NOVARTIS

Clinical Development

QVM149B (Indacaterol acetate / Glycopyrronium bromide / Mometasone furoate)

CQVM149B2306 / NCT03158311

A multicenter, partially-blinded, randomized, 24-week, parallel-group, non-inferiority, open-label active controlled study to compare the efficacy and safety of QVM149 with a free triple combination of salmeterol/fluticasone + tiotropium in patients with uncontrolled asthma

Statistical Analysis Plan (SAP)- Amendment 2

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		and other secondary/ [redacted] analysis		
17-Sep-19	Prior to DB lock	Update notable criteria for ECG	Final Amendment version 2	5.5

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List of abbreviations

ACQ-7	Asthma Control Questionnaire-7
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AQLQ	Asthma Quality of Life Questionnaire
AST	Aspartate Aminotransferase
b.i.d	twice a day
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CM	Concomitant Medication
CRF	Case Report/Record Form (paper or electronic)
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eDiary	Electronic Diary
FAS	Full analysis set
FEF	Forced Expiratory Flow
FEV_1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
GEE	Generalized Estimating Equation
GLY	Glycopyrronium Bromide
HTA	Health Technology Assessment
ICS	Inhaled Corticosteroid
IND	Indacaterol Acetate
LABA	Long Acting Beta-2 Agonist
LFT	Liver Function Test
LS	Least Square
MedDRA	Medical Dictionary for Regulatory Activities
MF	Mometasone Furoate
MID	Minimal Important Difference
MMRM	Mixed Model for Repeated Measurements
o.d.	Once a day
PD	Pharmacodynamics
PEF	Peak Expiratory Flow
PK	Pharmacokinetic
PPS	Per protocol set
PT	Preferred Term
QTc	Corrected QT interval
RAN	Randomized set
ROW	Rest of the World
SABA	Short Acting Beta2 Agonist

SAE	Serious Adverse Event
SAF	Safety analysis set
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SCS	Systemic Corticosteroids
[redacted]	[redacted]
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event

1 Introduction

This document contains details of the statistical methods that will be used in the phase IIIb clinical trial CQVM149B2306. This study is designed to demonstrate that the efficacy of two strengths of the fixed-dose combination product QVM149 (IND/GLY/MF 150/50/80 µg and IND/GLY/MF 150/50/160 µg) is non-inferior to the efficacy of the free combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg in patients with uncontrolled asthma.

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

Important information is given in the following sections and details are provided, as applicable, in section 5: Appendix.

1.1 Study design

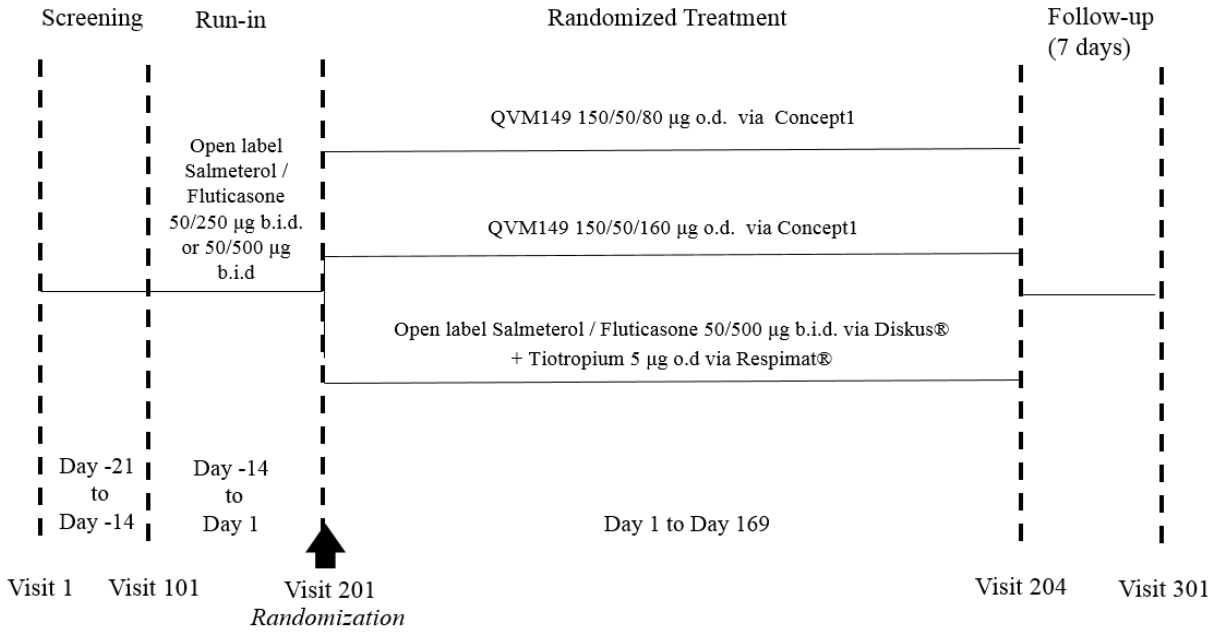
This study uses a multicenter, partially-blinded, randomized, 24-week, parallel-group, non-inferiority, open-label active controlled design (Figure 1).

Approximately 1251 male and female patients with uncontrolled asthma aged 18 and above will be randomized into the three treatment groups in a randomization ratio of 1:1:1, expecting approximately 417 patients in each of the treatment groups. It is intended that approximately 2085 patients will need to be screened in order to randomize approximately 1251 patients. Detailed information regarding sample size calculation is provided in section 3.

This study will enroll multi-nationally and patients will be stratified by previous ICS dose component of ICS/LABA therapy (medium or high) and region. Drop-outs after randomization will not be replaced.

No interim analysis for efficacy is planned in this study. An independent Data Monitoring Committee (DMC) will not be formed to review any blinded / semi-blinded data.

Figure 1 Study design



The study will consist of a screening period of up to 1-week, run-in period of 2-weeks, randomized treatment period of 24-weeks, and a follow-up of period of 1-week.

1.2 Study objectives and endpoints

All objectives will consider the following 2 comparison groups:

QVM149 150/50/80 µg o.d. delivered via Concept1 compared with open label salmeterol xinafoate/fluticasone propionate 50/500 µg b.i.d. delivered via Accuhaler® + tiotropium 5 µg o.d. delivered via Respimat®. QVM149 150/50/160 µg o.d. delivered via Concept1 compared with open label salmeterol xinafoate/fluticasone propionate 50/500 µg b.i.d. delivered via Accuhaler® + tiotropium 5 µg o.d. delivered via Respimat®

1.2.1 Study Objectives and Endpoints

Table 1-1

Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective • To demonstrate non-inferiority of either QVM149 high-dose or QVM149 medium-dose to comparator salmeterol/ fluticasone + tiotropium in terms of Asthma Quality of Life Questionnaire (AQLQ)	**Endpoint for primary objective** • Change from baseline in Asthma Quality of Life Questionnaire (AQLQ) total score after 24 weeks of treatment

Objective(s)	Endpoint(s)
Secondary Objectives • To evaluate efficacy of QVM149 high-dose and QVM149 medium-dose compared to salmeterol/ fluticasone + tiotropium in terms of Trough FEV_1 • To evaluate efficacy of QVM149 high-dose and QVM149 medium-dose compared to salmeterol/ fluticasone + tiotropium in terms of Asthma Quality of Life Questionnaire • To evaluate efficacy of QVM149 high-dose and QVM149 medium-dose compared to salmeterol/ fluticasone + tiotropium in terms of Asthma Control Questionnaire • To evaluate efficacy of QVM149 high-dose and QVM149 medium-dose compared to salmeterol/ fluticasone + tiotropium in terms of lung function	**Endpoints for secondary objectives** • Change from baseline in Trough FEV_1 after 24 weeks of treatment • Change from baseline in Asthma Control Questionnaire (ACQ-7) total score over 24 weeks of treatment • Change from baseline in Asthma Quality of Life Questionnaire (AQLQ) total score over 24 weeks of treatment • Percentage of patients achieving the minimal important difference (MCID) decrease from baseline ACQ-7 $\geq$ 0.5 over 24 weeks of treatment (responder rate) • Percentage of patients achieving the minimal important difference (MCID) change from baseline AQLQ $\geq$ 0.5 over 24 weeks of treatment (responder rate) • Change from baseline in FVC over 24 weeks of treatment • Change from baseline in Forced Expiratory Flow between 25% and 75% of Forced Vital Capacity (FEF_{25-75})

2 Statistical methods

2.1 Data analysis general information

The most recent version of SAS available in the statistical programming environment will be used for the analysis.

2.1.1 General definitions

Study treatment is the treatment administered in treatment period at visit 201.

The evaluations which have complete date and time values are assigned to pre or post-dose assessment based on the actual date/time. However, evaluations with missing date/time are assigned to their respective scheduled visit date and time given the visit number and time point are non-missing. If an evaluation scheduled as pre-dose is actually performed post-dose, or vice versa, the data will not be used for inferential analysis and summary statistics but will be included in the summaries of the notable values and extreme values.

Study day will be defined as the number of days since the date of first dose of study medication. The date of first dose of study medication will be defined as Day 1 and the day before the first dose of study medication was 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 has no study medication, the randomization date will be used instead of the date of first dose of study medication. Then, the randomization date is defined as Day 1 and the day prior to randomization is defined as Day -1.

2.1.1.1 Baseline definition

In general, baseline data is defined as the last assessment taken prior to the first dose of study drug at Day 1 (Visit 201).

Checks will be performed to ensure the assessments were indeed taken prior to the first dose of study drug on Day 1 (Visit 201). If this assessment is missing or not confirmed to be pre-dose, then last available non missing assessment will be used as baseline, if all the assessments prior to first drug administration are missing then the baseline will be set to missing without imputation.

Parameter	Baseline assessment	Detail
AQLQ-S [redacted]	Assessment on day 1 (Visit 201)	If assessment taken on day 1 (visit 201) prior to dosing are missing then baseline value will be set to missing without imputation.
ACQ-7	Assessment on day 1 (Visit 201)	If this assessment is missing or not confirmed to be pre-dose then last available non missing assessment will be used as baseline. If all the assessments prior to first drug administration are missing then baseline value will be set to missing without imputation.
[redacted]		

[redacted]

Lung function (FEV_1, FVC, FEV1 % predicted and FEF_{25-75})	Average of measurements taken at 45 min and 15 min prior to evening dosing on day 1 (Visit 201)	Checks will be performed to ensure both values were indeed 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 measurements are missing, then pre-SABA assessment on visit 101 will be used as baseline.

[redacted]

Laboratory data (hematology, clinical chemistry, urine analysis)	Last available assessment prior to dosing on day 1 (Visit 201)	
Vital signs (pulse rate and systolic and diastolic blood pressures)	Last available assessment prior to dosing on day 1 (Visit 201)	
Height and weight	Last available assessment prior to dosing on day 1 (Visit 201)	
ECG	Last available assessment prior to dosing on day 1 (Visit 201)	

2.1.1.2 Post-baseline measurement

Post-baseline measurements are defined as those assessments after the first dose of study drug.

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

Change from baseline = post baseline value – baseline value.

Detail descriptions for calculating post-baseline values are provided in the latter sections.

2.2 Analysis sets

The following analysis sets are defined:

- The randomized (RAN) set will consist of all patients who were assigned a randomization number, regardless of whether or not they actually received study medication. Patients in RAN will be analyzed according to the treatment they were randomized to. The RAN set will be used for a summary of patient disposition, demographics and baseline characteristics.
- The Full Analysis Set (FAS) will consist of all patients in the RAN set who received at least one dose of study medication. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization. The FAS will be used in the analysis of all efficacy variables.
- The Per-Protocol set (PPS) will include all patients in the FAS who did not have any major protocol deviations. The list of major protocol deviations is available in Appendix 5.8. Patients in the PPS will be analyzed according to the treatment they actually received. Patients who have taken ICS alone during the study as a treatment for any AE will be excluded from PPS. The PPS will be used for supportive and sensitivity analysis to assess robustness of the primary efficacy analysis.
- The Safety Analysis Set (SAF) will consist of all patients who received at least one dose of study medication. Patients will be analyzed according to the treatment they received. The SAF will be used in the analysis of all safety variables.

Note that the FAS and SAF are the same except that the SAF allows the inclusion of non-randomized patients who received study drug in error. Also, the FAS assign randomized treatment and the SAF assigned received treatment.

2.2.1 Subgroup of interest

The following exploratory subgroup analyses for AQLQ total score at Week 24 using MMRM will be performed (using the appropriate interaction term in the model and additional covariate as a fixed effect if necessary) for the FAS to explore the treatment effect in:

- Sex (male, female)
- Region (Asia, Europe, Latin America and Others)
- Age categories (18-39 years, 40-64 years and >=65 years)
- History of asthma exacerbation in the 12 months prior to screening (1, 2, 3, ≥ 4)
- Patients' prior therapies for at least 1 month prior to visit 1 (mid or high dose ICS/LABA; see Appendix 10 of the study protocol for the definition of ICS dose levels)

The subgroup analyses for patient's prior therapies prior to visit 1 (mid and high dose ICS/LABA) will also be performed for FEV_1 at Week 24.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number of patients will be summarized by treatment group for the RAN set. Further, for each study period (i.e., screening, run-in, randomized treatment phase, post treatment follow-up), the overall number of patients who entered, completed, and discontinued that phase will be summarized including the reasons for discontinuation.

Number of patients with protocol deviations will be summarized by deviation category (e.g., selection criteria not met, prohibited concomitant medication, key procedures not performed as per protocol) and treatment group. Protocol deviations that lead to exclusion from analysis sets will be listed by deviation category and treatment group.

The number of patients included in each analysis set will be tabulated by treatment group.

2.3.2 Patient demographics and baseline characteristics

Demographics and baseline characteristics will be summarized by treatment group using the RAN set. Summaries will include age, gender, race, ethnicity, height, weight, body mass index (BMI), relevant medical history, screening spirometry parameters: (FEV_1, FVC, FEV_1/FVC and FEF25-75), FEV_1 reversibility, % of predicted FEV_1, duration of asthma, history of asthma exacerbations, smoking history, prior concurrent medications (asthma-related and non-asthma-related), vital signs (systolic and diastolic blood pressure, pulse rate), QTc using Fridericia's correction and baseline AQLQ, ACQ-7, [redacted].

Continuous variables will be summarized using descriptive statistics (number of non-missing data, mean, standard deviation, median, first and third quartiles, minimum, and maximum) and categorical variables will be summarized in terms of the number and percentage of patients in each category including a category for missing data if any for the treatment group.
No statistical analyses will be provided for baseline comparability among the treatment group.
For two patients 2304004 and 2803009, their FEV1 reversibility values will be calculated from the last available value at unscheduled visits manually and will be added in the summary.

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

- Age: 18 – 39, 40 - 64 years, and ≥ 65 years;
- Region (Asia, Europe, Latin America and Others),
- BMI: ≤ 30.0 kg/m2 and > 30.0 kg/m2;
- Duration of asthma: < 1 year, 1 - 5 years, > 5 - 10 years, > 10 - 15 years, > 15 – 20 years, and > 20 years;
- Number of asthma exacerbations in the 12 months prior to the start of the study that required treatment: 0, 1, 2, 3, ≥ 4
- FEV1 reversibility %: <12%, >=12%
- AQLQ score: < 0.5, 0.5 - < 1, 1 - < 1.5, 1.5 - < 2, > 2
- ACQ-7: 1.5- < 2, 2 – < 2.5, ≥ 2.5 (< 1.5 will be added in case of protocol deviations)
- ICS component of background therapy (mid or high dose ICS/LABA)
- Baseline eosinophils blood count (low: < 300 cells/µL, high: ≥ 300 cells/µL)

Medical history will be coded with the Medical Dictionary for Regulatory Activities terminology (MedDRA) using the most recent version at the time of database lock. History/conditions will be summarized for the RAN set by primary system organ class and preferred term. Verbatim recorded history/conditions will be listed together with the coded terms, date of diagnosis/surgery and whether the problem was ongoing at start of the study.
In addition, medical histories/current medical conditions will be summarized by their status at baseline (current medical conditions, past medical conditions) and primary system organ class. Current medical conditions are defined as those which were reported as "Ongoing" at baseline.

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

2.4.1 Study treatment / compliance

2.4.1.1 Duration of exposure

Duration of exposure to study treatment will be calculated as the number of days starting from the first dose date up to and inclusive the last dose date. The duration of exposure will be summarized by treatment group for the safety set as a continuous variable with the standard descriptive statistics. In addition, the duration of exposure will be summarized with total patient years and the number (%) of patients who were exposed to study drug for the following categories <= 29 days, >29 days, >57 days, >85 days, >113 days, –>141 days and > 169 days.

If the patient's asthma symptoms are well controlled with stable lung function for 3 or more months and the patient is not at risk for an exacerbation, Tiotropium may be discontinued only in the "free combination" comparator arm (Salmeterol/fluticasone + Tiotropium). The number (%) of patients who were exposed to all three components of free triple combination will be presented for the time interval categories as described above.

2.4.2 Prior, concomitant and post therapies

Each medication, either an asthma or non-asthma medication, will have the start and end dates recorded on the eCRF. Separate tables will be provided for medications which were started and stopped prior to the first dose of study drug and medications which were taken concomitantly to the study drug (regardless of whether continued or started after the first dose of study drug).

Asthma medications will be summarized by the route of administration, the recorded prespecified drug subcategories (including types of combination) and the preferred terms. The summary will be repeated by showing ingredients instead of preferred terms. Non-asthma medications will be summarized by route of administration and preferred term. The summarization will be by treatment group in randomized set.

Surgical and medical procedures (non-drug therapies) will be coded using MedDRA and presentations will be done by MedDRA primary system organ class and preferred term, separately for prior procedures and those after start of study drug. The summarization will be by treatment group in randomized set.

Short acting beta2 agonist (SABA) rescue medication usage (mean number of puffs) during the run-in epoch will be summarized. Patients taking prohibited concomitant medications will be noted in the summary of protocol deviations. The summarization will be by treatment group in randomized set.

The number and proportion of patients who had their background asthma treatment escalated will be summarized by treatment group in the safety analysis set.

All summarizations will be by treatment group in the Safety Analysis Set.

2.5 Analysis of the primary and key secondary variable

2.5.1 Primary variable

The change from the baseline at week 24 for the AQLQ total score will be used as the primary endpoint

AQLQ(S) is a 32-item disease specific questionnaire designed to measure functional impairments that are most important to patients with asthma, with a recall time of two weeks and each question to be answered on a 7-point scale (1-totally limited/problems all the time, 7-not at all limited/no problems). It consists of 4 domains:

- 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)
- Total Score = Mean of Items 1 to 32 (32 items)

The AQLQ total score is defined as the mean response to all 32 questions. AQLQ assessment will be done at Day 113 and 169 (week 24, primary endpoint).

2.5.2 Statistical hypothesis, model, and method of analysis

2.5.2.1 Primary variable

The non-inferiority of QVM149 150/50/160 µg o.d. Versus free combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg and QVM149 150/50/80 µg o.d. versus free combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg, in terms of change from baseline in AQLQ total score, will be assessed by testing the following null hypothesis (H_1 & H_2) versus the alternative hypothesis (H_{a1} & H_{a2}):

H_1: QVM149 150/50/160 µg o.d. is inferior to free combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg in change from baseline for AQLQ total score at Week 24 ($\mu1 - \mu3 < -0.25$)

H_{a1}: QVM149 150/50/160 is non-inferior to free combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg in change from baseline for AQLQ total score at Week 24 ($\mu1 - \mu3 \geq -0.25$)

H_2: QVM149 150/50/80 µg is inferior to free combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg in change from baseline for AQLQ total score at Week 24 ($\mu2 - \mu3 < -0.25$)

H_{a2}: QVM149 150/50/80 is non-inferior to free combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg in change from baseline for AQLQ at total score Week 24 ($\mu2 - \mu3 \geq -0.25$)

where;
µ1 = Mean change from baseline for AQLQ total score at week 24 of QVM149 150/50/160 µg o.d. treatment;
µ2 = Mean change from baseline for AQLQ total score at week 24 of QVM149 150/50/80 µg o.d. treatment;
µ3 = Mean change from baseline for AQLQ total score at week 24 of free combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg;
-0.25 = Non-inferiority margin.

The primary variable will be analyzed using a mixed model for repeated measure (MMRM) on the FAS. The model will contain treatment, region (Asia, Europe, Latin America and Others), visit, background ICS/LABA (medium or high dose), baseline-by-visit interaction and treatment-by-visit interaction as fixed effects with baseline AQLQ total score as the covariate,

and center nested within region as a random effect. The within-patient correlation will be modeled using the unstructured covariance matrix in the mixed model. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom (Kenward and Roger,1997). If the model does not converge, then the compound symmetry covariance matrix will be used in the mixed model. Restricted maximum likelihood method will be used.

The least squares means of the treatment differences, standard errors, 97.5% (one-sided) CI, and one-sided p-values for NI test (adjusted and unadjusted) and nominal two-sided p-values at week 24 of each dose QVM149 vs. the combination of salmeterol/ fluticasone50/500 µg + tiotropium 5 µg, will be presented.

Non-inferiority of QVM149 will be claimed if the the multiplicity adjusted one-sided p-value is < 0.025.

An improvement of 0.5 points in AQLQ score is considered to be the minimally clinically important difference (MCID) in asthma. A non-inferiority margin of 0.25 points reduction in AQLQ score has been designated for the study based upon 50% of the MCID. If the MCID of 0.5 points reduction in the AQLQ is considered clinically important, it is reasonable to use a non-inferiority margin of one-half of this difference, which is 0.25 points.

2.5.3 Estimand Analysis

The estimand for this study is difference between the effect of initially randomized treatments had all patients remained on their randomized treatment throughout the study. The primary estimand will quantify the treatment effect based on on-treatment data. The primary estimand will account for different post-randomization events as follows:

- Use of rescue medications: Efficacy data collected during use of rescue medication will be used for analysis.
- Early discontinuation of study drug: The primary analysis will include on treatment data from all patients in FAS. Data collected after treatment discontinuation will be considered as missing.

2.5.4 Handling of missing values/censoring/discontinuations

The MMRM model, which is used for the analysis of primary variable is based on missing at random assumption for the missing values and assesses the treatment effects without explicit imputation. No imputation will be used for missing questions or missing total AQLQ score for primary analysis.

2.5.5 Supportive and Sensitivity analyses

As a sensitivity analysis, the following analyses will be performed:

- The same MMRM used for the primary objective will be performed with the missing values imputed using last observation carried forward (LOCF). The analysis will only be performed if there are less than 20% observations missing.

- The same MMRM model used for primary objective will be performed with on and off treatment data value at week 24/ day 169.
- The same MMRM used for the primary objective will be performed on the PPS. Primary variables will be analyzed using the same MMRM model as that of primary analysis using the data from all time-points (i.e. on and available off treatment data) on FAS.
- The same MMRM used in the primary analysis will be performed on all patients except for the patients who are "treatment failures" for whom only the data till the time the patient is not a treatment failure will be considered in the analysis while the data collected after being treatment failure will be considered as missing.
- The same MMRM model used in the primary analysis will be performed considering all patients in the QVM arms and only those patients in the loose triple arm who did not step down. This analysis will only be performed if more than 5% patients in the loose triple arm steps down.

2.5.6 Multiplicity adjustment

To control the family-wise type-I error rate at the one-sided 2.5% significance level, a multiple testing procedure based on the trimmedSimes test in Brannath et al. (2009) is used. The family for the overall type-I error rate control contains total 2 hypotheses for the primary endpoint, AQLQ. Denote the two hypotheses for the primary endpoint as H_1 and H_2 for comparing QVM149 150/50/160 µg o.d. Versus free combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg and QVM149 150/50/80 µg o.d. versus free combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg, in terms of change from baseline in AQLQ total score.

Below is a brief description of the testing procedure based on the trimmed Simes test in Brannath et al. (2009).

Let p_1 and p_2 are the corresponding p-values (1-sided, p-value related to NI hypotheses) of the two hypotheses of $H_1$and H_2.

Step 1: Retain both H_1 and H_2 if ANY p_i>=0.975 (i.e. Loose tripleis performing better than QVM) for i=1, 2, stop here; otherwise go to step 2;

Step 2: Reject H_1 and H_2 if p_i<0.025 for **BOTH** i=1, 2,and stop here; otherwise go to step 3;

Step 3: If neither step 1 or 2 applies, perform the Bonferroni test to H_1 and H_2. Thus reject H_1 if p_1<0.0125 and reject H_2 if p_2<0.0125 and stop.

For each of the two hypotheses, the corresponding testing statistic (estimated least square mean difference) follows normal distribution. Hence for H1 and H2, their corresponding testing statistics is assumed to follow jointly bivariate normal distribution. Therefore this testing procedure controls the overall type–I error rate at the 1-sided 0.025 level in the strong sense regardless if the bivariate normal distributions have positive or negative correlations as shown in Brannath et al (2009).

Other than the two analyses mentioned above for the primary endpoint (primary endpoint using FAS and PPS), all other analyses will be performed at the nominal 2-sided 0.05 level (2-sided) without multiplicity adjustment.

2.6 Analysis of secondary efficacy objective(s)

2.6.1 AQLQ Score, domains, and responders at each visit

Clinically important differences in scores between any two assessments have been determined by the authors of the AQLQ. Changes in scores of 0.5 are considered clinically meaningful; changes of 1.0 are considered as moderate and > 1.5 as large changes for any individual domain or for the overall summary score (Juniper 1994).
Change from baseline in Asthma Quality of Life Questionnaire (AQLQ) total score and each of the AQLQ domain (symptoms, emotions, exposure to environmental stimuli and activity limitation) over 24 weeks of treatment will be analyzed using MMRM model similar to primary endpoint. Appropriate baseline AQLQ domain scores will be used as covariate instead of baseline AQLQ total score in the model. .
The between-treatment comparison will be carried out using the adjusted mean (least-square mean) difference corresponding to the respective visit. Adjusted mean (LS mean) will be displayed for each treatment group along with the estimated treatment differences and the 95% confidence intervals and the two sided p-values by visit.

Percentage of patients achieving the minimal important difference (MCID) change from baseline AQLQ ≥ 0.5 over 24 weeks of treatment (responder rate) (i.e. increase of AQLQ total score of at least 0.5 from baseline) at post-baseline visits will be analyzed using the logistic regression model via the generalized estimating equations (GEE). The model will include terms for treatment, region, visit, background ICS/LABA (medium or high dose) , baseline-by-visit interaction and treatment-by-visit interaction as fixed effects, with baseline AQLQ total score as covariates. The within-patient correlation will be modeled using the unstructured covariance matrix in the GEE model. The estimated adjusted odds ratios of the treatment comparisons will be displayed along with the associated 95% (two- sided) confidence intervals and superiority p-values. For odds ratio, binomial distribution with logit link will be used and correlation structure will be “Unstructured”. The estimated risk ratios between the treatments will be displayed along with the associated 95% (two-sided) confidence intervals and superiority p-values.For risk ratios, modified Poisson regression model (Zou 2004) will be used in model with correlation structure as “unstructured”. This method leads to the robust error variance estimation and produce 95% CIS with the correct coverage.

2.6.2 ACQ-7 Score and responders at each visit

ACQ-7 questionnaire consists of five items to assess symptoms and activity limitations, one question to assess rescue medication use, and one question to assess airway caliber (FEV_1 % predicted). All seven items are scored on a 7-point Likert scale, with 0 indicating total control and 6 indicating poor control. The questions are equally weighted and the total score is the mean of the seven items.

