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 11 (27.27%)	1 / 9 (11.11%)	
occurrences (all)	3	1	
Skin and subcutaneous tissue disorders			
Injection related reaction			

subjects affected / exposed	5 / 11 (45.45%)	1 / 9 (11.11%)	
occurrences (all)	11	1	
Infections and infestations			
Infection upper respiratory tract			
subjects affected / exposed	5 / 11 (45.45%)	3 / 9 (33.33%)	
occurrences (all)	5	3	
urinary tract infection			
subjects affected / exposed	2 / 11 (18.18%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Gastroenteritis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 December 2017	Sponsor`s substantial amendment code number, version, date for the clinical trial concerned: (CURES, Version 1, 06. December 2016) Change or addition of principal investigator(s),co-ordinating investigator addition of a new site

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported