Clinical trial results:
A double-blind, placebo-controlled, study examining the effect of orally administered QAW039 (450 mg qd) on FEV1 and ACQ in non-atopic, asthmatic patients with a baseline, pre-bronchodilator FEV1 of 40-80% predicted, inadequately controlled with low dose ICS therapy

Summary

EudraCT number	2012-003995-38
Trial protocol	BE CZ
Global end of trial date	04 February 2016

Results information

Result version number	v1 (current)
This version publication date	15 February 2017
First version publication date	15 February 2017

Trial information

Trial identification

Sponsor protocol code	CQAW039A2214

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01836471
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals
Sponsor organisation address	CH - 4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharmaceuticals, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharmaceuticals, 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	04 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 February 2016
Global end of trial reached?	Yes
Global end of trial date	04 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the efficacy of QAW039 (450 mg qd) compared to placebo with respect to the change in trough FEV1 from baseline to 12 weeks of postbaseline treatment in non-atopic asthmatic patients who, at randomization, were inadequately controlled on low dose ICS (100 µg fluticasone bid) background therapy.

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:

Patients randomized to QAW039 (non-atopic and atopic) and Placebo (non-atopic and atopic) arms received fluticasone 100 µg as background therapy as powdered inhalation twice daily (AM and PM roughly 12 hours apart) at around the same times for the duration of the treatment period.
Patients randomized to Fluticasone 150 µg (atopic) as study treatment received powdered inhalation in one combined dosage from one inhaler (fluticasone 250 µg in total) twice daily (AM and PM roughly 12 hours apart) at around the same times for the duration of the treatment period.

Evidence for comparator: -

Actual start date of recruitment	28 May 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 16
Country: Number of subjects enrolled	Colombia: 13
Country: Number of subjects enrolled	Czech Republic: 15
Country: Number of subjects enrolled	Germany: 44
Country: Number of subjects enrolled	India: 18
Country: Number of subjects enrolled	Korea, Republic of: 21
Country: Number of subjects enrolled	Poland: 20
Country: Number of subjects enrolled	Romania: 63
Country: Number of subjects enrolled	South Africa: 29
Country: Number of subjects enrolled	United States: 95
Worldwide total number of subjects	334
EEA total number of subjects	158

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	274
From 65 to 84 years	60
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total of 939 subjects were screened, 679 entered the inhaled corticosteroid (ICS) tapering run-in, 345 subjects were randomized; eleven randomized subjects discontinued the study prior to start of study drug. Patient disposition and baseline characteristics were presented for 334 subjects (received study drug)

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	Investigator, Subject, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	QAW039 450 mg qd Non-atopic

Arm description:

QAW039 450 mg qd plus background ICS (100 µg fluticasone, bid). Non-atopic patients randomized in ratio of approximately 1:1 to QAW039 or placebo.

Arm type	Experimental
Investigational medicinal product name	QAW039 450 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

450 mg once daily (3 capsules of QAW039 150 mg taken with food in the morning)

Investigational medicinal product name	Fluticasone propionate 100 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use

Dosage and administration details:

Inhaled corticosteroid (ICS) fluticasone 100 µg dose strength inhaler (background therapy) taken morning and evening with approximately 12 hours between doses .

Arm title	Placebo Non-atopic

Arm description:

Placebo to QAW039 450 mg qd plus background ICS (100 µg fluticasone, bid). Non-atopic patients randomized in ratio of approximately 1:1 to QAW039 or placebo.

Arm type	Placebo
Investigational medicinal product name	QAW039 placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

The matching placebos for QAW039 were identical in appearance to their active counterparts. Dosage was QAW039 Placebo (3 capsules taken with food in the morning)

Investigational medicinal product name	Fluticasone propionate 100 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use

Dosage and administration details:

Inhaled corticosteroid (ICS) fluticasone 100 µg dose strength inhaler (background therapy) taken morning and evening with approximately 12 hours between doses .

Arm title	QAW039 450 mg qd Atopic

Arm description:

QAW039 450 mg qd plus background ICS (100 µg fluticasone, bid). Atopic patients randomized in ratio of approximately 1:1:1 to QAW039 or fluticasone or placebo.

Arm type	Experimental
Investigational medicinal product name	QAW039 450 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

450 mg once daily (3 capsules of QAW039 150 mg taken with food in the morning)

Investigational medicinal product name	Fluticasone propionate 100 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use

Dosage and administration details:

Inhaled corticosteroid (ICS) fluticasone 100 µg dose strength inhaler (background therapy) taken morning and evening with approximately 12 hours between doses .

Arm title	Fluticasone 150 µg bid Atopic

Arm description:

Fluticasone 150 µg plus background ICS (100 µg fluticasone, bid). Atopic patients randomized in ratio of approximately 1:1:1 to QAW039 or fluticasone or placebo.

Arm type	Active comparator
Investigational medicinal product name	Fluticasone propionate 250 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use

Dosage and administration details:

Inhaled corticosteroid (ICS) fluticasone 250 µg dose strength inhaler taken morning and evening with approximately 12 hours between doses. Background therapy of 100 µg included in 250 µg dose.

Arm title	Placebo Atopic

Arm description:

Placebo to QAW039 450 mg qd plus background ICS (100 µg fluticasone, bid). Atopic patients randomized in ratio of approximately 1:1:1 to QAW039 or fluticasone or placebo.

Arm type	Placebo
Investigational medicinal product name	QAW039 placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:	
The matching placebos for QAW039 were identical in appearance to their active counterparts. Dosage was QAW039 Placebo (3 capsules taken with food in the morning)	
Investigational medicinal product name	Fluticasone propionate 100 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use
Dosage and administration details:	
Inhaled corticosteroid (ICS) fluticasone 100 µg dose strength inhaler (background therapy) taken morning and evening with approximately 12 hours between doses .	

Number of subjects in period 1	QAW039 450 mg qd Non-atopic	Placebo Non-atopic	QAW039 450 mg qd Atopic
Started	93	94	51
Completed	82	85	49
Not completed	11	9	2
Consent withdrawn by subject	3	4	1
Physician decision	-	1	-
Non compliance with tx	1	1	-
Adverse event, non-fatal	6	3	1
Pregnancy	1	-	-
Lost to follow-up	-	-	-

Number of subjects in period 1	Fluticasone 150 µg bid Atopic	Placebo Atopic
Started	42	54
Completed	40	49
Not completed	2	5
Consent withdrawn by subject	-	2
Physician decision	-	-
Non compliance with tx	-	-
Adverse event, non-fatal	1	2
Pregnancy	-	-
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	QAW039 450 mg qd Non-atopic
Reporting group description:	
QAW039 450 mg qd plus background ICS (100 µg fluticasone, bid). Non-atopic patients randomized in ratio of approximately 1:1 to QAW039 or placebo.	
Reporting group title	Placebo Non-atopic
Reporting group description:	
Placebo to QAW039 450 mg qd plus background ICS (100 µg fluticasone, bid). Non-atopic patients randomized in ratio of approximately 1:1 to QAW039 or placebo.	
Reporting group title	QAW039 450 mg qd Atopic
Reporting group description:	
QAW039 450 mg qd plus background ICS (100 µg fluticasone, bid). Atopic patients randomized in ratio of approximately 1:1:1 to QAW039 or fluticasone or placebo.	
Reporting group title	Fluticasone 150 µg bid Atopic
Reporting group description:	
Fluticasone 150 µg plus background ICS (100 µg fluticasone, bid). Atopic patients randomized in ratio of approximately 1:1:1 to QAW039 or fluticasone or placebo.	
Reporting group title	Placebo Atopic
Reporting group description:	
Placebo to QAW039 450 mg qd plus background ICS (100 µg fluticasone, bid). Atopic patients randomized in ratio of approximately 1:1:1 to QAW039 or fluticasone or placebo.	

Reporting group values	QAW039 450 mg qd Non-atopic	Placebo Non-atopic	QAW039 450 mg qd Atopic
Number of subjects	93	94	51
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	70	73	45
From 65-84 years	23	21	6
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	51.9	53.5	50.3
standard deviation	± 14.33	± 14.37	± 12.75
Gender, Male/Female Units: Subjects			
Female	60	60	26
Male	33	34	25
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	2	3	3
Asian	15	16	4

Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	6	6	3
White	68	68	40
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Other	2	1	1
Subject population			
Non-atopic defined as history of perennial symptoms with no clear inhaled allergic trigger AND a negative skin prick test (< 3mm diameter above background) or a negative specific IgE (<0.35 IU eq./ml). Atopic/allergic defined as skin prick test (≥ 3mm diameter above background) or a positive specific IgE (e.g.,RAST/CAP) test (≥0.35 IU eq/ml)			
Units: Subjects			
Non-atopic	93	94	0
Atopic	0	0	51
Study Specific Characteristic | Duration of asthma			
Units: years			
arithmetic mean	14.88	12.82	24.69
standard deviation	± 12.349	± 12.196	± 17.446
Study Specific Characteristic | Percentage of predicted FEV1 (%) pre-bronchodilator			
Units: Percentage			
arithmetic mean	67.5446	65.7286	69.0662
standard deviation	± 11.81404	± 13.94056	± 12.16292
Study Specific Characteristic | ACQ-6 score			
Number of participants (n=92,94,51,42,54)			
Units: points			
arithmetic mean	1.7	1.53	1.55
standard deviation	± 0.762	± 0.745	± 0.665

Reporting group values	Fluticasone 150 µg bid Atopic	Placebo Atopic	Total
Number of subjects	42	54	334
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	41	45	274
From 65-84 years	1	9	60
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	48.2	48.2	
standard deviation	± 12.16	± 13.58	-

Gender, Male/Female Units: Subjects			
Female	23	25	194
Male	19	29	140
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	3	2	13
Asian	6	3	44
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	3	4	22
White	29	43	248
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Other	1	1	6
Subject population			
Non-atopic defined as history of perennial symptoms with no clear inhaled allergic trigger AND a negative skin prick test (< 3mm diameter above background) or a negative specific IgE (<0.35 IU eq./ml). Atopic/allergic defined as skin prick test (≥ 3mm diameter above background) or a positive specific IgE (e.g.,RAST/CAP) test (≥0.35 IU eq/ml)			
Units: Subjects			
Non-atopic	0	0	187
Atopic	42	54	147
Study Specific Characteristic | Duration of asthma Units: years			
arithmetic mean	27.78	24.09	
standard deviation	± 18.039	± 16.055	-
Study Specific Characteristic | Percentage of predicted FEV1 (%) pre-bronchodilator Units: Percentage			
arithmetic mean	68.7483	64.8709	
standard deviation	± 10.52156	± 12.97729	-
Study Specific Characteristic | ACQ-6 score			
Number of participants (n=92,94,51,42,54)			
Units: points			
arithmetic mean	1.68	1.72	
standard deviation	± 0.749	± 0.675	-

End points

End points reporting groups

Reporting group title	QAW039 450 mg qd Non-atopic
Reporting group description:	
QAW039 450 mg qd plus background ICS (100 µg fluticasone, bid). Non-atopic patients randomized in ratio of approximately 1:1 to QAW039 or placebo.	
Reporting group title	Placebo Non-atopic
Reporting group description:	
Placebo to QAW039 450 mg qd plus background ICS (100 µg fluticasone, bid). Non-atopic patients randomized in ratio of approximately 1:1 to QAW039 or placebo.	
Reporting group title	QAW039 450 mg qd Atopic
Reporting group description:	
QAW039 450 mg qd plus background ICS (100 µg fluticasone, bid). Atopic patients randomized in ratio of approximately 1:1:1 to QAW039 or fluticasone or placebo.	
Reporting group title	Fluticasone 150 µg bid Atopic
Reporting group description:	
Fluticasone 150 µg plus background ICS (100 µg fluticasone, bid). Atopic patients randomized in ratio of approximately 1:1:1 to QAW039 or fluticasone or placebo.	
Reporting group title	Placebo Atopic
Reporting group description:	
Placebo to QAW039 450 mg qd plus background ICS (100 µg fluticasone, bid). Atopic patients randomized in ratio of approximately 1:1:1 to QAW039 or fluticasone or placebo.	

Primary: Change from baseline in trough FEV1 (L) in non-atopic patients at Week 12 - full analysis set

End point title	Change from baseline in trough FEV1 (L) in non-atopic patients at Week 12 - full analysis set[1]
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. Data within 6 hr of rescue medication use is excluded from this analysis. For subjects with missing trough FEV1 (L) at Week 12, the last post baseline observation were used (LOCF). Estimates are from a mixed effects model with treatment, subject population (non-atopic vs. atopic), treatment by subject population interaction, baseline trough FEV1 and region as fixed effects and center nested within region as random effects. Full analysis set included all randomized subjects who received at least one dose of study drug.	
End point type	Primary
End point timeframe:	
baseline,12 weeks	

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: No statistical analysis was planned for this endpoint.

End point values	QAW039 450 mg qd Non-atopic	Placebo Non-atopic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	93		
Units: liter				
least squares mean (standard error)	0.05 (± 0.029)	0.03 (± 0.029)		

Statistical analyses

Statistical analysis title	QAW039 450 mg Non-atoopic vs placebo Non-atopic
Comparison groups	QAW039 450 mg qd Non-atopic v Placebo Non-atopic
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7269
Method	Mixed models analysis
Parameter estimate	least squares mean
Point estimate	0.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.5
upper limit	0.08
Variability estimate	Standard error of the mean
Dispersion value	0.038

Secondary: Change from baseline in trough FEV1 (L) in atopic patients at Week 12 - full analysis set

End point title	Change from baseline in trough FEV1 (L) in atopic patients at Week 12 - full analysis set[2]

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 FEV1 measurement taken prior to the first dose of randomized study drug. Data within 6 hr of rescue medication use is excluded from this analysis. For subjects with missing trough FEV1 (L) at Week 12, the last post baseline observation were used (LOCF). Estimates are from a mixed effects model with treatment, subject population (non-atopic vs. atopic), treatment by subject population interaction, baseline trough FEV1 and region as fixed effects and center nested within region as random effects. Full analysis set included all randomized subjects who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

baseline,12 weeks

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: No statistical analysis was planned for this endpoint.

End point values	QAW039 450 mg qd Atopic	Fluticasone 150 µg bid Atopic	Placebo Atopic	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	41	52	
Units: liter				
least squares mean (standard error)	0.06 (± 0.038)	0.01 (± 0.042)	0.05 (± 0.037)	

Statistical analyses

Statistical analysis title	QAW039 450 mg Atopic vs placebo Atopic
Comparison groups	QAW039 450 mg qd Atopic v Placebo Atopic
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	least sqares mean
Point estimate	0.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.08
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.05

Statistical analysis title	QAW039 450 mg Atopic vs fluticasone 150 µg Atopic
Comparison groups	QAW039 450 mg qd Atopic v Fluticasone 150 µg bid Atopic
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	least squares mean
Point estimate	0.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.04
upper limit	0.13
Variability estimate	Standard error of the mean
Dispersion value	0.054

Statistical analysis title	Fluticasone 150 µg Atopic vs placebo Atopic
Comparison groups	Fluticasone 150 µg bid Atopic v Placebo Atopic

Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	least squares mean
Point estimate	-0.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.13
upper limit	0.05
Variability estimate	Standard error of the mean
Dispersion value	0.053

Secondary: Change from baseline in trough FEV1 (L) in non-atopic compared to atopic patients at Week 12 - full analysis set

End point title	Change from baseline in trough FEV1 (L) in non-atopic compared to atopic patients at Week 12 - full analysis set

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 FEV1 measurement taken prior to the first dose of randomized study drug. Data within 6 hr of rescue medication use is excluded from this analysis. For subjects with missing trough FEV1 (L) at Week 12, the last post baseline observation were used (LOCF). Estimates are from a mixed effects model with treatment, subject population, treatment by subject population interaction, baseline trough FEV1 and region as fixed effects and center nested within region as random effects. Full analysis set included all randomized subjects who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

baseline,12 weeks

End point values	QAW039 450 mg qd Non-atopic	Placebo Non-atopic	QAW039 450 mg qd Atopic	Fluticasone 150 µg bid Atopic
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	93	50	41
Units: liter				
least squares mean (standard error)	0.05 (± 0.029)	0.03 (± 0.029)	0.06 (± 0.038)	0.01 (± 0.042)

End point values	Placebo Atopic			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: liter				
least squares mean (standard error)	0.05 (± 0.037)			

Statistical analyses

Statistical analysis title	FEV1 Non-atopic vs Atopic
Comparison groups	QAW039 450 mg qd Non-atopic v Placebo Non-atopic v QAW039 450 mg qd Atopic v Fluticasone 150 µg bid Atopic v Placebo Atopic
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9179
Method	Mixed models analysis

Secondary: Change from baseline in ACQ-6 score at Week 12 non-atopic and atopic patients at Week 12 - full analysis set

End point title	Change from baseline in ACQ-6 score at Week 12 non-atopic and atopic patients at Week 12 - full analysis set

End point description:

ACQ-6 consists of:5 items on symptoms, 1 item on rescue bronchodilator use, and 1 item on airway caliber (FEV1 % predicted). The ACQ was fully validated, including a minimal important difference (MID) or smallest change that could be considered clinically important (0.5). The ACQ was self-administered at the clinic and patients scored each item on a 7-point response scale: 0 = 'totally controlled' and 6 = 'severely uncontrolled.' Study staff scored question 7 based on % predicted FEV1 (ideally pre-bronchodilator). The total score=average of first 6 questions. Baseline=the ACQ-6 measurement taken prior to first dose of randomized study drug. The single missing score was interpolated by utilizing prior or subsequent completions of the questionnaire. Estimates were from a mixed effects model with treatment, subject population (non-atopic vs. atopic), treatment by subject population interaction, baseline ACQ-6 and region as fixed effects and center nested within region as random effects.

End point type	Secondary

End point timeframe:

baseline,12 weeks

End point values	QAW039 450 mg qd Non-atopic	Placebo Non-atopic	QAW039 450 mg qd Atopic	Fluticasone 150 µg bid Atopic
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	85	48	40
Units: score				
least squares mean (standard error)	-0.05 (± 0.077)	-0.03 (± 0.073)	-0.25 (± 0.096)	-0.35 (± 0.104)

End point values	Placebo Atopic			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: score				
least squares mean (standard error)	-0.18 (± 0.096)			

Statistical analyses

Statistical analysis title	QAW039 450 mg Non-atopic vs placebo Non-atopic
Comparison groups	QAW039 450 mg qd Non-atopic v Placebo Non-atopic
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	least squares mean
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.17
Variability estimate	Standard error of the mean
Dispersion value	0.098

Statistical analysis title	QAW039 450 mg Atopic vs placebo Atopic
Comparison groups	QAW039 450 mg qd Atopic v Placebo Atopic
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	least sqares mean
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.19
Variability estimate	Standard error of the mean
Dispersion value	0.128

Statistical analysis title	QAW039 450 mg Atopic vs fluticasone 150 µg Atopic
Comparison groups	QAW039 450 mg qd Atopic v Fluticasone 150 µg bid Atopic

Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	least squares mean
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.37
Variability estimate	Standard error of the mean
Dispersion value	0.134

Statistical analysis title	Fluticasone 150 µg Atopic vs placebo Atopic
Comparison groups	Fluticasone 150 µg bid Atopic v Placebo Atopic
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	least squares mean
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.134

Secondary: Change from baseline in ACQ-6 score at Week 12 non-atopic compared to atopic patients at Week 12 - full analysis set

End point title	Change from baseline in ACQ-6 score at Week 12 non-atopic compared to atopic patients at Week 12 - full analysis set

End point description:

ACQ-6 consists of:5 items on symptoms, 1 item on rescue bronchodilator use, and 1 item on airway caliber (FEV1 % predicted). The ACQ was fully validated, including a minimal important difference (MID) or smallest change that could be considered clinically important (0.5). The ACQ was self-administered at the clinic and patients scored each item on a 7-point response scale: 0 = 'totally controlled' and 6 = 'severely uncontrolled.' Study staff scored question 7 based on % predicted FEV1 (ideally pre-bronchodilator). The total score=average of first 6 questions. Baseline=the ACQ-6 measurement taken prior to first dose of randomized study drug. The single missing score was interpolated by utilizing prior or subsequent completions of the questionnaire. Estimates were from a mixed effects model with treatment, subject population (non-atopic vs. atopic), treatment by subject population interaction, baseline ACQ-6 and region as fixed effects and center nested within region as random effects.

End point type	Secondary

End point timeframe:

baseline,12 weeks

End point values	QAW039 450 mg qd Non-atopic	Placebo Non-atopic	QAW039 450 mg qd Atopic	Fluticasone 150 µg bid Atopic
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	85	48	40
Units: score				
least squares mean (standard error)	-0.05 (± 0.077)	-0.03 (± 0.073)	-0.25 (± 0.096)	-0.35 (± 0.104)

End point values	Placebo Atopic			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: score				
least squares mean (standard error)	-0.18 (± 0.096)			

Statistical analyses

Statistical analysis title	ACQ-6 Non-atopic vs Atopic
Comparison groups	QAW039 450 mg qd Non-atopic v Placebo Non-atopic v QAW039 450 mg qd Atopic v Fluticasone 150 µg bid Atopic v Placebo Atopic
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.793
Method	Mixed models analysis

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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	QAW039 450 mg qd
Reporting group description:	
QAW039 450 mg qd	
Reporting group title	Fluticasone 150 mcg bid
Reporting group description:	
Fluticasone 150 mcg bid	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Serious adverse events	QAW039 450 mg qd	Fluticasone 150 mcg bid	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 145 (1.38%)	0 / 42 (0.00%)	3 / 147 (2.04%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
CORONARY ARTERY DISEASE			
subjects affected / exposed	0 / 145 (0.00%)	0 / 42 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
PRESYNCOPE			
subjects affected / exposed	0 / 145 (0.00%)	0 / 42 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
ANAPHYLACTIC REACTION			

subjects affected / exposed	1 / 145 (0.69%)	0 / 42 (0.00%)	0 / 147 (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			
OVARIAN CYST			
subjects affected / exposed	1 / 145 (0.69%)	0 / 42 (0.00%)	0 / 147 (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			
HEPATIC STEATOSIS			
subjects affected / exposed	0 / 145 (0.00%)	0 / 42 (0.00%)	1 / 147 (0.68%)
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: 2 %

Non-serious adverse events	QAW039 450 mg qd	Fluticasone 150 mcg bid	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 145 (24.83%)	19 / 42 (45.24%)	35 / 147 (23.81%)
Investigations			
BLOOD TRIGLYCERIDES INCREASED			
subjects affected / exposed	1 / 145 (0.69%)	1 / 42 (2.38%)	0 / 147 (0.00%)
occurrences (all)	1	1	0
ELECTROCARDIOGRAM QT PROLONGED			
subjects affected / exposed	1 / 145 (0.69%)	2 / 42 (4.76%)	0 / 147 (0.00%)
occurrences (all)	1	2	0
Injury, poisoning and procedural complications			
LIGAMENT SPRAIN			
subjects affected / exposed	0 / 145 (0.00%)	1 / 42 (2.38%)	0 / 147 (0.00%)
occurrences (all)	0	1	0
WOUND			
subjects affected / exposed	0 / 145 (0.00%)	1 / 42 (2.38%)	0 / 147 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			

HEADACHE			
subjects affected / exposed	1 / 145 (0.69%)	0 / 42 (0.00%)	3 / 147 (2.04%)
occurrences (all)	1	0	4
SYNCOPE			
subjects affected / exposed	0 / 145 (0.00%)	1 / 42 (2.38%)	0 / 147 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
DENTAL CARIES			
subjects affected / exposed	0 / 145 (0.00%)	1 / 42 (2.38%)	0 / 147 (0.00%)
occurrences (all)	0	1	0
NAUSEA			
subjects affected / exposed	1 / 145 (0.69%)	1 / 42 (2.38%)	1 / 147 (0.68%)
occurrences (all)	1	1	1
Reproductive system and breast disorders			
DYSMENORRHOEA			
subjects affected / exposed	0 / 145 (0.00%)	1 / 42 (2.38%)	1 / 147 (0.68%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
ASTHMA			
subjects affected / exposed	10 / 145 (6.90%)	2 / 42 (4.76%)	13 / 147 (8.84%)
occurrences (all)	11	2	13
COUGH			
subjects affected / exposed	3 / 145 (2.07%)	0 / 42 (0.00%)	1 / 147 (0.68%)
occurrences (all)	3	0	1
PRODUCTIVE COUGH			
subjects affected / exposed	1 / 145 (0.69%)	0 / 42 (0.00%)	3 / 147 (2.04%)
occurrences (all)	1	0	3
Skin and subcutaneous tissue disorders			
DERMATITIS CONTACT			
subjects affected / exposed	0 / 145 (0.00%)	2 / 42 (4.76%)	0 / 147 (0.00%)
occurrences (all)	0	2	0
ECZEMA			
subjects affected / exposed	0 / 145 (0.00%)	1 / 42 (2.38%)	0 / 147 (0.00%)
occurrences (all)	0	1	0
ERYTHEMA			

subjects affected / exposed	0 / 145 (0.00%)	1 / 42 (2.38%)	0 / 147 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
HAEMATURIA			
subjects affected / exposed	0 / 145 (0.00%)	1 / 42 (2.38%)	0 / 147 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 145 (0.69%)	1 / 42 (2.38%)	1 / 147 (0.68%)
occurrences (all)	1	1	1
ARTHRITIS			
subjects affected / exposed	0 / 145 (0.00%)	1 / 42 (2.38%)	0 / 147 (0.00%)
occurrences (all)	0	1	0
MUSCULOSKELETAL PAIN			
subjects affected / exposed	0 / 145 (0.00%)	1 / 42 (2.38%)	0 / 147 (0.00%)
occurrences (all)	0	1	0
SYNOVIAL CYST			
subjects affected / exposed	0 / 145 (0.00%)	1 / 42 (2.38%)	0 / 147 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
ACUTE SINUSITIS			
subjects affected / exposed	0 / 145 (0.00%)	0 / 42 (0.00%)	3 / 147 (2.04%)
occurrences (all)	0	0	3
BRONCHITIS			
subjects affected / exposed	3 / 145 (2.07%)	0 / 42 (0.00%)	4 / 147 (2.72%)
occurrences (all)	3	0	4
CONJUNCTIVITIS VIRAL			
subjects affected / exposed	0 / 145 (0.00%)	1 / 42 (2.38%)	0 / 147 (0.00%)
occurrences (all)	0	1	0
INFLUENZA			
subjects affected / exposed	2 / 145 (1.38%)	0 / 42 (0.00%)	3 / 147 (2.04%)
occurrences (all)	3	0	3
NASOPHARYNGITIS			
subjects affected / exposed	5 / 145 (3.45%)	1 / 42 (2.38%)	3 / 147 (2.04%)
occurrences (all)	5	1	3
ORAL CANDIDIASIS			

subjects affected / exposed	0 / 145 (0.00%)	1 / 42 (2.38%)	1 / 147 (0.68%)
occurrences (all)	0	1	1
PHARYNGITIS			
subjects affected / exposed	1 / 145 (0.69%)	1 / 42 (2.38%)	0 / 147 (0.00%)
occurrences (all)	1	1	0
RHINITIS			
subjects affected / exposed	2 / 145 (1.38%)	2 / 42 (4.76%)	0 / 147 (0.00%)
occurrences (all)	2	2	0
SINUSITIS BACTERIAL			
subjects affected / exposed	3 / 145 (2.07%)	0 / 42 (0.00%)	0 / 147 (0.00%)
occurrences (all)	3	0	0
SKIN INFECTION			
subjects affected / exposed	0 / 145 (0.00%)	1 / 42 (2.38%)	0 / 147 (0.00%)
occurrences (all)	0	1	0
TONSILLITIS			
subjects affected / exposed	0 / 145 (0.00%)	1 / 42 (2.38%)	0 / 147 (0.00%)
occurrences (all)	0	1	0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	7 / 145 (4.83%)	1 / 42 (2.38%)	5 / 147 (3.40%)
occurrences (all)	7	1	5
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 145 (1.38%)	1 / 42 (2.38%)	3 / 147 (2.04%)
occurrences (all)	2	1	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2013	The following were added to prohibited medications: CYP3A4 inhibitors including boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin and voriconazole, CYP3A4 inducers including avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort and indomethacin
18 December 2014	The planned interim analysis (IA) for the study was removed. The closure of recruitment, once target patient numbers was met for the non-atopic and atopic groups of patients, was clarified. The definition of a positive pregnancy test in the exclusion criteria was updated. ACQ-6 was selected to be the key secondary variable because this form to align with other QAW039 studies. The interval of the data collection for rescue medication use via e-Diary was corrected from 12 hours to 24 hours. The definition of the pharmacokinetic (PK) analysis set was added. The definition of baseline values was clarified to be the values at the end of the initial 14-day, post-randomization placebo treatment period. These amendments were not considered to have affected the interpretation of study results as they were minor and occurred prior to study unblinding.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported