NOVARTIS

Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

QAW039

Clinical Trial Protocol CQAW039E12201

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

Statistical Analysis Plan (SAP)

Author(s): Personal Protected Data

Document type: SAP Documentation – NIBR

Document status: Final

Release date: 28-Apr-2020

Number of pages: 21

Commercially Confidential Information

Table of contents

List of tables

Commercially Confidential Information

1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial "CQAW039E12201".

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.2 Study reference documentation

The SAP is developed based on the study protocol v01 dated of 08Apr2019.

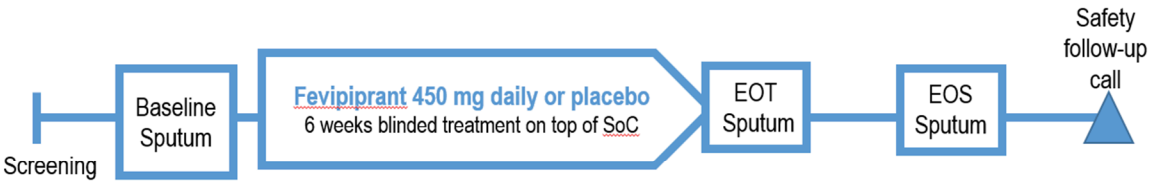
1.3 Study objectives

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	Endpoint(s) for primary objective(s)
• To assess the change from baseline in sputum eosinophil levels in COPD patients with eosinophilia after multiple oral doses of fevipiprant when compared to placebo	• Sputum eosinophil % of total cell count
Secondary objective(s)	Endpoint(s) for secondary objective(s)
• To assess the safety and tolerability of fevipiprant in COPD patients with eosinophilia	• Physical examination, ECG intervals, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), adverse events including COPD exacerbations
Exploratory objective(s)	Endpoint(s) for exploratory objective(s)

1.4 Study design and treatment

Figure 1-1 Study design



Key:
SoC: Standard of Care
EOT: End of Treatment
EOS: End of study

This is an exploratory, randomized, subject- and investigator-blind, placebo-controlled, parallel group, proof-of-mechanism study in COPD patients with eosinophilia, on standard of care therapy.

The study consists of a screening period during which the subject's phenotype and eligibility for the study will be assessed. All subjects will undergo induction of their sputum to examine

the baseline sputum cell counts. Subjects will be required to demonstrate both blood and sputum eosinophilia to be eligible for participation in the study:

- Peripheral eosinophilia is defined as circulating eosinophils ≥ 300 cells/μL of blood.
- Sputum eosinophilia is defined as sputum eosinophil count of ≥ 3% of total cell count on an induced sputum sample

Eligible subjects will be randomized 3:2 to active (QAW039 450 mg orally daily) vs. placebo arms. Randomization will be stratified by current smoking status (current vs. ex-smoker). Subjects will continue their standard of care COPD and other medications during the entire course of the study (provided they are not prohibited medications - see Protocol Section 6.2.2).

Subjects will receive multiple doses of fevipiprant for six weeks, with safety, efficacy/pharmacodynamic and pharmacokinetic assessments performed.

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

The study plans to recruit approximately 50 subjects (subjects who drop out from the study may be replaced so that 50 subjects complete the treatment period).

Study treatments are defined in the following table:

Table 1-2 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
QAW039 450mg	Tablet	Oral use	Double Blind supply; bottle	Sponsor (global)
QAW039 Placebo	Tablet	Oral use	Double Blind supply; bottle	Sponsor (global)

2 First interpretable results (FIR)

First interpretable results (FIR) will **not** be provided for this trial due to the early termination of the study.

3 Interim analyses

4 Statistical methods: Analysis sets

For subjects for which the actual treatment received does not match the randomized treatment the treatment actually received will be used for the analysis.

The safety set will include all subjects who received at least one dose of study drug. The safety set will be used in the analysis of all safety variables.

The PD analysis set will include all subjects with available PD data and no protocol deviations with relevant impact on PD data.

Available PD data definition: having baseline and at least one-post baseline non-missing sputum eosinophil values."

The analysis sets and protocol deviation codes are related as follows:

Commercially Confidential Information

5 Statistical methods for Pharmacokinetic (PK) parameters

Commercially Confidential Information

6 Statistical methods for Pharmacodynamic (PD) parameters

6.1 Primary objective

The primary objective of this study is to assess the change from baseline in sputum eosinophil levels in COPD patients with eosinophilia after multiple oral doses of fevipiprant when compared to placebo.

6.1.1 Estimand

Commercially Confidential Information

Commercially Confidential Information

6.1.2 Variables

The primary variable of the study is the change from baseline in sputum eosinophil percentage (SEP) at week 6. As sputum eosinophil percentage has been found to follow a log-normal distribution, the analysis will be based on log10-transformed scale. The baseline measurement is defined as sputum eosinophil percentage prior to the first dosing (on log10-transformed scale).

6.1.3 Descriptive analyses

Commercially Confidential Information

6.1.4 Statistical model, assumptions and hypotheses

Commercially Confidential Information

6.2 Secondary objectives

No pharmacodynamic secondary objective is planned.

6.3 Exploratory objectives

Commercially Confidential Information

7 Statistical methods for safety and tolerability data

Descriptive statistics will be used to provide an overview of the safety results. For categorical variables, frequencies, and percentages will be presented. The denominator for percentage will be based on the number of subjects appropriate for the purpose of analysis. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum).

7.1 Variables

Safety variables include adverse events including COPD exacerbations, vital signs (blood pressure, pulse rate, respiratory rate, and body temperature), ECG intervals, laboratory measurements, as well as subject demographics (age, sex, ethnicity, and BMI) baseline characteristics, medical history, protocol deviations, treatment information, concomitant medications, pregnancy,

7.2 Descriptive analyses

Baseline definition

Baseline values will be defined as the last measureable assessment prior to study treatment administration. Day 1 is defined as the date of first study drug administration. Study day is calculated relative to Day 1.

Subject demographics and other baseline characteristics

Demographic, including age, sex, ethnicity, and BMI, and other baseline data including, past medical history including smoking history, history of other respiratory diseases, IgE level, history of COPD exacerbations,

Commercially Confidential Information

Relevant medical history, current medical conditions, results of laboratory screens, and any other relevant information will be listed by treatment group and subject.

Subject disposition

A disposition summary will be presented for all subjects in the safety analysis set. This table will present the number and percentage of subjects who completed each study period and discontinued early for each period, along with the reasons for early discontinuation.

The number and percentage of subjects in each analysis set will be summarized by treatment group and period. All analysis set results will be presented in listings by subject. A separate listing of all subjects excluded from any analysis set and the reasons for their exclusion will be provided.

All study completion data will be listed by subject.

Treatment

Data for study drug administration and concomitant therapies will be listed by treatment group and subject.

Vital signs

All vital signs data will be listed by treatment, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

Table 7-1 Reference ranges for vital signs

Variable	Type of abnormality	Criterion
Sitting/Standing systolic blood pressure (mmHg)	High	≥140 mmHg
	Low	<90 mmHg
Sitting/Standing diastolic blood pressure (mmHg)	High	≥90 mmHg
	Low	<50 mmHg
Sitting pulse (bpm)	High	≥100 bpm

Respiratory Rate	Low	<12
	High	>25
	Low	<40 bpm
Temperature	High	>37.5° C
	Low	<35.0 ° C

ECG evaluations

All ECG data will be listed by treatment, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Table 7-2 Reference ranges for ECGs

Variable	Type of abnormality	Criterion
PR duration (msec)	High	> 200 msec
QRS duration (msec)	High	≥ 120 msec
QTcF (females) (msec)	High	> 460 msec
QTcF (males) (msec)	High	> 450 msec
Heart rate (bpm)	High	> 100 msec
	Low	<40 bpm

Clinical laboratory evaluations

All laboratory data will be listed by treatment, subject, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a subject with any abnormal values. Summary statistics will be provided by treatment and visit/time.

Adverse events

All information obtained on adverse events will be displayed by treatment and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system and treatment.

The number and percentage of subjects with adverse events by maximum severity of adverse events will be tabulated by body system and preferred term with a breakdown by treatment.

The number and percentage of subjects with adverse events classified as related to study drug will be tabulated by body system and preferred term with a breakdown by treatment.

COPD exacerbation AE

Adverse events related to COPD will also be analyzed separately as detailed below.

The number and percentage of subjects with any one AE preferred term corresponding to exacerbation of COPD will be summarized for each treatment group.

Commercially Confidential Information

7.3 Graphical presentation

Overlay plots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter) with each individual will be created.

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

8.2 Descriptive analysis

Commercially Confidential Information

8.3 Statistical model, assumptions and hypotheses

Commercially Confidential Information

8.4 Graphical presentation of results

Commercially Confidential Information