NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Fevipiprant

Trial Indication(s)

Chronic obstructive pulmonary disease (COPD) with eosinophilia

Protocol Number

CQAW039E12201

Protocol Title

A multi-center, proof-of-mechanism study of multiple, oral doses of fevipiprant (QAW039) in COPD patients with eosinophilia

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase 3

Study Start/End Dates

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

Study Completion Date: January 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 an exploratory, randomized, subject- and investigator-blind, placebo-controlled, parallel group, proof-of-mechanism study in COPD subjects with eosinophilia, on standard of care therapy. Standard of care (SoC) treatment in subjects with COPD typically includes a regimen of inhaled corticosteroid (ICS) plus one or more long acting bronchodilator (long-acting beta2-agonist (LABA) or long-acting antimuscarinic antagonist (LAMA)).

The study consisted of a screening period (including an optional pre-screen visit) during which the subject's phenotype and eligibility for the study were assessed. All subjects who met the eligibility criteria after the screening visit were to undergo induction of their sputum to examine the baseline sputum cell counts. Subjects were required to demonstrate both blood and sputum eosinophilia to be eligible for participation in the study.

Eligible subjects were randomized 3:2 to active (fevipiprant 450 mg oral daily) vs. placebo arms. Randomization was stratified by current smoking status (current vs. ex-smoker). Subjects were to continue their COPD standard of care and other medications during the entire course of the study. Subjects were to receive multiple doses of fevipiprant or placebo for six weeks.

Sputum induction was to be repeated at the end of the treatment period and at the end of the study (approximately 4 weeks after the last dose).

Centers

4 centers in 2 countries: Germany(3), United Kingdom(1)

Objectives:

The primary purpose of the proof-of-mechanism study was to determine whether fevipiprant (QAW039), when administered to COPD patients with eosinophilic airway inflammation on standard of care therapy, reduced the burden of sputum eosinophilia.

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

Fevipiprant (QAW039) was supplied as 450 mg film coated tablets. Participants received fevipiprant 450 mg oral once daily for 6 weeks.

Placebo was supplied as oral tablets. Participants received placebo oral once daily for 6 weeks.

Statistical Methods

The primary variable of the study was the change from baseline in sputum eosinophil percentage (SEP) based on log10-transformed scale at week 6. The treatment effect of the primary variable was to be analyzed using a Bayesian model with adjustments for baseline SEP and smoking status as covariates. Due to the limited sample size caused by early termination of the study, no inferential statistical analysis was conducted and only descriptive statistics could be calculated.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Acceptable and reproducible spirometry with post-bronchodilator FEV1/FVC < 0.7 and post-bronchodilator FEV1≥ 30 and ≤ 80% of predicted at the screening and baseline visits (GOLD stage II or III COPD).
2. Patients with a physician-diagnosed history of COPD for at least 1 year prior to screening visit, and a documented history of at least one COPD exacerbation within the year prior to screening visit and on a stable therapy regimen for COPD for at least 4 weeks prior to screening visit with inhaled glucocorticoid + one or more long acting bronchodilator.
3. Current or ex-smokers who have a smoking history of at least 10 pack-years (10 pack-years are defined as 20 cigarettes a day for

10 years, or 10 cigarettes a day for 20 years, or equivalent).
4. Circulating eosinophils ≥ 300 cells/µL blood AND sputum eosinophils ≥ 3% of total cell count during screening period.

Exclusion Criteria:
1. Patients with a past or current medical history of asthma.
2. Patients with a past or current medical history of conditions other than COPD or allergic rhinitis that could result in elevated sputum eosinophils (e.g., asthma, hypereosinophilic syndrome, Churg-Strauss Syndrome). Patients with known parasitic infestation within 6 months prior to screening are also excluded.
3. Patients who have had a respiratory tract infection or COPD worsening or systemic steroid use within 4 weeks prior to screening visit or between screening and randomization visits.
4. Patients with history of concomitant chronic or severe pulmonary disease (e.g., sarcoidosis, interstitial lung disease, cystic fibrosis, tuberculosis). Exception: patients with concomitant mild or moderate pulmonary hypertension or bronchiectasis are permitted to participate.
5. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective contraception (also called basic contraception)methods during the study.
6. Patients on any statin therapy with a CK level > 2 X ULN at screening.
7. Patients who have a clinically significant laboratory abnormality at the screening visit including (but not limited to):
• Total white blood cell count <2500 cells/uL
• AST or ALT > 2.0 X ULN or total bilirubin > 1.3 X ULN
• Estimated Glomerular Filtration Rate (eGFR) by the Modification of Diet in Renal Disease (MDRD) equation or Bedside Schwartz equation <55 mL/minute/1.73 m2.
8. Patients with any of the following cardiac related concerns:
• A resting QTcF (Fridericia) ≥450 msec (male) or ≥460 msec (female) at screening visit
• A history of familial long QT syndrome or known family history of Torsades de Pointe
• Receiving any medications or other agents known to prolong the QT interval
• patients with a history of moderate or severe uncontrolled tachyarrhythmias
• History of a clinically significant cardiovascular event within 1 year prior to the screening visit, such as acute myocardial infarction, congestive heart failure, unstable arrhythmia

