Sponsor

Novartis

Generic Drug Name

QAV680

Trial Indication(s)

Asthma

Protocol Number

CQAV680A2201

Protocol Title

A randomized, double-blind, two-way cross-over, proof-of-concept study to compare the efficacy, safety, pharmacokinetics and pharmacodynamics of two-week oral administration of QAV680 versus placebo, with an extended open-label inhaled corticosteroid period, in steroid-free, mild to moderate persistent asthma patients

Clinical Trial Phase

Phase II

Study Start/End Dates

30 Jan 2009 to 07 Oct 2009

Reason for Termination (If applicable)

Not Applicable

Study Design/Methodology

This was a multi centre, randomized, double-blind, placebo controlled, three period two-way cross-over study in symptomatic persistent steroid free asthma patients. Forty patients were to be randomized to one of two sequences relating to the first two treatment periods. In these periods patient received either QAV680 followed by placebo or placebo followed by QAV680 double-blinded. All patients received open-label inhaled fluticasone propionate Flutide miteTM (or equivalent oral dry powder inhalation) in the third period. Fluticasone propionate was used to validate the effect size of improvement in FEV1 compared to that seen in the literature.

Centers

8 centers in 2 countries: Germany (4) and India (4)

Objectives:

Primary objective:

- To assess the efficacy as measured by FEV1 change and safety of two-week administration of QAV680 (500 mg b.i.d. over 14 days) compared to placebo in mild to moderate persistent steroid free asthma patients.

Secondary objective:

- To assess the pharmacokinetics of multiple doses of QAV680 in asthma patients.
- To assess the pharmacodynamic effect of multiple doses of QAV680 on exhaled NO in asthma patients.
- To assess the effect of QAV680 on asthma control using assessments such as Asthma Control Questionnaire (ACQ) score, FEV1 variability data captured by PIKO-1 home monitoring device and the extent of inhaled salbutamol use as rescue medication

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

Subjects received QAV680 100 mg capsules for oral administration at a dose of 500 mg twice a day (b.i.d).

Statistical Methods

The main statistical analyses were restricted to the first two treatment periods (placebo and QAV680). Baseline FEV1 was defined as the average of the -45 and -15 min pre-dose measurements on day 1 of each period. Trough FEV1 was analyzed with an analysis-of-covariance model including treatment, sequence and period as fixed factors, baseline FEV1 as a covariate, and subject as a random effect. The mean trough FEV1 difference between QAV680 and placebo was estimated with a 90% confidence interval. An interim analysis was planned to be conducted when at least 24 patients had completed the first two treatment periods. This analysis was performed based on the analysis of FEV1, exhaled NO and salbutamol use and the methods used were identical to the main analyses. No changes were made to the study as a result of the interim analyses.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Male and female asthma patients aged between 18 and 55 years inclusive, who were diagnosed with symptomatic mild to moderate persistent asthma at least 6 months prior to the study start-defined by the NHLBI-Guidelines for the diagnosis and management of asthma (2002). These patients had to be steroid naive or off steroids and chromoglycate for at least 28 days prior to the study so that steroids did not mask any possible efficacious effects of the study drug.
- Patients weighed at least 45 kg to participate in the study, and had a body mass index (BMI) of >20 and ≤ 30 kg/m^2
- Participants in the study had to ensure that they could not become pregnant (for females) or that they did not father a child during the study.
- Study population to be in reasonably good health other than the diagnosis of asthma for this first study in patients with this indication.

Exclusion criteria:

- Smokers and patients with a history of drug or alcohol abuse within the 12 months prior to dosing were excluded from the study.
- No medications or dietary/food supplements were allowed, with the exception of paracetamol or short acting inhaled beta-agonists and stable use of medications for concomitant conditions such as hypertension, diabetes or hormone replacement therapy, but any patient requiring systemic corticosteroids for diseases other than asthma were excluded.

- Participation in any clinical investigation within four (4) weeks prior to initial dosing excluded patients from participating in the study.
- Patients with a recent history of life threatening asthma, a respiratory tract infection and/or exacerbation of asthma within 4 weeks prior to the first dose of study medication, or with other serious underlying diseases were excluded.
- Excluded patients included those with a history of clinically significant ECG abnormalities, recent and/or recurrent autonomic dysfunction, recent blood donation or blood loss of 400 ml or more, helminthic, ova or parasitic infections, significant illness within two weeks prior to initial dosing or history of allergies to drugs or to the study medication.
- Any surgical or medical condition which could significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which could jeopardize the subject in case of participation in the study was considered a reason for exclusion from the study.
- The patient should not have had evidence of impaired renal function or liver disease or liver injury as indicated by abnormal liver function tests (LFTs).
- Subjects with immunodeficiency diseases including a positive (HIV) or a positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result were excluded.
- Allergic disorders, pancreatic disease.
- Surgical and/or medical conditions which significantly effect ADME of the drug.
- Prior use of asthma medications (except SABA's) prior to 2 weeks of dosing.

Participant Flow Table

Patient disposition – n (%) of patients (Safety analysis set)

	QAV680/ placebo	Placebo/ QAV680	All patients
Patients			
Randomized	19 (100%)	21 (100%)	40 (100.0%)
Completed	15 (79%)	18 (86%)	33 (82.5%)
Discontinued	4 (21%)	3 (14%)	7 (17.5%)
Main cause of discontinuation			
Adverse event	0	1 (5%)	1 (2.5%)
Abnormal laboratory value	2 (11%)	0	2 (5.0%)
Subject withdrew consent	0	1 (5%)	1 (2.5%)
Lost to follow-up	2 (11%)	0	2 (5.0%)
Protocol deviation	0	1 (5%)	1 (2.5%)

Baseline Characteristics

Demographic and baseline data summary for all patients (safety analysis set)

		All randomized patients N=40
Age (years)	Mean (SD)	34 (8.9)
	Range	21 - 64
Gender - n(%)	Male	37 (92.5%)
	Female	3 (7.5%)
Race - n(%)	Caucasian	29 (72.5%)
	Black	1 (2.5%)
	Asian	10 (25.0%)
Weight (kg)	Mean (SD)	76.5 (13.45)
	Range	48.5 – 107.4
Height (cm)	Mean (SD)	177 (9.8)
	Range	159 - 200

Summary of Efficacy

Primary Outcome Result(s)

Summary of the statistical analysis of trough FEV1 on Day 15 (PD analysis set)

Analysis	Treatment	N	LS mean	90% CI	Contrast to Placebo* LS mean (90% CI)	P-value
Period 1 and 2 only	Placebo	37	3.31	3.22, 3.41		
	QAV680	38	3.26	3.17, 3.36	-0.05 (-0.18, 0.08)	0.51
Comparison with +ve control	Placebo	37	3.28	3.19, 3.38		
	FP	35	3.32	3.22, 3.42	0.04 (-0.10, 0.18)	0.67

LS = least squares. FP = fluticasone propionate, * adjusted for baseline covariate

For safety results please refer to the safety section.

Secondary Outcome Result(s)

Summary statistics of the plasma PK parameters for QAV680 on days 1 and 14 (PK analysis set)

Study Day		Tmax (hr)	Cmax (µg/mL)	Tlast (hr)	Clast (µg/mL)	AUCtau (hr.µg/mL)	Cav (µg/mL)	FL (%)	Rac (Cmax)	Rac (AUCtau)
1(n=37)**	Mean	-	6.11	11.8	0.0448	13.7	NA	NA	NA	NA
	SD	-	3.13	0.662	0.0264	8.73	NA	NA	NA	NA
	CV%	-	51.2	5.6	59.0	63.6	NA	NA	NA	NA
	Median	1.00	5.48	12.0	0.0370	10.5	NA	NA	NA	NA
	Range	0.50, 3.00	1.16, 15.3	8.00, 12.0	0.0142, 0.146	3.63, 41.2	NA	NA	NA	NA
14 (n=38)	Mean	-	5.96	NR	0.0789	13.7	1.14	531	1.29*	1.19*
	SD	-	2.79	NR	0.039	6.95	0.580	128	1.16	0.699
	CV%	-	46.8	NR	49.6	50.7	50.7	24.0	89.6	58.7
	Median	1.02	5.48	NR	0.0678	12.3	1.02	513	0.980	1.13
	Range	0.25, 3.02	1.74, 15.0	NR	0.0237,0.206	4.61,40.5	0.384, 3.37	279, 906	0.412, 6.25+	0.486, 4.64+

NR – Not reported, * only calculated for the 37 patients with both day 1 and day 14 data

**One patient's parameter values were excluded from inferential statistics due to very low QAV680 exposure on Day 1 (QAV680 Cmax 0.0557 µg/mL)
+ One Paitent's QAV680 AUCtau Day 1 was low (3.63 hr.µg/mL) compared to Day 14 (16.8 hr.µg/mL)

Statistical analysis of exhaled NO (ppb), PD analysis set.

Scheduled visit	N	Geometric Lsmean (90% CI) QAV680	N	Geometric Lsmean (90% CI) Placebo	Ratio of Geometric Lsmeans (90% CI) QAV680:Placebo	P-value
DAY7	37	26.59 (23.96, 29.51)	35	30.25 (27.20, 33.65)	0.88 (0.76, 1.02)	0.154
DAY15	38	31.03 (27.98, 34.41)	37	31.61 (28.48, 35.08)	0.98 (0.85, 1.14)	0.835

N is the number of subjects used in the analysis at each timepoint. Data were analyzed using a repeated measures ANCOVA model with period, day and treatment as fixed effects, the period by day and treatment by day interaction terms, pre-dose eNO on Day 1 as a covariate and subject and subject by period as random effects.

Statistical analysis of the standard deviation of FEV1 (L) from pikometry measurements over the 14 days of treatment, PD analysis set

Lsmean (90% CI)				Difference between Lsmeans (90% CI)	
N	QAV680	N	Placebo	QAV680-Placebo	P-value
38	0.31 (0.25, 0.37)	37	0.29 (0.23, 0.35)	0.02 (-0.05, 0.09)	0.559

N is the number of subjects used in the analysis at each timepoint. Data were analyzed using an ANOVA model including treatment, period and sequence as fixed effects, and subject as a random effect

Statistical analysis of cumulative salbutamol use, PD Analysis Set

Geometric Lsmean total number of puffs (90% CI)				Ratio (90% CI)	
N	QAV680	N	Placebo	QAV680:Placebo	P-value
38	1.93 (0.91, 4.11)	39	2.33 (1.27, 4.29)	0.83 (0.43, 1.60)	0.632

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 period and treatment and a random subject effect

Statistical analysis of the total score from the asthma control questionnaire (ACQ), PD Analysis Set

Scheduled visit	N	Lsmean (90% CI) QAV680	N	Lsmean (90% CI) Placebo	Difference of Lsmeans (90% CI) QAV680 - Placebo	P-value
DAY7	38	0.83 (0.70, 0.96)	38	0.88 (0.75, 1.01)	-0.05 (-0.21, 0.11)	0.597
DAY14	37	0.91 (0.78, 1.04)	37	0.82 (0.70, 0.95)	0.09 (-0.07, 0.25)	0.367

N is the number of subjects used in the analysis at each timepoint Data were analyzed using a repeated measures ANCOVA model with period, day and treatment as fixed effects, the period by day and treatment by day interaction terms, pre-dose total questionnaire score on Day 1 as a covariate and subject and subject by period as random effects.

Summary of Safety

Safety Results

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

	QAV680 500 mg N=38 n (%)	Placebo N=39 n (%)	FP N=35 n (%)
Subjects with AE(s)	18 (47.4)	15 (38.5)	11 (31.4)
System organ class			
Nervous system disorders	11 (28.9)	6 (15.4)	6 (17.1)
Infections and infestations	4 (10.5)	3 (7.7)	2 (5.7)
General disorders and administration site conditions	1 (2.6)	5 (12.8)	1 (2.9)
Gastrointestinal disorders	3 (7.9)	1 (2.6)	1 (2.9)
Injury, poisoning and procedural complications	1 (2.6)	1 (2.6)	2 (5.7)
Respiratory, thoracic and mediastinal disorders	2 (5.3)	1 (2.6)	1 (2.9)
Investigations	1 (2.6)	2 (5.1)	0
Eye disorders	1 (2.6)	0	1 (2.9)
Ear and labyrinth disorders	1 (2.6)	0	0
Musculoskeletal and connective tissue disorders	0	0	1 (2.9)

FP Fluticasone propionate

Incidence of AEs by preferred term (frequency 2 or more in any group) (Safety analysis set)

	QAV680 500 mg N=38 n (%)	Placebo N=39 n (%)	FP N=35 n (%)
Subjects with AE(s)	18 (47.4)	15 (38.5)	11 (31.4)
Preferred term			
Headache	10 (26.3)	6 (15.4)	5 (14.3)
Nasopharyngitis	2 (5.3)	2 (5.1)	2 (5.7)
Dizziness	1 (2.6)	1 (2.6)	2 (5.7)
Diarrhoea	2 (5.3)	1 (2.6)	0
Fatigue	1 (2.6)	2 (5.1)	0
Pain	0	3 (7.7)	0
Nasal congestion	2 (5.3)	0	0
Vomiting	2 (5.3)	0	0

FP Fluticasone propionate

Serious Adverse Events by System Organ Class

One patient experienced an abscess of pilonidal cyst (System organ class: infections and infestations) which was first reported on day 56 of the study when the patient was receiving placebo. The event was of moderate severity but not suspected to be related to the study drug. The patient was hospitalized for surgical intervention but not withdrawn from the study.

Other Relevant Findings

Not applicable

Date of Clinical Trial Report

31 Mar 2011