NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Fevipiprant

Trial Indication(s)

Nasal polyposis

Protocol Number

CQAW039A2322

Protocol Title

A multicenter, randomized, double-blind, parallel-group, placebo-controlled study of fevipiprant once daily plus standard-of-care (SoC) for assessment of the efficacy in reduction of nasal polyp size in patients with nasal polyposis and concomitant asthma.

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase 3

Study Start/End Dates

Study Start Date: March 2019 (Actual)
Primary Completion Date: May 2020 (Actual)
Study Completion Date: June 2020 (Actual)

Study Design/Methodology

This was a Phase 3b, proof-of-concept study with a randomized, multicenter, double-blind, placebo-controlled, parallel-group study design to determine the ability of fevipiprant plus standard of care (SoC) compared to placebo plus SoC to reduce the size of nasal polyps. The study enrolled adult male and female patients diagnosed with nasal polyposis with a nasal polyp score assessed by nasal endoscopy ≥ 4 at baseline with a minimum score of 2 in each nostril and a concomitant diagnosis of asthma. Patients who meet the inclusion/exclusion criteria were randomized in 1:1:1 ratio in either of the 3 arms fevipiprant 450 mg dose once daily (o.d.), fevipiprant 150 mg dose o.d. or placebo o.d. in addition to SoC (mometasone furoate spray).

The study included:

- a Screening period of 2 weeks to assess eligibility
- a Run-in period of 4 weeks where patients utilized mometasone furoate spray (200 µg once daily, administered as two 50 µg actuations into each nostril)
- a Treatment period of 16 weeks. Patients continued to use the mometasone furoate SoC throughout the treatment period.
- a Follow-up period of 2 weeks following the last dose of study drug to collect additional data for safety variables.

Centers

25 centers in 9 countries: Argentina(8), Belgium(2), Canada(2), Czech Republic(3), Germany(2), Netherlands(2), United States(1), Italy(3), Poland(2)

Objectives:

The primary objective was to demonstrate a difference in mean change from baseline in polyp size at Week 16, measured by the nasal polyp score (NPS, assessed by nasal endoscopy with central reading), between fevipiprant 150 mg or 450 mg once daily (o.d.) separately and placebo in subjects with nasal polyps with a polyp size score ≥ 4 at baseline.

The secondary objectives were:

- To evaluate the effect on symptoms as measured by the Nasal Congestion Score (NCS) with fevipiprant 150 mg or 450 mg o.d., compared with placebo.
- To evaluate the effect on quality of life as measured by the Sino-Nasal Outcome Test (SNOT 22) with fevipiprant 150 mg or 450 mg o.d., compared with placebo.
- To evaluate the effect on smell as measured by the University of Pennsylvania Smell Identification Test (UPSIT) with fevipiprant 150 mg or 450 mg o.d., compared with placebo.
- To evaluate the effect of fevipiprant 150 mg and 450 mg compared with placebo in terms of general safety/tolerability

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

Fevipiprant was supplied as tablets at dose strength of 150 mg and 450mg. Matching fevipiprant placebo was supplied as tablets. The investigational treatment (fevipiprant or placebo) was administered once daily for 16 weeks.

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

- Arm of fevipiprant 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 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 efficacy variable was analyzed using a mixed model repeated measures (MMRM) approach (fevipiprant 450 mg plus SoC and fevipiprant 150 mg plus SoC). The model included change from baseline to follow-up timepoints every 8 weeks through week 16 as response variables, fixed-effects factors for treatment, visit, treatment × visit interaction, nasal polyp score baseline value, and baseline × visit interaction. An unstructured correlation structure was assumed for the repeated measures within patients. Parameters were estimated using the restricted maximum likelihood method with the Newton- Raphson algorithm. The least square mean change in nasal polyp score from baseline to week 16 alongside with 95% confidence interval and the P-value corresponding to the least square mean difference are presented.

The change in Nasal Congestion Score (NCS) was be analyzed using an MMRM model with visit, treatment, interaction between visit and treatment and the baseline average NCS as covariates. The treatment group difference in terms of change from baseline at Week 16 in SNOT-22 was estimated using an MMRM model with change from baseline as the response variable, adjusted for visits (Week 4, 8, 12 and 16), treatment, interaction between visit and treatment and baseline SNOT-22. The treatment group difference in terms of change from baseline at Week 16 in UPSIT was estimated using an MMRM model with change from baseline as the response variable, adjusted for visits (week 4, 8, 12 and 16), treatment, interaction between visit and treatment and baseline UPSIT. The least square mean change in NCS, SNOT-22 and UPSIT from baseline to week 16 alongside with its 95% confidence interval and the P-value corresponding to the least square mean difference are presented.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Patients aged 18 years or more with a diagnosis of nasal polyps with Nasal polyp score >= 4 with minimum score of 2 in each nostril.
- Concomitant diagnosis of asthma for a period of at least 6 months prior to screening.
- Patients on stable asthma treatment of at least inhaled corticosteroids (any dose) alone for at least 6 months prior to screening or ICS for 6 months prior to screening with any required, inhaled medication (LABA, LAMA) added at least 6 weeks prior to screening.

Exclusion Criteria:
- Asthma exacerbation, within 6 weeks prior to screening, that required systemic corticosteroids, hospitalization or emergency room visit.
- Chronic/maintenance use of oral corticosteroids (OCS) defined as any continuous use of OCS for a period of 1 month or more, within 1 year of screening
- Use of biologics for asthma or any other indications, that has the potential to interfere/affect either asthma or nasal polyposis disease progression, within 6 months of screening.
- Use of medication for sino-nasal symptoms (antibiotics with or without OCS) within 30 days of screening or during the run-in period.
- Use of tetracycline or macrolide antibiotics specifically, within 8 weeks of screening.
- History of nasal surgery modifying the structure of the nose such that assessment of the nasal polyp score is not possible.
- Patients with baseline ACQ-5≥1.5

Participant Flow Table

Overall Study

	Fevipiprant 150 mg	Fevipiprant 450 mg	Placebo	Total
Arm/Group Description	Fevipiprant (QAW039) 150 mg once daily orally	Fevipiprant (QAW039) 450 mg once daily orally	Placebo once daily orally	
Started	32	34	32	98
Full Analysis Set (FAS)	31	32	28	91
Safety Analysis Set (SAF)	32	34	32	98
Completed	32	32	31	95

Not Completed	0	2	1	3
Subject decision	0	2	1	3

Baseline Characteristics

	Fevipiprant 150 mg	Fevipiprant 450 mg	Placebo	Total
Arm/Group Description	Fevipiprant (QAW039) 150 mg once daily orally	Fevipiprant (QAW039) 450 mg once daily orally	Placebo once daily orally	
Number of Participants [units: participants]	32	34	32	98
Age Continuous (units: years) Mean ± Standard Deviation				
	50.8±13.36	50.9±13.10	48.5±13.43	50.1±13.20
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)				
Female	16	15	12	43
Male	16	19	20	55
Race/Ethnicity, Customized (units: participants) Count of Participants (Not Applicable)				
White	32	34	31	97
Black	0	0	1	1

Primary Outcome Result(s)

Change from baseline in Nasal Polyp Score at Week 16

(Time Frame: Baseline, Week 16)

	Fevipiprant 150 mg	Fevipiprant 450 mg	Placebo
Arm/Group Description	Fevipiprant (QAW039) 150 mg once daily orally	Fevipiprant (QAW039) 450 mg once daily orally	Placebo once daily orally
Number of Participants Analyzed [units: participants]	31	32	28
Change from baseline in Nasal Polyp Score at Week 16 (units: score on scale) Least Squares Mean ± Standard Error			
	0.20 ± 0.224	-0.10 ± 0.216	0.14 ± 0.233

Statistical Analysis

Groups	Fevipiprant 150 mg, Placebo	
P Value	0.979	Adjusted p-value is reported. The adjusted p-value was obtained from the Dunnet Multiplicity Correction applied to control the Type I error for the primary analysis.
Method	Other Mixed Model for Repeated Measures (MMRM)	

Other Least Squares (LS) Mean	0.05	
Standard Error of the mean	0.323	
95 % Confidence Interval 2-Sided	-0.59 to 0.70	

Statistical Analysis

Groups	Fevipiprant 450 mg, Placebo	
P Value	0.656	Adjusted p-value is reported. The adjusted p-value was obtained from the Dunnet Multiplicity Correction applied to control the Type I error for the primary analysis.
Method	Other MMRM	
Other LS Mean	-0.25	
Standard Error of the mean	0.319	
95 % Confidence Interval 2-Sided	-0.88 to 0.39	

Secondary Outcome Result(s)

Change from baseline in Nasal Congestion Score at Week 16

(Time Frame: Baseline, Week 16)

	Fevipiprant 150 mg	Fevipiprant 450 mg	Placebo
Arm/Group Description	Fevipiprant (QAW039) 150 mg once daily orally	Fevipiprant (QAW039) 450 mg once daily orally	Placebo once daily orally
Number of Participants Analyzed [units: participants]	31	32	28
Change from baseline in Nasal Congestion Score at Week 16 (units: score on scale) Least Squares Mean ± Standard Error			
	-0.15 ± 0.172	-0.35 ± 0.171	-0.80 ± 0.181

Statistical Analysis

Groups	Fevipiprant 150 mg, Placebo	
P Value	0.012	Unadjusted p-value
Method	Other MMRM	
Other LS Mean	0.64	
Standard Error of the mean	0.249	

95 % Confidence Interval 2-Sided	0.15 to 1.14

Statistical Analysis

Groups	Fevipiprant 450 mg, Placebo	
P Value	0.074	Unadjusted p-value
Method	Other MMRM	
Other LS Mean	0.45	
Standard Error of the mean	0.248	
95 % Confidence Interval 2-Sided	-0.04 to 0.94	

Change from baseline in Quality of Life as assessed by the SNOT-22 questionnaire at Week 16

(Time Frame: Baseline, Week 16)

	Fevipiprant 150 mg	**Fevipiprant 450 mg**	**Placebo**
Arm/Group Description	Fevipiprant (QAW039) 150 mg once daily orally	Fevipiprant (QAW039) 450 mg once daily orally	Placebo once daily orally
Number of Participants Analyzed [units: participants]	31	32	28
Change from baseline in Quality of Life as assessed by the SNOT-22 questionnaire at Week			

16 (units: score on scale) Least Squares Mean ± Standard Error			
	-3.23 ± 3.349	-10.61 ± 3.358	-8.44 ± 3.571

Statistical Analysis

Groups	Fevipiprant 150 mg, Placebo	
P Value	0.288	Unadjusted p-value
Method	Other MMRM	
Other LS Mean	5.22	
Standard Error of the mean	4.881	
95 % Confidence Interval 2-Sided	-4.49 to 14.93	

Statistical Analysis

Groups	Fevipiprant 450 mg, Placebo	
P Value	0.661	Unadjusted p-value
Method	Other MMRM	
Other LS Mean	-2.17	
Standard Error of the mean	4.936	

95 % Confidence Interval 2-Sided	-11.99 to 7.65

Change from baseline in sense of smell as assessed by the University of Pennsylvania Smell Identification Test (UPSIT) at Week 16

(Time Frame: Baseline, Week 16)

	Fevipiprant 150 mg	Fevipiprant 450 mg	Placebo
Arm/Group Description	Fevipiprant (QAW039) 150 mg once daily orally	Fevipiprant (QAW039) 450 mg once daily orally	Placebo once daily orally
Number of Participants Analyzed [units: participants]	31	32	28
Change from baseline in sense of smell as assessed by the University of Pennsylvania Smell Identification Test (UPSIT) at Week 16 (units: score on scale) Least Squares Mean ± Standard Error			
	1.05 ± 1.242	4.95 ± 1.259	0.44 ± 1.315

Statistical Analysis

Groups	Fevipiprant 150 mg, Placebo	
P Value	0.735	Unadjusted p-value

Method	Other MMRM
Other LS Mean	0.61
Standard Error of the mean	1.809
95 % Confidence Interval 2-Sided	-2.98 to 4.21

Statistical Analysis

Groups	Fevipiprant 450 mg, Placebo	
P Value	0.015	Unadjusted p-value
Method	Other MMRM	
Other LS Mean	4.51	
Standard Error of the mean	1.821	
95 % Confidence Interval 2-Sided	0.89 to 8.13	

Safety Results

All-Cause Mortality

	Fevipiprant 150 mg N = 32	**Fevipiprant 450 mg N = 34**	**Placebo N = 32**

Arm/Group Description	Fevipiprant (QAW039) 150 mg once daily orally	Fevipiprant (QAW039) 450 mg once daily orally	Placebo once daily orally
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

No treatment emergent serious adverse events were reported for this study.

Other Adverse Events by System Organ Class

Time Frame	From first dose of study treatment until end of study treatment plus 2 weeks post treatment, up to Week 18.
Additional Description	Any sign or symptom that occurs during the study treatment plus 2 weeks post treatment.
Source Vocabulary for Table Default	MedDRA (23.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	0%

	Fevipiprant 150 mg N = 32	**Fevipiprant 450 mg N = 34**	**Placebo N = 32**
Arm/Group Description	Fevipiprant (QAW039) 150 mg once daily orally	Fevipiprant (QAW039) 450 mg once daily orally	Placebo once daily orally

Total participants affected	17 (53.13%)	13 (38.24%)	11 (34.38%)
Blood and lymphatic system disorders			
Iron deficiency anaemia	0 (0.00%)	1 (2.94%)	0 (0.00%)
Ear and labyrinth disorders			
Ear pain	1 (3.13%)	0 (0.00%)	0 (0.00%)
Tympanic membrane perforation	0 (0.00%)	1 (2.94%)	0 (0.00%)
Eye disorders			
Conjunctival haemorrhage	0 (0.00%)	1 (2.94%)	0 (0.00%)
Gastrointestinal disorders			
Diarrhoea	0 (0.00%)	0 (0.00%)	1 (3.13%)
Mouth ulceration	1 (3.13%)	0 (0.00%)	0 (0.00%)
Tongue discomfort	0 (0.00%)	0 (0.00%)	1 (3.13%)
Vomiting	1 (3.13%)	0 (0.00%)	0 (0.00%)
General disorders and administration site conditions			
Peripheral swelling	1 (3.13%)	0 (0.00%)	0 (0.00%)
Pyrexia	2 (6.25%)	0 (0.00%)	0 (0.00%)
Infections and infestations			
Acute sinusitis	0 (0.00%)	0 (0.00%)	1 (3.13%)
Bronchitis	0 (0.00%)	1 (2.94%)	0 (0.00%)

Ear infection	0 (0.00%)	0 (0.00%)	1 (3.13%)
Gastric infection	0 (0.00%)	0 (0.00%)	1 (3.13%)
Gastroenteritis viral	1 (3.13%)	0 (0.00%)	0 (0.00%)
Gingivitis	1 (3.13%)	0 (0.00%)	0 (0.00%)
Influenza	2 (6.25%)	1 (2.94%)	2 (6.25%)
Laryngitis	0 (0.00%)	1 (2.94%)	0 (0.00%)
Nasopharyngitis	1 (3.13%)	0 (0.00%)	2 (6.25%)
Oral herpes	1 (3.13%)	2 (5.88%)	0 (0.00%)
Otitis media	0 (0.00%)	1 (2.94%)	0 (0.00%)
Pharyngitis	0 (0.00%)	1 (2.94%)	0 (0.00%)
Sinusitis	3 (9.38%)	1 (2.94%)	2 (6.25%)
Tonsillitis	0 (0.00%)	1 (2.94%)	0 (0.00%)
Upper respiratory tract infection	1 (3.13%)	0 (0.00%)	0 (0.00%)
Viral upper respiratory tract infection	0 (0.00%)	0 (0.00%)	1 (3.13%)
Injury, poisoning and procedural complications			
Contusion	0 (0.00%)	1 (2.94%)	0 (0.00%)
Investigations			
Amylase increased	1 (3.13%)	0 (0.00%)	0 (0.00%)
Blood creatine phosphokinase increased	0 (0.00%)	0 (0.00%)	1 (3.13%)
Blood creatinine increased	1 (3.13%)	0 (0.00%)	0 (0.00%)
Lipase increased	2 (6.25%)	0 (0.00%)	0 (0.00%)

Weight increased	2 (6.25%)	0 (0.00%)	0 (0.00%)
Metabolism and nutrition disorders			
Decreased appetite	0 (0.00%)	1 (2.94%)	0 (0.00%)
Metabolic syndrome	1 (3.13%)	0 (0.00%)	0 (0.00%)
Musculoskeletal and connective tissue disorders			
Arthritis	1 (3.13%)	0 (0.00%)	0 (0.00%)
Bursitis	0 (0.00%)	1 (2.94%)	0 (0.00%)
Nervous system disorders			
Dizziness	1 (3.13%)	0 (0.00%)	0 (0.00%)
Facial paralysis	0 (0.00%)	1 (2.94%)	0 (0.00%)
Headache	2 (6.25%)	0 (0.00%)	0 (0.00%)
Renal and urinary disorders			
Pollakiuria	0 (0.00%)	1 (2.94%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders			
Asthma	2 (6.25%)	3 (8.82%)	1 (3.13%)
Cough	1 (3.13%)	0 (0.00%)	0 (0.00%)
Epistaxis	0 (0.00%)	1 (2.94%)	0 (0.00%)
Nasal congestion	2 (6.25%)	0 (0.00%)	0 (0.00%)
Oropharyngeal pain	1 (3.13%)	0 (0.00%)	0 (0.00%)
Paranasal sinus inflammation	0 (0.00%)	0 (0.00%)	2 (6.25%)
Respiratory disorder	0 (0.00%)	0 (0.00%)	1 (3.13%)

Rhinorrhoea	0 (0.00%)	1 (2.94%)	0 (0.00%)
Skin and subcutaneous tissue disorders			
Alopecia	0 (0.00%)	1 (2.94%)	0 (0.00%)
Scab	0 (0.00%)	0 (0.00%)	1 (3.13%)
Vascular disorders			
Hypertension	0 (0.00%)	1 (2.94%)	0 (0.00%)

Conclusion:

In conclusion, the efficacy objectives of this study were not met, and fevipiprant was well tolerated, with a safety profile similar to that of placebo.

No significant differences were observed between treatment arms for change from baseline for nasal polyp score by visit, nasal congestion score by visit, SNOT-22 score by visit, and in UPSIT score by visit.

Overall, the absolute number of treatment emergent adverse events (TEAEs) was low across the 3 treatment arms, although more TEAEs were reported in the 150 mg arm (53.1%) compared to the 450 mg arm (38.2%) and placebo arm (34.4%).

Date of Clinical Trial Report

23-Nov-2020