Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Pilot Study of Quilizumab in Patients With Refractory Chronic Spontaneous Urticaria (CSU)

Summary

EudraCT number	2013-003233-15
Trial protocol	DE
Global end of trial date	23 October 2014

Results information

Result version number	v1 (current)
This version publication date	17 February 2016
First version publication date	17 February 2016

Trial information

Trial identification

Sponsor protocol code	GX29107

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01987947
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com

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	07 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of quilizumab administered subcutaneously (SC) as add-on therapy for the treatment of adult participants (18 – 75 years old) who had been diagnosed with chronic spontaneous urticaria (CSU) and who remained symptomatic despite treatment with H1 antihistamines (including doses up to four times above the approved dose level) with or without leukotriene receptor antagonist (LTRA).

Protection of trial subjects:

This study was conducted in accordance with the United States (US) Food and Drug Administration (FDA) regulations, the International Conference on Harmonization E6 Guideline for Good Clinical Practice, and applicable local, state, and federal laws, as well as other applicable country laws. Approval from the Institutional Review Board (IRB)/Ethics Committee (EC) was obtained before study start and was documented in a letter to the investigator specifying the date on which the committee met and granted the approval. Sponsor also obtained approval from the relevant regulatory authority prior to starting the study.

Background therapy:

H1 antihistamines (including doses up to four times above the approved dose level) with or without leukotriene receptor antagonist (LTRA).

Evidence for comparator: -

Actual start date of recruitment	05 December 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	Canada: 15
Country: Number of subjects enrolled	Germany: 17
Worldwide total number of subjects	32
EEA total number of subjects	17

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)	30
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 47 participants from three centers in two countries (one site in Canada and two sites in Germany) were screened; of which 15 participants failed screening, and the remaining 32 participants were enrolled in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo matched to quilizumab SC injection on Day 1 and Day 29.

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:

Participants received three 1.5 milliliter (mL) SC injections at each of the two dosing visits.

Arm title	Quilizumab

Arm description:

Participants received quilizumab 450 milligrams (mg) SC injection on Day 1 and Day 29.

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

Dosage and administration details:

Participants received three 1.5 mL SC injections at each of the two dosing visits.

Number of subjects in period 1	Placebo	Quilizumab
Started	17	15
Completed	13	13
Not completed	4	2
Physician decision	1	-
Non-compliance	-	1
Withdrawal by subject	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to quilizumab SC injection on Day 1 and Day 29.	
Reporting group title	Quilizumab
Reporting group description:	
Participants received quilizumab 450 milligrams (mg) SC injection on Day 1 and Day 29.	

Reporting group values	Placebo	Quilizumab	Total
Number of subjects	17	15	32
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	41.8	44.7	
standard deviation	± 12.3	± 13.2	-
Gender categorical Units: Subjects			
Female	13	10	23
Male	4	5	9

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to quilizumab SC injection on Day 1 and Day 29.	
Reporting group title	Quilizumab
Reporting group description:	
Participants received quilizumab 450 milligrams (mg) SC injection on Day 1 and Day 29.	

Primary: Absolute Change From Baseline in Weekly Itch Severity Score at Week 20

End point title	Absolute Change From Baseline in Weekly Itch Severity Score at Week 20
End point description:	
The itch severity score was recorded once daily in the participant's diary, on a scale of 0 (none) to 3 (intense). The baseline weekly itch score was the sum of the daily itch scores over the 7 days prior to randomization (Day 1 visit). The weekly itch score was the sum of the daily scores over the last 7 days prior to the time point of interest. Total weekly itch severity score ranged from 0 to 21, where higher scores indicated more intense itching. Analysis was performed on modified intention-to-treat (mITT) population, defined as all participants who were randomized and received at least one dose of study drug. Missing data was imputed using worst observation carried forward (WOCF).	
End point type	Primary
End point timeframe:	
Baseline, Week 20	

End point values	Placebo	Quilizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	15		
Units: units on a scale				
arithmetic mean (standard deviation)	-3.8 (± 6.2)	-6.7 (± 7.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The LS mean was estimated using analysis of covariance (ANCOVA) model controlling for baseline weekly itch severity score and country.	
Comparison groups	Placebo v Quilizumab
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-3.3

