



Clinical trial results:

A Phase II, Multicenter, Randomized, Double-Blind, Placebo- Controlled Dose-Ranging Study of Xolair (Omalizumab) in Patients with Chronic Idiopathic Urticaria (CIU) Who Remain Symptomatic with Antihistamine Treatment (H1)

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2009-009498-87 |
| Trial protocol | DE |
| Global end of trial date | 07 January 2010 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 29 July 2016 |
| First version publication date | 29 July 2016 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | Q4577g |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00866788 |
| 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 2010 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 January 2010 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the efficacy of single doses of omalizumab compared with placebo in participants with refractory chronic idiopathic urticaria (CIU) receiving concomitant H1 antihistamine therapy. The secondary objectives were to evaluate the safety and efficacy of different dose levels of omalizumab in participants with refractory CIU, to evaluate the efficacy of omalizumab in participants with refractory CIU on the participant-reported, quality-of-life-related outcome measures and to evaluate the pharmacokinetics and pharmacodynamics of omalizumab in participants with refractory CIU.

Protection of trial subjects:

This study was conducted in accordance with the United States Food and Drug Administration (U.S. FDA) regulations, the International Conference on Harmonisation E6 Guideline for Good Clinical Practice, and applicable local, state, and federal laws, as well as other applicable country laws.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 26 March 2009 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Germany: 13 |
| Country: Number of subjects enrolled | United States: 77 |
| Worldwide total number of subjects | 90 |
| EEA total number of subjects | 13 |

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) | 5 |

| | |
|----------------------|----|
| Adults (18-64 years) | 80 |
| From 65 to 84 years | 5 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were screened from Week -2 to Week -1.

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, Data analyst |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Participants received a single subcutaneous placebo injection on Day 0 of the study. Participants remained on stable doses of their preallocation a chronic idiopathic urticaria (CIU) H1 antihistamine treatment throughout the study, and were provided diphenhydramine as rescue medication for pruritus relief on an as-needed basis.

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

Dosage and administration details:

Participants received a single subcutaneous placebo injection on Day 0 of the study.

| | |
|------------------|-------------------------------|
| Arm title | Omalizumab 75 milligrams (mg) |
|------------------|-------------------------------|

Arm description:

Omalizumab (Xolair) was administered subcutaneously on Day 0 of the study. Participants remained on stable doses of their preallocation CIU H1 antihistamine treatment throughout the study, and were provided diphenhydramine as rescue medication for pruritus relief on an as-needed basis.

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

Dosage and administration details:

75 mg of omalizumab (Xolair) was administered subcutaneously on Day 0 of the study.

| | |
|------------------|-------------------|
| Arm title | Omalizumab 300 mg |
|------------------|-------------------|

Arm description:

Omalizumab (Xolair) was administered subcutaneously on Day 0 of the study. Participants remained on stable doses of their preallocation CIU H1 antihistamine treatment throughout the study, and were provided diphenhydramine as rescue medication for pruritus relief on an as-needed basis.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|-----------------------------------|
| Investigational medicinal product name | Omalizumab |
| Investigational medicinal product code | |
| Other name | Xolair® |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: | |
| 300 mg of omalizumab (Xolair) was administered subcutaneously on Day 0 of the study. | |
| Arm title | Omalizumab 600 mg |

Arm description:

Omalizumab (Xolair) was administered subcutaneously on Day 0 of the study. Participants remained on stable doses of their preallocation CIU H1 antihistamine treatment throughout the study, and were provided diphenhydramine as rescue medication for pruritus relief on an as-needed basis.

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

Dosage and administration details:

600 mg of omalizumab (Xolair) was administered subcutaneously on Day 0 of the study.

| Number of subjects in period 1 | Placebo | Omalizumab 75 milligrams (mg) | Omalizumab 300 mg |
|---------------------------------------|---------|-------------------------------|-------------------|
| Started | 21 | 23 | 25 |
| Completed Week 4 | 20 | 18 | 23 |
| Completed | 15 | 17 | 23 |
| Not completed | 6 | 6 | 2 |
| Consent withdrawn by subject | 2 | 1 | - |
| Physician decision | - | - | 1 |
| Disease progression | 3 | 1 | 1 |
| Pregnancy | - | 1 | - |
| Adverse event | - | 2 | - |
| Lost to follow-up | 1 | 1 | - |

| Number of subjects in period 1 | Omalizumab 600 mg |
|---------------------------------------|-------------------|
| Started | 21 |
| Completed Week 4 | 20 |
| Completed | 16 |
| Not completed | 5 |
| Consent withdrawn by subject | 1 |
| Physician decision | 1 |
| Disease progression | - |
| Pregnancy | - |
| Adverse event | 1 |

| | |
|-------------------|---|
| Lost to follow-up | 2 |
|-------------------|---|

Baseline characteristics

Reporting groups

| | |
|---|-------------------------------|
| Reporting group title | Placebo |
| Reporting group description: Participants received a single subcutaneous placebo injection on Day 0 of the study. Participants remained on stable doses of their preallocation a chronic idiopathic urticaria (CIU) H1 antihistamine treatment throughout the study, and were provided diphenhydramine as rescue medication for pruritus relief on an as-needed basis. | |
| Reporting group title | Omalizumab 75 milligrams (mg) |
| Reporting group description: Omalizumab (Xolair) was administered subcutaneously on Day 0 of the study. Participants remained on stable doses of their preallocation CIU H1 antihistamine treatment throughout the study, and were provided diphenhydramine as rescue medication for pruritus relief on an as-needed basis. | |
| Reporting group title | Omalizumab 300 mg |
| Reporting group description: Omalizumab (Xolair) was administered subcutaneously on Day 0 of the study. Participants remained on stable doses of their preallocation CIU H1 antihistamine treatment throughout the study, and were provided diphenhydramine as rescue medication for pruritus relief on an as-needed basis. | |
| Reporting group title | Omalizumab 600 mg |
| Reporting group description: Omalizumab (Xolair) was administered subcutaneously on Day 0 of the study. Participants remained on stable doses of their preallocation CIU H1 antihistamine treatment throughout the study, and were provided diphenhydramine as rescue medication for pruritus relief on an as-needed basis. | |

| Reporting group values | Placebo | Omalizumab 75 milligrams (mg) | Omalizumab 300 mg |
|---------------------------------------|---------|-------------------------------|-------------------|
| Number of subjects | 21 | 23 | 25 |
| Age categorical Units: Subjects | | | |
| 12-<18 years | 2 | 2 | 1 |
| 18-<40 years | 7 | 10 | 12 |
| >=40 years | 12 | 11 | 12 |
| Gender categorical Units: Subjects | | | |
| Female | 17 | 15 | 17 |
| Male | 4 | 8 | 8 |

| Reporting group values | Omalizumab 600 mg | Total | |
|---------------------------------------|-------------------|-------|--|
| Number of subjects | 21 | 90 | |
| Age categorical Units: Subjects | | | |
| 12-<18 years | 0 | 5 | |
| 18-<40 years | 11 | 40 | |
| >=40 years | 10 | 45 | |
| Gender categorical Units: Subjects | | | |
| Female | 12 | 61 | |
| Male | 9 | 29 | |

End points

End points reporting groups

| | |
|---|-------------------------------|
| Reporting group title | Placebo |
| Reporting group description: Participants received a single subcutaneous placebo injection on Day 0 of the study. Participants remained on stable doses of their preallocation a chronic idiopathic urticaria (CIU) H1 antihistamine treatment throughout the study, and were provided diphenhydramine as rescue medication for pruritus relief on an as-needed basis. | |
| Reporting group title | Omalizumab 75 milligrams (mg) |
| Reporting group description: Omalizumab (Xolair) was administered subcutaneously on Day 0 of the study. Participants remained on stable doses of their preallocation CIU H1 antihistamine treatment throughout the study, and were provided diphenhydramine as rescue medication for pruritus relief on an as-needed basis. | |
| Reporting group title | Omalizumab 300 mg |
| Reporting group description: Omalizumab (Xolair) was administered subcutaneously on Day 0 of the study. Participants remained on stable doses of their preallocation CIU H1 antihistamine treatment throughout the study, and were provided diphenhydramine as rescue medication for pruritus relief on an as-needed basis. | |
| Reporting group title | Omalizumab 600 mg |
| Reporting group description: Omalizumab (Xolair) was administered subcutaneously on Day 0 of the study. Participants remained on stable doses of their preallocation CIU H1 antihistamine treatment throughout the study, and were provided diphenhydramine as rescue medication for pruritus relief on an as-needed basis. | |

Primary: Change in Urticaria Activity Score 7 (UAS7) From Baseline to Week 4

| | |
|---|---|
| End point title | Change in Urticaria Activity Score 7 (UAS7) From Baseline to Week 4 |
| End point description: The UAS is a composite diary-recorded score, which is the sum of the numeric severity intensity ratings (0 = none to 3 = intense) for 1) the number of wheals (hives) and 2) the intensity of the pruritus (itch). The UAS7 is the sum of the daily average UAS (morning and evening values) for 7 days. The maximum UAS7 score is 42. Intent-to-Treat population (all randomized participants). The last observation carried forward value was used if a participant's Week 4 diary data were completely missing. One participant from the omalizumab 600-mg group did not have any post-baseline data and was excluded from the primary analysis. | |
| End point type | Primary |
| End point timeframe: Baseline (based on the 7 days prior to randomization) and 4 weeks (Days 21-27) | |

| End point values | Placebo | Omalizumab 75 milligrams (mg) | Omalizumab 300 mg | Omalizumab 600 mg |
|--------------------------------------|-----------------|-------------------------------|-------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 23 | 25 | 20 |
| Units: scores on a scale | | | | |
| arithmetic mean (standard deviation) | -6.91 (± 9.84) | -9.79 (± 11.75) | -19.93 (± 12.38) | -14.56 (± 10.17) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Placebo v Omalizumab 75 milligrams (mg) |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1601 ^[1] |
| Method | van Elteren test |

Notes:

[1] - The p-value was based on the van Elteren test (stratified by baseline weight ≥ 80 or < 80 kg).

| | |
|---|-----------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Placebo v Omalizumab 300 mg |
| Number of subjects included in analysis | 46 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0003 ^[2] |
| Method | van Elteren test |

Notes:

[2] - The p-value was based on the van Elteren test (stratified by baseline weight ≥ 80 or < 80 kg).

| | |
|---|-----------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Placebo v Omalizumab 600 mg |
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0473 ^[3] |
| Method | van Elteren test |

Notes:

[3] - The p-value was based on the van Elteren test (stratified by baseline weight ≥ 80 or < 80 kg).

Secondary: Change in the Weekly Pruritus Score From Baseline to Week 4

| | |
|-----------------|---|
| End point title | Change in the Weekly Pruritus Score From Baseline to Week 4 |
|-----------------|---|

End point description:

The pruritus (itch) score was recorded by participants twice daily (morning and evening) based on the severity of itch over the last 12 hours, using a scale from 0 (none) to 3 (severe). The weekly pruritus score was the sum of average daily pruritus scores over the previous 7 days. The range of the weekly score is 0-21. Intent-to-Treat population (all randomized participants). The last observation carried forward value was used if a participant's Week 4 diary data were completely missing. One participant from the omalizumab 600-mg group did not have any post-baseline data and was excluded from the analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (based on the 7 days prior to randomization) and 4 weeks (Days 21-27)

| End point values | Placebo | Omalizumab 75 milligrams (mg) | Omalizumab 300 mg | Omalizumab 600 mg |
|--------------------------------------|-----------------|-------------------------------|-------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 23 | 25 | 20 |
| Units: scores on a scale | | | | |
| arithmetic mean (standard deviation) | -3.45 (± 5.22) | -4.5 (± 5.84) | -9.22 (± 5.98) | -6.46 (± 5.63) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Placebo v Omalizumab 75 milligrams (mg) |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.164 ^[4] |
| Method | van Elteren test |

Notes:

[4] - The p-value was based on the van Elteren test (stratified by baseline weight ≥ 80 or < 80 kg).

| | |
|---|-----------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Placebo v Omalizumab 300 mg |
| Number of subjects included in analysis | 46 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0005 ^[5] |
| Method | van Elteren test |

Notes:

[5] - The p-value was based on the van Elteren test (stratified by baseline weight ≥ 80 or < 80 kg).

| | |
|---|-----------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Placebo v Omalizumab 600 mg |
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0558 ^[6] |
| Method | van Elteren test |

Notes:

[6] - The p-value was based on the van Elteren test (stratified by baseline weight ≥ 80 or < 80 kg).

Secondary: Change in the Weekly Score for Number of Hives From Baseline to Week 4

| | |
|-----------------|--|
| End point title | Change in the Weekly Score for Number of Hives From Baseline to Week 4 |
|-----------------|--|

End point description:

The number of hives was recorded by participants twice daily (morning and evening) using a scale from 0 (no hives) to 3 (more than 12 hives). The weekly score of number of hives was the sum of the average daily scores over the previous 7 days, and ranged from 0 to 21. Intent-to-Treat population (all randomized patients). The last observation carried forward value was used if a patient's Week 4 diary data were completely missing. One subject from the omalizumab 600-mg group did not have any post-baseline data and was excluded from the analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (based on the 7 days prior to randomization) and 4 weeks (Days 21-27)

| End point values | Placebo | Omalizumab 75 milligrams (mg) | Omalizumab 300 mg | Omalizumab 600 mg |
|--------------------------------------|-----------------|-------------------------------|-------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 23 | 25 | 20 |
| Units: scores on a scale | | | | |
| arithmetic mean (standard deviation) | -3.46 (± 5.17) | -5.28 (± 6.91) | -10.71 (± 6.75) | -8.1 (± 6) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Omalizumab 75 milligrams (mg) v Placebo |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1411 ^[7] |
| Method | van Elteren test |

Notes:

[7] - The p-value was based on the van Elteren test (stratified by baseline weight ≥ 80 or < 80 kg).

| | |
|---|-----------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Placebo v Omalizumab 300 mg |
| Number of subjects included in analysis | 46 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0003 ^[8] |
| Method | van Elteren test |

Notes:

[8] - The p-value was based on the van Elteren test (stratified by baseline weight ≥ 80 or < 80 kg).

| | |
|-----------------------------------|-----------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Placebo v Omalizumab 600 mg |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0248 ^[9] |
| Method | van Elteren test |

Notes:

[9] - The p-value was based on the van Elteren test (stratified by baseline weight ≥ 80 or < 80 kg).

Secondary: Change in the Weekly Score for Sleep Interference From Baseline to Week 4

| | |
|-----------------|---|
| End point title | Change in the Weekly Score for Sleep Interference From Baseline to Week 4 |
|-----------------|---|

End point description:

The extent to which hives or itch interfered with participants' sleep was recorded once daily in the patient diary using a scale from 0 (no interference) to 3 (substantial interference, waking often). The weekly score of sleep interference was the sum of the daily scores over the previous 7 days, and ranged from 0 to 21. Intent-to-Treat population (all randomized patients). The last observation carried forward value was used if a patient's Week 4 diary data were completely missing. One subject from the omalizumab 600-mg group did not have any post-baseline data and was excluded from the analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (based on the 7 days prior to randomization) and 4 weeks (Days 21-27)

| End point values | Placebo | Omalizumab 75 milligrams (mg) | Omalizumab 300 mg | Omalizumab 600 mg |
|--------------------------------------|---------------------|-------------------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 23 | 25 | 20 |
| Units: scores on a scale | | | | |
| arithmetic mean (standard deviation) | -3.23 (\pm 5.93) | -3.9 (\pm 5.03) | -5.81 (\pm 5.36) | -6.85 (\pm 6.23) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Placebo v Omalizumab 75 milligrams (mg) |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5507 ^[10] |
| Method | van Elteren test |

Notes:

[10] - The p-value was based on the van Elteren test (stratified by baseline weight ≥ 80 or < 80 kg).

| | |
|-----------------------------------|-----------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Placebo v Omalizumab 300 mg |

| | |
|---|--------------------------|
| Number of subjects included in analysis | 46 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1525 ^[11] |
| Method | van Elteren test |

Notes:

[11] - The p-value was based on the van Elteren test (stratified by baseline weight ≥ 80 or < 80 kg).

| | |
|---|-----------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Placebo v Omalizumab 600 mg |
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0449 ^[12] |
| Method | van Elteren test |

Notes:

[12] - The p-value was based on the van Elteren test (stratified by baseline weight ≥ 80 or < 80 kg).

Secondary: Change in the Weekly Score for the Amount of Rescue Medication From Baseline to Week 4

| | |
|-----------------|--|
| End point title | Change in the Weekly Score for the Amount of Rescue Medication From Baseline to Week 4 |
|-----------------|--|

End point description:

Diphenhydramine 25mg was provided and used on an as-needed basis (maximum 3 times/day) as rescue medication. The weekly score for the amount of rescue medication is the sum of the daily scores for the amount of rescue medication used at each day in the week, and ranged from 0 to 21. Intent-to-Treat population (all randomized patients). The last observation carried forward value was used if a patient's Week 4 diary data were completely missing. One subject from the omalizumab 600-mg group did not have any post-baseline data and was excluded from the analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (based on the 7 days prior to randomization) and 4 weeks (Days 21-27)

| End point values | Placebo | Omalizumab 75 milligrams (mg) | Omalizumab 300 mg | Omalizumab 600 mg |
|--------------------------------------|---------------------|-------------------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 23 | 25 | 20 |
| Units: pills | | | | |
| arithmetic mean (standard deviation) | -1.38 (\pm 4.39) | -1.74 (\pm 4.48) | -2.64 (\pm 5.17) | -1.69 (\pm 3.56) |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Placebo v Omalizumab 75 milligrams (mg) |

| | |
|---|--------------------------|
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7261 ^[13] |
| Method | van Elteren test |

Notes:

[13] - The p-value was based on the van Elteren test (stratified by baseline weight \geq 80 or $<$ 80 kg).

| | |
|---|-----------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Placebo v Omalizumab 300 mg |
| Number of subjects included in analysis | 46 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.162 ^[14] |
| Method | van Elteren test |

Notes:

[14] - The p-value was based on the van Elteren test (stratified by baseline weight \geq 80 or $<$ 80 kg).

| | |
|---|-----------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Placebo v Omalizumab 600 mg |
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6504 ^[15] |
| Method | van Elteren test |

Notes:

[15] - The p-value was based on the van Elteren test (stratified by baseline weight \geq 80 or $<$ 80 kg).

Secondary: Number of Patients With Adverse Events by Severity

| | |
|-----------------|--|
| End point title | Number of Patients With Adverse Events by Severity |
|-----------------|--|

End point description:

The severity (i.e. intensity) of each Adverse Event (AE) was graded according to the following scale: Mild: Symptoms causing no or minimal interference with usual social and functional activities. Moderate: Symptoms causing greater than minimal interference with usual social and functional activities. Severe: Symptoms causing inability to perform usual social and functional activities. Additional AE data is provided in the AE section below. The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE. A "Serious" AE is defined below. Safety-Evaluable Population, which included all randomized participants who received any study drug. number (n) equals (=) number of participants analyzed in the specified category.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

16 weeks overall (data reported separately for "up to 4 weeks" and "Weeks 5 to 16")

| End point values | Placebo | Omalizumab 75 milligrams (mg) | Omalizumab 300 mg | Omalizumab 600 mg |
|--|-----------------|-------------------------------|-------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 23 | 25 | 21 |
| Units: participants | | | | |
| number (not applicable) | | | | |
| 4 Weeks - Any Adverse Event (n=21,23,25,21) | 10 | 8 | 12 | 10 |
| 4 Weeks - Mild (n=21,23,25,21) | 8 | 4 | 6 | 7 |
| 4 Weeks - Moderate (n=21,23,25,21) | 2 | 3 | 5 | 2 |
| 4 Weeks - Severe (n=21,23,25,21) | 0 | 1 | 1 | 1 |
| Follow-up period-Any adverse event (n=20,18,23,20) | 7 | 9 | 12 | 5 |
| Follow-up period-Mild (n=20,18,23,20) | 4 | 5 | 4 | 3 |
| Follow-up period-Moderate (n=20,18,23,20) | 2 | 2 | 6 | 1 |
| Follow-up period-Severe (n=20,18,23,20) | 1 | 2 | 2 | 1 |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Immunogenicity

| | |
|---|--|
| End point title | Number of Participants With Immunogenicity |
| End point description: | |
| Immunogenicity was measured by detection of anti-therapeutic antibodies (anti-omalizumab antibodies) using a fragment enzyme-linked immunosorbent assay (ELISA). Analysis was performed on safety-evaluable population. | |
| End point type | Secondary |
| End point timeframe: | |
| 16 weeks | |

| End point values | Placebo | Omalizumab 75 milligrams (mg) | Omalizumab 300 mg | Omalizumab 600 mg |
|-----------------------------|-----------------|-------------------------------|-------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 23 | 25 | 21 |
| Units: participants | | | | |
| number (not applicable) | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (C_{max}) of Omalizumab

| | |
|--|---|
| End point title | Maximum Observed Concentration (Cmax) of Omalizumab ^[16] |
| End point description: Cmax is the maximum (or peak) concentration of omalizumab in serum. The analysis was performed on Pharmacokinetic-Evaluable Population which included all randomized participants who received omalizumab and had pharmacokinetic data available. Here, number of participants analyzed = participants with available data for this outcome measure. | |
| End point type | Secondary |
| End point timeframe: Pre-dose and 2 hours post-dose on Days 0 and 3 of Week 0, Weeks 1, 2, 3, 4, 8, 12, 16 or early termination (up to Week 16) | |
| Notes: [16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Placebo group did not receive any omalizumab, therefore Cmax is not applicable. | |

| End point values | Omalizumab 75 milligrams (mg) | Omalizumab 300 mg | Omalizumab 600 mg | |
|--|-------------------------------|-------------------|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 22 | 23 | 20 | |
| Units: micrograms per milliliter (µg/mL) | | | | |
| arithmetic mean (standard deviation) | 11.4 (± 16.4) | 33.1 (± 10.4) | 67 (± 26.9) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Concentration (Tmax) of Omalizumab

| | |
|--|--|
| End point title | Time to Maximum Concentration (Tmax) of Omalizumab ^[17] |
| End point description: Tmax is the time to maximum concentration of omalizumab. Here, number of participants analyzed = participants with available data for this outcome measure. | |
| End point type | Secondary |
| End point timeframe: Pre-dose and 2 hours post-dose on Days 0 and 3 of Week 0, Weeks 1, 2, 3, 4, 8, 12, 16 or early termination (up to Week 16) | |
| Notes: [17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Placebo group did not receive any omalizumab, therefore Tmax is not applicable. | |

| End point values | Omalizumab 75 milligrams (mg) | Omalizumab 300 mg | Omalizumab 600 mg | |
|--------------------------------------|-------------------------------|-------------------|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 22 | 23 | 20 | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | 7.37 (± 3.72) | 8.01 (± 5.54) | 6.24 (± 3.51) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve from Time of Dosing Extrapolated to Infinity (AUC-Inf)

| | |
|-----------------|--|
| End point title | Area Under the Concentration-time Curve from Time of Dosing Extrapolated to Infinity (AUC-Inf) ^[18] |
|-----------------|--|

End point description:

AUCinf is the area under the concentration-time curve from time of dosing extrapolated to infinity. AUCinf was measured in microgram times day per milliliter ($\mu\text{g}\cdot\text{day}/\text{mL}$). The analysis was performed on Pharmacokinetic-Evaluable Population. Here, number of participants analyzed = participants with available data for this outcome measure.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose and 2 hours post-dose on Days 0 and 3 of Week 0, Weeks 1, 2, 3, 4, 8, 12, 16 or early termination (up to Week 16)

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Placebo group did not receive any omalizumab, therefore AUC-Inf is not applicable.

| End point values | Omalizumab 75 milligrams (mg) | Omalizumab 300 mg | Omalizumab 600 mg | |
|---|-------------------------------|-------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 18 | 22 | 19 | |
| Units: $\mu\text{g}\cdot\text{day}/\text{mL}$ | | | | |
| arithmetic mean (standard deviation) | 317 (\pm 99.6) | 1260 (\pm 580) | 2800 (\pm 1140) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Half-Life ($t_{1/2}$) of Omalizumab

| | |
|-----------------|--|
| End point title | Terminal Half-Life ($t_{1/2}$) of Omalizumab ^[19] |
|-----------------|--|

End point description:

Terminal Half-Life ($t_{1/2}$) is the time required for the serum concentration of omalizumab to decrease by half in the final stage of its elimination. The analysis was performed on Pharmacokinetic-Evaluable Population. Here, number of participants analyzed = participants with available data for this outcome measure.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose and 2 hours post-dose on Days 0 and 3 of Week 0, Weeks 1, 2, 3, 4, 8, 12, 16 or early termination (up to Week 16)

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Placebo group did not receive any omalizumab, therefore $t_{1/2}$ is not applicable.

| End point values | Omalizumab 75 milligrams (mg) | Omalizumab 300 mg | Omalizumab 600 mg | |
|--------------------------------------|-------------------------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 18 | 22 | 19 | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | 18.2 (± 4.76) | 17.1 (± 4.41) | 22.5 (± 5.9) | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were recorded from Day -7 until end of study at 16 weeks

Adverse event reporting additional description:

A Serious AE is any AE that is either: fatal, life threatening, requires or prolongs inpatient hospitalization, results in persistent or significant disability/incapacity, a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the study treatment or considered a significant medical event by the investigator.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Participants received a single subcutaneous placebo injection on Day 0 of the study. Participants remained on stable doses of their preallocation a CIU H1 antihistamine treatment throughout the study, and were provided diphenhydramine as rescue medication for pruritus relief on an as-needed basis.

| | |
|-----------------------|------------------|
| Reporting group title | Omalizumab 75 mg |
|-----------------------|------------------|

Reporting group description:

Omalizumab (Xolair) was administered subcutaneously on Day 0 of the study. Participants remained on stable doses of their preallocation CIU H1 antihistamine treatment throughout the study, and were provided diphenhydramine as rescue medication for pruritus relief on an as-needed basis.

| | |
|-----------------------|-------------------|
| Reporting group title | Omalizumab 300 mg |
|-----------------------|-------------------|

Reporting group description:

Omalizumab (Xolair) was administered subcutaneously on Day 0 of the study. Participants remained on stable doses of their preallocation CIU H1 antihistamine treatment throughout the study, and were provided diphenhydramine as rescue medication for pruritus relief on an as-needed basis.

| | |
|-----------------------|-------------------|
| Reporting group title | Omalizumab 600 mg |
|-----------------------|-------------------|

Reporting group description:

Omalizumab (Xolair) was administered subcutaneously on Day 0 of the study. Participants remained on stable doses of their preallocation CIU H1 antihistamine treatment throughout the study, and were provided diphenhydramine as rescue medication for pruritus relief on an as-needed basis.

| Serious adverse events | Placebo | Omalizumab 75 mg | Omalizumab 300 mg |
|--|----------------|------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 1 / 25 (4.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Omalizumab 600 mg | | |
|--|-------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 21 (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 300 mg |
|---|-----------------|------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 5 / 21 (23.81%) | 9 / 23 (39.13%) | 11 / 25 (44.00%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 23 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 1 | 0 | 4 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 23 (8.70%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 23 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 1 | 0 | 2 |
| Skin and subcutaneous tissue disorders | | | |
| Idiopathic urticaria | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 23 (4.35%) | 1 / 25 (4.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 23 (0.00%) | 0 / 25 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |

| | | | |
|--|---------------------|----------------------|----------------------|
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 4 | 4 / 23 (17.39%) 5 | 3 / 25 (12.00%) 3 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 2 / 23 (8.70%) 2 | 3 / 25 (12.00%) 3 |

| | | | |
|--|----------------------|--|--|
| Non-serious adverse events | Omalizumab 600 mg | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 8 / 21 (38.10%) | | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 3 / 21 (14.29%) 3 | | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | | |
| Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | | |
| Skin and subcutaneous tissue disorders Idiopathic urticaria subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | | |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | | |
| Upper respiratory tract infection | | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 2 / 21 (9.52%) | | |
| occurrences (all) | 2 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|--------------|---|
| 16 July 2009 | Study Q4577g was amended to consolidate the two CIU protocols for Germany and the United States into one single protocol covering both countries, per recommendation by Genentech's Product Development Regulatory. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported