NOVARTIS

Clinical Development

QAW039/Fevipiprant

CQAW039A2323 / NCT03629249

A 52-week, multicenter, randomized, double-blind, double-dummy, parallel-group, placebo-controlled study of fevipiprant once daily plus standard-of-care (SoC) for reduction of systemic corticosteroids (oral and parenteral) use in patients with severe asthma

Statistical Analysis Plan (SAP)

Author:	Trial Statistician, [redacted]

Document type:	SAP Documentation
Document status:	Final 1.1
Release date:	20-Apr-2020
Number of pages:	38

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
30-Nov-2018	Prior to DB lock	Creation of final version	N/A - First version	NA
20-Apr-2020	Prior to DB lock	Early termination of the study	[redacted]	Section 1.2
20-Apr-2020	Prior to DB lock	Early termination of the study	Removed all statistical analyses for secondary endpoints and changed to descriptive only	Section 2.7, 5.1, 5.2
20-Apr-2020	Prior to DB lock	Early termination of the study	Adjusted text in General Definitions and Baseline Characteristics.	Section 2.1
20-Apr-2020	Prior to DB lock	Early termination of the study	Removed all subgroup analyses	Section 2.2.1
20-Apr-2020	Prior to DB lock	Early termination of the study	Removed compliance to study treatment	Section 2.4.1, 2.4.1.2
20-Apr-2020	Prior to DB lock	Early termination of the study	Added definition of categories for cumulative duration of exposure	Section 2.4.1.1
20-Apr-2020	Prior to DB lock	Early termination of the study	Removed all supportive analyses	Section 2.5.4
20-Apr-2020	Prior to DB lock	Early termination of the study	Follow-up of deaths changed to last drug intake +7 days, changed follow-up of laboratory data to +7 days of last drug	Section 2.8.2, 2.8.3, Section 2.8.3.3

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			intake, newly occurring worsening of notable lab values removed	
20-Apr-2020	Prior to DB lock	Early termination of the study	Conversion of OCS to prednisolon equivalent added	Section 5.2
20-Apr-2020	Prior to DB lock	Early termination of the study	Definition of statistical analyses models not used anymore removed	Section 5

Table of contents

List of abbreviations

AE	Adverse event
CSR	Clinical Study report
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
MedDRA	Medical Dictionary for Drug Regulatory Affairs
o.d.	Once Daily
PK	Pharmacokinetics
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
SCS	Systemic Corticosteroids
SOC	System Organ Class
SoC	Standard of Care
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of study QAW039A2323, a 52-week phase IIIb, multicenter, randomized, double-blind, double-dummy, parallel-group, placebo-controlled study of fevipiprant once daily plus standard-of-care (SoC) for reduction of systemic corticosteroids (oral and parenteral) use in patients with severe asthma.

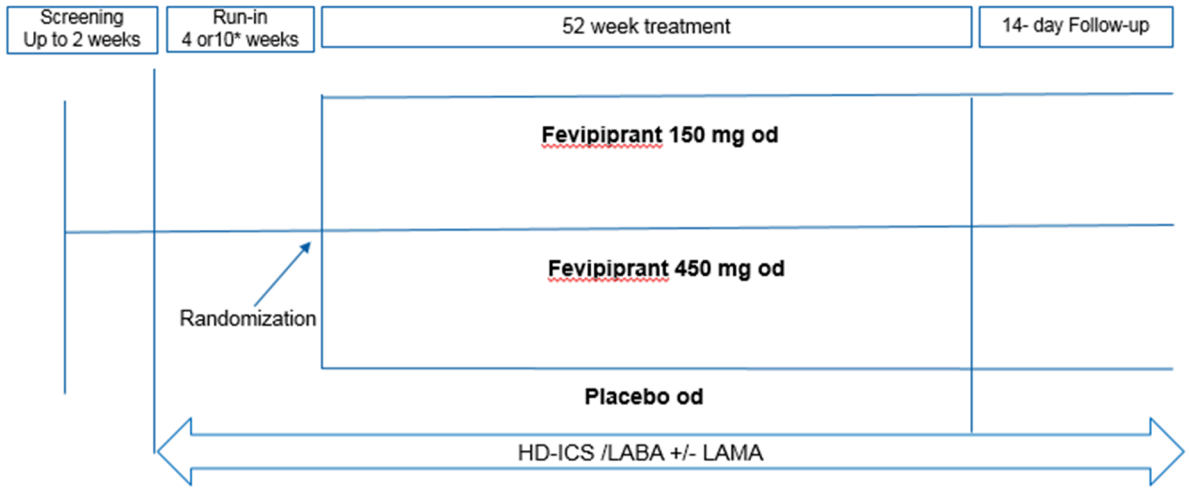
The content of this SAP is based on protocol QAW039A2323 version 01.

