Clinical trial results:
A 52-week, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of QAW039 when added to existing asthma therapy in patients with uncontrolled severe asthma

Summary

EudraCT number	2015-003172-67
Trial protocol	CZ SK ES IT NL GR
Global end of trial date	02 August 2019

Results information

Result version number	v1 (current)
This version publication date	16 February 2020
First version publication date	16 February 2020

Trial information

Trial identification

Sponsor protocol code	CQAW039A2314

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02563067
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, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 August 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In patients with severe asthma and high eosinophil counts (≥250 cells/µl) receiving standard-of-care asthma therapy:
- To demonstrate the efficacy (as measured by rate of moderate-to-severe asthma exacerbations) of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, at the end of the 52-week active-treatment period.

In all patients with severe asthma receiving standard-of-care asthma therapy:
- To demonstrate the efficacy (as measured by rate of moderate-to-severe asthma exacerbations) of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, at the end of the 52-week active-treatment period.

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	03 December 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 189
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Czech Republic: 56
Country: Number of subjects enrolled	Greece: 31
Country: Number of subjects enrolled	India: 76
Country: Number of subjects enrolled	Israel: 30
Country: Number of subjects enrolled	Italy: 70
Country: Number of subjects enrolled	Japan: 31
Country: Number of subjects enrolled	Lebanon: 9
Country: Number of subjects enrolled	Malaysia: 8
Country: Number of subjects enrolled	Mexico: 32
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Russian Federation: 89
Country: Number of subjects enrolled	Serbia: 36

Country: Number of subjects enrolled	Slovakia: 89
Country: Number of subjects enrolled	South Africa: 8
Country: Number of subjects enrolled	Spain: 45
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	United States: 50
Worldwide total number of subjects	877
EEA total number of subjects	302

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)	33
Adults (18-64 years)	699
From 65 to 84 years	145
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from centers in Argentina (18), Canada (5), Czech Republic (7), Greece (6), India (12), Israel (5), Italy (22), Japan (16), Lebanon (3), Malaysia (4), Mexico (3), Netherlands (4), Russian Federation (11), Serbia (4), Slovakia (11), South Africa (3), Spain (13), Taiwan (3) and the United States (19).

Pre-assignment

Screening details:

The study included a Screening period of up to 2 weeks and a Placebo Run-in period of 2 to 6 weeks, during which eligibility for randomization was determined

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	QAW039 150 mg

Arm description:

QAW039 150 mg once daily

Arm type	Experimental
Investigational medicinal product name	Fevipiprant
Investigational medicinal product code	QAW039
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

QAW039 150 mg once daily (one tablet of blinded QAW039 at 150 mg dosage strength to be given together with one tablet blinded placebo to QAW039 450 mg)

Arm title	QAW039 450 mg

Arm description:

QAW039 450 mg once daily

Arm type	Experimental
Investigational medicinal product name	Fevipiprant
Investigational medicinal product code	QAW039
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

QAW039 450 mg once daily (one tablet of blinded QAW039 at 450 mg dosage strength to be given together with one tablet blinded placebo to QAW039 150 mg)

Arm title	Placebo

Arm description:

Placebo once daily

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to QAW039 once daily (one tablet blinded placebo to QAW039 150 mg and one tablet blinded placebo to QAW039 450 mg)

Number of subjects in period 1	QAW039 150 mg	QAW039 450 mg	Placebo
Started	296	294	287
Completed	277	268	267
Not completed	19	26	20
Adverse event, serious fatal	-	1	1
Physician decision	-	1	3
Adverse event, non-fatal	2	1	-
Technical problems	-	1	-
Lost to follow-up	1	2	-
Subject/guardian decision	14	20	16
Lack of efficacy	1	-	-
Death after treatment period	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	QAW039 150 mg
Reporting group description: QAW039 150 mg once daily	
Reporting group title	QAW039 450 mg
Reporting group description: QAW039 450 mg once daily	
Reporting group title	Placebo
Reporting group description: Placebo once daily	

Reporting group values	QAW039 150 mg	QAW039 450 mg	Placebo
Number of subjects	296	294	287
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)	12	14	7
Adults (18-64 years)	237	232	230
From 65-84 years	47	48	50
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	49.8	49.6	50.9
standard deviation	± 14.60	± 15.25	± 14.16
Sex: Female, Male Units: Participants			
Female	165	178	177
Male	131	116	110
Race/Ethnicity, Customized Units: Subjects			
Caucasian	234	235	227
Black	6	4	1
Asian	44	41	41
Native American	2	2	4
Unknown	2	2	3
Other	8	10	11

Reporting group values	Total		
Number of subjects	877		

Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	33		
Adults (18-64 years)	699		
From 65-84 years	145		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	520		
Male	357		
Race/Ethnicity, Customized Units: Subjects			
Caucasian	696		
Black	11		
Asian	126		
Native American	8		
Unknown	7		
Other	29		

End points

End points reporting groups

Reporting group title	QAW039 150 mg
Reporting group description: QAW039 150 mg once daily	
Reporting group title	QAW039 450 mg
Reporting group description: QAW039 450 mg once daily	
Reporting group title	Placebo
Reporting group description: Placebo once daily	

Primary: Rate of moderate-to-severe Asthma Exacerbations during the 52-week treatment period in high eosinophils subpopulation

End point title	Rate of moderate-to-severe Asthma Exacerbations during the 52-week treatment period in high eosinophils subpopulation

End point description:

A severe asthma exacerbation is defined as treatment with 'rescue' systemic corticosteroids for greater than or equal to 3 days and
hospitalization; or treatment with 'rescue' systemic corticosteroids for greater than or equal to 3 days and emergency department visit
(greater than 24 hours*); or death due to asthma.
A moderate asthma exacerbation is defined as treatment with 'rescue' systemic corticosteroids for greater than or equal to 3 days either as an outpatient or in emergency department visits (Emergency department visit less than or equal to 24 hours). The high eosinophils subpopulation consists of all patients with blood eosinophil count ≥ 250 cells/µL at baseline.

End point type	Primary

End point timeframe:

52 weeks

End point values	QAW039 150 mg	QAW039 450 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	198	196	193	
Units: Events/year				
least squares mean (confidence interval 95%)	0.73 (0.57 to 0.94)	0.76 (0.59 to 0.99)	1.06 (0.84 to 1.33)	

Statistical analyses

Statistical analysis title	Logistic Regression
Comparison groups	QAW039 150 mg v Placebo

Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.059 [1]
Method	negative binomial regression model
Parameter estimate	Rate Ratio
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	0.96

Notes:

[1] - adjusted p-value, closed testing procedure across the primary and key secondary null hypotheses. Overall type I error rate controlled at two-sided 5%.

Statistical analysis title	Logistic Regression
Comparison groups	QAW039 450 mg v Placebo
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.114 [2]
Method	negative binomial regression model
Parameter estimate	Rate Ratio
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.01

Notes:

[2] - adjusted p-value, closed testing procedure across the primary and key secondary null hypotheses. Overall type I error rate controlled at two-sided 5%.

Primary: Rate of moderate-to-severe Asthma Exacerbations during the 52-week treatment period in overall population

End point title	Rate of moderate-to-severe Asthma Exacerbations during the 52-week treatment period in overall population

End point description:

A severe asthma exacerbation is defined as treatment with ‘rescue’ systemic corticosteroids for greater than or equal to 3 days and hospitalization; or treatment with ‘rescue’ systemic corticosteroids for greater than or equal to 3 days and emergency department visit (greater than 24 hours*); or death due to asthma.
A moderate asthma exacerbation is defined as treatment with ‘rescue’ systemic corticosteroids for greater than or equal to 3 days either as an outpatient or in emergency department visits (Emergency department visit less than or equal to 24 hours).

