Clinical trial results:
A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Safety Study of Xolair (Omalizumab) in Patients With Chronic Idiopathic Urticaria (CIU) who Remain Symptomatic Despite Treatment With H1 Antihistamines, H2 Blockers, and/or Leukotriene Receptor Antagonists

Summary

EudraCT number	2010-022784-35
Trial protocol	GB DE
Global end of trial date	22 November 2012

Results information

Result version number	v1 (current)
This version publication date	14 July 2016
First version publication date	09 August 2015

Trial information

Trial identification

Sponsor protocol code	GA00889 (Q4883)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01264939
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 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, 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	22 November 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 November 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a global, Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate the safety and efficacy of omalizumab administered subcutaneously as add on therapy for the treatment of adolescent and adult participants (12-75 years of age) diagnosed with CIU receiving concomitant therapy including H1 antihistamines at increased doses (up to four times the approved dose), H2 blockers, and/or leukotriene receptor antagonist (LTRAs).

Protection of trial subjects:

This study was conducted in accordance with the United States Food and Drug Administration (FDA) regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), Declaration of Helsinki, and applicable local, state, and federal laws, as well as other applicable country laws. The Clinical Study Protocol (CSP) and the Informed Consent Forms (ICFs) were reviewed and approved by an Independent Ethics Committee (IEC).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 February 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	United States: 270
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	New Zealand: 4
Country: Number of subjects enrolled	Singapore: 2
Worldwide total number of subjects	336
EEA total number of subjects	47

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	11
Adults (18-64 years)	303
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Randomized population: All randomized participants regardless of whether they received any study drug. One participant in the placebo group was withdrawn after randomization but before receiving treatment due to an adverse event. This participant is 1 of 18 in this reporting group who did not complete the study.

Period 1

Period 1 title	Overall trial (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 subcutaneously every 4 weeks during the 24-week double-blind treatment period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for cutaneous solution
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received placebo administered by subcutaneous (SC) injection every 4 weeks during the 24-week double-blind treatment period.

Arm title	Omalizumab

Arm description:

Participants received omalizumab 300 milligrams (mg) subcutaneously every 4 weeks during the 24-week double-blind treatment period.

Arm type	Experimental
Investigational medicinal product name	Omalizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for cutaneous solution
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 300 mg of omalizumab administered by SC injection every 4 weeks during the 24-week double-blind treatment period.

Number of subjects in period 1	Placebo	Omalizumab
Started	84	252
Completed	66	224
Not completed	18	28
Physician decision	1	1
Participant/Guardian decision	8	10
Disease progression	8	11
Adverse event, non-fatal	1	3
Lost to follow-up	-	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo subcutaneously every 4 weeks during the 24-week double-blind treatment period.	
Reporting group title	Omalizumab
Reporting group description:	
Participants received omalizumab 300 milligrams (mg) subcutaneously every 4 weeks during the 24-week double-blind treatment period.	

Reporting group values	Placebo	Omalizumab	Total
Number of subjects	84	252	336
Age categorical Units: Subjects			
Age continuous			
Modified intent-to-treat (mITT) Population: All randomized participants who received at least 1 dose of study drug. One participant (randomized to placebo) did not receive study drug and was not included in the mITT population.			
Units: years			
arithmetic mean	44.6	42.7	
standard deviation	± 14.9	± 13.9	-
Gender categorical Units: Subjects			
Female	56	186	242
Male	28	66	94

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo subcutaneously every 4 weeks during the 24-week double-blind treatment period.	
Reporting group title	Omalizumab
Reporting group description:	
Participants received omalizumab 300 milligrams (mg) subcutaneously every 4 weeks during the 24-week double-blind treatment period.	

Primary: Percentage of Participants With Adverse Events

End point title	Percentage of Participants With Adverse Events[1]
End point description:	
The percentage of participants with serious adverse events and other adverse events is summarized by Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and organ classes in the Reported Adverse Events section below. Safety population: All randomized participants who received at least 1 dose of study drug.	
End point type	Primary
End point timeframe:	
Baseline to the end of study (up to 40 weeks)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed because only descriptive statistics were planned as per protocol.

End point values	Placebo	Omalizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	252		
Units: Percentage of participants				
number (not applicable)	78.3	83.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 12 in the Weekly Itch Severity Score

End point title	Change From Baseline to Week 12 in the Weekly Itch Severity Score
End point description:	
The weekly itch severity score is the sum of the daily itch severity scores over 7 days and ranges from 0 to 21. The daily itch severity score is the average of the morning and evening scores on a scale of 0 (none) to 3 (severe). The Baseline weekly itch severity score is the sum of the daily itch severity scores over the 7 days prior to the first treatment. A higher itch severity score indicates more severe itching. A negative change score indicates improvement. mITT Population: All randomized participants who received at least 1 dose of study drug. One participant (randomized to placebo) did not receive study drug and was not included in the mITT population.	
End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Omalizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	252		
Units: Units on a scale				
arithmetic mean (standard deviation)	-4.01 (± 5.87)	-8.55 (± 6.01)		

Statistical analyses

Statistical analysis title	Change From Baseline in Weekly Itch Severity Score

Statistical analysis description:

The null hypothesis was that there was no difference between the placebo and the omalizumab 300 mg groups.

Comparison groups	Placebo v Omalizumab
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001 [3]
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	-4.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.97
upper limit	-3.08

Notes:

[2] - Covariates included in the analysis were baseline weekly itch severity score (less than [<] 13 versus [vs] greater than or equal to [≥] 13) and baseline weight (< 80 kilogram [kg] vs ≥80 kg).
[3] - Multiplicity plan applied to the efficacy endpoints provided strong control of the type I error rate at 0.05 level by pre-specifying the hierarchical order of the efficacy endpoint tests.

Secondary: Change From Baseline to Week 12 in the Urticaria Activity Score Over 7 Days (UAS7)

End point title	Change From Baseline to Week 12 in the Urticaria Activity Score Over 7 Days (UAS7)

End point description:

The UAS7 is the sum of the daily urticarial activity scores over 7 days and ranges from 0 to 42. The daily urticarial activity score is the average of the morning and evening urticarial activity scores and ranges from 0 to 6. The urticarial activity score is the sum of ratings on a scale of 0 to 3 (0 is equal to (=) none to 3 = intense/severe) for (1) the number of wheals (hives) and (2) itch intensity over the previous 12 hours, ranges from 0 to 6, and is measured twice daily (morning and evening). The Baseline score is the sum of the daily urticarial activity scores over the 7 days prior to the first treatment. A higher urticarial activity score indicates more urticaria activity. A negative change score indicates improvement. mITT Population: All randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Omalizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	252		
Units: Units on a scale				
arithmetic mean (standard deviation)	-8.5 (± 11.71)	-19.01 (± 13.15)		

Statistical analyses

Statistical analysis title	Change From Baseline to Week 12 in the UAS7

Statistical analysis description:

The null hypothesis was that there was no difference between the placebo and the omalizumab 300 mg groups.

Comparison groups	Placebo v Omalizumab
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.0001 [5]
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	-10.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.17
upper limit	-6.86

Notes:

[4] - Covariates included in the analysis were baseline UAS7 (< median vs ≥ median) and baseline weight (<80 kg vs ≥80 kg).

[5] - Multiplicity plan applied to the efficacy endpoints provided strong control of the type I error rate at 0.05 level by pre-specifying the hierarchical order of the efficacy endpoint tests.

Secondary: Change From Baseline to Week 12 in the Weekly Number of Hives Score

End point title	Change From Baseline to Week 12 in the Weekly Number of Hives Score

End point description:

The weekly hives score is the sum of the daily hives scores over 7 days and ranges from 0 to 21. The number of hives is measured twice daily (morning and evening) on a scale of 0 (none) to 3 (greater than [>] 12 hives per 12 hours). The daily hives score is the average of the morning and evening scores. The Baseline score is the sum of the daily hives scores over the 7 days prior to the first treatment. A higher score indicates more hives. A negative change score indicates improvement. mITT Population: All randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Omalizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	252		
Units: Units on a scale				
arithmetic mean (standard deviation)	-4.49 (± 6.33)	-10.46 (± 7.74)		

Statistical analyses

Statistical analysis title	Change From Baseline in Weekly Hives Score

Statistical analysis description:

The null hypothesis was that there was no difference between the placebo and the omalizumab 300 mg groups.

Comparison groups	Placebo v Omalizumab
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.0001 [7]
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	-5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.72
upper limit	-4.07

Notes:

[6] - Covariates included in the analysis were baseline weekly number of hives score (< median vs ≥ median) and baseline weight (<80 kg vs ≥80 kg).

[7] - Multiplicity plan applied to the efficacy endpoints provided strong control of the type I error rate at 0.05 level by pre-specifying the hierarchical order of the efficacy endpoint tests.

Secondary: Time to Minimally Important Difference (MID) Response in the Weekly Itch Severity Score by Week 12

End point title	Time to Minimally Important Difference (MID) Response in the Weekly Itch Severity Score by Week 12

End point description:

The time to the MID response is the number of weeks from the start of treatment (Baseline) until the time point at which the first MID response occurs. The MID response is defined as a reduction ≥ 5 points from Baseline in the weekly itch severity score. The weekly itch severity score is the sum of the daily itch severity scores over 7 days and ranges from 0 to 21. The daily itch severity score is the average of the morning and evening scores on a scale of 0 (none) to 3 (severe). The Baseline weekly itch severity score is the sum of the daily itch severity scores over the 7 days prior to the first treatment. A higher itch severity score indicates more severe itching. mITT Population: All randomized participants who received at least 1 dose of study drug. Only participants with a MID response were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Omalizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	252		
Units: Weeks				
median (confidence interval 95%)	5 (3 to 7)	2 (1 to 2)		

Statistical analyses

Statistical analysis title	Time to MID Response in Weekly Itch Severity Score

Statistical analysis description:

The null hypothesis was that there was no difference between the placebo and the omalizumab 300 mg groups.

Comparison groups	Placebo v Omalizumab
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	< 0.0001 [9]
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.47
upper limit	2.68

Notes:

[8] - Covariates included in the analysis were baseline weekly itch severity score (< 13 vs ≥ 13) and baseline weight (<80 kg vs ≥80 kg).
[9] - Multiplicity plan applied to the efficacy endpoints provided strong control of the type I error rate at 0.05 level by pre-specifying the hierarchical order of the efficacy endpoint tests.

Secondary: Percentage of Participants With a UAS7 Score Less Than or Equal to (≤) 6 at Week 12

End point title	Percentage of Participants With a UAS7 Score Less Than or Equal to (≤) 6 at Week 12

End point description:

The UAS7 is the sum of the daily urticarial activity scores over 7 days and ranges from 0 to 42. The daily urticarial activity score is the average of the morning and evening urticarial activity scores and ranges from 0 to 6. The urticarial activity score is the sum of ratings on a scale of 0 to 3 (0 = none to 3 = intense/severe) for (1) the number of wheals (hives) and (2) itch intensity over the previous 12 hours, ranges from 0 to 6, and is measured twice daily (morning and evening). The Baseline score is the sum of the daily urticarial activity scores over the 7 days prior to the first treatment. A higher urticarial activity score indicates more urticaria activity. mITT Population: All randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Omalizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	252		
Units: Percentage of participants				
number (not applicable)	12	52.4		

Statistical analyses

Statistical analysis title	% of Participants With a UAS7 Score ≤6 at Week 12

Statistical analysis description:

The null hypothesis was that there was no difference between the placebo and the omalizumab 300 mg groups.

Comparison groups	Placebo v Omalizumab
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	< 0.0001 [11]
Method	Cochran-Mantel-Haenszel

Notes:

[10] - Covariates included in the analysis were baseline UAS7 (< median vs ≥ median) and baseline weight (<80 kg vs ≥80 kg).
[11] - Multiplicity plan applied to the efficacy endpoints provided strong control of the type I error rate at 0.05 level by pre-specifying the hierarchical order of the efficacy endpoint tests.

Secondary: Percentage of Weekly Itch Severity Score MID Responders at Week 12

End point title	Percentage of Weekly Itch Severity Score MID Responders at Week 12

End point description:

The percentage of participants with an itch severity score at 12 Weeks at least 5 points lower than at Baseline. The weekly itch severity score is the sum of the daily itch severity scores over 7 days and ranges from 0 to 21. The daily itch severity score is the average of the morning and evening scores on a scale of 0 (none) to 3 (severe). The Baseline weekly itch severity score is the sum of the daily itch severity scores over the 7 days prior to the first treatment. A higher itch severity score indicates more severe itching. Modified intent-to-treat population: All randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Omalizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	252		
Units: Percentage of participants				
number (not applicable)	39.8	69.8		

Statistical analyses

Statistical analysis title	% of Weekly Itch Severity Score MID Responders

Statistical analysis description:

The null hypothesis was that there was no difference between the placebo and the omalizumab 300 mg groups.

Comparison groups	Placebo v Omalizumab
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	< 0.0001 [13]
Method	Cochran-Mantel-Haenszel

Notes:

[12] - Covariates included in the analysis were baseline weekly itch severity score (< 13 vs ≥ 13) and baseline weight (<80 kg vs ≥80 kg).
[13] - Multiplicity plan applied to the efficacy endpoints provided strong control of the type I error rate at 0.05 level by pre-specifying the hierarchical order of the efficacy endpoint tests.

Secondary: Change From Baseline to Week 12 in the Weekly Size of the Largest Hive Score

End point title	Change From Baseline to Week 12 in the Weekly Size of the Largest Hive Score

End point description:

The weekly size of the largest hive score is the sum of the daily size of the largest hive scores over 7 days and ranges from 0 to 21. The daily size of the largest hive score is assessed twice daily (morning and evening) on a scale of 0 (none) to 3 (> 2.5 cm). The daily size of the largest hive score is the average of the morning and evening scores. The Baseline weekly size of the largest hive score is calculated over the 7 days prior to the first treatment. A higher score indicates larger hives. A negative change score indicates a reduction in hive size. mITT Population: All randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Omalizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	252		
Units: Units on a scale				
arithmetic mean (standard deviation)	-3.09 (± 5.46)	-8.82 (± 7.23)		

Statistical analyses

Statistical analysis title	Change From Baseline in Largest Hive Score

Statistical analysis description:

The null hypothesis was that there was no difference between the placebo and the omalizumab 300 mg groups.

Comparison groups	Placebo v Omalizumab

Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	< 0.0001 [15]
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	-5.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.25
upper limit	-3.96

Notes:

[14] - Covariates included in the analysis were baseline weekly size of largest hive score (< median vs ≥ median) and baseline weight (< 80 kg vs ≥ 80 kg).
[15] - Multiplicity plan applied to the efficacy endpoints provided strong control of the type I error rate at 0.05 level by pre-specifying the hierarchical order of the efficacy endpoint tests.

Secondary: Change From Baseline in the Overall Dermatology Life Quality Index (DLQI) Score at Week 12

End point title	Change From Baseline in the Overall Dermatology Life Quality Index (DLQI) Score at Week 12

End point description:

The DLQI is a 10-item dermatology-specific health-related quality of life measure. Participants rated their dermatology symptoms as well as the impact of their skin condition on various aspects of their lives on a scale of 0 (not at all) to 3 (very much). The overall DLQI is the sum of the responses to the 10 items and ranges from 0 to 30. A lower score indicates a better quality of life. A negative change score indicates improvement. mITT Population: All randomized participants who received at least 1 dose of study drug and who had a DLQI score at Week 12.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo	Omalizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	216		
Units: Units on a scale				
arithmetic mean (standard deviation)	-5.11 (± 7.53)	-9.69 (± 6.85)		

Statistical analyses

Statistical analysis title	Change From Baseline in the Overall DLQI Score

Statistical analysis description:

The null hypothesis was that there was no difference between the placebo and the omalizumab 300 mg groups.

Comparison groups	Placebo v Omalizumab

Number of subjects included in analysis	280
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	< 0.0001 [17]
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	-4.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.28
upper limit	-3.06

Notes:

[16] - Covariates included in the analysis were baseline overall DLQI score (< median vs ≥ median) and baseline weight (<80 kg vs ≥80 kg).
[17] - Multiplicity plan applied to the efficacy endpoints provided strong control of the type I error rate at 0.05 level by pre-specifying the hierarchical order of the efficacy endpoint tests.

Secondary: Percentage of Angioedema-free Days From Week 4 to Week 12

End point title	Percentage of Angioedema-free Days From Week 4 to Week 12

End point description:

The percentage of angioedema-free days from Weeks 4 to 12 was defined as the number of days for which a participant responded "No" to the angioedema question in the daily diary divided by the total number of days with a non-missing diary entry, starting at the Week 4 visit and ending the day prior to the Week 12 visit. mITT Population: All randomized participants who received at least 1 dose of study drug. Participants who withdrew before the Week 4 visit or who had missing responses for more than 40% of the daily diary entries between the Week 4 visit and the Week 12 visit were not included in the analysis.

End point type	Secondary

End point timeframe:

Week 4 to Week 12

End point values	Placebo	Omalizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	224		
Units: Percentage of days				
arithmetic mean (standard deviation)	88.1 (± 18.9)	91 (± 21)		

Statistical analyses

Statistical analysis title	% of Angioedema-free Days From Week 4 to Week 12

Statistical analysis description:

The null hypothesis was that there was no difference between the placebo and the omalizumab 300 mg groups.

Comparison groups	Placebo v Omalizumab

Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.0006 [19]
Method	Stratified Wilcoxon

Notes:

[18] - Stratification variables included in the analysis were presence of angioedema at baseline (yes vs no) and baseline weight (<80 kg vs ≥80 kg).
[19] - Multiplicity plan applied to the efficacy endpoints provided strong control of the type I error rate at 0.05 level by pre-specifying the hierarchical order of the efficacy endpoint tests.

Secondary: Percentage of Complete Responders (UAS7 = 0) at Week 12

End point title	Percentage of Complete Responders (UAS7 = 0) at Week 12

End point description:

A complete responder was defined as a participant with a UAS7 score = 0 at Week 12. The UAS7 is the sum of the daily urticarial activity scores over 7 days and ranges from 0 to 42. The daily urticarial activity score is the average of the morning and evening urticarial activity scores and ranges from 0 to 6. The urticarial activity score is the sum of ratings on a scale of 0 to 3 (0 = none to 3 = intense/severe) for (1) the number of wheals (hives) and (2) itch intensity over the previous 12 hours, ranges from 0 to 6, and is measured twice daily (morning and evening). The Baseline score is the sum of the daily urticarial activity scores over the 7 days prior to the first treatment. A higher urticarial activity score indicates more urticaria activity. mITT Population: All randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Omalizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	252		
Units: Percentage of participants				
number (not applicable)	4.8	33.7		

Statistical analyses

Statistical analysis title	% of Complete Responders (UAS7 = 0) at Week 12

Statistical analysis description:

The null hypothesis was that there was no difference between the placebo and the omalizumab 300 mg groups.

Comparison groups	Placebo v Omalizumab
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	< 0.0001 [21]
Method	Cochran-Mantel-Haenszel

Notes:

[20] - Covariates included in the analysis were baseline UAS7 (< median vs ≥ median) and baseline weight (<80 kg vs ≥80 kg).
[21] - Multiplicity plan applied to the efficacy endpoints provided strong control of the type I error rate at 0.05 level by pre-specifying the hierarchical order of the efficacy endpoint tests.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported that started on or after the first treatment date through the end of the study (up to 40 weeks).

