NOVARTIS

Clinical Development

QAW039/Fevipiprant

CQAW039A2315 / NCT03052517

A 2-treatment period, randomized, placebo-controlled, multicenter parallel-group study to assess the safety of QAW039 when added to existing asthma therapy in GINA steps 3, 4 and 5 patients with uncontrolled asthma

Statistical Analysis Plan (SAP)

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Aug 18, 2017	*0.2*	*Country list and background therapy definition*	*Define the subgroup of background therapy as double therapy, triple therapy and other. Update the country list.*	
Sep 2, 2018	*Amd 0.3 draft*	*Protocol amendment*	[redacted]	
		Align with A2307/A2314, A2316/A2317 SAP wherever possible	*Remove shift table analysis*	
		Only cover first IA in this document	*Specify the scope of analysis*	
Nov 30, 2018	*Amd 0.4 draft*	*Subgroup*	*Revise the subgroups of interest.*	
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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
Mar 16, 2020	Amd 3	*Removed IA related wording, subgroup analyses of safety variables, and additional cuts at Week 26 and Week 52*		

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
Bid	bis in diem/twice a day
CM	Concomitant Medication
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
IA	Interim analysis
IVR	Interactive Voice Response
IWR	Interactive Web Response
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SCS	Systemic corticosteroid
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

This document contains details of the statistical methods that will be used in the final analysis of phase III clinical trial CQAW039A2315. Data will be analyzed 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

1.1.1 Study Design

This study is a 2-treatment period, randomized, multicenter parallel-group safety study (Figure 1-1). Treatment Period 1 is a 52-week, double-blind treatment period in which QAW039 or placebo is added to Global Initiative of Asthma (GINA) steps 3, 4 and 5 standard-of-care (SoC) asthma therapy. Treatment Period 2 is an optional 104-week, single-blind treatment period in which patients will receive QAW039 or placebo added to GINA steps 3, 4 and 5 SoC asthma therapy.

Note: For the purpose of this study, single-blind means investigators and patients will remain blinded while all Novartis personnel will be unblinded.

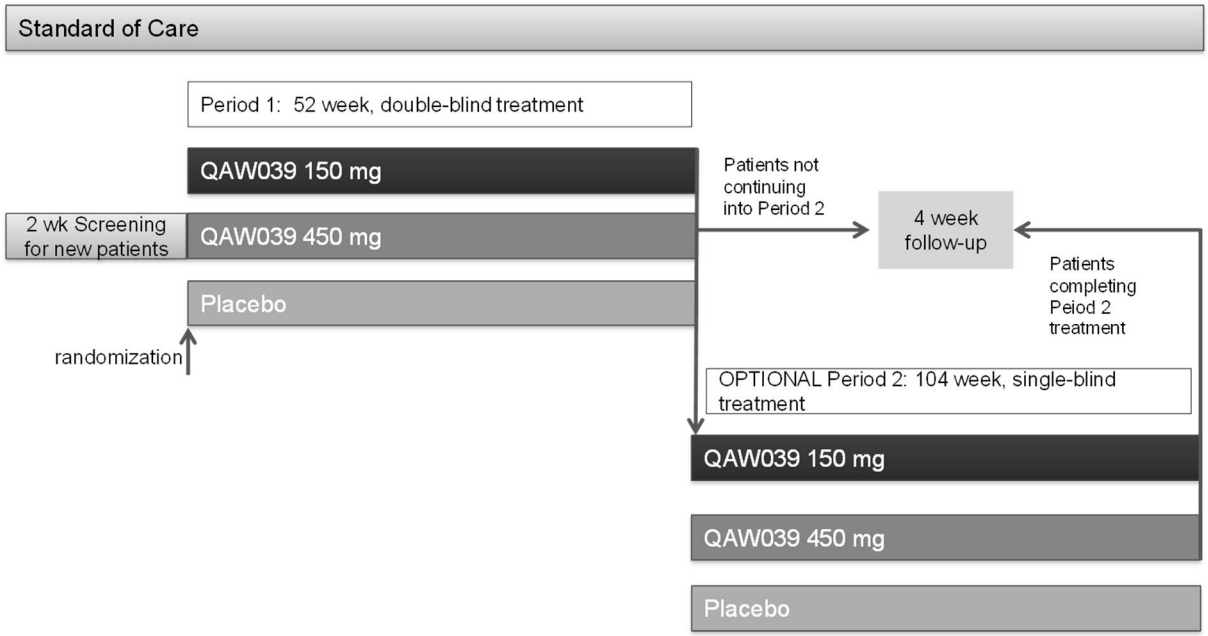
Two categories of patients will be enrolled:

- **Rollover patients:** patients completing a prior Phase 3 study (A2307, A2314, A2316, or A2317) of QAW039 on active study treatment (i.e., did not discontinue blinded study treatment prematurely); and

  New patients: patients with inadequately controlled asthma who had not previously participated in a study of QAW039.

Patients who successfully complete the treatment period of a prior Phase 3 study of QAW039 will be permitted to enter Study A2315 directly upon the completion of the treatment period of the prior study without completing an off drug follow-up period in the prior study. For these patients completing a prior Phase 3 study of QAW039, the last visit of the treatment period in the prior study and Visit 1 of Study 2315 will occur on the same day (i.e., on the last day of study drug treatment in the prior study). Additionally, for patients completing a prior Phase 3 study of QAW039, Visit 201 of Study 2315 will occur the following day (1 day after completion of the last visit of the treatment period of the prior study and Visit 1 of this study [Study A2315]) so that there is no interruption in study drug treatment.

Figure 1-1 Study design



1.1.2 Randomization scheme

Overall, there is an **approximately 85% chance patients will receive QAW039 in Study A2315.** For **patients who participated in a prior Phase 3 study**, there is **at least 57% chance a patient will remain on the same QAW039 dose** they received in the prior study in Study A2315.

Table 1-1 shows the randomized allocation of patients into treatment groups in Study A2315.

Table 1-1 Randomized Allocation of Patients into Treatment groups

Patients completing A PRIOR PHASE 3 STUDY OF QAW039: treatment allocation in Study A2315			
Prior study	Treatment group in prior study	Randomization ratio in Study A2315	Treatment group in Study A2315
CQAW039A2307 CQAW039A2314	450 mg once daily	5 1 1	QAW039 450 mg once daily QAW039 150 mg once daily Placebo
	150 mg once daily	1 5 1	QAW039 450 mg once daily QAW039 150 mg once daily Placebo
	Placebo	3 3 1	QAW039 450 mg once daily QAW039 150 mg once daily Placebo
CQAW039A2316 CQAW039A2317	150 mg once daily	2 4 1	QAW039 450 mg once daily QAW039 150 mg once daily Placebo

	Placebo	4 2 1	QAW039 450 mg once daily QAW039 150 mg once daily Placebo
Patients who HAVE NOT PREVIOUSLY PARTICIPATED IN A STUDY OF QAW039: treatment allocation in Study A2315			
Prior study	Treatment group in prior study	Randomization ratio in Study A2315	Treatment group in Study A2315
Not applicable	Not applicable	3 3 1	QAW039 450 mg once daily QAW039 150 mg once daily Placebo

Treatment randomization will be stratified at the regional level.

1.2 Study objectives and endpoints

1.2.1 Primary Objective

Treatment Period 1 (52-week treatment period):

In patients with moderate-to-severe asthma receiving SoC asthma therapy, to evaluate the long-term safety of QAW039 (150 mg once daily and 450 mg once daily), compared with placebo, as assessed by:

- treatment emergent adverse events (AEs);
- treatment emergent serious adverse events (SAEs); and
- study treatment discontinuations due to treatment emergent AEs.

Treatment Period 1 and Treatment Period 2 combined:

In patients with moderate-to-severe-asthma receiving SoC asthma therapy, to evaluate the long-term safety of QAW039 (150 mg once daily and 450 mg once daily), compared with placebo, as assessed by:

- treatment emergent AEs
- treatment emergent SAEs; and
- study treatment discontinuations due to treatment emergent AEs.

1.2.2 Secondary objective(s)

Treatment Period 1 (52-week treatment period):

In patients with moderate-to-severe asthma receiving SoC asthma therapy, to evaluate the long-term safety of QAW039 (150 mg once daily and 450 mg once daily), compared with placebo, as assessed by:

- the rate of patients with at least 1 treatment emergent AE by primary system organ class; and
- the rate of treatment emergent patient deaths and patient hospitalizations (any visit to the hospital requiring an overnight stay or an emergency room visit greater than 24 hours) due to an asthma exacerbation.

