NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Fevipiprant

Trial Indication(s)

Uncontrolled asthma

Protocol Number

CQAW039A2316

Protocol Title

A 12-week, multicenter, randomized, double-blind,
placebo-controlled study to assess the efficacy and safety of QAW039 when added to standard-of-care asthma therapy in patients with uncontrolled asthma

Clinical Trial Phase

Phase 3

Phase of Drug Development

III

Study Start/End Dates

Study Start Date: November 2017 (Actual)
Primary Completion Date: July 2019 (Actual)
Study Completion Date: July 2019 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This study used a randomized, multicenter, double-blind, placebo-controlled, parallel-group design, in which QAW039 150 mg or placebo were added to incoming standard-of-care asthma therapy. After a 1-week placebo run-in period, patients were randomized 1:1 to receive QAW039 150 mg or placebo in a 12-week treatment period. The target population represents a subset of patients with moderate asthma according to GINA 2016

Centers

111 centers in 10 countries: Slovakia (Slovak Republic)(7), Hungary(6), Germany(15), Argentina(21), United States(42), Turkey(7), South Africa(5), Saudi Arabia(2), Philippines(4), Mexico(2)

Objectives:

The primary: objective of this study was to demonstrate the efficacy of fevipiprant 150 mg once daily compared with placebo, as measured by change from baseline in pre-dose forced expiratory volume in 1 second (FEV1) at the end of the 12-week active-treatment period.

The secondary: objectives were to demonstrate the efficacy of fevipiprant 150 mg once daily, compared with placebo, on the following:

- daytime asthma symptoms over the 12-week active-treatment period.
- total daily short-acting β-agonist (SABA) use over the 12-week active-treatment period.
- change from baseline in Asthma Quality of Life Questionnaire (AQLQ+12) score at the end of the 12-week active-treatment period.
- Safety with respect to AEs, ECGs, vital signs, and laboratory tests.

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

The investigational treatments were QAW039 150 mg and matching placebo tablets to be taken once daily in the morning without regard to time of food intake.

The investigational treatment (tablets) were supplied in bottles by Novartis to the study sites. The matching placebos for QAW039 were identical in appearance and were identically packaged to their active counterparts.

Statistical Methods

The primary endpoint of the study was the change from baseline in pre-dose FEV1 (L) at the end of 12 weeks of treatment. The primary efficacy variable was analyzed using an analysis of covariance (ANCOVA) model with factors for treatment group, randomization strata [age group (<18 vs. ≥18 years), use or non-use of a second asthma controller medication at study entry, and region], as well as the baseline daytime asthma symptom score, baseline total daily SABA use and baseline pre-dose FEV1 as continuous linear covariates. The least squares mean ("adjusted mean") change from baseline for each treatment group, the difference in the LS mean changes between the two treatment groups, and the two-sided 95% confidence interval along with the p-value for the difference were obtained and combined from the primary analysis model.

The superiority of QAW039 vs placebo was established if the two-sided p-value is less than 0.05 and the 95% confidence intervals lie entirely to the right of 0 L.

The secondary efficacy endpoints were change from baseline in daytime asthma symptom score over 12 weeks of treatment, change from baseline in number of puffs of SABA taken per day over 12 weeks of treatment, and change from baseline in AQLQ+12 score at Week 12. The secondary efficacy endpoints were analyzed using the same ANCOVA model as for the primary endpoint (for the analysis of AQLQ+12 the AQLQ+12 baseline value was additionally included as a covariate).

The tests for the secondary variables were to be performed if statistical significance was achieved in the primary test. The local significance level for each secondary null hypothesis was determined based on the closed testing procedure used to control for the familywise type I error rate.

Missing data after discontinuation of double-blind study treatment was imputed using a jump to reference approach. Intermittent missing data prior to discontinuation of double-blind study treatment was imputed under a missing at random assumption.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
-A diagnosis of asthma (according to GINA 2016) for a period of at least 6 months.
-Treated with medium dose inhaled corticosteroid (ICS), or high dose ICS, or low dose ICS plus long- acting beta agonist (LABA), or low dose ICS plus leukotriene receptor antagonist (LTRA), or medium dose ICS plus LABA for at least 3 months prior to Visit 1 and the doses have been stable for at least 4 weeks prior to Visit 1.
-FEV1 of ≤85% for patients aged ≥18 years. FEV1 of ≤90% for patients aged 12 to <18 years.
-Daytime asthma symptom score (0 to 6 scale) of ≥1 per day during 4 of the last 7 days of the placebo run- in period.

-Total daily SABA use ≥1 puff per day during 4 of the last 7 days of the placebo run-in period.
-Demonstrated reversible airway obstruction.
-Asthma control questionnaire (ACQ) score ≥ 1.5.

Exclusion Criteria:
-Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days, whichever is longer.
-A resting QTcF (Fridericia) ≥450 msec (male) or
≥460 msec (female).
-Pregnant or nursing (lactating) women.
-Serious co-morbidities.
-Patients on >20 mg of simvastatin, > 40 mg of atorvastatin, >40 mg of pravastatin, or >2 mg of pitavastatin.

Other protocol-defined inclusion/exclusion criteria may apply.

Participant Flow Table

Overall Study

	QAW039	Placebo	Total
Arm/Group Description	QAW039 once daily	Placebo once daily	
Started	339	336	675
Completed	334	328	662
Not Completed	5	8	13
Technical Problems	1	0	1
Protocol deviation	0	1	1
Physician Decision	0	1	1
Death	0	1	1
Adverse Event	1	2	3

Subject/Guardian Decision	3	3	6

Baseline Characteristics

	QAW039	Placebo	Total
Arm/Group Description	QAW039 once daily	Placebo once daily	
Number of Participants [units: participants]	339	336	675
Age Continuous (units: Years) Mean ± Standard Deviation			
	48.1±15.15	47.7±15.40	47.9±15.26
Sex: Female, Male (units:) Count of Participants (Not Applicable)			
Female	217	216	433
Male	122	120	242
Race/Ethnicity, Customized (units: Participants)			
Caucasian	274	281	555
Black	18	12	30
Asian	39	34	73
Native American	1	0	1
Pacific Islander	2	0	2
Unknown	0	3	3
Other	5	6	11

Summary of Efficacy

Primary Outcome Result(s)

Change from baseline in pre-dose FEV1 at week 12

(Time Frame: Week 12)

	QAW039	Placebo
Arm/Group Description	QAW039 once daily	Placebo once daily
Number of Participants Analyzed [units: participants]	339	336
Change from baseline in pre-dose FEV1 at week 12 (units: Liters) Least Squares Mean ± Standard Error		
	0.112 ± 0.0167	0.071 ± 0.0169

Statistical Analysis

Groups	QAW039, Placebo
P Value	0.088
Method	ANCOVA

Mean Difference (Net)	0.0238
95 % Confidence Interval 2-Sided	-0.006 to 0.088

Secondary Outcome Result(s)

Change from baseline in daytime asthma symptom score

(Time Frame: 12 weeks)

	QAW039	Placebo
Arm/Group Description	QAW039 once daily	Placebo once daily
Number of Participants Analyzed [units: participants]	339	336
Change from baseline in daytime asthma symptom score (units: Score) Least Squares Mean ± Standard Error		
	-0.56 ± 0.036	-0.51 ± 0.037

Statistical Analysis

Groups	QAW039, Placebo
P Value	0.278
Method	ANCOVA

Mean Difference (Net)	-0.06
95 % Confidence Interval 2-Sided	-0.16 to 0.05

Change from baseline in daily use of SABA

(Time Frame: 12 weeks)

	QAW039	Placebo
Arm/Group Description	QAW039 once daily	Placebo once daily
Number of Participants Analyzed [units: participants]	339	336
Change from baseline in daily use of SABA (units: Number of puffs) Least Squares Mean ± Standard Error	-1.11 ± 0.075	-1.02 ± 0.076

Statistical Analysis

Groups	QAW039, Placebo
P Value	0.429
Method	ANCOVA
Mean Difference (Net)	-0.08
95 % Confidence Interval 2-Sided	-0.30 to 0.13

Change from baseline in Asthma Quality of Life (AQLQ+12) score

(Time Frame: Week 12)

	QAW039	Placebo
Arm/Group Description	QAW039 once daily	Placebo once daily
Number of Participants Analyzed [units: participants]	339	336
Change from baseline in Asthma Quality of Life (AQLQ+12) score (units: units on a scale) Least Squares Mean ± Standard Error		
	0.91 ± 0.048	0.89 ± 0.049

Statistical Analysis

Groups	QAW039, Placebo
P Value	0.777
Method	ANCOVA
Mean Difference (Net)	0.069
95 % Confidence Interval 2-Sided	-0.12 to 0.15

Summary of Safety

Safety Results

All-Cause Mortality

	QAW039 150 mg N = 339	Placebo N = 336
Arm/Group Description	QAW039 150 mg	Placebo
Total participants affected	0 (0.00%)	1 (0.30%)

Serious Adverse Events by System Organ Class

Time Frame	After signing informed consent to 30 days after last dose
Source Vocabulary for Table Default	MedDRA (22.0)
Assessment Type for Table Default	Systematic Assessment

	QAW039 150 mg N = 339	Placebo N = 336
Arm/Group Description	QAW039 150 mg	Placebo
Total participants affected	1 (0.29%)	5 (1.49%)

Infections and infestations		
Upper respiratory tract infection bacterial	0 (0.00%)	1 (0.30%)
Investigations		
Electrocardiogram T wave inversion	0 (0.00%)	1 (0.30%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Astrocytoma	0 (0.00%)	1 (0.30%)
Respiratory, thoracic and mediastinal disorders		
Asthma	1 (0.29%)	2 (0.60%)
Pulmonary embolism	0 (0.00%)	1 (0.30%)

Other Adverse Events by System Organ Class

Time Frame	After signing informed consent to 30 days after last dose
Source Vocabulary for Table Default	MedDRA (22.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	1%

	QAW039 150 mg N = 339	**Placebo N = 336**

Arm/Group Description	QAW039 150 mg	Placebo
Total participants affected	94 (27.73%)	102 (30.36%)
Gastrointestinal disorders		
Diarrhoea	2 (0.59%)	4 (1.19%)
General disorders and administration site conditions		
Fatigue	2 (0.59%)	4 (1.19%)
Infections and infestations		
Acute sinusitis	4 (1.18%)	1 (0.30%)
Bronchitis	12 (3.54%)	10 (2.98%)
Nasopharyngitis	13 (3.83%)	12 (3.57%)
Rhinitis	1 (0.29%)	5 (1.49%)
Upper respiratory tract infection	6 (1.77%)	10 (2.98%)
Upper respiratory tract infection bacterial	5 (1.47%)	5 (1.49%)
Viral upper respiratory tract infection	7 (2.06%)	6 (1.79%)
Investigations		
Blood creatine phosphokinase increased	2 (0.59%)	5 (1.49%)
Musculoskeletal and connective tissue disorders		
Arthralgia	1 (0.29%)	4 (1.19%)

Back pain	4 (1.18%)	4 (1.19%)
Nervous system disorders		
Headache	6 (1.77%)	7 (2.08%)
Respiratory, thoracic and mediastinal disorders		
Asthma	43 (12.68%)	45 (13.39%)
Cough	2 (0.59%)	5 (1.49%)
Nasal congestion	0 (0.00%)	4 (1.19%)
Rhinitis allergic	12 (3.54%)	6 (1.79%)
Vascular disorders		
Hypertension	1 (0.29%)	5 (1.49%)

Other Relevant Findings

Conclusion:

The primary objective of the study was not met: the difference in the change from baseline in pre-dose FEV1 (L) at Week 12 was not statistically significant between QAW039 and placebo.

The changes from baseline in mean daytime asthma symptoms, mean daily SABA use over the 12-week active treatment period, and AQLQ+12 score at Week 12 for QAW039 and placebo were not significantly different.
QAW039 was well tolerated, with a safety profile similar to that of placebo

Date of Clinical Trial Report

18-Dec-2019