Adverse event reporting additional description:

Safety population: All randomized participants who received at least 1 dose of study drug.
Multiple occurrences of a specific adverse event for a patient were counted once in the frequency for the adverse event.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Omalizumab

Reporting group description:

Participants received omalizumab 300 mg subcutaneously every 4 weeks during the 24-week double-blind treatment period .

Reporting group title	Placebo

Reporting group description:

Participants received placebo subcutaneously every 4 weeks during the 24 week treatment period.

Serious adverse events	Omalizumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 252 (7.14%)	5 / 83 (6.02%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Vascular disorders			
Intermittent claudication			
subjects affected / exposed	1 / 252 (0.40%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 252 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory distre			

subjects affected / exposed	0 / 252 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 252 (0.40%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 252 (0.40%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure increased			
subjects affected / exposed	1 / 252 (0.40%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Multiple drug overdose			
subjects affected / exposed	1 / 252 (0.40%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 252 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric ulcer			
subjects affected / exposed	1 / 252 (0.40%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			

subjects affected / exposed	1 / 252 (0.40%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 83 (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			
Angioedema			
subjects affected / exposed	4 / 252 (1.59%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	2 / 252 (0.79%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic urticaria			
subjects affected / exposed	1 / 252 (0.40%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 252 (0.40%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Viral infection			
subjects affected / exposed	1 / 252 (0.40%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 252 (0.40%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 252 (0.40%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 252 (0.40%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	1 / 252 (0.40%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal infection			
subjects affected / exposed	1 / 252 (0.40%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 252 (0.40%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Omalizumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	139 / 252 (55.16%)	39 / 83 (46.99%)	
Nervous system disorders			
Headache			
subjects affected / exposed	26 / 252 (10.32%)	6 / 83 (7.23%)	
occurrences (all)	44	18	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	15 / 252 (5.95%)	5 / 83 (6.02%)	
occurrences (all)	15	7	
Diarrhoea			
subjects affected / exposed	13 / 252 (5.16%)	5 / 83 (6.02%)	
occurrences (all)	13	5	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	11 / 252 (4.37%)	7 / 83 (8.43%)	
occurrences (all)	11	7	
Sinus congestion			
subjects affected / exposed	3 / 252 (1.19%)	5 / 83 (6.02%)	
occurrences (all)	3	7	
Skin and subcutaneous tissue disorders			
Idiopathic urticaria			
subjects affected / exposed	37 / 252 (14.68%)	10 / 83 (12.05%)	
occurrences (all)	54	14	
Urticaria			
subjects affected / exposed	14 / 252 (5.56%)	3 / 83 (3.61%)	
occurrences (all)	19	3	
Infections and infestations			
Sinusitis			
subjects affected / exposed	31 / 252 (12.30%)	7 / 83 (8.43%)	
occurrences (all)	43	9	
Nasopharyngitis			
subjects affected / exposed	27 / 252 (10.71%)	8 / 83 (9.64%)	
occurrences (all)	34	11	
Upper respiratory tract infection			

subjects affected / exposed	27 / 252 (10.71%)	4 / 83 (4.82%)	
occurrences (all)	34	5	
Urinary tract infection			
subjects affected / exposed	14 / 252 (5.56%)	1 / 83 (1.20%)	
occurrences (all)	16	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 2011	There were two region-specific changes in protocol which are summarized below: North America/Asia-Pacific protocol (Version 1.0): • The study entry criterion regarding women of childbearing potential was modified, i.e., women of child-bearing potential were excluded from enrollment in the study. • Nursing women were excluded from enrollment into the study. • The prescribed washout period after regular doxepin use prior to enrollment was reduced from 6 weeks to 14 days. European Union protocol (Version 1.1): • Nursing women were excluded from enrollment into the study. • The prescribed washout period after regular doxepin use prior to enrollment was reduced from 6 weeks to 14 days. • Additional minor changes were made for clarity and consistency.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported