NOVARTIS

Clinical Development

QAW039/Fevipiprant

CQAW039A2307 / NCT02555683

A 52-week, multicenter, randomized, double-blind, placebo controlled study to assess the efficacy and safety of QAW039 when added to existing asthma therapy in patients with uncontrolled severe asthma

Statistical Analysis Plan (SAP)

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List of abbreviations

ACQ	Asthma Control Questionnaire
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AM	ante meridiem
ANCOVA	Analysis of covariance
AQLQ+12	Asthma Quality of Life Questionnaire for 12 years and above
AR(1)	Autoregressive model of order 1
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
BMI	Body Mass Index
CM	Concomitant Medication
CSR	Clinical Study Report
DAR	Drug administration record
DMC	Data Monitoring Committee
DSPP	Development Safety Profiling Plan
ECG	Electrocardiography
eCRF	Electronic Case Report Form
[redacted]	[redacted]
FAS	Full Analysis Set
[redacted]	[redacted]
FEV1	Forced Expiratory Volume in 1 second
[redacted]	[redacted]
HRQOL	Health-Related Quality of Life
ICS	Inhaled Corticosteroid
IDR	Idiosyncratic drug reaction
IgE	Immunoglobulin E
ImmunoCAP^{R}	Specific IgE test
IRT	Interactive Response Technology
JRS	Japan Respiratory Society
LABA	Long-acting Beta-agonist
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene Receptor Antagonist
MAR	Missing at random
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MID	Minimally Important Difference
MMRM	Mixed Model Repeated Measures
OCS	Oral corticosteroids
[redacted]	[redacted]
PK	Pharmacokinetics
PM	post meridiem
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
QD	Qua'que di'e / once a day
PT	Preferred Term

QoL	Quality of Life
QTcF	Fridericia QT correction formula
RAN	Randomized set
RAST	Radioallergosorbent test
SABA	Short acting β2-agonist
SAE	Serious adverse event
SAF	Safety set
SAP	Statistical Analysis Plan
SCR	Screened set
SD	Standard Deviation
SGLT	Sodium glucose transporter
SGOT	Serum glutamic oxaloacetic transaminase
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
SOC	Standard of care
TBL	Total bilirubin
TFLs	Tables, Figures, Listings
Th2	Type 2 helper T
ULN	Upper Limit of Normal

1 Introduction

Data will be analyzed by the sponsor 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.

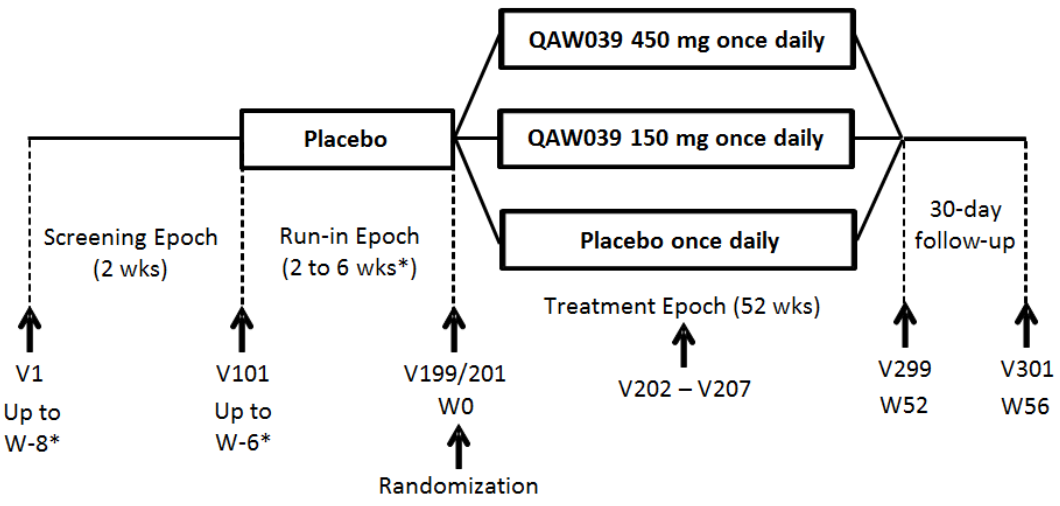
1.1 Study design

This study uses a randomized, multicenter, double-blind, placebo-controlled parallel-group study design in which QAW039 or placebo is added to GINA steps 4 and 5 asthma therapy (Figure 1-1).

The study will include:

- a Screening epoch of up to 2 weeks to assess eligibility;
- a Run-in epoch of approximately 2 weeks and a maximum of 6 weeks to collect baseline data for efficacy variables and compliance with the Electronic Peak Flow/ eDiary device (if a patient experiences an asthma exacerbation during the run-in epoch, the run-in epoch must be extended to 6 weeks to permit for resolution of the asthma exacerbation before randomization. The run-in epoch should only be extended beyond 2 weeks (+/- 5 days) for an asthma exacerbation.);
- a Treatment epoch of 52 weeks;
- a Follow-up epoch of 4 weeks, investigational and drug-free, following the last dose of study drug. Note: only applicable for patients not participating in the safety study CQAW039A2315.Popu;at

Figure 1-1 Study design



*flexible Run-in Epoch (2 to 6 weeks) to accommodate subjects with asthma exacerbations

Upon completion of the run-in epoch, all patients who met the eligibility criteria will be randomized to 1 of 3 treatments (QAW039 [150 mg or 450 mg once daily] or placebo once daily) in a ratio of 1:1:1. Randomized patients will stratified by their peripheral blood eosinophil counts (<250 cells/µl or ≥250 cells/µl), patient age (<18 years or ≥18 years), and

their baseline use or non-use of oral corticosteroids as part of their SoC asthma therapy at Visit 1. Treatment randomization will also be stratified at the regional level.

Clinic visits will be scheduled approximately 4 weeks after randomization and then at approximately 8-week intervals during the active-treatment epoch. Phone calls will occur at specified time points between visits occurring at 8-week intervals. A follow-up visit will occur approximately 4 weeks (i.e., approximately 30 days) following the last dose of study therapy to complete safety assessments and pregnancy testing (if applicable).

1.2 Study objectives and endpoints

Primary objective(s)

- In patients with severe asthma and high eosinophil counts (≥250 cells/µl) receiving SoC asthma therapy, to demonstrate the efficacy (as measured by rate of moderate-to-severe asthma exacerbations) of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, at the end of the 52-week active-treatment epoch.
- In all patients with severe asthma receiving SoC asthma therapy, to demonstrate the efficacy (as measured by rate of moderate-to-severe asthma exacerbations) of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, at the end of the 52-week active-treatment epoch.

Secondary objectives

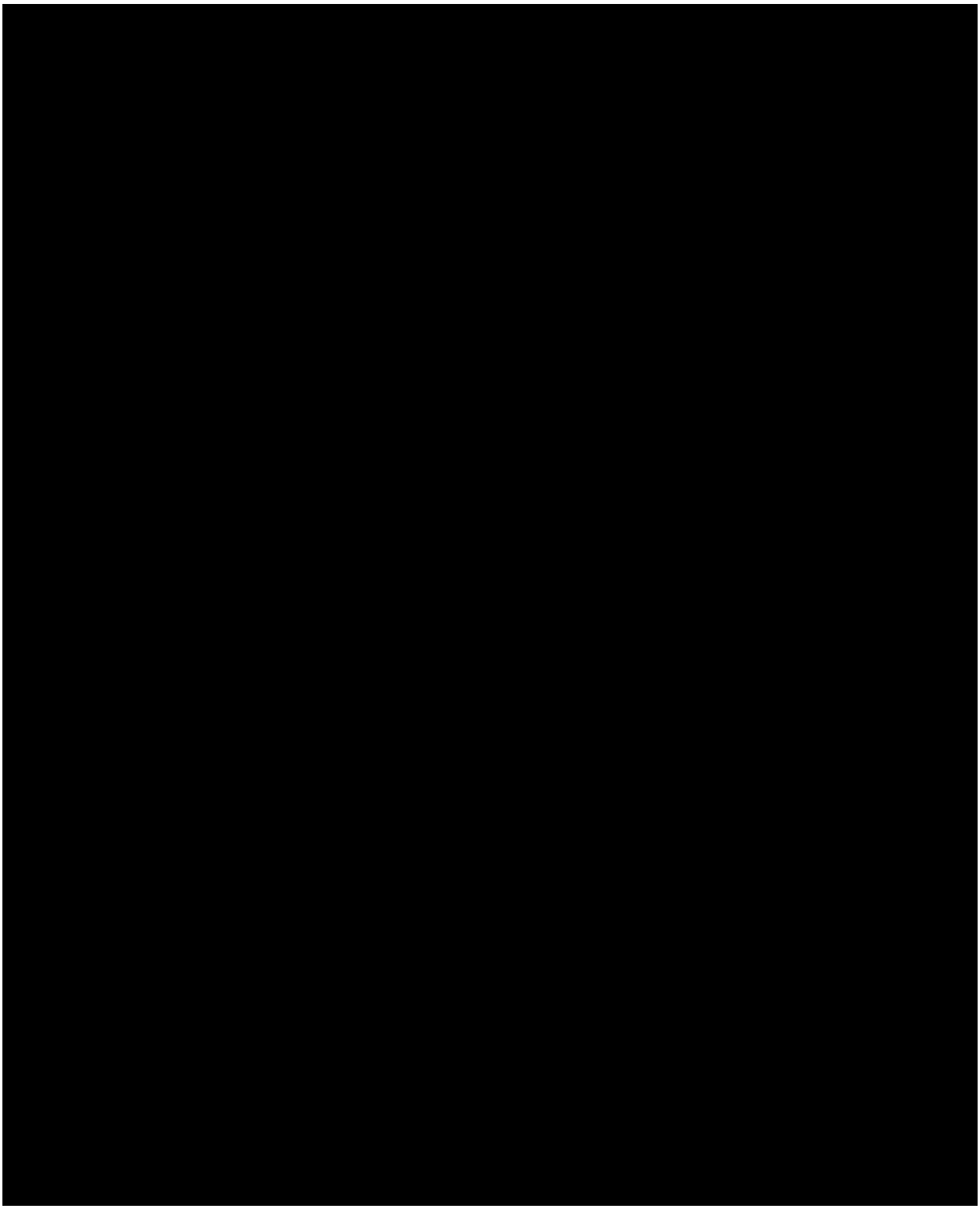
In patients with severe asthma and high eosinophil counts (≥250 cells/µl) receiving SoC asthma therapy:

- To demonstrate the efficacy of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, with respect to change from baseline in Asthma Quality of Life Questionnaire (AQLQ+12) scores at the end of the 52-week active-treatment epoch.
- To demonstrate the efficacy of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, with respect to change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at the end of the 52-week active-treatment epoch.
- To demonstrate the efficacy of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, with respect to change from baseline in pre-dose FEV1 at the end of the 52-week active-treatment epoch.
- To assess the safety of QAW039 (150 mg and 450 mg once daily), compared with placebo, with respect to adverse events, electrocardiograms (ECGs), vitals sign, laboratory tests and hypersensitivity reactions.

In all patients with severe asthma receiving SoC asthma therapy:

- To demonstrate the efficacy of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, with respect to change from baseline in Asthma Quality of Life Questionnaire (AQLQ+12) scores at the end of the 52-week active-treatment epoch.
- To demonstrate the efficacy of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, with respect to change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at the end of the 52-week active-treatment epoch.

- To demonstrate the efficacy of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, with respect to change from baseline in pre-dose FEV1 at the end of the 52-week active-treatment epoch.
- To assess the safety of QAW039 (150 mg and 450 mg once daily), compared with placebo, with respect to adverse events, electrocardiograms (ECGs), vitals sign, laboratory tests and hypersensitivity reactions.



[redacted]

2 Statistical methods

2.1 Data analysis general information

The final analysis will be performed by the sponsor. The most recent version of SAS and R available in the statistical programming environment will be used for the analysis. The interim analyses will be performed by a contracted CRO and the statistical analysis for the interim analyses will be planned in a separate document. In this document, 'study treatment' or 'study drug' will be used to refer to investigational therapy assigned to a patient. Specifically, for the double-blind treatment phase, study treatment refers to QAW039 or placebo as assigned to a patient at randomization.

2.1.1 Population

Unless otherwise specified, both the efficacy and safety analysis will be performed for the patients with eosinophil count ≥ 250 cells/µl (high eosinophils subpopulation) and the overall study population.

2.1.2 Study day

Study day is defined as the number of days since the date of first dose of study medication. 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.

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 study medication, the randomization date will be used instead of the date of first dose of study medication. In that case, the randomization date is defined as Day 1 and the day before the randomization is defined as Day -1.

2.1.3 Baseline definition

Data from unplanned visits prior to screening are not included in analysis.

For analysis purposes, the baseline value is defined to be the last result obtained at or prior to start of study medication (Day 1) for baseline demographics, medical history, lab values,vital signs and ECGs. Most variables will have their baseline at Day 1, unless otherwise specified. For assessments not performed at Day 1, the assessment at the screening visit or most recent assessment prior to start of study medication will be used as baseline.

- The baseline measurement of pre-dose FEV1 is defined as the mean of the two pre-bronchodilator FEV1 values taken in the clinic at 45 minutes and 15 minutes prior to the first dose of study drug on Day 1. If the pre-dose FEV1 is taken within 6 hours of

SABA use, or within 12 hours of twice-daily LABA (including fixed dose combinations of LABA and ICS) use, or 24 hours of once-daily LABA (including fixed dose combinations of LABA and ICS) use, or 24 hours of once-daily LAMA use, then the individual FEV1 value is set to missing.

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 first dose of study medication will be used for baseline.

- Vital signs include body temperature, pulse rate and systolic and diastolic blood pressures. Baseline vital signs are defined as the last assessment taken pre-dose on Day 1. Checks will be performed to ensure the assessments were indeed taken prior to the first dose of study drug on Day 1. If this assessment is missing or not confirmed to be pre-dose, the last value prior to the first dose will be used for baseline. Otherwise, the vital sign baseline will be set to missing without imputation.
- Baseline height and weight are defined to be the last result obtained at or prior to Day 1. Missing baseline values will not be imputed.
- Three ECG measurements are collected for each assessment. There are multiple assessments at different timepoints for a particular visit. For each timepoint an average of the three values are considered. Baseline ECG is defined as the average of the three values taken prior to the first dose of study drug on Day 1. Checks will be performed to ensure the ECGs were indeed obtained prior to the first dose of study drug. If the value on Day 1 is missing (or not confirmed to be pre-dose) then the average of the last values prior to the first dose will be used for baseline. Otherwise, the ECG baseline will be set to missing without imputation.
  Baseline ECG interpretation will be the value recorded pre-dose on Day 1, if present and confirmed to be pre-dose, otherwise the last interpretation prior to the first dose will be used
- Laboratory data include hematology, biochemistry and urinalysis. Baseline hematology, biochemistry and urinalysis are defined as the last assessment taken prior to first dose of study drug on Day 1. Checks will be performed to ensure baseline hematology, biochemistry and urinalysis laboratory values were indeed assessed pre-dose. 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.
- Baseline oral corticosteroid (OCS) use, atopic (yes/no) will be assessed Patients will be considered atopic, if they test positive for at least one allergen in the baseline RAST and/or ImmunoCAP test.
- 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.
- 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.

[redacted]

For e-dairy data, the morning assessment for Day 1 counts towards the baseline and the evening assessment for Day 1 counts as the treatment period.

2.1.4 Post-baseline measurement

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

2.1.5 Change from baseline

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

Change from baseline = post-baseline value – baseline value; and

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

2.1.6 Study completion and last contact

Study completion for a patient will occur after he/she has completed 52 weeks of treatment (through to Visit 299) or they have prematurely withdrawn. At sites participating in the Safety Study (CQAW039A2315), patients who successfully complete 52 weeks of treatment in this study ([redacted]) may be offered participation in the Safety Study (CQAW039A2315); patient participation in the Safety Study will be optional.

Patients not entering the safety study CQAW039A2315 will complete the follow-up epoch. 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.

2.1.7 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 occured closer to the planned study day of the missing scheduled visit than to the planned study day of any other scheduled visit. In this case the treatment discontinuation or study discontinuation visit will be treated as the scheduled visit for the purpose of all analyses so that no missing data imputation will be necessary. Otherwise the data from any scheduled visit that did not occur will be dealt with like any other missing data. If the treatment discontinuation or study discontinuation visit is not re-mapped to any

scheduled visit, it will be treated as an unscheduled visit that does not appear in by visit summaries.

2.2 Analysis sets

Screened set (SCR): All patients who provided informed consent.

Randomized set (RAN): This set will consist of all patients who were assigned a randomization number, regardless of whether or not they actually received study medication. Patients will be analyzed according to the treatment they were assigned to at randomization.

Full analysis set (FAS): All randomized patients who received at least one dose of study drug. It was considered reasonable to limit the FAS to patients who took trial medication, 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. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.

Per-protocol set (PPS): All patients in the FAS without any major protocol deviations such as violation of major entry criteria. Patients may also be considered censored for the PPS analysis at the time of major post-baseline protocol deviations. Major protocol deviations will be defined in the data review plan prior to database lock and the un-blinding of the study. Patients will be analyzed according to the treatment they received.

Safety set (SAF): All patients who received at least one dose of study drug. Patients will be analyzed according to the treatment they received. If the patient received more than one treatment they will be analyzed as randomized.

[redacted]

The analysis of the primary objective will be performed on the FAS. The PPS may be be used for the supportive analysis of the primary and the key secondary variables. 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.

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.

If an incorrect randomization stratum is inadvertently selected for a patients 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.

2.3 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 overall population and high eosinophil subpopulation. In addition, the number of patients randomized, completed and discontinued from the treatment period will be summarized for overall population, by country . Patients discontinued from the study will also be summarized with reasons for discontinuation. In addition, patients who discontinued study treatment but stay in the study will be summarized. 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.

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.

The number of subjects with protocol deviations will be tabulated by category and deviation for the RAN.

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).

2.3.2 Background and demographic characteristics

Patient demographics and baseline characteristics including
age, sex, race, ethnicity, height, weight, body mass index (BMI), relevant medical history, including smoking history, asthma duration, background asthma therapy, use of oral corticosteroids, pre- [redacted], percent predicted FEV1, ACQ-5 score, AQLQ+12 score, blood eosinophil count, number of exacerbations in the previous year and [redacted] will be summarized by treatment group for the FAS. Categorizations of age will include the categories of <18 years, >=18- <65 years and >=65 years of age.

Screening blood eosinophil counts will also be summarized as this reflects the randomization stratum.

Continuous variables will be summarized using descriptive statistics (mean, median, standard deviation, minimum and maximum, first and third quartiles) and categorical variables will be summarized in terms of the number and percentage of subjects in each category (a missing category will be included if required).

The number and percentage of patients on ICS at screening (concomitant medication start date on or before Visit 1 and end date after Visit 1) and the number and percentage of patients in each of the low, medium, high categories of ICS use at screening will be presented. The categorization of the dose of ICS can be done based on Appendix 7 in study protocol. The number of patients on OCS at screening (concomitant medication start date on or before Visit 1 and end date after Visit 1) and the average prednisone equivalent OCS dose among patients on OCS use at screening will be summarized. The prednisone equivalent OCS doses can be calculated based on Appendix 5.3.
Background asthma therapy will be categorized into GINA steps and will be summarized at screening. Background asthma therapy is defined as concomitant medication start date on or before Visit 1 and end date after Visit 1.

Derivation of the demographics and baseline characteristics

- Baseline values are as described in “Baseline measurements” section above.
- 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.

[redacted]. At visits with two pre-dose spirometry assessments the FEV1 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 Visit 1. 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.
- QTc will be calculated, by the third party vendors, from the QT interval and RR (in seconds) using Fridericia's formula (QTcF)

2.3.3 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology 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 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 the start of the study .

Current medical conditions are defined as those which were reported as "Ongoing" at baseline.

2.4 Subgroup of interest

Subgroup analyses will be performed for primary variable and key secondary variables on the on-study data (considering multiple imputations based on a combination of missing at random and jump-to-reference approaches as described in Sections 2.6.3 and 2.7.3) and for patients with eosinophil count ≥ 250 cells/µl and for the overall study population separately.

For subgroup analyses of primary variable or key secondary variables the same model as for the main analysis will performed by subgroup 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:

- age at entry into study (<18 years, >=18 years)
- Geographic region (The definition of geographic region will be same as the definition of region at the randomization e.g. North America, Latin America, Europe, China/AMAC)

- Blood Eosinophil counts at Visit 1 (< 250 cells/µl, ≥ 250 cells/µl). This subgroup is only considered for the analysis on overall study population.
- Use or non-use of oral corticosteroids as part of their SoC asthma therapy
- Gender (male, female)
- race (Caucasian, Black, Asian, other)
- number of asthma exacerbations in year prior to screening(2, 3, 4, ≥ 5): defined as per inclusion criteria in protocol. The categories for the variable may be updated depending on the number of patients and events in each treatment group.
- [redacted]
- Baseline IgE (≤100 IU/mL, >100 IU/mL)
- baseline %predicted FEV1 (> 70%, ≤ 70%)
- baseline FEV1 (tertiles 1, tertiles 2, tertiles 3)
- Baseline FEV1 reversibility demonstrated at the clinic (yes, no)
- Background asthma therapy (ICS plus number of controller therapies defined as 1, 2, 3+)
-
- Atopic asthma status at entry into study status (yes, no)
- [redacted]

Subgroup analyses contributing key regulatory information will be provided for each country or region in line with regulatory requirements.

Patients randomized to the study in the sites in China will be considered as the Chinese patients. Separate analyses on this subset of patients will be performed and the specific outputs will be marked by suffix ‘C’ in the study TFL shells.

[redacted]
Formal multiplicity adjusted testing on the subgroups will not be performed.

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

2.5.1 Study treatment / compliance

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

2.5.1.1 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). In addition, the duration of exposure will be summarized as a categorical variable classified into <4 weeks, >=4 to <12 weeks, >=12 to <26 weeks, >=26 to <52 weeks, >=52 weeks. Cumulative exposure will be summarized as a categorical variable classified into >=4 weeks, >=12 weeks, >=26 weeks, >=52 weeks.

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

2.5.1.2 Compliance

Compliance will be calculated as the percentage of days with study medication intake as per protocol 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 / (Day of the last known dose of study drug – Day 1 +1).

Compliance will be categorized as <80%, 80% -100%and summarized by treatment arm for each of the bottles separately based on the SAF.

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.

2.5.2 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”, “post-treatment” 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 treatment. Medications can be considered both prior and concomitant. Post treatment medication will be defined as any medication with start date after the end of treatment, including medications taken in the follow-up period.

Concomitant therapies will be recorded and summarized separately for asthma related medications, non-asthma related medications, surgical and medical procedures. 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.

SABA (short acting β2-agonist) usage (number of puffs) during the screening epoch will be summarized.
The total prednisone equivalent OCS dose associated with exacerbations taken by patients over the 52 week treatment period will be summarized and compared between treatment groups. A histogram will also be presented.

2.6 Analysis of the primary objective

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

2.6.1 Primary endpoint

The primary variable for this study is the number of moderate-to-severe asthma exacerbations experienced by each patient per patient year of follow-up. The start date of a moderate-to-severe asthma exacerbation recorded in the CRF is defined as the first day of 'rescue' systemic corticosteroid use, or the date of death if no rescue corticosteroids were taken prior to an asthma related death. The end of an exacerbation is defined as the last day of systemic corticosteroid use. The duration of follow-up in years will be calculated for each patient as (last date of scheduled visit in treatment epoch - treatment start date + 1 day)/365.25.

The following definitions of exacerbations are used in this study.
A severe asthma exacerbation is defined as

- treatment with 'rescue' systemic corticosteroids for greater than or equal to 3 days and hospitalization; or
- treatment with 'rescue' systemic corticosteroids for greater than or equal to 3 days* and emergency department visit (greater than 24 hours**); or
- death due to asthma.

A moderate asthma exacerbation is defined as treatment with 'rescue' systemic corticosteroids for greater than or equal to 3 days either as an outpatient or in emergency department visits (Emergency department visit less than or equal to 24 hours).

*In order to identify treatment with 'rescue' systemic corticosteroids for greater than or equal to 3 days, at least one of the following options should be marked on the Asthma Exacerbation episodes CRF page: "Systemic corticosteroid for >=3 days","Increase maintenance systemic corticosteroid for >=3 days","Single depot injection".

**An emergency room visit greater than 24 hours is considered to be a hospitalization.

Rules for combining multiple records to one continuous exacerbation episode

The asthma exacerbations will be collapsed and deemed one continuous episode for patients with multiple records on the asthma exacerbation CRF page if the start date of the next episode is within 7 days after the end of the previous exacerbation episode.. The start/end date as reported on the CRF will be used to collapse the events using the 7-day rule described below. Exacerbations will be collapsed if symptoms of the following exacerbation begun within 7 days of the previous episodes or episodes overlap based on start and end of symptoms.

Consider the case where a patient has two asthma exacerbations. If there are three or more exacerbations they are dealt with sequentially according to these rules.

- For asthma exacerbations without missing start and end dates, if the end of one exacerbation is seven or more days before the start date of the next exacerbation then they will be treated as two separate episodes. If the end of one exacerbation is less than seven days before the beginning of the next exacerbation (or they overlap) then they will be assumed to be one continuous episode. The earliest of the start dates and the latest of the end dates will be the start and end dates of the collapsed episode.

- For asthma exacerbations with missing end dates,
    - If the one which starts earlier has a missing end date and:
        - Start date is within 7 days of the start date of the next exacerbation, then the exacerbations will be combined as one episode. In this case, the start date of the collapsed episode is taken from the first exacerbation and the end date is from the second or last exacerbation.
        - Start date is greater than 7 or more days of the start date of the next exacerbation, then the exacerbations will be considered as two separate episodes.
    - If the later event has a missing end date and it is the last asthma exacerbation, then the second event is treated as ongoing at the end of trial.

For all efficacy analyses, collapsed exacerbations will be considered while uncollapsed exacerbations will be considered for all safety summaries and listings. Separate summaries based on observed and non-imputed on-study and on-treatment data will be presented.

Severity of the collapsed episode:

The severity of the collapsed episode is defined by whether the collapsed episode fulfils the severity criteria of the records contributing to the collapsed episode.
For all exacerbation efficacy parameters (described in Section 2.6 and Section 2.8) on-treatment data are defined as data on or after the first day of treatment with double-blind study medication, but before or on the day after the last day of treatment with double-blind study medication. For all exacerbation efficacy parameters 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 after the last day of treatment period.

2.6.2 Estimand for primary endpoint

The definition and rationale for the estimand for the primary endpoint are given in Table 2-1. 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 2.6.3.

Table 2-1 Summary of estimand for the primary endpoint

Population
Inadequately controlled severe asthma patients with high eosinophil counts (eosinophil count at screening ≥250 cells/µl)
Inadequately controlled severe asthma patients

Variables
Number of moderate-to-severe asthma exacerbations experienced by each patient per patient year of follow-up at the end of the 52-week active-treatment epoch

Intercurrent event	**Description**	**Strategy to handle event**	**Justification**
Discontinuation of study treatment but continuing in study	Patients who wish to discontinue active study medication will be asked to remain in the study and complete all study visits.	All data (including after treatment discontinuation) used.	Effect regardless of adherence to study drug (Treatment policy) is quantified
Discontinuation from study due to reasons likely to be related to study treatment	Reasons: adverse event, death, physician decision, subject/guardian decision	Analyzed assuming jump-to-reference (J2R) approach. Missing data imputed by MI under MAR for placebo and J2R for QAW treatment arms	Assume similar outcomes as Placebo patient
Discontinuation from study due to reasons unlikely to be related to study treatment	Reasons: pregnancy, study terminated by sponsor, technical problems, lost to follow-up	Analyzed assuming missing at random approach Missing data imputed by MI under MAR for placebo and QAW	Assume similar outcomes as if they had continued taking assigned treatment till trial end Hypothetical on-treatment value for reason not related to treatment (Hypothetical Strategy)

Summary measures
Relative risk ratio versus placebo for each of the two QAW039 doses

2.6.3 Statistical hypothesis, model, and method of analysis

2.6.3.1 Primary null hypotheses

The trial will be considered positive, if one or more of the two QAW039 doses demonstrate a statistically significant reduction in the rate of moderate-to-severe asthma exacerbations. As described below, the two doses will be tested in parallel and each dose may achieve statistically significant results irrespective of the results achieved by the other dose.

The primary null hypotheses are:

- $H_{0\ 450\ \text{eosinophil subgroup}}$: relative risk ratio for the QAW039 450 mg QD group versus placebo in patients with eosinophil count $\geq$ 250 cells/µl = 1,
- $H_{0\ 150\ \text{eosinophil subgroup}}$: relative risk ratio for the QAW039 150 mg QD versus placebo in patients with eosinophil count $\geq$ 250 cells/µl = 1,
- $H_{0\ 450\ \text{overall}}$: relative risk ratio for the QAW039 450 mg QD versus placebo in the overall study population = 1 and
- $H_{0\ 150\ \text{overall}}$: relative risk ratio for the QAW039 150 mg QD versus placebo in the overall study population = 1.

The primary alternate hypotheses are:

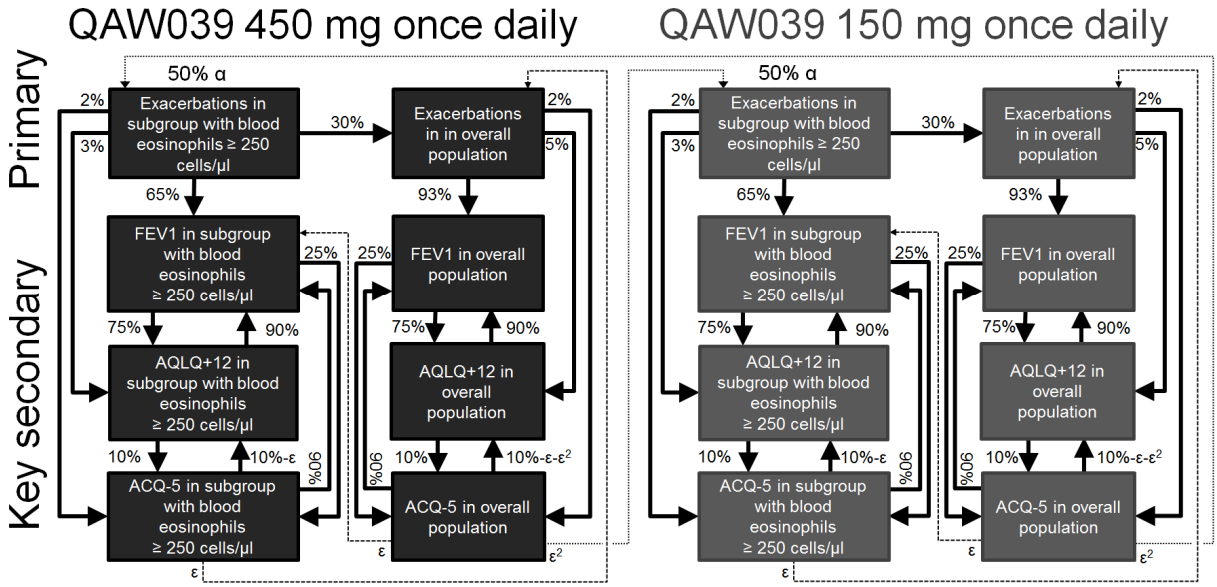
- $H_{A\ 450\ \text{eosinophil subgroup}}$: relative risk ratio for the QAW039 450 mg QD group versus placebo in patients with eosinophil count $\geq$ 250 cells/µl $\neq$ 1,
- $H_{A\ 150\ \text{eosinophil subgroup}}$: relative risk ratio for the QAW039 150 mg QD group versus placebo in patients with eosinophil count $\geq$ 250 cells/µl $\neq$ 1,
- $H_{A\ 450\ \text{overall}}$: relative risk ratio for the QAW039 450 mg QD group versus placebo in the overall study population $\neq$ 1 and
- $H_{A\ 150\ \text{overall}}$: relative risk ratio for the QAW039 150 mg QD group versus placebo in the overall study population $\neq$ 1.

The superiority of QAW039 over placebo will be considered confirmed if at least one of the four primary null hypotheses is rejected in favor of the respective two-sided alternative hypotheses and it demonstrated positive trends in favor of QAW039.

2.6.3.2 Familywise type I error rate control

The familywise type I error rate will be controlled at the two-sided 5% level across the primary and key secondary null hypotheses using the closed testing procedure specified by Figure 2-1 using the graphical method of Bretz, et al 2009. In this closed testing procedure the primary null hypothesis about exacerbations in the subset of patients with eosinophil count $\geq$ 250 cells/µl for each dose acts as a gatekeeper for the other null hypotheses for the same dose.

Figure 2-1 Closed testing procedure for primary and key secondary objectives



Vertices with associated weights denote the individual null hypotheses and their local significance levels (initially α is split 50%:50% across the primary null hypotheses regarding the subgroup with blood eosinophils ≥ 250 cells/µl for the 2 QAW039 doses). Directed edges between the vertices specify how the local significance levels are propagated in case of significant results. Dotted Dashed edges with a weight of ε indicate that the local significance level from the key secondary null hypotheses of a dose will only be propagated to the other population for the same dose, once all key secondary null hypotheses for a dose and population have been rejected. Dotted edges with a weight of ε^2 (much smaller than ε) indicate that the local significance level from the key secondary null hypotheses of a dose will only be propagated to the other dose, once all key secondary null hypotheses for a dose have been rejected.

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 QAW039 450 mg QD and QAW039 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 primary null hypothesis regarding the overall population for the same dose and the key secondary null hypotheses regarding the subgroup with blood eosinophils ≥ 250 cells/µl for that 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 key secondary null hypotheses regarding the overall population for that dose. Alpha will only be reassigned from the set of 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.

Once the primary null hypothesis for a dose and population has been rejected, all key secondary null hypothesis for that dose and population are tested and can be rejected irrespective of whether the other key secondary null hypotheses for that dose and population can be rejected. However, FEV1 will be initially given the highest local significance level due to its regulatory importance. Both adjusted and unadjusted p-values for all the endpoints, doses, populations stated in Figure 2-1 will be presented.

2.6.3.3 Summary statistics for the primary variable

The primary variable will be summarized by treatment group in terms of the mean rate (events per patient year of follow-up) overall, the distribution of patients by number of exacerbations

(i.e. the proportion of patients with 0, 1, 2, 3, 4, >=5… exacerbation episodes during the 52 week period for each treatment group) and using plots of Nelson's (1995) nonparametric estimate of the mean cumulative function on the on-study data. The plots of Nelson's nonparametric estimates will be calculated based on the independent censoring assumption. The components of the composite primary endpoint will be summarized for on-study and on-treatment data. The components include the following: severe exacerbations, exacerbations with 'rescue' systemic corticosteroids for greater than or equal to 3 days and hospitalization, treatment with 'rescue' systemic corticosteroids for greater than or equal to 3 days and emergency department visit (greater than 24 hours), death due to asthma, moderate exacerbations. Separate summaries based on observed and non-imputed on-study and on-treatment data will be presented. Based on the summary data, the difference in the rates of moderate to severe asthma exacerbations per patient year and resulting number of patients that needs to be treated for 1 year to prevent one exacerbation will also be reported with confidence intervals. The confidence interval for the difference in rates of exacerbations are presented and obtained using the normal approximation. (Liu et. al, 2006)

2.6.3.4 Statistical model for primary variable

These hypothesis tests, as well as point estimates and confidence intervals will be based on a negative binomial regression model with the natural logarithm of the duration of follow-up in years as an offset variable (Keene, et al 2007; Keene, et al 2008), treatment group, randomization strata (use or non-use of oral corticosteroids as part of SoC asthma therapy, patient age at Visit 1 [<18 years or ≥18 years], and when analyzing the overall population, peripheral blood eosinophil counts at Visit 1 [<250 cells/µl or ≥250 cells/µl] and region) as a fixed class effects, the natural logarithm of the number of asthma exacerbations in the 12 months prior to screening that required treatment per protocol and the baseline pre-dose FEV1 as a continuous linear covariate. When analyzing the subpopulation with baseline blood eosinophil counts ≥250 cells/µl, only the subpopulation data will be used for the analysis. Note that the duration of follow-up will be the planned duration of follow-up for all patients, because any missing data will be imputed as described in Section 2.6.3. The inclusion of the offset is nevertheless useful to make regression coefficients easier to interpret. Should despite the inclusion criteria a patient with no exacerbations in the 12 months prior to screening that required treatment per protocol be included in the trial, such a patient will be considered to have had 0.5 such exacerbations.

The ratios of the exacerbations for QAW039 to Placebo, the associated 95% confidence intervals and the p-values (adjusted and unadjusted) will be presented.

A negative binomial model will be used, because patient heterogeneity beyond that captured by the available patient-level covariates is expected. This can lead to over dispersed cumulative counts and zero inflation. A negative binomial model can better capture such heterogeneity than a Poisson model and can be seen as a Poisson model with the intensity distributed across patients according to a Gamma distribution (Keene, et al 2007).

Use of randomization strata in the analysis model

The variables ((use or non-use of oral corticosteroids as part of SoC asthma therapy, patient age at Visit 1 [<18 years or ≥18 years], and when analyzing the overall population, peripheral blood eosinophil counts at Visit 1 [<250 cells/µl or ≥250 cells/µl] and region) which constitute the randomization strata will be included separately in the analysis model. In case the model fails to converge then the following variables will be dropped in the following sequence: patient age at Visit 1 [<18 years or ≥18 years], region, use or non-use of oral corticosteroids as part of SoC asthma therapy and the models will be rerun till the model converges.

2.6.3.5 Handling of missing values/censoring/discontinuations

Despite all attempts to ensure complete follow-up for all patients, some patients may not be followed for asthma exacerbations for the whole planned study duration. Missing data will be imputed using a multiple imputation approach similar to the "missing at random and jump to reference" approach described by Keene et al. (2014).

The first step in implementing this approach is fitting a Bayesian hierarchical random effects Poisson model with non-informative priors to the data. This model will distinguish on- and off-treatment data for the QAW039 group and will include the same covariates as the primary model, as well as a log length of follow-up offset variable. Missing data on exacerbations in both treatment groups will then be imputed by simulation using independent pseudorandom draws from the posterior for the parameters of this model in the conditional distribution of the missing data given the observed data (including on-treatment and off-treatment data) as described by Keene et al. (2014). The imputation will use a mixture of the jump to reference and the missing at random approaches (Keene et al. 2014) and will distinguish the following three cases:

1. Missing data in QAW039 patients that discontinue treatment and are lost to follow-up due to (or following a treatment discontinuation due to) adverse event, death, physician decision and subject/guardian decision will be imputed assuming the same effect as the placebo group (Jump-to reference approch).
2. A continued treatment effect for QAW039 patients being lost to follow-up for reasons likely to be unrelated to study treatment (pregnancy, study terminated by sponsor, technical problems, lost to follow-up) will be assumed, i.e. for such patients postwithdrawal events will be imputed assuming MAR based on the event distribution of the arm patients were randomized to.
3. An unchanged event rate will be assumed for placebo patients with missing data. For the placebo patients events for time periods with missing data will be imputed assuming that missing data are missing at random

A large number of imputed datasets will be created, with their number chosen based on computational feasibility, but at least 1,000 based on the recommendation of Keene et al. (2014). Each dataset will be analyzed using the model described in Section 2.6.3 and the results will be combined on the log-scale using Rubin's rule (Barnard and Rubin 1999).

2.6.3.6 Supportive/sensitivity analyses

The primary analyses may be repeated for the PPS.

As a supportive analyses, the primary analyses will be repeated using a marginal approach (Bartlett 2018). Additionally, the differences in the rates of moderate-to-severe asthma exacerbations will be calculated based on the estimates obtained using the marginal approach.

An on-treatment analysis will also be conducted. In this analysis all moderate-to-severe asthma exacerbations will be counted, if the start date of the exacerbation is on or after the first day of treatment with double-blind study medication, but before or on the day after the last day of treatment with double-blind study medication. In this analysis a negative binomial regression model with the natural logarithm of the duration of on-treatment follow-up in years as an offset variable will be used. Two sided confidence intervals for the rate ratios will be computed based on the profile likelihood function. The duration of on-treatment follow-up in years will be calculated for each patient as (treatment end date - treatment start date + 1 day)/365.25 without taking into account treatment interruptions. Such a negative binomial model assumes that missing data after censoring either due to losses to follow-up or the end of treatment are missing at random conditional on the baseline covariates and the preceding data on events per follow-up time included in the analysis (Cook and Lawless 2007). Under this assumption the model implicitly imputes the missing data and the data censored at the end of treatment assuming a hypothetical situation of continued treatment with an unchanged on-treatment event rate for the patient (Committee for Medicinal Products for Human Use 2010). This analysis and missing data handling approach is in-line with the recently completed MENSA exacerbation trial for the monoclonal anti-interleukin-5 antibody mepolizumab in a similar population (Ortega, et al 2014). It is therefore the most appropriate analysis for a comparison of the results of the present trial to the MENSA trial.

In a tipping point analysis it will be explored by how much the rate of exacerbations post-study discontinuation would have had to increase in order to change the trial conclusions. Two dimensional tipping point analyses, allowing assumptions about the exacerbation rate post-study discontinuation on the two arms (active QAW treatment, placebo) to vary independently and including scenarios where dropouts on treatment have higher exacerbation rates than dropouts on control, will be perfomed.

As a worst reasonable case analysis a disappearing treatment effect for all patients that are lost-to-follow-up will be used (jump-to-reference). This is a sensitivity analysis for the effect of assuming a continued treatment effect for patients withdrawing from the study for reasons considered to be likely unrelated to study therapy (see Section 2.6.3.5.5)

In a further rank-based sensitivity analysis for the primary endpoint withdrawal from the trial and death will be directly treated as negative trial outcomes for patients. Patients that completed the trial will be ranked as having had a more favorable outcome than patients that withdrew from the trial, who will in turn be ranked as having had a more favorable outcome than patients that died. Within each of these categories patients will be ranked according to (number of exacerbations + 0.5)/patient years of follow-up. If patients in same category have same scores, then midranks are used. Compared to solely ranking patients according to the number of exacerbations or solely according to the duration of follow-up, this ensures that patients lost to follow-up very early in the trial without experiencing any exacerbations will not be ranked more favorably than patients that nearly completed the trial and only had 1, or 2 exacerbations, while also ensuring that a patient with 10 exacerbations that was lost to follow-up after 11

months and 1 day is not ranked as having a more favorable outcome than a patient with 0 exacerbations that was lost to follow-up after 11 months. A Wilcoxon rank-sum test stratified by randomization strata (Van Elteren test) will be used to analyze the ranked data.

The primary analyses of on-study data considering a multiple imputation framework based on a combination of missing at random and jump-to-reference approaches as described in Section 2.6.3 will also be conducted by subgroup including key demographic and disease related subgroups (See Section 2.4 for the details of subgroups). The results of the subgroup analyses will be displayed graphically in forest plots.

Summary of total prednisone equivalent OCS use (in grams) associated with moderate-to-severe on-treatment asthma exacerbations over 52 week treatment period by population will be presented.

2.7 Analysis of the key secondary objectives

2.7.1 Key secondary endpoints

The key secondary variables of this trial are the mean of the two pre-dose FEV1 assessments at the week 52 visit, AQLQ+12 and ACQ-5 at the end of the 52 week treatment period. Data from the preceding visits will be used primarily to describe the onset of action and for missing data imputation. The key secondary analyses for this study will be conducted for FAS.

2.7.1.1 Asthma Quality of Life Questionnaire for 12 years of age and older (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 2.6.3.5.

The minimal important difference (MID), defined as “the smallest difference 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).

2.7.1.2 Pre-dose FEV1

Pre-dose FEV1 is the average of two FEV1 assessments taken at approximately 45 minutes and approximately 15 minutes prior to the dosing of study drug at clinic visits.

Spirometry measurements deemed unacceptable (as defined by the masterscope) or affected by prohibited or rescue medication (as defined in the masterscope) will be censored (set to missing).

2.7.1.3 Asthma Control Questionnaire (ACQ-5)

The ACQ-5 measures asthma symptom control and consists of 5 items. Patients will be asked to recall their experiences during the past one week and to response items 1-6 (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheeze and rescue short-acting β2-agonist use) on a 7-point scale (0 – totally controlled, 6 – extremely poorly controlled). The ACQ-5 score calculated based on the 5 questions of the 5 most important symptoms. The 5 questions of the ACQ-5 are equally weighted. The ACQ-5 score is the mean of the responses to the 5 questions. The resultant score will be between 0 and 6.

The mean will be calculated as the sum of scores divided by the number of questions that were answered, as long as there were at least 4 questions answered and the missing question is not Question 1 ('On average, during the past week, how often were you woken by your asthma during the night?'). If Question 1 is missing or if there are less than 4 questions answered then the ACQ-5 score will be considered as missing and the data will be imputed using the imputation method described in Section 2.6.3.5.

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

For efficacy endpoints described in this Section and in Section 2.8 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.

For efficacy endpoints described in this Section and in Section 2.8 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.

2.7.2 Statistical hypothesis, model, and method of analysis

AQLQ+12, ACQ-5 and pre-dose FEV1 will be summarized by treatment for all visits. All the summaries will be based on observed and non-imputed on-treatment data.

The key secondary variables of AQLQ+12, ACQ-5 and pre-dose FEV1 will be analyzed using an analysis of covariance (ANCOVA) model with factors for treatment group, randomization strata, as well as the baseline AQLQ+12, baseline ACQ-5 and baseline pre-dose FEV1 as continuous linear covariates.

The null hypothesis will be tested for each dose group, each population (subgroup with peripheral blood eosinophil counts at Visit 1 ≥250 cells/µl or overall population) and each key secondary variable using this model versus the two-sided alternative hypotheses.

For each key secondary endpoint, each QAW039 dose and each population the null hypothesis is that the treatment difference compared to placebo at the week 52 visit = 0, while the alternative hypothesis is that the treatment difference to placebo at the week 52 visit ≠ 0.

2.7.3 Handling of missing values/censoring/discontinuations

Missing baseline AQLQ+12, ACQ-5 and pre-dose FEV1 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 randomised patients included in the FAS.

The FEV1 value analysed at each visit is based on the average of the two FEV1 assessments taken at 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.

Due translation errors some of the questions on ACQ-5, AQLQ+12 will be considered as missing. Questions with these errors were flagged by an external vendor and then excluded from the analysis datasets. These translation errors were due to some quality issues which were identified but did not impact patient outcomes. Such missing data are clearly missing for reasons unrelated to patient outcomes and will therefore be imputed under a missing at random assumption.

If there is intermittent missingness between two visits, then the missing values will be imputed under MAR assumption in all treatment arms.

Once these imputations are complete subsequent missing data will be imputed as follows:

1. Missing data in QAW039 patients that discontinue treatment and are lost to follow-up due to (or following a treatment discontinuation due to) adverse event, death, physician decision and subject/guardian decision will be imputed assuming the same effect as the placebo group (Jump-to reference approach).
2. A continued treatment effect for QAW039 patients being lost to follow-up for reasons likely to be unrelated to study treatment (pregnancy, study terminated by sponsor, technical problems, lost to follow-up) will be assumed, i.e. for such patients postwithdrawal events will be imputed assuming MAR based on the event distribution of the arm patients were randomized to.
3. A continued treatment effect for placebo patients being lost to follow-up for any reason i.e. for the placebo patients values for visits with missing data will be imputed assuming that missing data are missing at random

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)). These fit a Bayesian Normal repeated measures model to estimate parameters from the observed values and then use these to build possible predicted profiles for the unobserved values following withdrawal in a separate imputation model, one for each pattern of withdrawal. These profiles represent what we expect would happen to subjects after they withdraw. Missing values for an individual are then imputed based on the profile of predicted means that matches their treatment, and their

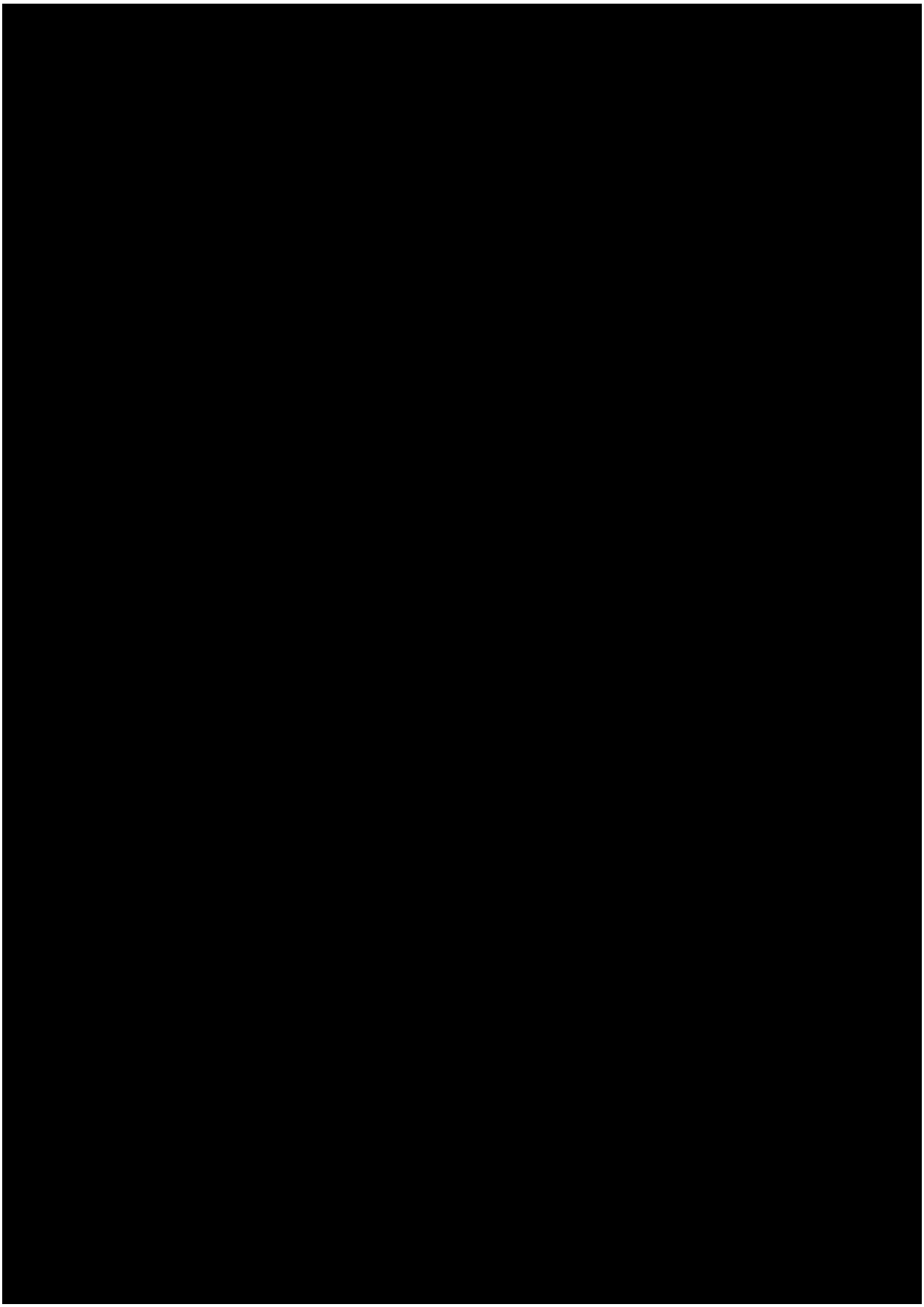
reason for, and time of, withdrawal. The complete datasets are then analysed using a univariate ANOVA at each visit with results summarized across imputations using Rubin's rules.

