NOVARTIS

Clinical Development

QAW039/Fevipiprant

QAW039A2322 / 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 polyp size in patients with nasal polyposis and concomitant asthma

Statistical Analysis Plan (SAP)

Author:	Trial Statistician, [redacted];

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
01-03-2019	Prior to DB lock	Creation of final version	N/A - First version	NA
20-04-2020	Prior to DB lock	Amendment 1	A sensitivity analysis added for UPSIT instrument to exclude patients from few sites (Documented in DHP),because the site peronnelfilled up this questionnaire by pencil instead pen.	Section 2.7.1.3
20-07-2020	Prior to DB lock	Amendment 2	Definition of full analysis set updated. Protocol deviation related to nasal endoscopy added.	Section 2.2 , Section 5.5

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
CM	Concomitant Medication
CSR	Clinical Study report
CTC	Common Toxicity Criteria
DMC	Data Monitoring Committee
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
IVR	Interactive Voice Response
IWR	Interactive Web Response
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NPS	Nasal Polyp Score
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
SAP	Statistical Analysis Plan
SoC	Standard of Care
SOC	System Organ Class
TFLs	Tables, Figures, Listings
UPSIT	University of Pennsylvania Smell Identification Test
WHO	World Health Organization

1 Introduction

The statistical analysis plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of study QAW039A2322, a phase IIIB, 16 week 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

The content of this SAP is based on the protocol of QAW039A2322 version v03.

The purpose of the statistical analysis plan is to describe the implementation of the statistical analysis planned in section 12 of the study protocol. Data will be analyzed by Novartis according to the data analysis section 12 of the protocol which is available in Appendix16.1.1 of the CSR. Important information is given in the following sections and the details will be provided, as applicable, in Appendix 16.1.9 of the CSR.

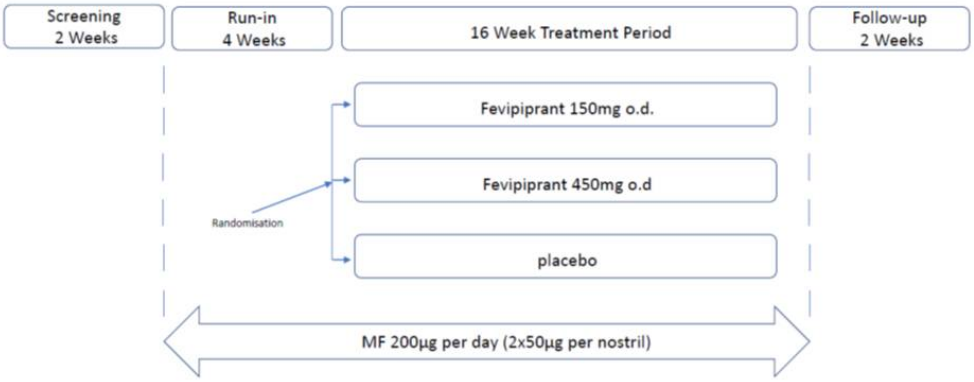
1.1 Study design

This study uses 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 Nasal Polyps in patients with asthma.

The study will include a Screening period of 2 weeks to assess eligibility followed by run-in period of 4 weeks where the patients will utilize Mometasone Furoate spray (200µg once daily administered as two 50µg actuations into each nostril) for baseline assessments treatment. The patients would then enter a treatment period of 16 weeks (with visits held every months 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.

The study will follow a 1:1:1 central randomization in each of the three arms (450 µg Fevipiprant+SoC , 150 µg Fevipiprant+SoC and Placebo)

The primary analysis will be performed after all patients have completed 16 weeks of study treatment or have discontinued early.



Approximately 93 patients will be enrolled into this study.

No formal interim analyses would be performed.

1.2 Study objectives and endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To compare the reduction in nasal polyps score (NPS, assessed by Nasal Endoscopy with central reading) after 16 weeks of treatment with fevipiprant + SoC (150mg or 450mg once daily, separately) versus placebo + SoC in patients with nasal polyps with a NPS ≥4.	• Reduction (in terms of change from baseline to week 16) in the Nasal Polyp Score, for fevipiprant (150mg or 450mg once daily, separately) as compared to placebo
,	
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the effect on symptoms as measured by the Nasal Congestion Score (NCS) with fevipiprant (150mg or 450mg once daily), compared with placebo.	• Reduction (in terms of change from baseline to week 16) in NCS for fevipiprant (150mg or 450mg once daily, separately) as compared to placebo.
• To evaluate the effect on Quality of Life as measured by the Sino-Nasal Outcome Test (SNOT 22) with fevipiprant (150mg or 450mg once daily), compared with placebo.	• Increase (in terms of change from baseline to week 16) in SNOT 22 for fevipiprant (150mg or 450mg 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 (150mg or 450mg once daily), compared with placebo.	• Increase (in terms of change from baseline to week 16) in UPSIT for fevipiprant (150mg or 450mg once daily, separately) as compared to placebo.

- To evaluate the general safety and tolerability of fevipiprant (150 mg and 450 mg, separately) as compared to placebo.
- Adverse events, ECG, vital signs and laboratory analysis following 16 weeks of treatment.

[redacted]

2 Statistical methods

This section contains information that will be used to draft CSR Section 9.7 on statistical analysis.

2.1 Data analysis general information

The final analysis will be performed by Novartis or a designated CRO. The most recent version of SAS and R software available in the statistical programming environment will be used for the analysis. There are no formal interim analysis to be performed.

2.1.1 Data included in the analysis

The analysis cut off date is defined as the date of last patient last visit during the 2 week follow-up period post the 16 weeks treatment period. The entire data collected up to the cut off date would be used under the scope of the analysis defined in the subsequent sections. All data with an assessment date or even start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'continuing at the cut-off date'. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings

2.1.2 General analysis conventions

Pooling of center: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small size of centers, no center effect will be assessed.
Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables by treatment group; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.
Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate

descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum) by treatment group.

2.1.3 General definitions

2.1.3.1 Study drug

In this document, 'study treatment' or 'study drug' will be used to refer to investigational therapy assigned to a patient. Specifically, for this double-blind trial,study treatment refers to QAW039 150 mg, QAW039 450 mg or placebo as assigned to a patient at randomization.

2.1.3.2 Date of first administration of study drug

The 'date of first administration of the study drug' is derived as the first date when a non zero dose of study drug is administered as per the Dosage Administration (e)CRF. The date of first administration of study treatment will also be referred as ***start of study treatment***.

2.1.3.3 Date of last administration of Study Drug

The 'date of last administration of the study drug' is derived as the last date when a non zero dose of study drug is administered as per the Dosage Administration (e)CRF.

2.1.3.4 Study Day

The study day, describes the day of the event or assessment date, relative to the reference start date.. The date of first administration of the study drug is defined as Day 1 and the day before the first administration of the study drug is defined as Day -1.

Therefore, for a particular date, study day will be calculated as follows :

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

The reference start date for safety assessments (e.g. adverse events, laboratory abnormality occurrence, vital sign measurements, dose interruption etc.) is the start of study treatment.

The reference start date for all other, non-safety assessments (i.e., eDiary, patient reported outcomes (PRO)) is the date of randomization.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

2.1.3.5 Time unit

A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375.

2.1.3.6 Baseline

For efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of randomization is taken as "baseline" value or "baseline" assessment. In the context of baseline definition, the efficacy evaluations also include PRO and performance status.

For safety evaluations, the last available assessment on or before the date of start of study treatment is taken as ''baseline" assessment.

If patients have no value as defined above, the baseline result will be missing.

- Vital signs include body temperature, pulse rate and systolic and diastolic blood pressures. Baseline vital signs are defined as the last available assessment taken pre-dose on Day 1. If this assessment is missing or not confirmed to be pre-dose, the last value prior to the first dose will be used for baseline. Otherwise, the vital sign baseline will be set to missing without imputation.

  Baseline height and weight are defined as the last measurements taken prior to first dose of study treatment. Missing baseline values will not be imputed.
- Baseline electrocardiogram (ECG) is defined as the last scheduled assessment taken prior to the first dose of study drug on screening. If the value on screening is missing (or not confirmed to be pre-dose), then the last value prior to the first dose will be used for baseline. Otherwise, the ECG baseline will be set to missing without imputation. Missing ECG baseline values will not be imputed.
- Laboratory data include hematology and biochemistry. Baseline hematology and biochemistry are defined as the last available assessment taken prior to first dose of study treatment on Day 1. If the pre-dose measurement on Day 1 is missing (or was not confirmed to be pre-dose), then the last value prior to the first dose will be used. Otherwise, the baseline laboratory data will be set to missing. Missing laboratory baseline values will not be imputed.

2.1.3.7 Post-baseline measurement

- Post baseline measurements are defined as those assessments after the start of study treatment.

2.1.3.8 Change from baseline

- When change from baseline is of interest, the following formula will be used for each scheduled visit and time-point where baseline and post-baseline values are both available:
- Change from baseline = post-baseline value – baseline value; and

- If baseline or post-baseline values are missing, then the change from baseline will be missing.

2.1.3.9 On-treatment assessment/event and observation periods

The overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period***: from day of patient's informed consent to the day before first administration of study treatment
2. ***on-treatment period***: from date of first administration of study treatment to date of last actual administration of any study treatment +1 day (including start and stop date)
3. ***post-treatment period***: starting at day 1 after last administration of study treatment.

Safety summaries (tables, figures) include data from the pre-treatment period (to display the baseline status e.g. for ECG) and the on-treatment period. Data from the post-treatment period with the exception of deaths should not be included unless requested from Health Authorities or external committees.

In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period, the so-called ***treatment-emergent*** AEs.

However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

2.1.3.10 Visit remapping and assessment windows

If a scheduled visit did not occur, the data from the treatment discontinuation or study discontinuation visit may be used as the data from the scheduled visit, if the treatment discontinuation or study discontinuation visit occurred closer to the planned study day of the missing scheduled visit than to the planned study day of any other scheduled visit. In this case the treatment discontinuation or study discontinuation visit will be treated as the scheduled visit for the purpose of all analyses so that no missing data imputation will be necessary. Otherwise the data from any scheduled visit that did not occur will be dealt with like any other missing data. If the treatment discontinuation or study discontinuation visit is not re-mapped to any scheduled visit, it will be treated as an unscheduled visit that does not appear in by-visit summaries.

2.1.3.11 Last contact date

The maximum of the date of last visit, date of last epoch completion, date of withdrawal of consent would be the date of last contact for the patient participating in the study.

The last contact date is defined as the latest complete date from the above list or the cut-off date whichever comes first. The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely

imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date.

2.2 Analysis sets

The **Screened Set (SCR)** will consist of all patients who provided infirmed consent

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 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 if the patient recieved more than one treatment, then the patient would be analyzed according to the randomized treatment.

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.

2.2.1 Subgroup of interest

No subgroups are defined in this study.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The following summaries will be provided overall and by treatment group: % based on the total number of FAS patients:

- Number of screened patients
- Number (%) of patients who were randomized
- Number (%) of patients who were randomized but not treated.
- Number (%) of patients who were treated
- Number (%) of patients who discontinued the study treatment phase

- Primary reason for study treatment phase discontinuation
- Number (%) of patients who have discontinued the study
- Reasons for discontinuation from the study.

Patient randomization numbers whether they completed or discontinued from the study will be listed, with date of last dose and primary reson for discontinuation, including the unblinding date if applicable.

2.3.2 Protocol Deviations

The number of subjects with protocol deviations will be tabulated by category and deviation for the FAS. Protocol deviations will be listed with date and study day of occurence and deviation.

2.3.3 Analysis sets

The number of subjects included in each analysis set will be tabulated . Reasons for exclusion from the analysis sets will be tabulated for FAS. Patient exclusion from analysis sets will be listed for all patients with reason for exclusion (including protocol deviations)

2.3.4 Demographics and baseline characteristics

Demographics and baseline characteristics will be summarized by treatment group using the FAS set. Summaries would include age, gender, race, ethnicity , heigh, weight , BMI and baseline ACQ-5. Continuous variables will be summarized using descriptive statistics (number of non-missing data, mean,standard deviation, median, first and third quartiles, minimum, and maximum) and categorical variables will be summarized in terms of the number and percentage of patients in each category including a category for missing data if any for the treatment group.

No statistical analyses will be provided for baseline comparability among the treatment groups.

Derivation of BMI :

- BMI is calculated as : BMI (kg/m^2) = weight (kg) /[Height(m) *Height (m)]

Medical history

Medical history will be coded with the Medical Dictionary for Regulatory Activities terminology (MedDRA) using the most recent version at the time of database lock. History/conditions as well as protocol solicited events for nasal polyposis will be summarized for the FAS set by primary system organ class and preferred term. Verbatim recorded history/conditions will be listed together with the coded terms, date of diagnosis/surgery and whether the problem was ongoing at start of the study.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Since the study has a double dummy design, each patient will be dispensed two bottles of study medication at the dispensing visits. Bottle 1 has study medication corresponding to 150 mg QAW039 or placebo and Bottle 2 has study medication corresponding to 450 mg QAW039 or placebo. Exposure and compliance will be presented on the SAF. Exposure will be presented for each treatment while compliance will be presented by treatment arm for each of the bottles separately.

The SAF will be used for the analyses of treatments.Categorical variables will be summarized as frequencies and percentages. For continuous data , mean , standard deviation , median , 25^{th} and 75^{th} percentiles, minimum and maximum will be presented.

2.4.1.1 Duration of exposure

Duration of exposure to a study drug will be calculated as the number of days between the first dose date and the last dose date exposed to that treatment over the specified period (expressed as: Duration of exposure (weeks) = (Date of last known dose of study drug – Date of first dose of study drug + 1)/7).

In addition, the duration of exposure will be summarized as a categorical variable classified into ≤ 4 weeks, > 4 – 8 weeks, > 8 – 12 weeks and > 12 weeks.

Dose administration data will be listed for patients in the SAF.

