Clinical trial results:
A multi-center, randomized, double blind, placebo and active-controlled study with exploratory dose-ranging, to investigate the efficacy and safety of 16 weeks treatment with subcutaneous QGE031 in asthma patients not adequately controlled with high-dose inhaled corticosteroids and long acting 2-agonists

Summary

EudraCT number	2012-002298-69
Trial protocol	FI SK CZ PT GB HU IT DE PL FR
Global end of trial date	21 January 2016

Results information

Result version number	v1 (current)
This version publication date	03 February 2017
First version publication date	03 February 2017

Trial information

Trial identification

Sponsor protocol code	CQGE031B2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01716754
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 January 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 January 2016
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 evaluate the efficacy of QGE031 240 mg s.c. every two weeks compared to matched placebo when added to existing asthma therapy by comparing the responder rates (response defined as a decrease of 0.5 or more of the Asthma Control Questionnaire7 (ACQ-7) score from baseline) following 16 weeks treatment in patients inadequately controlled on high dose inhaled corticosteroids plus long-acting β2-agonists (GINA treatment step 4). Inadequate control is defined as an ACQ-7 score of ≥1.5 at the end of the run-in epoch (Juniper et al 2006).

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:

At the screening visit all participants were provided with a short acting β2-agonist (salbutamol/albuterol) which they were instructed to use throughout the study as rescue medication on an 'as needed basis'. Participants were advised that between visits they could take their rescue medication for symptoms of intercurrent bronchospasm. In order to stabilize measurements, patients were instructed to abstain from taking rescue salbutamol/albuterol within 6 hours of the start of each spirometry visit unless absolutely necessary.

Evidence for comparator: -

Actual start date of recruitment	14 December 2012
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	Argentina: 59
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Czech Republic: 32
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 47
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Guatemala: 6
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	India: 9
Country: Number of subjects enrolled	Israel: 19
Country: Number of subjects enrolled	Italy: 22

Country: Number of subjects enrolled	Korea, Republic of: 28
Country: Number of subjects enrolled	Mexico: 12
Country: Number of subjects enrolled	Panama: 1
Country: Number of subjects enrolled	Poland: 26
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Romania: 39
Country: Number of subjects enrolled	Russian Federation: 43
Country: Number of subjects enrolled	Slovakia: 29
Country: Number of subjects enrolled	South Africa: 3
Country: Number of subjects enrolled	Turkey: 19
Country: Number of subjects enrolled	United States: 29
Worldwide total number of subjects	471
EEA total number of subjects	230

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)	420
From 65 to 84 years	50
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 471 participants were randomized to one of the 14 treatment groups. Of these, 5 participants did not receive study treatment. Therefore, the full analysis set (FAS) and safety set included 466 participants.

Pre-assignment

Screening details:

The treatment arms for QGE031 and placebo were pooled into high dose QGE031 (240 mg q2w, 240 mg q4w, 180 mg q2w and 120 mg q2w), low dose QGE031 (36 mg q2w and 18 mg 2qw) and Placebo Total (all QGE031 placebo and Omalizumab placebo arms).

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, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	QGE031 High dose

Arm description:

Participants received QGE031 240 mg q2w, 240 mg q4w, 180 mg q2w or 120 mg q2w.

Arm type	Experimental
Investigational medicinal product name	QGE031
Investigational medicinal product code	QGE031
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received QGE031 240 mg q2w, 240 mg q4w, 180 mg q2w or 120 mg q2w for 16 weeks.

Arm title	QGE031 Low dose

Arm description:

Participants received QGE031 36 mg q2w or 18 mg q2w.

Arm type	Experimental
Investigational medicinal product name	QGE031
Investigational medicinal product code	QGE031
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received QGE031 36 mg q2w or 18 mg q2w for 16 weeks.

Arm title	Omalizumab

Arm description:

Participants received omalizumab as per locally approved dosing table q2w or q4w.

Arm type	Active comparator

Investigational medicinal product name	Omalizumab
Investigational medicinal product code	
Other name	Xolair
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received omalizumab as per locally approved dosing table q2w or q4w for 16 weeks.

Arm title	Placebo total

Arm description:

Participants received matching placebo to QGE031 or Omalizumab.

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

Dosage and administration details:

Participants received matching placebo to QGE031 or Omalizumab for 16 weeks.

