Clinical trial results:
A randomized, double-blind, placebo-controlled, 28-week, multicenter study with a 8 weeks follow-up period to investigate the impact of subcutaneous omalizumab on quality of life measures and on the incidence and severity of angioedema in patients with chronic spontaneous urticaria and a history of angioedema who remain symptomatic with H1-antihistamine treatment.

Summary

EudraCT number	2011-004254-25
Trial protocol	DE
Global end of trial date	09 May 2014

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	13 August 2015

Trial information

Trial identification

Sponsor protocol code	CIGE025EDE16

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01723072
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis AG, 41 613241111,

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	09 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 May 2014
Global end of trial reached?	Yes
Global end of trial date	09 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate the superiority of Omalizumab 300 mg versus placebo in patients with moderate to severe CSU regarding QoL measures. This was done by evaluating the change of total CU-Q2oL scores in moderate to severe CSU patients with a history of angioedema and insufficient treatment response to a high dose of nsH1-antihistamines (second line treatment: up to 4 times of the approved nsH1-antihistamine dose). Scores were calculated from baseline (visit 2) to week 28 (visit 9) with secondary objective(s).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 91
Worldwide total number of subjects	91
EEA total number of subjects	91

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	88
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:
Eligible study patients were randomized in a 1:1 ratio

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Omalizumab

Arm description:
Omalizumab once a month via subcutaneous injection.

Arm type	Experimental
Investigational medicinal product name	Omalizumab
Investigational medicinal product code	IGE025
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:
patients received two injections of Omalizumab 150 mg every four weeks

Arm title	Placebo

Arm description:
Placebo of omalizumab once a month via subcutaneous injection

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:
patients received two injections of Placebo every four weeks

Number of subjects in period 1	Omalizumab	Placebo
Started	44	47
Completed	33	26
Not completed	11	21
Consent withdrawn by subject	7	13
Discon for rescue medication after wk 24	-	5

Unknown	4	3

Baseline characteristics

Reporting groups	
Reporting group title	Omalizumab
Reporting group description: Omalizumab once a month via subcutaneous injection.	
Reporting group title	Placebo
Reporting group description: Placebo of omalizumab once a month via subcutaneous injection	

Reporting group values	Omalizumab	Placebo	Total
Number of subjects	44	47	91
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)	0	0	0
Adults (18-64 years)	41	47	88
From 65-84 years	3	0	3
85 years and over	0	0	0
Age Continuous | Units: years			
arithmetic mean	44.9	41.1	
standard deviation	± 13.7	± 10.6	-
Gender, Male/Female Units: participants			
Male	14	14	28
Female	30	33	63
Age, Customized Units: Subjects			
<65 years	41	47	88
>=65 years	3	0	3
Study Specific Characteristic			
Body Mass Index group			
Units: Subjects			
<18.5	0	0	0
18.5-25	20	12	32
>25	24	35	59
Race/Ethnicity, Customized Units: Subjects			
Caucasian	42	46	88
Asian	1	1	2
Other	1	0	1
Study Specific Characteristic			

End points

End points reporting groups

Reporting group title	Omalizumab
Reporting group description:	
Omalizumab once a month via subcutaneous injection.	
Reporting group title	Placebo
Reporting group description:	
Placebo of omalizumab once a month via subcutaneous injection	

Primary: Mean change from baseline using Chronic urticaria quality of life questionnaire (CU-Q2oL) total scores during the study: unadjusted analysis and ANCOVA (LOCF) (FAS)

End point title	Mean change from baseline using Chronic urticaria quality of life questionnaire (CU-Q2oL) total scores during the study: unadjusted analysis and ANCOVA (LOCF) (FAS)
End point description:	
The CU-Q2oL is a questionnaire that measures the relative burden of chronic urticaria on subjective well-being. It consists of 23 questions in 3 domains (symptoms, general impairment, difficulties and problems due to urticaria). Patients are asked to respond how much they are troubled by each problem on a 5-point Likert scale (1= not at all to 5= very much). An overall score is calculated and normalized to a scale of 1 to 100.	
End point type	Primary
End point timeframe:	
Baseline/week 28	

End point values	Omalizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	47		
Units: score				
arithmetic mean (standard deviation)				
V3 (week 4)	-25.5 (± 21.3)	-6.4 (± 15.9)		
V5 (week 12)	-32.1 (± 21.8)	-12.1 (± 20.3)		
V7 (week 20)	-31.4 (± 23.7)	-16.2 (± 18.8)		
V9 (week 28)	-35.1 (± 24.2)	-13.9 (± 17.7)		
Follow-up (week 36)	-23.9 (± 23)	-14.7 (± 19.2)		

Statistical analyses

Statistical analysis title	CU-Q2oL Total Scores during study
Comparison groups	Omalizumab v Placebo

Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA

Secondary: Number of angioedema burdened days by study phase (observed cases with imputation)

End point title	Number of angioedema burdened days by study phase (observed cases with imputation)

End point description:

End point type	Secondary

End point timeframe:

Baseline/week 28

End point values	Omalizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	47		
Units: days				
arithmetic mean (standard deviation)				
Screening (Week -2 to -1)	5.2 (± 3.9)	6.8 (± 4.3)		
Treatment (Week 1 to 28)	14.6 (± 19.5)	49.5 (± 50.8)		
Follow-up (Week 29 to 36)	5.8 (± 9.1)	12.8 (± 16.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean time interval between successive angioedema episodes of the first 15 episodes

End point title	Mean time interval between successive angioedema episodes of the first 15 episodes

End point description:

End point type	Secondary

End point timeframe:

Baseline to week 28

End point values	Omalizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	47		
Units: days				
arithmetic mean (standard deviation)				
1st to 2nd episode (n=36/43)	20 (± 41.63)	7.8 (± 14.29)		
2nd to 3rd episode (n=30/42)	11 (± 19.52)	7.2 (± 10.16)		
3rd to 4th episode (n=28/39)	26.4 (± 50.73)	8.3 (± 13.24)		
4th to 5th episode (n=27/36)	14.9 (± 23.87)	8.6 (± 20.44)		
5th to 6th episode (n=25/34)	14.2 (± 20.54)	13.6 (± 30.09)		
6th to 7th episode (n=21/31)	11.2 (± 22.11)	7.5 (± 11.32)		
7th to 8th episode (n=15/29)	18.1 (± 29.41)	9.1 (± 17.58)		
8th to 9th episode (n=14/28)	10.7 (± 15.05)	8 (± 12.26)		
9th to 10th episode (n=11/26)	11.4 (± 20.16)	8.7 (± 12.26)		
10th to 11th episode (n=11/23)	11.5 (± 13.02)	8.5 (± 10.41)		
11th to 12th episode (n=10/21)	8.9 (± 9.42)	9.4 (± 13.89)		
12th to 13th episode (n=8/18)	6 (± 4.47)	4.3 (± 4.43)		
13th to 14th episode (n=8/18)	3.6 (± 3.02)	7.3 (± 4.56)		
14th to 15th episode (n=7/17)	6.9 (± 9.96)	10.1 (± 11.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change of AAS total week sum scores from baseline to week 28: unadjusted analysis and ANCOVA (observed cases with imputation)

End point title	Change of AAS total week sum scores from baseline to week 28: unadjusted analysis and ANCOVA (observed cases with imputation)

End point description:

A cumulative activity score, evaluated in the screening period and throughout the study. The records each evening on a daily basis symptoms of itch and hives into a patient diary.

End point type	Secondary

End point timeframe:

Baseline to week 28

End point values	Omalizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	47		
Units: AAS (Angioedema Activity Score)				
arithmetic mean (standard deviation)				
Diary week 4 (n=43,44)	-17.7 (± 20)	-5 (± 18.2)		
Diary week 12 (n=39,34)	-19 (± 22.4)	-9 (± 22.8)		
Diary week 20 (n=35,32)	-21.3 (± 21.6)	-16.9 (± 21)		
Diary week 28 (n=34, 32)	-20.6 (± 21.5)	-10.8 (± 21.3)		
Diary week 36 (n=-23, 16)	-9.6 (± 18.4)	-15.3 (± 20.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Diameter: acute swelling episodes within the screening period (Week -2 to -1)

End point title	Diameter: acute swelling episodes within the screening period (Week -2 to -1)

End point description:

End point type	Secondary

End point timeframe:

week -2 to -1

End point values	Omalizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	47		
Units: Number of episodes				
Acute swelling episode, Diameter <10cm	146	165		
Acute swelling episode, Diameter 10-20cm	54	99		
Acute swelling episode, Diameter >20cm	19	46		
unknown	12	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Diameter: acute swelling episodes at end of treatment (weeks 25 to 28)

End point title	Diameter: acute swelling episodes at end of treatment (weeks 25 to 28)

End point description:

End point type	Secondary

End point timeframe:

weeks 25 to 28

End point values	Omalizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	25		
Units: Number of episodes				
Acute swelling episode, Diameter <10cm	31	76		
Acute swelling episode, Diameter 10-20cm	0	94		
Acute swelling episode, Diameter 20cm	0	24		
unknown	0	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Diameter: acute swelling episodes at end of follow-up(weeks 33 to 36)

End point title	Diameter: acute swelling episodes at end of follow-up(weeks 33 to 36)

End point description:

End point type	Secondary

End point timeframe:

weeks 33 to 36

End point values	Omalizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	23		
Units: Number of episodes				
Acute swelling episode, Diameter <10cm	92	90		
Acute swelling episode, Diameter 10-20cm	28	58		
Acute swelling episode, Diameter >20cm	8	19		
unknown	17	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Shortness of breath: acute swelling episodes within the screening period

(weeks -2 to -1)

End point title	Shortness of breath: acute swelling episodes within the screening period (weeks -2 to -1)

End point description:

End point type	Secondary

End point timeframe:
weeks -2 to -1

End point values	Omalizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	47		
Units: number of episodes				
Shortness of breath: No	203	264		
Shortness of breath: Slightly	13	25		
Shortness of breath: Moderately	7	25		
Shortness of breath: Severely	1	7		
Unknown	7	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Shortness of breath: acute swelling episodes at end of treatment period (weeks 25 to 28)

End point title	Shortness of breath: acute swelling episodes at end of treatment period (weeks 25 to 28)

End point description:

End point type	Secondary

End point timeframe:
weeks 25 to 28

End point values	Omalizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	25		
Units: Number of episodes				
Shortness of breath: No	28	195		
Shortness of breath: Slightly	3	5		
Shortness of breath: Moderately	0	5		
Shortness of breath: Severely	0	0		
Unknown	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Shortness of breath: acute swelling episodes at end of follow-up period (weeks 33 to 36)

End point title	Shortness of breath: acute swelling episodes at end of follow-up period (weeks 33 to 36)

End point description:

End point type	Secondary

End point timeframe:

weeks 33 to 36

End point values	Omalizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	23		
Units: Number of episodes				
Shortness of breath: No	28	195		
Shortness of breath: Slightly	3	5		
Shortness of breath: Moderately	0	5		
Shortness of breath: Severely	0	0		
Unknown	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change of AE-Q2oL scores from baseline to week 28: unadjusted analysis and ANCOVA (observed cases)

End point title	Change of AE-Q2oL scores from baseline to week 28: unadjusted analysis and ANCOVA (observed cases)

End point description:

The AE-Q2oL is a questionnaire for patients suffering from angioedema. It consists of 29 questions relevant to angioedema and its specific impact on quality of life. Patients are asked to respond how much they are troubled be each problem on a 5-point Likert scale (1= does not apply to 5= very much). An overall score is calculated and a higher score indicates lower quality of life. A negative change score (week 28 score minus baseline score) indicates improvement.

End point type	Secondary

End point timeframe:

baseline to week 28

End point values	Omalizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	47		
Units: AE-QoL Score				
arithmetic mean (standard deviation)				
week 4 (n=38,36)	-26.5 (± 20.4)	-10.3 (± 21)		
week 12 (n= 35, 29)	-37.4 (± 23.8)	-20.4 (± 27.4)		
week 20 (n=34,27)	-37.1 (± 26.5)	-28.8 (± 22)		
week 28 (n=34, 25)	-41.4 (± 25.7)	-24.2 (± 24.3)		
follow-up, week 36 (n=33,23)	-27.2 (± 26.4)	-24.6 (± 23.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rescue medication during the treatment period

End point title	Rescue medication during the treatment period

End point description:

End point type	Secondary

End point timeframe:
baseline to 28 weeks

End point values	Omalizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	47		
Units: participants				
Any rescue medication	25	35		
Any nsH1 - antihistamine rescue medication	19	27		
Any clemastine rescue medication	12	26		
Any corticosteroid rescue medication	5	13		
Betamethasone	2	12		
Prednisolone	3	3		
Prednisolone succinate	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Days of rescue medication during the treatment period

End point title	Days of rescue medication during the treatment period

End point description:

End point type	Secondary

End point timeframe:
baseline to 28 weeks

End point values	Omalizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	47		
Units: days				
Any rescue medication	507	787		
Any nsH1 - antihistamine rescue medication	403	524		
Any clemastine rescue medication	92	236		
Any corticosteroid rescue medication	25	113		

Statistical analyses

No statistical analyses for this end point

Secondary: Days of rescue medication during the follow-up period

End point title	Days of rescue medication during the follow-up period

End point description:

End point type	Secondary

End point timeframe:
weeks 33 to 36

End point values	Omalizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	47		
Units: days				
Any rescue medication	165	118		
Any nsH1 - antihistamine rescue medication	158	85		
Any clemastine rescue medication	15	19		
Any corticosteroid rescue medication	0	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Change of UAS7 total scores from baseline to week 28: unadjusted analysis and ANCOVA (observed cases)

End point title	Change of UAS7 total scores from baseline to week 28: unadjusted analysis and ANCOVA (observed cases)

End point description:

End point type	Secondary

End point timeframe:
baseline to week 28

End point values	Omalizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	47		
Units: participants				
arithmetic mean (standard deviation)				
week 4	-12.6 (± 13.3)	-3 (± 9.4)		
week 12	-16.4 (± 14.3)	-4.4 (± 13.3)		
week 20	-15 (± 15)	-7.2 (± 14.7)		
week 28	-16.8 (± 14.8)	-6.5 (± 13.4)		
follow-up, week 36	-8.3 (± 15.3)	-6.2 (± 13.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change of DLQI scores from baseline to week 28: unadjusted analysis and ANCOVA (observed cases)

End point title	Change of DLQI scores from baseline to week 28: unadjusted analysis and ANCOVA (observed cases)

End point description:
change in Dermatology Quality of Life Index scores

End point type	Secondary

End point timeframe:
baseline to week 28

End point values	Omalizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	46		
Units: DLQI Score				
arithmetic mean (standard deviation)				
week 4	-8.3 (± 7.3)	-2.4 (± 6.9)		
week 12	-10.1 (± 7.5)	-3.9 (± 7.6)		
week 20	-9.5 (± 8.4)	-5.1 (± 8.3)		
week 28	-10.5 (± 8.3)	-5.6 (± 8)		
follow-up, week 36	-6.8 (± 8.6)	-5.4 (± 8.3)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo

Reporting group title	Omalizumab

Reporting group description:

Omalizumab

Serious adverse events	Placebo	Omalizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 47 (4.26%)	4 / 44 (9.09%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

subjects affected / exposed	0 / 47 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament injury			
subjects affected / exposed	1 / 47 (2.13%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 47 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 47 (2.13%)	0 / 44 (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			
Sciatica			
subjects affected / exposed	0 / 47 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 47 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 47 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			

subjects affected / exposed	0 / 47 (0.00%)	1 / 44 (2.27%)	
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	Placebo	Omalizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 47 (59.57%)	16 / 44 (36.36%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 47 (6.38%)	1 / 44 (2.27%)	
occurrences (all)	3	1	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 47 (8.51%)	4 / 44 (9.09%)	
occurrences (all)	5	8	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	4 / 47 (8.51%)	0 / 44 (0.00%)	
occurrences (all)	6	0	
Diarrhoea			
subjects affected / exposed	5 / 47 (10.64%)	3 / 44 (6.82%)	
occurrences (all)	6	4	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	6 / 47 (12.77%)	1 / 44 (2.27%)	
occurrences (all)	10	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 47 (8.51%)	0 / 44 (0.00%)	
occurrences (all)	4	0	
Back pain			
subjects affected / exposed	3 / 47 (6.38%)	3 / 44 (6.82%)	
occurrences (all)	4	4	
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	13 / 47 (27.66%) 17	9 / 44 (20.45%) 13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 September 2012	Issued before study start) was primarily written to address new legal requirements regarding market access, requiring provision of longer term data from the most diseased burdened patients. However, following feedback from participating centers, it became clear that this particular patient group was rare and difficult to recruit. Therefore, the amendment introduced the following changes: - Study population was reduced from 150 to 70 patients and, accordingly, the number of participating centers from 30 to 25. -For sample size calculation, acceptable power was reduced from 90 % to 84 % on a 2-sided, 5 % significance level. -Patients prematurely withdrawing the study were included in the FAS analysis. New additional patients were allowed to be enrolled to meet the target sample size of 70 evaluable (PP) patients.-Only one active arm (Omalizumab 300 mg) was compared to placebo; elimination of 150 mg Omalizumab arm. -Due to changes in the manufacturing process the study medication was delivered open-label, but the study itself remained double-blinded. The wording was changed accordingly. Changes were necessary to describe packaging of study drug. -Addition of MID-CU-Q2oL as explorative objective. Accordingly, an additional patient and physician questionnaire was included. Weekly UAS7 score was changed to twice-daily evaluation (US-system) to allow comparability with other globally available data-sets from phase III trials.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported