NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Fevipiprant

Trial Indication(s)

Asthma

Protocol Number

CQAW039A2323

Protocol Title

A 52-week, multicenter, randomized, double-blind, double-dummy, parallel-group, placebo-controlled study of fevipiprant once daily plus standard-of-care (SoC) for reduction of systemic corticosteroids (oral and parenteral) use in patients with severe asthma

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase 3

Study Start/End Dates

Study Start Date: December 2018 (Actual)
Primary Completion Date: February 2020 (Actual)
Study Completion Date: February 2020 (Actual)

Reason for Termination (If applicable)

Novartis terminated the study prematurely on 16-Dec-2019. This decision was based on results from completed studies (CQAW039A2307/ CQAW039A2314), which did not support further development of fevipiprant in asthma.

Study Design/Methodology

This was a randomized, multicenter, double-blind, double-dummy, placebo-controlled, parallel-group study to determine the ability of fevipiprant (QAW039) plus standard-of-care (SoC) compared with placebo plus SoC to reduce the use of systemic corticosteroids (SCS) in patients with severe asthma. The study included:

- a Screening period of up to 2 weeks to assess eligibility;
- a Run-in period of 4 or 10 weeks to evaluate maintenance of asthma control and to collect baseline safety data. The Run-in period was 4 weeks for patients coming with high-dose ICS/LABA (inhaled corticosteroids/long-acting beta-agonist) and 10 weeks for patients switching from mid-dose to high-dose ICS/LABA as per protocol during the run-in period;
- a Treatment period of 52 weeks. Upon completion of the Run-in period, all patients who met eligibility criteria were randomized to 1 of 3 treatment groups (fevipiprant 150 mg or 450 mg or placebo once daily) in a ratio 1:1:1. Randomized patients were stratified according to their peripheral blood eosinophil count (< 250 cells/µl or ≥ 250 cells/µl);
- a Follow-up period of 2 weeks following the last dose of study drug to collect additional data for safety variables.

Centers

122 centers in 21 countries: United States(9), Argentina(14), Germany(20), Spain(4), Czech Republic(7), United Kingdom(3), Greece(5), Belgium(4), Slovakia (Slovak Republic)(5), Russia(12), France(4), Hungary(10), Bulgaria(3), Turkey(1), Peru(4), Philippines(4), Colombia(5), Vietnam(3), Thailand(1), South Africa(2), Chile(2)

Objectives:

The primary objective of this study was to determine the efficacy of fevipiprant (150 mg and 450 mg once daily), compared with placebo, as add-on to SoC asthma therapy in terms of reduction in the use of systemic corticosteroids (SCS) over 52 weeks in patients with inadequately controlled severe asthma and high eosinophil counts (≥250 cells/ µl) and in the overall patient population regardless of eosinophil counts.

The secondary objectives were:

- To evaluate the effect of fevipiprant 150 mg and 450 mg and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy in the overall population in terms of:
  - Change from baseline in daytime and nighttime symptom scores
  - Change from baseline in Asthma Control Questionnaire (ACQ-5) total score
  - Change from baseline in Asthma Quality of Life Questionnaire (AQLQ+12) total score
  - Percentage of patients requiring ≥ 7.5 mg systemic corticosteroid dose in mg prednisone/prednisolone or equivalent per day continuously for at least 30 days
  - Percentage of patients with no SCS use
  - Percentage of patients with prescription of biologic therapy
- To evaluate the safety and tolerability of fevipiprant 150 mg and 450 mg and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy in the overall population.

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

Fevipiprant was supplied as tablets at dose strength of 150 mg and 450 mg. Matching fevipiprant placebo was supplied as tablets. The investigational treatment (fevipiprant or placebo) was administered once daily. The planned treatment period of 52 weeks was not completed by any patient due to the early termination of the trial. Patients were treated for a median time of 14 weeks in each group and a maximum of up to 36 weeks.

Since the tablets for fevipiprant 150 mg and 450 mg were not identical, treatment was double-dummy:

- Arm of fevipiprant (QAW039) 150 mg: one tablet of blinded fevipiprant at 150 mg dosage strength given together with one tablet blinded placebo to fevipiprant 450 mg.
- Arm of fevipiprant (QAW039) 450 mg: one tablet of blinded fevipiprant at 450 mg dosage strength given together with one tablet blinded placebo to fevipiprant 150 mg.
- Arm of placebo: one tablet blinded placebo to fevipiprant 150 mg and one tablet blinded placebo to fevipiprant 450 mg.

Statistical Methods

The primary endpoint was the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) over 52 weeks of treatment. The primary endpoint was analyzed in subpopulation of patients with eosinophil count ≥ 250 cells/µl and in overall population. The total systemic corticosteroid dose for 52 weeks was obtained as an annualized SCS dose.

The primary null hypotheses compared each dose, 150 mg and 450 mg fevipiprant, against placebo. The overall study population and the subgroup of patients with eosinophil count ≥ 250 cells/µl were compared separately. These 4 hypotheses were part of the testing procedure.

The familywise type I error rate was controlled at the two-sided 5% level across the primary null hypotheses using graphical approach.

The total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) over 52 weeks of treatment was analyzed using the Wilcoxon-Mann-Whitney rank sum test (Van Elteren test). The overall population analysis was stratified by randomization stratum – blood eosinophils levels (≥ 250 cells/µl and < 250 cells/µl). For the subgroup with blood eosinophils ≥ 250 cells/µl, the analysis did not include the stratification factor.

Due to the early study termination, the secondary endpoints are summarized using descriptive statistics and no imputations were done.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Patients with a diagnosis of asthma for a period of at least 3 months prior to Screening Visit with current asthma severity step 4 or 5 (GINA 2018)
- Currently on treatment with medium or high dose ICS/LABA +/- other controller (i.e.long-acting muscarinic antagonist (LAMA), leukotriene receptor antagonist (LTRA) etc. as per GINA) for a minimum of 6 weeks prior to Screening Visit
- At screening, patients with FEV1 of ≤80% of the predicted normal value for the patient, after withholding bronchodilators at Screening Visit and beginning of Run-In Visit
- An increase of ≥12% and ≥200 ml in FEV1 approximately 10 to 15 minutes after administration of 400 mcg of salbutamol/albuterol prior to randomization (documented historical reversibility was accepted).
- Demonstration of inadequate control of asthma based on an ACQ-5 score ≥1.5 at Screening Visit and Treatment Day 1 Visit
- Documented history of at least 1 asthma exacerbation within 1 year prior to enrollment

Exclusion Criteria:

- Asthma exacerbation, within 6 weeks prior to enrollment (screening) that required SCS, hospitalization, or emergency room visit
- Chronic/maintenance use of oral corticosteroids (OCS) for asthma (total OCS use days greater than 6 months; continuously or intermittently) within the last year
- Prior use of biologics that has potential to interfere/ affect asthma disease progression, in the previous 6 months from run-in period.
- Any contraindications of SCS use e.g. diabetes, narrow angle glaucoma, or any other as defined by the treating physician
- Pregnant or nursing (lactating) women
- Use of other investigational drugs within 5 half-lives of enrollment, or [within 30 days], whichever is longer

Participant Flow Table

Overall Study

	QAW039 150 mg	QAW039 450 mg	Placebo	Total
Arm/Group Description	QAW039 150 mg once daily orally	QAW039 450 mg once daily orally	Placebo to QAW039 once daily orally	
Started	201	201	202	604
Full Analysis Set (FAS)	201	200	201	602
Safety Set (SAF)	201	200	201	602
Completed	0	0	0	0
Not Completed	201	201	202	604
Study terminated by sponsor	197	197	194	588
Protocol deviation	0	2	5	7
Subject decision	1	1	3	5
Adverse Event	1	1	0	2
Death	1	0	0	1
Physician Decision	1	0	0	1

Baseline Characteristics

	QAW039 150 mg	QAW039 450 mg	Placebo	Total
Arm/Group Description	QAW039 150 mg once daily orally	QAW039 450 mg once daily orally	Placebo to QAW039 once daily orally	
Number of Participants [units: participants]	201	201	202	604
Age Continuous (units: years) Mean ± Standard Deviation				
	53.4±12.14	53.0±11.99	52.8±12.81	53.1±12.30
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)				
Female	121	136	125	382
Male	80	65	77	222
Race/Ethnicity, Customized (units: participants) Count of Participants (Not Applicable)				
White	180	176	174	530
Black or African American	2	2	2	6
Asian	10	12	9	31
American Indian or Alaska Native	3	5	13	21
Missing	6	6	4	16

Primary Outcome Result(s)

Total systemic corticosteroid dose in mg prednisone/prednisolone or equivalent over 52 weeks in the overall population

(Time Frame: 52 weeks)

	QAW039 150 mg	QAW039 450 mg	Placebo
Arm/Group Description	QAW039 150 mg once daily orally	QAW039 450 mg once daily orally	Placebo to QAW039 once daily orally
Number of Participants Analyzed [units: participants]	201	200	201
Total systemic corticosteroid dose in mg prednisone/prednisolone or equivalent over 52 weeks in the overall population (units: milligrams (mg)) Mean (Full Range)			
	219.67 (0 to 9241.27)	193.02 (0 to 5184.19)	223.22 (0 to 9552.69)

Statistical Analysis

Groups	QAW039 150 mg, Placebo
P Value	0.714
Method	Wilcoxon (Mann-Whitney)

Statistical Analysis

Groups	QAW039 450 mg, Placebo
P Value	0.734

Method	Wilcoxon (Mann-Whitney)

Total systemic corticosteroid dose in mg prednisone/prednisolone or equivalent over 52 weeks in the subpopulation of patients with high eosinophil count (≥ 250 cells/µl)

(Time Frame: 52 weeks)

	QAW039 150 mg	QAW039 450 mg	Placebo
Arm/Group Description	QAW039 150 mg once daily orally	QAW039 450 mg once daily orally	Placebo to QAW039 once daily orally
Number of Participants Analyzed [units: participants]	127	131	127
Total systemic corticosteroid dose in mg prednisone/prednisolone or equivalent over 52 weeks in the subpopulation of patients with high eosinophil count (≥ 250 cells/µl) (units: milligrams (mg)) Mean (Full Range)			
	210.88 (0 to 5352.80)	185.29 (0 to 5184.19)	212.66 (0 to 9552.69)

Statistical Analysis

Groups	QAW039 150 mg, Placebo
P Value	0.665
Method	Wilcoxon (Mann-Whitney)

Statistical Analysis

Groups	QAW039 450 mg, Placebo
P Value	0.910

Method	Wilcoxon (Mann-Whitney)

Secondary Outcome Result(s)

Change from baseline in daytime symptom scores

(Time Frame: Baseline, up to Week 29-32)

	QAW039 150 mg	QAW039 450 mg	Placebo
Arm/Group Description	QAW039 150 mg once daily orally	QAW039 450 mg once daily orally	Placebo to QAW039 once daily orally
Number of Participants Analyzed [units: participants]	201	200	201
Change from baseline in daytime symptom scores (units: score on scale) Mean ± Standard Deviation			
Week 1-4 (n = 185, 184, 187)	-0.12 ± 0.494	-0.12 ± 0.497	-0.09 ± 0.459
Week 5-8 (n= 162, 155, 159)	-0.21 ± 0.615	-0.25 ± 0.570	-0.17 ± 0.561
Week 9-12 (n= 134, 133, 136)	-0.29 ± 0.632	-0.36 ± 0.588	-0.17 ± 0.605
Week 13-16 (n= 98, 96, 95)	-0.32 ± 0.644	-0.37 ± 0.653	-0.17 ± 0.629
Week 17-20 (n= 67, 68, 69)	-0.30 ± 0.570	-0.35 ± 0.759	-0.12 ± 0.622
Week 21-24 (n= 41, 34, 39)	-0.31 ± 0.536	-0.49 ± 0.760	-0.07 ± 0.688
Week 25-28 (n= 19, 17, 20)	-0.13 ± 0.519	-0.65 ± 0.751	-0.14 ± 0.726
Week 29-32 (n= 6, 4, 9)	-0.54 ± 0.546	-0.83 ± 1.072	-0.20 ± 0.887

Change from baseline in nighttime symptom scores

(Time Frame: Baseline, up to Week 29-32)

	QAW039 150 mg	QAW039 450 mg	Placebo
Arm/Group Description	QAW039 150 mg once daily orally	QAW039 450 mg once daily orally	Placebo to QAW039 once daily orally
Number of Participants Analyzed [units: participants]	201	200	201
Change from baseline in nighttime symptom scores (units: score on scale) Mean ± Standard Deviation			
Week 1-4 (n= 185, 185, 188)	-0.08 ± 0.267	-0.05 ± 0.281	-0.07 ± 0.253
Week 5-8 (n= 163, 156, 159)	-0.11 ± 0.313	-0.12 ± 0.314	-0.13 ± 0.322
Week 9-12 (n= 136, 132, 135)	-0.15 ± 0.317	-0.19 ± 0.369	-0.12 ± 0.379
Week 13-16 (n= 101, 100, 96)	-0.19 ± 0.328	-0.18 ± 0.360	-0.12 ± 0.364
Week 17-20 (n= 70, 69, 69)	-0.21 ± 0.355	-0.18 ± 0.397	-0.17 ± 0.424
Week 21-24 (n= 43, 37, 41)	-0.17 ± 0.284	-0.16 ± 0.323	-0.14 ± 0.311
Week 25-28 (n= 20, 16, 20)	-0.17 ± 0.311	-0.29 ± 0.355	-0.15 ± 0.467
Week 29-32 (n= 8, 6, 9)	-0.12 ± 0.176	-0.46 ± 0.505	-0.24 ± 0.540

Change from baseline in ACQ-5 total score up to end of treatment visit

(Time Frame: Baseline, up to Week 28)

	QAW039 150 mg	QAW039 450 mg	Placebo
Arm/Group Description	QAW039 150 mg once daily orally	QAW039 450 mg once daily orally	Placebo to QAW039 once daily orally

Number of Participants Analyzed [units: participants]	201	200	201
Change from baseline in ACQ-5 total score up to end of treatment visit (units: score on scale) Mean ± Standard Deviation			
Week 6 (n= 166, 158, 160)	-0.74 ± 0.852	-0.94 ± 0.870	-0.85 ± 0.926
Week 12 (n= 120, 119, 119)	-0.97 ± 0.948	-1.11 ± 0.904	-1.05 ± 0.884
Week 20 (n= 60, 58, 53)	-1.08 ± 0.967	-1.13 ± 1.075	-1.22 ± 0.900
Week 28 (n= 19, 13, 15)	-1.14 ± 0.943	-1.52 ± 1.079	-1.15 ± 1.150

Change from baseline in AQLQ+12 total score up to end of treatment visit

(Time Frame: Baseline, up to Week 28)

	QAW039 150 mg	QAW039 450 mg	Placebo
Arm/Group Description	QAW039 150 mg once daily orally	QAW039 450 mg once daily orally	Placebo to QAW039 once daily orally
Number of Participants Analyzed [units: participants]	201	200	201
Change from baseline in AQLQ+12 total score up to end of treatment visit (units: score on scale) Mean ± Standard Deviation			
Week 6 (n= 166, 159, 162)	0.43 ± 0.757	0.43 ± 0.762	0.40 ± 0.854
Week 12 (n= 120, 119, 120)	0.55 ± 0.884	0.60 ± 0.876	0.52 ± 0.833
Week 20 (n= 60, 58, 53)	0.64 ± 0.903	0.67 ± 0.883	0.60 ± 0.867
Week 28 (n= 19, 13, 15)	0.43 ± 0.662	1.03 ± 1.178	0.55 ± 1.053

Percentage of patients requiring ≥ 7.5 mg systemic corticosteroid dose in mg prednisone/prednisolone or equivalent per day continuously for at least 30 days

(Time Frame: Up to 36 weeks)

	QAW039 150 mg	QAW039 450 mg	Placebo
Arm/Group Description	QAW039 150 mg once daily orally	QAW039 450 mg once daily orally	Placebo to QAW039 once daily orally
Number of Participants Analyzed [units: participants]	201	200	201
Percentage of patients requiring ≥ 7.5 mg systemic corticosteroid dose in mg prednisone/prednisolone or equivalent per day continuously for at least 30 days (units: participants) Count of Participants (Not Applicable)			
	1 (.5%)	0 (%)	0 (%)

Percentage of patients with no systemic corticosteroids use

(Time Frame: Week 36)

	QAW039 150 mg	QAW039 450 mg	Placebo
Arm/Group Description	QAW039 150 mg once daily orally	QAW039 450 mg once daily orally	Placebo to QAW039 once daily orally
Number of Participants Analyzed [units: participants]	201	200	201
Percentage of patients with no systemic corticosteroids use (units: participants) Count of Participants (Not Applicable)			
	170 (84.58%)	164 (82%)	168 (83.58%)

Percentage of patients with prescription of biologic therapy

(Time Frame: Up to 36 weeks)

	QAW039 150 mg	QAW039 450 mg	Placebo
Arm/Group Description	QAW039 150 mg once daily orally	QAW039 450 mg once daily orally	Placebo to QAW039 once daily orally
Number of Participants Analyzed [units: participants]	201	200	201
Percentage of patients with prescription of biologic therapy (units: participants) Count of Participants (Not Applicable)			
	1 (.5%)	1 (.5%)	0 (%)

Safety Results

All-Cause Mortality

	QAW039 150mg N = 201	QAW039 450mg N = 200	Placebo N = 201
Arm/Group Description	QAW039 150mg once daily orally	QAW039 450mg once daily orally	Placebo to QAW039 once daily orally
Total participants affected	1 (0.50%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse events (AEs) are presented from first dose of study treatment until last dose of study treatment plus 14 days post treatment. Serious AEs (including the All-Cause Mortality data table) are presented from first dose of study treatment until last dose of study treatment plus 30 days post treatment, up to maximum duration of 40 weeks.
Additional Description	Any sign or symptom that occurs during the study treatment plus 14 days post treatment for adverse events and 30 days post treatment for serious adverse events.
Source Vocabulary for Table Default	MedDRA (22.1)
Assessment Type for Table Default	Systematic Assessment

	QAW039 150mg N = 201	**QAW039 450mg N = 200**	**Placebo N = 201**
Arm/Group Description	QAW039 150mg once daily orally	QAW039 450mg once daily orally	Placebo to QAW039 once daily orally
Total participants affected	7 (3.48%)	5 (2.50%)	4 (1.99%)
Blood and lymphatic system disorders			
Anaemia macrocytic	0 (0.00%)	0 (0.00%)	1 (0.50%)
Cardiac disorders			
Arteriosclerosis coronary artery	0 (0.00%)	1 (0.50%)	0 (0.00%)
General disorders and administration site conditions			
Pyrexia	1 (0.50%)	0 (0.00%)	0 (0.00%)
Infections and infestations			
Cellulitis	0 (0.00%)	1 (0.50%)	0 (0.00%)

Pneumonia	0 (0.00%)	1 (0.50%)	0 (0.00%)
Viral upper respiratory tract infection	1 (0.50%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications			
Intentional product misuse	0 (0.00%)	1 (0.50%)	0 (0.00%)
Traumatic fracture	1 (0.50%)	0 (0.00%)	0 (0.00%)
Investigations			
Hepatic enzyme increased	0 (0.00%)	1 (0.50%)	0 (0.00%)
Musculoskeletal and connective tissue disorders			
Osteoarthritis	1 (0.50%)	0 (0.00%)	0 (0.00%)
Nervous system disorders			
Transient ischaemic attack	0 (0.00%)	1 (0.50%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders			
Asthma	3 (1.49%)	0 (0.00%)	3 (1.49%)
Vascular disorders			
Circulatory collapse	1 (0.50%)	0 (0.00%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	Adverse events (AEs) are presented from first dose of study treatment until last dose of study treatment plus 14 days post treatment. Serious AEs (including the All-Cause Mortality data table) are presented from first dose of study treatment until last dose of study treatment plus 30 days post treatment, up to maximum duration of 40 weeks.
Additional Description	Any sign or symptom that occurs during the study treatment plus 14 days post treatment for adverse events and 30 days post treatment for serious adverse events.
Source Vocabulary for Table Default	MedDRA (22.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	QAW039 150mg N = 201	**QAW039 450mg N = 200**	**Placebo N = 201**
Arm/Group Description	QAW039 150mg once daily orally	QAW039 450mg once daily orally	Placebo to QAW039 once daily orally
Total participants affected	48 (23.88%)	45 (22.50%)	44 (21.89%)
Infections and infestations			
Nasopharyngitis	13 (6.47%)	10 (5.00%)	13 (6.47%)
Respiratory, thoracic and mediastinal disorders			
Asthma	39 (19.40%)	41 (20.50%)	38 (18.91%)

Conclusion:

The study was terminated early by Novartis and therefore precludes any definitive statements regarding the results. Safety was not a factor in the decision to end the study early. Patients were treated up to a maximum of 36 weeks; none of the patients completed the planned observation time of 52 weeks.

The primary endpoint of the study was not met. There was no statistically significant difference in the use of SCS in the fevipiprant 150 mg vs placebo or in the fevipiprant 450 mg group vs placebo in the overall population or in the subgroup of patients with eosinophil count ≥ 250 cells/µl.

The changes from baseline in mean daytime and nighttime asthma symptoms, mean ACQ-5 total score, AQLQ+12 total score, proportion of patients ≥ 7.5 mg SCS use continuously for at least 30 days, the proportion of patients with no SCS use during the treatment period, and percentage of patients with prescription of biologic therapy were not different between the fevipiprant 150 mg, fevipiprant 450 mg, and placebo groups.

Overall, fevipiprant 150 mg and 450 mg were well tolerated, and most of the events were mild to moderate in severity. There was a slight imbalance for the number of adverse events in the 150 mg group (n=97, 48.3%) vs. the 450 mg (n=86, 43.0%) and placebo (n=82, 40.8%) but no clear pattern or trend could be identified, as the events were not driven by any specific preferred term/event type.

Date of Clinical Trial Report

9-Dec-2020