Patients in the randomized set who received any wrong study medications will be listed. These patients will be identified using the information recorded on the DAR page of the eCRF. If there is a record with reason = dispensing error, then the pack number will be used to identify whether or not the patient received the wrong study drug.

The number of patients with dose adjustments (interruption, or permanent discontinuation) and the corresponding reasons will be summarized for the study treatment .

2.4.1.2 Compliance

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 taking into account the duration of the drug interruptions.

Percentage of days with study medication intake = 100 x number of days with non-zero study treatment intake/(Day of last Treatment – Day1 +1).

Compliance will be categorized as <80% , 80-100%, >100% , and summarized by treatment arm for each of the pills separately based of the safety set.

2.4.2 Prior, concomitant and post therapies

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. More than one ATC class per medication is possible and the medication will be reported under all applicable classes.

Medications started and stopped prior to study drug and taken concomitantly will be summarized by treatment group in separate tables in the SAF. The medication will be classified into "prior", "concomitant" based on the start/end dates.

Prior: Any medication with a start date before Day 1.

Concomitant: Any medication with end date on or after Day 1 or ongoing at the end of trial or missing end date and start date before the end of the Treatment Epoch.

Medications can be considered both prior and concomitant.

Concomitant nasal polyp related medications will be summarized

All summaries will be by treatment group on the Safety Set.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary analysis of this study will be conducted according to the intention to treat principle and will be based on the FAS.

The primary population considered here are patients with nasal polyps with a Nasal Polyp Score (NPS) $\geq$4 (minimum of 2 per nostril) and a concommitant diagnosis of ashtma.

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 NPS 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 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.

2.5.2 Statistical hypothesis, model, and method of analysis

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.

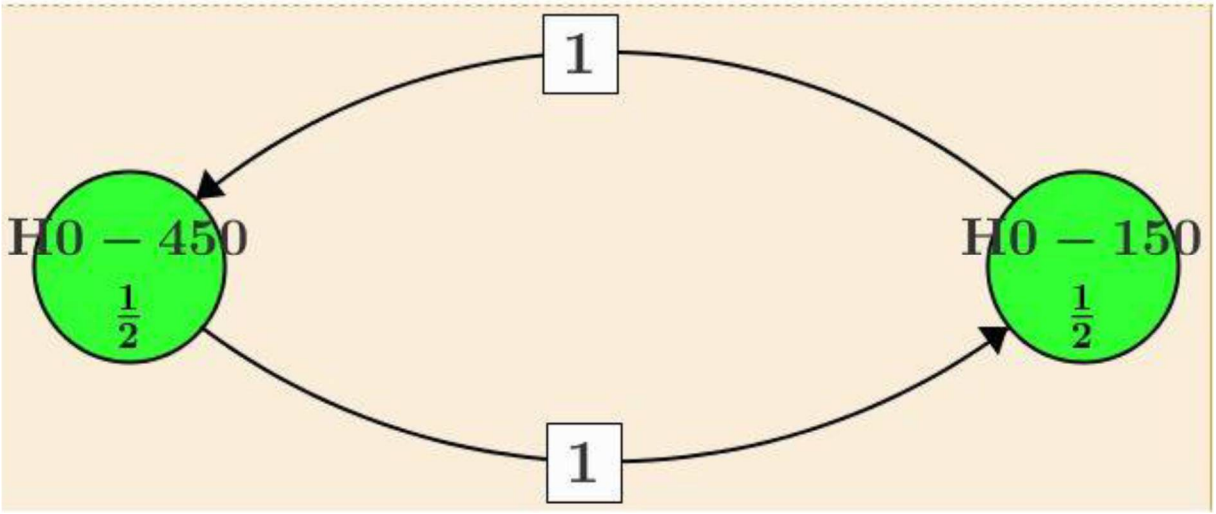
The primary alternative hypotheses are:

- $H_{A\,450}$: 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 2-1 (Bretz et al 2011). The Dunnett test will be used to test $H_{0\,450}$ and $H_{0\,150}$

Figure 2-1 Representation of Approach to Test Hypothesis



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 on or before the date of randomization. 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 8 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 by visit.

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

2.5.3 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.

2.5.4 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 covariates for treatment, visits and interaction between treatment and visit.

If the data suggests a logistic regression model is not the most appropriate for a responder analysis (*possible reasons may include majority of a particular response*) we will use additional analysis methods such as Cochran Mantel Haeszel test for the relative proportion of responders in each treatment arm and check whether there is a significant difference among them.

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.

2.6 Analysis of the key secondary objective

There are no key secondary endpoints defined.

2.6.1 Key secondary endpoint

2.6.2 Statistical hypothesis, model, and method of analysis

2.6.3 Handling of missing values/censoring/discontinuations

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

2.7.1.1 To evaluate the effect of symptoms as measured by the nasalcongestion 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. 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.

