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QAW039

Clinical Trial Protocol CQAW039E12201

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

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study procedures. Note: The SOM will not be a part of the Clinical Study Report.

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List of abbreviations

AE	adverse event
ALB	Albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen

CK	creatinine kinase
CMO&PS	Chief Medical Office & Patient Safety
COPD	Chronic obstructive pulmonary disease
CRF	Case Report/Record Form (paper or electronic)
CRTh2	Chemoattractant Receptor-homologous molecule expressed on Th2 cells (also called DP2)
CSR	Clinical study report
CV	coefficient of variation
DP2	Prostaglandin D2 receptor 2 (also called CRTh2)
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EOT	End of treatment
FEV1	Forced Expiratory Volume in one second
FSH	Follicle Stimulating Hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GOLD	Global Initiative for Chronic Obstructive Lung Disease
h	hour
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HFA	Hydrofluoroalkane
HIV	human immunodeficiency virus
hs-CRP	high-sensitivity C-reactive Protein
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled Corticosteroid
IDR	idiosyncratic drug reactions
IEC	Independent Ethics Committee
ILC-1	Innate Lymphoid Cell type 1

ILC-2	Innate Lymphoid Cell type 2
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine system
LABA	Long-acting Beta-agonist
LAMA	Long-acting muscarinic antagonist
LDH	lactate dehydrogenase
LFT	Liver function test

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MCID	Minimal clinically important difference
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)

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PT	prothrombin time
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
SAE	serious adverse event
SD	standard deviation
SEP	Sputum eosinophil percentage

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SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SoC	Standard of Care
SOM	Site Operations Manual
ULN	upper limit of normal
WOCBP	Women of child bearing potential

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last subject or at a later point in time as defined by the protocol
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug/treatment	The drug whose properties are being tested in the study
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Patient	An individual with the condition of interest
Personal data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer and does not allow any further collection of personal data

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Protocol summary

Protocol number	CQAW039E12201
Full Title	A multi-center, proof-of-mechanism study of multiple, oral doses of fevipiprant (QAW039) in COPD patients with eosinophilia
Brief title	A proof-of-mechanism study of multiple, oral doses of fevipiprant (QAW039) in COPD patients with eosinophilia
Sponsor and Clinical Phase	Novartis, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	There remains an unmet medical need for phenotype-driven therapy for patients with COPD who have evidence of eosinophilic airway inflammation despite treatment with standard of care medications. The purpose of this study is to determine whether fevipiprant (QAW039), when administered to COPD patients with eosinophilic airway inflammation on standard of care therapy, reduces the burden of sputum eosinophilia. In addition, the clinical safety and efficacy profile of fevipiprant in COPD patients with eosinophilia will support its further development in this population.
Primary Objective(s)	The primary objective of this study is to assess the change from baseline in sputum eosinophil levels (% of total count) in COPD patients with eosinophilia after multiple oral doses of fevipiprant when compared to placebo.
Secondary Objectives	To assess the safety and tolerability of fevipiprant in COPD patients with eosinophilia.
Study design	This is an exploratory, randomized, subject- and investigator-blind, placebo-controlled, parallel group, proof-of-mechanism study in COPD patients with eosinophilia. Patients should have moderate to severe COPD, with no past or current medical history of asthma, be on standard of care medications and demonstrate an eosinophilic phenotype, as defined by a sputum eosinophil count of ≥ 3% of the total cell count obtained from an induced sputum specimen and a peripheral eosinophil count ≥ 300 cells/µL of blood.
Key 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. Documented elevated peripheral blood eosinophil count ≥ 300 cells/µL blood either at the Screening visit or at any time in the preceding 3 months.

	Sputum eosinophils must be ≥ 3% of total cell count at the baseline sputum collection..
Key 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 or baseline visit. 7. Patients who have a clinically significant laboratory abnormality at the screening or baseline 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 m^2. 8. Patients with any of the following cardiac related concerns: • A resting QTcF (Fridericia) ≥450 msec (male) or ≥460 msec (female) at screening or baseline 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
Study treatment	• QAW039 450mg oral tablet • Matching placebo oral tablet
Key Efficacy assessments	• Sputum eosinophil % of total cell count
Key safety assessments	Physical examination, ECG, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), adverse event, and serious adverse event monitoring.

Other assessments	Commercially Confidential Information
Data analysis	The treatment effect of the primary variable will be assessed using the posterior difference between the treatment groups in the change from baseline in log10 sputum eosinophil percentage at week 6 using a Bayesian model with adjustment for baseline sputum eosinophil percentage and smoking status as covariates. A robust mixture prior for the placebo response (based on CQAW039A2208 study) will be used in the Bayesian analysis.
Key words	QAW039, Chronic obstructive pulmonary disease, COPD, sputum, eosinophilic, eosinophilia, prostaglandin D2 receptor, DP2, CRTh2, fevipiprant.

1 Introduction

1.1 Background

Chronic obstructive pulmonary disease (COPD) is characterized by persistent symptoms (e.g., dyspnea, cough) and airflow obstruction that is usually progressive (GOLD Guidelines 2018). The symptoms as well as airflow limitation in COPD are consequent to lung abnormalities (airway and/or alveolar) caused by exposure of the lungs to "noxious particles or gases" such as tobacco smoke (GOLD Guidelines 2018). COPD exacerbations are a major cause of poor health and death worldwide, and contribute to impaired health status (Seemungal et al 1998, Spencer et al 2004) and increased hospitalization costs (Andersson et al 2002) and predict mortality (Soler-Cataluña et al 2005).

The inflammation observed in COPD has generally been thought to be neutrophilic in origin (Tripple et al 2017). However, eosinophilic inflammation has been observed in the induced sputum of some patients with stable COPD (Tripple et al 2017, Saha and Brightling 2006), and blood eosinophil levels of 2% or greater appear to be associated with risk of exacerbations of COPD (Kerkhof et al 2017). Recently, the COPD Gene study showed that patients with moderate-to-severe COPD and blood eosinophil counts ≥300 cells/µl had an increased risk of exacerbations (Yun et al 2018). Eosinophilic airway inflammation may also be associated with underlying atopic disease, which may contribute to COPD symptoms and exacerbations (Jamieson et al 2013, Fattahi et al 2013). Therefore, as in asthma, eosinophilic inflammation may play a role in the pathophysiology of exacerbations in patients with COPD. An unmet medical need for phenotype-driven therapy exists for COPD patients who have evidence of eosinophilic inflammation despite treatment with standard of care medications such as inhaled glucocorticoids and long-acting bronchodilators.

The prostaglandin D2 receptor (DP2; also known as CRTh2) is a receptor for prostaglandin D2 which mediates the activation and migration of eosinophils, basophils and Th2 cells (Domingo et al 2018, Hirai et al 2001), as well as type 2 innate lymphoid (ILC-2) cells (Xue et al 2014). Fevipiprant (QAW039) is a potent, selective, competitive, reversible DP2 receptor antagonist currently in Phase 3 studies for the treatment of asthma. In a Phase 2 study of patients with severe asthma and sputum eosinophilia, treatment with fevipiprant resulted in improvement in measures of asthma control as well as a significant reduction in sputum eosinophils (Gonem et al 2016). A reduction in sputum eosinophils was observed in the same range with the anti-IL5 antibodies, mepolizumab (Pavord et al 2012) and reslizumab (Castro et al 2011) in asthma. Although fevipiprant has not been evaluated in patients with COPD to date, another DP2 receptor antagonist, AZD1981, has been evaluated in a small study in patients with moderate-to-severe COPD during which cellular and histological changes in the airways were evaluated. In this study, AZD1981, compared with placebo, significantly reduced sputum eosinophils (AstraZeneca, data on file) suggesting a potential mechanistic effect for a DP2 receptor antagonist in COPD.

In addition to reducing airway eosinophils, fevipiprant inhibits the migration and activation of type 2 innate lymphoid (ILC-2) cells, resident cells in the lung, which secrete IL-4, IL-5 and IL-13 in response to DP2 (Zhou et al 2018). ILC-2 cells also convert to ILC-1 cells, which are increased in patients with COPD and are associated with infection-induced COPD exacerbations, are a significant source of TNF-α and IFN-λ (Silver et al 2016).

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Given the above information on the potential role of the DP2 pathway in COPD, it is reasonable to evaluate fevipiprant's pharmacodynamic activity in COPD patients with eosinophilia.

1.2 Purpose

The primary purpose of this proof-of-mechanism study is to determine whether fevipiprant (QAW039), when administered to COPD patients with eosinophilic airway inflammation on standard of care therapy, reduces the burden of sputum eosinophilia similar to that seen in patients with asthma.

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2 Objectives and endpoints

Table 2-1 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)**

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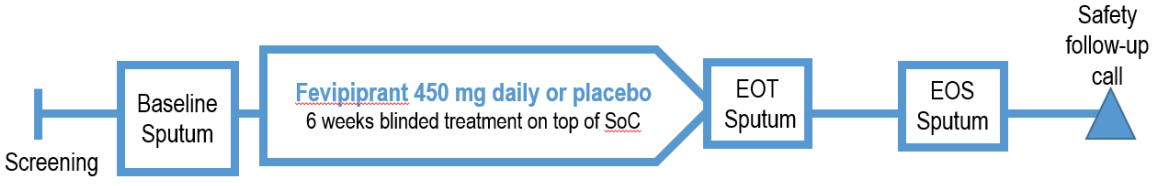
3 Study design

Figure 3-1 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.

Standard of care (SoC) treatment in patients with COPD typically includes a regimen of inhaled corticosteroid (ICS) plus one or more long acting bronchodilator (long-acting beta$_2$-agonist (LABA) or long-acting antimuscarinic antagonist (LAMA)). This can consist of double or triple inhaler therapy with short-acting bronchodilators taken as rescue medication on an "as needed" basis for symptoms. Rarely, systemic therapy with theophylline or roflumilast is added to the patient's daily medical regimen, which are permitted in the study. To be eligible for the study, subjects are required to be on a stable therapy regimen of inhaled corticosteroid (ICS) plus one or more long acting bronchodilator (long-acting beta2-agonist (LABA) and/or long-acting antimuscarinic antagonist (LAMA)) for at least four weeks prior to the screening. Subjects will be expected to continue their SoC therapy for the duration of the study.

The study consists of a screening period (including an optional pre-screen visit) during which the subject's phenotype and eligibility for the study will be assessed. All subjects who meet the eligibility criteria after the screening visit 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 a documented elevated peripheral blood eosinophil count ≥ 300 cells/μL of blood either at the Screening visit or at any time in the preceding 3 months (from an existing lab report or from a sample collected at the optional pre-screen visit – see Section 8.1.1 Eligibility screening for more details).
- 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 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).

Safety assessments will include physical examination, ECG, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), adverse event, and serious adverse event monitoring.

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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).

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4 Rationale

4.1 Rationale for study design

This exploratory, proof-of-mechanism study is designed to assess the pharmacodynamic, clinical safety and PK (drug concentrations) profiles of fevipiprant in COPD patients with eosinophilia. In order to optimize the rigor and integrity of the study and minimize bias, a randomized, subject- and investigator-blinded parallel group study design is used. This design is well-established in respiratory clinical trials (Snell et al 2013) and enables the study treatment to be given for an appropriate and practical length of time of 6 weeks to assess the efficacy and safety of the treatment (Gonem et al 2016).

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4.1.1 Rationale for choice of background therapy

Subjects will continue their standard of care for COPD and other medications (with the exception of prohibited medications outlined in Section 6.2.2) during the course of the study.

To be eligible for the study, subjects are required to be on a stable therapy regimen of inhaled corticosteroid (ICS) plus one or more long acting bronchodilator (long-acting beta$_2$-agonist (LABA) and/or long-acting antimuscarinic antagonist (LAMA)) for at least four weeks prior to the screening visit to minimize any impact of a change in background therapy on the endpoints

of the study. This is in line with standard of care treatment as described in the GOLD guidelines 2018 for patients with a history of exacerbations.

4.2 Rationale for dose/regimen and duration of treatment

Eosinophilic inflammation in the airway contributes to and drives exacerbations in a subset of patients with COPD as well as in asthma. A therapy that reduces sputum eosinophils in one indication should also do the same in the other. In the Phase 2 study CQAW039A2208, a 3.5-fold (~70%) reduction in sputum eosinophils was observed in patients with asthma relative to placebo after a daily oral dose of 450 mg over 12 weeks (Gonem et al 2016). The pharmacodynamic effect on sputum eosinophils was seen from 6 weeks onwards.

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Six week duration is considered sufficient to observe an improvement in key primary, secondary and exploratory endpoints of the study,

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4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Fevipiprant will be administered in addition to standard of care for COPD patients, with placebo control used to enable an unbiased comparison of safety and pharmacodynamic effects in active-treated subjects when compared to placebo-treated subjects.

4.4 Purpose and timing of interim analyses/design adaptations

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4.5 Risks and benefits

There is no benefit expected for subjects participating in this study.

The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring, subject and study level stopping rules, minimal study duration and periodic review of safety data by the clinical team. Study subjects are expected to continue their standard of care medications, which further reduces any potential risks.

Induction of sputum with isotonic or hypertonic saline can be associated with transient cough, breathing discomfort, chest pain, and worsening of lung function. These risks are minimized by pre-treatment with bronchodilators and close lung function monitoring during sputum induction, with stopping criteria for sputum induction and/or escalation of saline concentration. Subjects will only be discharged from the study center if symptoms and lung function recovery allow or upon evaluation by a responsible physician that it is safe to discharge the subject.

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Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and must agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

As of January 2018, over 2830 subjects have been exposed to fevipiprant in its clinical development program. Potential side effects of fevipiprant include: increased heart rate, non-serious arrhythmia such as palpitations, headache, diarrhea, nausea, vomiting, nasopharyngitis, somnolence and dizziness.

Cardiovascular risks will be monitored based on changes in vital signs, ECGs and biochemical parameters. Monitoring of liver function tests (LFT) and renal function will be conducted.

In humans, one major metabolite of fevipiprant has been identified which is formed by glucuronidation (acyl glucuronide) and partially binds to plasma proteins. In the literature, in vivo binding of acyl glucuronides to proteins has been reported to be associated with rare idiosyncratic drug reactions (IDRs), although a causal connection of protein adduction to IDRs remains uncertain. There have been no IDRs observed with fevipiprant treatment in completed clinical trials as of January 2018. Surveillance of adverse events for identification of IDRs will be conducted during the course of this study.

Taking fevipiprant at the doses used in this study with the cholesterol-lowering drug simvastatin has been shown to cause a small increase in the peak blood level of simvastatin. Subjects on doses of simvastatin > 20 mg, doses of atorvastatin >40 mg, doses of pravastatin >40 mg, or doses of pitavastatin > 2 mg per day, as well as subjects on any statins with high creatine kinase (CK) levels (> 2 X ULN (upper limit of normal)) at screening will be excluded from the study. Subjects on statin medication who are included in the study will have regular monitoring for relevant symptoms and be subject to discontinuation based on persistent myalgia and/or blood CK levels.

Kindly refer to the Investigator's Brochure for further guidance on the risk-benefit assessment of fevipiprant.

4.5.1 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of approximately 4 months from each subject as part of the study. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the Assessment Schedule (Table 8-1).

A summary blood log is provided in the Site Operations Manual (SOM). Instructions for all sample collection, processing, storage and shipment information is available in the Central Laboratory Manual.

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5 Population

The study population will comprise of approximately 50 male or female patients with moderate to severe COPD on standard of care medications. They must demonstrate an eosinophilic phenotype as defined by a sputum eosinophil count of ≥ 3% of the total cell count obtained from an induced sputum specimen and documented evidence of a peripheral eosinophil count ≥ 300 cells/μL of blood at the screening visit, or within three months prior to the screening visit.

Subject selection is to be established by checking through all inclusion and exclusion criteria following completion of all screening/baseline assessments. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects.

Deviation from **any** entry criterion excludes a subject from enrollment into the study.

Replacement subjects may be enrolled to replace subjects who discontinue the study for reasons other than safety.

Screening and Baseline safety laboratory tests can be repeated once, if deemed appropriate by the Investigator.

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
3. Male and female adult patients aged ≥ 40 to ≤ 80 years at screening visit.
4. 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). Note: re-testing is allowed once.
5. 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.

6. Patients 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.
7. Documented elevated peripheral blood eosinophil count ≥ 300 cells/μL blood either at the Screening visit or at any time in the preceding 3 months. Sputum eosinophils must be ≥ 3% of total cell count at the baseline sputum collection. Note: re-testing for each is allowed once.
8. 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).
9. Able to produce good quality induced sputum sample at the baseline sputum induction visit. Note: can be repeated once.

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study.

1. Patients with a past or current medical history of asthma.
2. History of hypersensitivity to any of the study treatments or study drug excipients (including milk or lactose) or to drugs of similar chemical classes.
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 the screening and randomization visits. Patients may be re-screened 4 weeks after recovery from their respiratory tract infection or COPD worsening or completion of steroid treatment.
4. Patients with a current or past 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.
5. 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.
6. Patients with a clinical diagnosis of α-1 anti-trypsin deficiency (heterozygous genotype may be enrolled).
7. Pregnant or nursing (lactating) women.
8. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during the study. Basic contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

- Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) if allowed as effective method of contraception by local regulations. For United Kingdom: with spermicidal foam/gel/film/cream/ vaginal suppository.
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS).

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

9. Patients with any of the following cardiac related concerns:
   - A resting QTcF (Fridericia) ≥450 msec (male) or ≥460 msec (female) at screening or baseline visit.
   - A history of familial long QT syndrome or known family history of Torsades de Pointes.
   - 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 arrhythmias.
   - 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.
10. Patients on any statin therapy with a CK level > 2 X ULN at screening or baseline visit.
11. Patients who have a clinically significant laboratory abnormality at the screening or baseline 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 m^2.

12. History of immunodeficiency diseases, or a positive HIV (ELISA and Western blot) test result at the screening visit.
13. Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV). A positive HBV surface antigen (HBsAg) test excludes a subject. Subjects with a positive HCV antibody test should have HCV RNA levels measured. Subjects with positive (detectable) HCV RNA should be excluded.
14. Patients who have a history of or current treatment for hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis or hepatic failure.
15. Any severe, progressive or uncontrolled, acute or chronic, medical or psychiatric condition, or other factors such as abnormal vital signs, ECG or physical findings, or clinically relevant abnormal laboratory values, that in the judgment of the investigator may increase the risk associated with study participation/treatment or may interfere with interpretation of study results, and thus would make the patient inappropriate for entry into or continuing the study.
16. Donation or loss of 400 ml or more of blood within 8 weeks prior to screening, or longer if required by local regulation.
17. History of drug or alcohol abuse within the 12 months prior to dosing.
18. At screening, history or symptoms of malignancy of any organ system (except for a history of basal cell carcinoma and/or up to 3 squamous cell carcinomas of the skin, if successful treatment has been performed, with no signs of recurrence; actinic keratosis, if present at screening, should be treated according to standard therapy before randomization), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
19. Patients on prohibited treatment listed in Table 6-2.
20. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of experimental drug at the time of enrollment, or within 30 days of last dose of experimental drug at the time of enrollment, whichever is longer; or longer if required by local regulations.

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing, and taking study treatment are outlined in the SOM.

6.1.1 Investigational and control drugs

Table 6-1 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)

6.1.2 Additional study treatments

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6.1.3 Treatment arms/group

Subjects will be assigned at or after visit 30 to one of the following two treatment arms/groups in a ratio of 3:2 active fevipiprant (QAW039) vs placebo.

6.2 Other treatment(s)

Oral contraception is permitted as a concomitant medication.

Prohibited medications are listed in Table 6-2.

6.2.1 Concomitant therapy

Subjects should remain on their baseline regimen of inhaled corticosteroid (ICS) plus one or more long acting bronchodilator (long-acting beta$_2$-agonist (LABA) or long-acting antimuscarinic antagonist (LAMA) from at least four weeks prior to the Screening visit through to the End of Study/Early Termination visit, with short-acting bronchodilators taken as rescue medication on an "as needed" basis for symptoms.

Other concomitant medications can continue during the study, provided they are not prohibited (see Table 6-2).

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded on the appropriate Case Report Forms.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

6.2.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed for the time defined in the 'Prohibition period'.

Table 6-2 Prohibited medication

Medication	Prohibition period	Action taken
> 20 mg simvastatin > 40 mg atorvastatin > 40 mg pravastatin > 2 mg pitavastatin	From 4 weeks prior to screening visit and for the duration of study (Rationale: Risk of over-exposure to concomitant medication due to OATP1B1 inhibition)	Exclude subject from study/Discontinue study treatment if initiated after randomization
Cyclosporin, rifampin, probenecid, ritonavir, valproic acid (i.e. medications blocking several pathways important for the elimination of QAW039 (broad range UGT inhibition and/or inhibition of OAT3, OATP1B3, MXR and Pgp))	From 4 weeks prior to screening visit and for the duration of study (Rationale: Risk of over-exposure to QAW039)	Exclude subject from study/Discontinue study treatment if initiated after randomization
Any medication or other agents, such as Azithromycin, known to significantly prolong the QT interval	From 4 weeks prior to screening visit and for the duration of study (Rationale: To avoid risk of QT prolongation)	Exclude subject from study/Discontinue study treatment if initiated after randomization
Systemic glucocorticoids	From 4 weeks prior to screening visit and for the duration of study (Rationale: Confounds primary objective)	Exclude subject from study/Discontinue study treatment if initiated after randomization

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6.2.3 Rescue medication

Unless clinically indicated, the type of rescue medication CCI a subject uses, the device used to deliver the medication (e.g., dry powder or HFA) and the way it is administered (e.g., with a spacer device) should not be adjusted. Commercially Confidential Information

6.2.4 Restriction for study subjects

For the duration of the study, subjects should be informed and reminded of the restrictions outlined in this section.

6.2.4.1 Dietary restrictions and smoking

Study participants should refrain from alcohol, caffeine and smoking for at least 4 hours prior to study visits. The study drug can be taken with or without food.

6.2.4.2 Other restrictions

- For women of childbearing potential, the contraception requirements as outlined in the Exclusion Criteria in Section 5.2
- No strenuous physical exercise (e.g. weight training, aerobics, football) until after the End of Study/Early Termination visit.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

The subject number assigned to a subject at screening remains the unique identifier for the subject throughout the study. For information on subject numbering, please see 'Subject numbering' section in the Site Operations Manual.

6.3.2 Treatment assignment, randomization

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Randomization will be stratified by current smoking status (current vs. ex smoker).

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

This is a subject and investigator-blinded study. Subjects, investigators and all site staff will remain blinded to study treatment throughout the study.

Unblinding a single subject at site for safety reasons (if necessary for subject management) will occur via an emergency system in place at the site.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

The sponsor may be unblinded to the study treatment at any time, especially in case of a safety concern.

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples.

The study statistician will be able to access the randomization list and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes. For example, unblinded summaries and unblinded individual data can be shared with the team for interim analyses.

Study programmers and other personnel involved in study data analysis (CCI)
are allowed to access treatment assignment information for the purpose of conducting analyses.

The clinical trial team is allowed to share unblinded results with other sponsor staff (e.g. decision boards) as required for internal decision making on the study or the project while the study is ongoing.

The sponsor does not intend to share unblinded data with study site staff or with study subjects while the study is ongoing.

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments are not permitted during the course of the study.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

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The total number of doses of study drug administered since the last visit will be recorded in the Dosage Administration Record eCRF.

6.6.2 Recommended treatment of adverse events

At present there is insufficient information to provide specific recommendations regarding treatment of adverse events (AEs). AEs should be treated per the judgement of the responsible physician.

Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- subject number

In addition, oral and written information must be provided to the subject on how to contact the investigator in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

If a subject has their treatment code revealed they should discontinue study treatment. They should continue to be followed up in the study, as outlined in Section 9.1.1.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under the investigational and control drugs section (Section 6.1.1).

Fevipiprant will be administered to the subject via the oral route of administration, both at the study site on visit days and administered at home. The site should remind subjects not to take their medication on the morning of a study visit, but to bring it with them to take at the study site, following completion of pre-dose assessments.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent, which then must be discussed with the subject.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

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A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

Subjects might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

Refer to the Site Operations Manual for a complete list of ICFs included in this study.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the Assessment Schedule (Table 8-1) or as close to the designated day/time as possible (visit windows are outline in the Site Operations Manual).

Notes:

- Baseline sputum and Baseline Visit can be combined, if this facilitates site scheduling.
- Sputum induction visits can be rescheduled/repeated if sputum induction is contraindicated/not possible or insufficient/poor quality sample is produced at the planned visit. A window of 3 days or more should occur between consecutive sputum induction assessments and the visit should occur within two weeks of the original planned visit.
- Assessments scheduled for a study visit can be split across multiple days to facilitate resourcing at site.
- Missed or rescheduled visits should not lead to automatic discontinuation.

Subjects who prematurely discontinue treatment/from the study will be encouraged to return for scheduled study visits depending on the cause for discontinuation (either scheduled as soon as possible and/or for the Early Termination visit approximately 28 days after their last treatment). The Investigator should contact Novartis for guidance.

At the End of Study/Early Termination visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

Table 8-1 Assessment Schedule

Period	Screening				Treatment							Follow-up	
Visit Name	Optional Pre-Screen	Screening	Baseline sputum induction	Baseline	Treatment							End of Study or Early Termination	Follow up Safety
Visit Numbers	1		20[1]	30[1]	100			110	120			1999	
Days	3 months to 1 day prior to Screening visit	-45 to -3*			1			21	42			70	100
Time (post-dose)	-	-	-	-	0h	2h	4h	0h	0h	2h	4h	-	-
Informed consent[8]	X	X											
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Inclusion / Exclusion criteria		S		S									
Demography		X											
Medical history, respiratory history, allergy history current medical conditions		X											
Smoking history		X											
Alcohol Test and Drug Screen		S											
Hepatitis and HIV Screen		S											
Physical Examination		S		S					S			S	
Vital Signs		X		X	X			X	X			X	
Electrocardiogram (ECG)		X		X	X			X	X			X	
Body Height		X											
Body Weight		X		X					X			X	
Pregnancy and assessments of fertility		X		X								X	
Clinical Chemistry		X		X				X	X			X	
Peripheral blood eosinophil count[6]	X[6]												
Hematology[7]		X		X				X	X			X	

Period	Screening				Treatment							Follow-up	
Visit Name	Optional Pre-Screen	Screening	Baseline sputum induction	Baseline	Treatment							End of Study or Early Termination	Follow up Safety
Visit Numbers	1		20[1]	30[1]	100			110	120			1999	
Days	3 months to 1 day prior to Screening visit	-45 to -3*			1			21	42			70	100
Time (post-dose)	-	-	-	-	0h	2h	4h	0h	0h	2h	4h	-	-
Urinalysis		X		X					X			X	
Blood sample for serum IgE level				X					X			X	
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Induced Sputum[7]			X							X		X	
Commercially Confidential Information													
Randomization				X									
Drug dispensation					X								
Study drug administered in clinic after pre-dose assessments are performed					X			X[2]	X[2]				
Commercially Confidential Information													
Innate lymphoid cells (blood)				X	X			X	X			X	
Commercially Confidential Information													
Prostaglandins (urine)				X	X	X[6]		X	X	X[6]		X	
Commercially Confidential Information													
Study completion information												X	
Adverse Events			X										

Period	Screening				Treatment							Follow-up	
Visit Name	Optional Pre-Screen	Screening	Baseline sputum induction	Baseline	Treatment							End of Study or Early Termination	Follow up Safety
Visit Numbers	1		20[1]	30[1]	100			110	120			1999	
Days	3 months to 1 day prior to Screening visit	-45 to -3*			1			21	42			70	100
Time (post-dose)	-	-	-	-	0h	2h	4h	0h	0h	2h	4h	-	-
Concomitant medications		X											
Safety Follow up Call													S

* Please see the Site Operations manual for details of turnaround time needed for each assessment.

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded as source data

[1] Baseline sputum and Baseline Visit can be combined

2 Site to remind patient ahead of the visit NOT to take their medication at home prior to the visit

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6 Optional sample

7 Due to diurnal variation in levels of eosinophils, recommend taking hematology and sputum sample in the morning

8 Informed consent needs to be collected at the optional prescreen visit or at the screening visit, but before study related assessments are performed

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8.1 Screening

It is permissible to re-screen a subject once if s/he fails the initial screening, if deemed feasible by the study site investigator. Subjects can be further rescreened; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis. Further information on re-screening is outlined in the Site Operations Manual.

8.1.1 Eligibility screening

Peripheral blood eosinophil level

All subjects must have documented elevated peripheral blood eosinophil count ≥ 300 cells/µL blood either at the Screening visit (central lab) or at any time in the preceding 3 months (local lab).

The historic value can be from an existing lab report, or from the optional pre-screen visit, where a hematology sample can be collected and analyzed locally, from 3 months to one day prior to the Screening visit. Alternatively, the value can be taken from the Screening central lab report.

HIV and Hepatitis markers

All subjects will be screened for HIV, HBV and HCV. See the Central Lab Manual for further details on assessments and methods.

Alcohol test, Drug screen

All subjects will be screened for substances of abuse and cotinine. See the Central Lab manual for further details on assessments and methods.

8.1.2 Information to be collected on screening failures

Information on what data must be collected for screening failures and further information on re-screening is outlined in the Site Operations Manual.

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data are to be collected on all subjects. Relevant medical history, respiratory and allergy history, including the number of COPD exacerbations in the prior year, known allergies, historic blood eosinophil levels (if applicable), smoking history/status and current medical conditions present before signing the informed consent will be recorded. Investigators will have the discretion to record abnormal test findings on the appropriate CRF whenever, in their judgment, the test abnormality occurred prior to the informed consent signature. Details are outlined in the Site Operations Manual.

The IgE level will be reported by the central lab.

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

8.3 Efficacy

Pharmacodynamic samples and measurements will be collected at the timepoints defined in the Assessment Schedule (Table 8-1). Follow instructions outlined in the Site Operations Manual and Central Laboratory Manual regarding sample collection, numbering, processing, and shipment and instructions.

Pharmacodynamic (PD) samples will be obtained and evaluated in all subjects at all dose levels, including the placebo group.

8.3.1 Sputum eosinophil % of total cell count

Sputum will be induced with isotonic or hypertonic saline with appropriate safety measures as per the Sputum induction protocol.

If sputum induction is contraindicated at the planned visit, or if insufficient/inadequate/poor quality sputum sample is obtained upon induction, the procedure can be repeated/rescheduled within two weeks after the planned visit (a window of 3 days or more should occur between consecutive sputum induction assessments).

If a repeat/reschedule of the sputum induction is necessary at the End of Treatment visit, the subject should continue to take their study medication until the assessment is repeated (up to a total of eight weeks treatment duration).

Induced sputum will be processed at site for the following analysis: 1. preparation of cytospin slides for differential cellular count (primary endpoint); 2. remaining supernatant from cytospin preparation used for biomarker assessments; 3. RNA profiling of sputum cells (if sufficient sputum plug samples are available).

Full details on the sputum induction process are provided in the Sputum induction protocol.

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8.3.3 Appropriateness of efficacy assessments

Induced sputum eosinophil count is an accepted endpoint within the respiratory community for interventions that target airway eosinophils.

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8.4 Safety and tolerability

Safety assessments are specified below with the Assessment Schedule (Table 8-1) detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE (Section 10).

The methods, assessment and specification for each assessment are detailed in the Site Operations Manual.

Table 8-2 Assessments & Specifications

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an adverse event must be recorded as an adverse event.
Vital signs	Vital signs include temperature, BP, pulse, respiratory rate measurements and pulse oximetry at rest.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

8.4.1 Laboratory evaluations

Screening and Baseline safety laboratory tests can be repeated once, if deemed appropriate by the Investigator.

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

Table 8-3 Laboratory test details

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils) absolute value and % of total cell count
Chemistry	Albumin, Alkaline phosphatase, ALT , AST , Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Total Bilirubin, (with Direct and Indirect Bilirubin assessments if above normal range), Total Cholesterol, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (non-fasting), Estimated Glomerular Filtration Rate (eGFR)
Urinalysis	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocytes , Nitrite, pH, Protein, Specific Gravity,)
	If Macroscopic Panel is abnormal, Microscopic Panel for RBC, WBC, epithelial cells, casts, crystals, bacteria and/or yeast
Immunology	IgE
HIV and Hepatitis markers	HIV Ab, HBsAg, HCV Ab (with RNA-PCR confirmation triggered in the event of a reactive/indeterminate HVC Ab result - will require a repeat sample to be collected)
Pregnancy Test	Serum / Urine pregnancy test - refer to 'Pregnancy and assessments of fertility', Section 8.4.3

8.4.2 Electrocardiogram (ECG)

Full details of all procedures relating to the ECG collection and reporting are contained in the Site Operations Manual.

PR interval, QRS duration, heart rate, RR interval, QT interval, QTcF

The Fridericia QT correction formula (QTcF) must be used for clinical decisions.

Unless auto-calculated by the ECG machine, the investigator must calculate QTcF at the Screening visit to assess eligibility. See the Site Operations Manual for additional details.

Clinically significant abnormalities must be reported as adverse events. See Section 16.1 for notable QTc values and action.

8.4.3 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile, i.e. women of child-bearing potential (WOCBP), will have pregnancy testing. A woman is considered post-menopausal and not of child-bearing potential if she reports 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile. Medical documentation of oophorectomy, hysterectomy, or tubal ligation, if available, must be retained as source documents. Subsequent hormone level assessment (FSH) to confirm the woman is not of child-bearing potential should also be available as source documentation if the subject has had surgical bilateral oophorectomy without a hysterectomy.

In WOCBP, at screening, a serum pregnancy test should be performed, while at other visits urinary pregnancy test will be performed. Additional pregnancy testing might be performed if requested by local requirements, any associated results will not be collected in the CRF.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

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8.5.3 Pharmacokinetics

PK samples will be collected at the visits defined in the Assessment Schedule (Table 8-1). Follow instructions outlined in the Central Laboratory Manual regarding sample collection, numbering, processing, and shipment.

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9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration. Discontinuation of study treatment can be decided by either the subject or the investigator.

Study treatment must be discontinued under the following circumstances:

- Subject decision - subjects may choose to discontinue study treatment for any reason at any time.
- The investigator believes that continuation would negatively impact the safety of the subject, the integrity of the trial or the risk/benefit ratio of trial participation.
- An adverse event graded as 'severe' or "serious" if it is considered related to study treatment.
- Any protocol deviation that results in a significant risk to the subject's safety.
- Pregnancy (see Section 8.4.3 and Section 10.1.4).
- Female subjects non-compliant with the chosen effective method of contraception during the study: The investigator must provide appropriate advice on the continued use of

effective contraception for at least one week (at least 5 half-lives of QAW039) after study drug discontinuation.

- Use of prohibited treatment as outlined in Table 6-2.
- COPD exacerbation requiring use of systemic steroids and/or antibiotics.
- Total white blood cell count <1000 cells/μL of blood.
- If a liver or renal event occurs, follow guidelines outlined in Section 16.2 and Section 16.3 regarding confirmation of safety monitoring signal and discontinuation of study treatment.
- If patients on statin therapy complain of persistent muscle pain without any obvious cause for greater than 3 days accompanied by increase in CK levels > 10xULN or persistent intolerable muscle pain regardless of the accompanying CK level.
- Moderate or severe hypersensitivity reaction occurs, including any of the following: anaphylaxis, fever, chills, urticaria, dyspnea, headache, myalgia, hypotension.
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study.
- The following deviations from the prescribed dose regimen for the study drug:

1. More than 10 missed doses
2. More than 7 consecutive missed doses

- The appropriate personnel from the site and Novartis will assess whether investigational drug treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

If discontinuation of study treatment occurs, the Investigator must determine the primary reason for the subject's premature discontinuation of study treatment and record this information on the Dosage Administration CRF.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.1.2, Withdraw of Informed Consent).

Subjects who prematurely discontinue from the study will be encouraged to return for scheduled study visits, depending on the cause for discontinuation (either scheduled as soon as possible and/or for the Early Termination visit approximately 28 days after their last treatment). The Investigator should contact Novartis for guidance. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in Section 9.1.3 (Lost to follow-up). This contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- new / concomitant treatments
- adverse events/Serious Adverse Events

The investigator/deputy must also contact the IRT to register the subject's discontinuation from study treatment.

9.1.1.1 Replacement policy

Subjects who discontinue due to reasons other than safety may be replaced.

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, **and**
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law.

For US: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Study stopping rules

Enrollment in the study will be placed on hold if any of the following occurs:

- Two or more similar study-drug related serious adverse events (SAEs)
- The Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the study on hold.

The study may resume following the safety review, if the Lead Investigator(s) and Sponsor agree it is safe to proceed.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, Novartis will contact the investigator with next steps, such as the subjects to be scheduled to be seen as soon as possible and to stop taking study drug, and to be treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. Depending on local regulations, the investigator or sponsor will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion assessments at the End of Study/Early Termination visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision. Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

All randomized subjects should have a safety follow-up call conducted 30 days after last administration of study treatment, or last study visit, whichever is later. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3 and SOM). Documentation of attempts to contact the subject should be recorded in the source documentation.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade:
- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities
2. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not change
- Drug interrupted/withdrawn

6. its outcome (i.e. recovery status or whether it was fatal)

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subjects with the underlying disease. Alert ranges for laboratory and other test abnormalities are referenced in Appendix 1.

Follow the instructions found in the Site Operations Manual for data capture methodology regarding AE collection for subjects that fail screening.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in COPD.
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the subject's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an

emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Screen Failures: If a subject fails screening (e.g. a subject who is screened but is not treated or randomized), SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

Randomized Subjects who discontinue prematurely: SAEs collected between the time a subject signs ICF until 30 days after the subject discontinued or stopped study treatment, or had their last study visit, whichever is later should be reported to Novartis/sponsor safety within 24 hours of learning of its occurrence.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Novartis Chief Medical Office and Patient Safety (CMO&PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate CRFs

Please refer to Table 16-1 in Appendix 2 Section 16.2 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Section 16.2 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events and guidance on how to document them are outlined in Section 9 (Appendix 3) of the Site Operations Manual.

- Repeat liver chemistry tests (i.e. ALT, AST, TBL, ALB, PT/INR, ALP and GGT) to confirm elevation. These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption* if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment Section 9.1.1 and Table 16-2), if appropriate.
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include repeat liver chemistry tests and additional investigation, based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

*Please see Section 9.1.1 for maximum duration of study drug interruption permitted.

10.2.2 Renal safety monitoring

The following categories of abnormal renal laboratory values have to be considered during the course of the study:

- Serum creatinine increase ≥ 25% compared to baseline during normal hydration status
- Urine protein-creatinine ratio (PCR) ≥1g/g or ≥100 mg/mmol, OR new onset dipstick proteinuria ≥ 3+ OR new onset dipstick hematuria ≥ 3+ (after excluding menstruation, UTI, extreme exercise, or trauma)

Abnormal renal event findings must be confirmed after ≤ 5 days after first notification of the result.

Every renal laboratory trigger or renal event as defined in Table 16-3 should be followed up by the investigator or designated personnel at the trial site as summarized in Appendix 3 (Section 16.3). Please also see Section 10 (Appendix 4) of the Site Operations Manual for further guidance.

*Please see Section 9.1.1 for maximum duration of study drug interruption permitted.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data entered into the eCRF is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and

adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Randomization codes and data about all study treatment (s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The safety set (SAF) will include all subjects who received at least one dose of study drug whether or not being randomized. 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.

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including medical history, respiratory history, PRO data and current medical conditions present before signing the informed consent will be listed and summarized descriptively by treatment group for the Safety set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment group.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

The concentration data will be summarized by means of descriptive statistics using the safety set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

12.4 Analysis of the primary endpoint(s)

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12.4.1 Definition of primary endpoint(s)

The primary variable of the study is the change from baseline in sputum eosinophil percentage 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).

12.4.2 Statistical model, hypothesis, and method of analysis

The treatment effect of the primary variable will be analyzed using a Bayesian model

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12.4.3 Handling of missing values/censoring/discontinuations

Induced sputum, from which the primary endpoint is derived, is collected only once post-treatment (at 6 weeks). Only trial completers will be included in the statistical model. Handling of missing values is not planned.

For other endpoints that are collected in multiple time points CCI
the repeated measures analysis includes all available information in terms of measurements at all times. If missing measurements are missing at random, an analysis of the available data provides consistent estimates of model parameters.

12.4.4 Sensitivity and Supportive analyses

12.4.4.1 Sensitivity analysis

The same Bayesian model stated in Section 12.4.2 will be repeated

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12.4.4.2 Supportive analysis

The proportion and timing of starting concomitant systemic steroids will be summarized and compared between treatment groups as the supplemental estimate of the primary estimand using safety data set.

12.5 Analysis of secondary endpoints

12.5.1 Safety endpoints

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

Adverse events

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

The number (and percentage) of subjects with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, and other significant adverse events leading to discontinuation.

The number and proportion of subjects with adverse events of special interest will be summarized by treatment group

A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

Vital signs (i.e. blood pressure and pulse rate) will be summarized with standard descriptive statistics of raw data and changes from baseline for each visit separately. The numbers of subjects with vital signs meeting the definition of notably abnormal will be presented by parameter.

ECG

1. PR, QRS, QT, QTcF, and RR intervals will be obtained from ECGs for each subject during the study. ECG data will be read and interpreted locally.
2. Categorical Analysis of QT/QTc interval data based on the number of subjects meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these subjects will be produced (by treatment group).

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

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

12.6 Analysis of exploratory endpoints

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12.7 Interim analyses

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12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Subjects will be randomized with a 3:2 ratio until approximately 50 subjects have completed the end of treatment visit, which equates to approximately 30 on fevipiprant and 20 on placebo. Subjects that drop out may be replaced.

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13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last subject last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values

The central laboratory will flag laboratory values falling outside of the normal ranges on the central laboratory reports. Investigators are responsible for reviewing these abnormal values for clinical significance, signing the laboratory reports to indicate their review, and reporting values considered clinically significant in the appropriate eCRF.

Any clinically significant abnormal laboratory value should be evaluated and followed-up by the investigator until normal or a cause for the abnormality is determined.

See Section 16.2 for specific liver event and laboratory test trigger definitions and follow-up requirements.

For ECGs, a notable QTc value is defined as a QTcF (Fridericia) interval of ≥450 msec for males or ≥460 msec for females – all such ECGs will require assessment for clinical relevance and continuance of the subject by the Investigator in consultation with Novartis.

16.2 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	2.5 x ULN < ALT / AST < 3 x ULN
	1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	ALT or AST ≥ 3 × ULN
	ALP > 2 × ULN (in the absence of known bone pathology)
	TBL > 2 × ULN (in the absence of known Gilbert syndrome)
	ALT or AST ≥ 2.5 x ULN **and** total bilirubin ≥ 1.5 x ULN
	Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)
	Any clinical event of jaundice (or equivalent term)
	Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: Hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal.

Table 16-2 Follow up requirements for liver events and laboratory triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[b] (frequency at investigator discretion)
ALT or AST		
≥ 3 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, medical history, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[b] (frequency at investigator discretion)
≥2.5 x ULN **and** total bilirubin ≥1.5xULN	• Discontinue the study drug and continue follow-up monitoring • Establish causality • Record the AE and contributing factors (e.g. conmeds, medical history, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[b] (frequency at investigator discretion)
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[b] (frequency at investigator discretion) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)

Criteria	Actions required	Follow-up monitoring
	• Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	
> 1.5 to ≤ 2 × ULN (subject is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the subject • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[b] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-3 Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h if possible Follow up within 2-5 days
Serum creatinine increase 50 % compared to baseline (Acute Kidney Injury)	Follow up within 24-48h if possible Consider drug interruption Consider subject hospitalization /specialized treatment
Urine Event	
Protein-creatinine ratio (PCR)≥1g/g or ≥100 mg/mmol Or New onset dipstick proteinuria ≥ 3+ Or New onset dipstick hematuria ≥ 3+ (after excluding menstruation, UTI, extreme exercise or trauma)	Confirm value after >24 hours but ≤ 5 days after first assessment Perform urine microscopy Consider drug interruption / discontinuation
For all renal events:	

1. Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed
2. Monitor subject regularly (frequency at investigator's discretion) until either:
   - Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or
   - Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.