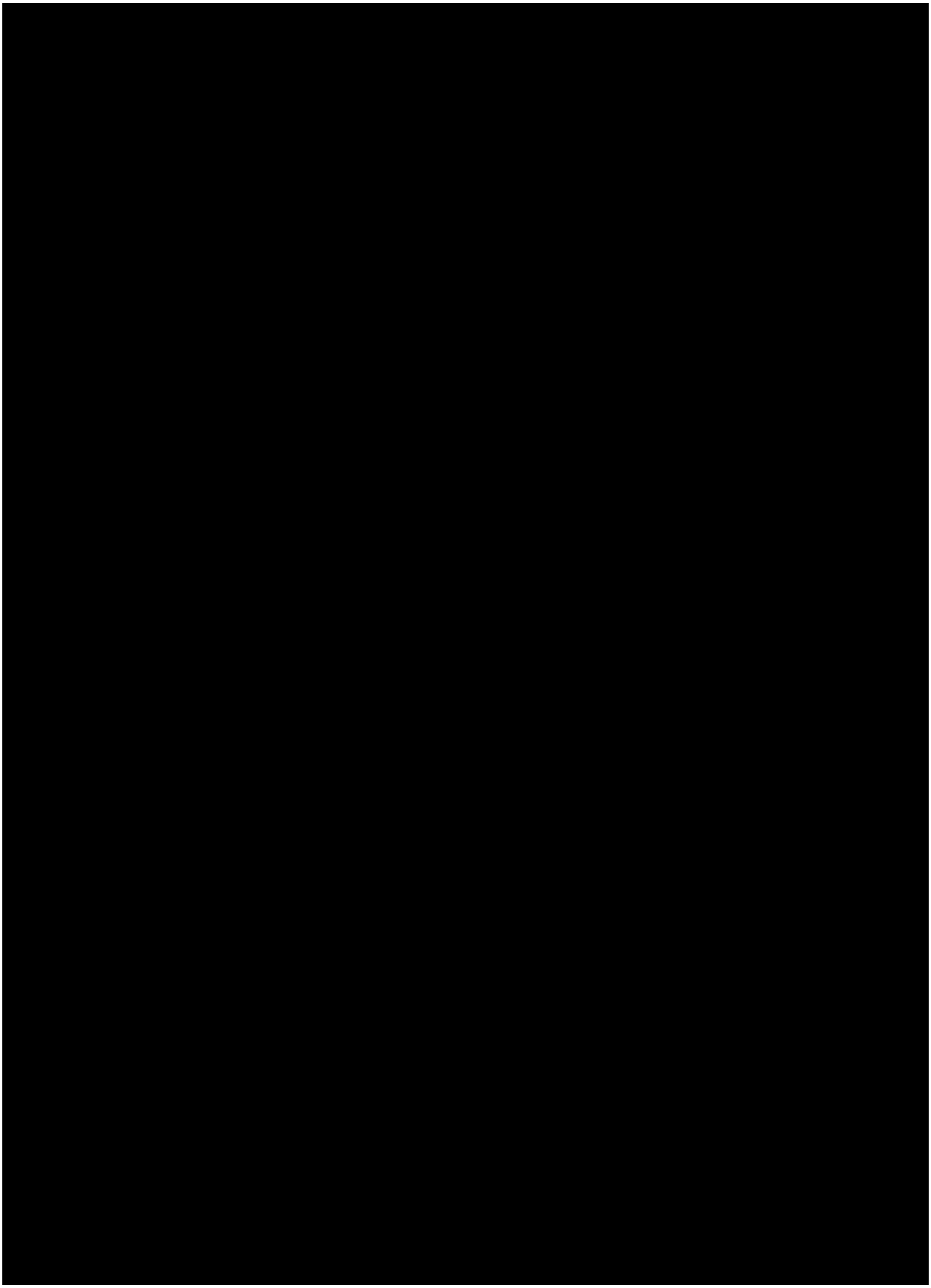
The test for the key secondary variables AQLQ+12, ACQ-5 and pre-dose FEV1 in patients with eosinophil count ≥ 250 cells/µl and for the overall population for each dose will be performed, if the primary null hypothesis has been rejected for the same dose for patients with eosinophil count ≥ 250 cells/µl and for the overall population, respectively. The local significance level for each secondary null hypothesis will be determined based on the closed testing procedure specified by Figure 2-1.

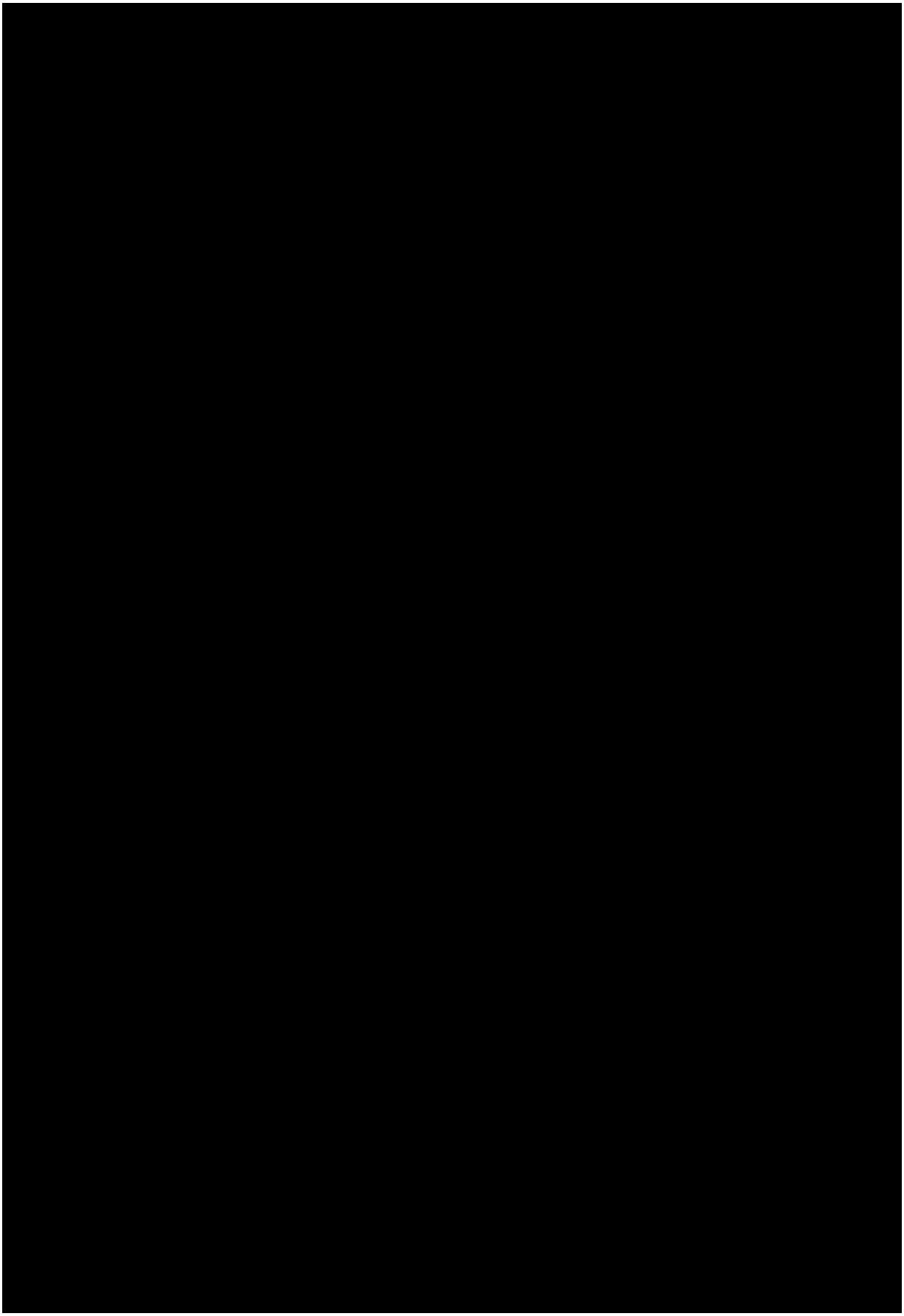
2.7.4 Supportive/sensitivity analysis for secondary endpoints

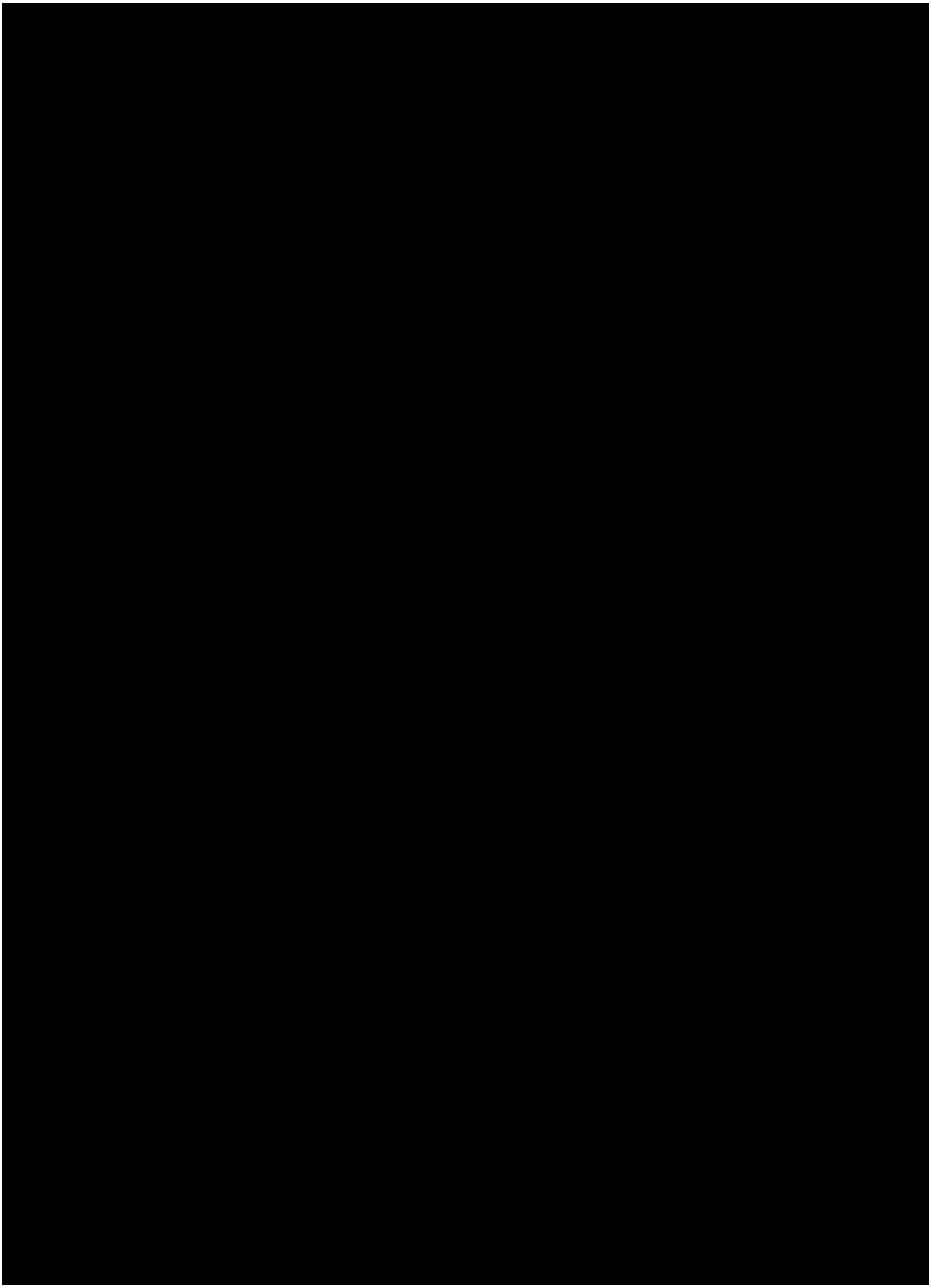
An on-treatment analysis of all visits will be conducted for the key secondary endpoints. In this analysis the measurements will be used, if the date of the measurement is on or after the first day of treatment with double-blind study medication, but before or on the day after the last day of treatment with double-blind study medication. The on-treatment analysis for the on-treatment values will use a MMRM with an unstructured covariance structure. If this model does not converge, a heterogeneous compound symmetric covariance structure will be used. These MMRMs will include treatment group, visit and randomization strata as fixed class effects, and the baseline AQLQ+12, baseline ACQ-5 and baseline pre-dose FEV1 as continuous linear covariates. Treatment group by visit interactions and baseline value (of the variable under analysis) by visit interactions will also be included in the model. Only observed on-treatment data will be used in this analysis. This model implicitly imputes unrecorded values and the data censored at the end of treatment assuming a hypothetical situation of continued treatment with an unchanged on-treatment effect.

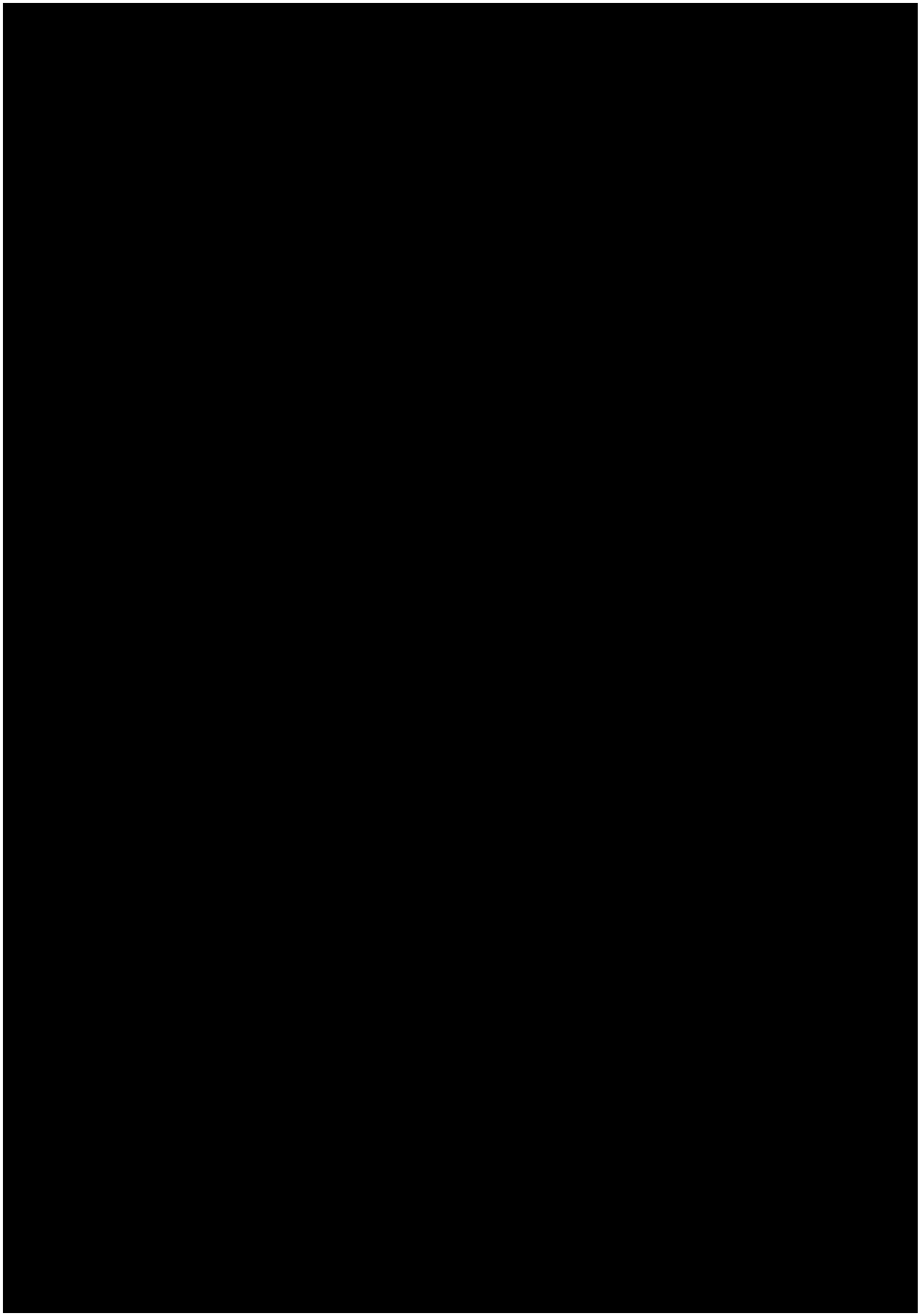
The analyses on key secondary variables on on-study data considering a considering multiple imputation framework based on a combination of missing at random and jump-to-reference approaches as described in Sections 2.7.3 will also be conducted by subgroup including key demographic and disease related subgroups (See Section 2.3 for the details of subgroups). The results of the subgroup analyses will be displayed graphically in forest plots.











2.9 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.

Unless otherwise specified, all safety summaries will be provided for patients with eosinophil count ≥ 250 cells/µl, and for the overall study population.

2.9.1 Adverse events (AEs)

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

Adverse events starting on or after the day of the first intake of study drug but not later than the last intake of study drug + 7 days will be classified as treatment emergent adverse events.

Serious adverse events starting on or after the day of the first intake of study drug but not later than the last intake of study drug + 30 days will be classified as treatment emergent serious 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 treatment-emergent adverse events (TEAEs) will be summarized by primary system organ class, preferred term, and treatment for

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

Missing AE severity will be assumed to be severe in the summary table. Relationship to study drug is coded as suspected for those adverse events where the study drug relationship is unknown.

2.9.1.1 Adverse events of special interest / grouping of AEs

Adverse events 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, SMQ (when applicable), preferred term and treatment. In addition, treatment emergent AEs of special interest that are considered serious will be summarized.

Treatment emergent and treatment related adverse events of special interest will be presented by risk category, preferred term and population. Also, treatment emergent adverse events of special interest will be presented by severity, risk category, preferred term and population.

2.9.1.2 Deaths

The number of deaths resulting from TEAEs will be summarized by SOC and PT. Death refers to treatment emergent adverse events with fatal outcome. All the deaths in the clinical database including those occurring during screening will be listed.

2.9.1.3 Adverse events reporting for safety disclosure

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than a certain threshold based on the final database and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term 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 $\leq$ 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 $\leq$ 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.

2.9.2 Laboratory data

Laboratory data consist of hematology, biochemistry and urinalysis measurements. Laboratory data measured after first intake of study drug and up to 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 on-treatment data will be included in the analyses regardless of rescue medication use. All data will be listed with abnormal values flagged.

2.9.2.1 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. The direction of interest for worst case post-baseline for selected hematology and biochemistry parameters is tabulated in Table 2-2. 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, scheduled visit and time-point, and treatment. Worst-case 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.

2.9.2.2 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 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.

2.9.2.3 Notable values

For selected laboratory parameters, abnormalities occurring at any time-point over the treatment period, considering all post-baseline on-treatment 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 clinically notable and also have a worse post-baseline value. For patients with a missing baseline value, any post-baseline notable value will be considered as newly occurring.

The criteria for clinically notable values are presented in Table 2-3.

Table 2-2 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 2-3 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	

Laboratory parameter (unit)	Bound for notably low values	Bound for notably high values
Female 12-65	0.32	
Female >=66	0.31	
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
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

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 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 which 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 2-4 for a summary of the notable values) for both populations.

Table 2-4 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 in the NCDS studies.

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 for both populations. 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 by population. The eDish plot will reflect the worst value of each of the parameters; they do not need to occur at the same visit.

2.9.3 Other safety data

2.9.3.1 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). 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, only listed. 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 will be summarized by parameter, and visit.

Clinically relevant and notable values

- The number and percentage of patients with newly occurring or worsening clinical notable QTcF values (The clinically notable ranges for QTcF are shown in Table 2-5) will be summarized at any time on treatment considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits.
- A summary table will also be produced for number and percentage of subjects with clinically relevant QT and QTcF intervals (irrespective of the timpoint) 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

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

Table 2-5 Clinical notable criteria for QTcF (Fridericia's formula)

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

Overall ECG interpretation

Using the morphologic determinations, the number and percentage of subjects with qualitative ECG abnormality will be summarized for each visit. The abnormality will be summarized by baseline condition (NO/YES) for each type of abnormality (i.e. newly occurring cases, or persistent/recurrent cases). The qualitative ECG abnormality will be determined by abnormality of Rhythm, Ectopy, Conduction, Morphology, Myocardial infarction, ST segment, T wave abnormalities, abnormal U wave. If patients does not have abnormality in any of the ECG records at baseline, then the baseline flag is considered as normal. If patients had at least once ECG abnormality at baseline, the baseline flag will be abnormal. Similarly for post baseline visits, if there is an abnormality in at least one of the records at any particular visit then ECG is considered to be abnormal at that visit. Number and percentage of patients with newly occuring or persistent/recurrent abnormalities in overall ECG interpretation at any time post-baseline will also be presented.

2.9.3.2 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 up to 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 2-6 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

- Number and percentage of patients with clinically relevant on-treatment vital signs values that occur at any time post-baseline:
    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.

for minimum and maximum post-baseline values.

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 2-6 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

2.9.3.3 Renal events

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

2.9.3.4 Liver events

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

[redacted]

[redacted]

2.12 Interim analysis

An independent Data Monitoring Committee will conduct periodic unblinded safety reviews of the accumulating data (including specific safety summaries for adolescent participants) from this trial and other Phase III trials of the QAW039 asthma development program to ensure safety of trial participants.

In addition, a single interim analysis for futility will be conducted to assess whether the study should be stopped for futility or safety, or whether treatment in one or more QAW039 dose groups should be discontinued for safety reasons. There will be no stopping for demonstrated efficacy prior to the completion of the study at either the unblinded safety reviews or the futility interim analysis, because a sufficiently large safety dataset is needed in addition to efficacy data. Therefore, no statistical adjustment will be made to the final analysis.

This interim analysis for futility will occur when approximately 200 patient-years of followup data have accumulated. The timing of the futility interim analysis may be modified based on the progress of recruitment, the logistics of arranging DMC meetings, the data accrual in other QAW039 asthma Phase III trials and additional external data that might become available.

Statistical methods for the interim analysis

Detailed statistical methods will be specified in a separate document. In general, statistical approaches will follow those outlined in this analysis plan. Patients administratively censored due to the analysis cut-off for the interim analysis will have their missing data imputed under a missing at random assumption unless they have discontinued treatment. This reflects that such patients are expected to continue treatment.

3 Sample size calculation

To be conservative a mean placebo event rate of 1.5 events per patient year of follow-up has been assumed for this study; this is a slightly lower rate than the 1.75 events per patient-year observed in the placebo group of the MENSA trial (Ortega, et al 2014) and the same event rate as assumed for the DREAM trial, although the actual DREAM placebo event rate was 2.4 events per patient year of follow-up (Pavord, et al 2012). A 40% reduction in the rate of asthma exacerbations per year in the QAW039 treatment compared to placebo has been assumed for the subgroup with high eosinophils $\geq$ 250 cells/µl for this study; this is considered to be highly clinically relevant and at the same time realistic based on the DREAM and MENSA trials conducted in similar patient populations. In the DREAM trial 75 mg mepolizumab reduced the number of asthma exacerbations per patient per year by 48%, 250mg mepolizumab by 39% and 750mg mepolizumab by 52% compared with placebo. In the MENSA trial intravenous mepolizumab reduced the number of asthma exacerbations per patient per year by 47% and subcutaneous mepolizumab by 53% compared with placebo. These relative risk reductions were taken into account, because the observed reduction in sputum eosinophils with QAW039 in Study CQAW039A2208 were similar to those observed with mepolizumab (Haldar, et al 2009; Pavord, et al 2012). On this basis it is postulated QAW039 may reduce the rate of asthma exacerbations to a similar extent as mepolizumab.

For the subgroup with eosinophils < 250 cells/µl a lesser relative risk reduction of 30% was assumed. However, it should be noted that the trial may produce a significant result with a smaller reduction in exacerbations than that assumed for power calculations and that such a reduction could still be considered clinically relevant.

As reported in online supplementary material for the MENSA publication the negative binomial dispersion parameter for the exacerbation rates was estimated to be 0.8 in the DREAM trial. In the DREAM trial approximately 15% of patients in the mepolizumab arms and 20% of patients in the placebo arm were lost to follow-up by the end of the 1-year trial, while in the 32 week MENSA trial only 6 to 8% of patients were lost across groups. Therefore, a constant exponential hazard rate over time for treatment discontinuation is assumed with 15% of patients off treatment by 1 year in the active treatment groups and the placebo group. No further treatment effect versus placebo has been assumed during the off-treatment, i.e. a mean event rate of 1.5 events per patient year has been assumed for patients after treatment discontinuation in both the QAW039 and placebo groups.

A 1:1:1 randomization was used, even though the power to demonstrate the superiority of at least one arm versus placebo would likely have been higher with an increased assignment to the placebo group, in order to not reduce the amount of efficacy and safety information for each QAW039 dose group.

Negative binomial counts were simulated based on the assumptions above and the testing procedure in Figure 2-1 was applied to each simulation result. For the purpose of evaluating the power for the primary trial objectives, it was assumed that none of the key secondary null hypotheses would be rejected.

For this study a two-sided significance level of 5% is used for testing. As shown in Table 3-1 188 patients per arm in the subpopulation with blood eosinophils ≥ 250 cells/µl and 282 patients per arm in the overall population corresponding to a total sample size of 846 patients provide greater than 80% power for demonstrating the superiority of each dose of QAW039 compared to placebo in the subpopulation with blood eosinophils ≥ 250 cells/µl and overall population under the described assumptions.

Table 3-1 Power for the primary variable

True relative risk reduction Upper row: Subpopulation Lower row: Other population		Power (%) Upper row: Subpopulation Lower row: Overall population			
450 mg (%)	150 mg (%)	450 mg	150 mg	At least one dose significant	All doses Significant
40 **30**	**40** **30**	**89%** **84%**	**89%** **84%**	**96%** **93%**	**82%** **75%**
40 20	40 20	89% 76%	89% 76%	96% 88%	82% 64%
40 0	40 0	89% 49%	89% 49%	96% 66%	82% 32%

Subpopulation means the subpopulation with blood eosinophils ≥ 250 cells/µl, while other population refers to the subpopulation with blood eosinophils < 250 cells/µl. Power results are based on 100,000 simulated trials per scenario. Only results for primary endpoints were simulated. For the purpose of evaluating the power for the primary trial objectives, it was assumed that none of the key secondary null hypotheses would be rejected. All simulations were performed in SAS 9.4.

If statistical significance is achieved in the primary test, the test for the key secondary variables pre-dose FEV1, AQLQ+12 and ACQ-5 will be performed. The local significance level for each secondary null hypothesis will be determined based on the closed testing procedure shown in Figure 2-1. For the power for each key secondary variable in the subpopulation with blood eosinophils ≥250 cells/µl and overall population, it was conservatively assumed that only the null hypothesis for the primary endpoint for the respective dose in the subpopulation and overall population would be rejected. For AQLQ+12 and ACQ5 the power was additionally calculated conditional on both the null hypothesis for the primary endpoint and pre-dose FEV1 for the respective dose in the subpopulation and overall population having been rejected. The power for each key secondary endpoint is shown in Table 3-2. However, note that the power for the key secondary endpoints will be higher once the null hypotheses relating to other key secondary variables or other doses have been rejected. For the power calculation of secondary endpoints no further treatment effect versus placebo has been assumed for patients with treatment discontinuation.

