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QAW039

Clinical Trial Protocol CQAW039A2322 / NCT03681093

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

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List of abbreviations

ACQ-5	asthma control questionnaire - 5 questions
ACR	albumin-creatinine ratio
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special interest
Alb	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AUC	area under the curve
AV	atrioventricular
BMI	body mass index
BSACI	British society for allergy and clinical immunology
BUN	blood urea nitrogen
CFR	code of federal regulation
CK	creatinine kinase
Cmax	maximum concentration
COAs	clinical outcome assessments
CPO	country pharma organisation
CRA	clinical research associate
CRF	case report/record form (paper or electronic)
CT	computerized tomography
CTT	clinical trial team
DAR	dose administration record
DMC	data monitoring committee
DP2	prostaglandin D2 receptor
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European medicines agency
ENT	ear, nose, throat
EOT	end of treatment
EU	European Union
FAS	full analysis sets
FCT	film-coated tablets
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity

[redacted]

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]

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

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
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)
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)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study.
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial subjects, regardless of randomization group, rescue medication, active drug run-ins etc.)
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
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
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
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)

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Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either 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 consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

[redacted]

Amendment 3

Amendment rationale

The protocol is being amended to provide clarification on the process for assessment of nasal endoscopy at baseline and management of protocol deviations in relation to the statistical analysis sets. These changes include:

- Changes in Section 8.3.1 to remove the constraint around the performance of the nasal endoscopy at the end of run-in/baseline visit along with confirming that patient eligibility will be based on the central reading score
- Change to the text in Section 12.1 to highlight that the Full Analysis Set will only comprise of patients with a baseline NPS ≥ 4, confirmed by central reading
- Addition of text in Section 12.4 to clarify that the central reading score is what will be used for the primary endpoint analysis
- Addition of text in Appendix 7 to clarify that the central reading score is the final determination of eligibility at both screening and end of run-in/baseline.

IRB Section

The changes described in this protocol have been classed as non-substantial and will not require additional IRB/HA approval, unless required by local regulations.

[redacted]

Amendment 2

Amendment rationale

The protocol is being amended to align the safety requirements with other studies in the QAW039 program. These changes include:

- Addition of exclusion criteria to align with other QAW039 studies in Section 5.2
- Update to contraception exclusion criteria to reference that any local deviations from the contraception requirements will apply and will be described within the patient informed consent form. Updates also included to align exclusion criteria with the prohibited medications in Table 6-2
- Update to asthma inclusion criteria throughout the protocol to remove reference to Global Initiative for Asthma (GINA) Step 3 in order to remove any contradiction and discrepancy with other QAW039 trials given this is a new population.
- Inclusion of Table 6-1 - Medications allowed under certain conditions - in Section 6.2.1
- Inclusion of renal safety monitoring in Section 10.2.2 and additional details as an appendix in Section 16.3
- Addition of urine pregnancy testing at each treatment visit
- Addition of liver event and renal event monitoring to each visit in Table 8-1
- Inclusion of clinical chemistry reflex testing in the event of elevated creatine kinase (CK) results in Table 8-4
- Addition of hemoglobin A1c (HbA1c) testing at Screening and end of treatment (EOT) with updates to Table 8-1 and Table 8-4

Changes to the protocol

The described changes in the aforementioned amendment rationale are implemented throughout the protocol in the sections noted.

The opportunity was also taken to make the following changes in the protocol:

- Changes made in Table 8-1 to clarify which assessments are performed prior to the start of treatment at the Week 1 visit. Other minor clarification changes also included in this table.
- Addition of patient withdrawal criteria in Section 9.1.1 relating to the need for nasal surgery during the trial, use of corticosteroids during the trial and also for persistent muscle pain, with or without elevated CK levels.
- Clarification of Nasal Endoscopy readings / assessments being performed centrally and locally
- Addition of sensitivity analyses in Section 12.4.4
- Typographical changes throughout for spelling/consistency.

IRB Section

A copy of this amended protocol will be sent to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Health Authorities.

[redacted]

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval, a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 1

Amendment rationale

The protocol is being amended based on health authority feedback - the following changes have been implemented:

- Added additional exclusion criteria to Section 5.2 to ensure that patients taking any of the prohibited medications outlined in Table 6-2 are appropriately excluded.

Changes to the protocol

The described changes in the aforementioned amendment rationale are implemented throughout the protocol in the sections noted.

The opportunity was also taken to amend typographical items in the protocol:

- Rewording of the text for the restriction on nasal corticosteroids in Table 6-2 to better clarify the specific types that are excluded along with the restricted statin therapies
- Minor revision to the wording in Section 8.3.3

[redacted]