End point type	Primary

End point timeframe:

52 weeks

End point values	QAW039 150 mg	QAW039 450 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	296	293	287	
Units: Events/year				
least squares mean (confidence interval 95%)	0.76 (0.62 to 0.92)	0.70 (0.57 to 0.87)	0.93 (0.76 to 1.12)	

Statistical analyses

Statistical analysis title	Logistic Regression
Comparison groups	QAW039 150 mg v Placebo
Number of subjects included in analysis	583
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.369 [3]
Method	negative binomial regression model
Parameter estimate	Rate Ratio
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.07

Notes:

[3] - adjusted p-value, closed testing procedure across the primary and key secondary null hypotheses. Overall type I error rate controlled at two-sided 5%.

Statistical analysis title	Logistic Regression
Comparison groups	QAW039 450 mg v Placebo
Number of subjects included in analysis	580
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.348 [4]
Method	negative binomial regression model
Parameter estimate	Rate Ratio
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1

Notes:

[4] - adjusted p-value, closed testing procedure across the primary and key secondary null hypotheses. Overall type I error rate controlled at two-sided 5%.

Secondary: Change From Baseline to Week 52 in Asthma Quality of Life Questionnaire for Participants 12 Years and Older (AQLQ+12) Score in high eosinophils subpopulation

End point title	Change From Baseline to Week 52 in Asthma Quality of Life

	Questionnaire for Participants 12 Years and Older (AQLQ+12) Score in high eosinophils subpopulation

End point description:

AQLQ is a 32-item instrument administered as a self-assessment. AQLQ+12 is a modified version of AQLQ developed to measure functional impairments of participants aged 12-70 years. It is divided into 4 domains: activity limitation, symptoms, emotional function, and environmental stimuli. Participants were asked to recall their experiences during the last 2 weeks and respond to each question on a 7-point scale (1=severe impairment, 7=no impairment), where higher scores indicated "better quality of life." Overall AQLQ+12 score is the mean of all 32 responses.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	QAW039 150 mg	QAW039 450 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	198	196	193	
Units: units on a scale				
least squares mean (standard error)	0.73 (± 0.061)	0.71 (± 0.062)	0.58 (± 0.062)	

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	QAW039 150 mg v Placebo
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.369 [5]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.32

Notes:

[5] - adjusted p-value, closed testing procedure across the primary and key secondary null hypotheses. Overall type I error rate controlled at two-sided 5%.

Statistical analysis title	ANCOVA
Comparison groups	QAW039 450 mg v Placebo
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.824 [6]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.3

Notes:

[6] - adjusted p-value, closed testing procedure across the primary and key secondary null hypotheses. Overall type I error rate controlled at two-sided 5%.

Secondary: Change from Baseline to Week 52 in Asthma Control Questionnaire-5 (ACQ-5) score in high eosinophils subpopulation

End point title	Change from Baseline to Week 52 in Asthma Control Questionnaire-5 (ACQ-5) score in high eosinophils subpopulation

End point description:

The ACQ-5 is a five-item, self-completed questionnaire, which is used as a measure of asthma control of a participant. The five questions (concerning nocturnal awakening, waking in the morning, activity limitation, shortness of breath and wheeze) enquire about the frequency and/or severity of symptoms over the previous week. The response options for all these questions range from zero (no impairment/limitation) to six (total impairment/ limitation) scale. ACQ-5 score range from 0 to 6. Higher scores indicates worsening of condition.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	QAW039 150 mg	QAW039 450 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	198	196	193	
Units: units on a scale				
least squares mean (standard error)	-0.92 (± 0.067)	-0.84 (± 0.068)	-0.75 (± 0.069)	

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	QAW039 150 mg v Placebo
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.369 [7]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.01

Notes:

[7] - adjusted p-value, closed testing procedure across the primary and key secondary null hypotheses. Overall type I error rate controlled at two-sided 5%.

Statistical analysis title	ANCOVA
Comparison groups	QAW039 450 mg v Placebo
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.824 [8]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.1

Notes:

[8] - adjusted p-value, closed testing procedure across the primary and key secondary null hypotheses. Overall type I error rate controlled at two-sided 5%.

Secondary: Change from Baseline to Week 52 in Pre-dose Forced Expiratory Volume in 1 second (FEV1) in high eosinophils subpopulation

End point title	Change from Baseline to Week 52 in Pre-dose Forced Expiratory Volume in 1 second (FEV1) in high eosinophils subpopulation

End point description:

Forced Expiratory Volume in one second (FEV1) is calculated as the volume of air forcibly exhaled in one second as measured by a spirometer. Baseline is defined as the last available FEV1 measurement taken prior to the first dose of randomized study drug.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	QAW039 150 mg	QAW039 450 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	198	196	193	
Units: Liter				
least squares mean (standard error)	0.192 (± 0.0306)	0.162 (± 0.0311)	0.124 (± 0.0313)	

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	QAW039 150 mg v Placebo

Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.369 [9]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.068
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.018
upper limit	0.154

Notes:

[9] - adjusted p-value, closed testing procedure across the primary and key secondary null hypotheses. Overall type I error rate controlled at two-sided 5%.

Statistical analysis title	ANCOVA
Comparison groups	QAW039 450 mg v Placebo
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.824 [10]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.038
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.048
upper limit	0.124

Notes:

[10] - adjusted p-value, closed testing procedure across the primary and key secondary null hypotheses. Overall type I error rate controlled at two-sided 5%.

Secondary: Change From Baseline to Week 52 in Asthma Quality of Life Questionnaire for Participants 12 Years and Older (AQLQ+12) Score in overall population

End point title	Change From Baseline to Week 52 in Asthma Quality of Life Questionnaire for Participants 12 Years and Older (AQLQ+12) Score in overall population

End point description:

AQLQ is a 32-item instrument administered as a self-assessment. AQLQ+12 is a modified version of AQLQ developed to measure functional impairments of participants aged 12-70 years. It is divided into 4 domains: activity limitation, symptoms, emotional function, and environmental stimuli. Participants were asked to recall their experiences during the last 2 weeks and respond to each question on a 7-point scale (1=severe impairment, 7=no impairment), where higher scores indicated "better quality of life." Overall AQLQ+12 score is the mean of all 32 responses.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	QAW039 150 mg	QAW039 450 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	296	293	287	
Units: units on a scale				
least squares mean (standard error)	0.62 (± 0.050)	0.67 (± 0.050)	0.55 (± 0.051)	

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	QAW039 150 mg v Placebo
Number of subjects included in analysis	583
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.824 [11]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.21

Notes:

[11] - adjusted p-value, closed testing procedure across the primary and key secondary null hypotheses. Overall type I error rate controlled at two-sided 5%.

Statistical analysis title	ANCOVA
Comparison groups	QAW039 450 mg v Placebo
Number of subjects included in analysis	580
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.824 [12]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.26

Notes:

[12] - adjusted p-value, closed testing procedure across the primary and key secondary null hypotheses. Overall type I error rate controlled at two-sided 5%.

Secondary: Change from Baseline to Week 52 in Asthma Control Questionnaire-5 (ACQ-5) score in overall population

End point title	Change from Baseline to Week 52 in Asthma Control Questionnaire-5 (ACQ-5) score in overall population

End point description:

The ACQ-5 is a five-item, self-completed questionnaire, which is used as a measure of asthma control of

a participant. The five questions (concerning nocturnal awakening, waking in the morning, activity limitation, shortness of breath and wheeze) enquire about the frequency and/or severity of symptoms over the previous week. The response options for all these questions range from zero (no impairment/limitation) to six (total impairment/ limitation) scale. ACQ-5 score range from 0 to 6. Higher scores indicates worsening of condition.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	QAW039 150 mg	QAW039 450 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	296	293	287	
Units: units on a scale				
least squares mean (standard error)	-0.83 (± 0.055)	-0.77 (± 0.055)	-0.70 (± 0.055)	

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	QAW039 150 mg v Placebo
Number of subjects included in analysis	583
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.824 [13]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.03

Notes:

[13] - adjusted p-value, closed testing procedure across the primary and key secondary null hypotheses. Overall type I error rate controlled at two-sided 5%.

Statistical analysis title	ANCOVA
Comparison groups	QAW039 450 mg v Placebo
Number of subjects included in analysis	580
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.824 [14]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.07

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.08

Notes:

[14] - adjusted p-value, closed testing procedure across the primary and key secondary null hypotheses. Overall type I error rate controlled at two-sided 5%.

Secondary: Change from Baseline to Week 52 in Pre-dose Forced Expiratory Volume in 1 second (FEV1) in overall population

End point title	Change from Baseline to Week 52 in Pre-dose Forced Expiratory Volume in 1 second (FEV1) in overall population

End point description:

Forced Expiratory Volume in one second (FEV1) is calculated as the volume of air forcibly exhaled in one second as measured by a spirometer. Baseline is defined as the last available FEV1 measurement taken prior to the first dose of randomized study drug.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	QAW039 150 mg	QAW039 450 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	296	293	287	
Units: Liter				
least squares mean (standard error)	0.153 (± 0.0247)	0.164 (± 0.0249)	0.103 (± 0.0250)	

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	QAW039 150 mg v Placebo
Number of subjects included in analysis	583
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.369 [15]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.019
upper limit	0.119

Notes:

[15] - adjusted p-value, closed testing procedure across the primary and key secondary null hypotheses. Overall type I error rate controlled at two-sided 5%.

Statistical analysis title	ANCOVA
Comparison groups	QAW039 450 mg v Placebo
Number of subjects included in analysis	580
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.595 [16]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.008
upper limit	0.13

Notes:

[16] - adjusted p-value, closed testing procedure across the primary and key secondary null hypotheses. Overall type I error rate controlled at two-sided 5%.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are presented from first dose of study treatment until last dose of study treatment plus 7 days, up to maximum duration of 56 weeks.

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	22.0

Reporting groups

Reporting group title	QAW039 150 mg

Reporting group description:

QAW039 150 mg

Reporting group title	Placebo

Reporting group description:

Placebo

Reporting group title	QAW039 450 mg

Reporting group description:

QAW039 450 mg

Serious adverse events	QAW039 150 mg	Placebo	QAW039 450 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 296 (6.76%)	18 / 287 (6.27%)	20 / 293 (6.83%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	1 / 296 (0.34%)	0 / 287 (0.00%)	0 / 293 (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
Ovarian neoplasm			
subjects affected / exposed	1 / 296 (0.34%)	0 / 287 (0.00%)	0 / 293 (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
Parathyroid tumour benign			

subjects affected / exposed	1 / 296 (0.34%)	0 / 287 (0.00%)	0 / 293 (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
Renal neoplasm			
subjects affected / exposed	0 / 296 (0.00%)	0 / 287 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 296 (0.00%)	1 / 287 (0.35%)	0 / 293 (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
Vascular disorders			
Arterial thrombosis			
subjects affected / exposed	1 / 296 (0.34%)	0 / 287 (0.00%)	0 / 293 (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
Lymphoedema			
subjects affected / exposed	0 / 296 (0.00%)	0 / 287 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	1 / 296 (0.34%)	0 / 287 (0.00%)	0 / 293 (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
Reproductive system and breast disorders			
Uterine enlargement			
subjects affected / exposed	0 / 296 (0.00%)	1 / 287 (0.35%)	0 / 293 (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
Uterine prolapse			

subjects affected / exposed	0 / 296 (0.00%)	0 / 287 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	8 / 296 (2.70%)	6 / 287 (2.09%)	6 / 293 (2.05%)
occurrences causally related to treatment / all	0 / 9	0 / 11	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	0 / 296 (0.00%)	0 / 287 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal polyps			
subjects affected / exposed	0 / 296 (0.00%)	0 / 287 (0.00%)	2 / 293 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 296 (0.00%)	0 / 287 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 296 (0.00%)	0 / 287 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture displacement			
subjects affected / exposed	0 / 296 (0.00%)	0 / 287 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 296 (0.00%)	1 / 287 (0.35%)	0 / 293 (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

Humerus fracture			
subjects affected / exposed	1 / 296 (0.34%)	0 / 287 (0.00%)	0 / 293 (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
Lower limb fracture			
subjects affected / exposed	1 / 296 (0.34%)	0 / 287 (0.00%)	0 / 293 (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
Lumbar vertebral fracture			
subjects affected / exposed	1 / 296 (0.34%)	0 / 287 (0.00%)	0 / 293 (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
Radius fracture			
subjects affected / exposed	0 / 296 (0.00%)	0 / 287 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seroma			
subjects affected / exposed	0 / 296 (0.00%)	0 / 287 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	1 / 296 (0.34%)	0 / 287 (0.00%)	0 / 293 (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
Cardiac disorders			
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 296 (0.00%)	1 / 287 (0.35%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nervous system disorders			
Brain hypoxia			
subjects affected / exposed	0 / 296 (0.00%)	0 / 287 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 296 (0.00%)	1 / 287 (0.35%)	0 / 293 (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
Eye disorders			
Ulcerative keratitis			
subjects affected / exposed	1 / 296 (0.34%)	0 / 287 (0.00%)	0 / 293 (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
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 296 (0.00%)	1 / 287 (0.35%)	0 / 293 (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
Abdominal pain upper			
subjects affected / exposed	1 / 296 (0.34%)	0 / 287 (0.00%)	0 / 293 (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
Inguinal hernia			
subjects affected / exposed	0 / 296 (0.00%)	1 / 287 (0.35%)	0 / 293 (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
Pancreatitis			
subjects affected / exposed	1 / 296 (0.34%)	0 / 287 (0.00%)	0 / 293 (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
Rectal haemorrhage			
subjects affected / exposed	0 / 296 (0.00%)	1 / 287 (0.35%)	0 / 293 (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
Vomiting			

subjects affected / exposed	1 / 296 (0.34%)	0 / 287 (0.00%)	0 / 293 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 296 (0.00%)	0 / 287 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver disorder			
subjects affected / exposed	0 / 296 (0.00%)	0 / 287 (0.00%)	1 / 293 (0.34%)
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 and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 296 (0.00%)	0 / 287 (0.00%)	1 / 293 (0.34%)
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 failure			
subjects affected / exposed	1 / 296 (0.34%)	0 / 287 (0.00%)	0 / 293 (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
Musculoskeletal and connective tissue disorders			
Gouty arthritis			
subjects affected / exposed	0 / 296 (0.00%)	1 / 287 (0.35%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 296 (0.34%)	1 / 287 (0.35%)	0 / 293 (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
Bronchitis			

subjects affected / exposed	0 / 296 (0.00%)	1 / 287 (0.35%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 296 (0.00%)	0 / 287 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 296 (0.00%)	1 / 287 (0.35%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal viral infection			
subjects affected / exposed	0 / 296 (0.00%)	1 / 287 (0.35%)	0 / 293 (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
Influenza			
subjects affected / exposed	0 / 296 (0.00%)	1 / 287 (0.35%)	0 / 293 (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
Pneumonia			
subjects affected / exposed	2 / 296 (0.68%)	3 / 287 (1.05%)	4 / 293 (1.37%)
occurrences causally related to treatment / all	0 / 2	0 / 3	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sinusitis			
subjects affected / exposed	1 / 296 (0.34%)	0 / 287 (0.00%)	0 / 293 (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
Tonsillitis			
subjects affected / exposed	0 / 296 (0.00%)	1 / 287 (0.35%)	0 / 293 (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
Upper respiratory tract infection			

subjects affected / exposed	0 / 296 (0.00%)	1 / 287 (0.35%)	0 / 293 (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
Urinary tract infection			
subjects affected / exposed	0 / 296 (0.00%)	0 / 287 (0.00%)	1 / 293 (0.34%)
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	0 / 296 (0.00%)	0 / 287 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	QAW039 150 mg	Placebo	QAW039 450 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	181 / 296 (61.15%)	180 / 287 (62.72%)	183 / 293 (62.46%)
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 296 (6.42%)	9 / 287 (3.14%)	21 / 293 (7.17%)
occurrences (all)	24	12	30
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	129 / 296 (43.58%)	145 / 287 (50.52%)	119 / 293 (40.61%)
occurrences (all)	267	319	214
Rhinitis allergic			
subjects affected / exposed	13 / 296 (4.39%)	9 / 287 (3.14%)	8 / 293 (2.73%)
occurrences (all)	18	10	10
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	13 / 296 (4.39%)	9 / 287 (3.14%)	5 / 293 (1.71%)
occurrences (all)	15	11	5
Infections and infestations			
Bronchitis			

subjects affected / exposed	37 / 296 (12.50%)	32 / 287 (11.15%)	30 / 293 (10.24%)
occurrences (all)	46	52	35
Influenza			
subjects affected / exposed	17 / 296 (5.74%)	13 / 287 (4.53%)	18 / 293 (6.14%)
occurrences (all)	19	15	21
Nasopharyngitis			
subjects affected / exposed	33 / 296 (11.15%)	26 / 287 (9.06%)	42 / 293 (14.33%)
occurrences (all)	40	33	48
Rhinitis			
subjects affected / exposed	10 / 296 (3.38%)	13 / 287 (4.53%)	15 / 293 (5.12%)
occurrences (all)	10	14	20
Upper respiratory tract infection			
subjects affected / exposed	18 / 296 (6.08%)	14 / 287 (4.88%)	16 / 293 (5.46%)
occurrences (all)	19	21	22
Upper respiratory tract infection bacterial			
subjects affected / exposed	10 / 296 (3.38%)	14 / 287 (4.88%)	8 / 293 (2.73%)
occurrences (all)	16	20	13
Viral upper respiratory tract infection			
subjects affected / exposed	20 / 296 (6.76%)	24 / 287 (8.36%)	28 / 293 (9.56%)
occurrences (all)	27	31	29

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 August 2015	A literature review identified additional statins that could interact with QAW039, and patients taking these statins were to be excluded from the study: - Text was added that indicated that patients on doses of simvastatin >20 mg, doses of atorvastatin >40 mg, doses of pravastatin >40mg, or doses of pitavastatin >2 mg per day should not be included in the study. - Statin doses less than or equal to these doses as well as other statins were permitted during the study.
19 May 2016	- Changed inclusion criterion #2 to allow for the lower age limit in the study to patients aged ≥12 years (or ≥ lower age limit allowed by health authority and/or ethics committee/institutional review board approvals). - Added an exclusion criterion for patients below the 3rd percentile for weight by age for adolescent patients aged 12 to <18 years to ensure malnourished adolescents were excluded. - Added an exclusion criterion for lactose and milk sensitivity since the placebo tablets include lactose - Added an exclusion criterion for patients with a history of conditions other than asthma that could result in elevated eosinophils (e.g., hypereosinophilic syndromes, Churg-Strauss Syndrome, eosinophilic esophagitis) and exclude patients with known parasitic infestation within 6 months prior to Visit 1. - Added country-required local contraception language for certain countries.
10 February 2017	Primarily updated renal guidelines and liver event and laboratory trigger definitions of Novartis were included. These changes included: - Updated definitions of urine events. - Updated follow-up requirements for liver events and laboratory triggers for ALT and AST (> 3 to ≤ 5 × ULN (patient is asymptomatic)).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported