Clinical trial results:
A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, DOSE-RANGING, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, RESPONSE DURATION AND SAFETY OF XOLAIR (OMALIZUMAB) IN PATIENTS WITH CHRONIC IDIOPATHIC URTICARIA (CIU) WHO REMAIN SYMPTOMATIC DESPITE ANTIHISTAMINE TREATMENT (H1)

Summary

EudraCT number	2010-022785-27
Trial protocol	FR DE DK IT ES
Global end of trial date	27 June 2012

Results information

Result version number	v1 (current)
This version publication date	08 April 2016
First version publication date	08 April 2016

Trial information

Trial identification

Sponsor protocol code	Q4882g

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01292473
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Genentech, Inc.
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
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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	29 August 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 June 2012
Global end of trial reached?	Yes
Global end of trial date	27 June 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of omalizumab compared with placebo in participants with refractory chronic idiopathic urticaria (CIU) receiving concomitant H1 antihistamine therapy

Protection of trial subjects:

This study was conducted in accordance with the United States (U.S.) Food and Drug Administration (FDA) regulations, 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. For example, the U.S. sites, investigators were trained in GCP according to Genentech and Quintiles standard operating procedures and a written commitment from investigators to comply with GCP was obtained. Approval from the independent ethics committee/institutional review board was obtained before study start-up and prior to implementation of any protocol amendments. The approval from the relevant competent authority prior to starting the study was also obtained. An Independent data monitoring committee was established to monitor safety and study conduct; the members of whom were external to the Sponsor and met at regular intervals (at least once every 6 months) until the end of the trial. A separate anaphylaxis review committee comprised of external experts in CIU and anaphylaxis was convened to clinically review anaphylaxis cases in a blinded fashion.

Background therapy:

All participants received standard-of-care H1 antihistamine treatment at approved doses during the screening, treatment, and follow-up periods. Diphenhydramine (25 mg) treatment was provided on an as-needed basis (up to a maximum of three doses in 24 hours, based on local regulations) during the screening, treatment, and follow-up periods. The medications approved for use in the countries outside the U. S. where the study was conducted were cetirizine 5 or 10 mg once per day (QD), levocetirizine dihydrochloride 2.5 or 5 mg QD, fexofenadine 60 mg twice per day or 180 mg QD, loratadine 10 mg QD, and desloratadine 5 mg QD. Medications for diseases other than CIU (asthma or gastroesophageal reflux disease) were permitted during the study.

Evidence for comparator: -

Actual start date of recruitment	10 March 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 234
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	Poland: 18
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	France: 3

Country: Number of subjects enrolled	Germany: 44
Country: Number of subjects enrolled	Italy: 4
Worldwide total number of subjects	322
EEA total number of subjects	83

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)	10
Adults (18-64 years)	294
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in six European countries along with Turkey and the U.S. from 11 Mar 2011 to 27 Jun 2012. A total of 466 participants were enrolled.

Pre-assignment

Screening details:

Out of 466 participants, 322 were randomized (79 in the Placebo group, 82 in the Omalizumab 75 mg group, 82 in the Omalizumab 150 mg group, and 79 in the Omalizumab 300 mg group). The most frequent reasons for screen failures were evidence of current drug or alcohol abuse, contraindications to diphenhydramine, and other.

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, Carer, Assessor

Blinding implementation details:

Study drug supplies were shipped blinded to each site. An individual not involved with evaluating the participant was identified to administer the study drug. There were no treatment assignment unblindings during the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received only placebo injections (i.e., no active treatment)

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

Dosage and administration details:

Participants received the placebo subcutaneously every 4 weeks on Day 1, Week 4, and Week 8 upon reconstitution with 1.4 mL sterile water for injection (SWFI). Doses of more than 150 mg were divided among multiple injection sites to limit injections to not more than 150 mg per site. Each placebo vial contained 145.5 mg sucrose, 2.8 mg L-histidine hydrochloride monohydrate, 1.8 mg L-histidine, and 0.5 mg polysorbate 20. Each vial was designed to deliver 150 mg of omalizumab in 1.2 mL after reconstitution with 1.4 mL SWFI, USP.

Arm title	Omalizumab 75 mg

Arm description:

Participants received at least one 75 mg omalizumab injection but no higher active dose level (150 mg or 300 mg) injections during the treatment period. Six participants were randomized to the Omalizumab 75 mg group received at least one dose of omalizumab 150 mg during the treatment period and were therefore included in the Omalizumab 150 mg group.

Arm type	Experimental
Investigational medicinal product name	Omalizumab
Investigational medicinal product code	RO5489789
Other name	Xolair
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 75 mg omalizumab subcutaneously on Day 1, Week 4, and Week 8, reconstituted with 1.4 mL SWFI. Each omalizumab vial contained 202.5 mg omalizumab, 145.5 mg sucrose, 2.8 mg, L-histidine hydrochloride monohydrate, 1.8 mg L-histidine, and 0.5 mg polysorbate 20. Each vial was designed to deliver 150 mg of omalizumab in 1.2 mL after reconstitution with 1.4 mL SWFI, USP.

Arm title	Omalizumab 150 mg

Arm description:

Participants who received at least one 150 mg omalizumab injection but no higher active dose level (300 mg) injections during the treatment period.

Arm type	Experimental
Investigational medicinal product name	Omalizumab
Investigational medicinal product code	RO5489789
Other name	Xolair
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 150 mg omalizumab subcutaneously on Day 1, Week 4, and Week 8, reconstituted with 1.4 mL SWFI. Each omalizumab vial contained 202.5 mg omalizumab, 145.5 mg sucrose, 2.8 mg, L-histidine hydrochloride monohydrate, 1.8 mg L-histidine, and 0.5 mg polysorbate 20. Each vial was designed to deliver 150 mg of omalizumab in 1.2 mL after reconstitution with 1.4 mL SWFI, USP.

Arm title	Omalizumab 300 mg

Arm description:

Participants received at least one 300 mg omalizumab injection during the treatment period. Two participants were randomized to the Omalizumab 300 mg group; however, they received one dose of omalizumab 150 mg during the treatment period.

Arm type	Experimental
Investigational medicinal product name	Omalizumab
Investigational medicinal product code	RO5489789
Other name	Xolair
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 300 mg omalizumab subcutaneously on Day 1, Week 4, and Week 8, with 1.4 mL SWFI. Each omalizumab vial contained 202.5 mg omalizumab, 145.5 mg sucrose, 2.8 mg, L-histidine hydrochloride monohydrate, 1.8 mg L-histidine, and 0.5 mg polysorbate 20. Each vial was designed to deliver 150 mg of omalizumab in 1.2 mL after reconstitution with 1.4 mL SWFI, USP.

Number of subjects in period 1	Placebo	Omalizumab 75 mg	Omalizumab 150 mg
Started	79	82	82
Completed	74	75	74
Not completed	5	7	8
Consent withdrawn by subject	3	4	2
Physician decision	-	1	-
Disease progression	-	1	3
Adverse event, non-fatal	1	-	1
Lost to follow-up	1	1	2

Number of subjects in period 1	Omalizumab 300 mg
Started	79
Completed	67
Not completed	12
Consent withdrawn by subject	3
Physician decision	-
Disease progression	6
Adverse event, non-fatal	1
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received only placebo injections (i.e., no active treatment)	
Reporting group title	Omalizumab 75 mg
Reporting group description:	
Participants received at least one 75 mg omalizumab injection but no higher active dose level (150 mg or 300 mg) injections during the treatment period. Six participants were randomized to the Omalizumab 75 mg group received at least one dose of omalizumab 150 mg during the treatment period and were therefore included in the Omalizumab 150 mg group.	
Reporting group title	Omalizumab 150 mg
Reporting group description:	
Participants who received at least one 150 mg omalizumab injection but no higher active dose level (300 mg) injections during the treatment period.	
Reporting group title	Omalizumab 300 mg
Reporting group description:	
Participants received at least one 300 mg omalizumab injection during the treatment period. Two participants were randomized to the Omalizumab 300 mg group; however, they received one dose of omalizumab 150 mg during the treatment period.	

Reporting group values	Placebo	Omalizumab 75 mg	Omalizumab 150 mg
Number of subjects	79	82	82
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)	2	4	2
Adults (18-64 years)	74	73	77
From 65-84 years	3	5	3
85 years and over	0	0	0
Gender categorical			
The majority of participants were female.			
Units: Subjects			
Female	55	61	65
Male	24	21	17

Reporting group values	Omalizumab 300 mg	Total	
Number of subjects	79	322	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	

Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	2	10	
Adults (18-64 years)	70	294	
From 65-84 years	7	18	
85 years and over	0	0	
Gender categorical			
The majority of participants were female.			
Units: Subjects			
Female	63	244	
Male	16	78	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received only placebo injections (i.e., no active treatment)	
Reporting group title	Omalizumab 75 mg
Reporting group description:	
Participants received at least one 75 mg omalizumab injection but no higher active dose level (150 mg or 300 mg) injections during the treatment period. Six participants were randomized to the Omalizumab 75 mg group received at least one dose of omalizumab 150 mg during the treatment period and were therefore included in the Omalizumab 150 mg group.	
Reporting group title	Omalizumab 150 mg
Reporting group description:	
Participants who received at least one 150 mg omalizumab injection but no higher active dose level (300 mg) injections during the treatment period.	
Reporting group title	Omalizumab 300 mg
Reporting group description:	
Participants received at least one 300 mg omalizumab injection during the treatment period. Two participants were randomized to the Omalizumab 300 mg group; however, they received one dose of omalizumab 150 mg during the treatment period.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
This population included participants who received at least one dose of either placebo or the study drug (omalizumab 75 mg/150 mg/ 300 mg according to the actual treatment received).	
Subject analysis set title	Modified intent to treat population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Modified intent to treat (mITT) population included all participants randomized in the study who received at least one dose of study drug.	
Subject analysis set title	Pharmacokinetic population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Pharmacokinetic (PK-evaluable) population included all randomized participants who received at least one dose of the study drug and had provided at least one serum sample for determination of omalizumab concentration.	

Primary: Mean change in weekly itch severity score from Baseline at Week 12

End point title	Mean change in weekly itch severity score from Baseline at Week 12
End point description:	
Weekly itch severity score is a component of the urticaria activity score over 7 days (UAS7). Daily itch severity score is the average of the morning and evening scores with use of a scale of 0 (none) to 3 (severe). Weekly itch severity score is the sum of the daily scores over 7 days; thus, the weekly score represents pruritus (itch) severity on a scale from 0 (minimum) to 21 (maximum). Negative value indicated decrease in mean weekly itch severity score from the baseline in all treatment groups during the 28-week study period. Change from Baseline was defined as itch severity score at Week 12 minus the baseline score and was calculated using baseline observation carried forward (BOCF) method. This analysis was performed on mITT population.	
End point type	Primary
End point timeframe:	
Baseline (Screening [Days -18 to -7]) and Week 12	

End point values	Placebo	Omalizumab 75 mg	Omalizumab 150 mg	Omalizumab 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	82	82	79
Units: Scores on a scale				
arithmetic mean (standard deviation)	-5.14 (± 5.58)	-5.87 (± 6.45)	-8.14 (± 6.44)	-9.77 (± 5.95)

Statistical analyses

Statistical analysis title	Change from Baseline in weekly itch severity score
Comparison groups	Placebo v Omalizumab 75 mg
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4637 [1]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.54
upper limit	1.16

Notes:

[1] - ANCOVA t-test was used to derive the 'p-value'.

Statistical analysis title	Change from Baseline in weekly itch severity score
Comparison groups	Placebo v Omalizumab 150 mg
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011 [2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.85
upper limit	-1.24

Notes:

[2] - ANCOVA t-test was used to derive the 'p-value'.

Statistical analysis title	Change from Baseline in weekly itch severity score
Comparison groups	Placebo v Omalizumab 300 mg

Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.49
upper limit	-3.13

Notes:

[3] - ANCOVA t-test was used to derive the 'p-value'.

Secondary: Mean change from Baseline in urticaria activity score over 7 days at Week 12

End point title	Mean change from Baseline in urticaria activity score over 7 days at Week 12

End point description:

The UAS7 is a composite of recorded score with numeric severity intensity ratings for the number of wheals (hives); and the intensity of the itch, measured twice daily (morning and evening). It was measured on a scale of 0 (none) to 3 (intense/severe) . Daily UAS is the average of morning and evening scores (range, 0−6 points/day) and the UAS7 is the sum of the daily UAS scores over 7 days (range, 0−42). Negative value indicated decrease in mean UAS from the baseline in all treatment groups during the 28-week study period. Change from Baseline was defined as urticaria activity score over 7 days at Week 12 minus the baseline score and was calculated using BOCF method. This analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline (Screening [Days -18 to -7]) and Week 12

End point values	Placebo	Omalizumab 75 mg	Omalizumab 150 mg	Omalizumab 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	82	82	79
Units: Scores on a scale				
arithmetic mean (standard deviation)	-10.36 (± 11.61)	-13.08 (± 12.67)	-17.89 (± 13.23)	-21.74 (± 12.78)

Statistical analyses

Statistical analysis title	Change from Baseline in UAS7 at Week 12
Comparison groups	Placebo v Omalizumab 75 mg

Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1575
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.53
upper limit	1.07

Statistical analysis title	Change from Baseline in UAS7 at Week 12
Comparison groups	Placebo v Omalizumab 150 mg
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.49
upper limit	-3.88

Statistical analysis title	Change from Baseline in UAS 7 at Week 12
Comparison groups	Placebo v Omalizumab 300 mg
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-12.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.13
upper limit	-8.66

Secondary: Mean change from Baseline in weekly number of hives score at Week 12

End point title	Mean change from Baseline in weekly number of hives score at Week 12

End point description:

Number of hives is measured twice daily (morning and evening), on a scale from 0 (none) to 3 (> 12 hives per 12 hours). Daily hives score is the average of morning and evening scores, and the weekly hives score is the sum of the daily hives scores over 7 days (range, 0−21). Change from Baseline was defined as itch severity score at Week 12 minus the baseline score and was calculated using BOCF method. This analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline (Screening [Days -18 to -7]) and Week 12

End point values	Placebo	Omalizumab 75 mg	Omalizumab 150 mg	Omalizumab 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	82	82	79
Units: Scores on a scale				
arithmetic mean (standard deviation)	-5.22 (± 6.56)	-7.21 (± 6.96)	-9.75 (± 7.28)	-11.97 (± 7.58)

Statistical analyses

Statistical analysis title	Change from Baseline in weekly number of hives
Comparison groups	Placebo v Omalizumab 75 mg
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0603
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.11
upper limit	0.09

Statistical analysis title	Change from Baseline in weekly number of hives
Comparison groups	Placebo v Omalizumab 150 mg
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.51

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.65
upper limit	-2.36

Statistical analysis title	Change from Baseline in weekly number of hives
Comparison groups	Placebo v Omalizumab 300 mg
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.26
upper limit	-4.93

Secondary: Median time to minimally important difference response in the weekly itch severity score by Week 12

End point title	Median time to minimally important difference response in the weekly itch severity score by Week 12

End point description:

The minimally important difference (MID) response for weekly itch severity score was defined as a reduction from Baseline in weekly itch severity score of >= 5 points. The time to weekly itch severity score MID response was defined as the time (in weeks) from Day 1 to the study week when weekly itch severity score MID response was first achieved. This analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Up to Week 12

End point values	Placebo	Omalizumab 75 mg	Omalizumab 150 mg	Omalizumab 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	82	82	79
Units: Number of weeks				
median (full range (min-max))	4 (1 to 12)	2 (0 to 12)	2 (1 to 12)	1 (1 to 12)

Statistical analyses

Statistical analysis title	Time to MID response in weekly itch severity score
Comparison groups	Placebo v Omalizumab 75 mg
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0478
Method	Cochran-Mantel-Haenszel
Parameter estimate	Hazard ratio (HR)
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	2.05

Statistical analysis title	Time to MID response in weekly itch severity score
Comparison groups	Placebo v Omalizumab 150 mg
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0101
Method	Cochran-Mantel-Haenszel
Parameter estimate	Hazard ratio (HR)
Point estimate	1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.12
upper limit	2.26

Statistical analysis title	Time to MID response in weekly itch severity score
Comparison groups	Placebo v Omalizumab 300 mg
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Hazard ratio (HR)
Point estimate	2.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.48
upper limit	3.03

Secondary: Number of participants with urticaria activity score 7 less than or equal to 6 at Week 12

End point title	Number of participants with urticaria activity score 7 less than or equal to 6 at Week 12

End point description:

The UAS7 less than or equal to (<=) 6 identifies participants whose conditions are considered clinically well controlled. The UAS is a composite of recorded scores with numeric severity intensity ratings on a scale of 0 (none) to 3 (intense/severe) for analysis of the number of wheals (hives) and the intensity of the itch, measured twice daily (morning and evening). Daily UAS is the average of morning and evening scores (range, 0−6 points per day) and the UAS7 is the sum of the daily UAS scores over 7 days (range, 0−42). Baseline UAS7 was calculated using data from the 7 days prior to the first treatment date. A higher UAS indicated more urticaria activity. A negative change score indicated improvement. This analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Omalizumab 75 mg	Omalizumab 150 mg	Omalizumab 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	82	82	79
Units: Number of participants	15	22	35	52

Statistical analyses

Statistical analysis title	Participants with UAS7 <= 6 at Week 12
Comparison groups	Placebo v Omalizumab 75 mg
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3419
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Participants with UAS7 <= 6 at Week 12
Comparison groups	Placebo v Omalizumab 150 mg
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001
Method	Cochran-Mantel-Haenszel

Statistical analysis title	participants with UAS7 <= 6 at Week 12
Comparison groups	Placebo v Omalizumab 300 mg
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Secondary: Number of participants with minimally important difference in weekly itch severity score at Week 12

End point title	Number of participants with minimally important difference in weekly itch severity score at Week 12

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. The MID response for weekly itch severity score was defined as a reduction from Baseline in weekly itch severity score of 5 points or more. This outcome measure shows number of participants classified as MID responders at Week 12, meaning their weekly itch severity scores at Week 12 were at least 5 points lower than that at the Baseline. This analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Omalizumab 75 mg	Omalizumab 150 mg	Omalizumab 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	82	82	79
Units: Number of participants	38	46	57	62

Statistical analyses

Statistical analysis title	Participants with weekly itch score MID response
Comparison groups	Placebo v Omalizumab 75 mg
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4366
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Participants with weekly itch score MID Response
Comparison groups	Placebo v Omalizumab 150 mg

Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0045
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Participants with weekly itch score MID response
Comparison groups	Placebo v Omalizumab 300 mg
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Secondary: Mean change from Baseline in the weekly size of the largest hive score at Week 12

End point title	Mean change from Baseline in the weekly size of the largest hive score at Week 12

End point description:

The size of the largest hive is assessed twice daily (morning and evening) on a scale of largest hive score (LHC) as 0 (none) to 3 (> 2.5 cm). The daily score is the average of the morning and evening scores. The weekly size of the largest hive score is the sum of the daily scores over 7 days, and ranges from 0 to 21. The Baseline weekly size of the largest hive score is the sum of daily scores over the 7 days prior to the first treatment and was calculated using BOCF method. A higher score indicates larger hives. A negative change score indicates a reduction in hive size. This analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline (Screening [Days -18 to -7]) and Week 12

End point values	Placebo	Omalizumab 75 mg	Omalizumab 150 mg	Omalizumab 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	82	82	79
Units: Scores on a scale				
arithmetic mean (standard deviation)	-4.04 (± 5.55)	-6.52 (± 6.33)	-7.84 (± 6.75)	-11 (± 7.18)

Statistical analyses

Statistical analysis title	Change from Baseline in the weekly size of the LHC
Comparison groups	Placebo v Omalizumab 75 mg

Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0082
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.32
upper limit	-0.65

Statistical analysis title	Change from Baseline in the weekly size of the LHC
Comparison groups	Placebo v Omalizumab 150 mg
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.61
upper limit	-1.9

Statistical analysis title	Change from Baseline in the weekly size of the LHC
Comparison groups	Placebo v Omalizumab 300 mg
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.03
upper limit	-5.27

Secondary: Mean change from Baseline in the overall dermatology life quality index

at Week 12

End point title	Mean change from Baseline in the overall dermatology life quality index at Week 12

End point description:

Dermatology life quality index (DLQI) is a 10-item dermatology-specific health-related quality of life measure. Participants rate 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 (high). 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. This analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline (Screening [Days -18 to -7]) and Week 12

End point values	Placebo	Omalizumab 75 mg	Omalizumab 150 mg	Omalizumab 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	82	82	79
Units: Scores on a scale				
arithmetic mean (standard deviation)	-6.09 (± 7.47)	-7.5 (± 7.16)	8.29 (± 6.31)	-10.15 (± 6.83)

Statistical analyses

Statistical analysis title	Change From Baseline in DLQI at Week 12
Comparison groups	Placebo v Omalizumab 75 mg
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1207
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.82
upper limit	0.45

Statistical analysis title	Change From Baseline in DLQI at Week 12
Comparison groups	Placebo v Omalizumab 150 mg

Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0215 [4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.64
upper limit	-0.38

Notes:

[4] - p-value is derived from ANCOVA t-test.

Statistical analysis title	Change From Baseline in DLQI at Week 12
Comparison groups	Placebo v Omalizumab 300 mg
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0004
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.85
upper limit	-1.73

Secondary: Mean percentage of angioedema-free days from Week 4 to Week 12

End point title	Mean 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 a participant reported as angioedema-free 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. This analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

From Week 4 to Week 12

End point values	Placebo	Omalizumab 75 mg	Omalizumab 150 mg	Omalizumab 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70[5]	71[6]	74[7]	74[8]
Units: Percentage of days				
arithmetic mean (standard deviation)	89.2 (± 19)	93.5 (± 14.9)	91.6 (± 17.4)	95.5 (± 14.5)

Notes:

[5] - Data is presented for the participants available at the time of assessment.

[6] - Data is presented for the participants available at the time of assessment.

[7] - Data is presented for the participants available at the time of assessment.

[8] - Data is presented for the participants available at the time of assessment.

Statistical analyses

Statistical analysis title	Percentage of angioedema-free days from W4 to W12
Comparison groups	Placebo v Omalizumab 75 mg
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1361
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided
lower limit	90
upper limit	97

Statistical analysis title	Percentage of angioedema-free days from W4 to W12
Comparison groups	Placebo v Omalizumab 150 mg
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0905
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided
lower limit	87.6
upper limit	95.6

Statistical analysis title	Percentage of angioedema-free days from W4 to W12
Comparison groups	Placebo v Omalizumab 300 mg

Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided
lower limit	92.1
upper limit	98.8

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 28 weeks	
Adverse event reporting additional description:	
Safety evaluable set: All randomized participants who received at least one dose of study drug (omalizumab or the placebo).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received only placebo injections (i.e., no active treatment)	
Reporting group title	Omalizumab 75 mg
Reporting group description:	
Participants received at least one 75 mg omalizumab injection, but no higher active dose level (150 mg or 300 mg) injections during the treatment period. Six participants were randomized to the Omalizumab 75 mg group received at least one dose of omalizumab 150 mg during the treatment period and were therefore included in the Omalizumab 150 mg group.	
Reporting group title	Omalizumab 150 mg
Reporting group description:	
Participants who received at least one 150 mg omalizumab injection but no higher active dose level (300 mg) injections during the treatment period.	
Reporting group title	Omalizumab 300 mg
Reporting group description:	
Participants received at least one 300 mg omalizumab injection during the treatment period. Two participants were randomized to the Omalizumab 300 mg group; however, they received one dose of omalizumab 150 mg during the treatment period.	

Serious adverse events	Placebo	Omalizumab 75 mg	Omalizumab 150 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 79 (2.53%)	1 / 76 (1.32%)	1 / 88 (1.14%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma in situ			
subjects affected / exposed	0 / 79 (0.00%)	0 / 76 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Tonsillectomy			

subjects affected / exposed	0 / 79 (0.00%)	0 / 76 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Haemorrhoids			
subjects affected / exposed	1 / 79 (1.27%)	0 / 76 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 79 (0.00%)	0 / 76 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 79 (0.00%)	1 / 76 (1.32%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Idiopathic urticaria			
subjects affected / exposed	0 / 79 (0.00%)	0 / 76 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 79 (0.00%)	0 / 76 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 79 (0.00%)	0 / 76 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	1 / 79 (1.27%)	0 / 76 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Omalizumab 300 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 79 (6.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma in situ			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Tonsillectomy			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Haemorrhoids			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Idiopathic urticaria			

subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urticaria			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	Omalizumab 75 mg	Omalizumab 150 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 79 (43.04%)	30 / 76 (39.47%)	39 / 88 (44.32%)
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 79 (6.33%)	4 / 76 (5.26%)	16 / 88 (18.18%)
occurrences (all)	5	5	20
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 79 (5.06%)	2 / 76 (2.63%)	4 / 88 (4.55%)
occurrences (all)	4	2	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 79 (3.80%)	4 / 76 (5.26%)	2 / 88 (2.27%)
occurrences (all)	3	4	2
Skin and subcutaneous tissue disorders			

Idiopathic urticaria			
subjects affected / exposed	2 / 79 (2.53%)	8 / 76 (10.53%)	6 / 88 (6.82%)
occurrences (all)	3	8	8
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 79 (5.06%)	1 / 76 (1.32%)	1 / 88 (1.14%)
occurrences (all)	4	1	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 79 (16.46%)	13 / 76 (17.11%)	12 / 88 (13.64%)
occurrences (all)	16	16	15
Upper respiratory tract infection			
subjects affected / exposed	7 / 79 (8.86%)	0 / 76 (0.00%)	2 / 88 (2.27%)
occurrences (all)	7	0	2
Influenza			
subjects affected / exposed	4 / 79 (5.06%)	5 / 76 (6.58%)	3 / 88 (3.41%)
occurrences (all)	4	5	3
Sinusitis			
subjects affected / exposed	2 / 79 (2.53%)	3 / 76 (3.95%)	1 / 88 (1.14%)
occurrences (all)	2	4	1
Bronchitis			
subjects affected / exposed	2 / 79 (2.53%)	4 / 76 (5.26%)	0 / 88 (0.00%)
occurrences (all)	2	6	0
Urinary tract infection			
subjects affected / exposed	1 / 79 (1.27%)	4 / 76 (5.26%)	3 / 88 (3.41%)
occurrences (all)	1	5	4

Non-serious adverse events	Omalizumab 300 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 79 (41.77%)		
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 79 (10.13%)		
occurrences (all)	8		
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed occurrences (all)	3 / 79 (3.80%) 5		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 2 / 79 (2.53%) 2		
Skin and subcutaneous tissue disorders Idiopathic urticaria subjects affected / exposed occurrences (all)	 4 / 79 (5.06%) 5		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	 4 / 79 (5.06%) 6		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 10 / 79 (12.66%) 15 6 / 79 (7.59%) 8 2 / 79 (2.53%) 2 6 / 79 (7.59%) 6 3 / 79 (3.80%) 3 0 / 79 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 2011	The purpose of the protocol amendment on 11 January 2011 was to modify the study design according to recommendations by the FDA, internal Genentech staff, and external experts. Secondary objective was modified as to provide information about recurrence of disease after withdrawal of omalizumab in participants with refractory CIU. The second treatment period, including the re-randomization portion was removed, accordingly secondary end-points were modified. The planned number of participants within each treatment group were changed from 80 in the Omalizumab treatment group and 60 in the Placebo group to 75 per group. The screening period was modified from 14−18 to 12−18 days prior to Day 1. Post-hoc analyses were conducted on the number of participants who achieved a complete response (UAS7 = 0), at Week 12 and at Week 28.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25046337