2.7.1.2 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. The treatment group difference in terms of change from baseline at Week 16 in

2.7.1.3 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 also indicates how the patient does in accordance to their age group and gender. The maximum score achievable on the scale is 40.

A sensitivity analysis would be performed excluding the patients from the sites for whom the UPSIT instrument was completed with pencil. This information would be recorded in the Data Handling Plan document.

2.7.2 Statistical hypothesis, model, and method of analysis

The treatment group difference in terms of change from baseline at Week 16 in UPSIT, SNOT 22 and Nasal Congestion Score will be estimated using an MMRM model with change from baseline as the response variable, and will be analysed similarly to the primary endpoint with appropriate baseline measurement .The least square mean change in scores for each of the questionnaires from baseline to week 16 alongside with 95% confidence interval and the P-value corresponding to the least square mean difference will be presented .

2.7.3 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.Safety analyses

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

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

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 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 1 day after the date of the last actual administration of any study treatment.

2.7.5 Adverse events (AEs)

.

Adverse events after informed consent including asthma exacerbations will be listed.

Adverse events starting on or after the day of the first intake of study drug and until the day after the last intake of study drug will be classified as treatment emergent adverse events. Adverse events that started during the study after informed consent and before the day of thefirst intake of study drug will be classified as prior adverse events and not included in tabulations of treatment emergent adverse events.

The number and percentage of patients who reported TEAEs will be summarized by primary system organ class (SOC), preferred term (PT), and treatment group for

- all adverse events (AEs)
- all AEs by maximum severity
- AEs suspected to be related to study drug
- AEs by standardized MedDRA query (SMQ) level serious AEs (SAEs)
- AEs leading to permanent study drug discontinuation
- Serious adverse events

Unless otherwise specified, primary system organ classes will be sorted alphabetically and, within each primary system organ class, the preferred terms will be sorted in descending order of frequency in the QAW039 150 mg once daily and QAW039 450 mg once daily treatment group. If a patient reported more than one AE with the same preferred term, the AE will be counted only once. If a patient reported more than one AE within the same primary system organ class, the patient will be counted only once at the system organ class level. In addition, the most frequent AEs will be presented by preferred term in descending order of frequency in the QAW039 150 mg QAW039 450 mg once daily treatment group.

Serious adverse events will also be summarized.

In addition, the most frequent AEs will be presented by preferred term in descending order of frequency in the QAW039 150 mg once daily treatment group.

All adverse events and related preferred terms and system organ class will be categorised using latest MedDRA version avilable at the time of data analysis.

2.7.5.1 Adverse events of special interest / grouping of AEs

The number and percentage of patients and treatment emergent adverse events of special interest will be summarized for each type of event with a break-down for each type of event by

SMQ(when applicable) and preferrred term. The Compound Case Retrieval Strategy (CRS) will be used to determine the MeDRA search criteria to be used to identify events of special interest.

2.7.5.2 Adverse events reporting for safety disclosure

For the legal requirements of clinicaltrials.gov, two required tables on TEAEs which are not SAEs with an incidence greater than a certain threshold based on the final database and on treatment emergent serious adverse events and SAEs suspected to be related to study drug will be provided by system organ class and PT on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study drug causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study drug / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study drug and SAEs irrespective of study drug relationship will be provided by SOC and PT.

2.7.6 Deaths

A summary of deaths will be presented by primary system organ class, preferred term, and treatment groups regardless of study drug relationship.

All the deaths in the clinical database incuding those occurring during screening will be listed, but only those between the first treatment and the last dose + 1 day will be included in summary tables. Additionally all deaths after first dose of study treatment will be tabulated by treatment group.

2.7.7 Laboratory data

Laboratory data consist of hematology and biochemistry measurements. Laboratory data measured after first intake of study drug and until the day after last intake of study drug are regarded as on-treatment data. Laboratory data measured more than 1 day after last intake of study drug are regarded as post-treatment data and will not be summarized. All data will be listed with abnormal values flagged.

2.7.7.1 Summary of change from baseline

For continuous laboratory parameters, the on-treatment change from baseline to the worst post-baseline values (including values from post-baseline unscheduled and premature discontinuation visits) will be summarized by laboratory parameter and treatment group with standard descriptive statistics.

2.7.7.2 Notable values

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

For a patient to meet the criterion of a newly occurring clinically notable value, the patient needs to have a baseline value which is not clinically notable for that parameter. For a patient to meet the criterion of a worsening clinically notable value, the patient needs to have a baseline value which is not clinically notable and also have a worse post-baseline value. For patients with a missing baseline value, any post-baseline notable value will be considered as newly occurring.

The criteria for clinically notable values are presented in Table 5.3.2.

Laboratory test units will be converted to standard units. Based on agreement within our standards, if we have a multi-region study the Blood Urea Nitrogen (BUN) / Urea test would be represented as BUN [mg/dL] for the regions used to conventional results (US, Latin America) and as Urea [mmol/L] for the regions used to SI (the international system of units) results. Therefore, both BUN and Urea parameters will be included in the data.

BUN is always reported as mg/dL and Urea as mmol/L. BUN and Urea are the same measurement in the lab and should be considered the same test. Hence, for the summary tables, it is expressed in SI units. Conversion to SI units includes the factor that incorporates a conversion from BUN to Urea as well as a conversion from mg/dL to mmol/L.

Listings of patients with notable laboratory values will be provided by laboratory parameter, treatment group, and patient number.

Additionally, box plot of change from baseline will be presented over time for ALT, AST, ALT/AST ratio, total bilirubin, creatinine, albumin,. ACR value will be considered missing if either the albumin or the creatinine values are missing. Similarly, PCR will be considered missing if either the protein or the creatinine values are missing.

2.8 Other safety data

2.8.1 ECG and cardiac imaging data

ECG measurements include heart rate, QT interval, RR interval, PR interval, QRS duration, and Fridericia's QTc (calculated as QTcF = QT / $3\sqrt{}$ RR (in seconds), where $3\sqrt{}$ denotes the cube root).

ECG data measured more than 1 day after last intake of study drug are regarded as post treatment data and will not be summarized. All data will be included in the analyses regardless of rescue medication use.

Clinically relevant values

- The number and percentage of patients with newly occurring or worsening clinical relevant QTcF values (see Table 2.8.1) summarized at any time on treatment considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits.

Table 2.8.1 Clinically relevant criteria for QTcF (Fridericia's formula)

ECG parameter (unit)	Clinically relevant range
Value considering newly occurring or worsening cases	
QTcF (msec)	≥ 450 (male)
QTcF (msec)	≥ 460 (female)
QTcF (msec)	> 500 (both)
Change from baseline	
QTcF	< 30
QTcF	30 – 60
QTcF	> 60

Clinically notable values

- A summary table will also be produced for number and percentage of subjects with notable QT and QTcF intervals (irrespective of the time point) using the following categories:
  a. any treatment emergent (new) QTcF or QT interval ≥ 450 ms – 480 ms, > 480 ms – 500 ms or > 500 ms
  b. QTcF or QT increase from baseline of ≥ 30 ms – < 60 ms, ≥ 60 ms
  c. QTcF and QT increase from baseline of ≥ 30 ms plus QTcF interval ≥ 450 ms, > 480 ms or > 500 ms
  d. QTcF increase from baseline of ≥ 60 ms plus QTcF interval ≥ 450 ms, > 480 ms or > 500 ms
- The number and percentage of subjects with noteworthy PR, QRS and HR interval changes will be reported using the below categories:
  a. New PR > 200 ms to <= 220 ms; and > 220 ms
  b. New QRS > 110 ms to <= 120 ms; and > 120 ms
  c. PR increase > 25% to a value > 200 ms
  d. QRS increase > 25% to a value > 120 ms
  e. HR decrease > 25% to a HR < 50 bpm
  f. HR increase > 25% to a HR > 100 bpm

2.8.2 Vital signs

Vital signs measurements include systolic and diastolic blood pressure (SBP and DBP), pulse rate, temperature, height and body weight. Vital signs data taken on or after the time of the first intake of study treatment and until the day after the last intake of study drug are regarded as on-treatment data. Vital signs data measured more than 1 day after last intake of study drug are

regarded as post-treatment data and will not be summarized. All data will be included in the analyses regardless of rescue medication use.
The following analyses will be performed by treatment group:

- the number and percentage of patients with newly occurring or worsening notable vital signs on-treatment values (see Table 2.8.2 for definition of notable values) summarized by parameter (except height), at any time on treatment considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits
- Vital signs will also be summarized by clinically relevant categories at the baseline and the week 16 visits :
    1. Pulse rate: < 40 bpm, 40 – 90 bpm, and > 90 bpm
    2. Systolic blood pressure: < 90 mm Hg, 90 – 140 mm Hg, and > 140 mm Hg
    3. Diastolic blood pressure: < 50 mm Hg, 50 – 90 mm Hg, and > 90 mm Hg.

The same approach as for notable laboratory values will be used to define a newly occurring notable vital sign value and a worsening notable vital sign value.
A listing of all patients with notable vital sign values and changes will be provided.

Table 2.8.2 Clinical notable criteria for vital signs

Vital sign parameter (unit)	Lower bound of clinically notable range	Upper bound of clinically notable range
Notable values		
Systolic blood pressure (mmHg)	< 75	> 200
Diastolic blood pressure (mmHg)	< 40	> 115
Pulse rate (bpm)	< 40	> 130
Notable change from baseline		
Systolic blood pressure (mmHg)	≤ 90 and decrease from baseline by ≥ 20	≥ 180 and increase from baseline by ≥ 20
Diastolic blood pressure (mmHg)	≤ 50 and decrease from baseline by ≥ 15	≥ 105 and increase from baseline by ≥ 15
Pulse rate (bpm)	≤ 50 and decrease from baseline by ≥ 15	≥ 120 and increase from baseline by ≥ 15
Weight (kg)	Decrease ≥ 7% from baseline	Increase ≥ 7% from baseline

2.9 Pharmacokinetic endpoints

Not Applicable

2.10 PD and PK/PD analyses

Not Applicable.

2.11 Patient-reported outcomes

Nasal Congestion Score, SNOT 22 and UPSIT are the Patient reported outcomes questionnaires that we would be collecting in this study. Endpoints related to these questionnaires and analysis method described in section 2.7.1.

2.12 Biomarkers

Not Applicable

2.14 Interim analysis

No interim analysis is planned.

3 Sample size calculation

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%.

4 Change to protocol specified analyses

Not Applicable

5 Appendix

5.1 Imputation rules

5.1.1 AE date imputation

Rules for imputing AE end dates are stated below. Date of last contact in the study has been defined as in Section 2.1.3.11.

1.If the AE end date month is missing, the imputed end date should be set to the earliest of the (date of last contact, 31DECYYYY, date of death).

2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (date of last contact, last day of the month, date of death).

3. If AE year is missing or AE is ongoing, the end date will not be imputed.

5.1.1.1 AE start date imputation

Rules for imputing the AE start date:

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not Used	MON	YYYY
Treatment Start Date	Not Used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) No Convention	(1) No Convention	(1) No Convention	(1) No Convention
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.c) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

Before imputing AE start date, find the AE start reference date.

1. If the imputed AE end date is complete and the imputed AE end date < treatment start date then AE start reference date = min(informed consent date, earliest visit date).
2. Else AE start reference date = treatment start date

Impute AE start date -

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
    a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
    b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
    a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
    b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).
4. If the AE start date year value is equal to the treatment start date year value:

a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.

b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).

c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete imputed AE end date is available and the imputed AE start date is greater than the imputed AE end date, then imputed AE start date should be set to the imputed AE end date.

5.1.2 Concomitant medication date imputation

5.1.2.1 Concomitant medication end date imputation

Rules for imputing the CM end date are stated below. Date of last contact in the study has been defined as in Section 2.1.3.10. Concomitant medication end dates will not be imputed for ongoing records.

1. If CM end day is missing and CM month/year are non-missing then impute CM day as the minimum of date of last contact and the last day of the month.
2. If CM end day/month are missing and CM year is non-missing then impute CM day as the minimum of date of last contact and the end of the year (31DECYYYY).
3. If CM day/month/year is missing then use the date of last contact + 1 day as the imputed CM end date.
4. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

5.1.2.2 Concomitant medication start date imputation

Rules for imputing the CM start date:

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial CMD Start Date	Not Used	MON	YYYY
Treatment Start Date	Not Used	TRTM	TRTY

The follwoing matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) Uncertain	(1) Uncertain	(1) Uncertain	(1) Uncertain
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.a) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
   a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).

b. Else if the CM month is not missing, the imputed CM start date is set to the midmonth point (15MONYYYY).

3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:
   a. If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).
   b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).
4. If the CM start date year value is equal to the treatment start date year value:
   a. And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior treatment start date.
   b. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
   c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete imputed CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.2 AEs coding/grading

The MedDRA version which will be available at the time of database lock, will be used for the coding purpose of the adverse events. For coding purpose of the concomitant medications, the available WHO-DD (World Health Organization-Drug Dictionary) version at the time of database lock, will be used.

5.3 Laboratory parameters derivations

The following table shows the criteria for clinically notable laboratory values. Not all parameters have notable criteria defined.

Table 5.3.1 Direction of interest for worst case value for laboratory parameters

Laboratory Parameter	Direction of interest for worst case value
A. Hematology	
Basophils	High
Eosinophils	High
Hematocrit	Low
Hemoglobin	Low
Lymphocytes	Low and high
Monocytes	High
Neutrophils	Low and high
Platelets	Low and high
RBC	Low
WBC total	Low and high
B. Chemistry	
Albumin	Low
Sodium	Low and High
Alkaline Phosphatase	High
ALT/SGPT	High
AST/SGOT	High
Bilirubin Total	High
Blood Urea Nitrogen (BUN)	High
CPK	High
Creatinine	High
Gamma GT	High
Glucose	Low and high
Potassium	Low and high
Uric acid	High

Table 5.3.2 Clinical notable criteria for selected laboratory tests

Laboratory parameter (unit)	Bound for notably low values	Bound for notably high values
Hematology		
Hematocrit (v/v)		
Male 12-17	0.34	
Male 18-65	0.37	
Male >=66	0.34	
Female 12-65	0.32	
Female >=66	0.31	

Laboratory parameter (unit)	Bound for notably low values	Bound for notably high values
Hemoglobin (g/L)		
Male 12-17	100	
Male >=18	110	
Female	95	
Thrombocytes (x10E^9/L	75	700
WBC's (x10^9/L)	2.8	16.0
Chemistry		
Alkaline Phosphatase (IU/L)	-	3xULN
Total Bilirubin (µmol/L)	-	34.2
Creatinine (µmol/L)		176.8
Potassium (mmol/L)	3	6
Glucose (mmol/L)	2.78	9.99
ALT/SGPT (U/L)	-	3 x ULN
AST/SGOT (U/L)	-	3 x ULN
BUN/ Urea (mmol/L)		9.99
Sodium (mmol/L)	125	160
Gamma GT (U/L)		3 x ULN
CPK (IU/L)		4 x ULN

5.4 Statistical models

5.4.1 Primary 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 following mixed model with repeated measures will be used for changes from baseline in the Nasal Polyp Score :

Change from baseline = intercept + treatment + visit + treatment * visit + NPS baseline value + NPS baseline value * visit + error

The random effect in the mixed model will be represented by the use of an unstructured covariance matrix for the within patient variability.

The SAS procedure MIXED will be used with the follwing code :

```
proc mixed data=...order=internal;
  **include schedule assessments/visits only;
  where avisitn in (201,208,216);
  class trt avisitn;
  model chg= trt avisitn trt*avisitn base base*avisitn /ddfm=kr;
  repeated avisitn/subject=usubjid type=un;
  lsmeans trt*avisitn/ cl diff;
```

```
adjust=DUNNET;
run;
```

where chg = change from baseline

trt = treatment (QAW 450 mg + SoC , QAW 150 mg +SoC , Placebo+SoC)

avisitn = visit (include scheduled visit and assesments only)

base = baseline Nasal Polyp Score

usubjid = unique subject identifier

Appropriate baseline values and visits will be included for each of the endpoints i.e. Nasal Congestion Score, SNOT-22 score and the UPSIT smell test score.

The default estimation method for the covariance parameters will be used, which is the restricted maximum likelyhood.

Results will be presented with least square means and standard errors (SE) for treatment effects and least square mean, SE, associated two sided 95% confidence interval , a two sided p-value for treatment contrast QAW-Placebo at each visit.

If the analysis fails to converge with an unstructured covariance matrix, either a compound symmetry (first choice) or the first order auto regressive (AR1) (second choice) covariance structure will be used.

5.4.2 Key secondary analysis

There are no key secondary endpoints for this study.

5.5 Rule of exclusion criteria of analysis sets

The following protocol deviations will lead to exclusion of patients from FAS, SCR or safety set :

PD Identifier	'PD Description' for reporting	CP_Exclude from analysis sets
INCL01A	Did not sign informed consent	Exclude from all analysis sets
INCL01B	Written informed consent obtained after date of a study assessment	All concerned assessments removed from SCR
TRT01	Received study drug but not randomized	Exclude from FAS and SAF (also evaluate on a case by case basis)
TRT02	Randomized but no study drug given	Patient did not recieve a study drug; then exclude

		from FAS and SAF; otherwise do not exclude from any population set
EXCL19	History of sinus or nasal surgery modifying the structure if the nose such that assessment of NPS via nasal endoscopy is not possible.	Exclude from all analysis sets
INCL02B	No current diagnosis of nasal polyposis	Exclude from all analysis sets
INCL02C	Diagnosis of nasal polyposis with polyp size score is less than 4 and a less than 2 score in each nostril, measured by nasal endoscopy at SCR and prior to randomization on Treatment Day 1.	Exclude from Full analysis set.

6 Reference

Bachert et al .(2016) Effect of Subcutaneous Dupilumab on Nasal Poly Burden in Patients With Chronic Sinusitis and Nasal Polyposis. A Randomized Clinical Trial . Journal of the American Medical Association ; Volume 315, Number 5 : 469-479

Bretz F, Maurer W, Brannath W et al. (2009) A graphical approach to sequentially rejective multiple test procedure. Statistics in Medicine; 28(4) : 586-604

Bretz F, Tamhane A , Dmitrienko A , Multiple Testing Problems in Pharmaceutical Statistics (2010) : CRC Press

Gaveart et al (2011) Mepolizumab, a humanized anti- IL-5 mAb, as a treatment option for severe nasal polyposis . Journal of Allergy and Clinical Immunology ; Volume 128 , Number 5 : 989-995

Niloofar Ramezani , Analyzing Corelated Data in SAS® , Paper 1251-2017 , SAS Institute Inc.