It was assumed that QAW039 achieves a difference of 150 mL against placebo in FEV1 after 52 weeks for patients that remain on treatment. A standard deviation (SD) of 380 mL was assumed for the analysis in FEV1. Given a 15% treatment discontinuation rate by week 52, the planned sample size will give 80% power for each dose in the subpopulation at the resulting local two-sided significance level of 1.625% and 90% power for each dose in the overall population at the resulting local two-sided significance level of 0.698%.

Assuming a clinically important true improvement of at least 0.5 in AQLQ+12 after 52 weeks treatment for patients that remain on treatment, a SD of 1 and 15% treatment discontinuation rate by week 52, the planned sample size per arm will provide 76% power for each dose in the subpopulation with blood eosinophils ≥ 250 cells/µl at the resulting local two sided significance level of 0.075% and 93% power for each dose in the overall population at the resulting local two-sided significance level of 0.038% after the respective primary null hypothesis has been rejected.

Assuming a difference of 0.5 against placebo in ACQ-5 after 52 weeks for patients without treatment discontinuation, a SD of 1.1, and a 15% treatment discontinuation rate by week 52, the planned sample size will give 59% power for each dose in the subpopulation at the resulting local two-sided significance level of 0.05% and 78% power for each dose in the overall population at the resulting two-sided local significance level of 0.015% after the respective primary null hypothesis has been rejected.

Table 3-2 Power of each dose for the analyses of key secondary variables

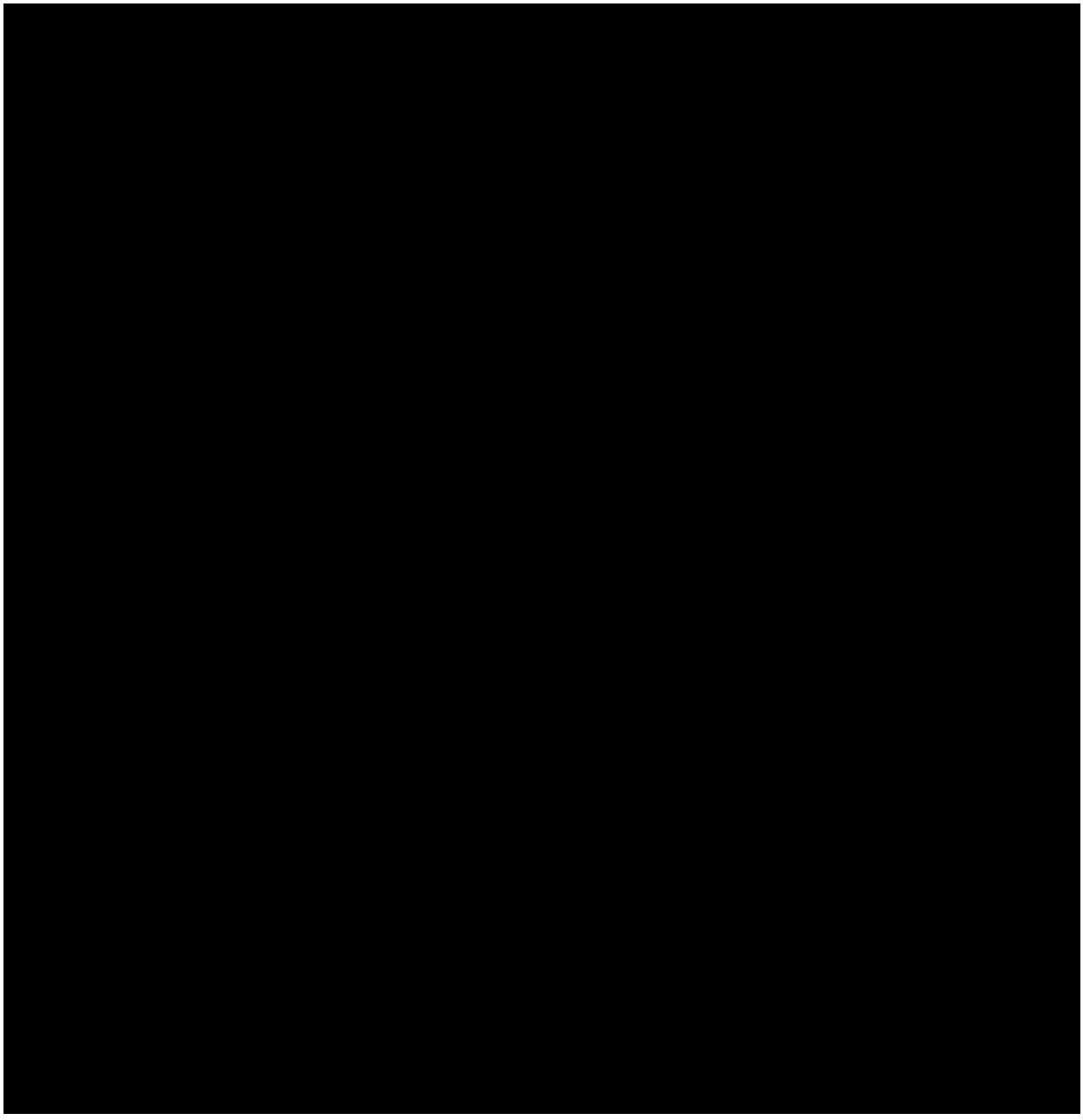
		Pre-dose FEV1	AQLQ+12	ACQ-5
Difference of effect (δ) for patients without treatment discontinuation		150 mL	0.5	0.5
SD (σ)		380 mL	1	1.1
Treatment discontinuation rate		15%	15%	15%
Subpopulation	Local two-sided significance level	1.625%	0.075%* 1.294%†	0.05%* 0.456%†
	Power	80%	76%* 95%†	59%* 81%†
Overall population	Local two-sided significance level	0.698%	0.038%* 0.561%†	0.015%* 0.189%†

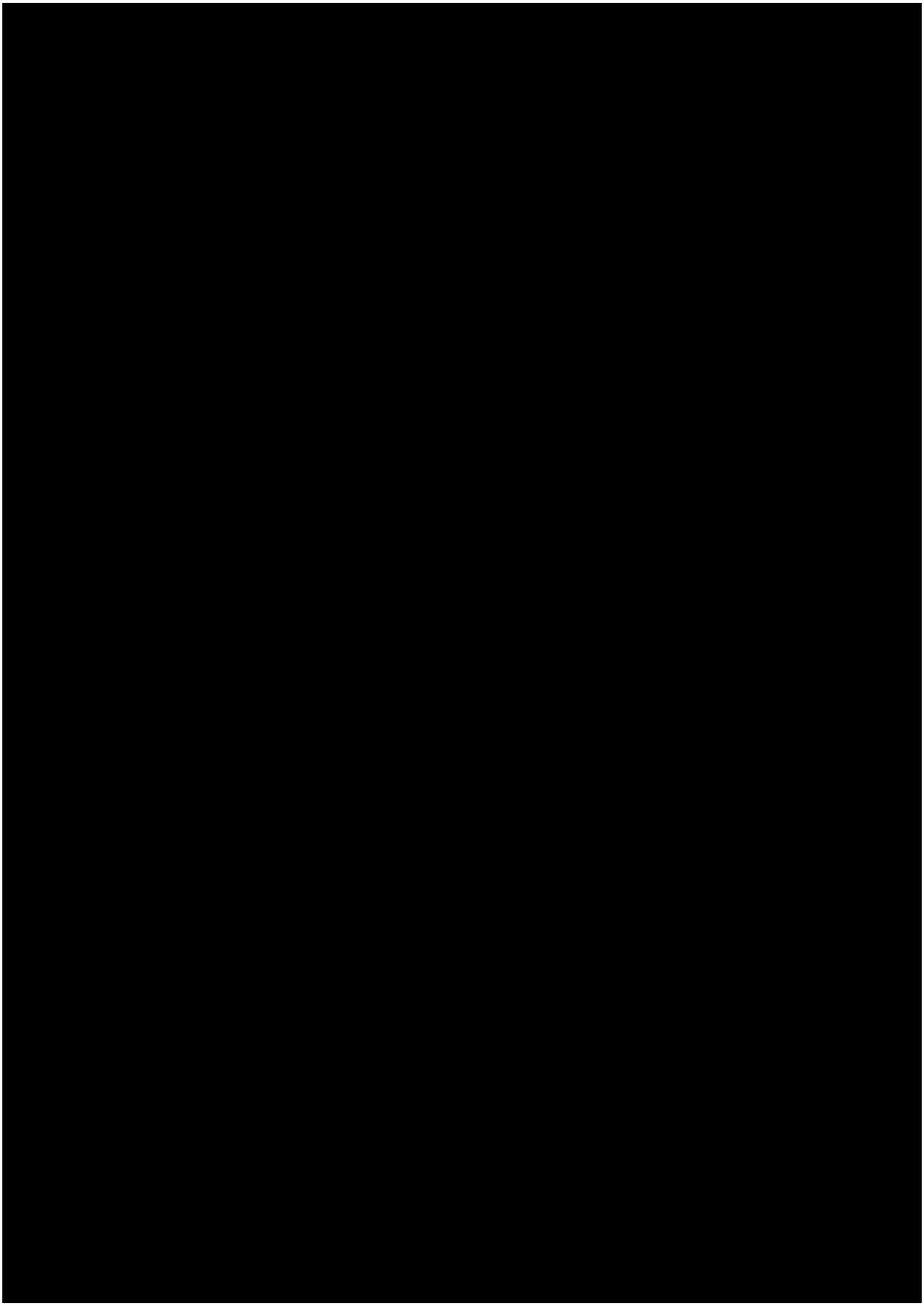
		Pre-dose FEV1	AQLQ+12	ACQ-5
	Power	90%	93%* 99%†	78%* 93%†

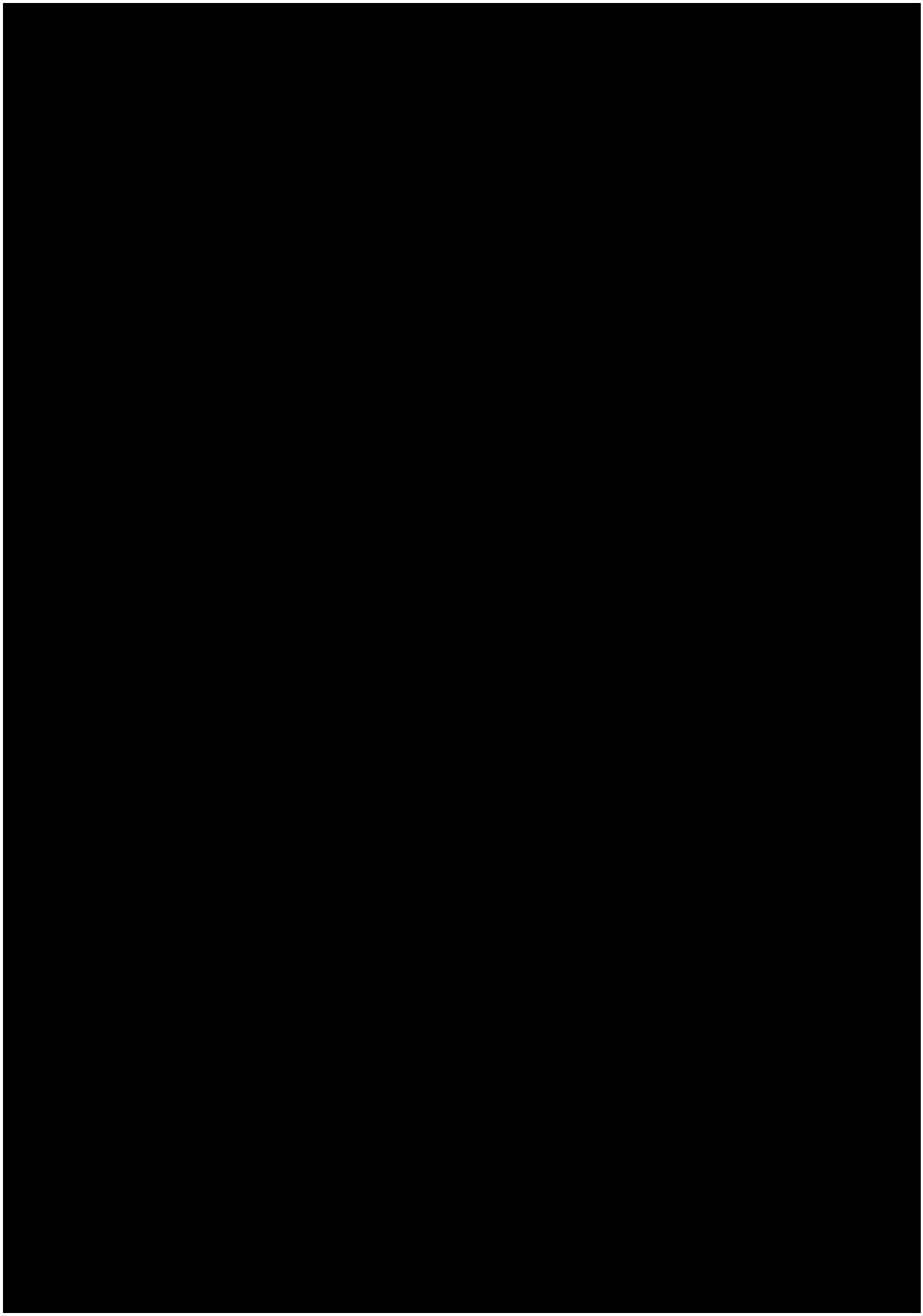
Subpopulation means the subpopulation with blood eosinophils ≥ 250 cells/µl.

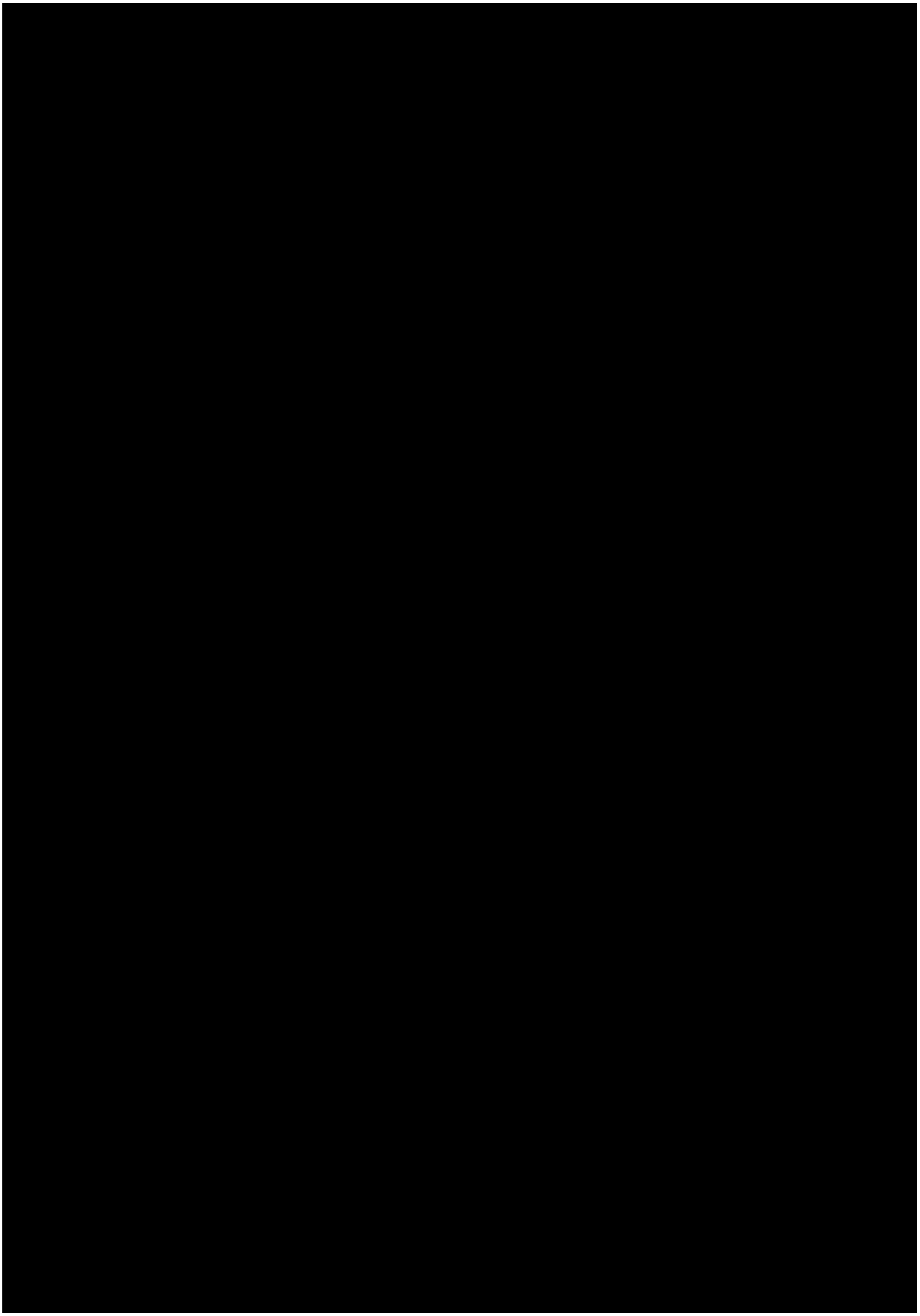
* For local two-sided significance level and power in AQLQ+12 and ACQ5 the upper row shows the value when only the null hypothesis for the primary endpoint for the respective dose in the subpopulation and overall population have been rejected.

† The lower row shows the value when both the null hypothesis for the primary endpoint and pre-dose FEV1 for the respective dose in the subpopulation and overall population have been rejected.









5.4 Safety variables

Safety summaries for patients with eosinophil count < 250 cells/µl will be summarized outside of CSR. The number and percentage of patients who reported treatment-emergent adverse events will be summarized by primary system organ class, preferred term, and treatment for all

6 Appendix

6.1 Imputation rules

6.1.1 AE date imputation

6.1.1.1 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 2.1.1.6 .

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.

6.1.1.2 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.

6.1.2 Prior and Concomitant medication date imputation

6.1.2.1 Concomitant medication end date imputation

Rules for imputing the CM end date are stated below. Date of last contact in the study has been defined as in Section 2.1.1.6. 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.

6.1.2.2 Concomitant medication start date imputation

Rules for imputing the CM start date:

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

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

The 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.

6.2 Statistical models

6.2.1 Primary analysis

6.2.1.1 Bayesian hierarchical random effects Poisson model

To perform the specified multiple imputation, a Bayesian random effects Poisson model will be fitted using Markov-Chain-Monte-Carlo (MCMC) methods. This model will be fitted to data that will have up to two records per patient:

1. a record for the time during which the patient is receiving double-blind study medication and
2. a record for any observed post-treatment follow-up during the double-blind study period after discontinuation of study treatment.

The linear predictor for the log-mean rate of the Poisson random effects model is as follows:

- intercept,
- a random subject effect on the intercept,
- treatment assigned at the time of randomization as a factor with the following levels
  - placebo or discontinued double-blind treatment,
  - QAW039 150 mg QD and
  - QAW039 450 mg QD,
- randomization strats as factors,
- natural logarithm of the number of exacerbations in the previous year that required treatment per protocol – using log(0.5) if there was no exacerbation – as a covariate,
- baseline FEV1 as a covariate, and
- the log follow-up in the time period covered by the record as an offset variable. This follow-up is either the on-treatment follow-up (during which the patient received double-blind study medication) for the first type of record for a patient, or the post-treatment follow-up during the double-blind study period for the second type of record for a patient.

If the baseline FEV1 value is missing, then mean of the non-missing baseline FEV1 values are considered. If the number of exacerbations in the previous year that required treatment per protocol is missing, then median of the non-missing values are considered.

The random subject effect on the intercept is the logarithm of a gamma distributed random variable with mean 1. The exponentiated random subject effects $\exp(U_i)|\kappa$ are independent identically distributed random variables that follow a gamma distribution with shape parameter $1/\kappa$ and rate parameter $1/\kappa$, where $\kappa>0$ is the dispersion parameter of the model. To improve the convergence of the MCMC sampler and to avoid numerical issues, we specify the random subject effect in terms of a latent random variable v_i, which satisties $u_i:=v_i \times \exp(0.5 \times \log \kappa) + \log \kappa$ subject $i=1,\ldots,n$. The log-probability density for the v_i is given by

$$f(v_1,\ldots,v_n;a) \quad - n\times(\text{lgamma}(a) + \log(a)/2) + \sum_{i=1,\ldots,n}(v_i\times\sqrt{a} - \exp(v_i/\sqrt{a})),$$

where lgamma is the log-gamma function and $a:=\exp(-\log \kappa)$.

Note that, if the model terms for a single subject did not differ between the records for a subject, this Poisson random effects model is a negative binomial model. The only difference

is that the Poisson random effects model explicitly includes random subject effects, which makes it easier to predict future time periods for the same subjects. In a negative binomial model these random effects have been integrated out, which has computational advantages.

6.2.1.2 Generating the multiple imputations

For patients, for whom some follow-up needs to be imputed, we then generate Poisson distributed random variables with a rate parameter based on the posterior of the Bayesian hierarchical model described above. The following two changes are made:

1. The offset becomes the logarithm of the follow-up time, for which data needs to be imputed for a patient.
2. The coefficient for the treatment effect will depend on the assumptions we wish to make in the imputation. In the primary analysis this differs from patient to patient depending on the reason for treatment discontinuation:
    - For a jump-to-reference imputation (J2R), we base it on the posterior for the placebo effect. In the primary analysis a J2R imputation will be used for patients that discontinue treatment and are lost to follow-up due to (or following a treatment discontinuation due to) lack of efficacy, adverse events or death.
    - For a missing-at-random (MAR) imputation, we based it on the posterior of the coefficient for the treatment group the patient is in. In the primary analysis a MAR imputation will be applied for patients being lost to follow-up for reasons likely to be unrelated to study treatment (e.g. lost to follow-up, withdrew consent).
    - For a tipping point analysis, we subtract a fixed value from the MCMC samples for the treatment group based on which we are imputing.

For each of the MCMC samples, we generate one imputation based on the sample from the posterior for the model parameters in that MCMC sample. The imputed datasets consist of these imputed number of extra events added to the observed number of events per patient. For all imputed datasets, the observed plus imputed follow-up is either the actual follow-up (for patients that completed the trial) or 1 year.

For the inferential analyses involving imputation in high eosinophil population (eosinophil count $\geq$ 250 cells/µl at screening), the imputation will be based on the subset of patients in the high eosinophil population only.

6.2.1.3 Analyzing the imputed data

The primary analysis model is fitted to each of the imputed datasets. The resulting log-mean rates and log-rate ratios – and the associated standard errors – will be combined across the imputations using Rubin's rule.

6.2.2 Key secondary analysis

The key secondary variables of this study are pre-dose FEV1, AQLQ+12 and ACQ-5 at the end of the 52 week treatment epoch. The imputation and analysis of these key 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 analysis of ACQ-5:

```
%part1A(Jobname=acqs
,Data=acqtests
,Subject=subjid
,Response=aval
,Time=visit
,Treat=trt01pn
,Covbytime= baseacq baseaqlq basefev
,Catcov=stratum
);
```

where subjid = subject identifier

aval = change from baseline in ACQ-5 value at a visit during the treatment epoch

visit = treatment period visit number

trt01pn = planned treatment

baseacq = baseline ACQ-5 value

baseaqlq = baseline AQLQ+12 value

basefev = baseline FEV1 value

stratum = randomization strata (peripheral blood eosinophil counts at Visit 1 for analyzing overall population(<250 cells/µl or ≥250 cells/µl), patient age (<18 years or ≥18 years), use or non-use of oral corticosteroids as part of SoC asthma therapy, region)

```
%part1B(Jobname=acqs
       ,Ndraws=1000
       ,thin=750
       ,seed=12345
       );


%part2A(Jobname=acqs_J2R
       ,inname=acqs
    ,methodV=Mymethod
       ,refV=Myreference
    );
```

where Mymethod = Method used to impute missing data: J2R for QAW patients who discontinued treatment for an adverse event, death, physician decision or subject/guardian decision and MAR otherwise.

Myreference = Placebo

```
%part2B(Jobname=acqs_J2R
       ,seed=832216);


%part3(Jobname=acqs_J2R
       ,ANTreat=trt01pn


       ,LsmOpt=OM
       ,label=Mixed MAR and J2R);
```

Results will be presented with Least Squares Mean (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.

6.3 Background asthma therapy

6.3.1 Prednisone equivalent OCS doses

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

6.4 Rule of exclusion criteria of analysis sets

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

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

Devation ID	Description of Deviation	Exclusion from Analyses
COMD02	Prohibited asthma related ConMed during run-in and treatment epoch	Exclude from PPS
EXCL12	Patient received high dose Inhaled Corticosteroids (ICS) prior to Visit 1 without Long-acting inhaled Beta-2 agonists (LABA) or alternate therapy.	Exclude from PPS
EXCL22	Patient receiving maintenance oral corticosteroids 3 months prior to Visit 1 and stable for 4 weeks prior to Visit 1, however without LABA (bid.) or alternate therapy	Exclude from PPS
EXCL25	Patient has a smoking history of > 10 pack years	Exclude from PPS
EXCL26	Patient had an asthma exacerbation within 6 weeks prior to Visit 1	Exclude from PPS
EXCL27	Respiratory Tract Infection or asthma worsening within 4 weeks prior to V1.	Exclude from PPS
EXCL29	Other investigational drug used within 30 days or 5 half-lives prior to Screening	Exclude from PPS
EXCL45	Prohibited Asthma Conmed taken during Run-In or treatment period.	Exclude from PPS

INCL04	Reversibility test is negative or missing or not performed as per protocol OR Hyperreactivity test is negative or missing or not performed as per protocol	Exclude from PPS
INCL05	Did not sign informed consent	Exclude from all analyses sets
INCL08	ACQ-5 score < 1.5 or missing	Exclude from PPS
INCL15	Patient did not have at least 2 asthma exacerbation(s) within 12 months prior to Visit 1 that required treatment with systemic corticosteroids or ER or hospitalization	Exclude from PPS
COMD06	Patient used prohibited asthma related ConMed during run-in and treatment epoch according to Protocol Version 2	Exclude from PPS
INCL23	Patient received medium or high dose ICS prior to Visit 1 which was not taken in combination with LABA or LAMA or LTRA or Theophylline or their combinations as required per Protocol v03.	Exclude from PPS
INCL24	Patient was not receiving medium or high dose Inhaled corticosteroids (ICS) prior to Visit 1 and throughout the study as required under protocol version 03.	Exclude from PPS

7 Reference

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