Treatment Period 1 and Treatment Period 2 combined:

In patients with moderate-to-severe-asthma receiving SoC asthma therapy, to evaluate the long-term safety of QAW039 (150 mg once daily and 450 mg once daily), compared with placebo, as assessed by:

- the rate of patients with at least 1 treatment emergent AE by primary system organ class; and
- the rate of treatment emergent patient deaths and patient hospitalizations (any visit to the hospital requiring an overnight stay or an emergency room visit greater than 24 hours) due to an asthma exacerbation.

2 Statistical methods

2.1 Data analysis general information

2.1.1 General definitions

2.1.1.1 Study treatment

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

- Name: QAW039
  - Formulation: tablet
  - Unit dose: 2 strengths: 150 mg and 450 mg
- Name: placebos to QAW039 150 mg and QAW039 450 mg
  - Formulation: tablet

- Unit dose: matching placebo to QAW039 150 mg, matching placebo to QAW039 450mg

The investigational treatment (tablets) will be supplied in bottles. The matching placebos for QAW039 will be identical in appearance to their active counterparts and will be identically packaged. No additional maintenance asthma treatment beyond investigational treatment will be provided for this trial.

Hence for this study the investigational treatment will be referred to as study treatment/drug. The date of the first administration of the investigational treatment (QAW039 or matching placebo) in Study A2315 is referred to as the date of first administration of study treatment in the study.

2.1.1.2 Study day

The first day of administration of randomized study treatment (first dose) is defined as Day 1. All other study days will be labeled relative to Day 1. 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.

2.1.1.3 Baseline definition

Baseline age will be defined as the age of the patient at study entry in Study A2315 for all patients. Baseline values of other variables are defined as follows for rollover patients and new patients, respectively.

Rollover patients: For laboratory, vital signs, and ECG variables, the last pre-treatment assessment in current study (A2315 baseline) will be used as a primary baseline value for safety monitoring purpose, and prior study baseline (i.e., the baseline value from the previous QAW039 Phase 3 study) will be used as a supplementary baseline value. For other variables, prior study baseline will be used.

New patients: the last pre-treatment assessment in the current study will be used as the baseline value.

Post-baseline measurements are defined as those assessments on or after the start of study treatment in Study A2315.

2.1.1.4 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.

2.1.1.5 Study completion and last contact

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol.

Study completion for a patient can occur after he/she has completed 52 weeks of treatment in Treatment Period 1, or after the additional 104 weeks of treatment in optional Treatment Period 2 (total of 156 weeks of treatment) or if they have prematurely withdrawn. Completion of the study will be when all randomized patients have met the definition of study completion described above and have completed the post-treatment follow-up visit.

For all patients/subjects a safety follow-up visit (visit 401) should be conducted (e.g. by telephone) 30 days after last visit (299, Week 52 for patients not continuing into Treatment Period 2 and visit 399, week 156 for patients completing Treatment Period 2).

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

2.1.1.6 Data pooling and assessment windows

If a scheduled visit did not occur, the data from the treatment discontinuation or study discontinuation visit may be used as the data from the scheduled visit, if the treatment discontinuation or study discontinuation visit occurred closer to the planned study day of the missing scheduled visit than to the planned study day of any other scheduled visit. In this case the treatment discontinuation or study discontinuation visit will be treated as the scheduled visit for the purpose of all analyses. 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.

[redacted]

2.2 Analysis sets

The screened set (SCR) will include all patients who provided informed consent.
The randomized set (RAN) will include all patients that were randomized to the study. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.

The full analysis set (FAS) will include all randomized patients who received at least one dose of study drug during this study. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.

The modified full analysis set (mFAS) will include all randomized patients in the FAS who either rolled over from Study A2307 or A2314 or were newly randomized. This analysis set consists of a more homogeneous group of patients with moderate-severe asthma.

The safety set (SAF) will include all patients who received at least one dose of study drug during this study. Patients will be analyzed according to the treatment they received during this study. If patients switch double-blind treatment during the study, they will be analyzed according to the treatment they have been randomized to.

The analysis of the primary and secondary safety variables will be performed on the SAF. The mFAS will be used for the analysis of all 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.

Protocol deviations will be defined in the data review plan document prior to database lock.

2.2.1 Subgroup of interest

Subgroup analyses will be performed for summaries of treatment emergent AE incidence rate and exposure adjusted AE incidence rate [redacted]:

[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 Chinese patients will be performed and the specific outputs will be marked by suffix 'C' in the study TFL shells. Patients randomized to the study in the sites in China, Japan, Taiwan, and Korea will be considered as Asian patients. Separate analyses on Asia region subgroup will be performed and the specific outputs will be marked by suffix 'AS' in the study TFL shells.

2.3 Patient disposition, demographics and other baseline characteristics

Patient demographics and baseline characteristics including age, sex, race, ethnicity, height, weight, body mass index (BMI), relevant medical history, smoking history, asthma duration, background therapies, pre- and post-bronchodilator FEV1, [redacted], percent predicted FEV1, [redacted], number of exacerbations in the previous year prior to screening will be summarized by treatment group for the SAF. Categorizations of age will include the categories of <18 years, >=18- <65 years and >=65 years of age. For rollover patients, summaries mentioning the number of patients who were adolescents (< 18 years age) at the start of the previous Phase 3 study but are adults (>= 18 years age) at the start of study A2315 will also be presented.

For rollover patients, relevant medical histories and adverse events that started and stopped in the prior phase 3 study will be recorded in Medical History CRF page of this study per investigator's judgement. Ongoing AEs in the prior phase 3 study will be recorded in Prior Study Adverse Event Outcome CRF page of this study and considered as medical history.

2.3.1 Patient disposition

The number of patients screened, randomized, completed and discontinued from the study (in overall treatment period, treatment period 1 and treatment period 2 separately) will be summarized on overall population and by source of patients (i.e., rollover patients from Study A2307/A2314, rollover patients from Study A2316/A2317, and new patients). In addition, a similar summary for overall population will be provided by country. Overall treatment period is defined as combined treatment period 1 and treatment period 2 (treatment period 1 only in the case of patients not continuing into treatment period 2). Patients discontinued from the study will be summarized with reasons for discontinuation. Rescreening information will also be summarized mentioning the number of patients who were rescreened and how many of them were randomized.

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

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

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

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

2.4.1 Study treatment / compliance

The duration of exposure, the number of patients randomized who completed the foreseen course of study medication and the number of patients who discontinued from the study medication will be summarized on overall population, by source of patients, by source of patients and prior treatment in a prior Phase 3 study. 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.

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 – <12 weeks, ≥ 12 – <26 weeks, ≥ 26 – <52 weeks, ≥ 52 – <104 weeks, ≥ 104 – <156 weeks, ≥ 156 weeks.

Patients in the randomized set who received any wrong study medications 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.

Study compliance will be calculated as the percentage of days with study medication intake (taking into account the duration of the drug interruptions) during the period from first intake to last intake.

Study compliance = 100 x number of days with study medication intake as per protocol/ (Day of the last treatment – Day 1 +1).

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

2.4.2 Prior, concomitant and post therapies

Medications started prior to study drug in Study A2315, taken concomitantly in Study A2315, and started following last study drug dose (if applicable) in Study A2315 will be summarized by treatment group in separate tables for the SAF. The medication will be classified into “prior”, “concomitant” based on the start/end dates.

Prior: Any medication with a start date before Day 1 in Study A2315.

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

Post: Any medication with start date after the end of treatment, including medications taken in the follow-up period. Medications can be considered both prior and concomitant.

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

Patients taking prohibited concomitant medications will be noted in the summary of protocol deviations.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

Primary endpoints for the study are:

Treatment Period 1:

- Time-to-first treatment emergent adverse events (AEs);
- Time-to-first treatment emergent serious adverse events (SAEs); and
- Time-to-first treatment emergent AE leading to discontinuation from study treatment.

of QAW039 (150 mg once daily and 450 mg once daily), compared with placebo in patients with moderate-to-severe asthma receiving SoC asthma therapy.

Treatment Period 1 and Treatment Period 2 combined:

- Time-to-first treatment emergent adverse events (AEs);
- Time-to-first treatment emergent serious adverse events (SAEs); and
- Time-to-first treatment emergent AE leading to discontinuation from study treatment.

of QAW039 (150 mg once daily and 450 mg once daily), compared with placebo in patients with moderate-to-severe asthma receiving SoC asthma therapy.

As this study has been early terminated, the primary endpoint will be analyzed in the way of combined treatment period 1 and treatment period 2. Treatment emergent AEs are defined as adverse events (including asthma exacerbations), starting on or after the day of the first intake of study drug in this study and until the earlier date out of: date of last intake of study drug +7 days (30 days in the case of a serious AE) and final visit.