Confidence interval	
level	90 %
sides	2-sided
lower limit	-7.2
upper limit	0.7

Secondary: Absolute Change From Baseline in Weekly Itch Severity Score at Week 4

End point title	Absolute Change From Baseline in Weekly Itch Severity Score at Week 4

End point description:

The itch severity score was recorded once daily in the participant's diary, on a scale of 0 (none) to 3 (intense). The baseline weekly itch score was the sum of the daily itch scores over the 7 days prior to randomization (Day 1 visit). The weekly itch score was the sum of the daily scores over the last 7 days prior to the time point of interest. Total weekly itch severity score ranged from 0 to 21, where higher scores indicated more intense itching. Analysis was performed on mITT population, defined as all participants who were randomized and received at least one dose of study drug. Missing data was imputed using WOCF.

End point type	Secondary

End point timeframe:

Baseline, Week 4

End point values	Placebo	Quilizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	15		
Units: units on a scale				
arithmetic mean (standard deviation)	-5.3 (± 5.8)	-6.4 (± 6.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The LS mean was estimated using ANCOVA model controlling for baseline weekly itch severity score and country.

Comparison groups	Placebo v Quilizumab
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-1.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	-4.9
upper limit	2

Secondary: Absolute Change From Baseline in Urticaria Activity Score 7 (UAS7) at Week 20

End point title	Absolute Change From Baseline in Urticaria Activity Score 7 (UAS7) at Week 20

End point description:

The urticaria activity score (UAS) was a composite diary score for the intensity of the itch and the number of wheals (hives), where the numeric severity intensity ratings were based on a scale of 0 (none) to 3 (intense/severe) for 1) the intensity of the itch; and 2) the number of wheals (hives). The UAS7 was the sum of the daily UAS over 7 days. Total UAS7 score ranged from 0 to 42, where higher scores indicated worse disease. Analysis was performed on mITT population, defined as all participants who were randomized and received at least one dose of study drug. Missing data was imputed using WOCF.

End point type	Secondary

End point timeframe:

Baseline, Week 20

End point values	Placebo	Quilizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	15		
Units: units on a scale				
arithmetic mean (standard deviation)	-7.4 (± 13.4)	-12.9 (± 14.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The LS mean was estimated using ANCOVA model controlling for baseline weekly itch severity score and country.

Comparison groups	Placebo v Quilizumab
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-5.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.1
upper limit	2.5

Secondary: Number of Participants With Anti-Therapeutic Antibodies (ATA)

End point title	Number of Participants With Anti-Therapeutic Antibodies (ATA)

End point description:

Number of participants positive for ATA was the number of post-baseline evaluable participants determined to have treatment-induced ATA or treatment-enhanced ATA during the study period. Participant with treatment-induced ATA was defined as a participant with a negative or missing baseline ATA result(s) and at least one positive post-baseline (P-B) ATA result. Participant with a treatment-enhanced ATA was defined as a participant with a positive ATA result at baseline who had one or more post-baseline titer results that are at least 0.60 titer units greater than the baseline titer result. Analysis was performed on participants who had at least one ATA assay results available.

End point type	Secondary

End point timeframe:

Baseline, Post-Baseline (28 weeks)

End point values	Placebo	Quilizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: participants				
Baseline: Positive ATA Sample (n=16,15)	0	1		
P-B: Treatment-induced ATA (n=16,14)	0	0		
P-B: Treatment-enhanced ATA (n=16,14)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 28 weeks	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1
Reporting groups	
Reporting group title	Placebo
Reporting group description: Participants received placebo matched to quilizumab SC injection on Day 1 and Day 29.	
Reporting group title	Quilizumab
Reporting group description: Participants received quilizumab 450 milligrams (mg) SC injection on Day 1 and Day 29.	

Serious adverse events	Placebo	Quilizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Quilizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 17 (41.18%)	8 / 15 (53.33%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of thyroid gland			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 17 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Dizziness			

subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Eye disorders			
Eye pruritus			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Enteritis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	3 / 17 (17.65%)	3 / 15 (20.00%)	
occurrences (all)	3	3	
Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Hypothyroidism			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Rheumatic disorder			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 17 (5.88%)	1 / 15 (6.67%)	
occurrences (all)	1	1	

Tonsillitis			
subjects affected / exposed	2 / 17 (11.76%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 17 (5.88%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Helicobacter infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported