NOVARTIS

Clinical Development

QAW039/fevipiprant

CQAW039A2316 / NCT03215758

A 12-week, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of QAW039 when added to standard-of-care asthma therapy in patients with uncontrolled asthma

Statistical Analysis Plan (SAP)

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Date	Reason for update	Section and title impacted (Current)
20-Jun-2019	Updated time window for eDiary data baseline	Table 2-1
	Added summary of estimand table for primary endpoint to explicitly describe the primary estimand	Table 2-2
	Provided more details on rank-based analysis	Section 2.5.5
	Added the responder analysis for AQLQ improvement	Section 2.6.3
	Updated the treatment emergent flags in order to maintain consistency with the submission documents	Section 2.7
	Updated rule of exclusion criteria of analysis sets	Section 6.4
16-Aug-2019	Extended box-plot to all laboratory parameters to investigate the tendency of treatment effect	Section 2.7.3.2
	Added more details to liver function tests including eDISH plot	Section 2.7.3.3
	Added analysis for renal events and liver events according to project level alignment	Section 2.7.5 and Section 2.7.6

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List of abbreviations

ACQ-5	Asthma Control Questionnaire
AE	Adverse event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AMAC	Asia-Pacific, Middle East and African Countries
ANCOVA	Analysis of Covariance
AQLQ	Asthma Quality of Life Questionnaire
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CM	Concomitant Medication
CRS	Case Retrieval Strategy
DAR	Dosage Administration Records
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FEV1	Forced Expiratory Volume in 1 Second
[redacted]	[redacted]
ICS	Inhaled Corticosteroid
IgE	Immunoglobulin E
IRT	interactive response technology
ITT	Intension-to-treat
LABA	Long Acting Beta-2 Agonist
LFT	Liver Function Test
MAR	Missing at Random
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mg	milligram
MI	Multiple Imputation
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not at Random
PD	Pharmacodynamics
PDS	Programming Dataset Specification
PEF	Peak Expiratory Flow
PK	Pharmacokinetics
PPS	Per protocol set
PR	Pulse Rate
PT	Preferred Term
Qd	Qua'que di'e / once a day
QTc	Corrected QT interval

QTcF	Fridericia QT correction formula
RAN	Randomized set
SABA	Short Acting Beta2 Agonist
SAE	Serious Adverse Event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SI	International System of Units
SoC	Standard of Care
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TFL	Tables, Figures, Listings
WHO-DD	World Health Organization- Drug Dictionary

1 Introduction

This document contains details of the statistical methods that will be used in the phase III clinical trial CQAW039A2316. This study is designed to determine efficacy and safety of QAW039 (150 mg once daily), compared with placebo, when added to standard-of-care (SoC) asthma therapy in adult and adolescent (≥12 years) patients with uncontrolled asthma with respect to change from baseline in FEV_1 at the end of 12 weeks of treatment.

Data will be analyzed according to Section 9 of the study protocol.

Important information is given in the following sections and details are provided, as applicable, in Section 6: Appendix.

1.1 Study design

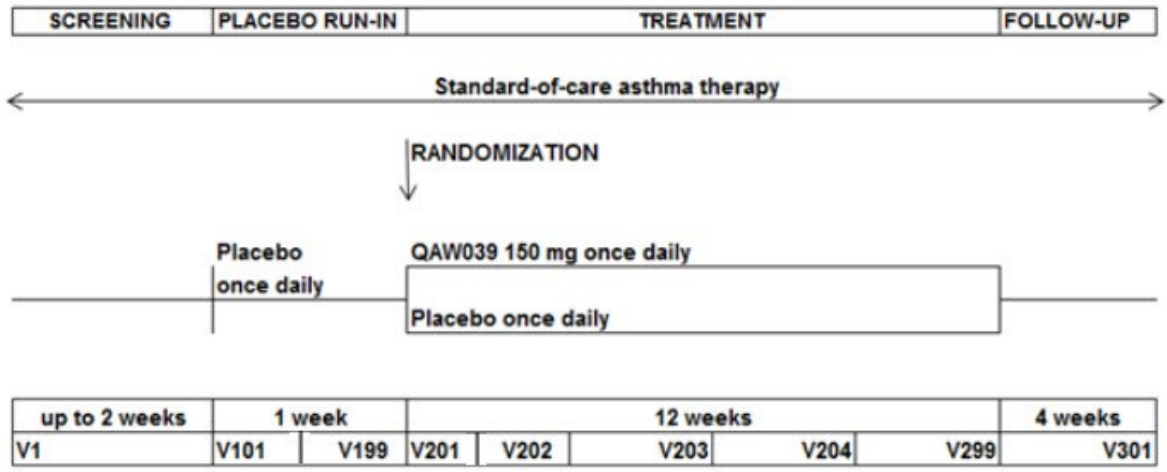
This study uses a randomized, multicenter, double-blind, placebo-controlled parallel-group study design in which QAW039 or placebo is added to incoming SoC asthma therapy (Figure 1).

The study will include:

- a Screening period of up to 2 weeks to assess eligibility. Patients will also practice completing the electronic peak expiratory flow (ePEF)/eDiary device during this period.
- a Placebo Run-in period of 1 week to collect baseline data for efficacy variables and compliance with the ePEF /eDiary device. Eligibility for randomization will be determined during the placebo run-in period.
- a Treatment period of 12 weeks; and
- a Follow-up period of 4 weeks, study drug-free, following the last dose of study drug.

Note: the follow-up period applies to all patients except those patients who enter the safety study (CQAW039A2315) directly after Visit 299.

Figure 1 Study design



1.2 Study objectives and endpoints

All objectives will consider the following comparison:

QAW039 (150 mg once daily) compared with placebo, when added to standard-of-care (SoC) asthma therapy in adult and adolescent (≥12 years) patients with uncontrolled asthma.

1.2.1 Study Objectives and Endpoints

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective To demonstrate the efficacy of QAW039 150 mg once daily as measured by change from baseline in pre-dose FEV_1 [in liters], compared with placebo, at the end of the 12-week active-treatment period.	**Endpoint for primary objective** Change from baseline in pre-dose FEV_1 (L) at week 12.
Secondary Objectives 1. To demonstrate the efficacy of QAW039 150 mg once daily, compared with placebo, on daytime asthma symptoms over the 12-week active-treatment period. 2. To demonstrate the efficacy of QAW039 150 mg once daily, compared with placebo, on total daily short-acting β-	**Endpoints for secondary objectives** 1. Change from baseline in daytime asthma symptom score over 12 weeks of treatment. 2. Change from baseline in number of puffs of SABA taken per day over 12 weeks of treatment.

Objective(s)	Endpoint(s)
agonist (SABA) use over the 12-week active-treatment period.	
3. To demonstrate the efficacy of QAW039 150 mg once daily, compared with placebo, on change from baseline in Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12) score at the end of the 12-week active-treatment period.	3. Change from baseline in AQLQ+12 score at week 12.
4. To assess the safety of QAW039 150 mg once daily, compared with placebo, with respect to adverse events (AE), electrocardiograms (ECGs), vital signs, and laboratory tests.	4. Summaries of treatment-emergent adverse events, systolic and diastolic blood pressure, pulse rate, body weight, RR interval, PR interval, QRS duration, heart rate, and Fridericia's QTc, laboratory values and change from baseline for continuous laboratory values.

2 Statistical methods

2.1 Data analysis general information

The statistical analysis will be performed by Novartis. The most recent version of SAS® (SAS Institute Inc., Cary, NC, USA) available in the statistical programming environment of Novartis will be used for the analysis.

2.1.1 General definitions

In this document, although investigational treatment is given in addition to background standard of care therapy, 'study medication', 'study treatment' or 'study drug' will be used to refer to investigational therapy assigned to a patient. Specifically, for the double-blind treatment period, study treatment refers to QAW039 or placebo as assigned to a patient at randomization.

The date of the first administration of the investigational treatment (QAW039 or matching placebo) is referred to as the date of first administration of study treatment in the study. The evaluations which have complete date and time values are assigned to pre or post-dose assessment based on the actual date/time. However, evaluations with missing date/time are assigned to their respective scheduled visit date and time given the visit number and time point are non-missing. If an evaluation scheduled as pre-dose is actually performed post-dose, or vice

versa, the data will not be used for inferential analysis and summary statistics but will be included in the summaries of the notable values and extreme values.

Study day will be defined as the number of days since the date of first dose of study medication. The date of first dose of study medication will be defined as Day 1 and the day before the first dose of study medication is defined as Day -1.

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

- for dates on or after the first date of study medication,

  Study day = Assessment date – Date of first dose of study medication + 1;

- for dates prior to the first date of study medication,

  Study day = Assessment date – Date of first dose of study medication.

If a patient never took any study medication, the randomization date will be used instead of the date of first dose of study medication. In this case, the randomization date is defined as Day 1 and the day prior to randomization is defined as Day -1.

2.1.1.1 Baseline definition

Data from unplanned visits prior to screening are not included in analysis. In general, baseline is defined as the last assessment taken prior to the first dose of study drug at Day 1 (Visit 201).

Checks will be performed to ensure the assessments were taken prior to the first dose of study drug on Day 1 (Visit 201). If the assessment is missing or not confirmed to be pre-dose, then the last available non-missing assessment will be used as baseline. Missing baseline pre-dose FEV1, daytime asthma symptoms, total daily SABA use and AQLQ+12 will be assumed to be missing at random as assessments are performed prior to any knowledge of treatment allocation and will be imputed using the mean value of all randomized patients.

Table 2-1 Baseline definition of analysis parameters

Parameter	Baseline assessment	Detail
ACQ-5, AQLQ [redacted]	Last assessment prior to the first dose of study drug on Day 1	If the Day 1 assessment is missing the last available assessment (scheduled or unscheduled) taken prior to the first dose of study drug will be used.

Lung function (FEV_1)	Average of the two FEV1 assessments taken at 45 minutes and 15 minutes prior to the first dose of study drug on Day 1	Checks will be performed to ensure both values were taken prior to the first dose of study drug. If one of the 45 and 15 min values is missing (or is not confirmed to be pre-dose) then the remaining non-missing value will be taken as the baseline. If both assessments are missing (or are not confirmed to be pre-dose) then the last available FEV1 measurement (scheduled or unscheduled) prior to Day 1 will be used for baseline.
eDiary data (Daytime asthma symptoms)	Average of the mean daytime asthma symptom score from Visit 101 to Day 1	The baseline score will be calculated as long as there are at least 4 days with non-missing eDiary data. Noted that the morning assessment for Day 1 counts towards the baseline.
[redacted]		
eDiary data (Total daily use of SABA)	Average of total daily SABA use from Visit 101 to Day 1	The baseline score will be calculated as long as at least 4 days with non-missing eDiary data. Noted that the morning assessment for Day 1 counts towards the baseline while the evening assessment for Day 1 counts as the treatment period.
[redacted]		

Laboratory data (hematology, clinical chemistry, urine analysis)	Last available assessment (scheduled or unscheduled) prior to dosing on Day 1	
Vital signs (pulse rate and systolic & diastolic blood pressures)	Last available assessment (scheduled or unscheduled) prior to dosing on Day 1	
Height and weight	Last available assessment (scheduled or unscheduled) prior to dosing on Day 1	
ECG	Last available assessment (scheduled or unscheduled) prior to dosing on Day 1	

2.1.1.2 Post-baseline measurement

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

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

Change from baseline = post baseline value – baseline value.

2.2 Analysis sets

The following analysis sets are defined:

- The screened set (SCR) will include all patients who provided informed consent.
- The randomized (RAN) set will consist of all patients who were assigned a randomization number, regardless of whether or not they actually received study medication. Patients in RAN will be analyzed according to the treatment they were randomized to.
- The Full Analysis Set (FAS) will consist of all randomized patients who received at least one dose of study medication. It was considered reasonable to limit the FAS to patients who took trial medication, because the decision on whether or not study drug is started will not be influenced by the treatment group assignment due to the effective treatment blinding procedures. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization. The FAS will be used for the analysis of all efficacy endpoints, and for the summaries of patient disposition, demographic and baseline characteristics.
- The Per-Protocol Set (PPS) will include all patients in the FAS who did not have any major protocol deviations such as violation of major entry criteria. Protocol deviations will be defined in the data review plan document prior to database lock and the un-blinding of the study. Protocol deviations leading to exclusion from analysis sets are

defined in Section 6.7. Patients in the PPS will be analyzed according to the treatment they actually received. The PPS may be used for supportive analysis of the primary efficacy endpoint.

- The Safety Set (SAF) will consist of all patients who received at least one dose of double-blind study drug. Patients will be analyzed according to the treatment they received. The SAF will be used in the analysis of all safety variables. If due to a dispensing error a patient erroneously receive received any study treatment which is different from the randomized treatment, the patient will be analyzed according to the treatment they were randomized to.

Note that the set of patients included in the FAS and SAF are the same except that the SAF allows the inclusion of non-randomized patients who receive study drug in error.

In cases where an incorrect randomization stratum is entered in the IRT (interactive response technology), the corrected stratum information as per the CRF data will be used for reporting and analysis.

2.2.1 Subgroup of interest

Subgroup analyses will be performed for primary endpoint and secondary endpoints using the same model as for the primary analysis (mentioned in section 2.5.3) but with additional model terms for the subgroup (if not already included in the model) and subgroup-by-treatment interaction terms. The subgroup variables are listed below:

Key demographic subgroups:

- Age at entry into study（<18, ≥18 years)
- Sex (Male, Female)
- Race (Caucasian, Black, Asian, Other)
- Geographic region (Europe, Latin America, North America, China/AMAC)
  The definition of geographic region will be same as the definition of region at the randomization

Disease related subgroups:

- Use or non-use of a second asthma controller medication
- Baseline FEV_1 (tertiles 1, tertiles 2, tertiles 3)
- Baseline %predicted FEV1 (> 70%, ≤ 70%)

Subgroup analyses will be conducted on the FAS for exploratory purposes. Formal multiplicity adjusted testing on the subgroups will not be performed.

Subgroup analyses contributing key regulatory information will be provided for relevant country or region to meet regulatory requirements. Analyses required to fulfil health authority commitments or submission requirements for specific countries will be reported separately and outside of CSR.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number of patients screened, randomized, completed and discontinued from the study will be summarized for each study phase (i.e., screening, run-in, and treatment). In addition, the number of patients randomized, completed and discontinued from the 12-week treatment period will be summarized by country. Screened set and its subset of patients who received placebo study medication during the run-in period will be used for screening period and run-in period disposition tables, respectively. RAN will be used for treatment disposition outputs. Patients discontinued from the 12-week treatment period will also be summarized with reasons for discontinuation. Patients who discontinued study treatment but stayed in the study will be considered as completing the 12-week treatment period. Patients who discontinued study treatment but stay in the study are defined as patients with the date of study discontinuation or Visit 299 - the end date of study treatment > 0. 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. Rescreening information will also be summarized mentioning the number of patients who were rescreened and how many of them were randomized.

Time to study discontinuation will be displayed graphically for each treatment group using a Kaplan-Meier curve for the FAS. The date of study discontinuation is defined as the maximum of the last known visit date for treatment period and the date of last dose of study medication. Patients who completed the study will be censored at the final study visit.

Number of patients with protocol deviations and protocol deviations that lead to exclusion from analysis sets will be tabulated by deviation category and treatment group for the RAN.

The number of patients included in each analysis set will be tabulated by treatment group for the RAN. Reasons for exclusions from analysis sets will be tabulated. Patient exclusion from analysis sets will be listed for all patients with reasons for exclusion (including protocol deviations).

2.3.2 Patient 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, [redacted], FEV_1 reversibility, duration of asthma, number of asthma exacerbations in prior year, atopic asthma at entry into the study (Yes/No), smoking history (never/former), number of pack years, baseline ACQ-5, baseline AQLQ+12, [redacted], and ICS use (alone, plus LABA, plus LTRA), ICS dose ranges (low, medium, high), [redacted] and daytime asthma symptom scores. Background asthma therapy will be categorized into GINA steps and will be summarized at baseline. Background asthma therapy is defined as concomitant medication start date on or before Visit 1 and end date after Visit 1. 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.

In addition, the following categorizations of continuous variables will be done:

- Age: <18, 18 to <65, and ≥65 years;
- BMI: ≤ 30.0 kg/m^2 and > 30.0 kg/m^2;
- Duration of asthma: < 1 year, 1 - 5 years, > 5 - 10 years, > 10 - 15 years, > 15 – 20 years, and > 20 years;
- Number of asthma exacerbations in prior year: 0, 1-2, 3, 4, ≥ 5
- pre-bronchodilator percent predicted FEV_1: <= 40 %, >40% - ≤ 50%, >50% - ≤ 60%, >60% - ≤ 70%, >70% - ≤ 80%, >80%
- ACQ-5: 1.5- < 2, 2 – < 2.5, ≥ 2.5 (< 1.5 will be added in case of protocol deviations)
- [redacted]

Derivation of the demographics and baseline characteristics

- BMI is calculated as: BMI (kg/m^2) = Weight (kg) / [Height (m) * Height (m)]
- Estimated number of pack years is calculated by the total years of smoking multiplied by cigarette packs smoked per day. This will be summarized as recorded on the eCRF. Smoking history in package years will be calculated as: (1 pack year = 20 cigarettes/day x 1 year or 10 cigarettes/day x 2 years).
- % of (pre-bronchodilator) predicted FEV_1 is obtained as a percentage of FEV_1 relative to the predicted normal value.
- FEV_1 reversibility is calculated as percentage increase of FEV_1 values after inhalation of bronchodilator relative to FEV_1 values prior to the inhalation. At visits with two pre-dose spirometry assessments, the FEV_1 from the 2nd pre-dose spirometry assessment (15 min prior to in-clinic witnessed study drug administration) should be considered the pre-bronchodilator FEV1 value. A patient is considered to have demonstrated reversibility at clinic at baseline if there is an increase of 12% and >=200 ml any particular visit prior to Day 1.
- 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.

- The total daily ICS dose at baseline will be categorized as low, medium, high based on the Appendix 6 in study protocol.

2.3.3 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

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 = Date of last known dose of study drug – Date of first dose of study drug + 1).

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

The number of patients who completed the 12-week study treatment and who discontinued prematurely will be shown including the reasons for discontinuation of study treatment. In addition, the duration of exposure will be summarized as a categorical variable classified into <4 weeks, >=4 to <12 weeks, >=12 weeks.

2.4.1.2 Compliance

Study drug compliance will be assessed. The overall compliance will be calculated 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 study medication intake as per protocol / (Date of last known dose of study drug – Day 1 + 1).

Compliance will be categorized as <80%, 80% -100% and summarized by treatment group for the safety set.

Time to study treatment discontinuation will be displayed graphically for each treatment group using a Kaplan-Meier curve for the SAF. The date of study treatment discontinuation is defined as the date of last dose of study medication. Patients who completed the study treatment will be censored at the final visit for treatment period.

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” and “post” 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 on or before the end of the Treatment ~~+ 1 day~~.

Post: Any medication with start date after the end of treatment ~~+ 1 day~~, including medications taken in the Follow-up Period.

Medications can be considered both prior and concomitant.

