



Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Fevipirant

Trial Indication(s)

Uncontrolled asthma

Protocol Number

CQAW039A2317

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

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Study Start Date: October 2017 (Actual)

Primary Completion Date: July 2019 (Actual)

Study Completion Date: August 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

144 centers in 17 countries: United States(47), Korea, Republic of(9), Spain(10), Canada(4), India(6), Israel(5), Sweden(3), Italy(5), Russia(14), Colombia(4), Brazil(8), Vietnam(3), Peru(6), Bulgaria(4), Hungary(7), Germany(8), Tunisia(1)

Objectives:

The primary objective of this study was to demonstrate the efficacy of fevipirant 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 fevipirant 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

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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.

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- 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	352	352	704
FAS	352	350 ^[1]	702
Completed	341	344	685
Not Completed	11	8	19
Protocol Deviation	1	0	1
Physician Decision	1	0	1
Lost to Follow-up	1	0	1
Adverse Event	1	0	1
Technical Problems	0	2	2

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Subject/Guardian Decision	7	6	13
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[1] Two patients in the placebo group were randomized in error and did not receive any study drug; for these patients the reason for discontinuation is given as “technical problems

Baseline Characteristics

	QAW039	Placebo	Total
Arm/Group Description	QAW039 once daily	Placebo once daily	
Number of Participants [units: participants]	352	352	704
Age Continuous (units: Years) Mean ± Standard Deviation	50.4±14.87	50.2±14.39	50.3±14.62
Sex: Female, Male (units:) Count of Participants (Not Applicable)			
Female	216	218	434
Male	136	132	268
Race/Ethnicity, Customized (units: Participants)			
Black	26	18	44
Asian	41	46	87
Native American	12	12	24
Pacific Islander	2	0	2
Other	55	58	113
Caucasian	216	216	432

Summary of Efficacy

Primary Outcome Result(s)

Change from baseline in pre-dose FEV1

(Time Frame: Week 12)

	QAW039	Placebo
Arm/Group Description	QAW039 once daily	Placebo once daily
Number of Participants Analyzed [units: participants]	352	350
Change from baseline in pre-dose FEV1 (units: Liters) Least Squares Mean ± Standard Error	0.126 ± 0.00177	0.157 ± 0.0177

Statistical Analysis

Groups	QAW039, Placebo
P Value	0.214
Method	ANCOVA
Mean Difference (Net)	-0.031

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95
 % Confidence Interval -0.080 to 0.018
 2-Sided

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]	352	350
Change from baseline in daytime asthma symptom score (units: Score) Least Squares Mean ± Standard Error	-0.55 ± 0.034	-0.45 ± 0.034

Statistical Analysis

Groups	QAW039, Placebo
P Value	0.035
Method	ANCOVA
Mean Difference (Net)	-0.10

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0.035
 % Confidence Interval -0.19 to 0.01
 2-Sided

Change from baseline in number of puffs of SABA taken per day
 (Time Frame: 12 weeks)

	QAW039	Placebo
Arm/Group Description	QAW039 once daily	Placebo once daily
Number of Participants Analyzed [units: participants]	352	350
Change from baseline in number of puffs of SABA taken per day (units: Number of puffs) Least Squares Mean ± Standard Error	-0.89 ± 0.066	-0.88 ± 0.066

Statistical Analysis

Groups	QAW039, Placebo
P Value	0.893
Method	ANCOVA
Mean Difference (Net)	0.093

95
 % Confidence Interval -0.20 to 0.17
 2-Sided

Change from baseline in Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12) score
 (Time Frame: Week 12)

	QAW039	Placebo
Arm/Group Description	QAW039 once daily	Placebo once daily
Number of Participants Analyzed [units: participants]	352	350
Change from baseline in Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12) score (units: units on a scale) Least Squares Mean \pm Standard Error	0.77 \pm 0.043	0.72 \pm 0.043

Statistical Analysis

Groups	QAW039, Placebo
P Value	0.448
Method	ANCOVA
Mean Difference (Net)	0.061
95 % Confidence Interval 2-Sided	-0.07 to 0.17

Summary of Safety

Safety Results

All-Cause Mortality

	QAW039 150 mg N = 352	Placebo N = 350
Arm/Group Description	QAW039 150 mg	Placebo
Total participants affected	0 (0.00%)	0 (0.00%)

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 = 352	Placebo N = 350
Arm/Group Description	QAW039 150 mg	Placebo
Total participants affected	7 (1.99%)	3 (0.86%)

Cardiac disorders

Acute myocardial infarction	0 (0.00%)	1 (0.29%)
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Gastrointestinal disorders

Upper gastrointestinal haemorrhage	1 (0.28%)	0 (0.00%)
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General disorders and administration site conditions

Non-cardiac chest pain	0 (0.00%)	1 (0.29%)
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Hepatobiliary disorders

Cholecystitis acute	1 (0.28%)	0 (0.00%)
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Infections and infestations

Cellulitis	1 (0.28%)	0 (0.00%)
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Urinary tract infection	1 (0.28%)	0 (0.00%)
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Injury, poisoning and procedural complications

Femur fracture	1 (0.28%)	0 (0.00%)
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Hip fracture	0 (0.00%)	1 (0.29%)
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Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Prostate cancer	1 (0.28%)	0 (0.00%)
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Respiratory, thoracic and mediastinal disorders

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Asthma 3 (0.85%) 0 (0.00%)

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 = 352	Placebo N = 350
Arm/Group Description	QAW039 150 mg	Placebo
Total participants affected	94 (26.70%)	116 (33.14%)
Infections and infestations		
Bronchitis	9 (2.56%)	6 (1.71%)
Influenza	4 (1.14%)	1 (0.29%)
Nasopharyngitis	10 (2.84%)	24 (6.86%)
Pharyngitis	5 (1.42%)	2 (0.57%)
Respiratory tract infection viral	5 (1.42%)	1 (0.29%)
Upper respiratory tract infection	7 (1.99%)	10 (2.86%)
Upper respiratory tract infection bacterial	3 (0.85%)	6 (1.71%)

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Viral upper respiratory tract infection	12 (3.41%)	8 (2.29%)
Injury, poisoning and procedural complications		
Contusion	0 (0.00%)	5 (1.43%)
Musculoskeletal and connective tissue disorders		
Back pain	7 (1.99%)	7 (2.00%)
Nervous system disorders		
Headache	5 (1.42%)	14 (4.00%)
Respiratory, thoracic and mediastinal disorders		
Asthma	46 (13.07%)	61 (17.43%)
Cough	2 (0.57%)	5 (1.43%)
Dyspnoea	3 (0.85%)	5 (1.43%)
Oropharyngeal pain	6 (1.70%)	4 (1.14%)
Rhinitis allergic	3 (0.85%)	5 (1.43%)
Wheezing	1 (0.28%)	4 (1.14%)

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.



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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

19-Dec-2019