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Generic Drug Name

QAW039A

Therapeutic Area of Trial

Mild to moderate persistent asthma

Approved Indication

NA

Protocol Number

QAW039A2201

Title

A randomized, placebo- controlled, parallel group study to assess the efficacy, safety, and pharmacokinetics of QAW039 in steroid-free patients with mild to moderate persistent asthma.

Study Phase

Phase II

Study Start/End Dates

14 Dec 2010 to 26 Sep 2011

Study Design/Methodology

This was a randomized, placebo controlled, parallel group study in one or two parts in patients with mild to moderate persistent asthma. Initially, the study was a double-blind comparison of 500 mg QAW039 and placebo (Part 1). An interim analysis was performed while the study was ongoing, when 63 patients had completed this part of the study and could have been stopped if a statistically significant effect was found with the primary endpoint. Otherwise, Part 2 of the study started where patients continued to be recruited for the double blind comparison of QAW039 and placebo. In addition it was intended that an open-label arm of patients treated with inhaled fluticasone propionate 200µg b.i.d. was also recruited in case the outcome of the interim analysis was negative. All patients participated in a screening period of up to 14 days, a 'weaning period' of a maximum of 28 days depending on the individual asthma treatment at screening, and a baseline visit. Patients who satisfied all the selection criteria were then randomized and entered a treatment period 28 days followed by a study completion visit within 7 days after the last dose of study drug.

Number of patients (planned and analyzed): It was planned to recruit up to 220 patients into the study (90 in the QAW039 group, 90 in the placebo group and 40 into the open-label fluticasone propionate group). A total of 170 patients were recruited (82 QAW039, 88 placebo), since the study was stopped prior to any patients being recruited into the fluticasone propionate group. All 170 patients were included in the safety analysis set, 166 (78 QAW039, 88 placebo) in the demographic data set, and 158 (74 QAW039, 84 placebo) into the efficacy (PD) data set.

Centers

Thirty centers in 7 countries: Germany (5 centers), Belgium (1 center), USA (20 centers), Romania (1 center), Bulgaria (1 center), Taiwan (1 center), South Korea (1 center)

Publication

Not Applicable.

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

QAW039 50 mg capsules for oral administration.

Statistical Methods

Trough FEV1 measurements from assessments on days 7, 14, 21, 28 and 29 were analyzed using a mixed model for repeated measurements, fitting treatment, visit, and treatment by visit interaction as fixed factors, Day 1 pre-dose trough as a continuous covariate, and subject as a repeated factor. The effect of baseline by time interaction was also explored in the model. Mean differences between each treatment group and placebo were estimated at Day 29 along with 90% confidence intervals.
One-sided P-values for the comparison of treatment vs. placebo were presented. P values less than 0.05 (1-sided) were regarded as statistically significant. No adjustment to p-values was made for the interim analysis.
As a secondary assessment, mean differences between each treatment group and placebo were also estimated using the above model along with 90% confidence intervals at Days7, 14 and 21.

Analysis methods for secondary objectives

Secondary efficacy assessments include:
• FEV1 at each individual time point following dosing on Day 28. This was used to assess the FEV1 peak effect.
• Area under the FEV1 effect curve 0-24 hours following the morning dose. Measurements from pikometry may have been used in this analysis where spirometry assessments were not available.
• eNO
• ACQ
• Serum IgE

Post treatment values of Area under the FEV1 effect curve, eNO, ACQ and serum IgE were analyzed using a mixed model for repeated measurements, fitting treatment, visit, and treatment by visit interaction as fixed factors, baseline value as a covariate, and subject as a repeated factor. The effect of baseline by time interaction was also explored in the model. Mean differences between each treatment group and placebo following 7, 14, 21 and 28 days' treatment were estimated along with 90% confidence intervals.

FEV1 values at each assessment time on Day 28/29 were analyzed using a mixed model for repeated measurements including treatment, time and treatment by time interaction as fixed factors, Day 1 pre-dose trough FEV1 as a continuous covariate, and subject as a repeated factor. The mean FEV1 difference between QAW039 and placebo was estimated with 90% confidence intervals at each time point.
Log transformations were used prior to analysis for eNO and any other parameters where the data indicated a lognormal distribution.
The frequency of salbutamol/Albuterol use over each of the visit intervals during the treatment period was compared between QAW039 and placebo using a log-linear Poisson model allowing for over dispersion.
The standard deviation of PEFR measurements collected over 28 days of treatment was derived for each patient and compared across treatment groups to determine if treatment with QAW039 resulted in improved asthma control. An analysis-of-variance model including treatment as a fixed factor was used to that effect. The time course of PEFR was plotted for morning and evening assessments, and analyzed using a repeated measures mixed effects model. The model included treatment and time as fixed factors, the treatment by time interaction terms, mean Baseline PEFR values as a covariate, and patient as a repeated effect.

Study Population: Inclusion/Exclusion Criteria and Demographics

Key inclusion criteria:

- male and post-menopausal female patients with mild to moderate asthma
- aged 18 to 65 years were eligible for this study as long as they
- weigh at least 45 kg and a body mass index (BMI) greater than 17 kg/m^2
- demonstrated FEV_1 reversibility at screening
- FEV_1 between 60 and 85% of the predicted normal value for the patient at baseline when LABA and steroid-weaned and to be symptomatic after weaning.

Key exclusion criteria:

- patients with severe persistent asthma, who had a history of life-threatening asthma or hospitalization for asthma exacerbation in the previous 6 months or were treated with systemic or high dose ICS, sustained release theophylline or had used a biologic agent for the treatment of asthma in the previous 6 months.
- history of any disease or illness other than asthma that required the use of systemic corticosteroids
- exposure to allergens that had the potential to worsen asthma symptoms,
- respiratory infections or serious underlying respiratory diseases.

Patient disposition

	QAW039 500 mg N=82 n (%)	Placebo N=88 n (%)	Total N=170 n (%)
Patients			
Completed	75 (91.5)	82 (93.2)	157 (92.4)
Discontinued	7 (8.5)	6 (6.8)	13 (7.6)
Main cause of discontinuation			
Adverse event(s)	1 (1.2)	1 (1.1)	2 (1.2)
Abnormal laboratory values	1 (1.2)	1 (1.1)	2 (1.2)
Unsatisfactory therapeutic effect	1 (1.2)	3 (3.4)	4 (2.4)
Patient withdrew consent	1 (1.2)	0	1 (0.6)
Administrative problems	1 (1.2)	1 (1.1)	2 (1.2)
Protocol deviation	2 (2.4)	0	2 (1.2)

Demographic Summary

		QAW039 500 mg N=78	Placebo N=88	Total N=166
Age (years)	Mean (SD)	41 (12.9)	42 (13.5)	42 (13.2)
	Range	19 - 65	19 – 65	19 - 65
Gender – n (%)	Male	59 (76)	59 (67)	118 (71)
	Female	19 (24)	29 (33)	48 929)
Race – n (%)	Caucasian	70 (90)	72 (82)	142 (86)
	Black	8 (10)	10 (11)	18 (11)
	Asian	0	1 (1)	1 (1)
	Native American	0	1 (1)	1 (1)
	Other	0	4 (4.5)	4 (2)
Weight (kg)	Mean (SD)	84.9 (18.26)	87.6 (19.74)	86.4 (19.05)
	Range	48.0 – 158.1	50.0 – 141.5	48.0 – 158.1
Height (cm)	Mean (SD)	173 (9.5)	173 (10.2)	173 (9.8)
	Range	144 – 196	152 – 198	144 – 198
BMI (kg/m²)	Mean (SD)	28.5 (5.81)	29.4 (5.79)	29.0 (5.80)
	Range	18.4 – 46.4	18.6 – 45.7	18.4 – 46.4

Outcome Measures

Primary outcome measures(s)

Change in trough forced expiratory volume in 1 second (FEV1) compared to placebo

	QAW039 mean	Placebo mean	QAW039 – placebo (90% CI)	P value*	LoC: T-C > 0	LoC T-C > 120 mL
Full PD analysis set	2.560	2.550	0.009 (-0.063, 0.082)	0.41	59.4%	0.7%

Secondary outcome measures(s)

Safety of a 28 day administration of QAW039 compared to placebo (reported on safety section of this document)

FEV_1 at FEV1 peak effect after 28 days administration of QAW039 compared to placebo

Scheduled Visit	N	QAW039 500 mg Lsmean (90% CI)	N	Placebo Lsmean (90% CI)	Difference between Lsmeans (90% CI) QAW039 500 mg-Placebo	One-sided P-value
DAY28*	63	2.763 (2.709, 2.817)	77	2.731 (2.682, 2.779)	0.032 (-0.041, 0.105)	0.233

* Peak is obtained using Day 28 and Day 29 data.
N is the number of subjects used in the analysis at each timepoint.
Data were analyzed using a repeated measures ANCOVA model including treatment, timepoint and treatment*timepoint as fixed effects, baseline FEV1 treated as a covariate and subject as a repeated factor.
Spirometry measurements taken within 6 hours of rescue medication were excluded from the analysis.

Area under the effect curve (0-24 hours) after 28 days administration of QAW039 compared to placebo

	QAW039 mean	Placebo mean	QAW039 – placebo (90% CI)	P value*
Full PD analysis set	2.668	2.602	0.066 (-0.008, 0.140)	0.070

Change in morning and evening peak expiratory flow rate (PEFR) as recorded by a home spirometry device longitudinally over 28 days of treatment with QAW039

Scheduled timepoint: Morning

Scheduled Visit	N	QAW039 500 mg Lsmean (90% CI)	N	Placebo Lsmean (90% CI)	Difference between Lsmeans (90% CI) QAW039 500 mg-Placebo	P-value
DAY1	62	389.6 (377.9, 401.4)	61	382.8 (371.1, 394.4)	6.9 (-9.7, 23.4)	0.494
DAY2	57	395.0 (382.9, 407.1)	66	398.8 (387.5, 410.0)	-3.8 (-20.3, 12.8)	0.707
DAY7	66	394.4 (382.9, 405.9)	64	388.6 (377.2, 400.0)	5.8 (-10.4, 22.0)	0.556
DAY14	60	393.3 (381.4, 405.2)	64	389.8 (378.4, 401.2)	3.5 (-13.0, 20.0)	0.727
DAY21	56	394.1 (381.9, 406.3)	61	391.5 (379.9, 403.1)	2.6 (-14.3, 19.5)	0.799
DAY28	54	378.6 (366.3, 391.0)	62	382.8 (371.3, 394.4)	-4.2 (-21.1, 12.7)	0.681

N is the number of subjects used in the analysis at each timepoint.
Data were analyzed using a repeated measures ANCOVA model including treatment, day and treatment*day as fixed effects, baseline PEFR treated as a covariate and subject as a repeated factor.

Scheduled timepoint: Evening

Scheduled Visit	N	QAW039 500 mg Lsmean (90% CI)	N	Placebo Lsmean (90% CI)	Difference between Lsmeans (90% CI) QAW039 500 mg-Placebo	P-value
DAY1	53	395.8 (382.4, 409.2)	65	390.8 (378.6, 403.0)	4.9 (-13.1, 23.0)	0.653
DAY2	55	420.9 (407.7, 434.1)	53	407.5 (394.4, 420.7)	13.4 (-5.3, 32.0)	0.238
DAY7	47	402.9 (388.9, 416.9)	63	394.0 (381.6, 406.3)	8.9 (-9.7, 27.6)	0.431
DAY14	50	414.6 (400.8, 428.3)	59	382.9 (370.2, 395.5)	31.7 (13.1, 50.3)	0.005
DAY21	45	409.5 (395.2, 423.7)	50	394.4 (380.9, 407.9)	15.1 (-4.5, 34.7)	0.206
DAY28	43	391.0 (376.5, 405.5)	61	379.9 (367.4, 392.4)	11.1 (-8.0, 30.2)	0.338

N is the number of subjects used in the analysis at each timepoint.
Data were analyzed using a repeated measures ANCOVA model including treatment, day and treatment*day as fixed effects, baseline PEFR treated as a covariate and subject as a repeated factor.

Rescue medication use over 28 days of treatment with QAW039

Visit	N	QAW039 500 mg Puffs per day (90% CI)	N	Placebo Puffs per day (90% CI)	Ratio (90% CI) QAW039 500 mg:Placebo	P-value
1-7	72	2.056 (1.731, 2.441)	82	1.917 (1.621, 2.266)	1.072 (0.844, 1.363)	0.631
7-14	71	2.111 (1.795, 2.483)	81	2.047 (1.754, 2.390)	1.031 (0.824, 1.290)	0.823
14-21	70	1.929 (1.625, 2.291)	79	2.018 (1.725, 2.363)	0.956 (0.757, 1.207)	0.750
21-28	70	1.748 (1.468, 2.080)	78	1.903 (1.628, 2.224)	0.919 (0.727, 1.160)	0.550

N is the number of subjects used in the analysis at each timepoint.
Data were analyzed using a log-linear poisson model allowing for over dispersion with fixed effects for treatment, visit treatment*visit.

Effect on asthma control using weekly Asthma Control Questionnaire (ACQ) scores during the 28 days of treatment with QAW039

N	QAW039 500 mg Lsmean (90% CI)	N	Placebo Lsmean (90% CI)	Difference between Lsmeans (90% CI) QAW039 500 mg-Placebo	One-sided P-value
70	1.74 (1.62, 1.86)	79	1.84 (1.72, 1.95)	-0.09 (-0.26, 0.07)	0.828

N is the number of subjects used in the analysis at each timepoint.
Data were analysed using an ANCOVA model including treatment, BMI and treatment*BMI as fixed effects and baseline treated as a covariate.

Pharmacodynamic effect as measured by eNO after 28 days administration of QAW039

Scheduled Visit	N	QAW039 500 mg Geometric lsmean (90% CI)	N	Placebo Geometric lsmean (90% CI)	Ratio of geometric lsmeans (90% CI) QAW039 500 mg:Placebo	One-sided P-value
DAY7	61	31.471 (29.539, 33.528)	58	35.059 (32.864, 37.400)	0.898 (0.820, 0.983)	0.025
DAY14	61	30.090 (27.917, 32.432)	58	33.768 (31.275, 36.459)	0.891 (0.800, 0.992)	0.039
DAY21	60	29.913 (27.744, 32.253)	55	35.016 (32.393, 37.852)	0.854 (0.767, 0.952)	0.009
DAY28	63	31.521 (29.015, 34.244)	58	32.805 (30.104, 35.749)	0.961 (0.853, 1.083)	0.290
DAY29	63	31.685 (28.940, 34.691)	54	34.331 (31.220, 37.752)	0.923 (0.809, 1.052)	0.157

N is the number of subjects used in the analysis at each timepoint.
Data were analyzed using a repeated measures ANCOVA model including treatment, day and treatment*day as fixed effects, baseline exhaled NO treated as a covariate and subject as a repeated factor.

Pharmacodynamic effect as measured by total serum IgE levels during the 28 days administration of QAW039.

Scheduled Visit	Geometric lsmean (90% CI) N	QAW039 500 mg	N	Placebo	Ratio of geometric lsmeans (90% CI) QAW039 500 mg:Placebo	One-sided P-value
DAY7	66	401.4 (392.0, 411.2)	80	406.1 (397.3, 415.0)	0.989 (0.957, 1.021)	0.279
DAY14	67	399.8 (387.3, 412.8)	78	401.1 (389.4, 413.1)	0.997 (0.954, 1.041)	0.453
DAY21	66	402.0 (388.5, 416.0)	76	402.4 (389.8, 415.4)	0.999 (0.953, 1.047)	0.488
DAY28	65	403.7 (370.7, 439.5)	77	415.1 (383.8, 448.8)	0.973 (0.866, 1.092)	0.345

N is the number of subjects used in the analysis at each timepoint.
Data were analyzed using a repeated measures ANCOVA model including treatment, day, treatment*day and baseline IgE*day as fixed effects, baseline IgE treated as a covariate and subject as a repeated factor.

Lack of clinical efficacy as measured by deterioration of asthma control during 28 days administration of QAW039 compared to placebo

Visit	Question number	Question		Question score	Change from baseline Question score
DAY28	2	Asthma symptoms when you woke up	n	70	70
			mean	1.9	-0.6
			SD	0.94	1.04
			minimum	0	-3
			median	2.0	-1.0
			maximum	4	2
	3	Limited were you in your activities	n	70	70
			mean	1.5	-0.6
			SD	1.07	1.03
			minimum	0	-3
			median	1.0	-0.5
			maximum	4	2
	4	Shortness of breath	n	70	70
			mean	1.9	-0.8
			SD	0.94	1.14
			minimum	0	-4
			median	2.0	-1.0
			maximum	4	2
	5	Wheeze	n	70	70
			mean	1.6	-0.6
			SD	1.07	1.09
			minimum	0	-4
			median	2.0	-1.0

Pharmacokinetics of multiple doses of QAW039

Treatment: QAW039 500 mg
Compound: QAW039, Matrix: Plasma, Analyte: QAW039

Profile day	Statistic	Tlast (h)	AUClast (h*ng/mL)	AUC0_24 (h*ng/mL)	Racc_AUC0_24	Racc_Cmax
1	n	73	73	73		
	Mean (SD)	22.9 (3.64)	12000 (5510)	12000 (5500)		
	CV% Mean	15.9	46.0	45.7		
	Geo-mean	22.4	10900	10900		
	CV% geo-mean	23.6	46.7	45.9		
	Median	24.0	11100	11100		
	[Min; Max]	[6.22; 24.3]	[3850; 28000]	[4130; 28000]		
28	n	71	71	70	66	67
	Mean (SD)	23.5 (2.45)	14300 (6090)	14300 (6090)	1.23 (0.271)	1.13 (0.719)
	CV% Mean	10.4	42.6	42.7	22.0	63.6
	Geo-mean	23.3	13100	13100	1.20	0.956
	CV% geo-mean	14.2	43.2	43.0	21.2	66.3
	Median	24.0	12300	12300	1.16	0.993
	[Min; Max]	[11.9; 25.1]	[4440; 31400]	[4440; 31400]	[0.732; 2.03]	[0.152; 4.99]

Safety Results

Incidence of AEs by Primary system organ class (Safety analysis set)

	QAW039 500 mg N=82 n (%)	Placebo N=88 n (%)
Patients with at least one AE	29 (35)	25 (28)
Primary system organ class (SOC)		
Nervous system disorders	12 (15)	12 (14)
Gastrointestinal disorders	11 (13)	2 (2)
General disorders & administration site conditions	3 (3)	3 (3)
Investigations	4 (5)	3 (3)
Infections & infestations	2 (2)	3 (3)
Respiratory, thoracic & mediastinal disorders	2 (2)	3 (3)
Injury poisoning and procedural complications	3 (4)	1 (1)
Musculoskeletal & connective tissue disorders	2 (2)	2 (2)
Cardiac disorders	2 (2)	1 (1)
Ear and labyrinth disorders	0	1 (1)
Metabolism and nutrition disorders	0	1 (1)
Psychiatric disorders	1 (1)	0
Skin & subcutaneous tissue disorders	0	1 (1)

AEs by SOC are presented in descending order of frequency in the total group.

Date of Clinical Trial Report

9 April 2013.

Date Inclusion on Novartis Clinical Trial Results Database

11 Nov 2013

Date of Latest Update