Concomitant therapies will be recorded and summarized separately for asthma related medications / non-drug therapies 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 placebo 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 and secondary endpoint

2.5.1 Primary endpoint

The definition and rationale for the estimand for the primary endpoint are given in Table 2-2. Novartis proposes the most informative estimand to be one that considers the maintenance treatment effect that could be expected in clinical practice. The statistical strategy to handle each intercurrent event is described in more detail in Section 2.5.4.

Table 2-2 Summary of estimand for the primary endpoint

Population
Male or female patients aged 12 years and older with asthma, who are uncontrolled with SoC therapy and receive at least one dose of study treatment. For this study, SOC is defined as ICS or ICS with a second controller medication (LABA or LTRA)

Variables
Change from baseline in pre-dose FEV_1 at the end of 12 weeks of treatment

Intercurrent event	**Description**	**Strategy to handle event**	**Justification**
Asthma medications with an effect on FEV_1 are taken within washout periods prior to spirometry assessment.	Allowed asthma medications (including SABA and SoC treatment) are taken within washout periods prior to spirometry assessment. Wash-out periods for allowed asthma medications prior to spirometry assessments are defined in Protocol Table 5-2.	A hypothetical strategy will be used for the days on which these medications are taken within the washout periods.	Asthma medications that taken within washout periods may have a transient impact on FEV_1 but interest is primarily in the effect of longer-term maintenance therapy.
Discontinuation of fevipiprant for any reason	Discontinuation of fevipiprant for any reason regardless of relation to fevipiprant	A treatment policy strategy will be used. All efforts will be made to retain patients in the trial and adhere to the schedule even after discontinuation of fevipiprant/placebo. Where those efforts are not successful, the missing observations will be imputed as described in Section 2.5.4	These patients may discontinue therapy in clinical practice. Any fevipiprant treatment effect would cease almost instantly after discontinuation of fevipiprant, and only SoC effect is expected.
Discontinuation of placebo for any reason	Discontinuation of placebo for any reason	A treatment policy strategy will be used. All efforts will be made to retain patients in the trial and adhere to the schedule even after discontinuation of fevipiprant/placebo. Where those efforts are not successful, the missing observations will be imputed as described in Section 2.5.4	In clinical practice, patients receive SoC without additional treatment and the approach for placebo reflects this.

Summary measures
mean difference in change from baseline in pre-dose FEV_1 (L) at week 12 between treatment groups

2.5.2 Secondary endpoints

The secondary endpoints are daytime asthma symptoms, total daily SABA use and AQLQ+12. Their definition and analysis is described in Section 2.6.

2.5.3 Statistical hypothesis, model, and method of analysis

2.5.3.1 Primary endpoint

The primary objective of the study is to evaluate superiority of QAW039 150 mg once daily over placebo (with SoC asthma therapy as the background therapy) by testing the following null hypothesis (H_0) versus the alternative hypothesis (H_a):
H_0: There is no difference in the change from baseline in pre-dose FEV_1 (L) at week 12 post-baseline for the patients treated with QAW039 150 mg once daily compared with placebo ($\mu_1 - \mu_2 = 0$)
H_a: There is a difference in the change from baseline in pre-dose FEV_1 (L) at week 12 post-baseline for the patients treated with QAW039 150 mg once daily compared with placebo ($\mu_1 - \mu_2 \neq 0$).
where;
μ_1 = Mean change from baseline in pre-dose FEV_1 (L) at week 12 of QAW039 150 mg once daily treatment;
μ_2 = Mean change from baseline in pre-dose FEV_1 (L) at week 12 of Placebo treatment;

The primary efficacy variable will be analyzed on the FAS using an analysis of covariance (ANCOVA) model with factors for treatment group, randomization strata [age group (<18 vs. ≥18 years), use or non-use of a second asthma controller medication at study entry, and region], as well as the baseline daytime asthma symptom score, baseline total daily SABA use and baseline pre-dose FEV_1 as continuous linear covariates. The variables contributing to the randomization strata (i.e. age group (<18 vs. ≥18 years), use or non-use of a second asthma controller medication at study entry, and region) are included separately in the model.

The least squares mean ("adjusted mean") change from baseline for each treatment group, the difference in the least squares (LS) mean changes between the two treatment groups (QAW039 150 mg – placebo), and the two-sided 95% confidence interval along with the p-value for the difference will be obtained and combined from the primary analysis model through the multiple imputation approach described in Section 2.5.4.

The superiority of QAW039 150 mg once daily to placebo as add on to SoC asthma therapy is established if the two-sided p-value is less than 0.05 and the 95% confidence intervals lie entirely to the right of 0 L.

Summary statistics for the primary endpoint

Summaries of observed absolute values and change from baseline in pre-dose FEV_1 (L) by treatment group and visit will be presented.

2.5.4 Handling of missing values/censoring/discontinuations

Retrieved data after the discontinuation of study drug (retrieved drop-out) will remain in the analysis without further imputation for all treatment groups.

Despite all attempts to ensure complete follow-up for all patients, some patients may not be followed for pre-dose FEV_1 for the whole planned study duration. Missing baseline pre-dose FEV_1 will be assumed to be missing at random (MAR) as assessments are performed prior to any knowledge of treatment allocation and will be imputated using the mean value of all randomized patients included in the FAS.

The FEV_1 value analyzed at each visit is based on the average of the two FEV_1 assessments taken at approximately 45 minutes and approximately 15 minutes prior to the dosing of study drug at clinic visits. In cases where one of the values is missing, this will be imputed within treatment group via multiple imputation and the average will be calculated based on the one available assessment and a second imputed assessment.

Once these imputations are complete, subsequent missing data will be imputed based on a jump-to-reference (J2R) approach according to following assumptions:

- Continued treatment effect will be imputed for QAW039 patients with intermittent missing data under a MAR assumption
- For QAW039 patients with missing data after discontinuation of double-blind treatment , imputation will be done based on placebo group under a J2R assumption
- Missing data in placebo group will be imputed under MAR assumption

The imputation and analysis will be implemented using the "five macros" available from www.missingdata.org.uk (for a full description see Carpenter et al (2013)). The first step in implementing this pattern mixture imputation approach is to fit a Bayesian Normal repeated measures model to estimate parameters from the observed on-study values (including on-treatment and off-treatment data). The model will include the same covariates as the primary model. Then use the estimated parameters to build possible predicted profiles for the unobserved values in a separate imputation model, one for each pattern of withdrawal. These profiles represent what we expect would happen to patients after they withdraw. Missing values for an individual are then imputed based on the profile of predicted means that matches their treatment, their time of withdrawal and other covariates. A large number of imputed datasets will be created, with their number chosen based on computational feasibility, but at least 1000. Observed and imputed data will be contrasted graphically. Each dataset will be analyzed using the model described in Section 2.5.3.1 and the results will be combined using Rubin's rule (Barnard and Rubin 1999) for final inference. A fuller description is given in the Section 6.6.1 of the Appendix.

Unless otherwise specified, for efficacy parameters, on-treatment data are defined as data on or after the first day of treatment with double-blind medication, but before or on the day of the last day of treatment with double-blind study medication; on-study data are defined as data on or after the first day of treatment with double-blind medication, but before or on the day of the last day of treatment period.

2.5.5 Supportive analyses

Sensitivity analysis

Two-dimensional tipping point analysis will be performed corresponding to the primary analysis on the FAS. Missing data after study treatment discontinuation will be firstly imputed in the same way as for the primary analysis. Then it will be explored by how much the imputed continuous missing data for the QAW039 treatment and the placebo arms would have had to change compared to the imputation values in the primary analysis in order to overturn conclusions from the primary analysis. After such tipping point(s) is determined, clinical judgment can be applied as to the plausibility of the assumptions underlying this tipping point. This methodology will provide a good picture of what it would take to overturn study conclusions based on varying assumptions about missing data.

Supplementary analysis

The primary efficacy variable will also be analyzed using a repeated measures (MMRM) analysis model in which treatment, age group (<18 vs. ≥18 years), use or non-use of a second asthma controller medication at study entry, region, visit and treatment-by-visit interaction will be included as fixed-effect factors, and baseline pre-dose FEV_1 value as well as the baseline daytime asthma symptom score, baseline total daily SABA use and visit-by-baseline FEV_1 as covariates. A common unstructured covariance matrix among visits for each treatment group will be used. If this model does not converge, a heterogeneous AR (1) covariance structure will be used. If this model still does not converge, a heterogeneous compound symmetry covariance structure will be used. The analysis will be performed based on all available on-treatment data up to week 12 and based on a likelihood method with an assumption of MAR for missing data assuming a hypothetical situation of continued treatment. On-treatment data is defined as all available data collected while patients took the study drug up to the week 12 visit. The estimated treatment differences for all treatment comparisons will be tabulated along with the associated 95% confidence intervals and their two-sided p-values.

Rank-based analysis

In a further rank-based supportive analysis for the primary endpoint, patients will be ranked from largest to smallest in the following sequence with high ranks denoting greater efficacy.

1. patients who completed the trial
2. patients who withdrew from the trial and did not die
3. patients who died

Note: death refers to adverse events with fatal outcome on-study.

Within category 1, patients with higher change from baseline FEV_1 at Week 12 will be ranked greater than patients with lower change from baseline. Patients who completed the trial with missing FEV_1 data at Week 12 will be ranked lower than anyone who completed the trial with non-missing FEV_1 data at Week 12. Within that, patients with higher change from baseline in FEV_1 at a later visit will get higher ranks. In case of ties in the visits with last available FEV_1 data, patients with higher change from baseline in FEV_1 are assigned a higher rank. In case of ties in the FEV_1 values, midranks will be used.

Within categories 2 and 3, patients that withdraw from the trial later will get higher ranks than patients that withdraw early. In cases in which patients withdraw at same study day, patients with higher change from baseline in FEV_1 at a later visit will get higher ranks. In case of ties in the FEV_1 values or no available post-baseline assessments of the primary variable, midranks will be used.

A Wilcoxon rank-sum test (Van Elteren test) stratified by age group (<18 vs. ≥18 years), use or non-use of a second asthma controller medication, and region will be used to analyze the ranked data.

Per-protocol analysis

The primary analysis may be repeated for the PPS.

2.5.6 Multiplicity adjustment

Familywise type I error rate control

The following null hypotheses are included in the testing strategy:

Primary objective: H1 (see Section 2.5.3.1)

Secondary objectives:

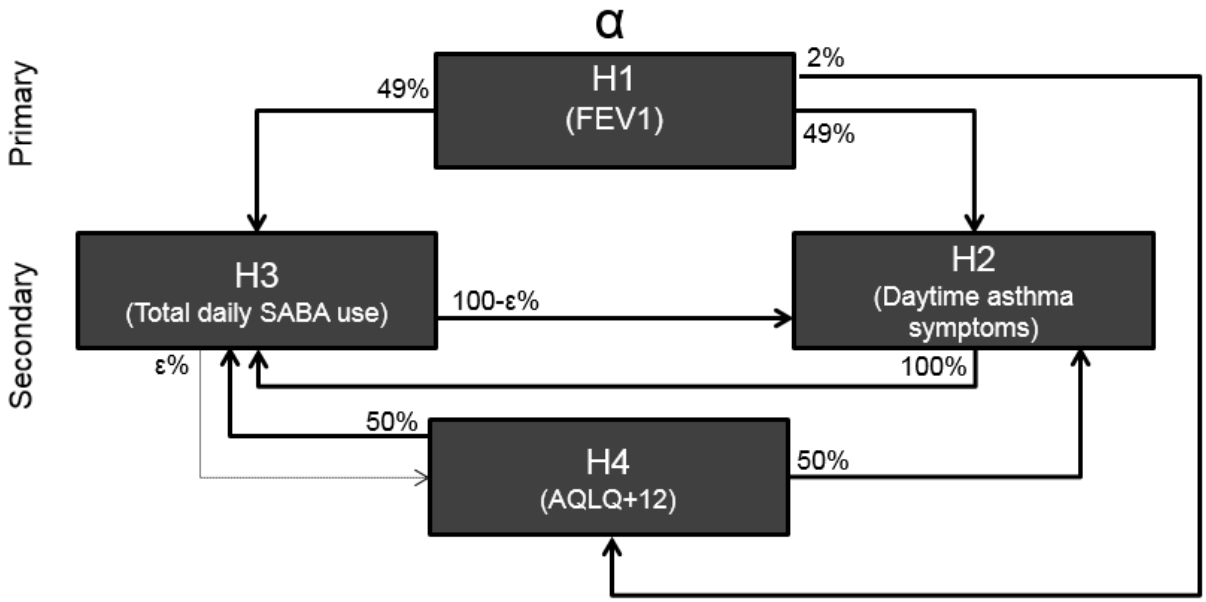
H2: QAW039 150 mg is not different to Placebo with respect to mean change from baseline in daytime asthma symptoms over the 12 weeks of treatment

H3: QAW039 150 mg is not different to Placebo with respect to mean change from baseline in total daily SABA use over the 12 weeks of treatment

H4: QAW039 150 mg is not different to Placebo with respect to change from baseline in AQLQ+12 at week 12

The familywise type I error rate will be controlled at the two-sided 5% level across the primary and secondary null hypotheses using the closed testing procedure shown in Figure 2 using the graphical method of Bretz et al 2009. In this closed testing procedure, the primary null hypothesis about pre-dose FEV_1 acts as a gatekeeper for the secondary null hypotheses.

Figure 2 Closed testing procedure for primary and secondary objectives



Vertices with associated weights denote the individual null hypotheses and their local significance levels. Directed edges between the vertices specify how the local significance levels are propagated in case of significant results. ε is set to a very small number in practice. Abbreviations: FEV1 (forced expiratory volume in 1 second); AQLQ+12 (asthma quality of life questionnaire for 12 years and older).

Initially, the alpha is assigned to the primary null hypothesis. Once the primary null hypothesis has been rejected, then 98% of the alpha will be distributed equally amongst the secondary null hypotheses of daytime asthma symptoms and total daily SABA use, respectively, and 2% of the alpha will be assigned to the null hypothesis for AQLQ+12. If one of the secondary null hypotheses is rejected, its local significance level will be propagated to the other secondary null hypotheses as illustrated in Figure 2.

2.6 Analysis of secondary efficacy objective(s)

2.6.1 Daytime asthma symptoms in patients

Daytime asthma symptoms are evaluated through four questions and each of them will be rated on a scale of 0 to 6. Higher scores indicate more severe asthma-related symptoms. A mean score will be calculated for the responses to 4 questions. The main analysis of the secondary endpoint of daytime symptoms will be performed for all patients over the entire age range (12 years and older).

The mean of change from baseline in the daytime symptom scores over the 12 weeks of treatment will be analyzed based on on-study data (including on-treatment and off-treatment data) using an analysis of covariance (ANCOVA) model in a similar fashion as the primary efficacy variable.

The model will include factors for treatment group, age group (<18 vs. ≥18 years), use or non-use of a second asthma controller medication at study entry, and region, as well as the baseline

daytime asthma symptom score, baseline total daily SABA use and baseline pre-dose FEV_1 as continuous linear covariates.

The least squares mean ("adjusted mean") change from baseline for each treatment group, the difference in the least squares mean changes between the two treatment groups (QAW039 150 mg – placebo), and the two-sided 95% confidence interval along with the superiority p-value for the difference will be obtained. This model will be fitted to each of multiple imputations generated using the approach described in Section 2.6.4.

In addition, the mean of change from baseline in the daytime symptom scores by 4-week intervals over the 12 weeks of treatment will be analyzed based on on-treatment data using a MMRM model in which treatment, age group (<18 vs. ≥18 years), use or non-use of a second asthma controller medication at study entry, region, interval and treatment-by-interval interaction will be included as fixed-effect factors, and baseline pre-dose FEV1 value as well as the baseline daytime asthma symptom score, baseline total daily SABA use and interval-by-baseline daytime asthma symptom score as covariates. A common unstructured covariance matrix among visits for each treatment group will be used. The analysis will be performed based on all available on-treatment data up to week 12. The estimated treatment differences for all treatment comparisons will be tabulated along with the associated 95% confidence intervals and their two-sided p-values.

Summaries of absolute values and change from baseline will be presented by 4-week intervals and overall 12 weeks of treatment based on on-treatment data.

The average score for each time interval is defined as the sum of daily scores divided by the number of days where eDiary records have been made on daytime score for that interval. The non-missing data within that interval will be used to calculate the mean value, as long as there are at least 4 days with non-missing eDiary data for baseline scores and 14 days with non-missing data for post-baseline scores in a 4-week period. Otherwise, the value will be set as missing for that interval. For Weeks 1 – 12, summary values will be calculated as long as a patient has at least 50% of their diary days and at least 42 diary days with evaluable data for that variable in the period of interest.

The asthma diary included in this study to measure daytime asthma symptoms was validated in studies of patients aged 18 to 65 years (Santanello et al 1997). It was subsequently included as a measure in placebo-controlled studies of montelukast in patients aged 15 years and older (Reiss et al. 1998 and Malmstrom et al. 1999) and shown to be responsive to both montelukast and inhaled beclomethasone therapy in this age range. Given the performance characteristics, particularly the responsiveness to asthma therapies, of the asthma diary are known for patients aged 15 years and older, a supportive analysis of the secondary endpoint of daytime symptoms will be included and be limited to patients aged 15 years and older.

2.6.2 Total daily use of SABA

Total daily use of SABA (the number of puffs taken in the previous 24 hours) by the patient will be analyzed using ePEF/ eDiary data. The mean of change from baseline in the total daily use of SABA over the 12 weeks of treatment will be analyzed based on on-study data (including on-treatment and off-treatment data) using an ANCOVA model in a similar fashion as the primary efficacy variable. The model will include factors for treatment group, age group (<18

vs. ≥18 years), use or non-use of a second asthma controller medication at study entry, and region, as well as the baseline daytime asthma symptom score, baseline total daily SABA use and baseline pre-dose FEV_1 as continuous linear covariates.

The least squares mean ("adjusted mean") change from baseline for each treatment group, the difference in the least squares mean changes between the two treatment groups (QAW039 150 mg – placebo), and the two-sided 95% confidence interval along with the superiority p-value for the difference will be obtained. This model will be fitted to each of multiple imputations generated using the approach described in Section 2.6.4.

In addition, the mean of change from baseline in the total daily use of SABA by 4-week intervals over the 12 weeks of treatment will be analyzed based on on-treatment data using a MMRM model in a similar fashion as mentioned in Section 2.6.1 except only one change is to replace interval-by-baseline daytime asthma symptom score interaction with interval-by-baseline total daily use of SABA interaction.

Summaries of absolute values and change from baseline will be presented by 4-week interval and overall 12 weeks of treatment based on on-treatment data. If the number of puffs of SABA use is missing but the rest of the eDiary has non-missing data, the number of puffs will be assumed zero. The total number of puffs of SABA use will be divided by the total number of days with non-missing SABA use data to derive the mean daily number of puffs of SABA use for each given visit interval (every 4 weeks). The non-missing data within that interval will be used to calculate the mean value, as long as there are at least 4 days with non-missing eDiary data for baseline scores and 14 days with non-missing data for post-baseline scores in a 4-week period. Otherwise, the value will be set as missing for that interval. If the number of puffs is missing for part of the day (either morning or evening) then a half day will be used in the denominator. For Weeks 1 – 12, summary values will be calculated as long as a patient has at least 50% of their diary days and at least 42 diary days with evaluable data for that variable in the period of interest.

2.6.3 AQLQ+12

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 2.6.4.

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).

The change from baseline in AQLQ+12 at week 12 will be analyzed using an ANCOVA model in a similar fashion as the primary efficacy variable, based on on-study data (including on-treatment and off-treatment data). The model will include factors for treatment group, age group (<18 vs. ≥18 years), use or non-use of a second asthma controller medication at study entry, and region, as well as the baseline daytime asthma symptom score, baseline total daily SABA use, baseline pre-dose FEV_1 , and baseline AQLQ as continuous linear covariates.

The least squares mean ("adjusted mean") change from baseline for each treatment group, the difference in the least squares mean changes between the two treatment groups (QAW039 150 mg – placebo), and the two-sided 95% confidence interval along with the superiority p-value for the difference will be obtained. This model will be fitted to each of multiple imputations generated using the same approach as for the primary analysis.

In addition, the mean of change from baseline in AQLQ +12 at Week12 will be analyzed based on on-treatment data using a MMRM model in which treatment, age group (<18 vs. ≥18 years), use or non-use of a second asthma controller medication at study entry, region, visit and treatment-by-visit interaction will be included as fixed-effect factors, and baseline pre-dose FEV1 value as well as the baseline daytime asthma symptom score, baseline total daily SABA use, baseline AQLQ and visit-by- baseline AQLQ as covariates. A common unstructured covariance matrix among visits for each treatment group will be used. The analysis will be performed based on all available on-treatment data up to week 12. The estimated treatment differences for all treatment comparisons will be tabulated along with the associated 95% confidence intervals and their two-sided p-values.

Summaries of absolute values and change from baseline will be presented by visit and by treatment group based on on-treatment data.

In addition, the proportion of patients with a change from baseline (improvement) in AQLQ+12 score of at least +0.5 unit based on on-treatment data will be analyzed using logistic regression by visit. The model will include treatment, age group (<18 vs. ≥18 years), use or non-use of a second asthma controller medication at study entry and region as a fixed class effects, and the baseline AQLQ+12 as continuous linear covariates. Estimates of the odds ratios between QAW039 group and placebo will be displayed along with associated 95% confidence intervals and two-sided p-values by visit.

2.6.4 Handling of missing values/censoring/discontinuations

Handling of missing daytime asthma symptom scores and total daily SABA use

The weekly mean will be calculated based on the non-missing post-baseline assessments as long as there are at least 4 days with non-missing data in a one-week period. Otherwise, the weekly mean will be set to missing. The multiple imputations will be carried out on the weekly mean data using J2R approach in a similar fashion as primary analysis described in Section 2.5.4. The completed weekly mean data after imputation will be used in the model to calculate the mean of change from baseline over 12 weeks of treatment.

Handling of missing AQLQ+12 values

The missing data of AQLQ+12 will be imputed using the same approach as primary analysis described in Section 2.5.4.

2.7 Safety analyses

All safety evaluation will be based on the safety analysis set.

2.7.1 Adverse events (AEs)

All adverse events, including asthma exacerbations, coded with MedDRA using the most actual version at the time of database lock, will be listed. Unless otherwise specified, summaries will include treatment-emergent adverse events (TEAEs) only. AEs starting on or after the time of the first intake of study drug and not later than 7 days (30 days in the case of a serious AE) after the last intake of study drug will be classified as a TEAE. For those patients who enter the safety study (CQAW039A2315) directly after Visit 299, AEs (including serious AEs) starting after Visit 299 will not be considered as TEAEs in this study as they will be reported in CQAW039A2315.

As a general rule of censoring, patients who either completed the study or discontinue treatment prematurely and without the event of interest will be censored at the minimum out of the dates of last medication intake + 30 days, final visit date, and date of death. 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
- AEs of special interest

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.

2.7.1.1 Adverse events of special interest / grouping of adverse events

AEs of special interest definitions are found in the compound electronic Case Retrieval Strategy (eCRS). The classification reflects the current version of the dSPP and might be updated based on review of accumulating data. To identify AEs of special interest at the time of the final analysis, the latest version of the eCRS where Core safety topic risk (SP) = 'Yes' or Other Search risk (OS) = 'Yes' will be used.

The number and percentage of patients with treatment emergent AEs of special interest will be summarized by risk category, PT and treatment. In addition, summaries will be provided for

- Treatment emergent AEs of special interest by maximum severity
- Treatment emergent serious AEs of special interest
- Treatment emergent AEs of special interest that are suspected to be related to study drug

2.7.1.2 AE reporting for CT.gov and EudraCT

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 TESAEs and SAEs suspected to be related to study treatment 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 treatment 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.

2.7.2 Deaths

The number of deaths resulting from TEAEs will be summarized by SOC and PT. All the deaths in the clinical database including those occurring during screening will be listed.

2.7.3 Laboratory data

Laboratory data consist of hematology, biochemistry and urinalysis measurements.

Laboratory data measured on or 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 included in the analyses regardless of rescue medication use. Results from local labs will be collected but not included in any analyses or summary tables because the reporting from local labs cannot be standardized. Results from central laboratories will be included in analyses and summary tables. Baseline laboratory data is defined in Section 2.1.1.1. The following sub-sections will describe the method of summary.

2.7.3.1 Summary of absolute values

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

The direction of interest for worst case post-baseline for selected hematology and biochemistry parameters is tabulated in Table 6-4-1. For continuous urinalysis parameters, the direction of interest is always High.

A frequency table of results for categorical on-treatment laboratory parameters will be produced. For categorical urinalysis laboratory parameters, a frequency table of results will be produced by laboratory parameter, scheduled visit and time-point, and treatment. Worst-case on-treatment post-baseline 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 that are flagged as greater than upper limit of quantification as 1.5, the values presented in summary tables should be multiplied by 1.5.

2.7.3.2 Summary of change from baseline

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

In order to observe the tendency of treatment effect on mean values, box plots by treatment arm for post-baseline values and worst case post-baseline will be presented on the change from baseline for all laboratory parameters. Albumin: Creatinine ratio (ACR) value will be considered missing if either the albumin or the creatinine values are missing. Similarly, Protein: Creatinine ratio (PCR) will be considered missing if either the protein or the creatinine values are missing.

2.7.3.3 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 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 6-4-2.

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.

Liver function tests

To evaluate potential drug-induced liver injury, newly occurring or worsening abnormalities in liver function tests will be evaluated (see Table 6-4-3 for a summary of the notable values).

When a criterion contains multiple laboratory parameters, the criterion will only be considered to be met when all conditions occur at the same time (i.e., in the same sample). A case where all criteria are met at a post-baseline time point but not met at baseline will be considered as newly occurring. A case will be considered as worsening if all the criteria are met at baseline and at least one component is worsening from baseline, irrespective of whether the other(s) are better.

The number and percentage of patients with newly occurring liver enzyme abnormalities any time post-baseline will be summarized. Listings of patients with notable liver function test lab values and liver events will be provided.

To evaluate drug induced serious hepatotoxicity eDish plots will be presented. The eDish plot will reflect the worst value of each of the parameters; they do not need to occur at the same visit.

2.7.4 Other safety data

2.7.4.1 ECG 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). Furthermore, an overall interpretation of the central cardiologist will be provided as well as a specification of abnormal findings.

ECG 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.

Summary of absolute values and change from baseline

Absolute values and change from baseline summarized by parameter, and visit.

Clinically notable values

- The number and percentage of patients with newly occurring or worsening clinical notable QTcF values (see Table 2-3) summarized by scheduled post-baseline visit and additionally at any time on treatment considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits.

Table 2-3 Clinically notable criteria for QTcF (Fridericia's formula)

ECG parameter (unit)	Clinically notable range
Value considering newly occurring or worsening cases	
QTc (msec)	≥ 450 (male)
QTc (msec)	≥ 460 (female)
QTc (msec)	> 500 (both)
Change from baseline	
QTc	1 - < 30
QTc	30 – 60
QTc	> 60

Clinically relevant values

- A summary table will also be produced for number and percentage of subjects with clinically relevant QT and QTcF intervals (irrespective of the time point) using the following categories:
  a. any treatment emergent (new) QTcF ≥ 450 ms – 480 ms, > 480 ms – 500 ms or > 500 ms
  b. QTcF increase from baseline of 30 ms – 60 ms, > 60 ms
  c. QTcF 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

Overall ECG interpretation

- Summary of ECG abnormalities will be produced on following variables: The number and percentage of subjects with newly occurring or persistent/recurrent on-treatment ECG abnormalities in overall ECG interpretation at any time point
  - The number and percentage of subjects with newly occurring or persistent/recurrent on-treatment ECG abnormalities by evaluation type and abnormality finding at any time point.

  If patients had at least once ECG abnormality at baseline, the baseline flag will be abnormal. Similarly, for post baseline visits, if patients had at least once ECG abnormality at a visit, then ECG is abnormal at that visit else normal.

- Patients with notable post-baseline ECG values will be listed. Box plots of ECG by scheduled visit and treatment for the parameters: QTcF and summary (mean) heart rate will be presented.

2.7.4.2 Vital signs

Vital signs measurements include systolic and diastolic blood pressure (SBP and DBP), pulse rate, 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 visit
- the number and percentage of patients with newly occurring or worsening notable vital signs on-treatment values (see Table 6-5-1 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.

Number and percentage of patients with clinically relevant on-treatment vital signs values that occur at any time post-baseline will be summarized for minimum and maximum post-baseline values.

2.7.5 Renal events

Summary of treatment emergent renal event overview data by treatment will be presented. All renal event overview data will be listed.

2.7.6 Liver events

Summary of treatment emergent liver event overview data by treatment will be presented. All liver event overview data will be listed.

2.8 Pharmacokinetic endpoints

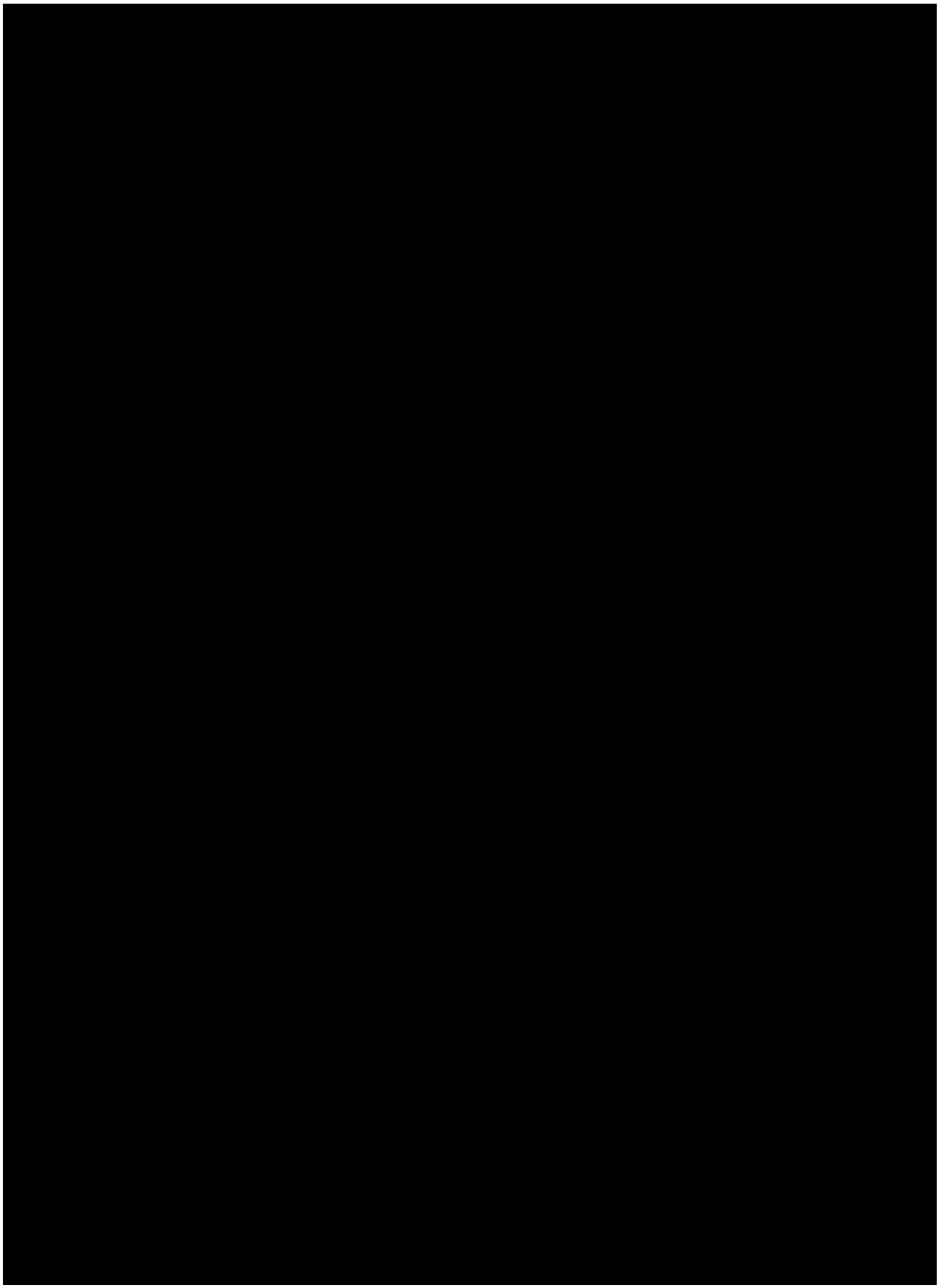
Not Applicable

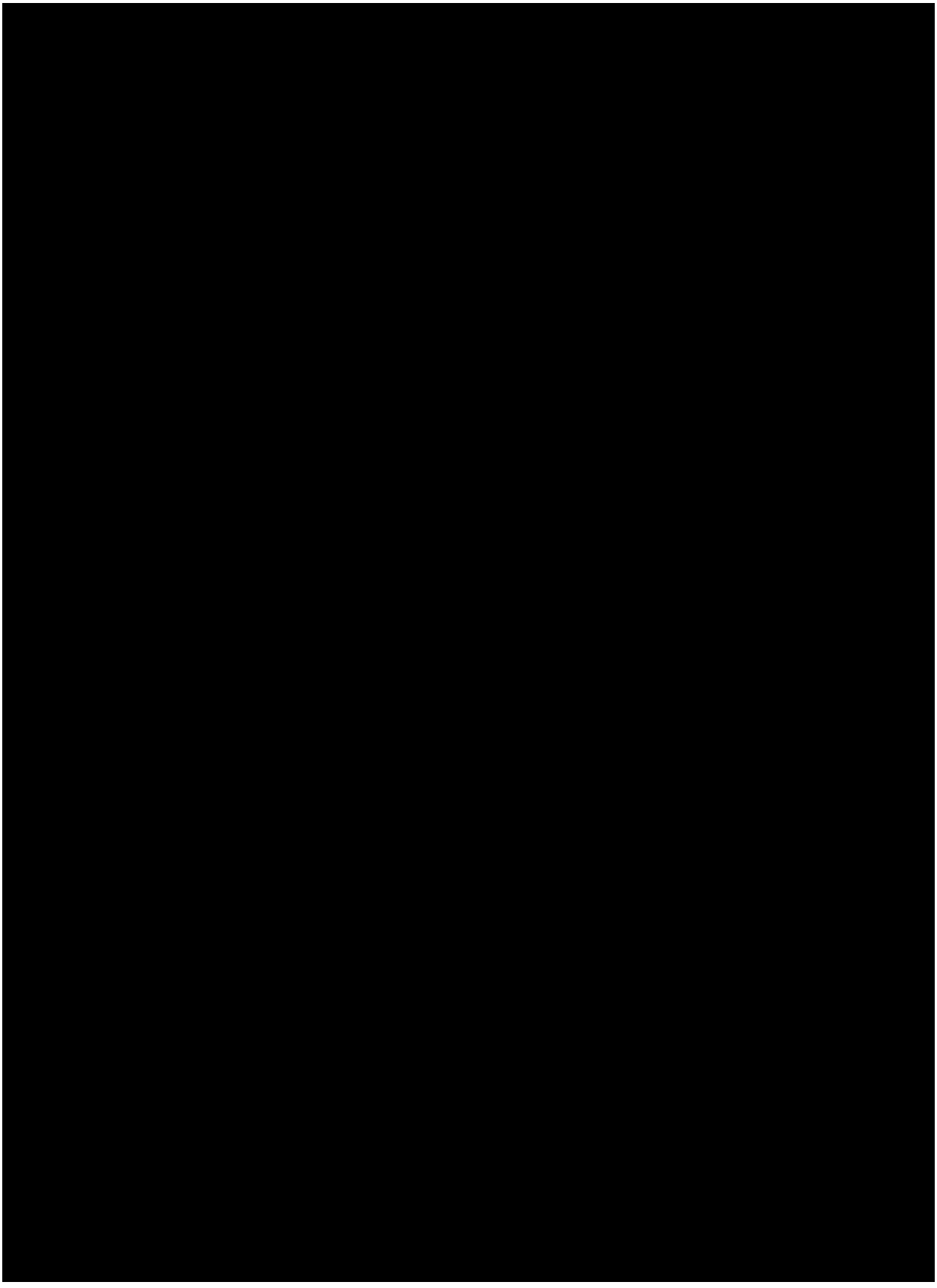
2.9 PD and PK/PD analyses

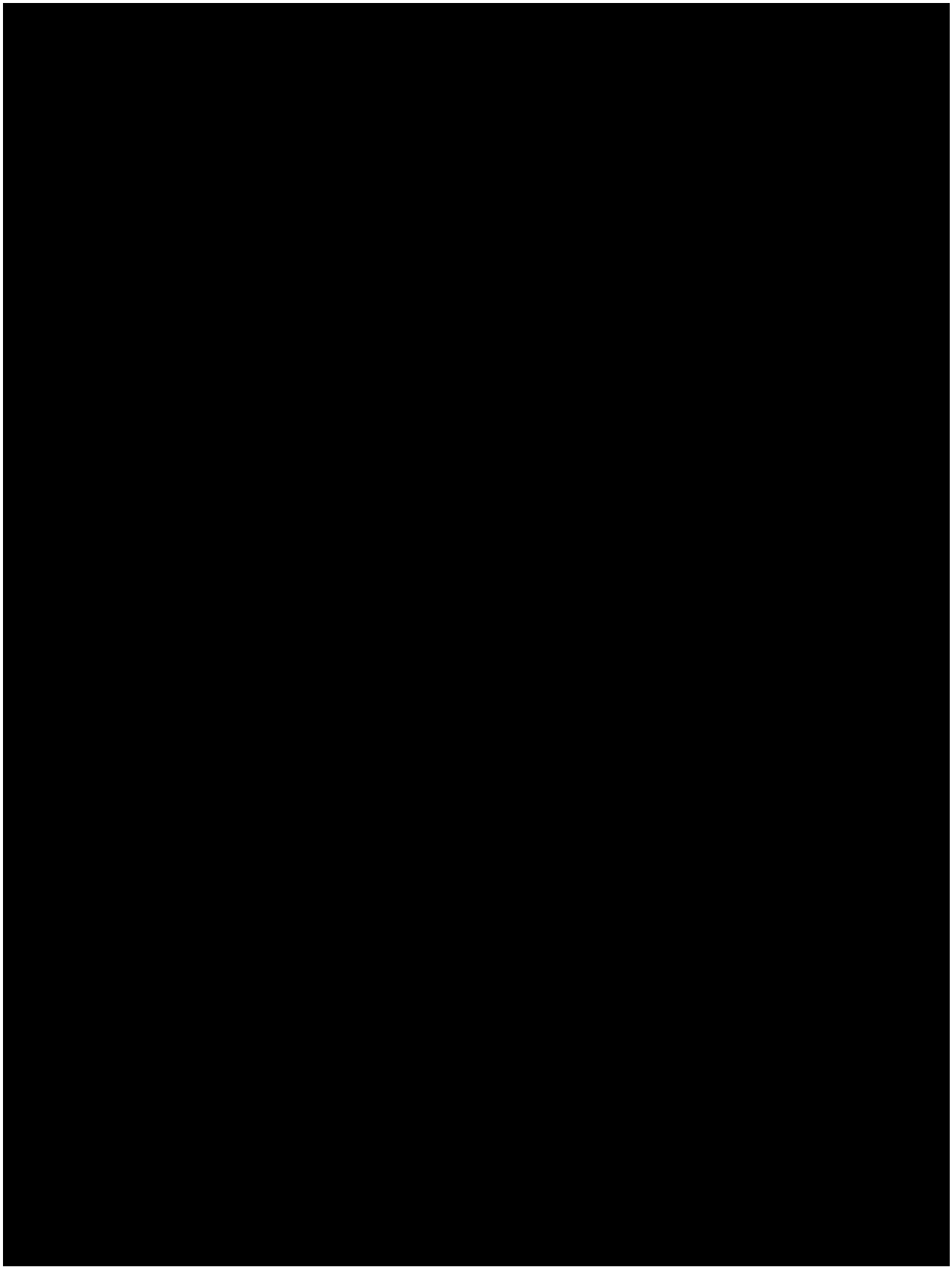
Not Applicable

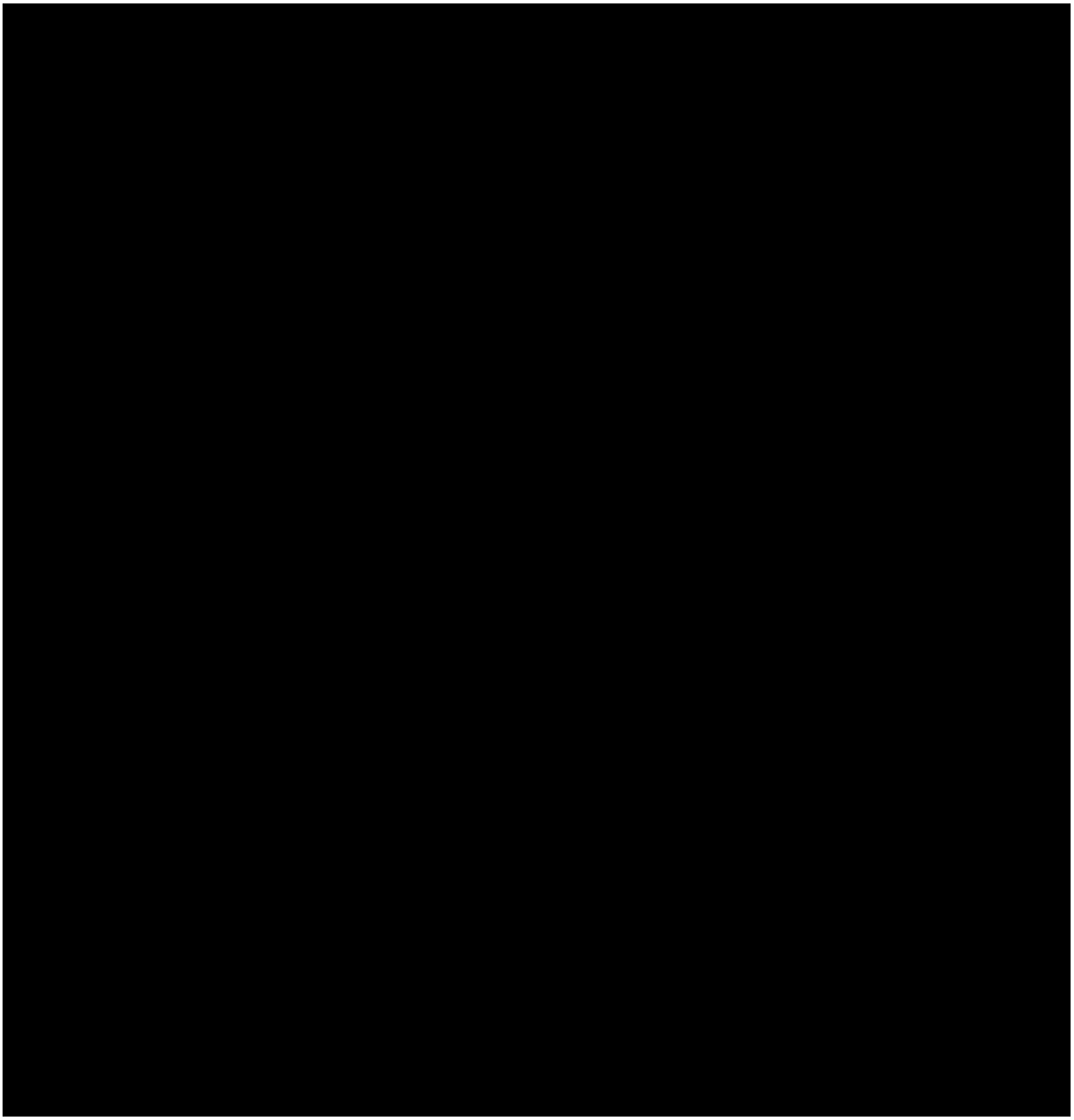
[redacted]

[redacted]









2.12 Interim analysis

No interim analysis for efficacy is planned in this study. An independent, external DMC has been set up to review safety data (including specific safety summaries for adolescent participants) for this trial. No statistical adjustment will be made to the final analysis.

3 Sample size calculation

The primary objective is to demonstrate that QAW039 150 mg is superior to placebo in pre-dose FEV1 following 12 weeks of post-baseline treatment. A difference of 112 mL in pre-dose FEV1 during treatment was assumed, which is similar to the model-averaged effect seen in

study QAW039A2206. The standard deviation (SD) of 380 mL and between-visit correlation for pre-dose FEV1 was based on study QAW039A2206 in a similar population. A treatment discontinuation rate of 15% was assumed based on QAW039A2206 and it was assumed that half of the patients discontinuing study treatment would have week 12 FEV1 values. Simulations were used to determine the sample size due to the complex J2R missing data imputation approach for the primary analysis.

Under the outlined assumptions, a sample size of 650 patients (325 per arm) would be needed to have 90% power to observe a statistically significant difference between QAW039 and placebo at the two-sided 5% significance level in the primary analysis as shown in Table 3-1. The table also shows the sensitivity of the power to deviations from the assumptions.

Table 3-1 Result of power simulations for the primary variable

Treatment effect (mL)	Discontinuation rate	Sample size	Power
112	15%	650	90.3
112	20%	650	85.9
100	15%	650	80.9

Based on 10,000 simulated trials per scenario and 250 multiple imputations for each trial. Simulations were conducted using SAS/STAT® 13.1 software, Version 9.4 of the SAS System for Linux.

Power for the secondary objectives

If statistical significance is achieved in the primary test, the tests for the secondary variables will be performed. The local significance level for each secondary null hypothesis will be determined based on the closed testing procedure shown in Figure 2.

As differences in FEV1 to placebo for QAW039 150 mg once daily and montelukast 10 mg once daily appeared to be of similar magnitudes in study QAW039A2206, the power calculations for the two secondary objectives (change from baseline in daytime asthma symptoms and change from baseline in total daily SABA use) are based on the assumptions from the results of two studies comparing montelukast 10 mg once daily with placebo (Reiss et al 1998, Malmstrom et al 1999). These studies suggest an averaged difference of 0.26 for change from baseline in daytime asthma symptoms between montelukast and placebo after 12 weeks of treatment and a SD of 0.94. The two studies also suggest an averaged difference of -1.34 point difference in the change from baseline in the number of daily SABA puffs between montelukast and placebo with a standard deviation of 3.82. We assume a clinically important true improvement of at least 0.5 in AQLQ+12 after 12 weeks of treatment for patients that remain on treatment and a standard deviation (SD) of 1. As shown in Table 3-2 all secondary endpoints have an adequate conditional power once the primary null hypothesis has been rejected, but will each have an even higher conditional power once the null hypotheses relating to the other secondary variables have been rejected.

Table 3-2 Power simulations for secondary variables

	Daytime asthma symptoms	Total daily rescue medication use	AQLQ+12
Difference of effect (δ)	-0.26	-1.34 number of puffs	0.5
SD (σ)	0.94	3.82 number of puffs	1
Local two-sided significance level once primary null hypothesis is rejected	0.0245	0.0245	0.001
Power	74%	97%	98%
Local two-sided significance level once primary and the other two secondary hypotheses are rejected	0.05	0.05	0.05
Power	83%	98%	> 99%

Power statements are based on 10,000 simulated trials per scenario and 250 multiple imputations using a jump-to-reference approach for each simulated trial. Simulations were conducted using SAS/STAT® 13.1 software, Version 9.4 of the SAS System for Linux. We assumed a treatment discontinuation rate of 15% with half of the patients discontinuing from study treatment completing the trial. The correlation structure was assumed the same as for the primary endpoint. Abbreviation: AQLQ+12 (asthma quality of life questionnaire for 12 years and older).