Any AEs that started during the study after informed consent and before the time of the first intake of study drug will be classified as a prior AE and not classified as treatment emergent AE. The time-to-first treatment emergent AE is defined as the time to the occurrence of an AE from the treatment start date, and computed as time to AE=AE start date – treatment start date +1 day. As a general rule of censoring, patients who either completed the study or discontinued

treatment prematurely or continued treatment and without the event of interest will be censored at the minimum out of the dates of last medication intake + 30 days, final visit date, and date of death. Time-to-first treatment emergent SAEs and time-to-first treatment emergent AEs leading to discontinuation from study treatment are defined in a similar manner as time-to-first treatment emergent AE.

The definition and rationale for the estimand for the primary endpoint are given in Table 2-1. The statistical strategy to handle each intercurrent event is described in more detail in Section 2.5.3.

Table 2-1 Summary of estimand for the primary endpoint

Population	Justification
Male or female patients aged 12 years and older with moderate-to-severe asthma on standard-of-care asthma therapy and receive at least one dose of study treatment, including two categories of patients: • Rollover patients: patients completing a prior Phase 3 study (A2307, A2314, A2316, or A2317) of fevipiprant; and • New patients: patients with inadequately controlled asthma who had not previously participated in a study of fevipiprant.	Fevipiprant (QAW039) is a Prostaglandin D2 receptor 2 (DP2) antagonist expected to provide benefit in asthma by impacting major effector cells and soluble factors driving airway inflammation in asthma. Treatment with fevipiprant should result in a decrease in these parameters of airway inflammation as well as a clinical improvement in asthma.

Variables	Justification
• Time-to-first treatment emergent AEs • Time-to-first treatment emergent SAEs and • Time-to-first treatment emergent AE leading to discontinuation from study treatment.	The primary endpoints provide safety assessments with respect to the timing of first occurrence of treatment emergent AEs, SAEs, and AEs leading to study treatment discontinuation.

Intercurrent event	Description	Strategy to handle event	Justification
Discontinuation of fevipiprant for any reason without experiencing a safety outcome as defined in the primary variables	Discontinuation of fevipiprant for any reason regardless of relation to fevipiprant without experiencing a safety outcome as defined in the primary variables	A hypothetical strategy will be used assuming a continued risk for a first event after study treatment discontinuation as described in Section 2.5.3	These patients may discontinue therapy in clinical practice. Any fevipiprant treatment effect would cease almost instantly after discontinuation of fevipiprant, and only SoC effect is expected. The safety outcomes would be no more or less likely to occur after discontinuation of fevipiprant.
Discontinuation of placebo for any reason without experiencing a safety outcome as defined in the primary variables	Discontinuation of placebo for any reason without experiencing a safety outcome as defined in the primary variables	A hypothetical strategy will be used assuming a continued risk for a first event after discontinuation of placebo as described in Section 2.5.3	In clinical practice patients receive SoC without additional treatment and the approach for placebo reflects this.

Summary measures
Hazard ratios comparing QAW039 450 mg once daily, QAW039 150 mg, once daily, and placebo treatments with regard to primary variables.

2.5.2 Statistical hypothesis, model, and method of analysis

The time-to-first treatment emergent AE will be considered from the start of study treatment for Study A2315 only and the clinical study report will be based solely on the data from Study A2315.

The primary variable will be analyzed by a Cox regression model stratified by randomization stratum (but not by region):

- patients on QAW039 150 mg once daily treatment in Studies QAW039A2307, QAW039A2314,
- patients on QAW039 450 mg once daily treatment in Studies QAW039A2307 and QAW039A2314,
- patients on placebo in Studies QAW039A2307 and QAW039A2314
- patients on QAW039 150 mg once daily treatment in Studies QAW039A2316 and QAW039A2317,
- patients on placebo in Studies QAW039A2316 and QAW039A2317,
- patients who have not previously participated in a study of QAW039,

and treatment group, severity of asthma (GINA treatment steps 3, 4, and 5), and region as fixed class effects.

Hazard ratios comparing QAW039 450 mg once daily, QAW039 150 mg, once daily, and placebo treatments with regard to time to first treatment emergent AEs and their corresponding 95% profile likelihood confidence intervals (CIs) will be presented. Time to first treatment emergent SAEs and time to first treatment emergent AEs leading to study treatment discontinuation, will be analyzed in a similar fashion.

If the model does not converge, then the primary variable will be analyzed similar to the primary analysis but after removing stratification factors from the model. Hence in case of non-convergence, primary variable will be analyzed by a Cox regression model having treatment group, severity of asthma (GINA treatment steps 3, 4, and 5), and region as fixed class effects. If then also the model does not converge the variable will be analyzed after removing region as a fixed class effect in the model. If the resulting model also fails to converge then the variable will be analyzed considering only treatment group as a fixed class effect in the Cox regression model. Efron's method for handling ties will be used.

Summary statistics for the primary variable(s)

Ascending Kaplan-Meier curves will be constructed by treatment arm on overall population and by source of patients. The number of subjects with an event, number of subjects remaining at risk in the treatment group, estimate of the event rate and its estimated standard error, as estimable, will be provided for each treatment group. Median time to event and quartiles including 95% confidence intervals will be summarized as well.

2.5.3 Handling of missing values/censoring/discontinuations

The primary Cox regression model will implicitly impute the censored data under the assumption of independent censoring (conditional on the baseline covariates). That is, a censored patient is assumed to be no more or less likely to experience an event in any future

time interval than other patients in the same stratum that continue to be at risk for a first event and that have the same model covariates. The implied assumption of a continued treatment effect after treatment discontinuation is considered conservative for the purpose of the evaluation of safety outcomes that are assumed to be more likely to occur while active treatment is ongoing.

2.6 Analysis of the key secondary objective

The study does not have any key secondary objectives.

2.7 Analysis of secondary efficacy objective(s)

The secondary objectives of the study are based on safety variables and hence no efficacy variables are stated in this section.

2.8 Safety analyses

The primary and secondary objectives of the study are based on safety variables. All safety data will be summarized for the SAF.

2.8.1 Adverse events (AEs)

Adverse events after informed consent including asthma exacerbations will be recorded. 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 following treatment emergent AE summaries will be produced by system organ class (SOC), preferred term (PT), treatment on overall population, by source of patients for:

1. all AEs,
2. all AEs by maximum severity,
3. suspected drug-related AEs,
4. AEs by standardized MedDRA query (SMQ) level
5. SAEs, and
6. AEs leading to permanent discontinuation of study-drug.

The number of patients experiencing an event, as well as the exposure-adjusted incidence rate (patients with events per 100 patient year of follow-up) will be provided in above summaries. Patient year of follow-up will be computed as (sum of the duration of exposure over patients, in days)/365.25. This method will account for the length of follow-up time under the assumption that events would occur with the same frequency at any point in time.

Summaries described above will also be produced by source of patients.

Post-treatment discontinuation AEs (events that start more than 7 days (30 days in the case of a serious AE) after the last intake of study drug) will be summarized separately in terms of number and percentage of patients with at least one AE.

Secondary endpoint: the rate of patients with at least one treatment emergent AE by primary system organ class

The number and proportion of patients with at least one treatment emergent AE by primary system organ class will be presented descriptively and analyzed using a logistic regression model stratified by randomization stratum (but not by region) and treatment group, severity of asthma (GINA treatment step 3, 4, and 5), and region as fixed class effects. Estimates of the odds ratios between QAW039 groups and placebo will be displayed along with associated 95% confidence intervals. Firth's penalized likelihood will be utilized for logistic regression for rare events.

Secondary endpoint: the rate of treatment emergent severe asthma exacerbation episodes requiring hospitalizations

In safety analysis, each record of asthma exacerbation episode will be considered as an adverse event regardless of the interval between two episodes, i.e., no collapsing of multiple records (this differs from how asthma exacerbations are included in efficacy analyses – see Section 2.13.1). Number of treatment emergent severe asthma exacerbation episodes requiring hospitalizations (any visit to the hospital requiring an overnight stay or an emergency room visit greater than 24 hours) will be summarized by source of patients.

Adverse events of special interest / grouping of AEs

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

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

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

AE reporting for CT.gov and EudraCT

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

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

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

2.8.2 Deaths

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

Secondary endpoint: the rate of patient deaths due to a treatment emergent asthma exacerbation

The number and percentage of deaths due to a treatment emergent asthma exacerbation will be summarized.

2.8.3 Laboratory data

Laboratory data consist of hematology, biochemistry and urinalysis. On-treatment laboratory data will be summarized. Laboratory data measured on or after first intake of study drug and until 7 days after last intake of study drug are regarded as on-treatment data. All data will be included in the analyses regardless of rescue medication use. The following sub-sections will describe the method of summary. For rollover patients, the last pre-treatment assessment in the current study (A2315 baseline) will be used in summary tables and figures. Prior study baseline will be considered as a supplementary baseline value presented in figures as well.

2.8.3.1 Summary of absolute values

For all continuous laboratory parameters, the absolute 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 treatment. The direction of interest for worst case post-baseline for selected hematology and biochemistry parameters is tabulated in Table 2-2.

For categorical urinalysis laboratory parameters, a frequency table of results will be produced by laboratory parameter, scheduled visit, and treatment for the whole study duration.

2.8.3.2 Summary of change from baseline

For continuous laboratory parameters, the change from baseline at each scheduled visit, and the 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 treatment with standard descriptive statistics.

2.8.3.3 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 missing value in baseline, any post-baseline notable value will be considered as newly occurring.

Guidelines for clinically notable criteria for laboratory tests are based on the FDA Guidelines for adults in SI units. The criteria for clinically notable values are presented in Table 2-3.

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 listings.

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.

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. If either albumin or protein or creatinine is below the limit of quantification then the raw values would be imputed and ratios will be computed.

Additionally, box plot over time for Albumin: Creatinine ratio (ACR), Protein: Creatinine ratio (PCR) will be presented. Box plot of creatinine change from baseline values for the post-baseline visits will also be presented. 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. Mean change from baseline in creatinine will be plotted for the post-baseline visits.

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 Male 18-65 Male >=66 Female 12-65 Female >=66	 0.34 0.37 0.34 0.32 0.31	
Hemoglobin (g/L) Male 12-17	 100	

Laboratory parameter (unit)	Bound for notably low values	Bound for notably high values
Male >=18 Female	110 95	
Thrombocytes (x10E^9/L	75	700
WBC's (x10^9/L)	2.8	16.0
Chemistry		
Alkaline Phosphatase (IU/L)	-	3xULN
Total Bilirubin (µmol/L)	-	34.2
Creatinine (µmol/L)		176.8
Potassium (mmol/L)	3	6
Glucose (mmol/L)	2.78	9.99
ALT/SGPT (U/L)	-	3 x ULN
AST/SGOT (U/L)	-	3 x ULN
BUN/ Urea (mmol/L)		9.99
Sodium (mmol/L)	125	160
Gamma GT (U/L)		3 x ULN
CPK (IU/L)		4 x ULN
Urinalysis		
Dipstick blood		≥ 2+
Dipstick glucose		≥ 2+
Dipstick leukocytes		≥ 2+
Dipstick protein		≥ 2+
v = volume, ULN = upper limit of normal		

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).

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 by source of patients. 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 source of patients and treatment in prior study for rollover for rollover patients. The eDish plot will reflect the worst value of each of the parameters; they do not need to occur at the same visit.

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.

2.8.4 Other safety data

2.8.4.1 ECG data

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

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

ECG data measured on or after first intake of study drug and until 7 days after last intake of study drug are regarded as on-treatment data. All on-treatment data will be included in the analyses regardless of rescue medication use. For rollover patients, the last pre-treatment assessment in the current study (A2315 baseline) will be used in summary tables and figures. Prior study baseline will be considered as a supplementary baseline value presented in figures as well.

Summary of absolute values and change from baseline

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

Clinically relevant values

- The number and percentage of patients with newly occurring or worsening clinical relevant QTcF values (see Table 2-5) summarized by scheduled post-baseline visit and additionally at any time on treatment considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits. Table 2-5 Clinically relevant criteria for QTcF (Fridericia's formula)

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

Clinically notable values

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

- The number and percentage of subjects with noteworthy PR, QRS and HR interval changes will be reported using the below categories:
  a. New PR > 200 ms to <= 220 ms; and > 220 ms
  b. New QRS > 110 ms to <= 120 ms; and > 120 ms
  c. PR increase > 25% to a value > 200 ms
  d. QRS increase > 25% to a value > 120 ms
  e. HR decrease > 25% to a HR < 50 bpm
  f. HR increase > 25% to a HR > 100 bpm

Overall ECG interpretation

- Summary of ECG abnormalities will be produced on following variables: the number and percentage of subjects with newly occurring or persistent/recurrent on-treatment ECG abnormalities in overall ECG interpretation at any time point.
- The number and percentage of subjects with newly occurring or persistent/recurrent on-treatment ECG abnormalities by evaluation type and abnormality finding at any time point.
  If patients had at least once ECG abnormality at baseline, the baseline flag will be abnormal. Similarly for post baseline visits, if patients had at least once ECG abnormality at a visit, then ECG is abnormal at that visit else normal.

Patients with notable post-baseline ECG values will be listed. Box plots of ECG by scheduled visit and treatment for each parameter will be presented.

2.8.4.2 Vital signs

Vital signs measurements include systolic and diastolic blood pressure (SBP and DBP), pulse rate, height and body weight. Vital signs data taken on or after first intake of study drug and until 7 days after 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. For rollover patients, the last pre-treatment assessment in the current study (A2315 baseline) will be used in summary tables and figures. Prior study baseline will be considered as a supplementary baseline value presented in figures as well.
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.
- Vital signs will also be summarized by clinically relevant categories:
  1. Pulse rate: < 40 bpm, 40 – 90 bpm, and > 90 bpm
  2. Systolic blood pressure: < 90 mm Hg, 90 – 140 mm Hg, and > 140 mm Hg
  3. Diastolic blood pressure: < 50 mm Hg, 50 – 90 mm Hg, and > 90 mm Hg.

The same approach as for notable laboratory values will be used to define a newly occurring notable vital sign value and a worsening notable vital sign value.

Table 2-6 Clinical notable criteria for vital signs

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

2.8.5 Renal events

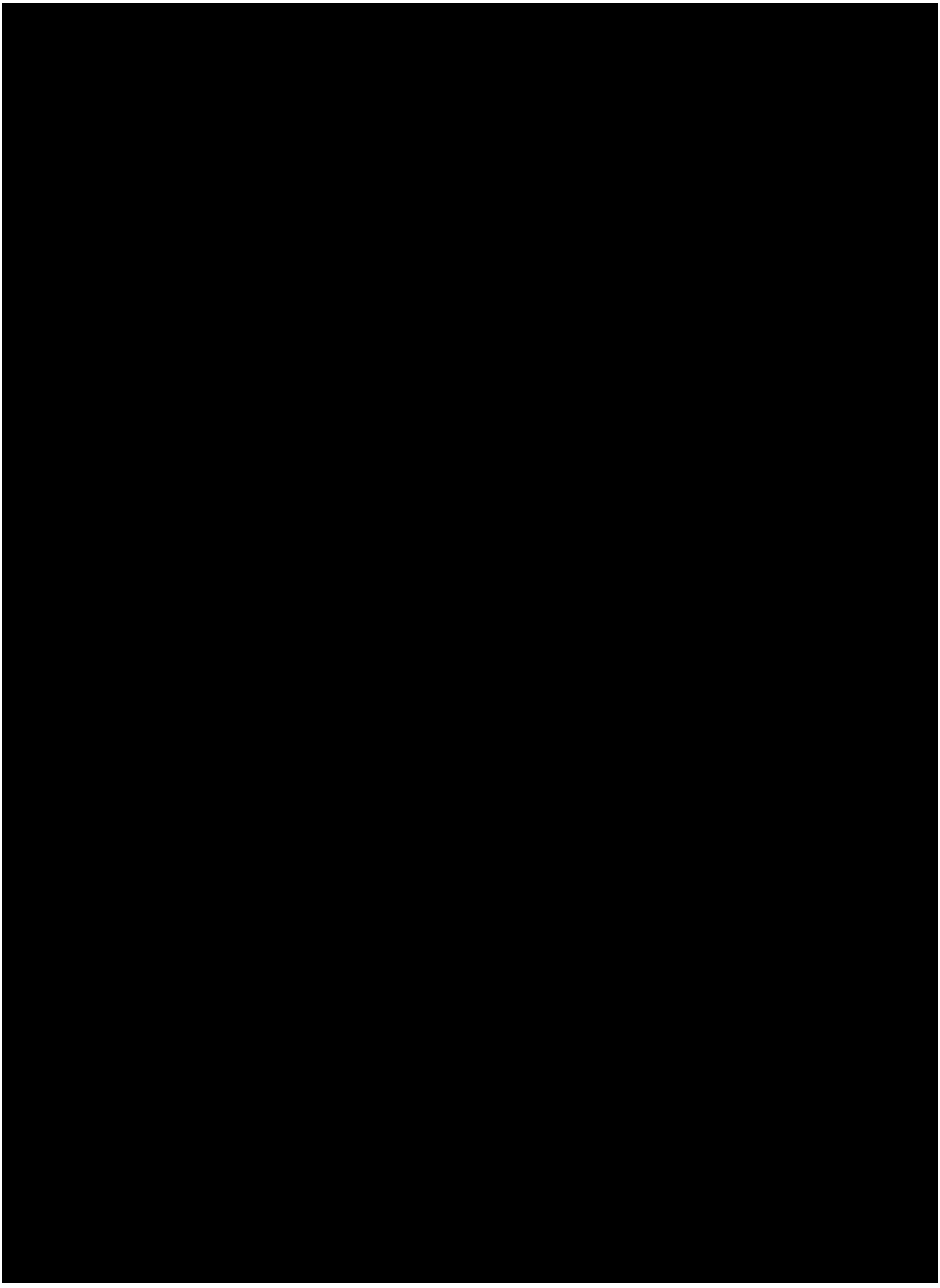
Summary of renal event overview data by treatment and source of patients will be presented.

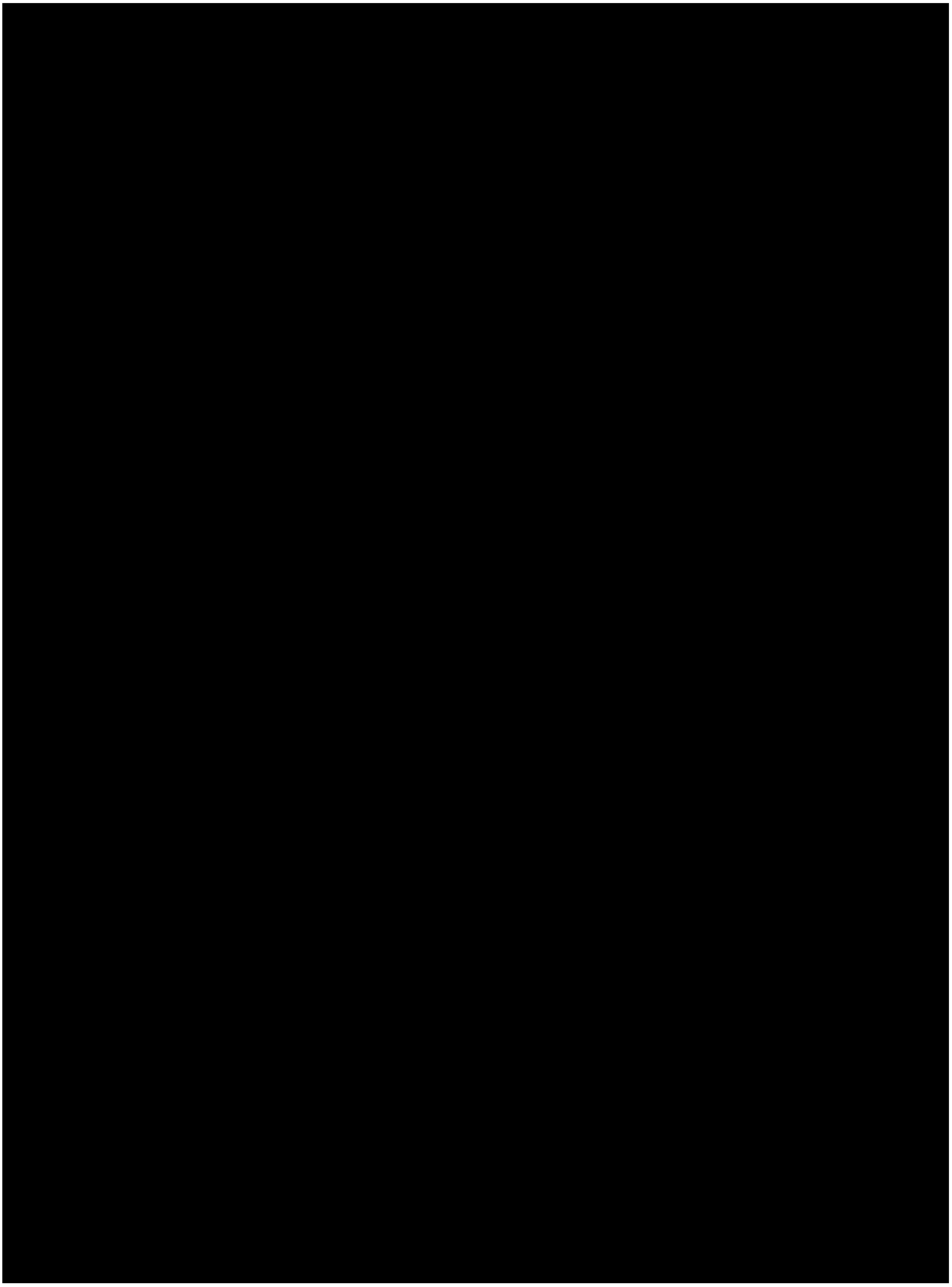
2.8.6 Liver events

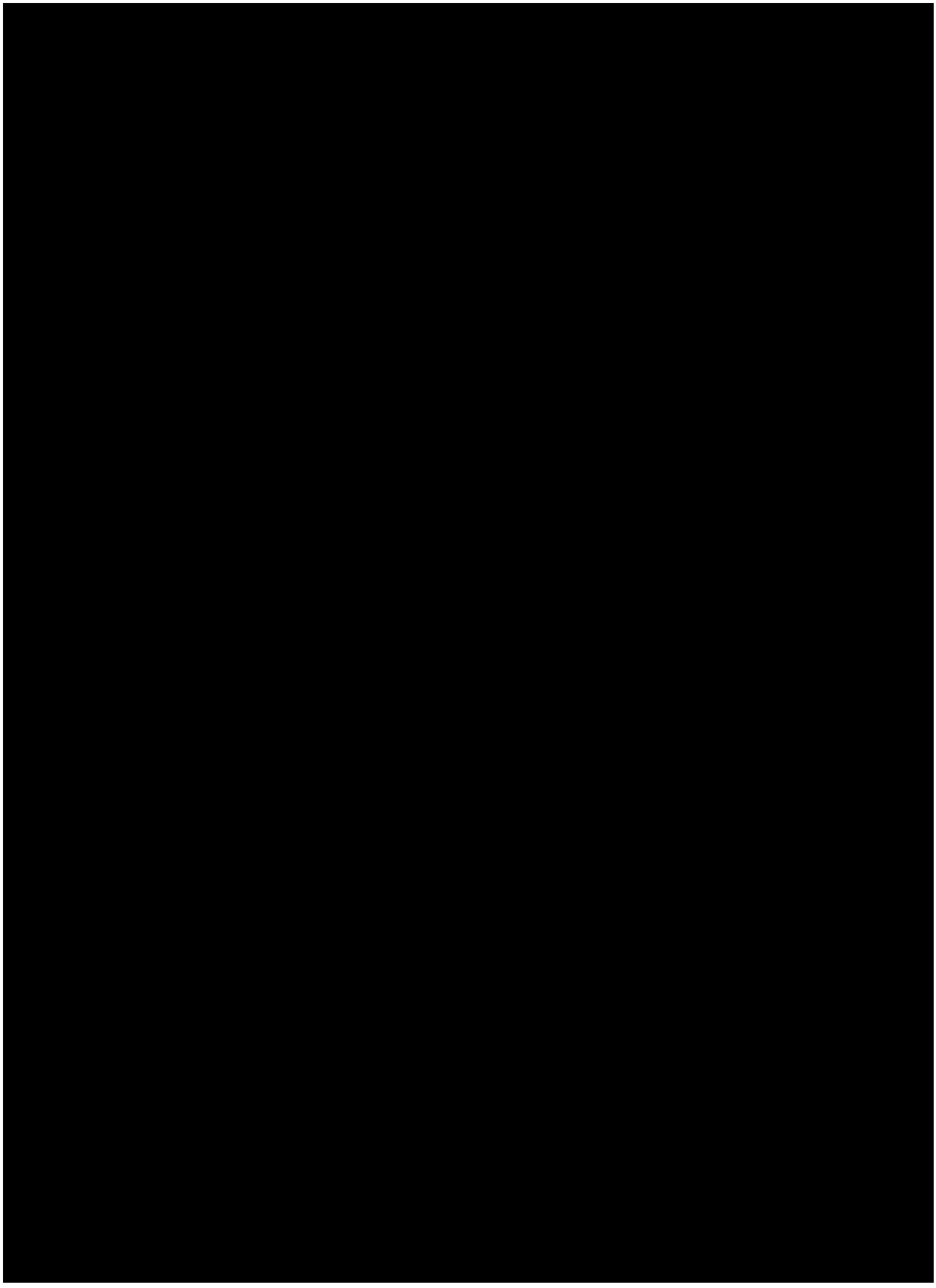
Summary of treatment emergent liver event overview data by treatment and source of patients will be presented. All liver event overview data will be listed.

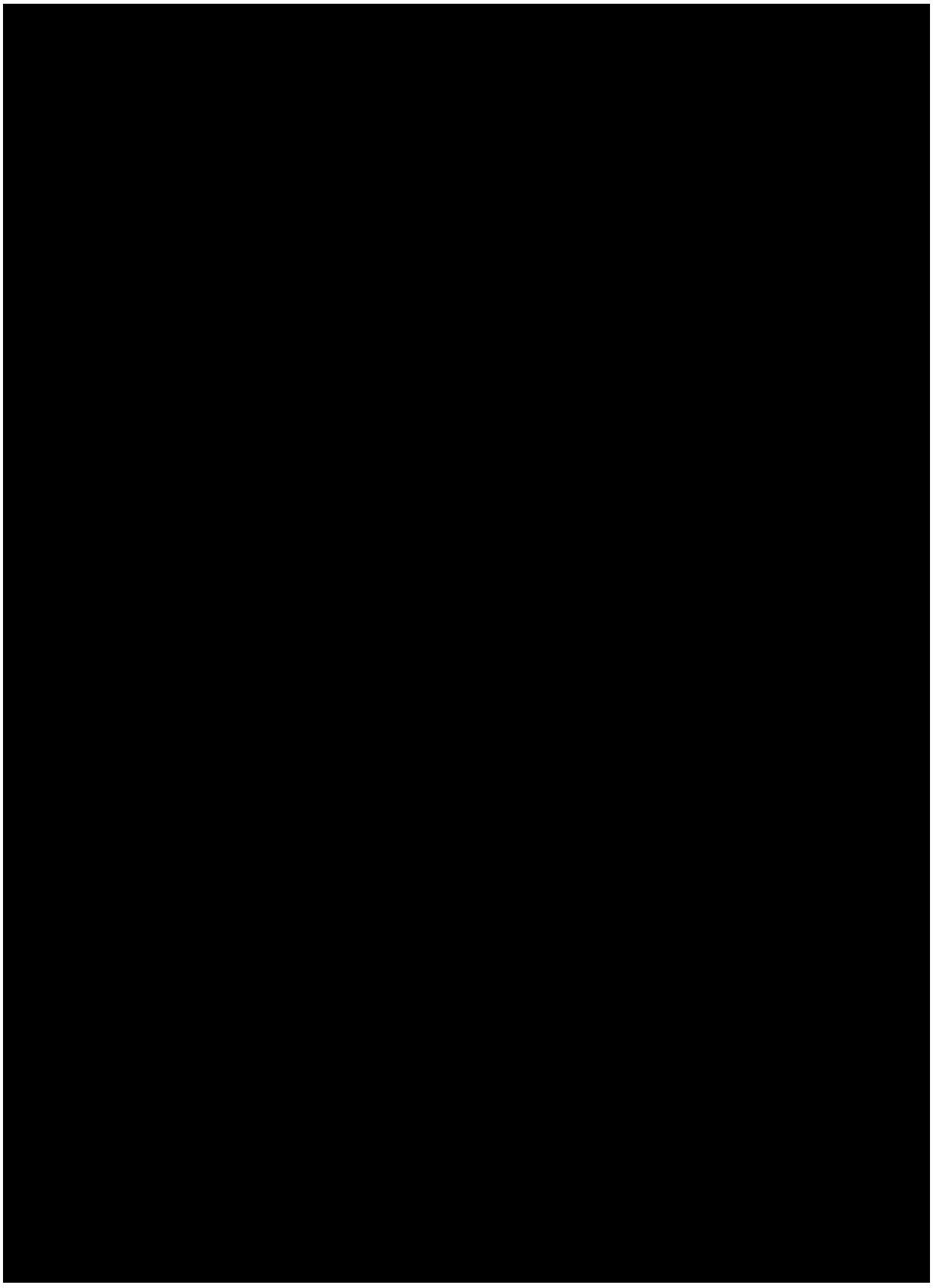
2.9 Pharmacokinetic endpoints

The study does not have any pharmacokinetic endpoints.









2.14 Other Interim analyses

An independent Data Monitoring Committee will conduct periodic unblinded safety reviews of the accumulating data from this study and other Phase 3 studies of the QAW039 asthma development program to ensure safety of study participants.

Periodic unblinded safety reviews by the DMC using data (including specific safety summaries for adolescent participants) from this study and other Phase 3 studies in the QAW039 asthma development program will be conducted. No stopping for demonstrated efficacy or safety prior to the completion of the study is foreseen, because the purpose of the study is to assess long-term safety. Thus, no statistical adjustment will be made to any of the interim analyses or the analysis after all patients have completed the study. No adjustment is foreseen to account for these different reporting times.

3 Sample size calculation

Approximately 1000 patients are expected to complete prior QAW039 Phase 3 studies and join the current Study A2315, based on the following assumptions.

- In the prior QAW039 Phase 3 studies, 85% of randomized patients are expected to complete the prior study and eligible for participation in the current study.
- It is estimated that 50% of those eligible patients from Studies A2307 and A2314 will enter in the current study.
- It is estimated that 25% of those eligible patients from Studies A2316 and A2317 will enter in the current study.

New patients (i.e., patients who have not previously participated in a study of QAW039) will also be recruited according to local regulatory requirements in certain countries. It is currently anticipated that approximately 570 newly recruited patients will be enrolled in the current study. Thus, the anticipated total sample size of this study is approximately 1,570 patients. This number of patients participating in the safety study will ensure 6-month exposure for each QAW039 dose clearly across the whole Phase 3 program in excess of the 300 to 600 patients (as well as in excess of 100 patients exposed for at least 1 year) suggested by ICH E1 at the time of the first regulatory submission for QAW039. The number of new patients and total patients may be subject to change depending on the actual participation of patients from prior QAW039 Phase 3 studies, the actual dropout rate in the current study and the local regulatory requirements.

While no formal hypothesis testing is foreseen for the primary safety objectives, if both QAW039 doses have a 50% relative hazard increase for treatment emergent events, compared with placebo, then there will be approximately > 99%, 94% and 38% power that the two-sided 95% confidence interval not adjusted for multiplicity for one of the two QAW039 doses would exclude no effect for the primary safety variables of time-to-first treatment emergent AE, time-to-first treatment emergent SAE, and time-to-first treatment emergent AE leading to study treatment discontinuation analyzed across Treatment Period 1 and Treatment 2 combined, respectively. The power was estimated using 10,000 simulations based on 1,570 patients being randomized into the current study. In addition, the sensitivity of the power is further assessed for different scenarios of sample size (1470 patients and 1670 patients).This power will be higher, if more patients are randomized (e.g., due to additional new patients being enrolled) or more patients completing prior Phase 3 studies of QAW039 elect to participate in the current study.

The underlying assumptions for the power simulations were an exponential censoring rate in the placebo group of 0.22 and of 0.16 in the QAW039 treatment groups. The assumptions on the exponential event rate in each treatment group are shown in Table 3-1. These assumptions are based on the, DREAM (Pavord et al. 2012) and MENSA (Ortega et al. 2014) trials, as well as a QAW039 Phase 2 study in moderate-to-severe asthma. The detailed power calculations are shown in the Table 3-2 and Table 3-3.

Table 3-1 Assumed placebo event rates for power calculations

Endpoint	Previous study patients were enrolled in or new patients	Assumed exponential event rate (per patient-year)
Rate of AEs	QAW039A2316/ QAW039A2317	3.01

	QAW039A2307/ QAW039A2314	2.86
	New patients	2.86
Rate of SAEs	QAW039A2316/ QAW039A2317	0.07
	QAW039A2307/ QAW039A2314	0.24
	New patients	0.24
Rate of AEs leading to study treatment discontinuation	QAW039A2316/ QAW039A2317	0.03
	QAW039A2307/ QAW039A2314	0.03
	New patients	0.03

Table 3-2 Power (%) for a non-multiplicity adjusted confidence interval to exclude no-difference versus placebo for the primary safety variables

Primary Endpoint	Treatment Period	QAW039 150 mg versus placebo	QAW39 450 mg versus placebo	Both QAW039 150 mg and 450 mg versus placebo	One of the two QAW039 doses versus placebo
Time-to-first AE	1	>99	>99	>99	>99
	1 & 2	>99	>99	>99	>99
Time-to-first SAE	1	65	65	54	76
	1 & 2	89	89	84	94
Time-to-first AE leading to study treatment discontinuation	1	16	16	9	22
	1 & 2	29	28	19	38

Power results are based on the sample size of 1570 randomized patients (1000 rollover patients plus 570 new patients).
Simulations were performed in SAS 9.4.

Table 3-3 power (%) for a non-multiplicity adjusted confidence interval to exclude no-difference versus placebo for the primary safety variables based on different sample size scenarios

Primary Endpoint	Treatment Period	QAW039 150 mg versus placebo	QAW39 450 mg versus placebo	Both QAW039 150 mg and 450 mg versus placebo	One of the two QAW039 doses versus placebo
Time-to-first AE	1	>99 >99	>99 >99	>99 >99	>99 >99
	1 & 2	>99 >99	>99 >99	>99 >99	>99 >99
Time-to-first SAE	1	62 68	62 68	50 57	73 79
	1 & 2	87 92	87 91	81 87	93 96
Time-to-first AE leading to study treatment discontinuation	1	14 17	14 16	8 10	21 23
	1 & 2	27 30	27 30	17 20	36 40

Power results in the upper rows are based on the sample size of 1470 randomized patients (1000 rollover patients plus 470 new patients).
Power results in the lower rows are based on the sample size of 1670 randomized patients (1000 rollover patients plus 670 new patients).
Simulations were performed in SAS 9.4.

4 Change to protocol specified analyses

- In protocol, the secondary endpoints are stated in one sentence, i.e., the rate of treatment emergent patient deaths and patient hospitalizations (any visit to the hospital requiring an overnight stay or an emergency room visit greater than 24 hours) due to an asthma exacerbation. In the analysis plan, the endpoints are presented separately:
  - The rate of patient deaths due to a treatment emergent asthma exacerbation
  - The rate of treatment emergent severe asthma exacerbation episodes requiring hospitalizations
- In protocol, it is mentioned that the treatment emergent adverse events and prior adverse events are defined based on the time of the adverse event and intake of study drug. However since the time of start and end of adverse events are not captured for this study, the definition has been updated considering only the day of the adverse event and intake of study drug.
- The supportive analyses specified in protocol Section 9.4.4 will be performed for exposure incidence rate summaries rather than the primary outcome.

- Non-treatment emergent adverse events (AEs) in post-treatment follow-up period will be summarized separately.
- AEs of special interest are only presented descriptively. Time-to-first-event analyses using Kaplan-Meier plots and Cox regressions as well as incidence for recurrent events per patient year will not be not presented.
- The secondary endpoint of the rate of patients with at least one treatment emergent AE by primary system organ class will be analyzed using a logistic regression model instead of a Cox regression model.
- Shift tables relative to the normal reference ranges to summarize the on-treatment change from baseline to post-baseline for each laboratory parameter or ECG parameter or vital sign assessments will not be presented.
- [redacted]
- In protocol, treatment emergent adverse events (TEAEs) were defined as AEs starting on or after the time of the first intake of study drug and until the day after the last intake of study drug. This definition was updated in analysis based on clinical and safety consideration as follows: adverse events (including asthma exacerbations), starting on or after the day of the first intake of study drug in this study and until the dates of last intake of study drug +7 days (30 days in the case of a serious AE) .
- [redacted]
- [redacted]
- Subgroup analyses on primary outcomes are removed.

[redacted]

6 Appendix

6.1 Imputation rules

6.1.1 Study drug

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

6.1.2 AE date imputation

6.1.2.1 AE end date imputation

Rules for imputing AE end dates are stated below. Date of last contact in the study is defined 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.

6.1.2.2 AE start date imputation

Rules for imputing the AE start date:

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

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

The following matrix explains the logic behind the imputation.

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

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

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

Impute AE start date -

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

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

5. 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. Prior and Concomitant medication date imputation

6.1.2.3 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.

6.1.2.4 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.

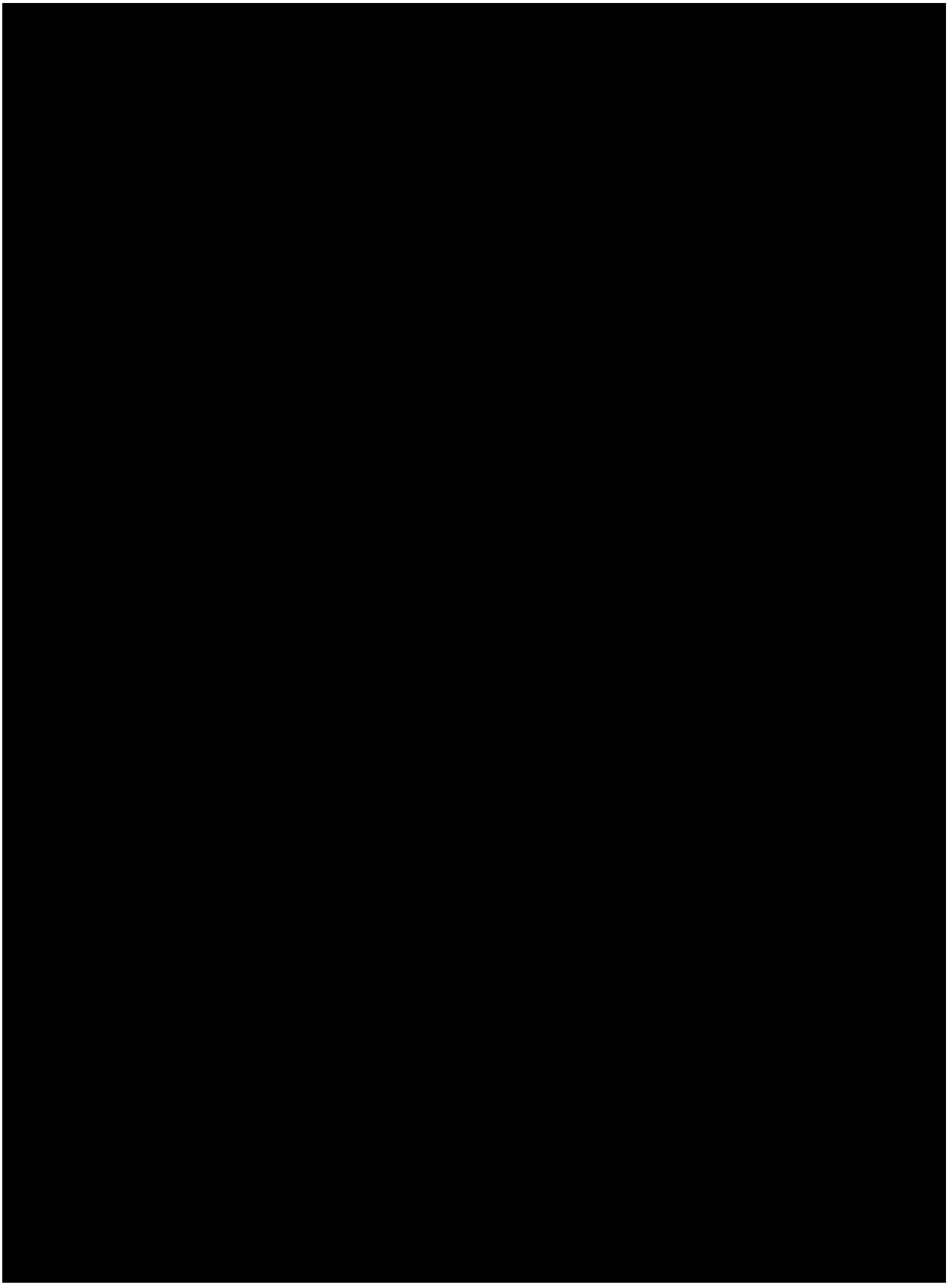
	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	**(1)** Uncertain	**(1)** Uncertain	**(1)** Uncertain	**(1)** Uncertain
YYYY < TRTY	**(2.a)** Before Treatment Start	**(2.b)** Before Treatment Start	**(2.b)** Before Treatment Start	**(2.b)** Before Treatment Start
YYYY = TRTY	**(4.a)** Uncertain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

