GCP	good clinical practice
GGT	gamma-glutamyl-transferase
GINA	global initiative for asthma
HbA1c	hemoglobin A1c
IB	Investigator's brochure
ICH	international conference on harmonization of technical requirements for registration of pharmaceuticals for human use
ICS	inhaled corticosteroids
IDR	idiosyncratic drug reactions
IEC	independent ethics committee
IgE	immunoglobulin E
IL5	interleukin 5
ILC2	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 bronchodilator
LAMA	long-acting muscarinic antagonist
LDH	lactate dehydrogenase
LFT	liver function test
LOCF	last observation carried forward
LTRA	leukotriene receptor antagonist
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDRD	modification of diet in renal disease
MedDRA	Medical dictionary for regulatory activities
MFS	mometasone furoate nasal spray
MMRM	mixed model repeated measures
MXR	multixenobiotic resistance
NCS	nasal congestion score
NIMP	non-investigational medicinal product
NP	nasal polyposis
NPS	nasal polyp score
NYHA	New York Heart Association
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCS	oral corticosteroids

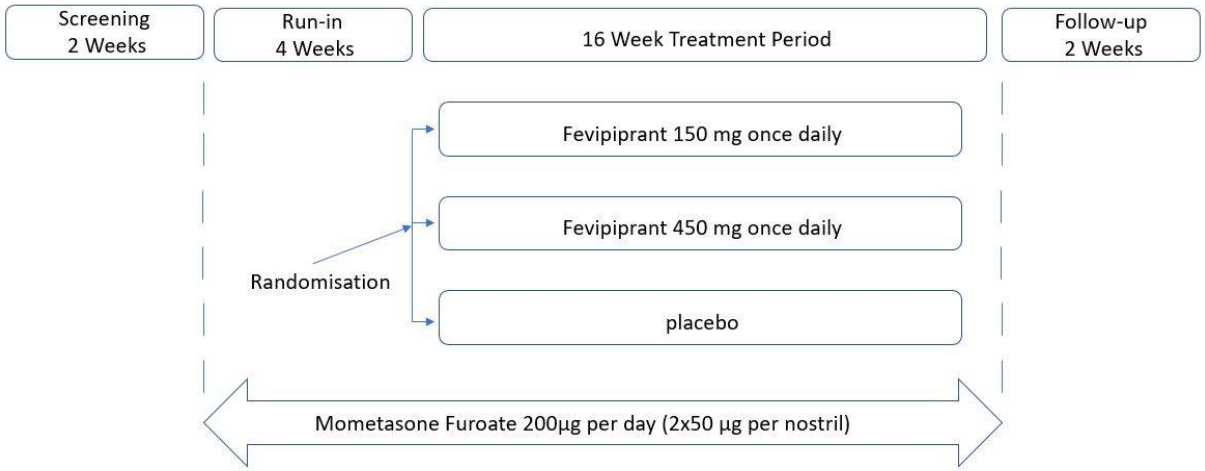
[redacted]

Objective(s)	Endpoint(s)
fevipiprant (150 mg or 450 mg once daily), compared with placebo.	mg once daily, separately) as compared to placebo.
[redacted]	

3 Study design

This is a Phase 3b, Proof-of-concept study with a randomized, multicenter, double-blind, placebo-controlled, parallel-group study design to determine the ability of fevipiprant plus SoC compared to placebo plus SoC to reduce the size of NPs. The study will include: Screening period of two weeks to assess eligibility; Run-in period of 4 weeks where patients will utilize mometasone furoate spray (200 µg once daily, administered as two 50 µg actuations into each nostril); Treatment period of 16 weeks (with visits held every month for study procedures); and a Follow-up period of two weeks following the last dose of study drug to collect additional data for safety variables. Patients will continue to use the mometasone furoate SoC throughout the Treatment period. Approximately 93 patients will be enrolled into this study. Please refer to Table 8-1 for the clinical visit schedule and the details of procedures to be performed at each visit.

Figure 3-1 Study Schematic



4 Rationale

4.1 Rationale for study design

The overall purpose of this study is to determine the ability of fevipiprant (150 mg and 450 mg once daily) plus SoC (mometasone furoate 200 µg daily), compared with placebo plus SoC, to reduce the size of nasal polyps during a 16 week Treatment period, assessed by nasal endoscopy

[redacted]

with central reading. The study will also determine if fevipiprant (150 mg and 450 mg once daily) plus SoC, compared with placebo plus SoC, can reduce symptoms and improve quality of life and smell, assessed via patient-reported outcomes (PROs) and the UPSIT.

4.1.1 Rationale for choice of background therapy

Mometasone furoate is the standard of care for nasal polyposis as per British society for allergy and clinical immunology (BSACI) treatment guidelines and will be utilized throughout the study, from the start of Run-in until the completion of treatment.

4.2 Rationale for dose/regimen and duration of treatment

QAW039 will be administered at doses of 150 mg and 450 mg once daily as oral film-coated tablets (FCTs) in this study. These doses have been selected for the ongoing asthma trials and are based on the following rationale:

The 450 mg once daily dose was selected because at a dose of 450 mg once daily, > 98% receptor occupancy is expected at steady state allowing inhibition of eosinophil migration over the entire treatment interval. Meanwhile in Study [CQAW039A2208], QAW039 caused significant reduction of sputum eosinophils in patients with severe eosinophilic asthma. The reduction in sputum eosinophils was comparable to that observed with the anti-IL5 antibodies, mepolizumab (Pavord et al 2012) and reslizumab (Castro et al 2011, Castro et al 2015).

A lower dose of 150 mg once daily was selected because it was the lowest dose of QAW039 with "maximal efficacy" on the endpoint of FEV1 in a prior dose-ranging study (Study [CQAW039A2206]) in patients with moderate-to-severe asthma (GINA treatment steps 4 and 5) as add-on to low-dose ICS. This dose is ½ log lower than the highest dose.

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

All patients in this study will receive mometasone furoate nasal spray (MFS) as SoC treatment with QAW039 or placebo administered as an add-on therapy. Patients currently using nasal corticosteroid drops or lavage will transfer on to MFS at the start of the Run-in period.

The use of placebo will permit the assessment of a reduction in nasal polyp score (NPS) along with improvement in symptoms, quality of life (QoL) and smell for patients treated with QAW039, in comparison to those on placebo, who will be on the nasal polyposis SoC therapy only. Additionally, the use of placebo will permit a controlled evaluation of the safety of QAW039.

This study does not include an active comparator since QAW039 will be given as an add-on therapy to standard of care therapy in patients with a NPS ≥ 4.

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable as no interim analysis will be performed on this study.

[redacted]

4.5 Risks and benefits

- QAW039 is a potent and highly selective oral DP2 receptor antagonist being developed as a potential therapy treatment for patients with severe asthma. DP2 is a receptor for PGD_2, which mediates the activation and migration of Th2 cells and eosinophils, some of the key inflammatory cell types in asthma. Recruitment of these cells into the lung is partly responsible for the intermittent airway obstruction, which leads to wheezing and shortness of breath characteristic of asthma.
- QAW039 is at least 300-fold selective for the DP2 receptor compared to other available prostanoid receptors and to cyclooxygenase-1 and cyclooxygenase-2, and it has been demonstrated to be a potent in-vitro inhibitor of human whole blood eosinophil activation and induction of Th2 cytokines. After oral dosing in rats, QAW039 inhibited pulmonary eosinophilia induced by the PGD_2 metabolite DK-PGD_2.
- The potential benefits of QAW039 therapy need to be balanced against its potential risks. The risk to patients in this study will be minimized by compliance with the inclusion/exclusion criteria and close clinical monitoring. All patients will remain on the background SoC asthma therapy they were taking at screening throughout the study.
- Women of child-bearing potential and sexually active males will 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 outlined in the exclusion criteria. If there is any question that the patient will not reliably comply, they should not be entered or continue in the study.
- The overall clinical experience with QAW039 includes 12 studies: 10 (6 in healthy volunteers and 4 in patients) have completed and 2 (in patients) are ongoing. The completed phase 2 studies consist of 3 in patients with asthma and 1 in patients with allergic rhinitis. The ongoing Phase 2 studies include one study in patients with asthma ([CQAW039A2214]) and 1 study in patients with atopic dermatitis ([CQAW039X2201]).
- QAW039 has been well tolerated in populations studied to date at total daily doses up to 500 mg given for up to 12 weeks. In the 10 completed studies, 16 patients reported 17 SAEs, no deaths due to SAEs were reported, and 5 discontinuations due to SAEs were reported. Of the 16 patients reporting SAEs, 12 patients reported 13 events, 2 patients reported 2 events and 2 patients reported 2 events in the QAW039, placebo, and montelukast treatment groups, respectively. There were no SAEs with a suspected causal relationship to QAW039. There have been no adverse events of idiopathic drug reactions.
- Cardiovascular risks: Transient, increases in heart rate were observed in a cardiovascular safety pharmacology study in dogs. These changes were not associated with any significant alterations in blood pressure, ECG interval duration, morphology or rhythm or any structural changes in cardiac tissues. No cardiac findings have been identified in the healthy volunteer and patient studies completed to date apart from an observed imbalance in the frequency of post-randomization cardiac adverse events in study [CQAW039A2206] with a higher incidence in the QAW039 treatment group (1.7%) compared with either placebo (0.7%) or montelukast (0%) treated patients. The cardiac events comprised a number of different non-serious arrhythmias and one serious adverse event of pericarditis not suspected to be related to study drug by the Investigator. Three of the events in the QAW039 treatment groups occurred during the washout period and

[redacted]

Table 8-1 Assessment Schedule

Period	Screening			Treatment					
Visit Name	Screening	Run-in[1]		Treatment				EOT or TD	Follow-up
Days	-42 to -28	-28 to -1	1	1	28	56	84	112	124
Weeks	-6 to -4	-4 to -1	1	1	4	8	12	16	18
Informed consent	X								
Inclusion / Exclusion criteria	X	X	X						
Demography	X								
Physical Examination	S							S	
Medical history/current medical conditions	X								
Surgeries and Procedures	X								
Prior medications	X								
Safety Follow up Call									S
ACQ-5	X								
Vital Signs	X	X	X		X	X	X	X	
Body Height	X								
Electrocardiogram (ECG)	X		X					X	
Body Weight	X								
Pregnancy Test (serum)	X								
Pregnancy Test (Urine)			S		S	S	S	S	
Hematology	X		X			X		X	
HbA1C	X							X	
Clinical Chemistry	X		X			X		X	
Urinalysis	X		X						
Check IMP Compliance					S	S	S	S	
Contact IRT (IVRS/IWRS)	S	S	S	S	S	S	S	S	
Randomization				S					

[redacted]

