Sponsor

Novartis Pharmaceuticals Corporation

Generic Drug Name

QAW039

Trial Indication(s)

Asthma

Protocol Number

CQAW039A2208

Protocol Title

A double-blind, placebo-controlled, study examining the effect of orally administered QAW039 on sputum eosinophil levels and other efficacy outcomes in patients with sputum eosinophilia and persistent asthma

Clinical Trial Phase

Phase II

Phase of Drug Development

Phase II

Study Start/End Dates

Study initiation date: 10-Feb-2012 (first patient first visit)

Study completion date: 25-Jun-2013 (last patient last visit)

Study Design/Methodology

This study used a 2-treatment arm (Placebo or QAW039), parallel-group, double-blind, randomized, placebo-controlled design.

After signing informed consent (Visit 1), patients underwent a 2-week placebo run-in period during which their clinical stability and suitability for randomisation were assessed. Asthma patients who were already receiving ICS or ICS-LABA therapy were the target population for this study. All patients were allowed to continue on their current therapy. At the baseline visit (visit 3) all eligible patients were randomized to QAW039 (225 mg b.i.d.) or placebo for a treatment duration of 12 weeks. At the end of the 12-week treatment period (visit 5), all patients received placebo until the 6-week post-treatment assessment (visit 6). Both during the run-in and wash-out periods, the study was single-blind because physicians were aware that patients were on placebo, however the 12-week treatment period was double-blind.

Visits to assess safety and efficacy were scheduled at 6, 12, and 18 weeks post-randomization. The assessment to address the primary objectives was performed at the end of the treatment period (week 12). A futility interim analysis was conducted when approximately 50% of the patients had completed their treatment phase with the additional purpose to facilitate planning of the QAW039 development program, but the trial was not stopped for futility.

Centers

One center in United Kingdom

Objectives:

Primary objective(s)

- The primary objective of this study was to demonstrate a statistically significant reduction in sputum eosinophil levels in inadequately controlled, moderate-to-severe asthmatics (GINA 2-5), with sputum eosinophilia after treatment with QAW039 for 12 weeks compared to placebo.

Secondary objectives

- To demonstrate that QAW039 provides significantly superior control of asthmatic symptoms as measured by the asthma control questionnaire (ACQ) compared to placebo.
- To assess safety and tolerability of QAW039 in this moderate-to-severe asthmatic population as compared to placebo.

Test Product (s), Dose(s), and Mode(s) of Administration

QAW039 was supplied in blister packs of two strengths: 25 mg (3 capsules to be taken orally morning and night) and 150 mg (1 capsule to be taken orally morning and night). The patients therefore took 225 mg twice daily for the period of the study.

The placebo was of identical appearance and was identically packaged.

Statistical Methods

The primary variable and the secondary variables related to ACQ were summarized by treatment and analyzed using an ANCOVA model with treatment as the fixed effect and the respective baseline value of the endpoints as well as maintenance OCS use (Yes/No) and bronchoscopy (yes/no) as covariates. As sputum eosinophil percentage had been found to follow a log-normal distribution, the primary analysis was based on the log-transformed scale with results back-transformed to present ratios of geometric means

The least squares means for each treatment group and for the treatment difference were presented along with associated 95% confidence interval and p-value (2-sided) for within and between group comparisons.

Primary Variable

The primary variable of the study was the change from baseline in sputum eosinophil percentage at week 12. As sputum eosinophil percentage had been found to follow a log-normal distribution, the analysis was based on log10-transformed scale. The baseline measurement was defined as sputum eosinophil percentage at Visit 3 (Day 1) prior to the first dosing (on log10-transformed scale). When no eosinophils were observed amongst the 400 cells on a slide, a proportion of 1/400 = 0.25% (the lower limit of detection by convention) was used instead of 0 in the analysis.

Secondary variable

The secondary variables included the change from baseline to week 12 in ACQ. The baseline was defined as the assessment measured at Visit 3 (Day 1) prior to the first dosing.

The ACQ measures asthma symptom control and consists of 7 items: 5 on symptom assessment, 1 on rescue bronchodilator use and 1 on airway calibre (FEV_1 % predicted). All 7 questions of the ACQ were equally weighted. Items 1-6 were scored along a 7-point response scale, where 0 = good controlled and 6 = poor controlled. The 7^{th} item on % predicted FEV_1 (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 at each visit was calculated as the sum of scores divided by the number of questions that were answered by the patient at the visit, as long as there were at least 6 questions answered and the missing item was neither question 1 nor question 7.

Handling of missing values/censoring/discontinuations

Missing data was imputed for the primary variable using last observation carried forward (LOCF). Only post-baseline observation was used for this purpose.

Only 1 missing item was allowed for scoring the ACQ and, preferably, this should not be question 1 or question 7. The single missing value could be interpolated by utilizing prior

or subsequent completions of the questionnaire. The averaged ACQ score was not imputed.

Safety variables

All safety endpoints (i.e. adverse events, laboratory data, vital signs, and ECG) were be summarized by treatment for all patients of the safety population. All data was included in the analysis regardless of rescue medication use.

Adverse events

All adverse events which started after the first dose of study medication were considered as a treatment emergent adverse event. Treatment emergent adverse events with the number and percentage of patients having any adverse event overall, by SOC and preferred term were provided for:

- all adverse events
- adverse events by maximum severity
- adverse events suspected by the investigator as study drug-related
- serious adverse events
- adverse events leading to permanent discontinuation of study drug

Other safety measurements

Laboratory, vital signs and electrocardiogram data were summarized with standard descriptive statistics for those measurements at baseline, post baseline and changes from baseline. Shift tables relative to the normal ranges for lab and vital signs, or qualitative assessments for ECG on the abnormality were provided in order to compare a patient's baseline and post-baseline conditions. The numbers and percentages of patients meeting the definition of notably abnormal values of those measurements were also presented by parameters and visits.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Males and females of any race who were over the age of 18 years at the time informed consent was obtained.
3. Physician diagnosis of asthma, as per GINA guidelines GINA guidelines and currently prescribed ICS or ICS-LABA therapy.
4. Patients who are demonstrated to have reversible airway obstruction, significant FEV1 variability or airway hyperresponsiveness (AHR), or who have shown such responses in previous test(s) within the last five years.
5. An ACQ score ≥ 1.5 at randomization or ≥ 1 exacerbations (requiring higher than the patient's normal dose of OCS or IV corticosteroids for ≥ 3 days) in the past 12

months. The definition of exacerbations includes episodes during which the patient self-administered higher doses of OCS as part of a documented self-management plan initiated by the patient's general practitioner or respiratory physician.

6. Patients currently on GINA step 2 to step 5 asthma therapies.
7. Sputum eosinophil count ≥ 2% at screening.

Exclusion Criteria:

1. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer.
2. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes (CRTH2 antagonists).
3. History of long QT syndrome or whose QTc interval (Fridericia's) is prolonged >450 msec for males and >470 msec for females at screening or baseline.
4. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
5. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL).
6. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the study treatment and for 5 days (5 half-lives) after treatment.
7. Acute illness other than asthma which, in the investigator's opinion, may compromise the well-being of the patient or study endpoint assessments at the start of the study
8. Patients who are considered unsuitable for inclusion by the assessing physician due to serious co-morbidities such as cancer, emphysema or significant bronchiectasis.
9. Recent (within 6 weeks of screening) or current lower respiratory tract infection.
10. Patients who have been hospitalized or required high-dose (>10mg prednisolone/day) oral corticosteroid (OCS) therapy within 6 weeks of the screening visit.
11. Patients with clinically significant laboratory abnormalities (not associated with the study indication) at screening.
12. Patients who have a clinically significant abnormality on a 12-lead ECG recorded within one month prior to or at screening.
13. Patients with a body mass index (BMI) < 17 or > 45 kg/m2.

Participant Flow Table

Patient disposition in treatment phase (Randomized Set)

Disposition/Reason	QAW039 N=30 n (%)	Placebo N=31 n (%)	Total N=61 n (%)
Randomized	30	31	61
Completed treatment phase	27 (90.0)	28 (90.3)	55 (90.2)
Discontinued prior to treatment phase completion	3 (10.0)	3 (9.7)	6 (9.8)
Primary reason for not completing treatment phase			
Adverse event	3 (10.0)	3 (9.7)	6 (9.8)
Abnormal laboratory value(s)	0	0	0
Abnormal test procedure result(s)	0	0	0
Unsatisfactory therapeutic effect	0	0	0
Subject's condition no longer requires study drug	0	0	0
Subject withdrew consent	0	0	0
Lost to follow-up	0	0	0
Administrative problems	0	0	0
Death	0	0	0
Patient's inability to use the device	0	0	0
Protocol deviation	0	0	0

N=number of subjects entering in the treatment phase.

This table shows the number of patients that withdrew from study participation. Patients continuing study assessments despite discontinuation of treatment are not counted in this table.

Patient disposition in washout phase (Randomized Set)

Disposition/Reason	QAW039 N=30 n (%)	Placebo N=31 n (%)	Total N=61 n (%)
Patients entered washout phase	27 (90.0)	28 (90.3)	55 (90.2)
Completed washout phase	27 (90.0)	27 (87.1)	54 (88.5)
Discontinued prior to washout phase completion	0	1 (3.2)	1 (1.6)
Primary reason for not completing washout phase			
Adverse event	0	1 (3.2)	1 (1.6)
Abnormal laboratory value(s)	0	0	0
Abnormal test procedure result(s)	0	0	0
Unsatisfactory therapeutic effect	0	0	0
Subject's condition no longer requires study drug	0	0	0
Subject withdrew consent	0	0	0
Lost to follow-up	0	0	0
Administrative problems	0	0	0
Death	0	0	0
Patient's inability to use the device	0	0	0
Protocol deviation	0	0	0

N=number of subjects entering in the treatment phase

This table shows the number of patients that withdrew from study participation. Patients continuing study assessments despite discontinuation of treatment are not counted in this table.

Baseline Characteristics

Demographic summary by treatment group (Randomized Set)

Demographic Variable	QAW039 N=30	Placebo N=31	Total N=61
Age (years)			
n	30	31	61
Mean	50.2	50.1	50.2
SD	16.56	12.39	14.47
Minimum	20.0	19.0	19.0
Q1	41.0	42.0	42.0
Median	53.0	52.0	53.0
Q3	62.0	60.0	61.0
Maximum	80.0	68.0	80.0
Sex			
Male	18 (60.0)	13 (41.9)	31 (50.8)
Female	12 (40.0)	18 (58.1)	30 (49.2)
Race			
Caucasian	28 (93.3)	28 (90.3)	56 (91.8)
Asian	2 (6.7)	3 (9.7)	5 (8.2)
Ethnicity			
Indian (Indian subcontinent)	2 (6.7)	3 (9.7)	5 (8.2)
Other	28 (93.3)	28 (90.3)	56 (91.8)
Weight (kg)			
n	30	31	61
Mean	88.1	83.8	85.9
SD	17.30	21.19	19.33
Minimum	58.7	51.4	51.4
Q1	79.5	68.9	75.0
Median	86.1	78.4	84.0
Q3	96.1	95.3	95.3
Maximum	130.0	147.3	147.3
Height (cm)			
n	30	31	61
Mean	168.6	167.7	168.2
SD	7.32	10.28	8.88
Minimum	156.0	152.0	152.0
Q1	165.0	159.0	161.0
Median	167.5	169.0	168.0
Q3	175.0	174.0	174.0
Maximum	181.0	195.0	195.0
BMI (kg/m2)			
n	30	31	61

Demographic Variable	QAW039 N=30	Placebo N=31	Total N=61
Mean	31.0	29.6	30.3
SD	5.86	5.96	5.91
Minimum	21.9	22.2	21.9
Q1	25.8	25.0	25.3
Median	29.3	27.5	28.9
Q3	35.8	31.2	34.1
Maximum	42.2	44.8	44.8

Height and weight are taken from Visit 2 vital signs evaluations.
BMI is calculated as: BMI (kg/m^2) = [weight (kg) (height (cm)/100].

Baseline disease characteristics by treatment group (Randomized Set)

	QAW039 N=30 n (%)	Placebo N=31 n (%)	Total N=61 n (%)
Smoking status - n (%)			
Ex-smoker	8 (26.7)	8 (25.8)	16 (26.2)
Never smoked	22 (73.3)	23 (74.2)	45 (73.8)
Estimated number of pack years			
n	8	8	16
Mean	4.7	4.6	4.6
SD	3.50	5.19	4.28
Minimum	0.2	0.1	0.1
Q1	2.0	0.8	1.0
Median	4.8	1.5	3.3
Q3	6.5	9.5	8.5
Maximum	11.0	13.0	13.0
Time (years) since stopped smoking			
n	8	8	16
Mean	28.8	18.5	23.6
SD	16.31	14.96	16.02
Minimum	1.0	3.0	1.0
Q1	18.5	4.5	6.0
Median	30.5	17.0	27.0
Q3	40.0	33.0	35.0
Maximum	51.0	36.0	51.0
Duration of asthma (years)			
n	30	31	61
Mean	31.8	29.0	30.4
SD	18.87	16.20	17.48
Minimum	7.0	4.0	4.0
Q1	19.0	12.0	17.0
Median	25.0	33.0	29.0
Q3	48.0	38.0	40.0
Maximum	71.0	57.0	71.0
Use of (OCS) + Bronchoscopy - n (%)			
OCS+Bronchoscopy	5 (16.7)	4 (12.9)	9 (14.8)
OCS+No Bronchoscopy	2 (6.7)	3 (9.7)	5 (8.2)
No OCS+Bronchoscopy	13 (43.3)	14 (45.2)	27 (44.3)
No OCS+No Bronchoscopy	10 (33.3)	10 (32.3)	20 (32.8)
ICS use - n (%)			
Yes	3 (10.0)	4 (12.9)	7 (11.5)
No	27 (90.0)	27 (87.1)	54 (88.5)

	QAW039 N=30 n (%)	Placebo N=31 n (%)	Total N=61 n (%)
ICS + LABA use - n (%)			
Yes	21 (70.0)	20 (64.5)	41 (67.2)
No	9 (30.0)	11 (35.5)	20 (32.8)
ICS + LABA + OCS use - n (%)			
Yes	7 (23.3)	6 (19.4)	13 (21.3)
No	23 (76.7)	25 (80.6)	48 (78.7)
Baseline ACQ score			
n	30	31	61
Mean	1.9	2.2	2.1
SD	0.81	0.91	0.87
Minimum	0.3	0.3	0.3
Q1	1.1	1.4	1.4
Median	2.1	2.0	2.1
Q3	2.4	3.0	2.7
Maximum	3.4	3.9	3.9
% sputum eosinophil count (%)			
n	29	29	58
Mean	13.9	13.1	13.5
SD	20.77	15.16	18.03
Minimum	0.3	0.3	0.3
Q1	3.0	1.8	1.8
Median	5.0	5.3	5.1
Q3	13.5	26.8	19.8
Maximum	78.5	45.3	78.5
FeNO (ppb)			
n	30	31	61
Mean	37.5	46.9	42.3
SD	24.43	41.19	34.05
Minimum	7.0	11.0	7.0
Q1	16.0	21.0	18.0
Median	29.0	28.0	28.0
Q3	58.0	62.0	58.0
Maximum	92.0	173.0	173.0

Duration of asthma is calculated as date of asthma first diagnosed until Visit.
ACQ overall score is average of 6 questions & categorized pre-bronchodilator FEV1 (% Predicted FEV1) at visit 3.

Summary of Efficacy

Primary Outcome Result(s)

Geometric mean of sputum eosinophils at weeks 6, 12 and 18 (Full analysis set)

	N		Baseline Geometric Mean (CV%)		Ratio of Geometric Means vs. baseline (95% CI)			
Week	QAW	Placebo	QAW	Placebo	QAW	Placebo	Ratio for QAW vs. Placebo (95% CI)	p-value
Visit 4 - Baseline	28	29	5.343 (300.217)	4.296 (372.733)	0.240 (0.139,0.415)	0.616 (0.357,1.063)	0.390 (0.1972, 0.7711)	0.0077
Visit 5 - Baseline	27	28	4.914 (274.065)	4.352 (398.555)	0.221 (0.124,0.394)	0.769 (0.428,1.382)	0.288 (0.1370, 0.6038)	0.0014
Visit 6 - Baseline	25	24	5.350 (266.732)	4.863 (314.754)	0.694 (0.375,1.285)	0.666 (0.338,1.312)	1.043 (0.4627, 2.3491)	0.9182
Visit 6 - Visit 5	25	23	1.059 (259.002)	3.277 (366.873)	2.613 (1.491,4.579)	1.359 (0.719,2.571)	1.922 (0.8720, 4.2373)	0.1027
Visit 5 - Baseline (LOCF)	29	30	5.418 (287.648)	4.646 (391.443)	0.223 (0.129,0.385)	0.775 (0.451,1.330)	0.288 (0.1435, 0.5773)	0.0007

CV=Coefficient of Variation, CI = confidence interval.

Model: change in log10 transformed sputum eosinophil (5) = treatment, OCS(Yes/No), bronchoscopy (yes/no) and log (base 10) transformed baseline sputum eosinophil as covariate.

Estimated LS means (log base 10) and difference between estimated LS means are back transformed to original scale to present geometric means (GM) and ratio of GM.

CV% is calculated as 100 * square root of (exp (SD on log scale^2) – 1), where SD is the MSE obtained from the log10 scale.

LOCF = Last observation carried forward. Only data collected at week 6 & afterwards can be used for 12 week LOCF.

Secondary Outcome Result(s)

ACQ7 without LOCF: Estimated Difference in treatment effects using ANCOVA Model for all patients-Full analysis set

	N		Baseline Mean (SE)*		LS Mean of Change (SE)			
	--		--		--			
Week	QAW	Placebo	QAW	Placebo	QAW	Placebo	Treatment Difference (QAW vs. Placebo) (95% CI)	p-value
Visit 4 - Baseline	29	31	1.909 (0.1533)	2.221 (0.1635)	-0.182 (0.1427)	0.028 (0.1418)	-0.210 (-0.5784, 0.1577)	0.2571
Visit 5 - Baseline	27	30	1.913 (0.1499)	2.181 (0.1638)	-0.235 (0.1779)	0.168 (0.1792)	-0.402 (-0.8606, 0.0564)	0.0843
Visit 6 - Baseline	27	26	1.913 (0.1499)	2.082 (0.1711)	0.316 (0.1647)	0.068 (0.1751)	0.248 (-0.1878, 0.6834)	0.2584
Visit 6 - Visit 5	27	26	1.688 (0.1676)	2.174 (0.2440)	0.453 (0.1554)	0.056 (0.1663)	0.397 (-0.0206, 0.8143)	0.0619

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Model: change in ACQ = treatment, OCS (Yes/No), bronchoscopy(yes/no)and baseline ACQ score as covariates.
Score: 0 = good control of asthma, 6 = poor control of asthma.
The overall score is the average of 6 questions and the categorized pre-bronchodilator FEV1 (in % of Predicted FEV1), of which at least 6 had to be available.
Baseline is defined as the ACQ average score at visit 3.
ACQ7: The overall score is the average of the first 7 questions.
* For comparison Visit 6 – Visit 5, baseline is presented as Visit 5 mean.

Summary of Safety

Safety Results

Adverse events, by primary system organ class, preferred term, and treatment during the Post-Randomization period-Safety analysis set

PERIOD: 12 WEEK TREATMENT + 6 WEEK WASH OUT PERIOD

Primary system organ class Preferred term	QAW039 N=29 n (%)	Placebo N=32 n (%)	Total N=61 n (%)
Number of subjects with at least one AE	24 (82.8)	26 (81.3)	50 (82.0)
Blood and lymphatic system disorders	**2 (6.9)**	**0**	**2 (3.3)**
Lymphadenopathy	1 (3.4)	0	1 (1.6)
Thrombocytopenia	1 (3.4)	0	1 (1.6)
Cardiac disorders	**0**	**1 (3.1)**	**1 (1.6)**
Angina pectoris	0	1 (3.1)	1 (1.6)
Eye disorders	**0**	**2 (6.3)**	**2 (3.3)**
Eye pain	0	1 (3.1)	1 (1.6)
Vision blurred	0	1 (3.1)	1 (1.6)
Gastrointestinal disorders	**5 (17.2)**	**8 (25.0)**	**13 (21.3)**
Diarrhoea	3 (10.3)	3 (9.4)	6 (9.8)
Vomiting	2 (6.9)	1 (3.1)	3 (4.9)
Abdominal pain	1 (3.4)	1 (3.1)	2 (3.3)
Abdominal pain upper	0	1 (3.1)	1 (1.6)
Dyspepsia	1 (3.4)	0	1 (1.6)
Gingival pain	0	1 (3.1)	1 (1.6)
Irritable bowel syndrome	0	1 (3.1)	1 (1.6)
Mouth ulceration	0	1 (3.1)	1 (1.6)
Nausea	0	1 (3.1)	1 (1.6)
General disorders and administration site conditions	**3 (10.3)**	**2 (6.3)**	**5 (8.2)**
Chest discomfort	2 (6.9)	1 (3.1)	3 (4.9)
Facial pain	0	1 (3.1)	1 (1.6)
Fatigue	1 (3.4)	0	1 (1.6)
Oedema peripheral	1 (3.4)	0	1 (1.6)
Immune system disorders	**0**	**1 (3.1)**	**1 (1.6)**
Seasonal allergy	0	1 (3.1)	1 (1.6)
Infections and infestations	**11 (37.9)**	**10 (31.3)**	**21 (34.4)**
Nasopharyngitis	3 (10.3)	5 (15.6)	8 (13.1)
Lower respiratory tract infection	2 (6.9)	2 (6.3)	4 (6.6)
Ear infection	1 (3.4)	2 (6.3)	3 (4.9)
Sinusitis	2 (6.9)	0	2 (3.3)

PERIOD: 12 WEEK TREATMENT + 6 WEEK WASH OUT PERIOD

Primary system organ class Preferred term	QAW039 N=29 n (%)	Placebo N=32 n (%)	Total N=61 n (%)
Fungal infection	1 (3.4)	0	1 (1.6)
Impetigo	1 (3.4)	0	1 (1.6)
Influenza	1 (3.4)	0	1 (1.6)
Pharyngitis	0	1 (3.1)	1 (1.6)
Tonsillitis	0	1 (3.1)	1 (1.6)
Upper respiratory tract infection	0	1 (3.1)	1 (1.6)
Injury, poisoning and procedural complications	**5 (17.2)**	**2 (6.3)**	**7 (11.5)**
Post procedural complication	2 (6.9)	0	2 (3.3)
Ankle fracture	0	1 (3.1)	1 (1.6)
Concussion	0	1 (3.1)	1 (1.6)
Contusion	1 (3.4)	0	1 (1.6)
Fall	1 (3.4)	0	1 (1.6)
Hand fracture	1 (3.4)	0	1 (1.6)
Procedural nausea	1 (3.4)	0	1 (1.6)
Investigations	**2 (6.9)**	**2 (6.3)**	**4 (6.6)**
Blood bilirubin increased	1 (3.4)	0	1 (1.6)
Blood glucose increased	0	1 (3.1)	1 (1.6)
C-reactive protein increased	1 (3.4)	0	1 (1.6)
Electrocardiogram T wave inversion	0	1 (3.1)	1 (1.6)
Haematocrit decreased	1 (3.4)	0	1 (1.6)
Haemoglobin decreased	1 (3.4)	0	1 (1.6)
Platelet count increased	1 (3.4)	0	1 (1.6)
Metabolism and nutrition disorders	**2 (6.9)**	**0**	**2 (3.3)**
Hypercholesterolaemia	2 (6.9)	0	2 (3.3)
Musculoskeletal and connective tissue disorders	**3 (10.3)**	**3 (9.4)**	**6 (9.8)**
Muscle spasms	2 (6.9)	0	2 (3.3)
Arthralgia	1 (3.4)	0	1 (1.6)
Back pain	0	1 (3.1)	1 (1.6)
Joint swelling	0	1 (3.1)	1 (1.6)
Musculoskeletal chest pain	0	1 (3.1)	1 (1.6)
Nervous system disorders	**3 (10.3)**	**8 (25.0)**	**11 (18.0)**
Headache	2 (6.9)	6 (18.8)	8 (13.1)
Lethargy	0	2 (6.3)	2 (3.3)
Amnesia	0	1 (3.1)	1 (1.6)
Dizziness	0	1 (3.1)	1 (1.6)
Dysgeusia	1 (3.4)	0	1 (1.6)

PERIOD: 12 WEEK TREATMENT + 6 WEEK WASH OUT PERIOD

Primary system organ class Preferred term	QAW039 N=29 n (%)	Placebo N=32 n (%)	Total N=61 n (%)
Renal and urinary disorders	**2 (6.9)**	**0**	**2 (3.3)**
Pollakiuria	2 (6.9)	0	2 (3.3)
Reproductive system and breast disorders	**0**	**1 (3.1)**	**1 (1.6)**
Breast cyst	0	1 (3.1)	1 (1.6)
Respiratory, thoracic and mediastinal disorders	**12 (41.4)**	**15 (46.9)**	**27 (44.3)**
Asthma	10 (34.5)	8 (25.0)	18 (29.5)
Cough	2 (6.9)	4 (12.5)	6 (9.8)
Oropharyngeal pain	0	4 (12.5)	4 (6.6)
Dyspnoea	1 (3.4)	2 (6.3)	3 (4.9)
Rhinorrhoea	0	2 (6.3)	2 (3.3)
Nasal congestion	0	1 (3.1)	1 (1.6)
Pulmonary mass	1 (3.4)	0	1 (1.6)
Sputum increased	1 (3.4)	0	1 (1.6)
Skin and subcutaneous tissue disorders	**1 (3.4)**	**1 (3.1)**	**2 (3.3)**
Eczema	1 (3.4)	0	1 (1.6)
Rash	0	1 (3.1)	1 (1.6)
Surgical and medical procedures	**0**	**1 (3.1)**	**1 (1.6)**
Elective surgery	0	1 (3.1)	1 (1.6)
Vascular disorders	**0**	**1 (3.1)**	**1 (1.6)**
Hypertension	0	1 (3.1)	1 (1.6)

A subject with multiple adverse events within a primary system organ class is counted only once in the total row.
*Post procedural complications were related to bronchoscopy.
A subject with multiple occurrences of an AE under one treatment is counted only once in this AE category for that treatment.
Primary system organ classes are presented in alphabetical order; preferred terms are sorted within system organ class in descending frequency of AEs in the Total column.
MedDRA Version 16.1 has been used for the reporting of adverse events.
Post-Randomization period includes both 12 Week treatment and 6 Week washout period, which are presented separately as well as combined
AEs up to 7 days after the last dose of study drug or last visit whichever is later are included for 12 WEEK TREATMENT + 6 WEEK WASH OUT PERIOD.

Deaths, other serious adverse events or adverse events leading to discontinuations – n (%) of patients -Safety analysis set

PERIOD: 12 WEEK TREATMENT + 6 WEEK WASH OUT PERIOD	QAW039 N=29 n (%)	Placebo N=32 n (%)	Total N=61 n (%)
Patients with AE(s)	24 (82.8)	26 (81.3)	50 (82.0)

PERIOD: 12 WEEK TREATMENT + 6 WEEK WASH OUT PERIOD	QAW039 N=29 n (%)	Placebo N=32 n (%)	Total N=61 n (%)
Death	0	0	0
SAE(s)	0	0	0
Discontinued study drug due to AE(s)	5 (17.2)	4 (12.5)	9 (14.8)
Withdrawn from study due to AE(s)	3 (10.3)	4(12.5)	7 (11.5)

Other Relevant Findings

Summary statistics of Day 42 and Day 84 concentrations for QAW039 and CCN362

Day	Scheduled sampling time	Statistic	Concentration (ng/mL) QAW039	Concentration (ng/mL) CCN362
42	**Pre-dose**	N	23	23
		Mean (SD)	156 (177)	348 (318)
		CV% mean	113.0	91.4
84	**Pre-dose**	N	24	25
		Mean (SD)	148 (117)	385 (362)
		CV% mean	79.3	94.0
	3 h post dose	N	25	25
		Mean (SD)	888 (535)	2210 (1260)
		CV% mean	60.2	57.1

ACQ7 without LOCF: Estimated Difference in treatment effects using ANCOVA Model by subgroups-FAS

Sub group	Week	LS Mean of Change (SE) -- QAW	LS Mean of Change (SE) -- Placebo	Treatment Difference (QAW vs. Placebo) (95% CI)	p-value
ACQ >= 1.5	Visit 5 - Baseline	-0.368 (0.2231)	0.195 (0.2349)	-0.564 (-1.118, -0.009)	0.0464
ACQ < 1.5	Visit 5 - Baseline	0.064 (0.3718)	0.068 (0.3787)	-0.004 (-0.840, 0.832)	0.9924

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Model: change in ACQ = treatment, OCS (Yes/No), bronchoscopy(yes/no), subgroup, subgroup*treatment as covariates.
Score: 0 = good control of asthma, 6 = poor control of asthma.
The overall score is the average of 6 questions and the categorized pre-bronchodilator FEV1 (in % of Predicted FEV1), of which at least 6 had to be available.
Baseline is defined as the ACQ average score at visit 3.
LOCF = Last observation carried forward. Only data collected at week 6 & afterwards can be used fro 12 week LOCF.
ACQ7: The overall score is the average of the first 7 questions.

Date of Clinical Trial Report
13 June 2014

Date of Initial Inclusion on Novartis Clinical Trial Results website
23 Jun 2014

Date of Latest Update