4 Change to protocol specified analyses

- Section 9.2 in the study protocol states that the age of the patient will be calculated from the date of birth to date of Visit 1. However, since date of birth is not captured on the CRF page and age (in years) at the time of informed consent is entered into CRF, there is no need to re-calculate age.
- Shift tables relative to the normal reference ranges to summarize the on-treatment change from baseline to post-baseline for each laboratory parameter or ECG parameter or vital sign assessments will not be presented.
- Study protocol defines treatment emergent adverse events as those events starting on or after the time of the first intake of study drug and until the day after the last intake of study drug. However, in order to maintain consistency with the submission documents, for analysis purposes the following updated definitions are considered:

  AEs starting on or after the time of the first intake of study drug and not later than 7 days (30 days in the case of a serious AE) after the last intake of study drug will be classified as a TEAE.
- Added the responder analysis for AQLQ improvement
- Added more details to liver function tests including eDISH plot
- Added analysis for renal events and liver events according to project level alignment
- The following analyses, though pre-specified in the protocol, may not be critical for decision making purposes and hence will be reported outside of CSR:
  - [redacted]

- In protocol 9.4.4, supportive analysis for the primary endpoint based on other missing data imputation approaches: pattern mixture approach combining the jump to reference and missing at random approaches by distinguishing reasons for discontinuation of treatment and retrieved dropout imputation approach.
- In protocol Section 9.4.4, subgroup analyses for BMI, number of exacerbations in the previous year, ACQ tertiles, [redacted].
- Summaries on post-treatment discontinuation events to be produced for adverse events and serious adverse events by system organ class and preferred term.

[redacted]

6 Appendix

This appendix gives details about statistical methods in addition to the report text. All analyses will be performed by using SAS Version 9.4.

Note: The SAS version that will be actual on the NOVARTIS platform at the time when the study is completed will be stated here.

6.1 Imputation rules

6.1.1 Study drug

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

6.1.2 AE date imputation

Rules for imputing AE end date or start date will be provided in Programming Dataset Specification (PDS) document in details.

6.1.3 Concomitant medication date imputation

Rules for imputing concomitant medication start or end dates will be provided in Programming Dataset Specification (PDS) document in details.

6.1.3.1 Prior therapies date imputation

Rules for imputing the prior therapies end date or start date will be provided in Programming Dataset Specification (PDS) document in details.

6.1.3.2 Post therapies date imputation

Rules for imputing the post therapies end date or start date will be provided in Programming Dataset Specification (PDS) document in details.

6.2 AEs and Concomitant medications 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.

6.3 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.

6.4 Laboratory parameters derivations

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

Table 6-4-1 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 6-4-2 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 aged 12-17	0.34	
Male aged 18-65	0.37	
Male aged >=66	0.34	
Female aged 12-65	0.32	
Female aged >=66	0.31	

Laboratory parameter (unit)	Bound for notably low values	Bound for notably high values
Hemoglobin (g/L)		
Male aged 12-17	100	
Male aged >=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

Table 6-4-3 Notable liver function test values

Criterion
ALT > 3 x ULN ALT > 5 x ULN ALT > 8 x ULN ALT > 10 x ULN ALT > 20 x ULN
ALT or AST > 3 x ULN ALT or AST > 5 x ULN ALT or AST > 8 x ULN ALT or AST > 10 x ULN ALT or AST > 20 x ULN
Total Bilirubin > 1 x ULN Total Bilirubin > 1.5 x ULN Total Bilirubin > 2 x ULN Total Bilirubin > 3 x ULN
ALP > 1.5 x ULN ALP > 2 x ULN ALP > 3 x ULN ALP > 5 x ULN
ALT or AST > 3 x ULN and Total Bilirubin > 1.5 x ULN ALT or AST > 3 x ULN and Total Bilirubin > 2 x ULN ALT or AST > 5 x ULN and Total Bilirubin > 2 x ULN ALT or AST > 8 x ULN and Total Bilirubin > 2 x ULN ALT or AST > 10 x ULN and Total Bilirubin > 2 x ULN ALT or AST > 20 x ULN and Total Bilirubin > 2 x ULN
ALP > 3 x ULN and Total Bilirubin > 2 x ULN ALP > 5 x ULN and Total Bilirubin > 2 x ULN
ALT or AST > 3 x ULN and Total Bilirubin > 2 x ULN and ALP ≤ 2 x ULN (Hy's law)
ALT or AST > 3 x ULN and (nausea or vomiting or fatigue or general malaise or abdominal pain or (rash and eosinophilia))*

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ALP=alkaline phosphatase; ULN=upper limit of normal. *Based on the signs/symptoms information as recorded on the liver events eCRF, not the adverse events eCRF.

6.5 Vital signs – definition of clinically notable and relevant values

The following table shows the clinical notable criteria for vital signs.

Table 6-5-1 Vital signs - clinical notable values

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

6.6 Statistical methodology and assumptions

SAS codes for all statistical methodology described in this section will be included in Table, Figure, Listing (TFL) Shells as programming note.

6.6.1 Multiple imputations for primary and secondary variables

The imputation and analysis of primary and secondary variables will be implemented using the "five macros" available from www.missingdata.org.uk (for a full description see Carpenter et al (2013)). The purpose and activities of each of the five macros is described below.

Part1A declares the parameter estimation model and checks consistency with the input dataset. It builds a master dataset which holds details of the current job and also builds indexes for the classification variables, which may be either numeric or character.

Part1B fits the parameter estimation model using the MCMC procedure and draws a pseudo-independent sample from the joint posterior distribution for the linear predictor parameters and the covariance parameters.

Part2A calculates the predicted mean under MAR, and under MNAR for each subject based on their withdrawal pattern once for each draw of the linear predictor parameter estimates. The choice of MNAR is controlled by the method used, which may vary from subject to subject.

Part2B imputes the intermediate missing values using MAR and the trailing missing values using MNAR, by deriving the conditional distribution for the missing values conditional on the observed values and covariates, using the appropriate sampled covariance parameter estimates.

Part3 carries out a univariate ANOVA analysis at selected time points usually based on the same covariates as the parameter estimation model. It then combines the least-squares means and their differences using the MIANALYZE procedure to provide final results.

This is example code to implement the primary analysis:

```
%part1A(Jobname=fev1
,Data=RE
,Subject=subjid
,Response=aval
,Time=visit
,Treat=trt01pn
,Covbytime= basefev basescore basesaba
,Catcov=stratum
,
);
```

Where subjid = subject identifier

aval = change from baseline in FEV1 value at visit during the treatment epoch

visit = treatment period visit number

trt01pn = planned treatment

basefev = baseline FEV1 value

basescore = baseline daytime asthma symptom score
basesaba = baseline total daily SABA use

stratum = randomization strata (patient age (<18 years or ≥18 years), use or not use a second asthma controller at study entry, region)

```
%part1B(Jobname=fev1
,Ndraws=1000
,thin=750
,seed=12345
);
%part2A(Jobname=fev1_J2R
,inname=fev1
,methodV=Mymethod
,refV=Myreference
);
```

where Mymethod = Method used to impute missing data: J2R for QAW patients who discontinued treatment and MAR otherwise. Myreference = Placebo

```
%part2B(Jobname=fev1_J2R
,seed=832216);

%part3(Jobname=fev1_J2R
,ANTreat=trt01pn
,label=Mixed MAR and J2R);
```

Results will be presented as Least Squares Means (LSM) and standard errors (SE) for treatment effects and LSM, SE, associated two-sided 95% confidence interval, and two-sided p-value for all relevant treatment contrasts.

6.7 Rule of exclusion criteria of analysis sets

Subject classification in the analysis sets (FAS, Safety, Per Protocol, SCR, and RAN) will be based on protocol deviation specifications and non-protocol deviation classification criteria as following.

Table 6-7-1 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses
INCL01a	Informed consent was not obtained	SCR, RAN, FAS, PPS, SAF
INCL02	Age < 12 years	PPS
INCL03	No current diagnosis of Asthma of at least 6 months prior to V1	PPS
INCL05a	For patients aged >= 18 years, % predicted FEV1 was not <= 85% at both V1 & V101	PPS
INCL05b	For patients aged 12 years to <18 years, % predicted FEV1 was not <= 90% at V1 & V101	PPS
INCL05c	Spirometry done for assessing study eligibility is not meeting ATS/ERS criteria for acceptability or repeatability.	PPS
INCL08	Reversibility not demonstrated before randomization	PPS
EXCL01	Other investigational drug used within 30 days or within 5 half-lives prior to Screening	PPS
EXCL10b	Smoking history of greater than 10 pack years	PPS
EXCL11	Patient had an asthma exacerbation requiring systemic corticosteroids, hospitalization, or emergency room visit within 6 weeks prior to Visit 1	PPS

Deviation ID	Description of Deviation	Exclusion in Analyses
EXCL12	Patient had an asthma exacerbation requiring systemic corticosteroids, hospitalization or emergency room visit during the screening or placebo run-in periods.	PPS
EXCL13	Patients had respiratory tract Infection or asthma worsening within 4 weeks prior to V1.	PPS
COMD01	Prohibited asthma related ConMed during treatment epoch	PPS
COMD04	Permitted asthma related medication not taken as allowed under certain conditions during treatment epoch	PPS
COMD05	Baseline asthma medication or their dose was changed after Visit 1	PPS
OTH04	Patient randomized in error	PPS

Table 6-7-2 Subject Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
SCR	INCL01a,	NA
RAN	INCL01a	NA
FAS	INCL01a	Not in RAN; Randomized and no double-blind study drug taken
PPS	INCL01a,INCL02,INCL03, INCL05a,INCL05b,INCL05c, INCL08,EXCL01,EXCL10b, EXCL11,EXCL12, EXCL13,COMD01,COMD04 ,COMD05,OTH04	Not in FAS;
SAF	INCL01a	No double-blind study drug taken

7 Reference

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