Period	Screening			Treatment					
Visit Name	Screening	Run-in[1]		Treatment				EOT or TD	Follow-up
Days	-42 to -28	-28 to -1	1	1	28	56	84	112	124
Weeks	-6 to -4	-4 to -1	1	1	4	8	12	16	18
Study Drug Dispensation				S	S	S	S		
Study drug administration				Daily					
SoC/Rescue Medication Dispense		S	S	S	S	S	S		
Adverse Events	X	X	X		X	X	X	X	X
Serious Adverse Events	X	X	X		X	X	X	X	X
Concomitant medications	X	X	X		X	X	X	X	X
Liver Event Monitoring[2]	X	X	X	X	X	X	X	X	X
Renal Event Monitoring[3]	X	X	X	X	X	X	X	X	X
Nasal Endoscopy[4]	X		X			X		X	
Nasal Congestion Score Questionnaire	X	X	X		X	X	X	X	
QoL Questionnaire (SNOT-22)	X	X	X		X	X	X	X	
Smell Assessment (UPSIT)	X	X	X		X	X	X	X	
Study completion information								X	
[redacted]									

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
[1] Assessments at Run-in Day 1 will be performed prior to Randomization. Run-in Day 1 and the Treatment Day 1 visit will take place on the same day if the patient is randomized
[2] Please refer to protocol Section 10.2.1
[3] Please refer to protocol Section 10.2.2
[4] Nasal polyp score will be determined by central reading.
[5] [redacted]
[6] For patient familiarization with device only.

[redacted]

8.3.2.2 Quality of Life (SNOT-22)

For this study, the SNOT-22 questionnaire (listed in Section 16.5) will be used to assess any improvement in the patients quality of life. The questionnaire consists of 22 questions relating to various quality of life indicators and answers are scored from 0 (no problem) to 5 (problem as bad as it can be) with questions relating to the patients experience in the previous 2 weeks.

The test will be self-administered by the patient via a tablet computer at the clinic visits outlined in Table 8-1 and takes only a few minutes to complete. The final outcome is a total score from 0 to 110.

8.3.3 Smell (UPSIT)

For this study, any change in the patients sense of smell will be assessed using the University of Pennsylvania Smell Identification Test. The test comprises of a kit which will be supplied to sites. The test includes 4 workbooks, each of which contains 10 microencapsulated (scratch and sniff) odors with forced choice responses accompanying each test item. The sites will also be supplied with the relevant instruction manual and scoring key.

The test is administered at the clinic visits and usually takes 10-15 minutes to complete. The result is a score out of 40 and this will be captured within the Clinical Database by the site personnel.

8.3.4 Appropriateness of efficacy assessments

The efficacy assessments outlined above are deemed to be sufficient for the objectives of the study.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section.

Table 8-3 Physical Assessments

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. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. 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 first administration of investigational drug which meet the definition of an Adverse Event must be recorded as an adverse event.

[redacted]

Assessment	Specification
Vital signs	Vital signs include blood pressure and pulse measurements. After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.
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

Samples for safety will be collected as per the assessment schedule in Table 8-1 . A central laboratory will be used for analysis of all specimens detailed in this section. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to Investigators in the laboratory manual.

Details on clinically notable laboratory findings are defined in Section 16.1 .

Table 8-4 Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Other).
Clinical Chemistry	Albumin, Alkaline phosphatase, ALT , AST , Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, CK-MB and Troponin I (in response to CK results outside of the normal range), HbA1c (collected at Screening visit and EOT only), Direct Bilirubin, Total Bilirubin, Total Cholesterol, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose.
Urinalysis	Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells) - if required. Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) Urine chemistry and microscopic examination of the urine will be performed by the central laboratory as delineated in Section 10.2.2 "Renal Safety Monitoring" and Section 16.3 "Specific Renal Alert Criteria and Actions and Event Follow-up"
Coagulation	International normalized ratio (INR), activated partial thromboplastin time (APTT)
Pregnancy Test	Serum / Urine pregnancy test

8.4.2 Electrocardiogram (ECG)

ECGs will be measured according to the assessment schedule in Table 8-1. ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Single 12-lead ECGs will be collected using the sites own ECG machines and key parameters and the original trace available within the source data.

[redacted]

For any ECGs with subject safety concerns, two additional ECGs must be performed to confirm the safety finding. A monitoring or review process should be in place for clinically significant ECG findings throughout the study and especially at baseline before administration of study treatment. Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate.

Any identifier details must be redacted e.g subject initials, date of birth.

8.4.3 Pregnancy

All pre-menopausal women who are not surgically sterile will have serum/urine pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

8.4.4 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

COAs are utilised on this study for assessment of study eligibility and also as part of the secondary study objectives. Those COAs related to the study objectives and efficacy are documented in protocol Section 8.3.2.

The remaining COAs used on this study are documented as follows.

8.5.1.1 Asthma Control Questionnaire (ACQ-5)

In this study the ACQ-5 will be used as Exclusion criterion at screening in order to identify those subjects who are currently symptomatic and who may exacerbate during the Run-in or treatment periods.

The ACQ-5 will be self-administered at the clinic during the screening visit and it only takes a few minutes to complete. Patients will be asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0=no impairment, 6=maximum impairment). The questions are equally weighted and the ACQ-5 score is the mean of the 5 questions and therefore between 0 (totally controlled) and 6 (severely uncontrolled) (Juniper et al 1999; Juniper et al 2005) (Section 16.6).

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the patient or the Investigator.

The Investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Study treatment must be discontinued under the following circumstances:

- Withdrawal of informed consent (and the Investigator must prematurely withdraw the patient from the study);
- Pregnancy;
- 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 and follow up with the subject as appropriate at least to the end of this period;
- Any protocol deviation that results in a significant risk to the patient's safety;
- Liver laboratory test abnormality / event (see Section 16.2):
  - Abnormal liver laboratory results requiring discontinuation – refer to Table 16-1 - Section 16.2 ;
- If the Investigator considers it appropriate after the confirmation of a liver safety monitoring signal:

[redacted]

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

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

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn

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 14 days (or 5 half-lives or end of study visit, whichever is longer) following the last dose of study treatment

Information about adverse drug reactions for the investigational drug can be found in the Investigator 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

[redacted]

10.1.3 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days following the last administration of study treatment 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.

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 Chief Medical Office and Patient Safety 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.

10.1.4 Pregnancy reporting

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. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study 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.

[redacted]

12.4.1 Definition of primary endpoint(s)

The primary endpoint for this study is the mean change in terms of reduction in polyp size as measured by the nasal polyp score (NPS) from baseline to week 16, for patients treated with fevipiprant (150 mg or 450 mg once daily, separately) as compared to placebo.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary endpoint for this study is the efficacy in terms of change from baseline in the nasal polyp score of fevipiprant 450 mg plus SoC and fevipiprant 150 mg plus SoC over placebo plus SoC. The primary null hypotheses are:

- $H_{0\,450}$: the reduction in the polyp size at 16 weeks from the baseline as measured by the NPS in fevipiprant 450 mg QD plus the SoC is less than or equal to the reduction in the polyp size as measured by the NPS in placebo plus the SoC for the population.
- $H_{0\,150}$: the reduction in the polyp size at 16 weeks from the baseline as measured by the NPS in fevipiprant 150 mg QD plus the SoC is less than or equal to the reduction in the polyp size as measured by the NPS in placebo plus the SoC for the population.

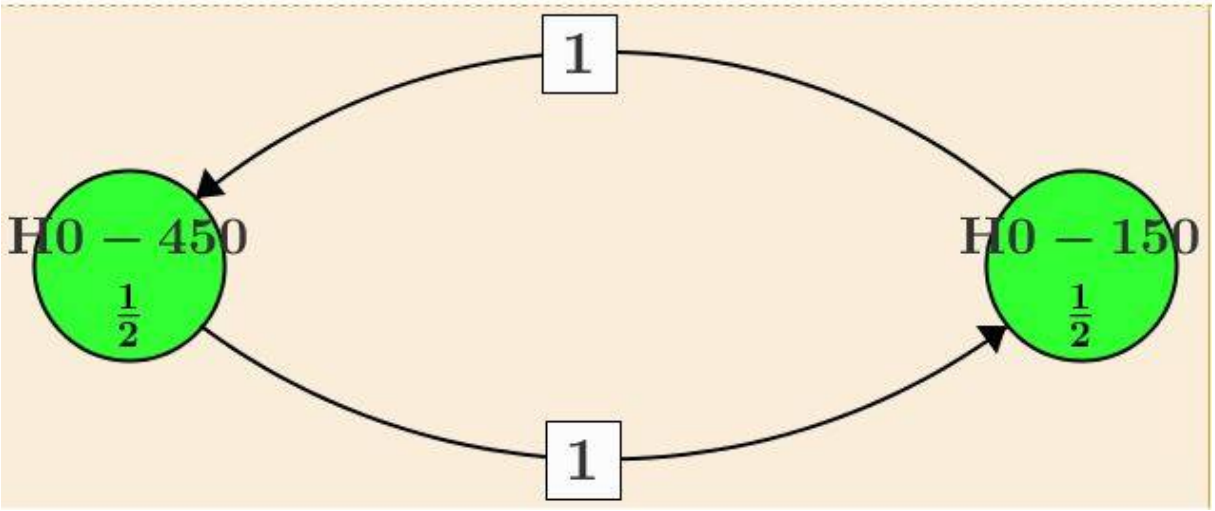
The primary alternative hypotheses are:

- $H_{A\,450}$: the reduction in the polyp size at 16 weeks from the baseline as measured by the NPS in fevipiprant 450 mg QD plus the SoC is greater than the reduction of the polyp size as measured by the NPS in placebo plus the SoC for the population
- $H_{A\,150}$: the reduction in the polyp size at 16 weeks from the baseline as measured by the NPS in fevipiprant 150 mg QD plus the SoC is greater than the reduction of the polyp size as measured by the NPS in placebo plus the SoC for the population

Familywise Type I error rate control

The familywise type I error rate will be controlled at a 1-sided 2.5% level across the primary null hypothesis using graphical approach specified by Figure 12-1 (Bretz et al 2011). The Dunnett test will be used to test $H_{0\,450}$ and $H_{0\,150}$

Figure 12-1 Representation of Approach to Test Hypotheses



[redacted]

Vertices with associated weights denote the individual null hypotheses and their local significance levels (initially the alpha is split 50%:50% across the primary null hypotheses regarding the two dose levels. Directed edges between the vertices specify how the local significance levels are propagated in case of significant results.

Statistical model for primary variable

The primary efficacy endpoint is mean change in nasal polyp score from baseline to Week 16.

Baseline NPS is defined as the last measurement performed before the first dose of study drug. The absolute change from baseline NPS values will be defined as the NPS at the timepoint minus the NPS at baseline.

The primary efficacy variable will be analyzed using a mixed model repeated measures (MMRM) approach (fevipiprant 450 mg plus SoC and fevipiprant 150 mg plus SoC). The model will include change from baseline to follow-up timepoints every 4 weeks through week 16 as response variables, fixed-effects factors for treatment, visit, treatment × visit interaction, nasal polyp score baseline value, and baseline × visit interaction. An unstructured correlation structure will be assumed for the repeated measures within patients. Parameters will be estimated using the restricted maximum likelihood method with the Newton- Raphson algorithm. The least square mean change in nasal polyp score from baseline to week 16 alongside with 95% confidence interval and the P-value corresponding to the least square mean difference will be presented. The change in the least square mean will also be plotted against the visits to look at the general trend of the values across the visits.

The absolute change from baseline in NPS will be summarized by treatment arm and timepoint

12.4.3 Handling of missing values/censoring/discontinuations

Despite all attempts to ensure complete follow-up for all patients, some patients may not be followed for nasal polyp size for the whole planned study duration of 16 weeks. The primary analysis will be done using a Mixed Model Repeated Measures (MMRM) approach. Under the assumption that the missing values are missing at random (MAR), this provides asymptotically unbiased and consistent estimates of the treatment effects.

12.4.4 Sensitivity and Supportive analyses

Sensitivity Analysis 1: A responder analysis of patients achieving a reduction of at least 1 in the Nasal Polyp score would be performed using a logistic regression, including terms for treatment, visits and interaction between treatment and visit.

Sensitivity Analysis 2: The primary efficacy endpoint will be evaluated using the MMRM approach after imputing the Nasal Polyp Scores following surgery, only for patients who are considered as study withdrawals due to undergoing surgical procedures, by using the last observation carried forward (LOCF) technique. All other missing values will be imputed under the MAR approach within the MMRM model.

Sensitivity Analysis 3: The primary efficacy endpoint will be evaluated using the MMRM approach after imputing the Nasal Polyp Scores following surgery only for patients who are considered as study withdrawals due to undergoing surgical procedures, by using the worst

SNOT-22 will be estimated using an MMRM model with change from baseline as the response variable, adjusted for visits (Week 4, 8, 12 and 16), treatment, interaction between visit and treatment and baseline SNOT-22.

The least square mean change in SNOT-22 Score from baseline to week 16 alongside with 95% confidence interval and the P-value corresponding to the least square mean difference will be presented.

To evaluate the effect on smell as measured by the university of Pennsylvania smell identification test (UPSIT) with fevipiprant (150 mg or 450 mg, once daily) ,compared to placebo, in terms of increase in smell score from baseline to Week 16.

The university of Pennsylvania smell identification test (UPSIT) is a test for smell identification to test an individuals olfactory response. The test is a measure of an individual's ability to detect odor. It consists of 4 workbooks of 10 questions, giving a total of 40 questions. On each page, there is a different "scratch and sniff" strip which are embedded with a microencapsulated odorant. There is also a four choice multiple choice question on each page. The scents are released using a pencil. After each scent is released, the patient smells the level and detects the odor from the four choices. There is an answer column on the back of the test booklet, and the test is scored out of 40 items. The score is compared to scores in a normative database from 4000 normal individuals, this tells the level of absolute smell function. The score also indicates how the patient does in accordance to their age group and gender. The maximum score achievable on the scale is 40.

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

To evaluate the general safety and tolerability of fevipiprant (150 mg and 450 mg, separately) as compared to placebo.

Safety and tolerability assessments were based on the incidence of adverse events and serious adverse events, as well as vital signs, clinical laboratory evaluation, and 12-lead electrocardiogram findings.

12.5.1 Safety Variables

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group. Safety summaries will be primarily based on on-treatment data with selected tables also presented for the all data after the first intake of study drug, while all databased safety data will be listed. The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment.

Adverse events

Adverse events starting on or after the time of first intake of study drug and until the 30 days after the last intake of study drug will be classified as treatment-emergent adverse events. Any adverse events that started during the study after informed consent before the time of first intake

[redacted]

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 (**defines as last patient 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 (SOPs) 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.

[redacted]

Criteria	Actions required	Follow-up monitoring
> 3 × ULN accompanied by symptoms[b]	• 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 γGT until resolution[c] (frequency at Investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
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 • 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 γGT until resolution[c] (frequency at Investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • 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 γGT until resolution[c] (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](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia [c]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.

[redacted]

16.4 Appendix 4: Nasal Congestion Score Questionnaire

Figure 16-1 Nasal Congestion Score

1. Is your nose blocked? [a]

   0 = Not at all 1 = Mild 2 = Moderate 3 = Severe

2. Is your sense of smell reduced?

   0 = Not at all 1 = Mild 2 = Moderate 3 = Severe

3. Do you have a runny nose?

   0 = Not at all 1 = Mild 2 = Moderate 3 = Severe

4. Do you feel dripping at the back of the nose?

   0 = Not at all 1 = Mild 2 = Moderate 3 = Severe

[a] The Nasal Congestion Score (NCS) will be assessed with Question 1 only.

[redacted]

16.5 Appendix 5: SNOT-22 Questionnaire

Figure 16-2 SNOT-22 Questionnaire

I.D.:_____ **SINO-NASAL OUTCOME TEST (SNOT-22)** DATE:_____

Below you will find a list of symptoms and social/emotional consequences of your rhinosinusitis. We would like to know more about these problems and would appreciate your answering the following questions to the best of your ability. There are no right or wrong answers, and only you can provide us with this information. Please rate your problems as they have been over the past two weeks. Thank you for your participation. Do not hesitate to ask for assistance if necessary.

