Clinical trial results:
A randomized, open label, parallel-group, international, multicenter study evaluating persistency of response to omalizumab during 32 weeks treatment given as add on to optimized asthma therapy in adult and adolescent patients with severe allergic asthma, who remain inadequately controlled despite GINA (2004) Step 4 therapy

Summary

EudraCT number	2005-001099-11
Trial protocol	GB NO IE ES DK SE DE HU PT IT BE GR
Global end of trial date	23 September 2008

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	15 August 2015

Trial information

Trial identification

Sponsor protocol code	CIGE025A2425

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00264849
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 Pharma AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 September 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 September 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate persistency in treatment responder classification between assessments at 16 and 32 weeks after starting omalizumab therapy given as add on to optimized asthma therapy in patients who remained uncontrolled despite GINA (2004) Step 4 therapy. Treatment response was defined by at least marked improvement of overall asthma control as assessed by physician Global Evaluation of Treatment Effectiveness.

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. The subjects were treated with β-2 agonist (salbutamol or terbutaline) for rescue medication from symptoms of intercurrent bronchospasm or during asthma exacerbation, inhaled via any device e.g. MDI Accuhaler, Rotacaps, Turbuhaler and Ventidisks. If rescue medication was taken prior to a spirometric assessment, the investigator was notified by the subject. Home use of nebulized β-2 agonist (salbutamol 2.5-5 milligram (mg) or terbutaline 5-10 mg) was allowed for treatment. Symptomatic subjects despite nebulization contacted trial personnel immediately for further evaluation, each nebulization was recorded on subject's diary/note book.

Background therapy:

Subjects were receiving any of the following background therapies (Oral and/or inhaled corticosteroids (ICS),Long-acting inhaled β-2 agonists (LABA), Fixed dose combinations of ICS and LABA) at least 3 months prior to screening with doses adjusted according to best clinical practice during the 32 weeks treatment:
1. Oral and ICS: Subjects inhaled moderate to high dose of corticosteroids more than or equal to (≥)800 microgram (mcg) beclomethasone dipropionate (BDP) or equivalent prior to the 2 qualifying asthma exacerbations, required treatment with systemic corticosteroids for at least 3 months prior to screening . Doses of ICS more than (>)1000 mcg BDP or equivalent, were taken for at least the last 4 weeks of the run-in period.
2. LABA: Subjects were to have taken LABA at least 3 months prior to screening and remain on unchanged dose during the last 4 weeks of run-in. Subjects were not allowed LABA medication within 12 hours prior to visit for reversibility and spirometric assessment.
3. Fixed dose combinations of ICS and LABA: Subjects were allowed with fixed combination (budesonide/formoterol and fluticasone/salmeterol) with a dose of ICS ≥ 800 mcg BDP or equivalent. Doses of inhaled corticosteroid (ICS) more than (>)1000 mcg BDP or equivalent, were taken for at least the last 4 weeks of the run-in period. Fixed dose combination medication should have been taken after spirometry measurements. Additional medications for treatment of the patient's allergic asthma exacerbations already established prior to the final 4 weeks of the run in period were allowed in this study

Evidence for comparator: -

Actual start date of recruitment	22 November 2005
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	Norway: 1
Country: Number of subjects enrolled	Spain: 39
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	United Kingdom: 36
Country: Number of subjects enrolled	Belgium: 21
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	Germany: 48
Country: Number of subjects enrolled	Hungary: 30
Country: Number of subjects enrolled	Italy: 99
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Israel: 16
Country: Number of subjects enrolled	Poland: 40
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	Turkey: 35
Worldwide total number of subjects	400
EEA total number of subjects	331

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)	368
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 106 centres in 14 countries.

Pre-assignment

Screening details:

A total of 768 subjects were screened, out of which 406 were provided with treatment. Out of 406 treated subjects, 2 subjects treated with optimized asthma treatment (OAT) + omalizumab were non-randomised and discontinued due to administrative problems.

Pre-assignment period milestones

Number of subjects started	404[1]
Number of subjects completed	400

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 2
Reason: Number of subjects	Protocol deviation: 1
Reason: Number of subjects	lost to follow up: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Out of 406 treated subjects, 2 subjects treated with optimized asthma treatment (OAT) + omalizumab were nonrandomised and discontinued due to administrative problems.

Period 1

Period 1 title	Randomized patients (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The study was open label, hence no blinding was performed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Optimized Asthma Treatment (OAT) + Omalizumab

Arm description:

Subjects received omalizaumab (150 mg; 225 mg; 300 mg or 375 mg) through subcutaneous (s.c) route for 2-4 weeks based on their body weight and immunoglobulin E (IgE) levels.
Subjects with body- weight between 90-150 kilograms (kg), received 300 mg of omalizumab for omalizumab for 4 weeks (if pre-treatment IgE
level was between 30-100 international units per milliliter [IU/mL]) and for 2 weeks (if pre-treatment Ig E level was between 200-300 IU/mL).

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:

Omalizumab 150 mg administered s.c. after reconstitution with 1.4 ml Sterile Water for Injection. The dose administered was individualized for each subject based on the body weight.

Arm title	Optimized Asthma Treatment (OAT)

Arm description:

During the 32 weeks treatment phase , subjects continued to receive OAT were evaluated and optimized according to GINA guidelines established during the run-in period of the study. The subjects were treated with moderate to high dose ICS (BDP 1000 mcg or equivalent dose), regular LABA, or fixed combination of ICS and LABA.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Optimized Asthma Treatment (OAT) + Omalizumab	Optimized Asthma Treatment (OAT)
Started	272	128
Completed	253	106
Not completed	19	22
Adverse event, serious fatal	-	1
Consent withdrawn by subject	7	9
Adverse event, non-fatal	7	2
Unsatisfactory therapeutic effect	1	6
Lost to follow-up	-	1
Protocol deviation	4	3

Baseline characteristics

Reporting groups	
Reporting group title	Optimized Asthma Treatment (OAT) + Omalizumab
Reporting group description:	
Subjects received omalizaumab (150 mg; 225 mg; 300 mg or 375 mg) through subcutaneous (s.c) route for 2-4 weeks based on their body weight and immunoglobulin E (IgE) levels. Subjects with body- weight between 90-150 kilograms (kg), received 300 mg of omalizumab for omalizumab for 4 weeks (if pre-treatment IgE level was between 30-100 international units per milliliter [IU/mL]) and for 2 weeks (if pre-treatment Ig E level was between 200-300 IU/mL).	
Reporting group title	Optimized Asthma Treatment (OAT)
Reporting group description:	
During the 32 weeks treatment phase , subjects continued to receive OAT were evaluated and optimized according to GINA guidelines established during the run-in period of the study. The subjects were treated with moderate to high dose ICS (BDP 1000 mcg or equivalent dose), regular LABA, or fixed combination of ICS and LABA.	

Reporting group values	Optimized Asthma Treatment (OAT) + Omalizumab	Optimized Asthma Treatment (OAT)	Total
Number of subjects	272	128	400
Age categorical Units: Subjects			
12-17 years	5	0	5
18-54 years	189	92	281
55-64 years	61	26	87
65-75 years	17	10	27
Age continuous			
Mod ITT			
Units: years			
arithmetic mean	45.6	45.7	
standard deviation	± 13.04	± 12.57	-
Gender categorical Units: Subjects			
Female	183	76	259
Male	89	52	141

End points

End points reporting groups

Reporting group title	Optimized Asthma Treatment (OAT) + Omalizumab

Reporting group description:

Subjects received omalizaumab (150 mg; 225 mg; 300 mg or 375 mg) through subcutaneous (s.c) route for 2-4 weeks based on their body weight and immunoglobulin E (IgE) levels.
Subjects with body- weight between 90-150 kilograms (kg), received 300 mg of omalizumab for omalizumab for 4 weeks (if pre-treatment IgE
level was between 30-100 international units per milliliter [IU/mL]) and for 2 weeks (if pre-treatment Ig E level was between 200-300 IU/mL).

Reporting group title	Optimized Asthma Treatment (OAT)

Reporting group description:

During the 32 weeks treatment phase , subjects continued to receive OAT were evaluated and optimized according to GINA guidelines established during the run-in period of the study. The subjects were treated with moderate to high dose ICS (BDP 1000 mcg or equivalent dose), regular LABA, or fixed combination of ICS and LABA.

Primary: Persistency rate of response and non-response, as based on investigator's Global Evaluation of Treatment Effectiveness

End point title	Persistency rate of response and non-response, as based on investigator's Global Evaluation of Treatment Effectiveness[1]

End point description:

Treatment response of omalizumab was assessed by investigator based on GETE, a five point scale that evaluated change in asthma control/symptoms (1: excellent for complete control of asthma, 2: good for marked improvement of asthma, 3: moderate for discernible, but limited improvement of asthma, 4: poor for no appreciable change, and 5: worsening of asthma). Responders were defined as subjects scaling excellent or good and non-responders as moderate, poor or worsening assessed at 16 weeks and 32 weeks. The primary analysis was performed in the modified intent to treat (ITT) population, defined as all randomized subjects with at least one post-baseline efficacy assessment. Here, "Number of subjects analysed" were subjects assessed for persistency of response if they were responders at Week 16 and had a second GETE obtained ≥ 4 weeks after the Week 16 assessment or discontinued prematurely for unsatisfactory therapeutic effect ≥ 4 weeks after the Week 16 assessment.

End point type	Primary

End point timeframe:

Week 16, Week 32

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistics for this end point was planned for selected arm only.

End point values	Optimized Asthma Treatment (OAT) + Omalizumab	Optimized Asthma Treatment (OAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	28		
Units: Percentage of subjects				
number (confidence interval 95%)	91.4 (87.4 to 95.5)	64.3 (46.5 to 82)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects by Investigator's Global Evaluation of Treatment Effectiveness (GETE) category at Week 16 and Week 32

End point title	Number of subjects by Investigator's Global Evaluation of Treatment Effectiveness (GETE) category at Week 16 and Week 32

End point description:

Responders were defined as subjects scaling excellent or good at 16 weeks and still at 32 weeks. Response for subjects were assessed by investigator based on completion of a GETE, which was a five point scale that evaluates change in asthma control/symptoms (excellent for complete control of asthma, good for marked improvement of asthma, moderate for discernible, but limited improvement of asthma, poor for no appreciable change, and worsening for asthma). The analysis was performed in the modified ITT population.

End point type	Secondary

End point timeframe:

Week 16, Week 32

End point values	Optimized Asthma Treatment (OAT) + Omalizumab	Optimized Asthma Treatment (OAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	128		
Units: Number of subjects				
Week 16: Excellent	35	1		
Week 16: Good	155	28		
Week 16: Moderate	57	24		
Week 16: Poor	13	34		
Week 16: Worsening	1	6		
Week 16: Missing	11	35		
Week 32: Excellent	73	1		
Week 32: Good	126	24		
Week 32: Moderate	45	31		
Week 32: Poor	13	39		
Week 32: Worsening	2	9		
Week 32: Missing	13	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects by Subject's Global Evaluation of Treatment Effectiveness (GETE) category at Week 16 and Week 32

End point title	Number of subjects by Subject's Global Evaluation of Treatment Effectiveness (GETE) category at Week 16 and Week 32

End point description:

Responders were defined as subjects scaling excellent or good at 16 weeks and still at 32 weeks. Response for subjects were evaluated by subjects based on completion of a GETE, which was a five point scale that evaluates change in asthma control/symptoms (excellent for complete control of asthma, good for marked improvement of asthma, moderate for discernible, but limited improvement of asthma, poor for no appreciable change, and worsening for asthma). The analysis was performed in the modified ITT population.

End point type	Secondary

End point timeframe:

Week 16, Week 32

End point values	Optimized Asthma Treatment (OAT) + Omalizumab	Optimized Asthma Treatment (OAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	128		
Units: Number of subjects				
Week 16: Excellent	54	4		
Week 16: Good	139	29		
Week 16: Moderate	53	23		
Week 16: Poor	15	33		
Week 16: Worsening	1	5		
Week 16: Missing	10	34		
Week 32: Excellent	80	2		
Week 32: Good	127	27		
Week 32: Moderate	38	28		
Week 32: Poor	12	38		
Week 32: Worsening	2	8		
Week 32: Missing	13	25		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of persistent treatment non-responders based on Investigator's Global Evaluation of Treatment Effectiveness (GETE) score at both Week 16 and Week 32

End point title	Percentage of persistent treatment non-responders based on Investigator's Global Evaluation of Treatment Effectiveness (GETE) score at both Week 16 and Week 32

End point description:

Treatment response was assessed by investigator based on GETE, a five point scale that evaluated change in asthma control/symptoms (1: excellent for complete control of asthma, 2: good for marked improvement of asthma, 3: moderate for discernible, but limited improvement of asthma, 4: poor for no appreciable change, and 5: worsening for asthma). Non-responders were defined as moderate, poor or worsening assessed at 16 weeks and 32 weeks. The analysis was performed in the modified ITT population. Here, "Number of subjects analysed" were subjects assessed for persistency of non-response if they were non-responders at Week 16 and had second GETE obtained ≥ 4 weeks after the week 16 assessment or discontinued prematurely for unsatisfactory therapeutic effect ≥ 4 weeks after the week 16 assessment.

End point type	Secondary
End point timeframe: Week 16, Week 32	

End point values	Optimized Asthma Treatment (OAT) + Omalizumab	Optimized Asthma Treatment (OAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	63		
Units: Percentage of subjects				
number (confidence interval 95%)	62 (50.7 to 73.3)	90.5 (83.2 to 97.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Predicted Forced Expiratory Volume for 1 Second (FEV1)

End point title	Percent Predicted Forced Expiratory Volume for 1 Second (FEV1)

End point description:

FEV1 was defined as the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation, measured through spirometry testing. The subject's predicted FEV1 value was calculated according to Crapo standards (Males: Predicted FEV1 = 0.0414*height – 0.0244*age – 2.190 and Females: Predicted FEV1 = 0.0342*height – 0.0255*age – 1.578, where height was in cm). The analysis was performed in modified ITT population. Here, 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary
End point timeframe: Weeks 16, Week 32	

End point values	Optimized Asthma Treatment (OAT) + Omalizumab	Optimized Asthma Treatment (OAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	128		
Units: Percent predicted FEV1				
least squares mean (confidence interval 95%)				
Week 16 (n= 258, 106)	68.4 (66.2 to 70.5)	64.8 (61.8 to 67.8)		
Week 32 (n= 266, 121)	68.1 (65.8 to 70.5)	63.7 (60.6 to 66.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Asthma Control Questionnaire (ACQ) overall score at Week 16 and Week 32

End point title	Change from baseline in Asthma Control Questionnaire (ACQ) overall score at Week 16 and Week 32

End point description:

Asthma Control Questionnaire (ACQ), has 7 questions, each with a 7 point scale (0 – good control, 6 – poor control). The average score will be calculated as the total of all 7 questions divided by 7 (or the number of questions that were answered at the time point as long as there are at least 4 questions answered). A negative change in score indicated improvement in symptoms. The analysis was performed in modified ITT population. Here 'n' signifies those subjects with valid ACQ measurements at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Weeks 16, Week 32

End point values	Optimized Asthma Treatment (OAT) + Omalizumab	Optimized Asthma Treatment (OAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	128		
Units: Units on a scale				
least squares mean (confidence interval 95%)				
Week 16 (n= 249, 104)	-0.78 (-0.92 to -0.63)	-0.11 (-0.31 to 0.1)		
Week 32 (n= 238, 104)	-0.91 (-1.07 to -0.76)	-0.04 (-0.26 to 0.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with clinically significant asthma exacerbations during the 32 week treatment period

End point title	Percentage of subjects with clinically significant asthma exacerbations during the 32 week treatment period

End point description:

A clinically significant asthma exacerbation was defined as a worsening of asthma requiring treatment with rescue systemic (oral or IV) corticosteroids. The initiation of the rescue systemic corticosteroids

was marked as the start of asthma exacerbation and cessation of the rescue systemic corticosteroids was marked as the end. Duplicated, or overlapped by at least one day with another episode, or nested within another exacerbation episode,were considered as single exacerbation. The analysis was performed in the modified ITT population.

End point type	Secondary

End point timeframe:

Day 1 up to Weeks 32

End point values	Optimized Asthma Treatment (OAT) + Omalizumab	Optimized Asthma Treatment (OAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	128		
Units: Percentage of subjects				
number (not applicable)				
0 asthma exacerbation	67.3	50		
1 asthma exacerbation	21.3	27.3		
2 asthma exacerbation	6.6	13.3		
3 asthma exacerbation	3.3	4.7		
>= 4 asthma exacerbation	1.5	4.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with severe asthma exacerbations during the 32 week treatment period

End point title	Percentage of subjects with severe asthma exacerbations during the 32 week treatment period

End point description:

Subjects with clinically significant severe asthma exacerbation fulfilled any of the following criteria: required treatment with rescue systemic (oral or IV) corticosteroids, or resulted in hospitalization or required an emergency department visit, or resulted in >30% fall from personal best in peak expiratory flow for two successive days. The analysis was performed in the modified ITT population.

End point type	Secondary

End point timeframe:

Day 1 up to Week 32

End point values	Optimized Asthma Treatment (OAT) + Omalizumab	Optimized Asthma Treatment (OAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	128		
Units: Percentage of subjects				

number (not applicable)				
0 asthma exacerbations severe	84.6	77.3		
1 asthma exacerbations severe	11.8	13.3		
2 asthma exacerbations severe	1.8	5.5		
3 asthma exacerbations severe	0.7	1.6		
>= 4 asthma exacerbations severe	1.1	2.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with hospital admissions, emergency room visits and unscheduled clinical visits due to asthma exacerbations

End point title	Percentage of subjects with hospital admissions, emergency room visits and unscheduled clinical visits due to asthma exacerbations

End point description:

Combined total of unscheduled visits was determined for each subject as the total number of hospital admissions, emergency room visits and unscheduled outpatient clinical visits due to asthma exacerbations. Only the most serious type of asthma exacerbation was included for multiple type of visit on same day, while all visits were counted when visits occurred on different dates for single asthma exacerbation. The analysis was performed in the modified ITT population.

End point type	Secondary

End point timeframe:

Day 1 up to Week 32

End point values	Optimized Asthma Treatment (OAT) + Omalizumab	Optimized Asthma Treatment (OAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	128		
Units: Percentage of subjects				
number (not applicable)				
0 combined unscheduled visits	83.1	67.2		
1 combined unscheduled visits	9.6	9.4		
2 combined unscheduled visits	3.7	13.3		
3 combined unscheduled visits	1.5	6.3		
>= 4 combined unscheduled visits	2.2	3.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline in oral steroid dose at Weeks 16 and Week 32

End point title	Percentage change from baseline in oral steroid dose at Weeks 16 and Week 32

End point description:

The dose of oral steroid measured was the maintenance dose of the subjects and not the dose to treat an asthma exacerbation. A negative change from baseline indicated improvement. The analysis was performed in the modified ITT population. Here, "Number of subjects analysed" were subjects evaluable for change from baseline in oral steroid dose at week 16 and week 32, for each arm. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 32

End point values	Optimized Asthma Treatment (OAT) + Omalizumab	Optimized Asthma Treatment (OAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	23		
Units: Prednisolone equivalent mg/day				
arithmetic mean (standard deviation)				
Week 16 (n= 56, 19)	-20.1 (± 63.08)	36.8 (± 212.03)		
Week 32 (n= 59, 23)	-45 (± 50.22)	18.3 (± 85.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects by type of dose change for systemic steroids at Weeks 16 and Week 32

End point title	Percentage of subjects by type of dose change for systemic steroids at Weeks 16 and Week 32

End point description:

Subjects with systemic steroids were defined as those who used systemic steroids throughout the entire treatment period (Weeks 16 and Week 32). Dose of systemic steroids was expressed in prednisolone equivalent mg/day. Removed subjects were defined as subjects who removed from systemic steroids during treatment period and not provided with dose, maintained as subjects with unchanged or increased dose and decreased as subjects with decreased dose. The analysis was performed in the modified ITT population.Here, "Number of subjects analysed" were subjects evaluable for change from baseline in oral steroid dose at week 16 and week 32, for each arm. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 32

End point values	Optimized Asthma Treatment (OAT) + Omalizumab	Optimized Asthma Treatment (OAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	23		
Units: Percentage of subjects				
number (not applicable)				
Week 16 - Removed systemic steroids (n= 56, 19)	17.9	10.5		
Week 32 - Removed systemic steroids (n= 59, 23)	32.2	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Asthma Quality of Life Questionnaire (AQLQ) overall score at Week 15 and Week 31

End point title	Change from baseline in Asthma Quality of Life Questionnaire (AQLQ) overall score at Week 15 and Week 31

End point description:

Asthma Quality of Life Questionnaire (AQLQ) was 32 item questionnaire defined in 4 domains (symptoms, activity limitation, emotional function and environmental exposure). Each question was answered on a 7 point scale (1–totally limited/problems all the time to 7–not at all limited/no problems). The overall AQLQ score was the mean of all 32 responses (a minimum domain / overall score of 1 = Severely impaired whereas a maximum domain / overall score of 7 = not impaired at all). A positive change from baseline score indicated improvement. The analysis was performed in the modified ITT population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 15, Week 31

End point values	Optimized Asthma Treatment (OAT) + Omalizumab	Optimized Asthma Treatment (OAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	128		
Units: Units on a scale				
least squares mean (confidence interval 95%)				
Overall Score: Week 15 (n= 214, 92)	0.9 (0.73 to 1.07)	0.03 (-0.2 to 0.27)		
Overall Score: Week 31 (n= 224, 97)	1.06 (0.88 to 1.24)	-0.07 (-0.31 to 0.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in EuroQual 5-Dimension health status questionnaire (EQ-5D) utility index and health state assessment at Week 15 and Week 31

End point title	Change from baseline in EuroQual 5-Dimension health status questionnaire (EQ-5D) utility index and health state assessment at Week 15 and Week 31

End point description:

The utility-based EQ-5D questionnaire was in two parts and provides a generic measure of health for clinical and economic appraisal. The health state classification part contains 5 questions each with 3 categories (no problem, moderate problem, severe problems). The visual analogue scale was measured from 0 (worst imaginable health state) to 100 (best imaginable health state). A positive change from baseline score indicated improvement.The analysis was performed in the modified ITT population. Here 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 15, Week 31

End point values	Optimized Asthma Treatment (OAT) + Omalizumab	Optimized Asthma Treatment (OAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	128		
Units: Units on a scale				
least squares mean (confidence interval 95%)				
EQ-5D Utility Index Score: Week 15 (n= 212 ,90)	0.071 (0.038 to 0.105)	0.002 (-0.044 to 0.049)		
EQ-5D Utility Index Score: Week 31 (n= 194, 81)	0.091 (0.051 to 0.132)	0.064 (0.008 to 0.121)		
Health State Assessment: Week 15 (n= 211, 89)	8.2 (4.7 to 11.8)	-0.4 (-5.4 to 4.6)		
Health State Assessment: Week 31 (n= 194, 80)	9.3 (5.2 to 13.4)	-2.8 (-8.5 to 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in percent overall Work Impairment due to asthma symptoms at Week 31

End point title	Change from baseline in percent overall Work Impairment due to asthma symptoms at Week 31

End point description:

Work Productivity and Activity Impairment-Allergic Asthma (WPAI-AA) questionnaire, covered 6 questions relating to hours missed from work and work productivity in the previous 7 days. Overall work impairment due to asthma problems was derived from the proportion of hours missed from work due to

asthma and the degree to which asthma problems affected productivity while working. A negative change indicated improvement. The analysis was performed in the modified ITT population. Here, "Number of subjects analysed" were subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 31

End point values	Optimized Asthma Treatment (OAT) + Omalizumab	Optimized Asthma Treatment (OAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	34		
Units: Percent impairment				
arithmetic mean (standard deviation)	-21.4 (± 26.79)	0 (± 29.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in percent Activity Impairment due to asthma symptoms at Week 31

End point title	Change from baseline in percent Activity Impairment due to asthma symptoms at Week 31

End point description:

Work Productivity and Activity Impairment-Allergic Asthma (WPAI-AA) questionnaire, covered 6 questions relating to hours missed from work and work productivity in the previous 7 days. Activity impairment due to asthma problems was derived from the subjects assessment of the degree to which asthma problems affected regular activities. A negative change indicated improvement. The analysis was performed in the modified ITT population. Here, "Number of subjects analysed" were subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 31

End point values	Optimized Asthma Treatment (OAT) + Omalizumab	Optimized Asthma Treatment (OAT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	80		
Units: Percent impairment				
arithmetic mean (standard deviation)	-17.2 (± 24.36)	-0.1 (± 24.05)		

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 are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	Optimized Asthma Treatment
Reporting group description:	
Optimized Asthma Treatment	
Reporting group title	Optimized Asthma Treatment + Omalizumab
Reporting group description:	
Optimized Asthma Treatment + Omalizumab	

Serious adverse events	Optimized Asthma Treatment	Optimized Asthma Treatment + Omalizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 128 (13.28%)	29 / 274 (10.58%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast neoplasm			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibroadenoma of breast			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			

subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Intra-uterine death			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyp			
subjects affected / exposed	1 / 128 (0.78%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 128 (0.78%)	0 / 274 (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	14 / 128 (10.94%)	15 / 274 (5.47%)	
occurrences causally related to treatment / all	0 / 14	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status asthmaticus			
subjects affected / exposed	1 / 128 (0.78%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Chest injury			
subjects affected / exposed	0 / 128 (0.00%)	2 / 274 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 128 (0.00%)	2 / 274 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured coccyx			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Road traffic accident			
subjects affected / exposed	0 / 128 (0.00%)	3 / 274 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Melaena			
subjects affected / exposed	1 / 128 (0.78%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 128 (0.78%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 128 (0.78%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			

subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperparathyroidism			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
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			
Arthralgia			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 128 (0.78%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 128 (0.78%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 128 (1.56%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lower respiratory tract infection			
subjects affected / exposed	1 / 128 (0.78%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 128 (0.00%)	1 / 274 (0.36%)	
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	Optimized Asthma Treatment	Optimized Asthma Treatment + Omalizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 128 (51.56%)	151 / 274 (55.11%)	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 128 (7.03%)	33 / 274 (12.04%)	
occurrences (all)	26	92	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	51 / 128 (39.84%)	82 / 274 (29.93%)	
occurrences (all)	52	85	
Cough			
subjects affected / exposed	4 / 128 (3.13%)	14 / 274 (5.11%)	
occurrences (all)	6	19	
Oropharyngeal pain			
subjects affected / exposed	1 / 128 (0.78%)	14 / 274 (5.11%)	
occurrences (all)	1	15	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 128 (0.00%)	14 / 274 (5.11%)	
occurrences (all)	0	19	
Infections and infestations			
Bronchitis			
subjects affected / exposed	7 / 128 (5.47%)	13 / 274 (4.74%)	
occurrences (all)	10	14	
Influenza			
subjects affected / exposed	4 / 128 (3.13%)	18 / 274 (6.57%)	
occurrences (all)	4	22	
Nasopharyngitis			
subjects affected / exposed	9 / 128 (7.03%)	38 / 274 (13.87%)	
occurrences (all)	14	52	
Lower respiratory tract infection			
subjects affected / exposed	8 / 128 (6.25%)	16 / 274 (5.84%)	
occurrences (all)	14	20	
Upper respiratory tract infection			

subjects affected / exposed	6 / 128 (4.69%)	17 / 274 (6.20%)	
occurrences (all)	7	20	
Sinusitis			
subjects affected / exposed	7 / 128 (5.47%)	10 / 274 (3.65%)	
occurrences (all)	12	18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 June 2006	• The secondary objective to further evaluate the best individual or combination of clinical measures for evaluating treatment response to omalizumab treatment was introduced • The dose of omalizumab to be given every 4-weeks for a body weight >30-40 and baseline IgE >200-300 international units per millilitre(IU/ml) to 225 mg, was introduced to be consistent with the approved dosing schedule • Total IgE measurement at randomisation visit was added

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported