Clinical trial results:
A Phase IV, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Persistency of Response with or without Xolair after Long-Term Therapy (XPORT)

Summary

EudraCT number	2016-001001-16
Trial protocol	Outside EU/EEA
Global end of trial date	14 August 2013

Results information

Result version number	v1 (current)
This version publication date	07 January 2017
First version publication date	07 January 2017

Trial information

Trial identification

Sponsor protocol code	Q4777n

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01125748
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	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, 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	14 August 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a randomised, double-blind, placebo-controlled, 2-arm, 1-year study of subjects who completed the EXCELS study (NCT00252135) and had received long-term treatment with Xolair. In addition, subjects who did not participate in the EXCELS study but received long-term (~5 years) treatment with Xolair were allowed to enter the study.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy:

Subjects could receive 1 or more of the following medications as concomitant asthma therapy: Inhaled corticosteroids; long acting beta-agonists; zafirlukast or other leukotriene receptor antagonist; zileuton or other 5-lipoxygenase enzyme inhibitors; oral, inhaled, and/or nasal anticholinergic therapy; mast-cell stabilizers; theophyllines; chronic oral corticosteroids, defined as a minimum dose of oral prednisone of 2 to 40 mg/day or 5 to 80 mg every other day.

Evidence for comparator: -

Actual start date of recruitment	12 May 2010
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	United States: 176
Worldwide total number of subjects	176
EEA total number of subjects	0

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)	1
Adults (18-64 years)	151

From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects, who previously completed the EXCELS study and received long-term treatment with omalizumab (Xolair). In addition, subjects, who did not participate in the EXCELS study but received long-term (~5 years) treatment with omalizumab. Continuous omalizumab exposure was required prior to enrollment in this study.

Pre-assignment

Screening details:

Eligible subjects were randomised in a 1:1 ratio to continue to receive omalizumab (Xolair) at the same dose and dosing interval as administered prior to enrollment to this study (continuation group) or to receive placebo at the same dosing interval as omalizumab (Xolair) was administered prior to enrollment to this study (discontinuation group).

Period 1

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

Blinding implementation details:

The treatment designation for subjects reaching the primary efficacy endpoint (one protocol-defined severe asthma exacerbation) was unblinded to allow appropriate clinical intervention. Subjects who had their treatment designation unblinded remained in the study for ongoing evaluation of safety and were allowed to continue on study drug known to be omalizumab (or to start study drug known to be omalizumab if they were in the placebo group).

Arms

Are arms mutually exclusive?	Yes
Arm title	Omalizumab

Arm description:

Subjects received omalizumab subcutaneously at the same dose and dosing interval as administered prior to enrollment in this study. The dose of omalizumab was either a minimum of 0.008 milligrams/kilogram/Immunoglobulin E (mg/kg/IgE) (International Units/millilitre [IU/mL]) every 2 weeks or a minimum of 0.016 mg/kg/IgE (IU/mL) every 4 weeks for 48 weeks.

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:

Omalizumab was administered subcutaneously at the same dose and dosing interval as administered prior to enrollment. The dose of omalizumab was either a minimum of 0.008 mg/kg/IgE (IU/mL) every 2 weeks or a minimum of 0.016 mg/kg/IgE (IU/mL) every 4 weeks for 48 weeks.

Arm title	Placebo

Arm description:

Subjects received matching placebo subcutaneously at the same dosing interval as omalizumab was administered prior to enrollment in this study.

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:

Placebo contained the same ingredients as the omalizumab formulation, excluding omalizumab, and was administered subcutaneously at the same dosing interval as omalizumab was administered prior to enrollment in this study, which was every 2 weeks or every 4 weeks for 48 weeks.

Number of subjects in period 1	Omalizumab	Placebo
Started	88	88
Completed	78	74
Not completed	10	14
Consent withdrawn by subject	2	4
Physician decision	8	7
Adverse event, non-fatal	-	2
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Omalizumab
Reporting group description:	
Subjects received omalizumab subcutaneously at the same dose and dosing interval as administered prior to enrollment in this study. The dose of omalizumab was either a minimum of 0.008 milligrams/kilogram/Immunoglobulin E (mg/kg/IgE) (International Units/millilitre [IU/mL]) every 2 weeks or a minimum of 0.016 mg/kg/IgE (IU/mL) every 4 weeks for 48 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo subcutaneously at the same dosing interval as omalizumab was administered prior to enrollment in this study.	

Reporting group values	Omalizumab	Placebo	Total
Number of subjects	88	88	176
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)	1	0	1
Adults (18-64 years)	78	73	151
From 65-84 years	9	15	24
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	51.14	51.86	
standard deviation	± 11.73	± 13.25	-
Gender categorical Units: Subjects			
Female	63	60	123
Male	25	28	53

End points

End points reporting groups

Reporting group title	Omalizumab

Reporting group description:

Subjects received omalizumab subcutaneously at the same dose and dosing interval as administered prior to enrollment in this study. The dose of omalizumab was either a minimum of 0.008 milligrams/kilogram/Immunoglobulin E (mg/kg/IgE) (International Units/millilitre [IU/mL]) every 2 weeks or a minimum of 0.016 mg/kg/IgE (IU/mL) every 4 weeks for 48 weeks.

Reporting group title	Placebo

Reporting group description:

Subjects received matching placebo subcutaneously at the same dosing interval as omalizumab was administered prior to enrollment in this study.

Primary: Percentage of Subjects Not Experiencing a Protocol-Defined Severe Exacerbation During the Study

End point title	Percentage of Subjects Not Experiencing a Protocol-Defined Severe Exacerbation During the Study

End point description:

A protocol-defined severe exacerbation was a clinically significant worsening of asthma which, in the clinical judgment of the investigator, required at least 1 of the following: (1) Initiation of systemic corticosteroid treatment (tablets, suspension, or injection) or an increase in the level of systemic corticosteroid treatment from a stable maintenance dose for at least 3 days (For patients taking chronic oral corticosteroids, a protocol-defined severe exacerbation was any clinically significant worsening of asthma requiring ≥ 3 days of treatment with at least a 20 mg increase in the average daily dose of oral prednisone or a comparable dose of systemic corticosteroids) or (2) a hospitalization or emergency room visit because of asthma requiring systemic corticosteroids. The Intent-to-treat (ITT) population included all randomised subjects based on randomised treatment groups regardless of actual treatment.

End point type	Primary

End point timeframe:

Baseline to end of study (up to 52 weeks)

End point values	Omalizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	88		
Units: Percentage of subjects				
number (confidence interval 95%)	67 (57.2 to 76.9)	47.7 (37.3 to 58.2)		

Statistical analyses

Statistical analysis title	Mean Difference between Arms
Comparison groups	Omalizumab v Placebo

Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	19.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	5
upper limit	33.6

Secondary: Time to the First Protocol-defined Severe Exacerbation

End point title	Time to the First Protocol-defined Severe Exacerbation

End point description:

A protocol-defined severe exacerbation was a clinically significant worsening of asthma which, in the clinical judgment of the investigator, required at least 1 of the following: (1) Initiation of systemic corticosteroid treatment (tablets, suspension, or injection) or an increase in the level of systemic corticosteroid treatment from a stable maintenance dose for at least 3 days (for subjects taking chronic oral corticosteroids, a protocol-defined severe exacerbation was any clinically significant worsening of asthma requiring ≥ 3 days of treatment with at least a 20 mg increase in the average daily dose of oral prednisone or a comparable dose of systemic corticosteroids) or (2) a hospitalization or emergency room visit because of asthma requiring systemic corticosteroids. The ITT population included all randomised subjects based on randomised treatment groups regardless of actual treatment.

End point type	Secondary

End point timeframe:

Baseline to end of study (up to 52 weeks)

End point values	Omalizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	88		
Units: Weeks				
arithmetic mean (confidence interval 95%)	21.7 (14.41 to 29.03)	16.6 (11.9 to 21.26)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline to end of study (up to 52 weeks)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Omalizumab

Reporting group description:

Subjects received omalizumab subcutaneously at the same dose and dosing interval as administered prior to enrollment in this study. The dose of omalizumab was either a minimum of 0.008 mg/kg/IgE (IU/mL) every 2 weeks or a minimum of 0.016 mg/kg/IgE (IU/mL) every 4 weeks for 48 weeks. The safety population for omalizumab exposure included all subjects who received at least one injection of omalizumab while on study. In addition, subjects from the placebo arm who 'crossed over' and were given omalizumab after an unblinding exacerbation were included.

Reporting group title	Placebo

Reporting group description:

Subjects received matching placebo subcutaneously at the same dosing interval as omalizumab was administered prior to enrollment in this study. The safety population included all subjects who received at least one injection of placebo while on study.

Serious adverse events	Omalizumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 121 (8.26%)	8 / 88 (9.09%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 121 (0.83%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mueller's mixed tumour			
subjects affected / exposed	0 / 121 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Laceration			

subjects affected / exposed	1 / 121 (0.83%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 121 (0.83%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 121 (0.83%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Spontaneous haematoma			
subjects affected / exposed	1 / 121 (0.83%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dyskinesia oesophageal			
subjects affected / exposed	1 / 121 (0.83%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 121 (0.83%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eosinophilic oesophagitis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	6 / 121 (4.96%)	4 / 88 (4.55%)	
occurrences causally related to treatment / all	2 / 6	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 121 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 121 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc degeneration			
subjects affected / exposed	1 / 121 (0.83%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 121 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 121 (0.00%)	1 / 88 (1.14%)	
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	98 / 121 (80.99%)	71 / 88 (80.68%)	
Nervous system disorders			

Headache			
subjects affected / exposed	5 / 121 (4.13%)	3 / 88 (3.41%)	
occurrences (all)	7	3	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	36 / 121 (29.75%)	33 / 88 (37.50%)	
occurrences (all)	62	38	
Rhinitis allergic			
subjects affected / exposed	1 / 121 (0.83%)	7 / 88 (7.95%)	
occurrences (all)	1	8	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 121 (4.96%)	2 / 88 (2.27%)	
occurrences (all)	7	2	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	13 / 121 (10.74%)	11 / 88 (12.50%)	
occurrences (all)	15	15	
Bronchitis			
subjects affected / exposed	9 / 121 (7.44%)	8 / 88 (9.09%)	
occurrences (all)	10	9	
Sinusitis			
subjects affected / exposed	27 / 121 (22.31%)	13 / 88 (14.77%)	
occurrences (all)	36	18	
Upper respiratory tract infection			
subjects affected / exposed	24 / 121 (19.83%)	11 / 88 (12.50%)	
occurrences (all)	28	12	
Urinary tract infection			
subjects affected / exposed	6 / 121 (4.96%)	6 / 88 (6.82%)	
occurrences (all)	13	7	
Viral upper respiratory tract infection			
subjects affected / exposed	6 / 121 (4.96%)	3 / 88 (3.41%)	
occurrences (all)	6	3	
Gastroenteritis viral			
subjects affected / exposed	6 / 121 (4.96%)	1 / 88 (1.14%)	
occurrences (all)	7	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2010	Protocol Q4777n was amended to increase the percent allowance of missed doses from the beginning of EXCELS to enrollment to XPORT (from 10% to 25%); and from maximum of 1 to maximum of 2 doses within the last 6 months before being randomised into XPORT. The original inclusion criteria which required "no more than 3 months between completion of EXCELS and the screening visit for XPORT" has been removed. Subjects should have continued to receive Xolair therapy between completion of EXCELS and enrollment to XPORT to be eligible for this study. In addition, Serious Adverse Events (SAE) reporting period has been updated to 24 hours for all SAE types.
12 July 2011	Protocol Q4777n was amended to allow subjects to enter the study who did not participate in EXCELS but received long-term (~5 years) treatment with Xolair. Additional minor changes have been made to improve clarity and consistency.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported