



Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

The oral CRTh2 antagonist QAW039 (fevipiprant): A phase II study in uncontrolled allergic asthma



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ARTICLE INFO

Article history:

Received 18 December 2015

Received in revised form

16 June 2016

Accepted 19 June 2016

Available online 21 June 2016

Keywords:

Asthma

Chemoattractant receptor-homologous

molecule expressed on Th2 cells

Clinical trial

ABSTRACT

Background: There is an unmet medical need for allergic asthma patients who are uncontrolled on conventional therapies. The aim of this study was to collect efficacy and safety data for QAW039, an oral chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTh2) receptor antagonist, for the treatment of asthma.

Methods: This was an exploratory phase II, double-blind, randomized, placebo-controlled multi-center study. Patients with mild-to-moderate uncontrolled allergic asthma (N = 170) were either without or weaned off inhaled corticosteroids (ICS) and long-acting β -agonists (LABA) and randomized (1:1) to QAW039 (500 mg once daily) or to placebo for 28 days.

Results: Overall, 157 patients completed the study. There were no significant differences between QAW039 and placebo for trough forced expiratory volume in 1 s (FEV₁) or Asthma control questionnaire (ACQ) in the total population. Subgroup analyses demonstrated that patients with a FEV₁ <70% of predicted at baseline treated with QAW039 had significant improvement compared with placebo in trough FEV₁ (QAW039- Placebo [Δ] = 207 mL; 90% confidence interval [CI]: 96, 319; P = 0.002) and ACQ7 (Δ = -0.41; 90%CI: -0.69, -0.13; P = 0.009). QAW039 reached a mean maximum concentration (C_{max}) of 3440 ng/mL on day 28 at a median T_{max} of 1 h (range 0.5–4 h). Most adverse events (AEs) were mild/moderate and balanced between both groups, with no serious AEs.

Conclusions: In the general study population, no improvement in lung function was observed with QAW039. However, a subgroup analysis revealed that patients with greater severity of airflow limitation (FEV₁ < 70%) had improved lung function and asthma control when treated with QAW039. QAW039 also demonstrated a favorable safety profile.

Trials registration: [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01253603) NCT01253603.

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1. Background

Asthma is a chronic lung disease that affects 235–330 million people worldwide [1]. It is characterized by chronic airway inflammation and bronchial hyper-responsiveness and is clinically defined by a history of respiratory symptoms, such as chest tightness, shortness of breath, wheezing and cough, that vary over time and in intensity [2]. Asthma is a heterogeneous disease that is

associated with a range of different phenotypes, which can be linked to age of onset, specific triggers and type of inflammation (eosinophilic, neutrophilic and pauci-granulocytic phenotypes) [3]; and can be further defined by endotypes [4].

Patients with asthma who are poorly controlled or poorly compliant with current medication, such as inhaled corticosteroids (ICS) and long-acting β -agonists (LABA), constitute a population with a significant health and economic burden [5]. There is an unmet medical need across all asthma severities, as observed in a large scale global insight study by Rabe et al., [6]. This study demonstrated that across all severities there was a higher use of quick-relief medication (short-acting bronchodilators) compared to preventative medication, which is suggestive of poor asthma control. Over 80% of patients with uncontrolled asthma have poor adherence with regular inhaled therapy [7]. Therefore, there is a need to develop new therapies to achieve asthma symptom control and reduce exacerbations. Unlike biologics, the administration of these therapies should be convenient for the patient (e.g. oral administration, once daily dosing) and without the side effects associated with steroids [8].

Prostaglandin D₂ (PGD₂), an arachidonic acid metabolite, is produced mainly by mast cells [9], but other leukocytes such as dendritic cells [10] and Th2 cells [11] can also produce this eicosanoid. PGD₂ has long been associated with the allergic inflammatory responses; with high levels of PGD₂ being produced in response to allergens [12]. It has been demonstrated that after an antigen challenge, PGD₂ levels are increased within the airways of patients with asthma [13]. IgE-stimulated mast cells have been shown to produce PGD₂ [9], which in turn signals through the classical PGD₂ receptor 1 (DP₁) and the DP₂, also known as the chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTh2), [14]. The DP₁ receptor mediates vascular effects of PGD₂ [15], while CRTh2 mediates the inflammatory effects [14,16,17]. Due to its role in allergic diseases, there is interest in developing CRTh2 inhibitors [18]. During the recent years, there has been an evolution in the field of CRTh2 antagonists, with some of them being discontinued and others being moved forward to late-stage clinical development [19,20].

QAW039 (fevipiprant) is a selective, potent, reversible, and competitive CRTh2 antagonist [21]. Previous data from phase I studies have shown that QAW039 was safe and well tolerated across a range of doses and exhibited favorable pharmacokinetic attributes with peak plasma levels achieved 1-to-3 hours after dosing and a half-life of 18.6–20.2 h [22]. More recently it has been demonstrated that QAW039 can impact directly on key immune cells associated with asthma [23] and is effective at modulating eosinophilic airway inflammation in patients with high sputum eosinophils [24].

This trial was designed as the first proof-of-concept study with QAW039, set out to assess the clinical response of once daily dosing of QAW039 (500 mg) over 28 days in steroid-free patients with mild-to-moderate persistent allergic asthma.

2. Methods

2.1. Study design

This was an exploratory phase II, double-blind, randomized, placebo-controlled multi-center study in patients with mild-to-moderate persistent allergic asthma. The first patient was enrolled on December 14th, 2010, and the last patient completed the study on September 26th, 2011.

The study consisted of a screening period of up to 14 days and a weaning period (LABA and ICS withdrawal) of up to 28 days. The weaning period was conducted in a stepwise tapering of the

patient's asthma medication every 7 days (Fig. 1). Further information is provided in the Data in Brief.

The treatment period consisted of a baseline day followed by 28 days of treatment (Fig. 1). At baseline, all patients were assessed and patients deemed eligible were randomized 1:1 to receive either QAW039 (500 mg once daily) or placebo.

Two previous safety, tolerability and pharmacokinetic studies in healthy volunteers [22,25] have demonstrated that QAW039 doses up to 500 mg were well tolerated with a PK profile potentially allowing once daily dosing. The use of QAW039 at 500 mg once daily in this study was based on previous observations from these studies, which suggested that this dose administered repeatedly over 28 days would produce blood concentrations sufficient to elicit a clinical effect [22,25].

More details on study drug administration are provided in the Data in Brief. This study is registered with ClinicalTrials.gov as NCT01253603.

2.2. Patients

This study enrolled male or post-menopausal female asthma patients aged 18–65 years with a history of mild-to-moderate allergic asthma diagnosed in accordance with GINA 2010 report [26]. All patients at screening weighed at least 45 kg, with a body mass index (BMI) greater than 17 kg/m². Patients had forced expiratory volume in 1 s (FEV₁) reversibility (an increase of $\geq 12\%$ and ≥ 200 mL in FEV₁) at screening and a FEV₁ of $\geq 60\%$ and $\leq 85\%$ of the predicted normal value at baseline, and were symptomatic post weaning period. A positive skin prick test within 12 months of screening to aeroallergens or allergens specific to locality was required. Patients must have had an asthma control questionnaire (ACQ) score of at least 1.5 at baseline, and be able to communicate well with the Investigator. Key exclusion criteria were: women of childbearing potential, patients who smoked in the previous 6 months or had a smoking history >10 pack-years, patients who had a history of life-threatening asthma or who had a significant illness two weeks prior to initial dosing. Detailed inclusion and exclusion criteria are provided in the Data in Brief (Table 1). Post screening, the following allergy/asthma medication were prohibited: Systemic corticosteroids, long-acting muscarinic antagonists (LAMAs), short acting anti-cholinergics, LABAs, LABA/ICS combinations, theophylline and other xanthines, leukotriene antagonists, inhaled cromolyn or nedocromil. Patients were excluded or discontinued from the study if they received treatment with: systemic corticosteroids, beta-adrenergic blockers, aspirin above daily doses of >81 mg, non-steroidal anti-inflammatory drugs (except for acetaminophen and ibuprofen) or other investigational drugs. Indomethacin was not allowed after screening since it has activity on the CRTh2 receptor. Furthermore, at screening, patients who had a previous exposure to a biological agent for asthma in the last six months were also excluded.

All patients provided written informed consent. The study protocol was approved by the local ethics committees and was undertaken in accordance with good clinical practice guidelines and the Declaration of Helsinki.

2.3. Assessments and outcomes

Spirometry measurements were taken at specified time points (Screening, Baseline, Days 1, 7, 14, 21 and 28) during the treatment period and were assessed by a central reader, resulting in values for FEV₁, forced vital capacity (FVC) in absolute terms and as % predicted. FEV₁ was also measured on Day 29 for the primary endpoint trough FEV₁ (the mean of the FEV₁ measured at 23 h 15 min and 23 h 45 min post-dose on Day 28) of QAW039 compared with

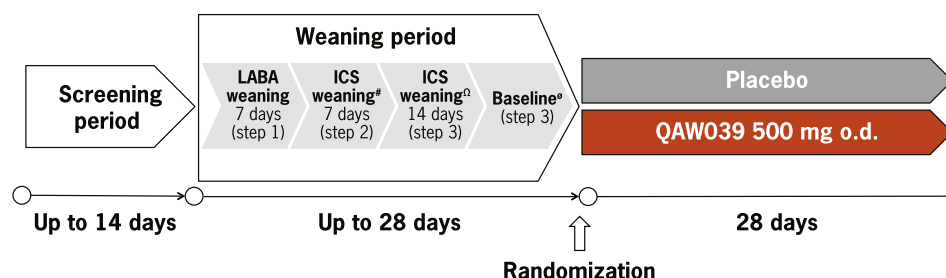


Fig. 1. Study Design. The patient's asthma medication was weaned every 7 days in a stepwise manner. Patients not on LABA and/or ICS who had stopped their asthma controller therapies did not undergo the weaning period. ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; #, medium dose to low dose ICS; Ω, low dose to ICS withdrawal; *, final day of ICS weaning; o.d., once daily.

placebo.

Key secondary endpoints: the safety of QAW039 compared with placebo was assessed by monitoring adverse events (AEs), including severity of the event. Drug efficacy was measured by peak FEV₁ and the area under the effect curve from 0 to 24 h (AUC_{0–24h}); changes in morning and evening peak expiratory flow rate (PEFR) which were recorded by a home spirometry device longitudinally; the use of rescue medication (salbutamol/albuterol) and asthma control which was evaluated using weekly Asthma Control Questionnaire (ACQ7) scores. Other endpoints were the pharmacodynamics (PD) effect, as measured by fractional exhaled nitric oxide (FeNO) or by total serum IgE levels and the assessment of the pharmacokinetics (PK) of QAW039.

2.4. Interim analyses

As per protocol, an unblinded interim analysis (first interim analysis, IA1) was performed when 63 patients (33 treated with QAW039 and 30 with placebo) completed the 28 day study to evaluate proof-of-concept on PD analysis set. The interim analysis tested the treatment effect in trough FEV₁ and other lung function parameters, FeNO, ACQ7 and frequency of rescue medication. No statistically significant effect on the primary endpoint was observed but there was a trend for efficacy on the key endpoints (FEV₁ and ACQ7) observed in patients with low FEV₁% predicted or in other sub-groups (ACQ high/low [$>/\leq$ median ACQ at baseline (BL) in the total population], eosinophil (Eos) high [$>300 \mu\text{L}$] or low [$\leq 150 \mu\text{L}$], FeNO high/low [$>/\leq$ median BL FeNO at BL in the total population], IgE high/low [$>/\leq$ median IgE level at BL in the total population] and combinations of these groups). The recruitment continued during and after this interim analysis.

A second interim analysis (unplanned) was performed after 127 patients had completed the study (61 treated with QAW039 and 66 with placebo). A positive result for the primary endpoint, trough FEV₁, was observed in the subgroup analysis set FEV₁ (% predicted) $< 70\%$, so the study was stopped with 170 patients recruited into the QAW039 and placebo groups. Unblinded data from this second interim analysis indicated that a further 17 subgroup analysis sets (Table 1) needed to be included in the final analysis. A post-hoc analysis of all PD variables was carried out using these subgroup analysis sets. The subgroup analysis sets were defined according to the patient's baseline values.

2.5. Statistical methods

All patients who received at least one dose of the study drug were included in the safety data analysis. The PD analysis set included all patients with evaluable PD/PK data, excluding 12 patients who did not satisfy entry criteria but were randomized. The number of patients included in each of the analysis sets is provided

in Table 1.

The primary endpoint, mean trough FEV₁, was analyzed using a linear model for repeated measurements, fitting treatment, visit, and treatment-by-visit interaction as fixed factors, and Day 1 pre-dose trough as a continuous covariate. Missing data from patients was not imputed. The residual dependence of repeated subject measurements was modelled with an unstructured covariance matrix. Mean differences between each treatment group and placebo were estimated at all visits along with 90% confidence intervals (CI). One-sided P-values for the comparison of treatment vs. placebo were presented with p-values < 0.05 regarded as statistically significant. A Sample size of 130 evaluable patients (65 in each treatment arm) would provide approximately 80% power to detect a difference of 150 mL in trough FEV₁ between QAW039 and placebo, assuming a one-sided alpha level of 0.05 and a between-patient standard deviation (SD) of 341 mL based on data from another clinical study (data not shown). The overall dropout rate was expected to be approximately 25% at the end of the study. It was planned that 90 patients would be randomized to both treatment arms.

For secondary endpoints, unless otherwise stated, the mean differences between each treatment group and placebo were estimated using the same model as the primary analysis along with 90% CI at Days 7, 14, 21, 28 and 29. Spirometry measurements taken within 6 h of use of rescue medication were excluded from all statistical analysis. The PK parameters were determined from plasma and/or urine concentration and descriptive statistics of PK parameters included mean, SD, CV%, minimum and maximum. All safety endpoints were summarized by treatment for the safety set, which included all patients who received at least one dose the study drug. SAS version 9.3 was used to perform all the statistical analyses.

3. Results

3.1. Patients

Of the 170 patients that were randomized, 157 (92.4%) completed the study (QAW039 $n = 75$, placebo $n = 82$) (Fig. 2). A similar percentage of patients completed both treatment arms (91.5% completion rate for QAW039 compared with 93.2% for placebo).

3.2. Patient demographics and baseline characteristics

Patient demographics were comparable between both treatment arms (Table 2). The majority of patients were male (76% in QAW039 and 67% in placebo) and Caucasian (86%).

Baseline characteristics in the PD analysis set were generally well balanced across both arms (Table 2). There was a slight

Table 1
Number (%) of patients in the subgroup analysis sets.

Patient analysis set	QAW039 500 mg	Placebo	Total
	N = 82	N = 88	N = 170
	n (%)	n (%)	n (%)
Safety	82 (100)	88 (100)	170 (100)
Demography ^a	78 (95)	88 (100)	166 (98)
PK ^b	78 (95)	0	75 (44)
PD ^c	74 (90)	84 (96)	158 (93)
Subgroup analysis sets^d			
Tertile of FEV ₁ (% predicted)			
Upper tertile (>76.1%)	26 (36)	26 (31)	52 (33)
Middle tertile (68.7–76.1%)	25 (34)	28 (33)	53 (34)
Lower tertile (<68.7%)	22 (30)	30 (36)	52 (33)
FEV ₁ (% predicted) < 70%	28 (38)	37 (44)	65 (41)
Steroid weaned	36 (49)	31 (37)	67 (42)
Steroid naïve	38 (51)	53 (63)	91 (58)
Naïve + lower tertile of FEV ₁ (% predicted) < 70%	11 (15)	19 (23)	30 (19)
Eosinophils >300/μL	21 (29)	25 (30)	46 (29)
Eosinophils ≤300/μL	52 (71)	59 (70)	111 (71)
Eosinophils >150/μL	54 (74)	64 (76)	118 (75)
Eosinophils ≤150/μL	19 (26)	20 (24)	39 (25)
IgE > median	40 (57)	36 (44)	76 (50)
IgE ≤ median	30 (43)	46 (56)	76 (50)
IgE high + eos. >300/μL	15 (22)	9 (11)	24 (16)
FeNO > median	34 (49)	35 (52)	69 (50)
FeNO ≤ median	35 (51)	33 (49)	68 (50)
FEV ₁ (% predicted) < 70% excl. IA1	15 (21)	29 (35)	44 (28)

Denominator to calculate percentage for subgroup analysis sets based on PD analysis set.

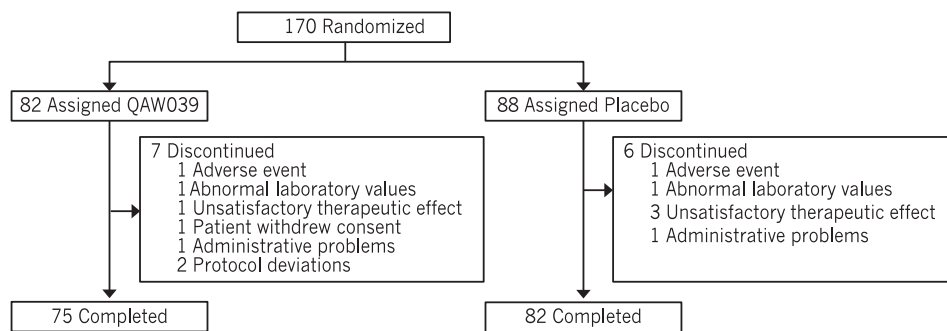
FEV₁, forced expiratory volume in 1 s; AUC, area under the curve; ACQ7, asthma control questionnaire derived from 7 questions; Eos, eosinophil; FeNO, exhaled nitric oxide; ppb, parts per billion; IA1, first interim analysis.

^a Demography analysis set excludes 2 double completers and 2 patients with no drug in PK sample.

^b 3 subjects had not day 1 PK data but did have data on Day 28.

^c PD analysis set excludes an additional 12 subjects who did not satisfy entry criteria but were randomized.

^d Subgroups were defined according to baseline values. Total population median IgE = 166 mg/L; Total population median FeNO = 32 ppb; High IgE = IgE > median (166 mg/L).

**Fig. 2.** Study profile.

imbalance in steroid status as there were more steroid-naïve patients allocated to the QAW039 treatment arm (49%) than to placebo (37%), and there were more patients who were weaned off steroids allocated to the placebo (63%) than to the QAW039 treatment arm (51%). IgE at baseline was highly variable in both groups ranging from 7 to 32,729 μg/L. The baseline demographics and disease characteristics of FEV₁ (% predicted) < 70% patient subgroup are displayed in Table 3.

3.3. Assessments and outcomes from primary PD and PK analysis

The analysis of the primary endpoint, trough FEV₁, at day 29, in the overall PD set was comparable between QAW039 and placebo (treatment difference QAW039–placebo (Δ) = 9 mL, 90% CI: –63, 82 mL; $P = 0.41$) (Table 4). Analysis of FEV₁AUC_{0–24h} at day 28/29 showed a difference between treatment with QAW039 and

placebo, but it was not statistically or clinically significant ($\Delta = 66$ mL, 90% CI: –8, 140 mL; $P = 0.07$) (Table 4). Similarly, within the PD analysis set, the ACQ7 score reported by patients treated with QAW039 was comparable with placebo group ($\Delta = -0.12$, 90% CI: –0.29, 0.04; $P = 0.11$) (Table 4).

Differences between QAW039 and placebo for PEFR (morning and evening) and FeNO were comparable on Day 28 and 29, respectively (Data in Brief, Tables 2 and 3, respectively). A treatment effect was observed between QAW039 and placebo on the evening of Day 14 for PEFR and on Day 7, 14 and 21 for FeNO (Data in Brief, Tables 2 and 3, respectively). Analysis of total serum IgE and rescue medication use showed no statistical difference between the two treatment arms (Data in Brief, Tables 4 and 5, respectively).

QAW039 had median T_{max} values of 1.08 h and 1.13 h on Days 1 and 28, respectively (Data in Brief, Table 6) and reached a mean maximum concentration (C_{max}) of 3440 ng/mL on Day 28. The

Table 2
Patient demographic and baseline characteristics.

	QAW039 500 mg o.d. (n = 78)	Placebo (n = 88)	Total (N = 166)
Age, years (SD)	41 (12.9)	42 (13.5)	42 (13.2)
Male, n (%)	59 (76)	59 (67)	118 (71)
Race, n (%)			
Caucasian	70 (90)	72 (82)	142 (86)
Black	8 (10)	10 (11)	18 (11)
Asian	0	1 (1)	1 (1)
Other	0	4 (4.5)	4 (2)
Native American	0	1 (1)	1 (1)
Weight (kg)	84.9 (18.26)	87.6 (19.74)	86.4 (19.05)
Height (cm)	173 (9.5)	173 (10.2)	173 (9.8)
BMI (kg/m ²)	28.5 (5.81)	29.4 (5.79)	29.0 (5.80)
FEV ₁ (L) ^a	2.59 (0.646)	2.50 (0.713)	2.54 (0.682)
FEV ₁ (% predicted) ^a	71.5 (7.11)	71.8 (6.46)	71.6 (6.75)
FEV ₁ reversibility (%) ^a	20.9 (9.0)	24.1 (13.7)	22.6 (11.8)
Steroid status, n (%) ^a			
Naive	36 (49%)	31 (37%)	67 (42%)
Withdrawn	38 (51%)	53 (63%)	91 (58%)
ACQ total score ^a	2.20 (0.451)	2.21 (0.476)	2.21 (0.463)
IgE (μg/L), median (range) ^a	183 (11–32,720)	134 (7–5728)	166 (7–32,720)

Data are mean ± standard deviation, unless otherwise stated.

o.d., once daily; SD, standard deviation; kg, kilogram; cm, centimeter; kg/m², kilogram per meter squared; FEV₁, forced expiratory volume in 1 s; ACQ, asthma control questionnaire.^a Baseline characteristics were summarized using the PD analysis set.**Table 3**
Patient demographic and baseline characteristics of FEV₁ (% predicted) < 70% patient subgroup.

	QAW039 500 mg o.d. (n = 28)	Placebo (n = 37)	Total (N = 65)
Age, years (SD)	43 (12.9)	44 (11.8)	44 (12.2)
Male, n (%)	20 (71)	22 (60)	42 (65)
Race, n (%)			
Caucasian	27 (96)	29 (78)	56 (86)
Black	1 (4)	6 (16)	7 (35)
Asian	0	1 (3)	1 (2)
Other	0	1 (3)	1 (2)
Weight (kg)	87.4 (14.09)	89.3 (20.16)	88.5 (17.70)
Height (cm)	172 (9.9)	172 (11.2)	172 (10.6)
BMI (kg/m ²)	29.8 (5.46)	29.9 (5.60)	29.9 (5.50)
FEV ₁ (L)	2.42 (0.651)	2.23 (0.632)	2.34 (0.639)
FEV ₁ (% predicted)	68.0 (6.25)	67.6 (4.36)	67.8 (5.22)
FEV ₁ reversibility (%)	22.2 (9.7)	24.5 (10.3)	23.5 (10.0)
Steroid status, n (%)			
Naive	13 (46%)	16 (43%)	29 (45%)
Withdrawn	15 (54%)	21 (57%)	36 (55%)
ACQ total score	2.18 (0.441)	2.19 (0.345)	2.19 (0.386)
IgE (μg/L), median (range)	193 (22–2445)	123 (57–3253)	151 (7–3253)

Data are mean ± standard deviation, unless otherwise stated.

o.d., once daily; SD, standard deviation; kg, kilogram; cm, centimeter; kg/m², kilogram per meter squared; FEV₁, forced expiratory volume in 1 s; ACQ, asthma control questionnaire.**Table 4**
Primary and secondary efficacy outcomes in full PD analysis set.

	QAW039 (n = 74)	Placebo (n = 84)	Treatment difference QAW039-placebo (90% CI)	P value*
Trough FEV ₁ (L)	2.560	2.550	0.009 (−0.063, 0.082)	0.41
FEV ₁ AUC _{0–24h} (L)	2.668	2.602	0.066 (−0.008, 0.140)	0.070
ACQ7 total score	1.73	1.85	−0.12 (−0.29, 0.04)	0.110

Data are least square means (LSM).

FEV₁, forced expiratory volume in 1 s; AUC, area under the curve; ACQ7, asthma control questionnaire derived from 7 questions; CI, confidence intervals.

*One-sided P value.

mean AUC_{tau} ratio (Day 28 AUC_{0–24h}/Day1 AUC_{0–24h}) for QAW039 was 1.2 (Data in Brief, Table 6). Approximately 17% of the dose was excreted unchanged in urine, with a mean renal clearance of approximately 7 L/hour.

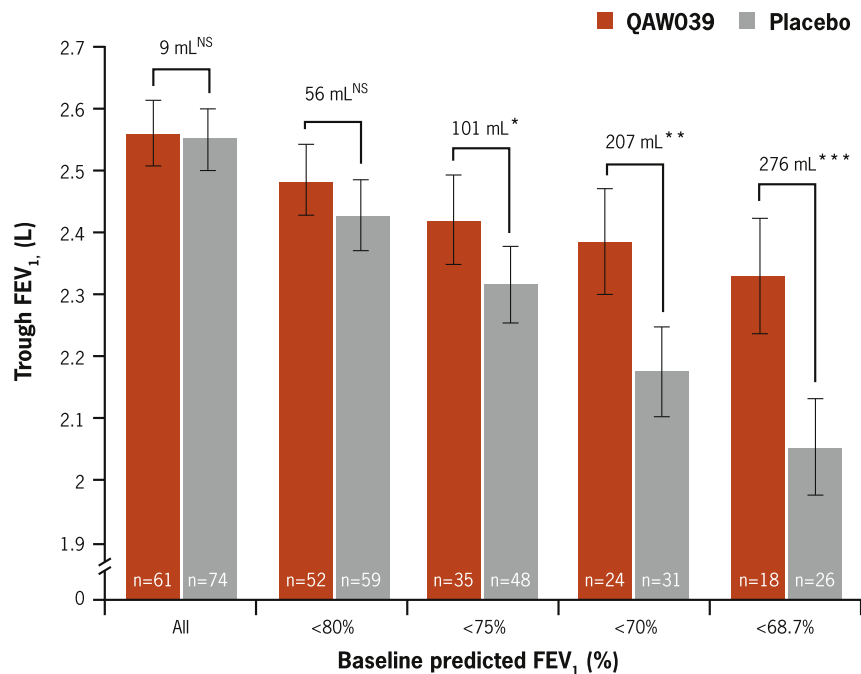
3.4. Assessments and outcomes from subgroup analysis sets

The post hoc analysis of the subgroup analysis sets revealed that the largest treatment effects were observed in subgroups based on low FEV₁ (% predicted) at baseline (Table 5).

Table 5Summary of the statistical analysis in subgroups.^a

	Treatment difference QAW039–placebo (least squares mean, 90% CI)		
	Trough FEV ₁ (L)	FEV ₁ AUC _{0–24h} (L)	ACQ7
Upper tertile of FEV ₁ % predicted (>76.1%)	–0.112 (–0.236, 0.011) ^{NS}	–0.020 (–0.116, 0.076) ^{NS}	0.21 (–0.03, 0.46) ^{NS}
Middle tertile of FEV ₁ % predicted (68.7–76.1%)	–0.083 (–0.200, 0.034) ^{NS}	–0.080 (–0.191, 0.031) ^{NS}	–0.18 (–0.48, 0.12) ^{NS}
Lower tertile of FEV ₁ % predicted (<68.7%)	0.276 (0.154, 0.398) ^{**}	0.341 (0.192, 0.489) ^{**}	–0.43 (–0.73, –0.13) [*]
FEV ₁ (% predicted) < 70%	0.207 (0.096, 0.319) [*]	0.240 (0.109, 0.371) [*]	–0.41 (–0.69, –0.13) [*]
Steroid weaned	–0.009 (–0.126, 0.108) ^{NS}	0.075 (–0.053, 0.202) ^{NS}	–0.34 (–0.61, –0.06) [*]
Steroid naïve	0.023 (–0.074, 0.119) ^{NS}	0.071 (–0.026, 0.168) ^{NS}	–0.02 (–0.22, 0.18) ^{NS}
Naïve + lower tertile of FEV ₁ (% predicted) < 70%	0.314 (0.162, 0.465) ^{**}	0.338 (0.163, 0.513) [*]	–0.30 (–0.71, 0.10) ^{NS}
Eosinophils >300/μL	0.025 (–0.112, 0.161) ^{NS}	0.089 (–0.036, 0.214) ^{NS}	–0.19 (–0.50, 0.13) ^{NS}
Eosinophils ≤300/μL	–0.003 (–0.090, 0.084) ^{NS}	0.040 (–0.049, 0.130) ^{NS}	–0.09 (–0.29, 0.11) ^{NS}
Eosinophils >150/μL	0.007 (–0.085, 0.099) ^{NS}	0.052 (–0.041, 0.145) ^{NS}	–0.19 (–0.37, –0.01) [*]
Eosinophils ≤150/μL	–0.021 (–0.116, 0.075) ^{NS}	0.053 (–0.040, 0.147) ^{NS}	0.08 (–0.31, 0.46) ^{NS}
IgE > median	0.057 (–0.051, 0.166) ^{NS}	0.093 (–0.015, 0.201) ^{NS}	–0.26 (–0.51, –0.01) ^{NS}
IgE ≤ median	–0.046 (–0.151, 0.060) ^{NS}	0.043 (–0.073, 0.159) ^{NS}	0.07 (–0.17, 0.32) ^{NS}
High IgE + Eos. >300/μL	0.063 (–0.138, 0.264) ^{NS}	0.133 (0.017, 0.249) [*]	0.03 (–0.49, 0.56) ^{NS}
FeNO > median	0.087 (–0.035, 0.209) ^{NS}	0.188 (0.053, 0.322) [*]	–0.30 (–0.58, –0.01) [*]
FeNO ≤ median	–0.064 (–0.159, 0.030) ^{NS}	–0.051 (–0.150, 0.048) ^{NS}	0.05 (–0.16, 0.26) ^{NS}
FEV ₁ (% predicted) < 70% excl. IA1	0.269 (0.126, 0.412) [*]	0.258 (0.107, 0.408) [*]	–0.60 (–0.97, –0.23) [*]

*P < 0.05; **P < 0.001; NS, not significant.

FEV₁, forced expiratory volume in 1 s; AUC, area under the curve; ACQ7, asthma control questionnaire derived from 7 questions; Eos, eosinophil; FeNO, Fractional exhaled nitric oxide; ppb, parts per billion; IA1, first interim analysis.^a Subgroups were defined according to baseline values. Total population median IgE = 166 mg/L; Total population median FeNO = 32 ppb; High IgE = IgE > median (166 mg/L).**Fig. 3.** Improvement in mean trough FEV₁ classified per baseline predicted FEV₁ subgroups. Data are least square means ± 90% confidence intervals. Numbers shown represent patient number per treatment group. *P < 0.05; **P < 0.01; ***P < 0.0001; NS, not significant for QAW039 vs. placebo.

Patients treated with QAW039 whose baseline FEV₁ (% predicted) was <70% showed a clinically and statistically meaningful improvement compared with placebo (Δ = 207 mL, 90% CI: 96, 319 mL; P = 0.002) (Table 5) (Fig. 3). Over the 29 days period, a difference between placebo and QAW039 was observed at Day 14, and was maintained until Day 29 (Fig. 4).

A sensitivity analysis was carried out to determine if the subgroup results seen at the first interim analysis (IA1) could be replicated without including the IA1 patients. The improvement observed in the subgroup IA1 was statistically and clinically meaningful compared with placebo (Δ = 269 mL, 90% CI: 126,

412 mL, P = 0.002). Patients treated with QAW039 who had a FEV₁ (% predicted) < 68.7% (lower tertile of FEV₁% predicted) had a statistically significant improvement in trough FEV₁ when compared with placebo (Δ = 276 mL, 90% CI: 154, 398 mL; P < 0.001) (Fig. 3). The treatment effect of QAW039 on trough FEV₁ was reduced with a decrease in severity as observed for patients with a baseline FEV₁ <75% (Δ = 101 mL, 90% CI: 5, 197 mL; P = 0.04) and FEV₁ <80% (Δ = 56 mL, 90% CI: (–23, 136 mL; P = 0.1) (Fig. 3).

QAW039 demonstrated statistically significant improvement in FEV₁ AUC_{0–24h} in the FEV₁ (% predicted) < 70% analysis set when compared with placebo (Δ = 240 mL, P = 0.002) (Table 5). Similar

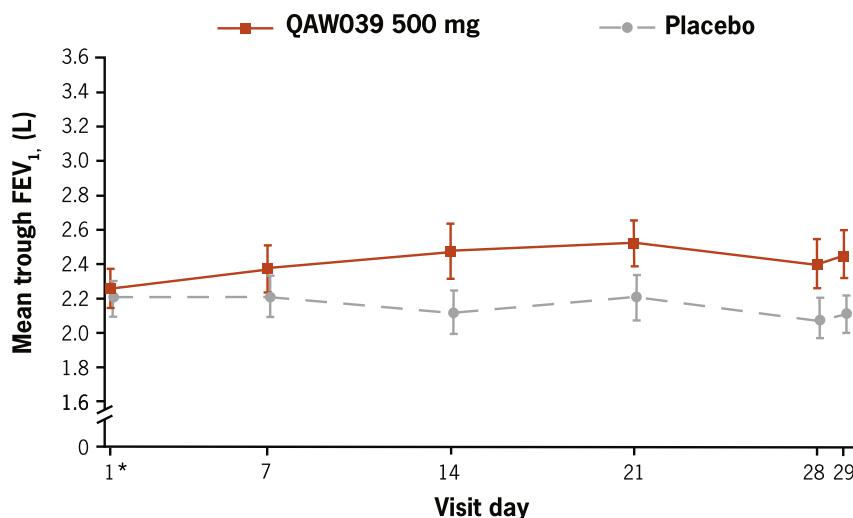


Fig. 4. Trough FEV₁ in patients with a baseline FEV₁ (% predicted) < 70% over 28 days. Data are arithmetic means ± standard errors. *Baseline is defined as the average of the –45 min and pre-dose measurements on days 1. QAW039 (n = 24) and placebo (n = 30) at Day 29.

results were observed in patients within the analysis sets IgE high + eosinophils >300/μL ($\Delta = 133$ mL, $P = 0.03$) and FeNO > median ($\Delta = 188$ mL, $P = 0.01$) (Table 5).

No differences were observed in FeNO in the patient population with baseline FEV₁ (% predicted) < 70% (Data in Brief, Table 3). However, serum IgE levels showed a statistical difference between QAW039-treated patients and placebo treated patients at Day 14 in this subgroup (Data in Brief, Table 4).

As with the analysis of FEV₁, the largest improvement in ACQ7 (negative treatment difference) was observed in the analysis sets with low baseline FEV₁ (% predicted) (Table 5). The analysis set of patients with a baseline FEV₁ (% predicted) < 70% analysis receiving QAW039 demonstrated an improvement in ACQ total score that started on Day 7 after, continued to Day 21 and was maintained to Day 28 ($\Delta = -0.41$, $P = 0.009$) (Table 5 and Fig. 5). When compared with placebo, most of the improvement was observed on Day 7, with no further improvement over the rest of the study period (Fig. 5). Statistically significant improvements with QAW039 compared with placebo at Day 28 were also observed in FeNO > median analysis set ($\Delta = -0.30$, $P = 0.04$) (Table 5).

3.5. Safety

A total of 54 (32%) patients experienced at least one adverse event (AE), with the incidence of adverse events slightly higher with the QAW039 (35%) than with the placebo (28%) (Table 6). Headache was the most common AE experienced by patients who received QAW039 (11%), which was comparable to the rate reported by patients in the placebo treatment arm (10%). Other AEs had an incidence rate below 4% (Table 6). No deaths and no SAEs were reported in this study.

4. Discussion

In this study, QAW039, a once daily CRTh2 antagonist, was compared with a placebo in patients with mild-to-moderate uncontrolled allergic asthma. Analysis of the primary endpoint, trough FEV₁, demonstrated no difference between QAW039 and placebo. Similarly, analysis of key secondary endpoints, FEV₁AUC_{0–24h} and ACQ7, showed no difference between QAW039 and placebo. Additional subgroup analysis, defined at the first

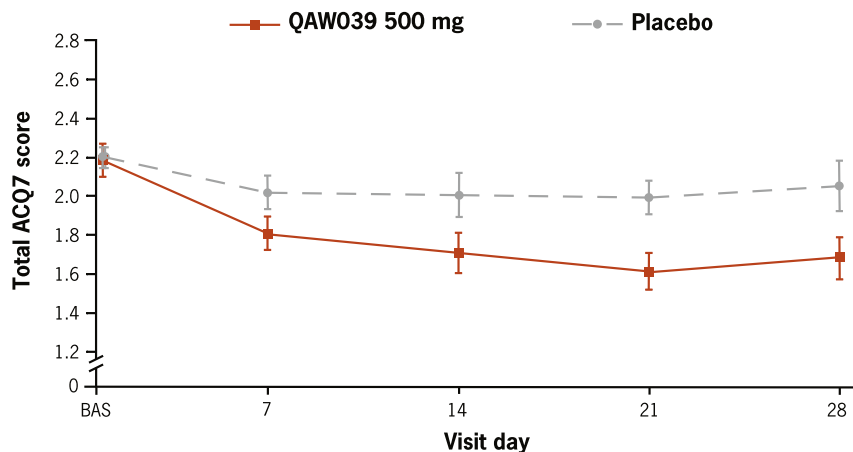


Fig. 5. ACQ7 score for patients with a baseline FEV₁ (% predicted) < 70% over 28 days. Data are arithmetic means ± standard errors. BAS, Baseline.

Table 6

Number (%) of adverse events, serious adverse events (Safety analysis set).

	QAW039 (n = 82)	Placebo (n = 88)
Patients with at least one AE, n (%)	29 (35)	25 (28)
Any AE in ≥ 2% of any group (Preferred Term), n (%)		
Headache	9 (11)	9 (10)
Somnolence	3 (4)	2 (2)
Vomiting	3 (4)	1 (1)
Bradycardia	2 (2)	1 (1)
Fatigue	2 (2)	1 (1)
Blood creatine phosphokinase increased	2 (2)	1 (1)
Lipase increased	2 (2)	0
Diarrhea	2 (2)	0
Muscle spasms	2 (2)	0
Worsening of allergic rhinitis	2 (2)	0
Back pain	1 (1)	2 (2)
SAEs, n (%)	0	0
Deaths, n (%)	0	0

AE, adverse events; SAE, serious adverse events.

interim analysis, demonstrated that patients with a low FEV₁ (% predicted) had statistically significant improvement in trough FEV₁ and FEV₁AUC_{0–24h} when compared with placebo. Finally, statistically significant improvement in ACQ7 at Day 28 between QAW039 and placebo was observed in patients with baseline FEV₁ (% predicted) < 70%, suggesting that this subgroup of asthma patients could benefit from treatment with QAW039.

Current asthma maintenance controller medicines consist of ICS and LABA bronchodilators [2]. There is some evidence that there are issues with patients adhering to inhaled medications [27], and side effects have been reported with ICS, when administered in high doses for an extended period of time [28]. Ultimately, there is an unmet need to develop novel therapies that can improve outcomes for patients with asthma (improved efficacy and better control of disease). Development of CRTh2 antagonists, like QAW039, offers huge potential for the treatment of asthma due to these molecules targeting a key inflammatory pathway. Previously, QAW039 has been reported to modulate key immune cells associated with asthma [23]. Clinical studies involving the use of other CRTh2 antagonists have reported varied results [29–31]. Examining the effect of QAW039 once daily in the overall study population demonstrated that QAW039 had no significant effect on the primary endpoint, trough FEV₁, or on the other secondary endpoints (FEV₁AUC_{0–24h} and ACQ7). PK evaluation of QAW039 demonstrated similar results to those observed previously [22], whereby peak concentrations were reached around 1 h post dose, with modest accumulation in plasma after repeat dosing. A post hoc analysis was carried out to further determine if certain subgroups of patients demonstrated a clinical and statistical significant response to QAW039. Subgroup analyses can identify treatment effect when there is heterogeneity in disease, but caution is needed when interpreting the subsequent results [32]. This analysis suggested that there are certain cohorts of asthma patients who may benefit from once daily administration of QAW039. It was observed that patients with a baseline FEV₁ (% predicted) < 70% and treated with QAW039 had a significant improvement of 207 mL in trough FEV₁ over patients treated with placebo ($P = 0.002$). This result was larger than the protocol-defined clinically relevant effect of 150 mL. QAW039 also resulted in significant increases in FEV₁ AUC_{0–24h} when compared with placebo in patients with a baseline FEV₁ (% predicted) < 70%.

Uncontrolled asthma represents a major problem to many asthma patients [33,34]. Asthma control can be ascertained using standardized questionnaires like ACQ7. Previous studies have had varied results regarding the impact that CRTh2 antagonists had on asthma control [29–31]. The subgroup analysis in this study

suggested that the improvement in lung function also translated into improved asthma control. A difference in ACQ7 at Day 28 between QAW039 and placebo of –0.41 was observed in patients with a baseline FEV₁ (% predicted) < 70% ($P = 0.009$). Similar improvements in ACQ7 were reported in uncontrolled patients with eosinophilic asthma [24].

The evolution of CRTh2 antagonists as a viable treatment option for asthma is occurring, with more potent drugs such as once daily oral tablets emerging, of which QAW039 is an example. While some CRTh2 antagonists have been discontinued due to mixed results [19], the data reported here for QAW039 is in line with other previously published data on other CRTh2 antagonists, which have demonstrated clinical efficacy [29,31,35,36]. Recently there has been a direct in vitro comparison of QAW039 with another CRTh2 antagonist, OC000459 [37]. In this study, it was observed that OC000459 dissociated thirty times faster from the CRTh2 receptor. This could equate to over fifty percent of OC000459 being displaced from the CRTh2 receptor, in the time it takes for eosinophils to pass through the asthmatic lung. In direct contrast, less than 1.2% of QAW039 would likely become displaced during the same time frame. Such differences in the properties of CRTh2 antagonists may account for differences observed for clinical efficacy. Regarding the target population of asthmatics for the CRTh2 antagonist, previously with OC000459, it has been observed that different subgroups may be responsive [35]. So far, the FEV₁ subgroup identified in this study has not been previously described. Based on the data presented here, and the strong mechanistic data from another phase 2 study [38], we think the more severe asthma patients would benefit the most from QAW039. While not observed in this study, QAW039 impact on eosinophilic inflammation has been documented. A recent study in patients with severe and eosinophilic asthma with a sputum eosinophil count ≥ 2% at baseline, has shown that QAW039 induced a fall in sputum eosinophils of 71% after 12 weeks of treatment [38]. Taken together, these data may suggest that asthma patients with more severe disease, in which eosinophils play key role might have better outcomes with QAW039 treatment. Further investigation is required to establish and confirm the findings of this and other studies, and to determine if the strong reduction in sputum eosinophils translates into clinical efficacy in patients with severe eosinophilic asthma. Regarding QAW039 impact on current treatment pillars in asthma, such as ICS, there is no published data on comparing these two treatments. However, QAW039 thus far has shown to lack the side effects associated with ICS, while also being an oral convenient (once daily) drug.

QAW039 demonstrated a good safety profile, with the overall

incidence of AEs comparable to placebo. Most AEs reported were mild or moderate, not related to the study drug, and resolved during the study. No SAEs and no deaths were observed.

There are limitations to this study that have to be acknowledged. First, the primary and secondary endpoints were not met when analyzed in the total population. A subgroup analysis suggested that some patients may benefit from QAW039. Several subgroup analyses were conducted (Table 1), and hence results must be interpreted with caution. There was no comparison with an active comparator like montekulast or ICS. The duration of the study provides limited safety data. Restricting the inclusion to more severe asthma patients might have resulted in a greater difference between QAW039 and placebo. Finally, we did not analyze additional biomarkers (e.g. soluble blood markers or cellular markers) in this study.

5. Conclusions

QAW039 is safe and well tolerated in patients with mild-to-moderate uncontrolled allergic asthma. Post hoc analysis suggests that patients with FEV₁ (% predicted) < 70% might benefit from once daily QAW039. Further studies are required to determine and confirm these observations reported here.

Acknowledgments

The authors also acknowledge all clinical investigators and study coordinators at the participating centers and all subjects who participated in the study. This work was funded by Novartis Pharma AG, Basel, Switzerland. The authors would also like to acknowledge the contributions of David Bergin and Danielle Corbett, Expert Scientific Writers at Novartis, for providing writing and editorial assistance (funded by Novartis). This manuscript is dedicated to the memory of Dr Sheldon Spector.

List of abbreviations

ACQ	Asthma control questionnaire
AEs	adverse events
AUC	area under the effect curve
BMI	body mass index
CI	Confidence interval
CRTh2	chemoattractant receptor-homologous molecule expressed on Th2 cells
CV	coefficient of variation
DP ₁	PGD ₂ receptor 1
DP ₂	PGD ₂ receptor 2
FeNO	Fractional exhaled nitric oxide
FEV ₁	forced expiratory volume in 1 s
FVC	forced vital capacity
IA1	first interim analysis
ICS	inhaled corticosteroids
LABA	long-acting β -agonists
LAMA	long-acting muscarinic antagonist
PEFR	peak expiratory flow rate
PD	pharmacodynamics
PK	pharmacokinetics
PGD ₂	Prostaglandin D2
SAEs	serious adverse events
SD	standard deviation

Competing interests

This trial was funded by Novartis Pharma AG, Basel Switzerland. VJE, BM and MW are employees of Novartis. TAP has nothing to

declare. DM has nothing to declare. SFW reports grants from Novartis, grants from Pulmagen, grants from Teva, grants from GlaxoSmithKline, grants from Asta-Zeneca, grants from Mylan, grants from Roxane. SS reports stock and mutual funds in GlaxoSmithKline and Merck; has received grant support from TKL, Perrigo, Targacept, Genentech, Novartis, Sanofi-Aventis, AstraZeneca, GlaxoSmithKline, Amgen, Merck, Boehringer Ingelheim, and Sunovion; and is a speaker/moderator for the American College of Allergy, Asthma, and Immunology. WO reports that she was an employee of Novartis Pharmaceuticals, Horsham, United Kingdom at the time of this study and is currently an employee of Takeda Development Center Europe, London, United Kingdom. PG reports he was an employee of Novartis Pharmaceuticals, Horsham, United Kingdom at the time of this study and is currently an employee of Takeda Pharmaceuticals Europe, London, United Kingdom. JB reports advisory board, lecture fees, compensation for conduct of clinical trials paid to insaf Respiratory Research Institute from Almirall Hermal, Novartis and AstraZeneca; compensation for conduct of clinical trials paid to insaf Respiratory Research Institute from TEVA, Mundipharma, Sterna AG, Boehringer Ingelheim and GSK; and advisory board and/or lecture fees from Berlin Chemie, Mennarini, Pohl Boskamp.

Author contribution

TAP, DM, SFW, SS and JB were study investigators. VJE, TAP, DM, SFW, SS, BM, WO, PG, and JB contributed to the conception and design of the study. BM oversaw the statistical analyses. MW and PG oversaw the pharmacokinetic analyses. All authors contributed to the analysis and interpretation of the data. All authors contributed to the preparation of this manuscript and were involved in the development of the outline, review of all drafts, the final approval, and the decision to submit the manuscript.

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