1. Considering how severe the problem is when you experience it and how often it happens, please rate each item below on how "bad" it is by circling the number that corresponds with how you feel using this scale: →	No Problem	Very Mild Problem	Mild or slight Problem	Moderate Problem	Severe Problem	Problem as bad as it can be		5 Most Important Items
1. Need to blow nose	0	1	2	3	4	5		○
2. Nasal Blockage	0	1	2	3	4	5		○
3. Sneezing	0	1	2	3	4	5		○
4. Runny nose	0	1	2	3	4	5		○
5. Cough	0	1	2	3	4	5		○
6. Post-nasal discharge	0	1	2	3	4	5		○
7. Thick nasal discharge	0	1	2	3	4	5		○
8. Ear fullness	0	1	2	3	4	5		○
9. Dizziness	0	1	2	3	4	5		○
10. Ear pain	0	1	2	3	4	5		○
11. Facial pain/pressure	0	1	2	3	4	5		○
12. Decreased Sense of Smell/Taste	0	1	2	3	4	5		○
13. Difficulty falling asleep	0	1	2	3	4	5		○
14. Wake up at night	0	1	2	3	4	5		○
15. Lack of a good night's sleep	0	1	2	3	4	5		○
16. Wake up tired	0	1	2	3	4	5		○
17. Fatigue	0	1	2	3	4	5		○
18. Reduced productivity	0	1	2	3	4	5		○
19. Reduced concentration	0	1	2	3	4	5		○
20. Frustrated/restless/irritable	0	1	2	3	4	5		○
21. Sad	0	1	2	3	4	5		○
22. Embarrassed	0	1	2	3	4	5		○

2. Please mark the most important items affecting your health (maximum of 5 items)_____ ↑

[redacted]

16.6 Appendix 6: ACQ-5 Questionnaire

Figure 16-3 Asthma Control Questionnaire - 5 - Page 1

ASTHMA CONTROL QUESTIONNAIRE
(SYMPTOMS ONLY)

For further information:

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December 2002

[redacted]

Figure 16-4 Asthma Control Questionnaire - 5 - Page 2

ASTHMA CONTROL QUESTIONNAIRE© Page 1 of 1

Please answer questions 1 - 5

Circle the number of the response that best describes how you have been during the past week.

1.	On average, during the past week, how often were you **woken by your asthma** during the night?	0 Never 1 Hardly ever 2 A few times 3 Several times 4 Many times 5 A great many times 6 Unable to sleep because of asthma
2.	On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?	0 No symptoms 1 Very mild symptoms 2 Mild symptoms 3 Moderate symptoms 4 Quite severe symptoms 5 Severe symptoms 6 Very severe symptoms
3.	In general, during the past week, how **limited were you in your activities** because of your asthma?	0 Not limited at all 1 Very slightly limited 2 Slightly limited 3 Moderately limited 4 Very limited 5 Extremely limited 6 Totally limited
4.	In general, during the past week, how much **shortness of breath** did you experience because of your asthma?	0 None 1 A very little 2 A little 3 A moderate amount 4 Quite a lot 5 A great deal 6 A very great deal
5.	In general, during the past week, how much of the time did you **wheeze**?	0 Not at all 1 Hardly any of the time 2 A little of the time 3 A moderate amount of the time 4 A lot of the time 5 Most of the time 6 All the time

SYMPTOMS ONLY MODIFIED 30 JAN 04 NORTH AMERICAN ENGLISH

[redacted]

16.7 Appendix 7: Nasal Endoscopy

Nasal Endoscope will be performed at the clinic using either a flexible fiber optic endoscope or a rigid endoscope. Polyps will be evaluated using the following scale:

Polyp Score	Polyp Size
0	No polyps
1	Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate
2	Polyps reaching below the lower border of the middle turbinate
3	Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate
4	Large polyps causing complete obstruction of the inferior nasal cavity

Note: Scoring system is used to evaluate polyp size in each nasal passage by means of video nasal endoscopy. Nasal polyp score is the sum of unilateral polyp scores for each nasal passage.The scoring is modified to accommodate patients who have had a middle turbinectomy, such that the polyp must reach the top of the inferior turbinate to be graded as Score 2.

If the patient has polyps between the middle turbinate and septum meaning that polyps are coming from posterior ethmoid cells, one point was added, but not if the polyp scale was already confirmed. The grade of polyps in each nasal cavity of all patients will be taken into account in the results.

A video of each endoscopy will be recorded and initially saved locally within the clinical site. For endoscopy procedures performed at screening, the initial assessment of eligibility will be performed locally by the Investigator with the video files then uploaded for assessment of the NPS and confirmation of eligibility by central reading. This should be confirmed before the patient enters the run-in period. The endoscopy will be assessed at the end of the run-in with baseline NPS assigned locally by the Investigator. Should the Investigator deem the patient eligible for randomization then the baseline video will be uploaded for central reading assessment. The final result from the central readers **must** be received to re-confirm eligibility, prior to randomization. Upon confirmation of eligibility, the endoscopy assessments from Treatment Day 1 onwards, will also be uploaded to the vendors cloud based system for central reading assessment of the NPS. Should this upload not be possible due to local restrictions or logistics, the endoscopy video will be posted to the vendor on an encrypted USB drive. The vendor will utilize two independent experts who will each review the video and assign a score for NPS for that patient at the specific timepoint. Should there not be an agreement between the two reviewers, a third review will act as adjudicator and will make the final decision on the NPS.

Full training on the use of the vendors cloud based system will be provided.

[redacted]

P-gp	P-glycoprotein
PASS	power analysis software
PCR	protein-creatinine ratio
PK	pharmacokinetic
PRO	patient-reported outcome
PT	prothrombin time
QMS	quality management system
QoL	quality of life
QTc	QT interval
QTcF	QT interval - Fridericia correction
RoW	rest of world
SABA	short-acting bronchodilator
SAE	serious adverse event
SAF	safety analysis set
sCr	serum creatinine
SCS	systemic corticosteroids
SD	standard deviation
SNOT-22	sino-nasal outcome test - 22 questions
SoC	standard of care
SOP	standard operating procedure
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin
Th2	T helper cell type 2
UK	United Kingdom
ULN	upper limit of normal
UPSIT	University of Pennsylvania smell identification test
US	United States
USB	universal serial bus
WHO	world health organization
WoC	withdrawal of consent

resolved on treatment. Based on the inability to identify discernable trends with QAW039 dose, regimen, time-of-onset, patient age and gender, concomitant medication, event type and following detail ECG review, it was considered that these were most probably coincidental events without a causal association to study drug. A formal QTc study has not been completed for QAW039. Monitoring for changes in vital signs, ECGs and biochemical parameters will be conducted.

- Liver toxicity: Dose-dependent increases in liver weights with concomitant hepatocellular hypertrophy were the primary findings during 2- and 13-week toxicity studies in mice. These changes were considered to be a species-specific adaptive metabolic response with no relevance for humans. Liver toxicity findings have not been identified in the healthy volunteer and patient studies completed to date. Monitoring of liver function tests (LFTs) will be conducted as described in Section 16.2 of this protocol.
- Potential risk of idiosyncratic drug reactions CCN362 is an acylglucuronide metabolite of QAW039 and its potential to covalently bind to plasma proteins, such as albumin, was demonstrated in the human ADME (Absorption, distribution, metabolism, excretion) study of QAW039 ([CQAW039A2104]). 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 (Regan et al 2010). There have been no IDRs observed with QAW039 treatment in completed clinical trials. Surveillance of adverse events for identification of IDRs will be conducted.
- Drug-drug interactions: QAW039 and CCN362 did not show any relevant inhibition or induction of the cytochrome P450 isoenzymes or inhibition of ubiquitous efflux transporters. The most potent in-vitro inhibition by QAW039 was found for OATP1B1, but clinically only a small impact was observed at 450 mg/day (~2-fold increase in Cmax of simvastatin acid and rosuvastatin without change in AUC). Based on these data, as well as recommendations in the simvastatin label, simvastatin doses of > 20 mg per day should not be co-administered with QAW039; no relevant impact on the disposition of other co-medications are expected with QAW039 dosed up to 450 mg/day. Patients on doses of simvastatin > 20 mg, doses of atorvastatin > 40 mg, doses of pravastatin > 40mg, or doses of pitavastatin > 2 mg per day (Elsby et al 2012, Deng et al 2008, Noé et al 2007, and Kalliokoski and Niemi 2009), as well as patients on any statins with high CK levels (> 2 X upper limit of normal (ULN)) at screening (Visit 1) will be excluded from the study. Furthermore, patients 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 blood CK levels (Jacobson 2008).
- Overall, the safety profile of QAW039 has been favorable across studies. Three Phase 2 studies in patients with asthma demonstrated the effect of QAW039 across the range of asthma severities (mild to severe). For detailed information on the studies described below, please refer to the Investigator's Brochure (IB).

[redacted]

8.1 Screening

Patients will be scheduled to attend for the screening visit within 14 days of the scheduled start of the Run-in period. It is permissible to re-screen a patient if he/she fails the initial screening; however, each case must be discussed and agreed with Novartis on a case-by-case basis.

8.1.1 Information to be collected on screening failures

Subjects who signed an informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the screening phase (see SAE Reporting Section, Section 10.1.3 for reporting details). If the subject fails to be randomized, the IRT must be notified within 2 days of the screen fail that the subject was not randomized.

Subjects who are randomized and fail to start treatment, e.g. subjects randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Subject demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include:

- Date of birth (where allowed by local legislation)
- Age (calculated)
- Sex
- Race and ethnicity
- Patients initials (where allowed by local legislation)
- Height and Weight
- BMI (calculated)
- Baseline physical examination (not databased other than in the context of relevant medical history)
- Vital signs
- Date of diagnosis of asthma
- Relevant medical history/ current medical condition present before signing the informed consent
- Asthma Control (ACQ-5)
- Prior concomitant medication (Both asthma/NP related and non-asthma/NP related)

8.3 Efficacy

The following assessments of efficacy will be performed:

- Nasal Polyp Score
- Patient-reported Outcomes (NCS and SNOT-22)

[redacted]

  - ALT or AST ≥ 5xULN, **or**
  - ALT or AST ≥ 2.5xULN **and** total bilirubin (TBL) ≥ 1.5xULN (Section 16.2);
- 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;
- Premature unblinding of study treatment for a patient for any reason; please refer to Section 6.6.2 ;
- Total white blood cell count < 1000 cells/µL;
- Patient requires SCS/OCS use for a period of more than 5 consecutive days during the study. Any OCS/SCS use in addition to this allowed 5 days of treatment will result in withdrawal;
- If patients on statin therapy complain of persistent muscle pain without any obvious cause for greater than 3 days, accompanied by an increase in CK levels >10xULN or persistent intolerable muscle pain, regardless of the accompanying CK level;
- If a patient undergoes nasal surgery, including but not limited to the following: treatment of nasal polyposis, septal deviation correction, turbinectomy, para-nasal sinus drainage, nasal plastic surgery, hypophysis tumor nasal approach.
- If a patient develops a medical condition, that requires consistent use of prohibited treatment as per Section 6.2.2 or if patient exhibits a behavior of non-compliance regarding prohibited medication.

If discontinuation of study treatment occurs, the Investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information.

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 withdraw of informed consent section,). **Where possible, they should return for the assessments indicated** in the Assessment schedule (Table 8-1).

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

- new/concomitant treatments including OCS use
- adverse events/Serious Adverse Events

If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail or letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule. The information already collected during the study including your samples will still be used according to applicable laws

[redacted]

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 included in Section 16.1.

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:

1. routine treatment or monitoring of the studied indication, not associated with any deterioration in condition under study
2. 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
3. social reasons and respite care in the absence of any deterioration in the subject's general condition
4. 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.

[redacted]

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 Dose Administration Record (DAR) eCRF (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 - Appendix 2 in Section 16 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Section 16.1- Appendix 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 are outlined in Table 16-2 - Appendix 2. Repeat liver function test (LFT) 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.

[redacted]

observed score for that patient. All other missing values will be imputed under the MAR approach within the MMRM model.

12.5 Analysis of secondary endpoints

The secondary objectives include:

To evaluate the effect of symptoms as measured by the nasal congestion score with fevipiprant (150 mg or 450 mg once daily, separately) as compared to placebo, in terms of reduction in NCS from baseline to week 16.

Nasal congestion is defined as the objective restriction of the nasal cavity airflow caused by mucosal pathology and or by mucosal secretions when anatomical variations have been excluded. The nasal congestion score is calculated based on the responses from the patients in Question 1 from the nasal congestion questionnaire outlined in Section 16.4. The questionnaire has four questions relating to the symptoms of nasal obstruction with each question having four categories ranging from 0-3, where the scores relate to the degree of severity as follows:

- 0 = Not at all
- 1 = Mild
- 2 = Moderate
- 3 = Severe

The score however is calculated based on the response to the first question in the questionnaire.

The change in Nasal Congestion Score (NCS) will be analyzed using an MMRM model with visit, treatment, interaction between visit and treatment and the baseline average NCS as covariates. The least square mean change in Nasal Congestion Score from baseline to week 16 alongside with 95% confidence interval and the P-value corresponding to the least square mean difference will be presented.

To evaluate the effect on quality of life as measured by the sino-nasal outcome test (SNOT-22) with fevipiprant (150 mg or 450 mg once daily, separately) , compared to placebo, in terms of increase in QoL score from baseline to Week 16.

SNOT-22 measures the quality of life in patients facing nasal obstructions (Section 16.5). There are 22 items available on the questionnaire. Each item in the questionnaire are followed by five options to choose from:

- 0 = No problem
- 1 = Very Mild Problem
- 2 = Mild or slight Problem
- 3= Moderate problem
- 4 = Severe Problem
- 5 = Problem as bad as it can be.

The scores for each of the items are added to get a total out of 110, with 110 being the worst signifier of quality of life. Also the questionnaire has the option for the patient to select the five most important items affecting their health which are analyzed separately to give a rating across the patients The treatment group difference in terms of change from baseline at Week 16 in

[redacted]

of the study drug will be classified as a prior adverse event and not included in tabulations of treatment emergent adverse events.

The following treatment emergent adverse event summaries will be produced,

- overall by system organ class and preferred term,
- overall by system organ class and preferred,
- overall by system organ class, preferred term and maximum severity,
- suspected drug related adverse events by system organ class and preferred term, and
- adverse events leading to permanent discontinuation of study drug by system organ class and preferred term.

Serious adverse events, non-serious adverse events, adverse events requiring dose adjustment or study-drug interruption adverse events requiring additional therapy during the on-treatment period will be summarized.

The adverse events of special interest (AESI) will be listed and summarized by treatment group.

Vital signs

All vital signs data will be listed by treatment group, On-treatment notable vital signs abnormalities will be summarized by treatment group.

12-lead ECG

The notable ECG abnormalities will be summarized for following ECG variables,QT interval, RR interval, PR interval, QRS duration, heart rate, and Friedericia's QTc.

Clinical laboratory evaluations

All laboratory data will be listed with abnormal values flagged.

All laboratory parameter values will be classified into one of the four mutually exclusive groups (low, normal, high, and low + high).

For selected laboratory parameters, the number and percentage of patients with newly occurring or worsening on-treatment laboratory abnormalities meeting the clinically notable will be summarized by laboratory parameter at any time-point over the treatment period, considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits. Patients with any newly occurring or worsening on-treatment value meeting the clinically notable criteria will be counted under the applicable criteria.

[redacted]

12.7 Interim analyses

No formal interim analysis will be performed in this trial.

[redacted]

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.

[redacted]

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 Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥50% compared to baseline	Follow up within 24-48h if possible Consider study treatment interruption Consider patient hospitalization /specialized treatment
Urine Event	
Albumin-creatinine ratio (ACR) ≥1g/g or ≥100 mg/mmol; Protein-creatinine ratio (PCR) ≥1g/g or ≥100 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider study treatment interruption / or discontinuation
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor patient 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.	