Data will be analyzed by Novartis or a contracted contract research organization (CRO) according to the data analysis section 9 of the study protocol which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and 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, double-dummy, placebo-controlled, parallel-group study design to determine the ability of fevipiprant plus SoC compared with placebo plus SoC to reduce the use of systemic corticosteroids (SCS) in patients with severe asthma. The study will include:

- a Screening period of up to 2 weeks to assess eligibility;
- a Run-in period of 4 or 10 weeks to evaluate maintenance of asthma control and to collect baseline safety data. Upon completion of the Run-in period, all patients who met eligibility criteria will be randomized to 1 of 3 treatment groups (Fevipiprant 150 mg or Fevipiprant 450 mg or placebo once daily) in a ratio 1:1:1. Randomized patients will be stratified according to their peripheral blood eosinophil count (< 250 cells/µl or ≥ 250 cells/µl). Patients coming with high-dose ICS/LABA will have 4 weeks of run-in period and 10 weeks of run in period will be allowed for patients switching from mid-dose to high-dose ICS/LABA as per protocol;
- a Treatment period of 52 weeks 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 allow for flexible therapy, meaning that patients can be escalated or de-escalated on their SoC therapy or add any other controller.

Study completion for a patient will occur after he/she has completed 52 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 52 weeks of treatment and the post- treatment follow-up visit.

Approximately 669 patients will be randomized in the study.

The primary analysis will be conducted upon study completion.

There is no interim analysis planned for this study.

1.2 Study objectives and endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	***Endpoint(s) for primary objective(s)***
• In patients with severe asthma and high eosinophil counts (≥ 250 cells/µl) receiving flexible SoC asthma therapy, to demonstrate a reduction in the use of SCS with fevipiprant (150 mg or 450 mg once daily), compared with placebo	• Total systemic corticosteroid dose in mg prednisone/prednisolone or equivalent over 52 weeks of treatment
• In all patients with severe asthma receiving flexible SoC asthma therapy, to demonstrate a reduction in the use of SCS with fevipiprant (150 mg or 450 mg once daily), compared with placebo	• Total systemic corticosteroid dose in mg prednisone/prednisolone or equivalent over 52 weeks of treatment
Secondary objective(s)	***Endpoint(s) for secondary objective(s)***

• To evaluate the effect of fevipiprant 150 mg and 450 mg and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy in terms of difference in daytime and nightime symptom scores	• Change from baseline in daytime and nightime symptom scores over 52 weeks of treatment by treatement group
• To evaluate the efficacy fevipiprant 150 mg or 450 mg and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy, with respect to change from baseline in Asthma Control Questionnaire (ACQ-5) in the overall population	• Change from baseline in Asthma Control Questionnaire (ACQ-5) total score over 52 weeks of treatment
• To evaluate the effect of fevipiprant 150 mg and 450 mg and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy in terms of Asthma Related Quality of Life Questionnaire (AQLQ+12) in the overall population	• Change from baseline in Asthma Related Quality of Life Questionnaire (AQLQ+12) total score over 52 weeks of treatment
• To evaluate the effect of fevipiprant 150 mg and 450 mg and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy in terms of proportion of patients receiving continuous SCS during ≥ 30 days, at ≥ 7.5mg/day of prednisolone or equivalent in the overall population	• Proportion of patients requiring ≥ 7.5mg systemic corticosteroid dose in mg prednisone/prednisolone or equivalent per day continuously for at least 30 days
• To evaluate the safety and tolerability of fevipiprant 150 mg and 450 mg and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy in the overall population	• Adverse events, ECG, vital signs and laboratory analysis over 52 weeks of treatment
• To evaluate the effect of fevipiprant 150 mg and 450 mg and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy in terms of proportion for patients with no SCS use from the overall population	• Proportion of patients with no SCS use over 52 weeks of treatment
• To evaluate the effect of fevipiprant 150 mg and 450 mg and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy in terms of time to first prescription of biologic therapy in the overall population	• Time to first prescription of biologic therapy from first dose of study treatment received over 52 weeks of treatment

2 Statistical methods

2.1 Data analysis general information

The final efficacy analysis will be performed by Novartis or a designated CRO. The most recent version of SAS or R software will be used to perform all data analyses and to generate tables, figures and listings.

Data included in the analysis

The analysis cut-off date for the primary analysis of study data will be established after all randomized patients have completed 52 weeks of treatment or have discontinued study, or study

terminatde by sponsor. All statistical analyses will be performed using all data collected in the database up to the data cutoff date. All data with an assessment date or event 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.

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.

2.1.1 General definitions

Study drug

For this double blind trial, study treatment refers to QAW039 150 mg, QAW039 450 mg or placebo as assigned to a patient at randomization.

Date of first administration study treatment

The date of first administration of study treatment is derived as the first date when a nonzero dose of study treatment was administered as per the Dosage Administration CRF. The date of first administration of study treatment will also be referred as ***start of study treatment***.

Date of last administration of study treatment

The date of last administration of study treatment is defined as the last date when a nonzero dose of study treatment was administered as per Dose Administration (e)CRF.

Study day

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

The study day is calculated as:

- 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., SCS use, eDiary, patient reported outcomes (PRO) (AQLQ and ACQ) and biologic therapy administered during the treatment period) 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.

Time unit

A year length is defined as 365.25 days. 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. If duration is reported in years, duration in days will be divided by 365.25.

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 eDiary, PRO, biologic therapy.

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.