Number of subjects in period 1	QGE031 High dose	QGE031 Low dose	Omalizumab
Started	199	40	135
FAS	199	40	131
Safety set	199	40	131
Completed	188	36	121
Not completed	11	4	14
Adverse event, serious fatal	-	-	-
Physician decision	1	-	-
Consent withdrawn by subject	5	-	4
Adverse event, non-fatal	4	2	2
Protocol deviation	-	2	7
Non-compliance with study treatment	-	-	1
Lost to follow-up	1	-	-

Number of subjects in period 1	Placebo total
Started	97
FAS	96
Safety set	96
Completed	89
Not completed	8
Adverse event, serious fatal	1
Physician decision	-
Consent withdrawn by subject	3

Adverse event, non-fatal	1
Protocol deviation	2
Non-compliance with study treatment	-
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	QGE031 High dose
Reporting group description:	
Participants received QGE031 240 mg q2w, 240 mg q4w, 180 mg q2w or 120 mg q2w.	
Reporting group title	QGE031 Low dose
Reporting group description:	
Participants received QGE031 36 mg q2w or 18 mg q2w.	
Reporting group title	Omalizumab
Reporting group description:	
Participants received omalizumab as per locally approved dosing table q2w or q4w.	
Reporting group title	Placebo total
Reporting group description:	
Participants received matching placebo to QGE031 or Omalizumab.	

Reporting group values	QGE031 High dose	QGE031 Low dose	Omalizumab
Number of subjects	199	40	135
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	0
Adults (18-64 years)	176	37	121
From 65-84 years	22	3	14
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	47.6	46	46.8
standard deviation	± 13.86	± 12.38	± 13.35
Gender, Male/Female Units: Subjects			
Female	113	20	92
Male	86	20	43

Reporting group values	Placebo total	Total	
Number of subjects	97	471	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	

Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	1	
Adults (18-64 years)	86	420	
From 65-84 years	11	50	
85 years and over	0	0	
Age Continuous			
Units: Years			
arithmetic mean	48.6		
standard deviation	± 12.8	-	
Gender, Male/Female			
Units: Subjects			
Female	63	288	
Male	34	183	

End points

End points reporting groups

Reporting group title	QGE031 High dose
Reporting group description:	
Participants received QGE031 240 mg q2w, 240 mg q4w, 180 mg q2w or 120 mg q2w.	
Reporting group title	QGE031 Low dose
Reporting group description:	
Participants received QGE031 36 mg q2w or 18 mg q2w.	
Reporting group title	Omalizumab
Reporting group description:	
Participants received omalizumab as per locally approved dosing table q2w or q4w.	
Reporting group title	Placebo total
Reporting group description:	
Participants received matching placebo to QGE031 or Omalizumab.	
Subject analysis set title	QGE031 240 mg q2w
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received QGE031 240 mg q2w.	
Subject analysis set title	Placebo to QGE031 240 mg q2w
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received placebo to QGE031 240 mg q2w	
Subject analysis set title	QGE031 240 mg q2w
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received QGE031 240 mg q2w.	
Subject analysis set title	Placebo to QGE031 240 mg q2w
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received placebo to QGE031 240 mg q2w	
Subject analysis set title	Placebo to QGE031 240 mg q2w
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received placebo to QGE031 240 mg q2w	
Subject analysis set title	QGE031 240 mg q2w
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received QGE031 240 mg q2w.	

Primary: Percentage of QGE031 participants with clinically important improvement of <= -0.5 in the Asthma Control Questionnaire 7 (ACQ-7) score compared to placebo

End point title	Percentage of QGE031 participants with clinically important improvement of <= -0.5 in the Asthma Control Questionnaire 7 (ACQ-7) score compared to placebo[1]

End point description:

The ACQ-7 measures asthma symptom control and consisted of 7 items: 5 on symptom assessment, 1 on rescue bronchodilator use and 1 on airway caliber (FEV1 % predicted). All 7 questions of the ACQ were equally weighted. Items 1-6 scored along a 7-point response scale, where 0 = good controlled and 6 = poor controlled. The 7th item on % predicted FEV1 (pre-bronchodilator) was scored by clinic staff on a 7-point scale (0 – > 95%; 1 – 90-95%; 2 – 80-89%; 3 – 70-79%; 4 – 60-69%; 5 – 50-59%; 6 – < 50%). The average score of the 7 questions was calculated as the sum of scores divided by the number

of questions that were answered by the participants, as long as there were at least 6 questions answered and the missing items were neither question 1 nor question 7.

End point type	Primary

End point timeframe:

Week 16

Notes:

[1] - 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: Statistical analysis does not apply to this end point.

End point values	Omalizumab	QGE031 240 mg q2w	Placebo to QGE031 240 mg q2w	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	131	114	49	
Units: Percentage of participants				
number (not applicable)	69.17	63.16	70.21	

Statistical analyses

Statistical analysis title	Clinically important improve. of <= -0.5 in ACQ-7
Comparison groups	QGE031 240 mg q2w v Placebo to QGE031 240 mg q2w
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.576
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	1.78

Statistical analysis title	Clinically important improve. of <= -0.5 in ACQ-7
Comparison groups	Omalizumab v QGE031 240 mg q2w
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.556
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.52

Secondary: Change from baseline in ACQ-7 score

End point title	Change from baseline in ACQ-7 score[2]

End point description:

The ACQ-7 measures asthma symptom control and consisted of 7 items: 5 on symptom assessment, 1 on rescue bronchodilator use and 1 on airway caliber (FEV1 % predicted). All 7 questions of the ACQ were equally weighted. Items 1-6 scored along a 7-point response scale, where 0 = good controlled and 6 = poor controlled. The 7th item on % predicted FEV1 (pre-bronchodilator) was scored by clinic staff on a 7-point scale (0 – > 95%; 1 – 90-95%; 2 – 80-89%; 3 – 70-79%; 4 – 60-69%; 5 – 50-59%; 6 – < 50%). The average score of the 7 questions was calculated as the sum of scores divided by the number of questions that were answered by the participants, as long as there were at least 6 questions answered and the missing items were neither question 1 nor question 7. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12, 16 and 28

Notes:

[2] - 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: Statistical analysis does not apply to this end point.

End point values	Omalizumab	Placebo to QGE031 240 mg q2w	QGE031 240 mg q2w	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	131	49	120	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=122,115,46)	-0.6 (± 0.705)	-0.48 (± 0.834)	-0.51 (± 0.709)	
Week 8 (n=122,110,46)	-0.78 (± 0.687)	-0.62 (± 0.735)	-0.68 (± 0.678)	
Week 12 (n=118,110,46)	-0.83 (± 0.737)	-0.71 (± 0.724)	-0.78 (± 0.738)	
Week 16 (n=120,114,48)	-0.89 (± 0.734)	-0.79 (± 0.733)	-0.75 (± 0.817)	
Week 28 (n=115,114,47)	-0.59 (± 0.842)	-0.63 (± 0.744)	-0.62 (± 0.81)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with a change from baseline in ACQ-7 score less than -1.1

End point title	Percentage of participants with a change from baseline in ACQ-7 score less than -1.1[3]

End point description:

The ACQ-7 measures asthma symptom control and consisted of 7 items: 5 on symptom assessment, 1 on rescue bronchodilator use and 1 on airway caliber (FEV1 % predicted). All 7 questions of the ACQ were equally weighted. Items 1-6 scored along a 7-point response scale, where 0 = good controlled and 6 = poor controlled. The 7th item on % predicted FEV1 (pre-bronchodilator) was scored by clinic staff on a 7-point scale (0 – > 95%; 1 – 90-95%; 2 – 80-89%; 3 – 70-79%; 4 – 60-69%; 5 – 50-59%; 6 – < 50%). The average score of the 7 questions was calculated as the sum of scores divided by the number of questions that were answered by the participants, as long as there were at least 6 questions answered and the missing items were neither question 1 nor question 7.

End point type	Secondary

End point timeframe:

Week 16

Notes:

[3] - 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: All arms do not apply to this end point.

End point values	Omalizumab	QGE031 240 mg q2w	Placebo to QGE031 240 mg q2w	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	120	114	47	
Units: Percentage of participants				
number (not applicable)	36.67	40.35	34.04	

Statistical analyses

Statistical analysis title	Change from baseline in ACQ-7 score less than -1.1
Comparison groups	QGE031 240 mg q2w v Placebo to QGE031 240 mg q2w
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.483
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	2.86

Statistical analysis title	Change from baseline in ACQ-7 score less than -1.1
Comparison groups	Omalizumab v QGE031 240 mg q2w

Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.261
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	2.44

Secondary: Change from baseline in Asthma Quality of Life Questionnaire (AQLQ) score

End point title	Change from baseline in Asthma Quality of Life Questionnaire (AQLQ) score[4]

End point description:

The AQLQ is a 32-item disease specific questionnaire designed to measure functional impairments that are most important to participants with asthma. The 32 items in the AQLQ were divided into four domain-specific scores and a total score as follows: Activity limitations = Mean of Items 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32 (11 items); Symptoms = Mean of Items 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30 (12 items); Emotional function = Mean of Items 7, 13, 15, 21, 27 (5 items); Environmental stimuli = Mean of Items 9, 17, 23, 26 (4 items); and Overall Score = Mean of Items 1 to 32 (32 items). Each item of the AQLQ was equally weighted and scored along a 7-point scale, where 1 indicates maximal impairment and 7 indicates no impairment. Thus, higher scores indicate better asthma-related quality of life. The mean overall score ranged from 1 to 7. A positive change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 28

Notes:

[4] - 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: Statistical analysis does not apply to this end point.

End point values	Omalizumab	QGE031 240 mg q2w	Placebo to QGE031 240 mg q2w	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	122	114	48	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 16 (n=122,114,48)	0.79 (± 0.853)	0.53 (± 0.878)	0.66 (± 0.624)	
Week 28 (n=121,114,47)	0.48 (± 0.871)	0.44 (± 0.899)	0.63 (± 0.826)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean number of puffs of morning, evening and

total daily asthma rescue medication

End point title	Change from baseline in mean number of puffs of morning, evening and total daily asthma rescue medication[5]

End point description:

Participants recorded their use of rescue medication into an electronic diary (eDiary). A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Week 16

Notes:

[5] - 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: All arms do not apply to this end point.

End point values	Omalizumab	Placebo to QGE031 240 mg q2w	QGE031 240 mg q2w	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	122	48	117	
Units: Number of puffs				
least squares mean (standard error)				
Morning	-0.39 (± 0.073)	-0.34 (± 0.113)	-0.28 (± 0.072)	
Evening	-0.33 (± 0.084)	-0.33 (± 0.126)	-0.31 (± 0.082)	
Overall	-0.73 (± 0.148)	-0.64 (± 0.226)	-0.56 (± 0.145)	

Statistical analyses

Statistical analysis title	Change from baseline in mean number of puffs

Statistical analysis description:

Morning

Comparison groups	Placebo to QGE031 240 mg q2w v QGE031 240 mg q2w
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.604
Method	Repeated measures mixed model

Statistical analysis title	Change from baseline in mean number of puffs

Statistical analysis description:

Morning

Comparison groups	Omalizumab v QGE031 240 mg q2w

Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26
Method	Repeated measures mixed model

Statistical analysis title	Change from baseline in mean number of puffs
Statistical analysis description: Evening	
Comparison groups	Placebo to QGE031 240 mg q2w v QGE031 240 mg q2w
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.937
Method	Repeated measures mixed model

Statistical analysis title	Change from baseline in mean number of puffs
Statistical analysis description: Evening	
Comparison groups	Omalizumab v QGE031 240 mg q2w
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.88
Method	Repeated measures mixed model

Statistical analysis title	Change from baseline in mean number of puffs
Statistical analysis description: Overall daily	
Comparison groups	Placebo to QGE031 240 mg q2w v QGE031 240 mg q2w
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.762
Method	Repeated measures mixed model

Statistical analysis title	Change from baseline in mean number of puffs
Statistical analysis description: Overall daily	
Comparison groups	Omalizumab v QGE031 240 mg q2w

Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.408
Method	Repeated measures mixed model

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.

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	18.0

Reporting groups

Reporting group title	QGE031 High dose
Reporting group description: QGE031 High dose	
Reporting group title	QGE031 Low dose
Reporting group description: QGE031 Low dose	
Reporting group title	Omalizumab
Reporting group description: Omalizumab	
Reporting group title	Placebo Total
Reporting group description: Placebo Total	

Serious adverse events	QGE031 High dose	QGE031 Low dose	Omalizumab
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 199 (4.52%)	3 / 40 (7.50%)	1 / 131 (0.76%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 199 (0.50%)	0 / 40 (0.00%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 199 (0.50%)	0 / 40 (0.00%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 199 (0.50%)	0 / 40 (0.00%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 199 (0.50%)	0 / 40 (0.00%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal laceration			
subjects affected / exposed	0 / 199 (0.00%)	0 / 40 (0.00%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	1 / 199 (0.50%)	0 / 40 (0.00%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 199 (0.00%)	0 / 40 (0.00%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Haemorrhagic anaemia			
subjects affected / exposed	0 / 199 (0.00%)	0 / 40 (0.00%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			

subjects affected / exposed	0 / 199 (0.00%)	1 / 40 (2.50%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 199 (0.50%)	0 / 40 (0.00%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 199 (0.50%)	1 / 40 (2.50%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal dysplasia			
subjects affected / exposed	0 / 199 (0.00%)	0 / 40 (0.00%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 199 (0.00%)	0 / 40 (0.00%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 199 (0.00%)	0 / 40 (0.00%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 199 (0.00%)	0 / 40 (0.00%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			

subjects affected / exposed	0 / 199 (0.00%)	1 / 40 (2.50%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 199 (0.50%)	0 / 40 (0.00%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	1 / 199 (0.50%)	0 / 40 (0.00%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 199 (0.50%)	0 / 40 (0.00%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 199 (0.50%)	0 / 40 (0.00%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impetigo			
subjects affected / exposed	1 / 199 (0.50%)	0 / 40 (0.00%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 199 (0.50%)	0 / 40 (0.00%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 199 (0.50%)	0 / 40 (0.00%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Urinary tract infection			
subjects affected / exposed	0 / 199 (0.00%)	0 / 40 (0.00%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 199 (0.50%)	0 / 40 (0.00%)	0 / 131 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 96 (5.21%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vaginal laceration			

subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ventricular arrhythmia			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Haemorrhagic anaemia			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 96 (1.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 96 (2.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Laryngeal dysplasia			

subjects affected / exposed	1 / 96 (1.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	1 / 96 (1.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Skin and subcutaneous tissue disorders				
Urticaria				
subjects affected / exposed	1 / 96 (1.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Haematuria				
subjects affected / exposed	0 / 96 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal colic				
subjects affected / exposed	0 / 96 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	0 / 96 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bursitis				
subjects affected / exposed	0 / 96 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc protrusion				
subjects affected / exposed	0 / 96 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Impetigo			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 96 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 96 (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	QGE031 High dose	QGE031 Low dose	Omalizumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	91 / 199 (45.73%)	17 / 40 (42.50%)	43 / 131 (32.82%)
General disorders and administration site conditions			
Injection site reaction			

subjects affected / exposed	57 / 199 (28.64%)	5 / 40 (12.50%)	19 / 131 (14.50%)
occurrences (all)	159	8	48
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	44 / 199 (22.11%)	13 / 40 (32.50%)	19 / 131 (14.50%)
occurrences (all)	65	24	26
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	16 / 199 (8.04%)	2 / 40 (5.00%)	9 / 131 (6.87%)
occurrences (all)	20	2	10
Viral upper respiratory tract infection			
subjects affected / exposed	6 / 199 (3.02%)	2 / 40 (5.00%)	2 / 131 (1.53%)
occurrences (all)	6	3	2

Non-serious adverse events	Placebo Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 96 (36.46%)		
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	5 / 96 (5.21%)		
occurrences (all)	10		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	27 / 96 (28.13%)		
occurrences (all)	33		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 96 (9.38%)		
occurrences (all)	13		
Viral upper respiratory tract infection			
subjects affected / exposed	6 / 96 (6.25%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 August 2012	Following additional internal Novartis review, it was noted that any reference to "ligelizumab" as the generic name for QGE031 should be removed, as at the time of the protocol this INN has not yet been recommended. The protocol was therefore amended to remove this text from the cover page. An error in timing of ACQ and spirometry assessments was also noted. The ACQ-7 questionnaire requires entry of FEV1 data and therefore needed to align with scheduled spirometry; ACQ and spirometry assessments prior to randomization were not aligned in the original protocol. To ensure clarity, additional errors and inconsistencies had also been corrected following vendor and internal feedback received post protocol finalization.
14 March 2013	During the set-up of study, it had become known that epinephrine auto-injectors may not be available or may not be able to be imported into all countries participating in the study. Therefore the protocol was amended to allow epinephrine use as per local standard of care for treatment of anaphylaxis. Also, following completion of reproductive toxicity studies, the requirement for contraception for female study participants had been limited to effective contraception instead of highly effective contraception. Also, following feedback from Ethics Committees, it was decided to add an exclusion criterion for patients with a history of generalized urticaria or with an acute urticarial episode at time of screening or during run-in. Further changes to the protocol were made to correct inconsistencies as follows: a) The Assessment Schedule was updated accordingly to be consistent with this timing of assessments. b) The use of permitted asthma medications was clarified. c) Similarly, the withdrawal criterion regarding use of prohibited medication had been updated. d) The instructions to the unblinded pharmacist preparing the syringes with study drug were updated. e) Guidance on the disposal of expired and unused rescue medication was added to the protocol. f) Also, when using the eDiary to monitor the occurrence of asthma worsening symptoms relative to a drop in PEF, it has been decided not to refer the patient's predicted PEF but only to the patient's personal best PEF measurements. The protocol was updated to this effect. g) minor changes and corrections of typographical errors were made.
04 June 2013	In Europe, conditional approval only was received for Protocol Amendment 2 under the Voluntary Harmonisation Procedure (VHP) (Ref. VHP20125/SA1). The approval was conditioned to uphold the requirement of highly effective methods of contraception; this was changed to effective methods of contraception in Amendment 2, following completion of reproductive toxicity studies. The EMA therefore suggested keeping the original contraceptive language. A request was received from Central Ethics Committees that every patient with any two grade 3 unexpected hypersensitivity reactions (as defined by WAO) would immediately discontinue drug. This criterion had been added. Some of the in/exclusion criteria were furthered specified as follows: a) The requirement for historical asthma exacerbations had been reduced to 1 exacerbation in last 12 months instead of 2 exacerbations within last 2 years. b) The requirement for patients to be on maintenance LABA b.i.d. had been specified further to allow equivalent once daily LABA dosing. c) To better define what is meant with uncontrolled diabetes, the exclusion criterion on diabetes had been updated to exclude patients with uncontrolled diabetes if they have an HbA1C of 7% or more. d) The exclusion criterion for clinically significant laboratory abnormalities had been further specified to indicate these should only be excluded if they are not compatible with the natural history of atopic asthma. e) Finally, a couple of inconsistencies between the protocol synopsis and full text and between the informed consent and protocol text have been corrected to further improve the overall quality of the document.

17 December 2013	The inclusion and exclusion criteria in this protocol were revised with the aim to reduce the screen failure rate, make the eligibility criteria more realistic and to prevent excluding suitable patients. The opportunity was taken to also make the following changes to the protocol: Following advice gathered during a recent expert advisory board, there was the desire to assess the impact of IgE suppression on mast cells and the opportunity was taken to collect urine samples for relevant biomarker assessments. Furthermore, an additional blood sample was collected for bio-banking to possibly assess currently non-specified biomarkers in future (a serum sample was already collected for this purpose, in addition, a plasma sample was collected and stored). Also, a non-allergen specific basophil activation assay (BAA) had recently become available and as part of this amendment additional serum samples were to be collected to assess the effect of QGE031 treatment on the sensitivity of basophils to stimulation. These samples were to be collected at selected sites only; at these sites also other additional samples for biomarker assessments, in particular for assessing FcR1 and CD23 receptor expression, their IgE occupancy levels and IgE levels on B cells, were to be collected at relevant time points. For all future studies with QGE031, the injection site was no longer be restricted to deltoid region in the arm or thigh if arm was not possible, but instead arms, thighs or abdomen were allowed. This change was also implemented in this study. Some updates had been made to the lists with prohibited and allowed medications to allow medications that were not expected to have any interactions with QGE031 or interpretation of the study. Finally, an extension to this study was being set up, CQGE031B2201E1, and a reference to this extension study was included in this protocol.
09 June 2014	One inclusion criteria and one exclusion criteria in the protocol were, following recent feedback from participating study physicians and detailed internal discussions, respectively, updated with the aim to reduce the screen failure rate, make the eligibility criteria more realistic and to prevent excluding suitable patients.
22 April 2015	This amendment included two additional Adjudication Committees (ACs); one for the assessment of neoplastic events and one for cardiovascular and cerebrovascular (CCV) events. While there is no known mechanism linking IgE suppression to CCV events or malignancy, statistically non-significant imbalances of these events have been identified in selected omalizumab data-sets and had been reflected in some Xolair country labeling. In order to closely monitor any potential relationship between IgE suppression and these events, and to strengthen patient safety in this trial and future trials, Novartis had decided to institute a CCV and a neoplastic adjudication committee. The other key change in this amendment was the removal of some exploratory biomarkers from the study protocol. The high number of biomarkers sampled and the required shipping conditions had frequently been reported as very cumbersome and too complex by the sites. In order to facilitate study conduct and to support protocol execution at the sites, Novartis decided to remove some of the exploratory biomarkers from the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported