Sponsor

Novartis

Generic Drug Name

QAW039

Trial Indication(s)

Asthma

Protocol Number

CQAW039A2206

Protocol Title

A randomized, placebo-controlled, dose-ranging, multi-center trial of QAW039 (1-450 mg p.o.) to investigate the effect on FEV1 and ACQ in patients with moderate-to-severe, persistent, allergic asthma, inadequately controlled with ICS therapy

Clinical Trial Phase

Phase IIb

Phase of Drug Development

Phase II

Study Start/End Dates

Study initiation date: 25-Aug-2011 (first patient first visit)

Study completion date: 12-Nov-2013 (last patient last visit)

Study Design/Methodology

The study had 15 treatment arms in a in a parallel-group, double-blind, placebo-controlled design with montelukast as an active comparator. The target population for the study included asthma patients who received prior ICS or ICS-LABA therapy.

At the time of randomization, all patients were on 200 µg budesonide bid as background therapy. At baseline, eligible patients who were uncontrolled on ICS therapy alone were randomized to 1 of the 15 treatment arms and entered into the 12 week treatment period. During the 12-week treatment period, the patients received QAW039, montelukast, or placebo. At the end of treatment period, all the patients were allocated to placebo and were followed up during an active drug washout period for additional 4 weeks.

Centers

186 centers in 22 countries: Argentina (14), Austria (5), Bulgaria (3), Canada (1), Colombia (5), France (5), Great Britain (3), Greece (3), Guatemala (5), Hungary (9), India (8), Italy (2), Japan (41), Mexico (7), Netherlands (2), Peru (7), Poland (2), Romania (9), Russia (7),Turkey (3), USA (37), South Africa (7)

Publication

None

Objectives:

Primary objective(s)

- The primary objective of this study was to demonstrate a clinically significant improvement in morning forced expiratory volume in 1 second FEV1 in moderate to severe allergic asthmatics inadequately controlled by ICS therapy treated with QAW039 for 12 weeks compared to placebo.

Secondary objectives

- To demonstrate that QAW039 provides significantly superior control of asthmatic symptoms in these patients as measured by the ACQ, compared to placebo
- To estimate the onset of efficacy as measured by spirometry assessments and the (ACQ) after 2, 4, 8 and 12 weeks of treatment
- To characterize the dose response relationship among QAW039 doses with respect to trough FEV1 after 12 weeks of treatment
- To assess safety and tolerability of QAW039 in a moderate to severe asthmatic population, particularly with regard to vital signs, electro cardiogram (ECG), heart rate, laboratory tests and adverse events (AEs), as compared to placebo
- To compare the efficacy of QAW039 to that of montelukast as an add-on therapy to ICS in inadequately controlled moderate-to-severe asthmatics
- To assess the effect of QAW039 on asthma symptoms as measured by the Juniper asthma control diary (JACD).

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

QAW039 was given in 13 different dose levels and regimens orally and montelukast (capsule, 10 mg qd orally) was used as active comparator. QAW039 capsules were supplied to investigators at four different dose strengths (1mg, 10mg, 25mg and 150mg) to generate the 13 dose levels (1, 3, 10, 30, 50, 75, 150, 300, and 450 mg once daily (qd) and 2, 25, 75, and 150 mg twice daily (bid)). In total there were 15 treatment arms where patients received QAW039, montelukast or placebo. Placebos were generated for both QAW039 and montelukast and dispensed appropriately.

Statistical Methods

The primary efficacy variable was analyzed on the modified full analysis set using the Multiple Comparison Procedures and Modelling methodology. First the data was analyzed using a linear mixed effects model to obtain covariate adjusted treatment effects and the corresponding variance covariance matrix. These were the basis for (1) multiple contrast tests with multiplicity adjustment to test whether there was a non-flat dose-response and (2) 10,000 parametric bootstrap samples. On each of these 10,000 bootstrap samples a set of candidate dose response models (Emax, Sigmoid Emax and Linear in the primary analysis) were fitted with the best fitting model chosen based on the generalized Akaike Information Criterion. Sensitivity analyses included analyses exploring non-monotonic dose response models.

Missing trough FEV1 values including those recorded up to 6 hours after rescue medication were imputed using the last-observation-carried-forward.

Safety data. Descriptive summaries of safety data were produced.

Pharmacokinetics: The descriptive statistics (mean, standard deviation, median) of PK parameters of QAW039 (Cmax, AUC0-6h and AUClast) were analyzed and reported. For the assessment of dose-proportionality, the log transformed PK data was analyzed using mixed effect model with log transformed dose as covariate and region as fixed effect.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

Patients who met the following criteria were included:

- Written informed consent before performing any assessment
- Aged between 18 and 65 years old at the time of obtaining informed consent
- Physician diagnosis of asthma, as per GINA (2009) guidelines, and currently prescribed ICS therapy
- Patients with a pre-bronchodilator FEV1 value of 40% to 80% of individual predicted value at screening and at randomization. The value at the randomization being within 15% of the screening FEV1 and the results of spirometry

meeting the American Thoracic society /European Respiratory society (ATS/ERS) criteria for acceptability and repeatability

- Patients were allergic or atopic, as diagnosed historically or at screening Visit 3 by either a skin prick test or a positive specific IgE test
- Patients demonstrated to have reversible airway obstruction or airways hyper-reactivity (AHR) or had shown either of such responses in previous test(s) within the last 5 years.
- An ACQ score ≥1.5 at randomization.

Exclusion criteria

Patients who met the following criteria were excluded:

- Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever was longer
- History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes (CRTh2 antagonists)
- History of life-threatening asthma, including a history of significant hypercarbia (pCO2>45mmHg), prior intubation, respiratory arrest, or seizures as a result of asthma
- History of long QT syndrome or patients whose current QTc interval (Fridericia's) is prolonged (> 450 msec) at screening,
- History of malignancy of any organ system, respiratory tract infection within 4 weeks of the screening visit, or serious co-morbidities
- 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)
- Women of child-bearing potential. All women physiologically capable of becoming pregnant, must have used effective contraception during the study and for 5 days (5 half-lives) after treatment.
- Current smokers or ex-smokers who stopped smoking within 6 months prior to screening or have a smoking history ≥10 pack years.

Participant Flow Table

Patient disposition (Randomized set)*

Disposition/Reason	QAW039 450 mg qd (N=134) n (%)*	Montelukast 10 mg qd (N=139) n (%)*	Placebo (N=137) n (%)*	QAW039 Total (N=782) n (%)%	QAW039 low dose (N=206) n (%)*	QAW039 mid dose (N=224) n (%)*	QAW039 top dose (N=218) n (%)*
Completed	107 (79.9)	113 (81.3)	111 (81.0)	653 (83.5)	171 (83.0)	194 (86.6)	181 (83.0)
Discontinued	26 (19.4)	24 (17.3)	25 (18.2)	121 (15.5)	33 (16.0)	26 (11.6)	36 (16.5)
Primary reason for discontinuation							
Adverse Event(s)	14 (10.4)	5 (3.6)	16 (11.7)	58 (7.4)	12 (5.8)	15 (6.7)	17 (7.8)
Abnormal laboratory value(s)	0	1 (0.7)	1 (0.7)	4 (0.5)	2 (1.0)	1 (0.4)	1 (0.5)
Abnormal test procedure result(s)	1 (0.7)	1 (0.7)	2 (1.5)	5 (0.6)	1 (0.5)	2 (0.9)	1 (0.5)
Unsatisfactory therapeutic effect	1 (0.7)	1 (0.7)	1 (0.7)	6 (0.8)	2 (1.0)	0	3 (1.4)
Subject withdrew consent	6 (4.5)	10 (7.2)	2 (1.5)	17 (2.2)	7 (3.4)	1 (0.4)	3 (1.4)
Lost to follow-up	2 (1.5)	1 (0.7)	2 (1.5)	9 (1.2)	0	2 (0.9)	5 (2.3)
Administrative problems	0	3 (2.2)	0	6 (0.8)	1 (0.5)	3 (1.3)	2 (0.9)
Patients inability to use the device	1 (0.7)	0	0	2 (0.3)	1 (0.5)	0	0
Protocol deviation	1 (0.7)	2 (1.4)	1 (0.7)	14 (1.8)	7 (3.4)	2 (0.9)	4 (1.8)

N= Number of patients randomized per treatment group

- QAW039 low dose: Combination of 1 mg qd, 3 mg qd, 2 mg bid, 10 mg qd.
- QAW039 mid dose: Combination of 30 mg qd, 50 mg qd, 25 mg bid, 75 mg qd.
- QAW039 top dose: Combination of 150 mg qd, 75 mg bid, 300 mg qd, 150 mg bid.

QAW039A total: Combination of all QAW039 doses

*The percentages do not add up to 100% as about 1% of the patients were randomized in error and no data is available for these patients in study completion record.

Baseline Characteristics

Demographic summary by treatment group (Safety set)

Demographic Variable	QAW039 450 mg qd (N=133)	Montelukast 10 mg qd (N=133)	Placebo (N=136)	QAW039 Total (N=765)	QAW039 low dose (N=201)	QAW039 mid dose (N=219)	QAW039 top dose (N=212)	Total (N=1034)
Age group (years) - n (%)								
< 65	131 (98.5)	130 (97.7)	134 (98.5)	757 (99.0)	199 (99.0)	216 (98.6)	211 (99.5)	1021 (98.7)
>= 65	2 (1.5)	3 (2.3)	2 (1.5)	8 (1.0)	2 (1.0)	3 (1.4)	1 (0.5)	13 (1.3)
Age (years)								
n	133	133	136	765	201	219	212	1034
Mean (SD)	45.8 (12.51)	44.5 (11.25)	44.6 (12.46)	45.0 (12.27)	45.2 (12.14)	45.6 (12.14)	43.5 (12.34)	44.9 (12.16)
Median (Min - Max)	46.0 (18-65)	45.0 (19-65)	45.5 (18-65)	46.0 (18-65)	46.0 (19-65)	46.0 (19-65)	45.5 (18-65)	46.0 (18-65)
Sex - n (%)								
Female	73 (54.9)	78 (58.6)	79 (58.1)	440 (57.5)	119 (59.2)	119 (54.3)	129 (60.8)	597 (57.7)
Male	60 (45.1)	55 (41.4)	57 (41.9)	325 (42.5)	82 (40.8)	100 (45.7)	83 (39.2)	437 (42.3)
Race - n (%)								
Asian	29 (21.8)	27 (20.3)	28 (20.6)	180 (23.5)	49 (24.4)	50 (22.8)	52 (24.5)	235 (22.7)
Black	7 (5.3)	2 (1.5)	2 (1.5)	25 (3.3)	2 (1.0)	5 (2.3)	11 (5.2)	29 (2.8)
Caucasian	74 (55.6)	78 (58.6)	82 (60.3)	427 (55.8)	119 (59.2)	124 (56.6)	110 (51.9)	587 (56.8)
Native american	5 (3.8)	8 (6.0)	8 (5.9)	42 (5.5)	10 (5.0)	15 (6.8)	12 (5.7)	58 (5.6)
Other	18 (13.5)	18 (13.5)	16 (11.8)	91 (11.9)	21 (10.4)	25 (11.4)	27 (12.7)	125 (12.1)
Ethnicity								
Chinese	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)
Hispanic/Latino	32 (24.1)	33 (24.8)	34 (25.0)	151 (19.7)	38 (18.9)	40 (18.3)	41 (19.3)	218 (21.1)
Indian (Indian subcontinent)	13 (9.8)	14 (10.5)	14 (10.3)	82 (10.7)	25 (12.4)	20 (9.1)	24 (11.3)	110 (10.6)
Japanese	16 (12.0)	13 (9.8)	13 (9.6)	95 (12.4)	24 (11.9)	27 (12.3)	28 (13.2)	121 (11.7)
Mixed Ethnicity	4 (3.0)	3 (2.3)	4 (2.9)	26 (3.4)	11 (5.5)	5 (2.3)	6 (2.8)	33 (3.2)

Demographic Variable	QAW039 450 mg qd (N=133)	Montelukast 10 mg qd (N=133)	Placebo (N=136)	QAW039 Total (N=765)	QAW039 low dose (N=201)	QAW039 mid dose (N=219)	QAW039 top dose (N=212)	Total (N=1034)
Other	68 (51.1)	69 (51.9)	71 (52.2)	410 (53.6)	103 (51.2)	126 (57.5)	113 (53.3)	550 (53.2)
Weight (kg)								
n	133	133	136	765	201	219	212	1034
Mean (SD)	76.80 (16.616)	76.07 (17.512)	75.33 (15.563)	75.92 (17.584)	76.66 (19.017)	75.14 (16.503)	75.48 (17.913)	75.86 (17.308)
Median (Min - Max)	78.00 (40.0-119.3)	72.30 (41.0-120.0)	73.00 (45.0-123.0)	75.00 (40.0-137.0)	75.00 (40.0-130.0)	73.00 (45.0-128.6)	73.05 (43.0-137.0)	74.00 (40.0-137.0)
Height (cm)								
n	133	133	136	765	201	219	212	1034
Mean (SD)	165.9 (10.71)	165.8 (10.21)	165.7 (9.94)	165.7 (10.39)	164.6 (10.21)	166.7 (10.11)	165.7 (10.60)	165.7 (10.30)
Median (Min - Max)	165.0 (145-194)	165.0 (144-187)	165.6 (144-195)	165.0 (141-197)	163.0 (141-191)	167.0 (142-196)	165.0 (143-197)	165.0 (141-197)
BMI (kg/m2)								
n	133	133	136	765	201	219	212	1034
Mean (SD)	27.775 (5.0297)	27.546 (5.3507)	27.422 (5.1147)	27.520 (5.3414)	28.120 (5.7478)	26.946 (4.9629)	27.385 (5.4747)	27.511 (5.3084)
Median (Min - Max)	27.548 (17.54-39.78)	26.673 (17.36-40.54)	27.155 (17.30-43.13)	26.665 (17.09-44.29)	27.472 (17.09-42.19)	25.945 (17.15-40.03)	26.463 (17.28-44.29)	26.732 (17.09-44.29)
BMI Category - n (%)								
<=30kg/m2	92 (69.2)	94 (70.7)	100 (73.5)	540 (70.6)	138 (68.7)	158 (72.1)	152 (71.7)	734 (71.0)
>30kg/m2	41 (30.8)	39 (29.3)	36 (26.5)	225 (29.4)	63 (31.3)	61 (27.9)	60 (28.3)	300 (29.0)

Height and weight are taken from Visit 1 vital signs evaluations.
BMI is calculated as: BMI(kg/m^2) = [weight(kg)/(height(cm)/100)^2].
QAW039 low dose: Combination of 1 mg qd, 3 mg qd, 2 mg bid, 10 mg qd.
QAW039 mid dose: Combination of 30 mg qd, 50 mg qd, 25 mg bid, 75 mg qd.
QAW039 top dose: Combination of 150 mg qd, 75 mg bid, 300 mg qd, 150 mg bid.
QAW039A total: Combination of all QAW039 doses

Disease characteristics by treatment group (Safety set)

	QAW039 450 mg qd (N=133)	Montelukast 10 mg qd (N=133)	Placebo (N=136)	QAW039 Total (N=765)	QAW039 low dose (N=201)	QAW039 mid dose (N=219)	QAW039 top dose (N=212)	Total (N=1034)
Duration of asthma (years)								
n	133	133	136	765	201	219	212	1034
Mean (SD)	21.2 (15.03)	22.2 (15.49)	20.7 (13.65)	20.0 (14.57)	20.5 (14.47)	20.5 (14.88)	18.4 (13.99)	20.4 (14.58)
Median (Min - Max)	18.5 (0.4-53.9)	19.6 (0.3-54.7)	18.2 (0.2-54.6)	17.6 (0.1-62.6)	19.4 (0.5-60.9)	17.4 (0.3-62.6)	14.8 (0.1-61.8)	17.8 (0.1-62.6)
Smoking History - n (%)								
Current smoker	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Ex-smoker	23 (17.3)	18 (13.5)	25 (18.4)	135 (17.6)	39 (19.4)	37 (16.9)	36 (17.0)	178 (17.2)
Never smoked	109 (82.0)	115 (86.5)	111 (81.6)	629 (82.2)	162 (80.6)	182 (83.1)	176 (83.0)	855 (82.7)
Estimated number of pack years								
n	24	18	25	136	39	37	36	179
Mean (SD)	5.2 (2.74)	3.5 (3.00)	3.7 (2.38)	4.5 (4.02)	3.7 (3.00)	4.2 (3.10)	5.1 (6.02)	4.3 (3.75)
Median (Min - Max)	5.0 (0.3-9.6)	2.8 (0.3-10.0)	4.5 (0.0-7.5)	4.0 (0.0-36.0)	3.8 (0.0-9.0)	4.0 (0.0-9.5)	4.0 (0.0-36.0)	4.0 (0.0-36.0)
Time since stopped smoking (years)								
n	23	18	25	135	39	37	36	178
Mean (SD)	15.7 (14.95)	13.0 (9.87)	13.1 (11.66)	15.3 (12.82)	16.6 (12.63)	16.0 (11.84)	13.1 (12.81)	14.8 (12.38)
Median (Min - Max)	10.2 (0.5-49.3)	11.0 (1.6-35.7)	9.7 (0.6-40.6)	11.5 (0.5-49.3)	16.0 (0.7-41.3)	13.9 (0.8-44.6)	8.6 (0.7-41.4)	11.1 (0.5-49.3)
Baseline ACQ score								
n	132	133	136	760	199	219	210	1029
Mean (SD)	2.2 (0.52)	2.3 (0.55)	2.2 (0.54)	2.2 (0.55)	2.2 (0.50)	2.3 (0.59)	2.2 (0.58)	2.2 (0.55)
Median (Min - Max)	2.1 (1.4-3.9)	2.1 (0.9-3.7)	2.1 (0.7-4.0)	2.1 (0.6-5.0)	2.1 (0.6-4.0)	2.3 (1.1-5.0)	2.1 (1.3-4.4)	2.1 (0.6-5.0)

	QAW039 450 mg qd (N=133)	Montelukast 10 mg qd (N=133)	Placebo (N=136)	QAW039 Total (N=765)	QAW039 low dose (N=201)	QAW039 mid dose (N=219)	QAW039 top dose (N=212)	Total (N=1034)
Quartiles (1 - 3)	(1.9-2.6)	(1.9-2.6)	(1.9-2.6)	(1.9-2.6)	(1.9-2.4)	(1.9-2.6)	(1.7-2.6)	(1.9-2.6)
Baseline ACQ score - n (%)								
1st tertile	50 (37.6)	43 (32.3)	48 (35.3)	259 (33.9)	72 (35.8)	63 (28.8)	74 (34.9)	350 (33.8)
2nd tertile	43 (32.3)	49 (36.8)	50 (36.8)	283 (37.0)	81 (40.3)	82 (37.4)	77 (36.3)	382 (36.9)
3rd tertile	39 (29.3)	41 (30.8)	38 (27.9)	218 (28.5)	46 (22.9)	74 (33.8)	59 (27.8)	297 (28.7)
ICS dose - n (%)								
≤ 800 µg Budesonide (or equivalent per day)	122 (91.7)	125 (94.0)	131 (96.3)	718 (93.9)	188 (93.5)	203 (92.7)	205 (96.7)	974 (94.2)
> 800 µG Budesonide (or equivalent per day)	11 (8.3)	8 (6.0)	5 (3.7)	47 (6.1)	13 (6.5)	16 (7.3)	7 (3.3)	60 (5.8)
ICS status - n (%)								
Step Neutral	34 (25.6)	39 (29.3)	38 (27.9)	220 (28.8)	63 (31.3)	58 (26.5)	65 (30.7)	297 (28.7)
Step Up	27 (20.3)	40 (30.1)	33 (24.3)	180 (23.5)	51 (25.4)	49 (22.4)	53 (25.0)	253 (24.5)
Step Down	72 (54.1)	54 (40.6)	65 (47.8)	365 (47.7)	87 (43.3)	112 (51.1)	94 (44.3)	484 (46.8)

Duration of asthma is calculated as date of asthma first diagnosed until Visit 1.

Time since stopped smoking is calculated as, (date of screening visit – date of stopping smoking) / 365.25

ACQ score is the average of all 7 questions

The baseline ACQ score is the last available non-missing pre-dose value.

- QAW039 low dose: Combination of 1 mg qd, 3 mg qd, 2 mg bid, 10 mg qd.
- QAW039 mid dose: Combination of 30 mg qd, 50 mg qd, 25 mg bid, 75 mg qd.
- QAW039 top dose: Combination of 150 mg qd, 75 mg bid, 300 mg qd, 150 mg bid.

QAW039 total: Combination of all QAW039 doses

Step Down ICS status: The patient is controlled at screening and received Medium dose ICS ± LABA or High dose ICS ± LABA.

Step Neutral dose status: The patient is controlled at screening and received Low dose ICS + other (e.g. LABA, LTRA etc.)

Summary of Efficacy

Primary Outcome Result(s)

Testing a dose-response signal for trough FEV1 (L), after 12 weeks of treatment (Modified Full analysis set)
Parameter: FEV1 (LOCF with Baseline FEV1 as covariate)

Model	T-Statistics	Unadjusted p-value (one sided)	Adjusted p-value* (one sided)
Emax model with half of maximum effect at 5 mg	2.97	0.0015	0.0039*
Emax model with half of maximum effect at 20 mg	3.00	0.0014	0.0035*
Emax model with half of maximum effect at 50 mg	2.78	0.0027	0.0074*
EMAX model with half of maximum effect at 120 mg	2.39	0.0084	0.0218*
Sigmoid Emax model with half of maximum effect at 100 mg and hill coefficient 6	2.14	0.0163	0.0393
Sigmoid Emax model with half of maximum effect at 170 mg and hill coefficient 4	1.16	0.1226	0.2395
Sigmoid Emax model with half of maximum effect at 80 mg and hill coefficient 3	2.41	0.0079	0.0207*
Sigmoid Emax model with half of maximum effect at 290 mg and hill coefficient 5	0.33	0.3706	0.5794
Linear model	1.25	0.1057	0.2121

FEV1 (L) after 12 weeks of treatment was used as the response variable.
Observations with missing values are imputed using LOCF, from last post baseline value on or after week 4.
* indicates that the model is significantly different from a flat dose-response model, with an adjusted one-sided p-value less than or equal to 0.025.
Adjusted p-values were obtained by adjusting for multiple comparisons of the above dose-response models with a flat dose-response model.

Dose-response results of trough FEV1 (L) based on model-averaged method over all models in the candidate set after 12 weeks of treatment (Modified Full analysis set)

Parameter: FEV1 (LOCF with Baseline FEV1 as covariate)

Treatment		Absolute increase over Placebo	95% CI	Percentage of projected effect of maximum QAW039	95% CI
QAW039	1 mg qd	0.0054	(0.0000, 0.1473)	4.9	(0.0, 99.6)
QAW039	3 mg qd	0.0189	(0.0000, 0.1610)	16.8	(0.0, 100.0)
QAW039	10 mg qd	0.0476	(0.0000, 0.1647)	42.4	(0.0, 100.0)
QAW039	30 mg qd	0.0881	(0.0000, 0.1685)	95.5	(0.0, 100.0)
QAW039	50 mg qd	0.0954	(0.0000, 0.1697)	98.2	(0.8, 100.0)
QAW039	75 mg qd	0.1019	(0.0009, 0.1708)	99.1	(16.7, 100.0)
QAW039	150 mg qd	0.1078	(0.0029, 0.1725)	99.9	(33.3, 100.0)
QAW039	300 mg qd	0.1097	(0.0065, 0.1739)	100.0	(66.7, 100.0)
QAW039	2 mg bid	0.0027	(0.0000, 0.1113)	5.8	(0.0, 82.6)
QAW039	25 mg bid	0.1043	(0.0004, 0.1668)	100.0	(11.4, 105.2)
QAW039	75 mg bid	0.1104	(0.0016, 0.1713)	100.0	(40.4, 170.0)
QAW039	150 mg bid	0.1122	(0.0036, 0.1753)	100.0	(67.3, 221.9)
QAW039	450 mg qd	0.1107	(0.0104, 0.1746)		
Montelukast	10 mg qd	0.1324	(0.0427, 0.2252)	119.3	(32.1, 227.1)

CI = confidence interval.
Model averaging process is based on three candidate model families.
All estimates were obtained through 10000 bootstrap samples analyzed using three candidate model families.
Percentage of projected effect of maximum QAW039 dose = (Effect of this QAW dose /Effect of QAW 450 mg qd) x 100%.
Maximum theoretical effect is the maximum effect estimated using model averaging method.

Trough FEV1 (L) after 12 weeks of treatment, comparison of QAW039 with Placebo and Montelukast, using linear mixed effect model (Modified Full analysis set)

Parameter:FEV1 (LOCF with Baseline FEV1 as covariate)

		LS mean		Difference to Placebo			Difference to Montelukast		
Treatment		Estimate	95% CI	Estimate	95% CI	p-value	Estimate	95% CI	p-value
QAW039	1 mg qd	2.066	(1.956, 2.176)	0.075	(-0.048, 0.198)	0.2296	-0.058	(-0.180, 0.063)	0.3477
QAW039	3 mg qd	2.078	(1.967, 2.189)	0.087	(-0.035, 0.209)	0.1609	-0.046	(-0.167, 0.074)	0.4513
QAW039	10 mg qd	1.993	(1.878, 2.108)	0.002	(-0.125, 0.129)	0.9760	-0.132	(-0.258, -0.005)	0.0412
QAW039	30 mg qd	2.082	(1.974, 2.190)	0.091	(-0.027, 0.210)	0.1311	-0.042	(-0.161, 0.076)	0.4819
QAW039	50 mg qd	2.043	(1.932, 2.153)	0.052	(-0.071, 0.175)	0.4072	-0.082	(-0.204, 0.041)	0.1909
QAW039	75 mg qd	2.102	(1.995, 2.209)	0.111	(-0.007, 0.230)	0.0652	-0.022	(-0.140, 0.096)	0.7119
QAW039	150 mg qd	2.155	(2.047, 2.263)	0.164	(0.044, 0.285)	0.0075	0.031	(-0.089, 0.150)	0.6137
QAW039	300 mg qd	2.111	(2.005, 2.216)	0.120	(0.003, 0.237)	0.0442	-0.014	(-0.130, 0.103)	0.8198
QAW039	2 mg bid	1.977	(1.869, 2.085)	-0.014	(-0.135, 0.107)	0.8230	-0.147	(-0.267, -0.027)	0.0161
QAW039	25 mg bid	2.136	(2.032, 2.240)	0.145	(0.030, 0.260)	0.0133	0.012	(-0.103, 0.126)	0.8409
QAW039	75 mg bid	2.170	(2.055, 2.285)	0.179	(0.052, 0.307)	0.0059	0.046	(-0.081, 0.173)	0.4790
QAW039	150 mg bid	2.054	(1.948, 2.161)	0.064	(-0.054, 0.181)	0.2871	-0.070	(-0.187, 0.047)	0.2414
QAW039	450 mg qd	2.068	(1.995, 2.142)	0.077	(-0.012, 0.167)	0.0901	-0.056	(-0.145, 0.032)	0.2120
Montelukast 10 mg		2.124	(2.052, 2.196)	0.134	(0.045, 0.222)	0.0033			
Placebo		1.991	(1.917, 2.064)				-0.134	(-0.222, -0.045)	0.0033

CI = confidence interval.
All estimates were obtained through linear mixed effect model with treatment, region as fixed effects, with either baseline % predicted FEV1 (first page) or baseline absolute FEV1 (second page) as covariate and center nested within region as random effect.
The baseline FEV1 is defined as the average of two FEV1 assessments taken in the clinic at 50 min and 15 min prior to the first study drug administration.

Secondary Outcome Result(s)

Change from baseline in ACQ score, comparison of QAW039 with Placebo and Montelukast, using linear mixed effect model by visit (Modified Full analysis set)

Parameter: ACQ7 overall score at week 12

Treatment		LS mean		Difference to Placebo			Difference to Montelukast		
		Estimate	95% CI	Estimate	95% CI	p-value Estimate	Estimate	95% CI	p-value Estimate
QAW039	1 mg qd	-0.758	(-0.954, -0.561)	-0.127	(-0.351, 0.098)	0.2682	-0.078	(-0.300, 0.144)	0.4905
QAW039	3 mg qd	-0.636	(-0.836, -0.436)	-0.005	(-0.230, 0.220)	0.9669	0.044	(-0.179, 0.267)	0.6992
QAW039	10 mg qd	-0.603	(-0.806, -0.399)	0.029	(-0.202, 0.259)	0.8072	0.077	(-0.152, 0.306)	0.5077
QAW039	30 mg qd	-0.612	(-0.805, -0.420)	0.019	(-0.197, 0.235)	0.8634	0.068	(-0.149, 0.284)	0.5400
QAW039	50 mg qd	-0.529	(-0.722, -0.337)	0.102	(-0.119, 0.323)	0.3652	0.151	(-0.068, 0.370)	0.1775
QAW039	75 mg qd	-0.617	(-0.805, -0.428)	0.015	(-0.200, 0.229)	0.8940	0.063	(-0.151, 0.277)	0.5618
QAW039	150 mg qd	-0.653	(-0.847, -0.460)	-0.022	(-0.243, 0.199)	0.8430	0.026	(-0.194, 0.246)	0.8141
QAW039	300 mg qd	-0.721	(-0.908, -0.533)	-0.089	(-0.303, 0.124)	0.4117	-0.041	(-0.253, 0.171)	0.7062
QAW039	2 mg bid	-0.681	(-0.872, -0.490)	-0.050	(-0.270, 0.170)	0.6586	-0.001	(-0.219, 0.217)	0.9936
QAW039	25 mg bid	-0.563	(-0.745, -0.381)	0.068	(-0.141, 0.277)	0.5228	0.117	(-0.091, 0.324)	0.2700
QAW039	75 mg bid	-0.737	(-0.950, -0.523)	-0.105	(-0.345, 0.134)	0.3884	-0.057	(-0.294, 0.181)	0.6396
QAW039	150 mg bid	-0.548	(-0.731, -0.365)	0.083	(-0.126, 0.293)	0.4358	0.132	(-0.077, 0.340)	0.2149
QAW039	450 mg qd	-0.666	(-0.795, -0.537)	-0.035	(-0.200, 0.131)	0.6823	0.014	(-0.150, 0.178)	0.8659
Montelukast 10 mg		-0.680	(-0.806, -0.554)	-0.049	(-0.213, 0.115)	0.5605			
Placebo		-0.631	(-0.761, -0.502)				0.049	(-0.115, 0.213)	0.5605

CI = confidence interval.
All estimates were obtained through linear mixed effect model with treatment and region as fixed effects, baseline ACQ score and baseline % predicted FEV1 as covariates and center nested within region as random effect.
The baseline ACQ score is defined as the ACQ score obtained on day 1.
The baseline FEV1 is defined as the average of two FEV1 assessments taken in the clinic at 50 min and 15 min prior to the first study drug administration.

Change from baseline in ACD score, comparison of QAW039 with Placebo and Montelukast, using repeated measures linear mixed effect model by timepoint (Modified Full analysis set)

Parameter: Average ACD score, Visit: Week 8-12

Treatment		LS mean Estimate	LS mean 95% CI		Difference to Placebo Estimate	Difference to Placebo 95% CI		Difference to Placebo p-value Estimate	Difference to Montelukast Estimate	Difference to Montelukast 95% CI		Difference to Montelukast p-value Estimate
QAW039	1 mg qd	-0.308	(-0.485,	-0.130)	-0.078	(-0.283,	0.128)	0.4577	0.001	(-0.201,	0.204)	0.9890
QAW039	3 mg qd	-0.167	(-0.368,	0.034)	0.063	(-0.158,	0.284)	0.5765	0.142	(-0.077,	0.361)	0.2027
QAW039	10 mg qd	-0.320	(-0.513,	-0.126)	-0.090	(-0.310,	0.131)	0.4239	-0.011	(-0.229,	0.208)	0.9237
QAW039	30 mg qd	-0.169	(-0.351,	0.013)	0.061	(-0.142,	0.264)	0.5549	0.140	(-0.062,	0.343)	0.1747
QAW039	50 mg qd	-0.149	(-0.338,	0.040)	0.081	(-0.134,	0.296)	0.4590	0.160	(-0.052,	0.373)	0.1389
QAW039	75 mg qd	-0.235	(-0.417,	-0.054)	-0.006	(-0.208,	0.197)	0.9572	0.074	(-0.128,	0.276)	0.4742
QAW039	150 mg qd	-0.340	(-0.522,	-0.157)	-0.110	(-0.317,	0.097)	0.2982	-0.031	(-0.237,	0.175)	0.7708
QAW039	300 mg qd	-0.280	(-0.460,	-0.101)	-0.050	(-0.252,	0.151)	0.6232	0.029	(-0.171,	0.229)	0.7774
QAW039	2 mg bid	-0.244	(-0.415,	-0.073)	-0.014	(-0.214,	0.185)	0.8892	0.065	(-0.133,	0.263)	0.5181
QAW039	25 mg bid	-0.229	(-0.404,	-0.053)	0.001	(-0.196,	0.198)	0.9895	0.081	(-0.115,	0.276)	0.4198
QAW039	75 mg bid	-0.136	(-0.326,	0.055)	0.094	(-0.121,	0.310)	0.3909	0.173	(-0.041,	0.388)	0.1121
QAW039	150 mg bid	-0.215	(-0.381,	-0.049)	0.015	(-0.175,	0.205)	0.8783	0.094	(-0.095,	0.283)	0.3283
QAW039	450 mg qd	-0.308	(-0.428,	-0.188)	-0.078	(-0.230,	0.074)	0.3147	0.001	(-0.149,	0.152)	0.9865
Montelukast 10 mg		-0.309	(-0.428,	-0.191)	-0.079	(-0.231,	0.073)	0.3070				
Placebo		-0.230	(-0.352,	-0.108)					0.079	(-0.073,	0.231)	-0.3070

CI = confidence interval.
All estimates were obtained through repeated measures linear mixed effect model with treatment, region and visit as fixed effects, baseline mean ACD score as covariate, visit by treatment and visit by baseline mean ACD score as interaction effects, center nested within region as random effect and patient as repeatedfactor. Baseline mean ACD score is defined as mean ACD score calculated prior to day 1

Summary of Safety

Safety Results

Number (%) of patients with AEs by primary system organ class (SAF) during treatment period

Primary system organ class	QAW039 450 mg qd (N=133)	Montelukast 10 mg qd (N=133)	Placebo (N=136)	QAW039 Total (N=765)	QAW039 low dose (N=201)	QAW039 mid dose (N=219)	QAW039 top dose (N=212)
Any primary system organ class	65 (48.9)	63 (47.4)	68 (50.0)	367 (48.0)	104 (51.7)	103 (47.0)	95 (44.8)
Blood and lymphatic system disorders	2 (1.5)	2 (1.5)	0 (0.0)	5 (0.7)	2 (1.0)	0 (0.0)	1 (0.5)
Cardiac disorders	4 (3.0)	0 (0.0)	1 (0.7)	13 (1.7)	3 (1.5)	3 (1.4)	3 (1.4)
Ear and labyrinth disorders	1 (0.8)	0 (0.0)	1 (0.7)	5 (0.7)	2 (1.0)	2 (0.9)	0 (0.0)
Endocrine disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.5)	0 (0.0)	0 (0.0)
Eye disorders	0 (0.0)	0 (0.0)	2 (1.5)	7 (0.9)	0 (0.0)	3 (1.4)	4 (1.9)
Gastrointestinal disorders	15 (11.3)	21 (15.8)	10 (7.4)	75 (9.8)	16 (8.0)	29 (13.2)	15 (7.1)
General disorders and administration site conditions	6 (4.5)	5 (3.8)	1 (0.7)	27 (3.5)	4 (2.0)	9 (4.1)	8 (3.8)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	3 (2.2)	3 (0.4)	1 (0.5)	0 (0.0)	2 (0.9)
Immune system disorders	1 (0.8)	1 (0.8)	1 (0.7)	2 (0.3)	0 (0.0)	1 (0.5)	0 (0.0)
Infections and infestations	26 (19.5)	39 (29.3)	31 (22.8)	188 (24.6)	56 (27.9)	48 (21.9)	58 (27.4)
Injury, poisoning and procedural complications	6 (4.5)	3 (2.3)	5 (3.7)	24 (3.1)	7 (3.5)	5 (2.3)	6 (2.8)
Investigations	6 (4.5)	2 (1.5)	7 (5.1)	36 (4.7)	10 (5.0)	11 (5.0)	9 (4.2)
Metabolism and nutrition disorders	5 (3.8)	4 (3.0)	1 (0.7)	13 (1.7)	4 (2.0)	2 (0.9)	2 (0.9)
Musculoskeletal and connective tissue disorders	4 (3.0)	6 (4.5)	3 (2.2)	38 (5.0)	13 (6.5)	10 (4.6)	11 (5.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.5)	0 (0.0)
Nervous system disorders	11 (8.3)	13 (9.8)	9 (6.6)	53 (6.9)	13 (6.5)	13 (5.9)	16 (7.5)
Psychiatric disorders	1 (0.8)	1 (0.8)	2 (1.5)	5 (0.7)	2 (1.0)	2 (0.9)	0 (0.0)
Renal and urinary disorders	3 (2.3)	3 (2.3)	1 (0.7)	9 (1.2)	2 (1.0)	1 (0.5)	3 (1.4)

Primary system organ class	QAW039 450 mg qd (N=133)	Montelukast 10 mg qd (N=133)	Placebo (N=136)	QAW039 Total (N=765)	QAW039 low dose (N=201)	QAW039 mid dose (N=219)	QAW039 top dose (N=212)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	4 (2.9)	2 (0.3)	1 (0.5)	1 (0.5)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	17 (12.8)	13 (9.8)	20 (14.7)	92 (12.0)	19 (9.5)	28 (12.8)	28 (13.2)
Skin and subcutaneous tissue disorders	8 (6.0)	4 (3.0)	4 (2.9)	26 (3.4)	4 (2.0)	7 (3.2)	7 (3.3)
Surgical and medical procedures	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.5)	0 (0.0)	0 (0.0)
Vascular disorders	3 (2.3)	3 (2.3)	2 (1.5)	8 (1.0)	5 (2.5)	0 (0.0)	0 (0.0)

A subject with multiple adverse events within a primary system organ class is counted only once in the total row.

Number (%) of patients reporting common AEs (greater than or equal to 5%* in any group) by preferred term (SAF) during treatment period

Preferred term	QAW039 450 mg qd (N=133)	Montelukast 10 mg qd (N=133)	Placebo (N=136)	QAW039 Total (N=765)	QAW039 low dose (N=201)	QAW039 mid dose (N=219)	QAW039 top dose (N=212)
Any AE	65 (48.9)	63 (47.4)	68 (50.0)	367 (48.0)	104 (51.7)	103 (47.0)	95 (44.8)
Nasopharyngitis	5 (3.8)	8 (6.0)	6 (4.4)	52 (6.8)	11 (5.5)	21 (9.6)	15 (7.1)
Headache	10 (7.5)	8 (6.0)	8 (5.9)	37 (4.8)	9 (4.5)	9 (4.1)	9 (4.2)
Asthma exacerbation#	6 (4.5)	6 (4.5)	6 (4.4)	34 (4.4)	9 (4.5)	8 (3.7)	11 (5.2)
Upper respiratory tract infection	3 (2.3)	11 (8.3)	4 (2.9)	27 (3.5)	9 (4.5)	7 (3.2)	8 (3.8)
Asthma#	6 (4.5)	4 (3.0)	10 (7.4)	26 (3.4)	4 (2.0)	5 (2.3)	11 (5.2)
Pharyngitis	1 (0.8)	5 (3.8)	4 (2.9)	22 (2.9)	9 (4.5)	8 (3.7)	4 (1.9)
Influenza	2 (1.5)	4 (3.0)	3 (2.2)	20 (2.6)	6 (3.0)	4 (1.8)	8 (3.8)
Diarrhoea	1 (0.8)	1 (0.8)	2 (1.5)	16 (2.1)	3 (1.5)	8 (3.7)	4 (1.9)
Sinusitis	3 (2.3)	5 (3.8)	3 (2.2)	14 (1.8)	5 (2.5)	2 (0.9)	4 (1.9)
Viral upper respiratory tract infection	3 (2.3)	1 (0.8)	0 (0.0)	12 (1.6)	6 (3.0)	2 (0.9)	1 (0.5)
Nausea	3 (2.3)	4 (3.0)	4 (2.9)	11 (1.4)	2 (1.0)	5 (2.3)	1 (0.5)
Cough	0 (0.0)	1 (0.8)	0 (0.0)	8 (1.0)	2 (1.0)	4 (1.8)	2 (0.9)
Dizziness	1 (0.8)	1 (0.8)	1 (0.7)	7 (0.9)	1 (0.5)	1 (0.5)	4 (1.9)
Abdominal pain	0 (0.0)	2 (1.5)	1 (0.7)	6 (0.8)	2 (1.0)	4 (1.8)	0 (0.0)
Gastrooesophageal reflux disease	0 (0.0)	1 (0.8)	0 (0.0)	5 (0.7)	0 (0.0)	2 (0.9)	3 (1.4)

Preferred term	QAW039 450 mg qd (N=133)	Montelukast 10 mg qd (N=133)	Placebo (N=136)	QAW039 Total (N=765)	QAW039 low dose (N=201)	QAW039 mid dose (N=219)	QAW039 top dose (N=212)

Asthma and asthma exacerbation AE terms could both be reported for the same patient. Asthma and/ or asthma exacerbation was reported for 12 (9.0%) QAW039 450mg QD, 9 (6.8%) montelukast, 14 (10.3%) placebo, 55 (7.2%) QAW039 total doses, 12 (6.0%) QAW039 low dose, 12 (5.5%) QAW039 medium dose, and 19 (9.0%) QAW039 top dose patients
Note that the ≥5% cutoff also applies to treatment arms which are not shown.
A subject with multiple adverse events is counted only once in the total row.
A subject with multiple occurrences of an AE under one treatment is counted only once in that AE category for that treatment.
*Note that the ≥5% cutoff also applies to treatment arms which are not shown in this table only displays the largest of these treatment groups).

Deaths, other serious or clinically significant adverse events or related discontinuations –n (%) of patients (SAF)

	QAW039 450 mg qd (N=133) n (%)	Montelukast 10 mg qd (N=133) n (%)	Placebo (N=136) n (%)	QAW039 Total (N=765) n (%)	QAW039 low dose (N=201) n (%)	QAW039 mid dose (N=219) n (%)	QAW039 top dose (N=212) n (%)
Patients with serious or other significant events	19 (14.3)	11 (8.3)	27 (19.9)	108 (14.1)	28 (13.9)	28 (12.8)	33 (15.6)
Patients who died	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with at least one SAE	3 (2.3)	1 (0.8)	2 (1.5)	13 (1.7)	4 (2.0)	4 (1.8)	2 (0.9)
Patients with at least one clinically significant AE	18 (13.5)	10 (7.5)	26 (19.1)	102 (13.3)	27 (13.4)	25 (11.4)	32 (15.1)
Patients who discontinued from study due to AEs	14 (10.5)	5 (3.8)	16 (11.8)	60 (7.8)	12 (6.0)	16 (7.3)	18 (8.5)
Discontinued from study due to SAEs	0 (0.0)	0 (0.0)	1 (0.7)	4 (0.5)	1 (0.5)	2 (0.9)	1 (0.5)
Discontinued from study due to non-serious AEs	14 (10.5)	5 (3.8)	15 (11.0)	56 (7.3)	11 (5.5)	14 (6.4)	17 (8.0)
Discontinued from study due to clinically significant AEs	10 (7.5)	4 (3.0)	13 (9.6)	41 (5.4)	10 (5.0)	8 (3.7)	13 (6.1)

- QAW039 low dose: Combination of 1 mg qd, 3 mg qd, 2 mg bid, 10 mg qd.
- QAW039 mid dose: Combination of 30 mg qd, 50 mg qd, 25 mg bid, 75 mg qd).
- QAW039 top dose: Combination of 150 mg qd, 75 mg bid, 300 mg qd, 150 mg bid).

QAW039 total: Combination of all QAW039 doses

Other clinically significant AEs comprised at least one of the following AEs drug-related hepatic disorders, tachyarrhythmia (supraventricular and ventricular tachyarrhythmias), cardiac failure, and MedDRA high level term “platelet analyses”.

Other Relevant Findings

None

Conclusion:

In summary, CQAW039A2206 study achieved its primary endpoint in demonstrating a clinically and statistically significant effect on trough FEV1 at 12 weeks over placebo in patients with moderate-to-severe, persistent, atopic asthma uncontrolled on low-dose ICS. There was no change in symptom control or quality-of-life either with QAW039 or the positive control, montelukast.

QAW039 appears to be well-tolerated without particular safety issues. SAEs and AEs appeared to be evenly distributed across QAW039, montelukast and placebo treatment groups. The pattern of AEs was in line with the indication of moderate to severe asthma patients. Efficacy and safety results were broadly similar in Japanese patients compared with the global population suggesting that no obvious ethnic sensitivity for this population was present in this study.

Date of Clinical Trial Report

14 October 2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

12 November 2014

Date of Latest Update

Reason for Update