Patients coming with medium dose of SoC will have 10 weeks of run-in period. For those patients the last 4 weeks of run-in period will be used for baseline calulcations in and effort to standarize the groups with the patients coming with high dose of SoC (4 weeks of run-in period)

Parameter	Baseline Assessment	Details
Vital Signs	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.	
Height and Weight	Baseline height and weight is defined as the last available measurement taken prior to first dose of study drug. Missing baseline values will not be imputed.	
ECG	Baseline 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. For baseline ECG interpretation, there will only be one assessment at each time-point, and, hence, this will be used as the baseline ECG interpretation (screening value if present, otherwise the last value prior to the first dose).	ECG is collected as single 12 lead ECG, not as a triplet.
Laboratory data	Baseline hematology, biochemistry and urinalysis are defined as the last scheduled assessment taken prior to first dose of study drug 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.	
AQLQ+12	Baseline AQLQ+12 score is defined as AQLQ+12 score obtained on Day 1. If the AQLQ+12 score on Day 1 is missing then the last available AQLQ+12 score prior to Day 1 will be used. If the AQLQ+12 score is missing on Day 1 and on all visits before Day 1, the respective baseline value will be set to missing.	AQLQ assessments are taken during run-in and day 1.
ACQ-5	Baseline ACQ-5 score is defined as ACQ-5 scores obtained on Day 1. If the ACQ-5 score on Day 1 is missing then the last available ACQ-5 score prior to Day 1 will be used. If the ACQ-5 score is missing on Day 1 and on all visits before Day 1, the respective baseline value will be set to missing.	ACQ assessments are taken during screening and on day 1.
e-Diary daytime and night time asthma symptoms	For e-diary data (daytime and night time asthma symptoms) which are collected daily, the mean score for the baseline is calculated from Visit 101 to Day 1) will be considered as the baseline mean score. The non-missing data within that interval will be used to calculate the mean value	Note that the morning assessment for Day 1 counts towards the baseline (as a part of run-in). However, the evening assessment for Day 1 counts as the treatment period (not as a part of run-in).

	as long as there are at least 75% days in the period with non-missing e-diary data. Since these measurements are collected at both morning and evening at Day 1, the morning assessment for Day 1 counts towards the baseline (as a part of run-in) while the evening assessment counts as the treatment period.	

Post-baseline measurement

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

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.

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 (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.

Visit remapping and assessment windows

If a scheduled visit did not occur, then the data from the treatment discontinuation or study discontinuation visit may be used as the data from the scheduled visit. This is done 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.

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 include all patients who provided informed consent.

The randomized set (RAN) will include all patients that were randomized. Data from these patients will be analyzed according to the treatment to which the patient was assigned at randomization.

The full analysis set (FAS) will include all randomized patients who received at least one dose of study treatment. It was considered reasonable to limit the FAS to patients who took study treatment, because the decision on whether or not treatment is started will not be influenced by the treatment group assignment due to the effective treatment blinding procedures described in protocol Section 5.4. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.

The safety set (SAF) will include all patients who received at least one dose of study treatment. Patients will be analyzed according to the treatment they received.

The analysis of the primary objective 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.

If an incorrect randomization stratum is inadvertently selected for a patient by the investigator in the IRT, patients will still be included in all analyses. The corrected stratum information as per the CRF data will be used in any analysis models.

2.2.1 Subgroup of interest

NA

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 RAN 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 and whether they completed or discontinued from the study will be listed, with date of last dose and primary reason 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 RAN. Protocol deviations will be listed with date and study day of occurrence and deviation.

2.3.3 Analysis sets

The number of subjects included in each analysis set will be tabulated. Reasons for exclusions from analysis sets will be tabulated for RAN. Patient exclusion from analysis sets will be listed for all patients with reasons 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 will include age, gender, race, ethnicity, height, weight, BMI, pre- and post-bronchodilator FEV_1, percent predicted FEV_1, FEV_1 reversibility, duration of asthma, number of asthma exacerbations in prior year, smoking history (never/former), number of pack years, baseline ACQ-5, baseline AQLQ+12 and Peripheral blood eosinophils. 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.

Blood eosinophil counts will also be summarized for the SCR. The baseline blood eosinophil will be considered as the eosinophil value at Visit 1. If the value at Visit 1 is missing then the baseline value will be considered as the first assessment after Visit 1 and prior to first dose of study medication, unless there is no value before randomization, in which situation, it will be missing.

Background asthma therapy will be categorized into GINA steps and will be summarized at baseline.

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

Derivation of the demographics and baseline characteristics

- BMI is calculated as: BMI (kg/m^2) = Weight (kg) / [Height (m) * Height (m)]
- Duration of asthma is calculated from the date of asthma first diagnosed recorded on the eCRF until the 1st visit. If the date is missing in day and/or month, it will be imputed as follows. If the year is before the first visit, the missing days will be imputed as the first of the month and the missing months will be imputed as July. If the year is the current year of the first visit, the missing days will be imputed as the first of the month and the missing months will be imputed as January.

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 asthma 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 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.

2.4.1.1 Duration of exposure

Duration of exposure to a treatment 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). The duration of exposure will be summarized by treatment group for the safety set as a continuous variable with the standard descriptive statistics.

In addition, the duration of exposure and cumulative exposure will be summarized as a categorical variable classified into ≤ 4 weeks, > 4 – 12 weeks, > 12 – 20 weeks, > 20 – 28 weeks, > 28 – 36 weeks, > 36 – 44 weeks, > 44 weeks or ≥ 4 weeks, ≥ 12 weeks, ≥ 20 weeks, ≥ 28 weeks, ≥ 36 weeks, ≥ 44 weeks, ≥ 52 weeks, respectively.

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

2.4.1.2 Compliance

NA

2.4.2 Prior, concomitant and post therapies

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 therapies will be recorded and summarized separately for asthma related medications and other medications.Concomitant therapies will be recorded and summarized separately for asthma related medications and other medications. Concomitant asthma related medications will be summarized by pre-defined category. Concomitant medications not related to asthma will be summarized by pharmacological (ATC) class and preferred term. More than one ATC class per medication is possible and the medication will be reported under all applicable classes.

Short acting beta2 agonist (SABA) rescue medication usage (mean number of puffs) during the screening/run-in period will be summarized. Patients taking prohibited concomitant medications will be noted in the summary of protocol deviations.

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 endpoint for this study is total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) over 52 weeks of treatment. The primary endpoint is analysed using FAS.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary endpoint will be analyzed in subpopulation of patients with eosinophil count ≥ 250 cells/µl and in overall population. The primary null hypotheses are:

- $H_{01\ 450\ \text{eosinophil subgroup}}$: the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in Fevipiprant 450 mg QD plus SoC is equivalent

to the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in placebo plus SoC in patients with eosinophil count ≥ 250 cells/µl

- $H_{02\ 150\ \text{eosinophil subgroup}}$: the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in Fevipiprant 150 mg QD plus SoC is equivalent to the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in placebo plus SoC in patients with eosinophil count ≥ 250 cells/µl
- $H_{03\ 450\ \text{overall population}}$: the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in Fevipiprant 450 mg QD plus SoC is equivalent to the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in placebo plus SoC for the overall population
- $H_{04\ 150\ \text{overall population}}$: the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in Fevipiprant 150 mg QD plus SoC is equivalent to the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in placebo plus SoC for the overall population

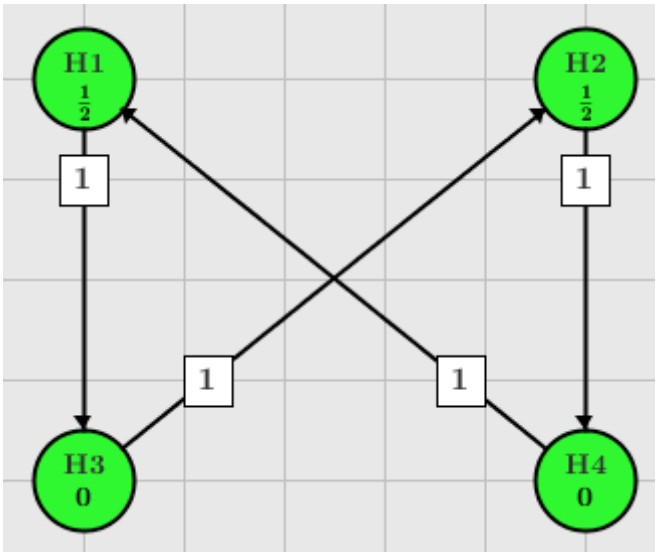
The primary alternate hypotheses are:

- $H_{A1\ 450\ \text{eosinophil subgroup}}$: the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in Fevipiprant 450 mg QD plus SoC is different to the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in placebo plus SoC in patients with eosinophil count ≥ 250 cells/µl
- $H_{A2\ 150\ \text{eosinophil subgroup}}$: the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in Fevipiprant 150 mg QD plus SoC is different to the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in placebo plus SoC in patients with eosinophil count ≥ 250 cells/µl
- $H_{A3\ 450\ \text{overall population}}$: the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in Fevipiprant 450 mg QD plus SoC is different to the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in placebo plus SoC for the overall population
- $H_{A4\ 150\ \text{overall population}}$: the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in Fevipiprant 150 mg QD plus SoC is different to the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in placebo plus SoC for the overall population

Familywise type I error rate control

The familywise type I error rate will be controlled at the two-sided 5% level across the primary null hypotheses using graphical approach specified by Figure 2-1 (Bretz et al 2009).

Figure 2-1 Closed testing procedure for primary objectives



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 subgroup with blood eosinophils ≥ 250 cells/µl for the 2 fevipiprant doses). Directed edges between the vertices specify how the local significance levels are propagated in case of significant results.

Initially, 50% of the alpha is assigned to each of the primary null hypotheses regarding the subgroup with blood eosinophils ≥ 250 cells/µl for the Fevipiprant 450 mg QD and Fevipiprant 150 mg QD doses, respectively. Once this first primary null hypothesis for a dose has been rejected, the alpha will be distributed to the other null hypothesis regarding the overall population for the same dose. If the null hypothesis regarding the primary endpoint for the overall population is rejected for a dose, then alpha is reassigned to the primary null hypotheses regarding the subgroup with blood eosinophils ≥ 250 cells/µl for the other dose. Alpha will only be reassigned from the null hypotheses for a dose to the null hypotheses for the other dose once all null hypotheses for the dose to which the alpha was originally assigned have been rejected.

Statistical model for primary variable

The total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) over 52 weeks of treatment will be analyzed using the Wilcoxon-Mann-Whitney rank sum test (Van Elteren test). For overall population analysis will be stratified by randomization stratum – blood eosinophils levels (≥ 250 cells/µl and < 250 cells/µl). For subgroup with blood eosinophils ≥ 250 cells/µl, analysis will not include stratification factor. The summary statistics for total SCS dose by treatment group will be provided.

The primary estimand will quantify the treatment effect based on on-treatment data. The total SCS dose data will be aggregated into monthly data for analysis. The primary estimand will account for different post-randomization events as follows:

- Use of rescue medications: Efficacy data collected during use of rescue medication will be used for analysis.

- Early discontinuation of study drug (prior to completing 52 weeks of treatment period): For the patients discontinuing study drug early, the total SCS dose for 52 weeks will be obtained as annualized SCS dose. For example if patient took 280 mg for 7 months then for 12 months patient will be taking 280*12/7=480mg total SCS dose.
- Use of biologics prior to discontinuation of treatment: Efficacy data collected during the use of biologics will be set to missing, since use of biologics can confound efficacy data. Biologics are usually taken for long period of time. Thus, after replacing SCS dose with missing, patient will not have data available for remaining duartion of the study. The total SCS dose will be obtained as annualized dose as explained above.

2.5.3 Handling of missing values/censoring/discontinuations

Some patients may discontinue early and may not complete the entire study duration. For the patients discontinuing treatment early, the total SCS dose for 52 weeks will be obtained as annualized SCS dose. For example if patient took 280 mg for 7 months then for 12 months patient will be taking 280*12/7=480mg total SCS dose. Efficacy data collected during the use of biologics will be set to missing, since use of biologics can confound efficacy data. After replacing SCS dose with missing, patient will not have data available for all 12 months, thus total SCS dose will be obtained as annualized dose.

-

2.6 Analysis of the key secondary objective

There is no key secondary objective.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

2.7.1.1 Proportion of patients with no SCS use over 52 weeks of treatment or during on-treatment period

The proportion of patients with no SCS use in individually observed on-treatment time will be presented. Patients will be considered as non-responders if patient takes SCS dose in observed period of treatment.

2.7.1.2 Proportion of patients requiring ≥ 7.5mg systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) per day continuously for at least 30 days

This is a composite endpoint where patients requiring ≥ 7.5mg systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) per day continuously for at least 30 days in 52 weeks treatment period or during on-treatment period are considered as responders. Patients will be considered as non-responders if patient do not satisfy either of the conditions.

2.7.1.3 Summary of Change from baseline in Asthma Related Quality of Life Questionnaire (AQLQ+12) total score during on-treatment period

The 32 items in the AQLQ+12 are divided into 4 domain-specific scores and a total score as follows:

- Symptoms = Mean of Items 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30 (12 items)
- Activity limitation = Mean of Items 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32 (11 items)
- Emotional function = Mean of Items 7, 13, 15, 21, 27 (5 items)
- Environmental Stimuli = Mean of Items 9, 17, 23, 26 (4 items)
- Overall Score = Mean of Items 1 to 32 (32 items)

Each item of the AQLQ+12 is equally weighted and scored along a 7-point scale, where 1 indicates maximal impairment and 7 indicates no impairment. Thus, higher scores indicate better asthma-related HRQOL (Health-Related Quality of Life). There is a mean score calculated for each of the four domains, as well as an overall quality-of-life score, which is the mean score of all 32 items. The resultant overall scores will be between 1 and 7.

The developer suggests no more than 10% of missing data. This means no more than 3 missing responses for the overall score and no more than 1 missing response per domain. For the symptoms and activity domain scores, one missing value per domain is allowed. For the emotional function and environmental stimuli domain scores, no missing values are allowed. If these limits for missing questions are exceeded, the variable will be considered missing and will be imputed as described in Section 2.7.3.

The minimal important difference (MID), defined as "the smallest difference in score which patients perceive as beneficial and would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management," of 0.5 has been established for this questionnaire as clinically significant (Juniper, et al 1994).

2.7.1.4 Summary of change from baseline of Asthma Control Questionnaire (ACQ-5) total score during on-treatment period

In this study, the ACQ-5 will be used to assess improvements in asthma symptom control. The original ACQ consists of 7 items: 5 items on symptom assessment, 1 item on rescue bronchodilator use, and 1 item on airway calibre (% FEV1 predicted). As the Spirometry assessments are performed centrally, the rescue bronchodilator use and % FEV1 predicted are not included in the version of ACQ chosen for this study.

The ACQ-5 will be self-administered at the clinic 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 2005a).

A score of 1.5 at baseline indicates patients who entered the study had inadequately controlled asthma (Juniper et al 2006). In addition, the minimal important difference (MID) or smallest change that can be considered clinically important is 0.5.

2.7.1.5 Proportion of patients with prescription of biologic treatment

The proportion of patients with any prescription of biologic therapy during the on-treatment period will be presented. Events which occur during on-treatment period will be included.

2.7.1.6 Summary of change from baseline of daytime and nighttime symptom scores by 4-week intervals during on-treatment period

The daytime and night time symptom scores will be collected using validated electronic patient diary. Scoring of measures: A range of response categories for each question from 0 to 6 (0 – totally controlled, 6 – extremely poorly controlled) is used in the daytime asthma symptom scale. Response categories ranging from 0 (indicating no awakening with asthma symptoms) to 3 (indicating awake all night) are used in the nocturnal diary scale. Daily daytime symptom scores will be computed as the average of the avaiable scores on four questions on the daytime symptom scale.

The mean daytime asthma symptom scores/nighttime symptom score will be calculated for each patient for each 4 week visit interval and over on-treatment period. The average score for each time interval is defined as the sum of daily scores (based on all the available questions) divided by the number of days where ediary records have been made on nighttime/daytime score for that visit interval. The non-missing data within each 4 week interval in treatment period will be used to calculate the mean value, as long as there are at least 14 days with non-missing e-diary data (based on all the available questions) in a 4-week period. Otherwise, the value will be set as missing.

2.7.2 Statistical hypothesis, model, and method of analysis

The analysis of all secondary endpoints will be based on on-treatment data (that is from first dose of study treatment till last dose of study treatment + 1).

The proportion of patients with no SCS use during on-treatment will be summarized by treatment. groups.

The proportion of patients requiring $\geq$ 7.5mg systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) per day continuously for at least 30 days within the on-treatment period will be summarized by treatment in overall population.

AQLQ+12, ACQ-5 and change from baseline in daytime and nighttime score will be summarized by treatment for all visits. All the summaries will be based on observed on-treatment data and non-imputed data.

2.7.3 Handling of missing values/censoring/discontinuations

No imputation will be done for secondary endpoints.

2.8 Safety analyses

All safety data will be summarized for the safety set. 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 safety data will be listed.

2.8.1 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 7 days 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 the first 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 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 once daily treatment group.

2.8.1.1 Adverse events of special interest / grouping of AEs

The number and percentage of patients with 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 preferred term. The Compound Case Retrieval Strategy (CRS) will be used to determine the MedDRA search criteria to be used to identify events of special interest.

2.8.1.2 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 treatment / 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 treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.2 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 + 7 day will be included in summary tables. Additionally all deaths after first dose of study drug will be tabulated by treatment group.

2.8.3 Laboratory data

Laboratory data consist of hematology, biochemistry and urinalysis measurements.
Laboratory data measured after first intake of study drug and until 7 days after last intake of study drug are regarded as on-treatment data. Laboratory data measured more than 7 days 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.

2.8.3.1 Summary of absolute values

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

The direction of interest for worst post-baseline for selected hematology and biochemistry parameters is tabulated in Table 6.3.1. For continuous urinalysis parameters, the direction of interest is always High.

For categorical laboratory parameters and categorical urinalysis parameters, a frequency table of results will be produced by laboratory parameter and treatment. Worst post-baseline on-treatment values (including values from post-baseline unscheduled and premature discontinuation visits) will also be included.

For summary tables and figures on laboratory parameters considering values, which are lower or greater than the limit of quantification, the following approach will be taken. For values which are flagged as lower than the lower limit of quantification, the values presented in summary tables should be multiplied by 0.5 and for values which are flagged as greater than upper limit of quantification as 1.5, the values presented in summary tables should be multiplied by 1.5.

2.8.3.2 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.

2.8.3.3 Notable values

For selected laboratory parameters, abnormalities occurring at any time-point over the on-treatment period, considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits will be summarized.

The criteria for clinically notable values are presented in Table 6.3.2.

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. This is necessary because BUN is Urea Nitrogen, not Urea and there are two nitrogens in each urea molecule. The factor of 0.357 converts BUN in mg/dL to Urea in 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, urine albumin, urine protein, urine albumin/creatinine ratio (ACR), urine protein/creatinine ratio (PCR). 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.

2.8.4 Other safety data

2.8.4.1 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	
QTc (msec)	≥ 450 (male)
QTc (msec)	≥ 460 (female)
QTc (msec)	> 500 (both)
Change from baseline	
QTc	< 30
QTc	30 – 60
QTc	> 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

Patients with notable post-baseline ECG values will be listed.

2.8.4.2 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 drug and until 7 days after the last intake of study drug are regarded as on-

treatment data. Vital signs data measured more than 7 days 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:

- absolute on-treatment values and change from baseline summarized by parameter, and 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:
    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 value considering newly occurring or worsening cases		
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

PROs such as AQLQ+12 and ACQ-5 will be analysed as part of secondary endpoints.

2.12 Biomarkers

Not applicable.

2.13 Other Exploratory analyses

NA

2.14 Interim analysis

Not applicable.

3 Sample size calculation

The historical data (US Marketscan database) shown in Table 3.1 indicates that the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) across patients is not normal; rather the distribution is skewed; hence using a normal distribution assumption is not appropriate. In addition, the proportion of patients with 0 total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) is quite high (>30%) therefore a transformation that could normalize the distribution is not feasible. As a consequence, a non-parametric method based on rank analysis will be used to analyze the primary end-point. The formula developed for the Wilcoxon-Mann-Whitney test adjusting for ties (Zhao et al 2008) has been used to estimate the sample size. A 1:1:1 randomization was used. There are four hypotheses to be tested for primary endpoint as stated in Section xxx.

Table 3.1 Frequency distribution of dose to display (non-normal) distribution of US Marketscan database

	HD ICS/LABA+LAMA 6 weeks		HD ICS/LABA+LTRA 6 weeks		HD ICS/LABA 6 weeks	
Outcomes	n=1562		n=7409		n=18471	
Dose Category (Count/%)						
0 (0mg)	533	34.1%	2901	39.2%	8211	44.5%
1 (>0 - 50 mg)	5	0.3%	20	0.3%	46	0.2%
2 (>50 - 100 mg)	25	1.6%	90	1.2%	214	1.2%
3 (>100 - 150 mg)	107	6.9%	595	8.0%	1376	7.4%
4 (>150 - 200 mg)	62	4.0%	358	4.8%	904	4.9%
5 (>200 - 250 mg)	90	5.8%	335	4.5%	808	4.4%
6 (>250 - 300 mg)	50	3.2%	313	4.2%	789	4.3%
7 (>300 - 350 mg)	40	2.6%	184	2.5%	426	2.3%
8 (>350 - 400 mg)	47	3.0%	216	2.9%	608	3.3%
9 (>400 - 450 mg)	44	2.8%	219	3.0%	519	2.8%
10 (>450 - 500 mg)	34	2.2%	181	2.4%	396	2.1%
11 (>500 - 550 mg)	24	1.5%	141	1.9%	308	1.7%
12 (>550 - 600 mg)	39	2.5%	221	3.0%	479	2.6%

13 (>600 - 650 mg)	19	1.2%	99	1.3%	237	1.3%
14 (>650 - 700 mg)	16	1.0%	80	1.1%	214	1.2%
15 (>700 - 750 mg)	28	1.8%	103	1.4%	252	1.4%
16 (>750 mg)	399	25.5%	1353	18.3%	2684	14.5%

table_9_2Table 3.2 represents the selected scenario for the null and alternative hypothesis and the sample size under a 90% power and an overall alpha two sided of 5%. As we have two doses to test, the alpha considered for the sample size is 2.5% two sided.

Under the assumptions specified above and scenarios described in Table 3.2, 134 patients per arm in the subpopulation with eosinophils count ≥ 250 cells/µl and 201 patients per arm in the overall population corresponding to a total sample size of 603 patients provide greater than 90% power for primary null hypotheses. Assuming 10% treatment discontinuation rate, a total of 669 patients are needed.

Table 3.2 Fevipiprant single dose EOS≥ 250 cells/µl

alpha 2.5% power 90%	**0-50mg/year**	**>50-150 mg/year**	**>150-300 mg/year**	**>300-450 mg/year**	**>450-600 mg/year**	**>600 mg/year**	**High EoS**	**Full population**	**+10 %**
Placebo	42.7%	8.8%	13.5%	8.4%	6.6%	20.0%	-	-	-
Fevi	60.0%	15.0%	9.0%	3.0%	3.0%	10.0%	402	603	669

We have looked also at other possible distributions for both fevipiprant and placebo under a power of 80% or 90% and alpha 0.025 two sided. table_9_3Table 3.3 provides other scenarios for the placebo and the Fevi group. Even if we deviate from the original scenario, other possible distributions provide still good power.

Table 3-3 Other scenario investigated for Fevipiprant single dose EOS≥ 250 cells/µl

alpha 2.5%	**0-50mg/year**	**>50-150 mg/year**	**>150-300 mg/year**	**>300-450 mg/year**	**>450-600 mg/year**	**>600 mg/year**	**Power under the assumption of 134 pts per arm**
Placebo	0.0%	10.0%	25.0%	25.0%	15.0%	25.0%	-
Scenario 1 Fevi	5.0%	25.0%	25.0%	20.0%	10.0%	15.0%	96%
alpha 2.5%	**0-50mg/year**	**>50-150 mg/year**	**>150-300 mg/year**	**>300-450 mg/year**	**>450-600 mg/year**	**>600 mg/year**	
Placebo	20.0%	5.0%	20.0%	10.0%	15.0%	30.0%	-
Scenario 2 Fevi	35.0%	20.0%	30.0%	5.0%	5.0%	5.0%	100%

alpha 2.5%	**0-50mg/year**	**>50-150 mg/year**	**>150-300 mg/year**	**>300-450 mg/year**	**>450-600 mg/year**	**>600 mg/year**	
Placebo	42.7%	8.8%	13.5%	8.4%	6.6%	20.0%	-
Scenario 3 Fevi	57.0%	18.0%	9.0%	3.0%	3.0%	10.0%	85%
Scenario 4 Fevi	55.0%	14.0%	14.0%	5.0%	3.0%	9.0%	75%
alpha 2.5%	**0-50mg/year**	**>50-150 mg/year**	**>150-300 mg/year**	**>300-450 mg/year**	**>450-600 mg/year**	**>600 mg/year**	
Placebo	0.0%	10.0%	25.0%	25.0%	15.0%	25.0%	-
Scenario 5 Fevi	5.0%	25.0%	20.0%	20.0%	12.0%	18.0%	82%

Based on clinical judgment different scenarios are considered in the above table

The following formula to calculate the sample size has been used (Zhao et al 2008):

$$N = \frac{(Z_{\alpha/2} + Z_{\beta})^2 (1 - \sum_{c=1}^{D} ((1-t)p_c + tq_c)^3)}{12t(1-t)(\sum_{c=2}^{D} p_c \sum_{d=1}^{c-1} q_d + 0.5 \sum_{c=1}^{D} p_c q_c - 0.5)^2}$$

Where

N is the total sample size for a 2 arm trial.

t is the randomization ratio

p_c are the % of patients in category c for the experiment arm

q_c are the % of patients in category c for the control arm

D is number of categories

4 Change to protocol specified analyses

The primary endpoint will be analyzed as specified in the protocol for the CSR and is detailed in this SAP. As the study is treminated early by sponsor, most of the patients don't have sufficient follow up and most of the data will not be matured enough do the analysis as defined in the protocol, due to that all secondary endpoints will be analyzed descriptively.

NA

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Missing/partial start date or end date of study drug will not be imputed.

5.1.2 AE date imputation

5.1.2.1 AE end date imputation

Rules for imputing AE end dates are stated below. Date of last contact in the study has been defined as in Section 2.1.1.

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.

5.1.2.2 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.

5.1.3 Prior and Concomitant medication date imputation

5.1.3.1 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 2.1.1. 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.

5.1.3.2 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 following 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 mid-month 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 Conversion of OCS to prednisolon equivalent

Prednisone 5 mg is comparable to

Drug	Dose	Conversion factor
Deflazacort	6 mg	0.83
Triamcinolone	4 mg	1.25
Dexamethasone	0.75 mg	6.67
Methylprednisolone	4 mg	1.25
Prednisolone	5 mg	1
Betamethasone	0.75 mg	6.67
Prednisone	5 mg	1
Hydrocortisone	20 mg	0.25
Fluocortolone	5 mg	1
Meprednisone	4 mg	1.25

5.3 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.

5.4 Laboratory parameters derivations

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

Table 6.3.1 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 6.3.2 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
Urinalysis		
Dipstick blood		≥ 2+
Dipstick glucose		≥ 2+
Dipstick leukocytes		≥ 2+
Dipstick protein		≥ 2+

v = volume, ULN = upper limit of normal

5.5 Statistical models

5.5.1 Primary analysis

A Van Elteren test will be used to analyze the ranked data with stratifications. The SAS procedure PROC FREQ will be used for this analysis. The test can be done by defining a stratified, three-way table and using the CMH and SCORES=MODRIDIT options. In the TABLE statement, the variable(s) defining the strata appear first, followed by the treatment variable and finally the response variable.

5.6 Rule of exclusion criteria of analysis sets

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

PD Identifier	'PD Description' for Reporting	CP_Exclude from analysis set
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 excluded from SCR
TRT01	Received study drug but not randomized	Exclude from RAN, FAS and SAF (also evaluate on case by case basis)
TRT02	Randomized but no study drug given	Patient did not receive a study drug then exclude from FAS and SAF; otherwise do not exclude from any population set
TRT04	Double blind study drug taken prior to baseline FEV1 assessment	Do not consider FEV1 baseline value for analysis
WITH01	Patient not withdrawn from the study even after Withdrawal of informed consent.	Include data up to withdrawal of consent in all analysis sets
WITH07	Blind broken and study drug not stopped	Data before unblinding can be used for efficacy ; otherwise use all data for safety

6 Reference

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

Juniper EF, Guyatt GH, Willan A, et al (1994) Determining a minimal important change in a disease-specific Quality of Life Questionnaire. J Clin Epidemiol p. 81-7.

Juniper EF, O'Byrne PM, Guyatt GH, et al (1999) Development and validation of a questionnaire to measure asthma control. Eur. Respir. J. p. 902-7.

Juniper EF, Svensson K, Mörk AC, et al (2005)a Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med p. 553-8.

Juniper EF, Bousquet J, Abetz L et al., GOAL Committee (2006) Identifying ‘well-controlled’ and ‘not well-controlled’ asthma using the Asthma Control Questionnaire. Respir Med; 100: 616- 621.

Zhao YD (2006) Sample size estimation for the van Elteren test—a stratified Wilcoxon–Mann–Whitney test. Statistics in Medicine; 25:2675–2687

Zhao YD, Rahardja D, Qu Y (2008) Sample size calculation for the Wilcoxon-Mann-Whitney test adjusting for ties. Stat Med p. 462-468.