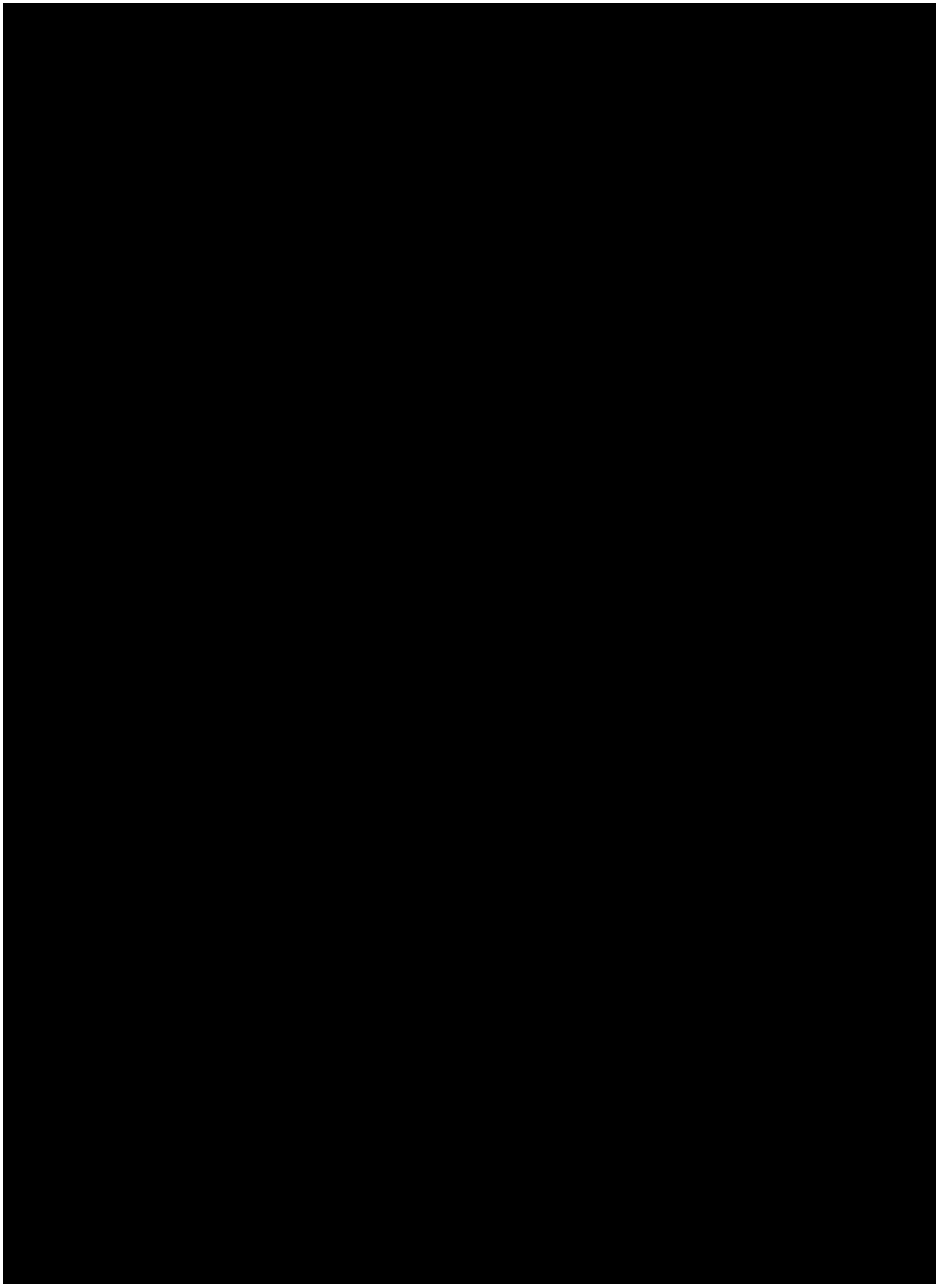
1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
    a. If the CM month is missing, the imputed CM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

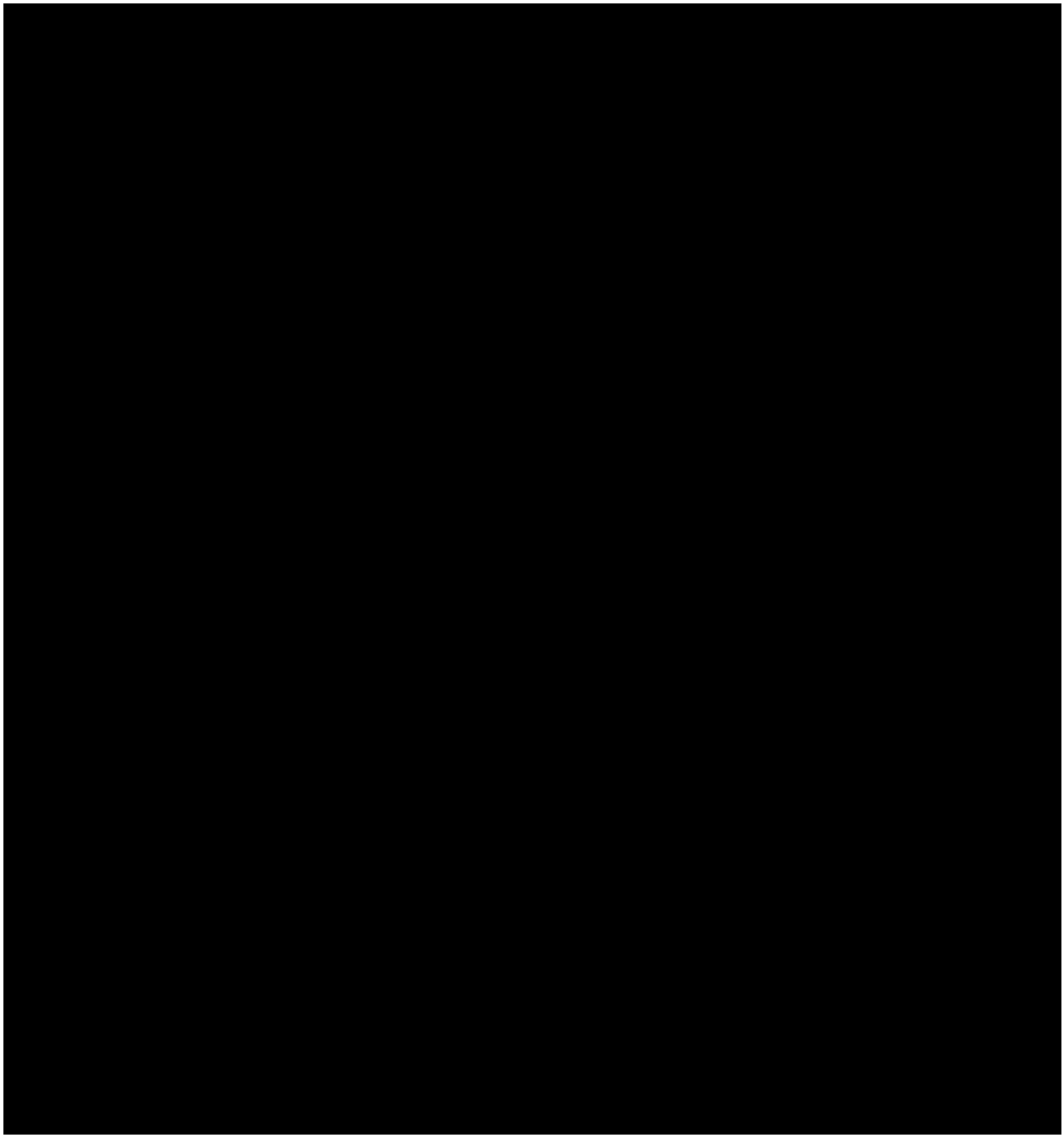
If complete imputed CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

6.2 AEs and Concomitant medications coding/grading

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







6.4 Background asthma therapy

6.4.1 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

6.5 Rule of exclusion criteria of analysis sets

The following protocol deviations will be considered as major and will lead to exclusion of patients from analysis sets:

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

Deviation ID	Description of Deviation	Exclusion in Analyses
INCL01ab	Patient did not sign informed consent for EPOCH 1	Exclude from all analysis sets for epoch 1 data
INCL01ba	Patient did not sign informed consent for EPOCH 2	Exclude from all analysis sets for epoch 2 data

6.6 Atopic and non-atopic status

RAST or ImmunoCAP test at Screening visit will be used to determine the atopic and non-atopic status. If at least one allergen test (including 'Other') is positive, the patient is atopic, otherwise the patient is non-atopic.

7 Reference

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