• Patients who, in the judgment of the investigator have a clinically significant ECG abnormality such as (but not limited to) sustained ventricular tachycardia, or clinically significant second or third degree AV block without a pacemaker

Participant Flow Table

Overall Study

	QAW039 450 mg	Placebo	Total
Arm/Group Description	QAW039 (fevipiprant) 450 mg once daily for 6 weeks administered orally as a tablet.	Placebo once daily for 6 weeks administered orally as a tablet.	
Started	6	3	9
Completed	4	2	6
Not Completed	2	1	3
Study terminated by Sponsor	2	1	3

Baseline Characteristics

	QAW039 450 mg	Placebo	Total
Arm/Group Description	QAW039 (fevipiprant) 450 mg once daily for 6 weeks administered orally as a tablet.	Placebo once daily for 6 weeks administered orally as a tablet.	
Number of Participants [units: participants]	6	3	9
Age Continuous (units: Years) Mean ± Standard Deviation			
	63.5±9.71	67.3±6.35	64.8±8.53
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)			
Female	1	1	2
Male	5	2	7
Race/Ethnicity, Customized (units: Participants) Count of Participants (Not Applicable)			
Asian	0	1	1
White	6	2	8

Primary Outcome Result(s)

Change from baseline in sputum eosinophil percentage based on log-10 transformed scale at Week 6

(Time Frame: Baseline, Week 6)

	QAW039 450 mg	Placebo
Arm/Group Description	QAW039 (fevipiprant) 450 mg once daily for 6 weeks administered orally as a tablet.	Placebo once daily for 6 weeks administered orally as a tablet.
Number of Participants Analyzed [units: participants]	3	2
Change from baseline in sputum eosinophil percentage based on log-10 transformed scale at Week 6 (units: Percentage) Mean ± Standard Deviation		
	-0.43373 ± 0.39740	-0.06689 ± 0.43094

Safety Results

All-Cause Mortality

	QAW039 450mg N = 6	Placebo N = 3	Total N = 9
Arm/Group Description	QAW039 (fevipiprant) 450 mg once daily for 6 weeks administered orally as a tablet.	Placebo once daily for 6 weeks administered orally as a tablet.	Total
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

No serious adverse events were reported.

Other Adverse Events by System Organ Class

Time Frame	Adverse events were collected from first dose of study treatment until last dose plus 30 days, up to a maximum of 72 days.
Additional Description	Any signs or symptoms that occurs during study treatment plus the 30 days post treatment.
Source Vocabulary for Table Default	MedDRA (22.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	0%

	QAW039 450mg N = 6	**Placebo N = 3**	**Total N = 9**
Arm/Group Description	QAW039 (fevipiprant) 450 mg once daily for 6 weeks administered orally as a tablet.	Placebo once daily for 6 weeks administered orally as a tablet.	Total
Total participants affected	4 (66.67%)	2 (66.67%)	6 (66.67%)
Infections and infestations			
Nasopharyngitis	1 (16.67%)	0 (0.00%)	1 (11.11%)
Injury, poisoning and procedural complications			
Fall	0 (0.00%)	1 (33.33%)	1 (11.11%)
Foot fracture	1 (16.67%)	1 (33.33%)	2 (22.22%)
Joint injury	0 (0.00%)	1 (33.33%)	1 (11.11%)

Nervous system disorders			
Headache	1 (16.67%)	0 (0.00%)	1 (11.11%)
Psychiatric disorders			
Insomnia	1 (16.67%)	0 (0.00%)	1 (11.11%)
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease	1 (16.67%)	0 (0.00%)	1 (11.11%)
Vascular disorders			
Orthostatic hypotension	0 (0.00%)	1 (33.33%)	1 (11.11%)

Conclusion:

Efficacy could not be assessed in this study due to early termination. Fevipiprant was generally safe and well tolerated.

Date of Clinical Trial Report

30-Jul-2020