Protocol summary

Protocol number	CQAW039A2322
Full Title	A multicenter, randomized, double-blind, parallel-group, placebo-controlled study of fevipiprant once daily plus standard-of-care (SoC) for assessment of the efficacy in reduction of nasal polyp size in patients with nasal polyposis and concomitant asthma.
Brief title	Study of efficacy of fevipiprant in patients with nasal polyposis and asthma
Sponsor and Clinical Phase	Novartis Phase 3b
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Nasal polyposis is a common disorder, affecting up to 4% of the population. Although the causes remain unclear, nasal polyposis has been associated with a number of conditions including, asthma, infection, cystic fibrosis and aspirin sensitivity. Nasal polyposis with concomitant asthma has a prevalence ranging from 2%-66% although it is usually in the region of 30% of those nasal polyposis patients who are referred to (ear, nose, throat) ENT departments. The purpose of this study is to evaluate the efficacy and safety of fevipiprant 150 mg and 450 mg compared to placebo in the reduction of nasal polyps size and the effect on symptoms, quality of life and smell via patient-reported outcomes in patients with nasal polyposis (NP) and concomitant asthma.
Primary Objective(s)	• In patients with nasal polyps with a polyp size score ≥ 4 at baseline, to demonstrate a difference in mean change from baseline in polyp size at Week 16, measured by the nasal polyp score (NPS, assessed by nasal endoscopy with central reading), between fevipiprant (150 mg or 450 mg once daily, separately) and placebo
Secondary Objectives	• To evaluate the effect on symptoms as measured by the nasal congestion score (NCS) with fevipiprant (150 mg or 450 mg once daily), compared with placebo following 16 weeks of treatment. • To evaluate the effect on quality of life as measured by the Sino-Nasal Outcome Test - 22 (SNOT-22) with fevipiprant (150 mg or 450 mg once daily), compared with placebo following 16 weeks of treatment. • 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 with placebo following 16 weeks of treatment. • To evaluate the effect of fevipiprant 150 mg and 450 mg compared with placebo in terms of general safety/tolerability following 16 weeks of treatment.
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 2 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 2 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.
Population	The study population will consist of approximately 93 male and female patients aged 18 and above, diagnosed with nasal polyposis with nasal polyp size score ≥ 4 (nasal polyp score, assessed by nasal endoscopy) with a minimum score of 2 in each nostril; and a concomitant diagnosis of asthma.
Key Inclusion criteria	• Written informed consent must be obtained before any assessment is performed. • Patients aged ≥ 18 years with a diagnosis of nasal polyposis with nasal polyp size score ≥ 4 and a minimum score of 2 in each nostril, measured by nasal endoscopy at screening and prior to randomization on Run-in/Treatment Day 1 (to ensure no reduction in NPS following the use of the mometasone furoate SoC therapy). • Patients with a concomitant diagnosis of asthma for a period of at least 6 months prior to screening. • Have been on a stable asthma treatment regimen of at least inhaled corticosteroids (ICS, any dose), alone for at least 6 months prior to Screening or ICS for 6 months prior to Screening with any other required inhaled asthma medication (long-acting bronchodilator (LABA), long-acting muscarinic antagonist (LAMA)) added at least 6 weeks prior to Screening.
Key Exclusion criteria	• Asthma exacerbation, within 6 weeks prior to Screening that required systemic corticosteroids, hospitalization, or emergency room visit. When patients experience an exacerbation between screening and the end of the 4 week Run-in period, and prior to randomization, they will be considered screen failures and can be eligible for re-screening only once the required 6 weeks post-exacerbation window has passed. • Chronic/maintenance use of oral corticosteroids (OCS) defined as any continuous use of OCS for a period of 1 month or more within 1 year of Screening. • Use of biologics (omalizumab, mepolizumab, reslisumab, dupilumab, benralizumab etc., for asthma or any other indications) that has potential to interfere/affect asthma or NP disease progression, within 6 months of the start of the Run-in period. • Use of medication for sino-nasal symptoms (antibiotics with or without OCS) within 30 days of Screening or during the Run-in period. • Any contra-indications to inhaled or nasal steroids e.g. narrow angle glaucoma, or any other as decided by the Investigator. • History of nasal surgery (including polypectomy) within 6 months prior to screening. • Patients with asthma control questionnaire - 5 questions (ACQ-5) ≥ 1.5 at Screening
Study treatment	• QAW039 150 mg and QAW039 450 mg once daily • Matching placebo to QAW039 150 mg and QAW039 450 mg once daily
Efficacy assessments	• Assessment of nasal polyp score by nasal endoscopy • Assessment of nasal congestion using the nasal congestion score questionnaire • Assessment of quality of life using the SNOT-22 questionnaire • Assessment of smell using the university of Pennsylvania smell identification test

[redacted]

Key safety assessments	• Medical history and physical examination • Adverse events (AEs) including serious adverse events (SAEs) • Vital signs • Electrocardiogram (ECG) • Laboratory evaluations (hematology, blood chemistry, urinalysis) • Pregnancy (female patients)
Data analysis	Approximately 93 patients will be randomized in 1:1:1 ratio in either of the 3 arms fevipiprant 450 mg dose, fevipiprant 150 mg dose or placebo in addition to standard of care. **Primary Objective:** The primary aim of the study is to evaluate a change in nasal polyp size with fevipiprant (150mg or 450mg once daily, separately) as compared to placebo. This will be evaluated by using the NPS) which is assessed by nasal endoscopy. The total NPS is recorded as the sum of the right and left nostril scores with a range of 0 to 8. A decrease in the NPS is considered a favorable outcome. The analysis of the primary endpoint will be conducted according to the intention to treat principle using the full analysis set (FAS) population and using a mixed model repeated measures (MMRM) approach. **Secondary Objectives:** • **Nasal Congestion Score:** The change in NCS will be analyzed using an MMRM model. • **Quality of Life (SNOT-22):** The treatment group difference in terms of change from baseline at Week 16 in SNOT-22 will be estimated using an MMRM model. • **Smell (UPSIT):** The treatment group difference in terms of change from baseline at Week 16 in UPSIT will be estimated using an MMRM model. • **Safety and Tolerability:** 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.
Key words	Efficacy and safety of QAW039, nasal polyp score, nasal congestion score, quality of life, smell, nasal polyposis, concomitant asthma, female and male patients ≥ 18 years

[redacted]

1 Introduction

1.1 Background

The purpose of this study is to evaluate the efficacy and safety of fevipiprant 150 mg and 450 mg compared to placebo in the reduction of nasal polyps size and the effect on symptoms, quality of life and smell via patient-reported outcomes in patients with nasal polyposis and concomitant asthma.

Nasal Polyposis (NP) is a common disorder, affecting up to 4% of the population. Although the causes remain unclear, NP has been associated with a number of conditions including asthma, infection, cystic fibrosis and aspirin sensitivity. The polyps themselves are benign lesions arising from the mucosa of the nasal cavity, which present typically as single or multiple polypoid masses, causing symptoms including nasal obstruction, anosmia, post nasal drip, rhinorrhea and, less commonly, facial pain (Newton and Ah-See 2008). NP is diagnosed either by a clinical examination or more commonly via nasal endoscopy. Computerized tomography (CT) scans are useful but do not provide optimal understanding of the disease extension, as the polyps can be indistinguishable of the anatomy, so endoscopic direct observation is more accurate for diagnosis. Treatment can range from the use of corticosteroid nasal sprays (e.g. mometasone furoate) to surgical interventions. It is common for patients to have relapses, requiring repeated surgeries.

NP with concomitant asthma has a prevalence ranging from 2%-66% (Orlandi et al 2016), usually considered in the range of 30% of the NP patients for those referred to ENT departments (Larsen); and it is 58% in those patients with a nasal polyps score ≥ 4 (Bachert et al 2016). Nasal polyp score is assessed by nasal endoscopy using the following scale (Gevaert et al 2013):

Table 1-1 Nasal Polyp 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

Prostaglandin D2 (PGD_2) is one of the major prostanoid inflammatory mediators identified in airway inflammatory diseases. The PGD_2 type 2 receptor (DP2) usually mediates these pro-inflammatory effects. There is evidence that the DP2 pathway and PGD_2 have an effect on NP physiopathology:

- The in-vitro study by Perez-Novo et al showed that in nasal polyps taken from 10 patients there was an increased release of PGD_2. Pre-treatment with IgE/anti-IgE was significantly impacted by pre-incubation with diclofenac. This suggests that in immunologically activated NP tissue, PGD_2 produced by mast cells promotes the migration of Th2 cells through a DP2 dependent mechanism (Pérez-Novo et al 2010).

[redacted]

- The study by Mjosberg et al showed that tissue taken from nasal polyps in patients with chronic rhinosinusitis contained larger proportions of DP2 than mucosa from uninflamed nasal cavities from healthy donors (Mjösberg et al 2011).
- It has been shown that the expression of DP2 receptors is associated with the pathophysiology of Chronic Rhinosinusitis along with NP formation (Yamamoto et al 2009).
- Elevated percentages of mast cells are found in the sino-nasal mucosa of chronic rhinosinusitis patients with NPs (Shaw et al) when compared to a healthy control group.

Fevipiprant (QAW039) is a DP2 competitive antagonist in investigation in severe asthma. It exerts its effect by binding to DP2 receptors on eosinophils, Th2 and ILC2 cells in the blood and tissues; thus, inhibiting migration and activation of these cells into the airway tissues and reducing the release of pro-inflammatory cytokines (Chevalier et al 2005). It is proposed that fevipiprant will also be a suitable treatment for NP. Moreover it's once daily oral regimen could increase compliance when compared with the current standard of care of nasal sprays.

1.2 Purpose

A Phase 3b Proof-of-Concept study to evaluate the efficacy of fevipiprant (QAW039) (150 mg and 450 mg once daily) compared with placebo, as add-on to mometasone furoate treatment standard-of-care (SoC), in reducing endoscopic nasal polyp score (NPS) and nasal congestion score (NCS) in adult (≥ 18 years) patients with nasal polyposis (NP) and concomitant asthma.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

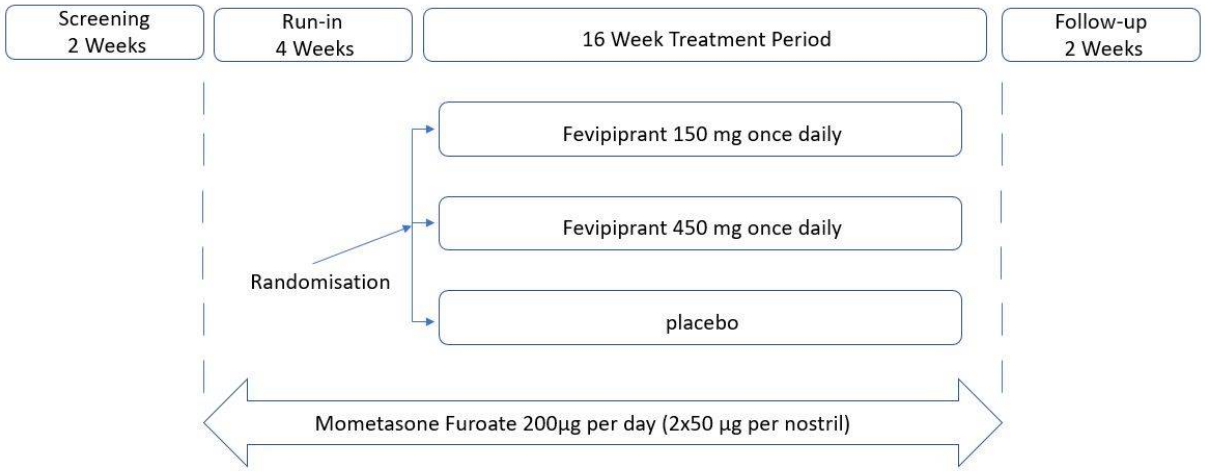
Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• In patients with nasal polyps with a polyp size score ≥ 4, to demonstrate a difference in mean change from baseline in polyp size at week 16, measured by the nasal polyp score (NPS, assessed by nasal endoscopy with central reading), between fevipiprant (150 mg or 450 mg once daily, separately) and placebo.	• Reduction (in terms of change from baseline to week 16) in NPS for fevipiprant (150 mg or 450 mg once daily, separately) as compared to placebo.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the effect of fevipiprant 150 mg and 450 mg compared with placebo in terms of general safety/tolerability	• Adverse events, ECG, vital signs and laboratory analysis following 16 weeks of treatment.
• 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), compared with placebo.	• Increase (in terms of change from baseline to week 16) in QoL score for fevipiprant (150 mg or 450 mg once daily, separately) as compared to placebo.
• To evaluate the effect on Smell as measured by the University of Pennsylvania Smell Identification Test (UPSIT) with fevipiprant (150 mg or 450 mg once daily), compared with placebo.	• Increase (in terms of change from baseline to week 16) in Smell score for fevipiprant (150 mg or 450 mg once daily, separately) as compared to placebo.
• To evaluate the effect on symptoms as measured by the Nasal Congestion Score (NCS) with	• Reduction (in terms of change from baseline to week 16) in NCS for fevipiprant (150 mg or 450

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

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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]

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]

5 Population

The study population will consist of approximately 93 male and female patients aged 18 and above, diagnosed with nasal polyposis with polyps size ≥ 4 (nasal polyp score, assessed by nasal endoscopy) with a minimum score of 2 in each nostril; and a concomitant diagnosis of asthma.

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. Patients aged ≥ 18 years with a diagnosis of nasal polyposis with polyp size score ≥ 4 and a minimum score of 2 in each nostril, measured by nasal endoscopy at screening and prior to randomization on Run-in/Treatment Day 1 (to ensure no reduction in NPS following the use of the mometasone furoate SoC therapy).
3. Patients with a concomitant diagnosis of asthma for a period of at least 6 months prior to screening.
4. Have been on a stable asthma treatment regimen of at least inhaled corticosteroids (any dose), alone for at least 6 months prior to Screening or ICS for 6 months prior to screening with any other required, inhaled asthma medication (LABA, LAMA) added at least 6 weeks prior to Screening.

5.2 Exclusion criteria

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

1. Asthma exacerbation, within 6 weeks prior to screening that required systemic corticosteroids, hospitalization, or emergency room visit. When patients experience an exacerbation between screening and the end of the 4-week Run-in period, and prior to randomization, they will be considered screen failures and can be eligible for re-screening only once the required 6 weeks post exacerbation window has passed.
2. Chronic/maintenance use of oral corticosteroids (OCS) or systemic corticosteroids (SCS) defined as any continuous use of OCS/SCS for a period of 1 month or more within 1 year of Screening.
3. Patients who, in the judgement 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.
4. Patients with a history of familial long QT syndrome or known family history of Torsades de Pointes.
5. Patients with a resting QTcF (Fridericia) ≥ 450 msec (males) or ≥ 460 msec (females) at screening.
6. Use of biologics (omalizumab, mepolizumab, reslisumab, dupilumab, benralizumab etc., for asthma or any other indications) that has potential to interfere/affect asthma or NP disease progression, within 6 months of the start of the Run-in period.
7. Use of medication for sino-nasal symptoms (antibiotics with or without OCS) within 30 days of Screening or during the Run-in period.

[redacted]

8. Use of tetracycline (e.g. doxycycline) or macrolide antibiotics specifically within the 8 weeks prior to the start of the Run-in period due to the influence they have on Nasal Polyps.
9. Any contra-indications to inhaled or nasal steroids e.g. narrow angle glaucoma, or any other as decided by the Investigator.
10. Pregnant or nursing (lactating) women
11. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of investigational drug. 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). For UK: 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, then local regulations apply and will be described in the informed consent form.
12. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
13. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes.

14. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
15. Patients who are unable to follow instructions to complete the study, either because of mental or physical conditions.
16. Patients with a terminal disease, or conditions that may impede the timely completion of the study as decided by the investigator.
17. Patients with a diagnosis of Cystic Fibrosis
18. History of nasal surgery (including polypectomy) within 6 months prior to screening.
19. History of sinus or nasal surgery modifying the structure of the nose such that assessment of NPS via nasal endoscopy is not possible.
20. Patients with a diagnosis of ciliary dyskinesia
21. Patients with allergic fungal sinusitis as diagnosed from previous surgery or from CT scan.
22. Patients with ACQ-5 $\geq$ 1.5 at Screening
23. Uncontrolled epistaxis requiring surgical or procedural intervention, including nasal packing, within 2 months of screening
24. Concomitant conditions that interfere with evaluation of the primary endpoint:
    - Marked nasal septal deviation occluding one or both nostrils
    - Ongoing rhinitis medicamentosa
    - Acute sinusitis, nasal infection or upper respiratory tract infection during run-in period.
25. Initiation of or change in immunotherapy or aspirin desensitization for allergies within 3 months prior to Screening or during the Run-in period.
26. Patients receiving any medications in the classes listed in Table 6-2 should be excluded unless they meet the criteria as specified in Table 6-2.
27. Patients on >20 mg of simvastatin, > 40 mg of atorvastatin, >40 mg of pravastatin, or >2 mg of pitavastatin 7 days prior to run-in visit. Statin doses less than or equal to these doses as well as other statins will be permitted during the study
28. Patients on any statin therapy with a CK level >2 X ULN at Screening Visit
29. Patients receiving any medications in the classes listed in Table 6-1 should be excluded unless the medication has been stabilized for the specified period and the stated conditions have been met
30. Patients receiving any medications or other agents known to prolong the QT interval.
31. Patients with any chronic condition of the respiratory tract which in the opinion of the investigator may interfere with study evaluation or optimal participation in the study.
32. Patients with a history of chronic lung disease other than asthma, including (but not limited to) chronic obstructive pulmonary disease, bronchiectasis, (non-clinically significant bronchiectasis may be allowed provided recent [within 3 months prior to Screening Visit] CT scan proof is available), sarcoidosis, interstitial lung disease, and tuberculosis.

[redacted]

33. Patients with uncontrolled diabetes having an HbA1c test result ≥8% at the Screening Visit laboratory test.
34. Patients who have a clinically significant laboratory abnormality at the Screening laboratory test including (but not limited to):
    - Total white blood cell count <2500 cells/µL
    - AST or ALT>2.0 X ULN or total bilirubin >1.3 X ULN
    - Estimated Glomerular Filtration Rate (eGFR) by the Modification of Diet in Renal Disease (MDRD) equation or Bedside Schwartz equation <55 mL/minute/1.73 m2
35. Patients who, in the judgement of the investigator, have a clinically significant condition such as (but not limited to) unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, arrhythmia, uncontrolled hypertension, cerebrovascular disease, neurodegenerative diseases, or other neurological disease, uncontrolled hypo- and hyperthyroidism and other autoimmune diseases, hypokalemia, hyperadrenergic state, or ophthalmologic disorder or patients with a medical condition that might compromise patient safety or compliance, interfere with evaluation, or preclude completion of the study.
36. Patients who have smoked or inhaled any substance other than asthma medications within the 6 month period prior to Screening, or who have a smoking history of greater than 10 pack years (Note:10 pack years = 1 pack /day x 10 yrs., or ½ pack/day x 20 yrs.).
37. Patients with a history of myocardial infarction within 12 months of Screening.
38. Patients with serious co-morbidities including, but not limited to, neurodegenerative diseases, rheumatoid arthritis and other autoimmune diseases.
39. Patients with a history of alcohol or drug abuse within 12 months prior to Screening.
40. Patients with a weight <30 kg.
41. Patients with a known history of non-compliance to medication.
42. Patients with a history of being unable to swallow tablets.
43. 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.
44. Patients with a history of immunodeficiency disease or hepatitis B or hepatitis C.
45. No person directly associated with the administration of the study is allowed to participate as a study subject.
46. No family member of the investigational study staff is allowed to participate in this study.
47. History of lactose or milk sensitivity.
48. Patients with a history of conditions other than asthma that could result in elevated eosinophils (e.g., hypereosinophilic syndromes, Churg-Strauss Syndrome, eosinophilic esophagitis). Patients with known parasitic infestation within 6 months prior to Screening are also excluded.
49. Patients requiring SCS use for conditions other than asthma (chronic or intermittent) or nasal polyposis.

No additional exclusions may be applied by the Investigator, in order to ensure that the study population will be representative of all eligible subjects

[redacted]

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

The following investigational treatment will be supplied by Novartis to the study sites:

- Name: fevipiprant (labeled as QAW039)
- Formulation: tablet
- Unit dose: 2 strengths: 150 mg and 450 mg

Please refer to the Investigator's Brochure for composition of the fevipiprant tablets.

- Name: fevipiprant placebo
- Formulation: tablet
- Unit dose: matching placebo to fevipiprant 150 mg, matching placebo to fevipiprant 450 mg

Please refer to the Investigator's Brochure for composition of the placebo tablets.

The investigational treatment (tablets) will be supplied in bottles. The matching placebos for fevipiprant will be identical in appearance to their active counterparts and will be identically packaged.

6.1.2 Additional study treatments

At the start of the Run-in period, all patients will be provided with mometasone furoate nasal spray (no specific brand required) as the SoC for use during the study. This will either be supplied to the Investigator sites by Novartis or sourced locally and reimbursed by Novartis. All patients will remain on their current asthma treatment for the duration of the study (with the exception of LTRAs, which should be discontinued prior to patients entering the Run-in period). Patients will also be provided with short-acting β2-agonists (SABAs), (salbutamol/albuterol/other SABA) which they will be instructed to use throughout the study as rescue medication to treat asthma symptoms on an 'as needed basis'. SABAs will either be supplied to the Investigator sites by Novartis or sourced locally and reimbursed by Novartis.

Should patients develop any sino-nasal exacerbations during the course of the study, the treating physician should follow their normal treatment regimen with systemic corticosteroids and/or antibiotics.

6.1.3 Treatment arms/group

Subjects will be assigned at the randomization visit to one of the following 3 treatment arms in a ratio of 1:1:1.

During the Run-in period, all patients will receive the NP SoC treatment only - Mometasone Furoate 200 µg once daily, administered as two 50 µg actuations into each nostril.

For the treatment period, patients will be assigned to one of three treatment arms as follows in a 1:1:1 ratio:

[redacted]

- QAW039 150 mg once daily (one tablet of blinded QAW039 at 150 mg dosage strength to be given together with one tablet blinded placebo to QAW039 450 mg).
- QAW039 450 mg once daily (one tablet of blinded QAW039 at 450 mg dosage strength to be given together with one tablet blinded placebo to QAW039 150 mg).
- Placebo to QAW039 once daily (one tablet blinded placebo to QAW039 150 mg and one tablet blinded placebo to QAW039 450 mg).

Patients will be instructed to take their investigational treatment (QAW039 or placebo) once daily in the morning without regard to time of food intake.

6.1.4 Treatment duration

The planned duration of the study treatment period is 16 weeks from the point of randomization. Subjects will take their assigned study treatments along with the NP SoC which will be supplied to patients at the start of the Run-in period. The patients will administer the SoC only, during the Run-in period and then administer both the SoC and the study treatment, during the 16-week Treatment period.

6.2 Other treatment(s)

All patients will be provided with short-acting β2-agonists (SABAs) (salbutamol/albuterol/other SABA) which they will be instructed to use throughout the study as rescue medication on an 'as needed basis.'

6.2.1 Concomitant therapy

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 (CRFs). The medications in Table 6-1 are only permitted under the circumstances given and this table is not considered all-inclusive.

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

Table 6-1 Medications allowed under certain conditions

Class of medication	Conditions
Short-acting β2-agonist (SABA)	Rescue medication to be taken as needed
SCS for treatment of symptoms of asthma or NP	One treatment of up to 5 consecutive days allowed during the study. SCS should not be administered within the 2 weeks prior to nasal endoscopy
Maintenance Immunotherapy for allergies	Stable dose for at least 3 months prior to Screening and the dose remains stable throughout the study
Inactivated influenza vaccine, pneumococcal vaccine or any other inactivated vaccine	Not administered with 48 hour prior to a study visit
Topical corticosteroids for treatment of eczema	Recommended doses and dosage regimens

[redacted]

Class of medication	Conditions
Antihistamines (e.g. loratadine, cetirizine)	Stable for at least 1 month prior to Screening visit and dose remains stable throughout the study
Nasal anticholinergic	Treatment regimen has been stable for at least 1 month prior to Screening visit. In the case of as needed use, providing an established pattern of use, has been documented
Nasal or ophthalmological preparations of nedocromil	
Nasal or ophthalmological preparations of antihistamines	

6.2.2 Prohibited medication

Use of the treatments displayed in the below table is NOT allowed after screening. Each concomitant drug must be individually assessed against all exclusion criteria and the tables below to see if it is allowed. If in doubt, the Investigator should contact the Novartis medical monitor or designee before randomizing a patient or allowing a new medication to be started. This table is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria. These medications are also prohibited if administered for other indications.

Table 6-2 Prohibited Medication

Medication	**Prohibition period** (Minimum cessation prior to Run-in)
Other investigational drugs	30 days or 5 half-lives, whichever is longer
Oral and Nasal Decongestants (more than 3 weeks total use)	30 days
Live attenuated vaccine	30 days
Simvastatin > 20 mg, atorvastatin > 40 mg, pravastatin > 40 mg, or pitavastatin > 2 mg total daily dose	7 days
Other DP2 antagonists (e.g., ramatroban)	7 days or 5 half-lives whichever is longer
Short-acting anticholinergics	8 hours
Fixed combinations of short-acting β2 agonists and short-acting anticholinergics	8 hours
Systemic mast cell stabilizers (e.g.,cromoglycate, nedocromil, ketotifen)	7 days
Monoclonal antibodies, investigational or approved, for the treatment of asthma (e.g., omalizumab)	6 months
Nasal corticosteroids in the form of drops, sprays that are administered via devices (e.g. OptiNose device or stents) or lavage	8 weeks
Tetracyclic or macrolide antibiotics	8 weeks
Rifampin, probenecid, ritonavir and 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 P-gp)).	7 days
Methotrexate, gold salts, cyclosporine, troleandomycin, azathioprine, other immuno-modulator drugs or immuno-modulatory monoclonal antibodies	6 months
Systemic (oral, intravenous, intramuscular) corticosteroids for non-asthma conditions	3 months

[redacted]

Medication	**Prohibition period** (Minimum cessation prior to Run-in)
Leukotriene receptor antagonists (LTRA)	Stopped at beginning of Run-in period

6.2.3 Rescue medication

At the start of the Run-in period, all patients will be provided with a SABA (such as salbutamol 100 mcg or albuterol 90 mcg) which they will be instructed to use throughout the study as rescue medication on an 'as needed basis'. Patients will be advised that between visits they could take their rescue medication for symptoms of asthma. Rescue medication (i.e., SABAs) will either be supplied to the Investigator sites locally by the Novartis country pharma organization (CPO) or sourced locally and reimbursed by Novartis. Nebulized salbutamol/albuterol is not allowed as rescue medication and will not be supplied.

Should patients develop any sino-nasal exacerbations during the course of the study, the treating physician should follow their normal treatment regimen with systemic corticosteroids and/or antibiotics. Short term oral or nasal decongestants may also be utilised as a rescue therapy however the assessment of NPS must not be performed within 3 days of their use.

Use of rescue medication must be recorded on the concomitant medications in the CRF.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available.

6.3.2 Treatment assignment, randomization

At randomization visit, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The Investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify unique medication numbers for the first packages of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

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 patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient 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 Supplies using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

[redacted]

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

6.4 Treatment blinding

Subjects, Investigator staff, persons performing the assessments, and clinical trial team (CTT) will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study, (2) the identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

A double-dummy design is used because the identity of the study treatment cannot be disguised, as the drug products are visibly different.

Unblinding will occur in the case of subject emergencies and at the conclusion of the study.

Table 6-3 Blinding and unblinding plan

	Time or Event		
Role	**Randomization list generated**	**Treatment allocation & dosing**	**Safety event (single subject unblinded)**
Subjects	B	B	B
Site staff	B	B	B
Unblinded site staff e.g. pharmacy staff *(specify)*	B	B	B
Drug Supply and Randomization Office	UI	UI	UI
Unblinded Pharmacovigilance sponsor staff	UI	UI	UI
Statistician/statistical programmer/ data analysts (e.g. biomarker, PK)	B	B	B
Independent committees used for assessing interim results, if required (e.g. DMC)	NA	NA	NA
All other sponsor staff not identified above (trial team, project team, management & decision boards, support functions)	B	B	B

Key:

UI: Allowed to be unblinded on individual subject level

B: Remains blinded

NA: Not applicable to this study

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted and should any such changes in dosing regimen occur during the study then the patients will be excluded unless highlighted as a rescue therapy within other sections of the protocol.

[redacted]

6.5.1 Dose modifications

For subjects who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are not permitted and the patients will be withdrawn from the study.

6.5.2 Follow-up for toxicities

Not applicable.

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.

Compliance will be assessed by the Investigator and/or study personnel at each visit using pill counts and information provided by the subject. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

All doses of study drug taken at the clinic visits must be from the newly assigned medication bottles, **except at the end of treatment** (EOT) **visit when the medication returned by the patient should be used.**

6.6.2 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 Novartis 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/code break cards at any time in case of emergency. The Investigator will provide:

- protocol number
- name
- subject number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that unblinding

[redacted]

can be performed at any time. Following any emergency breaking of the blind, the subject will be withdrawn from the study.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the subject, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

The Investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients/subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the Investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the Investigator folder at each site.

6.7.1.2 Handling of additional treatment

The following non-study treatment has to be monitored specifically:

- Mometasone furoate 200 µg used as SoC
- SABA (such as salbutamol 100 µg)

The non-investigational treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designees have access. Clinical supplies are to be dispensed only in accordance with the protocol.

[redacted]

The Investigator must maintain an accurate record of the shipment and dispensing of the non-investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all unused non-study treatments and packaging at the end of the study or at the time of discontinuation from the study.

6.7.2 Instruction for prescribing and taking study treatment

Study treatment will be double-blind, double-dummy, and placebo-controlled during the treatment period. QAW039 will be supplied as tablets. Since the tablets for QAW039 150 mg and QAW039 450 mg are not identical, treatment will be double-dummy and patients will take 2 tablets of study medication (one tablet of blinded QAW039 at 150 mg dosage strength to be given together with one tablet blinded placebo to QAW039 450 mg or one tablet of blinded QAW039 at 450 mg dosage strength to be given together with one tablet blinded placebo to QAW039 150 mg or one tablet blinded placebo to QAW039 150 mg and one tablet blinded placebo to QAW039 450 mg) once daily as described below.

During the Run-in period, all patients will start treatment with mometasone furoate 200 µg daily, administered as 2 50 µg into each nostril, in the morning. Patients will continue to use their standard asthma therapy, as needed.

If a patient experiences an asthma exacerbation during the Run-in period, the patient is considered Run-in failure and can be re-screened only once 6 weeks have passed after full recovery from the exacerbation.

At the Randomization Visit (Treatment Day 1) patients will be randomized to receive one of the three study treatments:

- QAW039 150 mg once daily
- QAW039 450 mg once daily
- placebo once daily

The treatment period will continue for a period of 16-weeks and patients will continue to take the mometasone furoate SoC in addition to the study treatments, during the treatment period. The investigational treatment will be dispensed in medication packs (bottles) at each clinic visit during the treatment epoch with enough medication supplied to cover the period between patient visits and to allow for late visits and other unforeseen events. All dosages prescribed and dispensed to the patient must be recorded in the appropriate section of the CRF.

At clinic visits, patients will receive a witnessed dose of study medication. These in-clinic witnessed doses will be given after the completion of all pre-dose assessments (see Section 8) and should be given at approximately the same time at each clinic visit. Between clinic visits, patients will take study medication once daily in the morning. Patients will be instructed to take their study medication at approximately the same time each morning.

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

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

[redacted]

7 Informed consent procedures

Eligible patients/subjects may only be included in the study after providing signed (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if applicable after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the informed consent document or a separate assent form. 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 patient source documents.

Novartis will provide to Investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the Investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

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 requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

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 and then must be discussed with the subject.

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

8 Visit schedule and assessments

Assessment schedule lists all of the assessments and indicates with an "X" or an "S", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation with those events marked by an "X" being captured in the CRF/Clinical Database and those marked with an "S" will be captured in source documentation only.

Patients should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

[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]

8.1 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]

- Smell (UPSIT)

8.3.1 Nasal Polyp Score

The nasal polyp score is assessed four times during the study by nasal endoscopy. The initial assessment will be performed at screening to assess the patient's eligibility on the study. Patients will be deemed eligible with a NPS ≥ 4 with a minimum score of at least 2 in one nostril, determined by central reading at screening and prior to randomization, using the following scale (Gevaert et al 2013):

Table 8-2 Nasal Polyp 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

NPS will be re-assessed at Treatment Day 1 to both re-confirm eligibility for the study but also for a baseline measurement. The central reading result must be received for the baseline assessment, prior to randomization. At the 8 and 16-week treatment visits, NPS will again be re-assessed for efficacy. The readings from the endoscopies performed will be uploaded for central reading for NPS determination.

The nasal endoscopy may be performed on a different day from the other study procedures as long as this is performed within approximately 5 days of the original scheduled visit.

Note that the nasal endoscopy procedure should not be performed within 3 days of any concomitant use of oral or nasal decongestants.

8.3.2 Patient Reported Outcomes

A patient reported outcome (PRO) is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else. Patient reported outcomes may provide quantitative information for patients regarding the 'impact on daily life', which is of key importance, for patients and their physicians and also for health technology assessments. In this study, two PROs are used to assess the improvement in symptoms (nasal congestion score) and quality of life (SNOT-22). All PROs should be completed prior to any other assessments (especially the nasal endoscopy) to avoid any influence on the responses.

8.3.2.1 Symptoms (Nasal Congestion Score)

The nasal congestion score is assessed via a questionnaire where the patients are asked "Is your nose blocked?" with responses ranging from 0 = not at all, to 3=severe. The test is performed within the clinic at the visits outlined in Table 8-1 on a tablet computer and the questionnaire is outlined in Section 16.4.

[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]

  - 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]

The Investigator must also contact the IRT to register the patient's discontinuation from study treatment.

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 or 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 their 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 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 patient welfare and safety. Should early termination be necessary, patients must be seen as soon as possible (provide instruction for contacting the

[redacted]

patient, when the patient should stop taking drug, when the patient should come for a final visit) and treated as a prematurely withdrawn patient. 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 patient's interests. The Investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol. Study completion for a patient will occur after he/she has completed 16-weeks of treatment (through the follow-up visit) or they have prematurely withdrawn. Completion of the study will be when all randomized patients have completed 16 weeks of treatment and the post-treatment follow-up visit.

Patients who have been screened when enrolment target has been met will be allowed to proceed onto study participation.

For all patients a safety follow-up visit should be conducted (e.g. by telephone) 14 days after last visit (Week 16). The information to be collected at this follow up visit includes adverse events, concomitant medications and SAEs.

When the patient has completed all scheduled study assessments or prematurely withdrawn from the study, the Investigator must contact the IRT to record the patient completion /discontinuation and complete applicable eCRF .

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.

[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]

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]

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]

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]

- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
- These investigations can include 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 the procedures performed must be recorded as appropriate in the CRF

10.2.2 Renal safety monitoring

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

Serum event:

- Confirmed (after ≥24 hours) increase in serum creatinine (sCr) of ≥25% compared to baseline during normal hydration status

Urine event:

- Albumin-creatinine ratio (ACR) ≥1g/g or ≥100 mg/mmol.
- Protein-creatinine ratio (PCR) ≥1g/g or ≥100 mg/mmol.

Every renal laboratory trigger or renal event as defined in Table 16-3 - Appendix 3 should be followed up by the investigator or designated personnel at the trial site as summarized in Section 16 .

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 using fully validated software that conforms to US CFR 21 Part 11 requirements. Investigator site staff will not be given access to the electronic data capture (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 is 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.

[redacted]

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 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.

Laboratory samples will be processed by a central lab and the results will be provided electronically to Novartis.

The PROs will be recorded on site by patients on tablet computers and the database from the vendor will be provided electronically to Novartis. The videos of the nasal endoscopies will be provided to the vendor (either by upload to a cloud server or postage of encrypted USB drives) for central reading. Videos will be read by two independent reviewers to assign the nasal polyp score with a third adjudicating reader making the decision on NPS should the original two readers not agree during their assessment.

[redacted]

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 development 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 (i.e. eCRFs) 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

[redacted]

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

The primary efficacy and safety analyses will be conducted at the time the trial ends. All data captured in the study up to the end of study will be analyzed and reported.

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

12.1 Analysis sets

The Full Analysis Set (FAS) will be comprised of all randomized patients who meet both of the following criteria:

- Received at least one dose of study treatment
- Have a baseline NPS score ≥ 4 as measured by the central reader.

According to the intent to treat principle, subjects will be analyzed according to the treatment they have been assigned to at the randomization. However, if patients received study treatment without being randomized into the study they will be excluded from the FAS.

The Safety Analysis Set (SAF) includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received, where treatment received is defined as the randomized/assigned treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received.

The analysis of the primary objectives will be performed on the FAS. The FAS will be used for the analysis of all other efficacy variables. The SAF will be used in the analysis of all safety variables.

[redacted]

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation (SD), median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also 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 Analysis Set will in general be used for the analyses of treatments. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure (expressed in weeks), the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics.

The number of patients with dose adjustments (reductions, interruption, or permanent discontinuation) and the corresponding reasons will be summarized for the study treatment. Compliance with study medication over the course of the entire study will be summarized as the percentage of days with study medication intake during the period from first intake to last intake.

All fevipiprant dosing data will be listed.

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 in the Safety Analysis Set.

Concomitant nasal polyp related medications will be summarized by pre-defined category.

12.4 Analysis of the primary endpoint(s)

The primary aim of the study is to evaluate a change in nasal polyp size with fevipiprant (150 mg or 450 mg once daily, separately) as compared to placebo. This will be evaluated by using the nasal polyp score (NPS) which is assessed by nasal endoscopy and determined by central reading. The total NPS is recorded as the sum of the right and left nostril scores with a range of 0 to 8 . A decrease in the NPS is considered a favorable outcome.

The analysis of the primary endpoint will be conducted according to the intention to treat principle using FAS population.

[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.

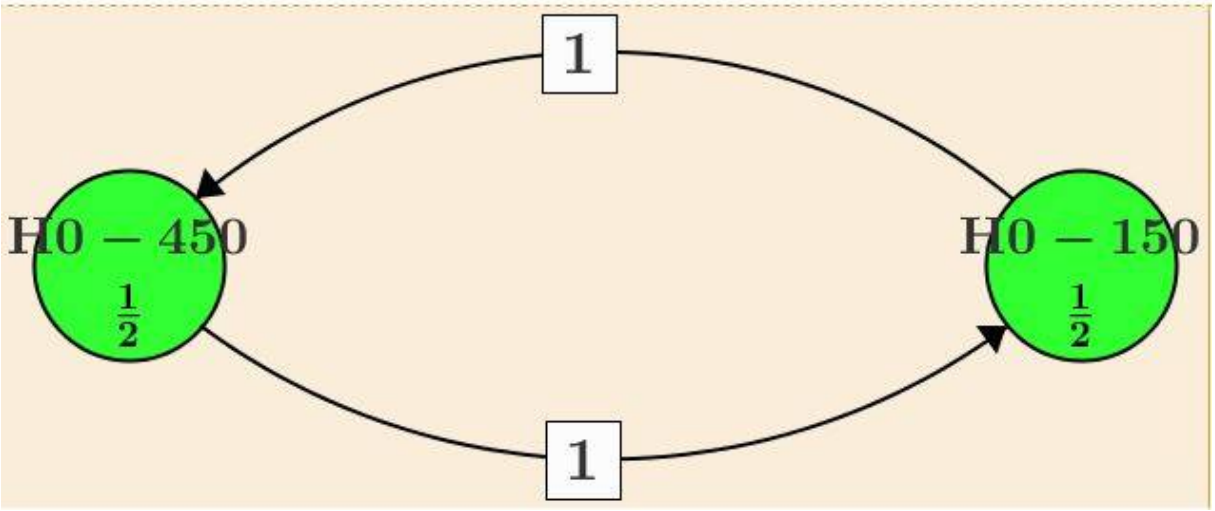
The primary alternative hypotheses are:

- $H_{A\,450}$: 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

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]

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]

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]

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Based on clinical judgement a mean reduction of 1.5 in polyp score (as measured by the NPS) can be expected with fevipiprant (450 mg and 150 mg) and SoC as compared to Placebo and SoC. Considering this factor, the sample size was calculated under an 80% power and 1.25% one sided alpha for comparison of each of the two dose levels of fevipiprant and SoC with placebo and SoC. A 10% dropout rate is considered as appropriate with reference to prior studies (omalizumab study by Gevaert et al 2013 and dupilumab study by Bachert et al 2016). From prior literature standard deviation of 1.8 is considered as appropriate for the change of score from baseline at 16 weeks in Nasal Polyp Score.

The sample size calculation was performed using the software PASS 2008 using inequality tests using difference of two independent means with equal variance.

The randomization will be performed in a 1:1:1 ratio for the two separate doses level of fevipiprant (450 mg and 150 mg) and the placebo arm. Under these assumptions (effect size = 1.5, equal SD = 1.8,power = 80% for each arm individually, one-sided alpha = 0.0125 and dropout = 10%), the total sample size yielded was 93 with 31 patients in each arm.

The sample size provides a power of 80% for each comparison but since we will be testing correlated hypothesis using a Dunnet's test, this is a lower bound on the power. The real power is expected to be higher if in at least one of the 2 dosages i.e. fevipiprant 150 mg or fevipiprant 450 mg, the standardized effect size (in other words, keeping the assumption of an SD of 1.8 in each group) is equal to the clinically significant value of 1.5 and there is some treatment benefit in the other groups as well. However, if the effect size is equal to 1.5 in both of the groups, the power will be substantially higher i.e. around 93%

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 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

[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]

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]

15 References

References are available upon request

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

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 electronic case report form (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. See** Section 16.3 **for specific renal alert criteria and actions.**

For electrocardiograms (ECGs), a notable QTc value is defined as a QTcF (Fridericia) interval of ≥450 msec for males or ≥460 msec for females. All ECGs will be assessed locally at site and with assessment of clinical relevance and continuance of the patient being confirmed by the Investigator.

[redacted]

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	• 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN
	• ALP > 2 × ULN (in the absence of known bone pathology)
	• TBL > 2 × ULN (in the absence of known Gilbert syndrome)
	• ALT or AST > 3 × ULN and INR > 1.5
	• 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)
	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	• 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 γGT until resolution[c] (frequency at Investigator discretion)
ALT or AST		
> 8 × ULN	• 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 × ULN and INR > 1.5	• 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)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • 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)

[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]

16.3 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.	

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

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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]