The first 6 questions of the ACQ-7 should be completed by the patient based on one recall over the prior week. The last question should be completed by the investigator at the site using data from the MasterScope spirometer.
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 6 questions answered and the missing question is neither

Question 1 ('On the average, during the past week, how often were you woken by your asthma during the night?') nor Question 7. Missing ACQ score will not be imputed explicitly.
Change from baseline in ACQ-7 total score over 24 weeks of treatment will be analyzed using the MMRM model similar to primary endpoint with baseline ACQ-7 score will be used as covariate instead of baseline AQLQ total score in the model.

Adjusted mean (LS mean), the least squares means of the treatment differences, standard errors, 95% (two-sided) CI, and superiority p-values at each visit of each dose QVM149 vs. the combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg, will be displayed.
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 6 questions answered and the missing question is neither Question 1 ('On the average, during the past week, how often were you woken by your asthma during the night?') nor Question 7.

Percentage of patients achieving the minimal important difference (MID) change from baseline ACQ-7 $\geq$ 0.5 decrease over 24 weeks of treatment (responder rate) (i.e. decrease of ACQ-7 score of at least 0.5 from baseline) at post-baseline visits will be analyzed using the same logistic regression model via GEE specified for the AQLQ analysis except that baseline ACQ-7 score will be used as the covariate in the model, instead of the baseline AQLQ total score. The estimated adjusted odds ratios of the treatment comparisons will be displayed along with the associated 95% (two- sided) confidence intervals and superiority p-values. For odds ratio, binomial distribution with logit link will be used and correlation structure will be "Unstructured". The estimated risk ratios between the treatments will be displayed along with the associated 95% (two-sided) confidence intervals and superiority p-values. For risk ratios, modified Poisson regression model as described above will be used in model with correlation structure as "unstructured".

Percentage of patients achieving the change from baseline ACQ-7 $\geq$ 0.75 decrease over 24 weeks of treatment (responder rate) (i.e. decrease of ACQ-7 score of at least 0.75 from baseline) at post-baseline visits will be analyzed using the same logistic regression model via GEE specified for the AQLQ analysis except that baseline ACQ-7 score will be used as the covariate in the model, instead of the baseline AQLQ total score. The estimated adjusted odds ratios of the treatment comparisons will be displayed along with the associated 95% (two- sided) confidence intervals and p-values. The estimated risk ratios of the treatment comparisons will be displayed along with the associated 95% (two-sided) confidence intervals and superiority p-values.

2.6.3 Spirometry data at each visit

Change from baseline in Trough FEV_1 at week 24 of treatment will be analyzed using the same MMRM model as specified for the primary variable on FAS. Trough FEV_1 is calculated as average of 15 min and 45 min pre-dose measurements. Baseline FEV_1 will be used as covariate in the model. The least squares means of the treatment differences, standard errors, 95% (two-

sided) CI, and p-values (nominal) at week 24 of each dose QVM149 vs the combination of salmeterol/fluticasone 50/500 µg + tiotropium 5 µg will be presented.

Trough FEV_1 will also be analyzed using the same MMRM model as specified above, where the between-treatment comparison will be carried out using the adjusted mean (least-square mean) difference corresponding to the respective visit. Adjusted mean (LS mean) will be displayed for each treatment group along with the estimated treatment differences and the 95% confidence intervals and the two sided p-values by visit.

Similar analyses will be performed for FVC and FEF25-75. Change from baseline in the spirometry values will be also analyzed using the same MMRM model.

2.7 Safety analyses

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

For safety data, post-baseline measurements comprise recordings up to the last dose of study drug + 7 days for laboratory, ECG, vital signs, non-serious AE and up to the last dose of study drug + 30 days for SAEs and death.

2.7.1 Adverse events (AEs)

All adverse events including asthma exacerbations, coded with MedDRA using the most actual version at the time of database lock, will be listed. In general, summaries will include treatment-emergent adverse events (TEAEs) only.
TEAEs are those adverse events starting on or after the time of the first inhalation of study drug but not later than 7 days (30 days in the case of SAE) after the last administration of study drug. Any adverse events that started during the study before the time of the first inhalation of study drug will be classified as a prior adverse event.

The number and percentage of patients who reported TEAEs will be summarized by primary system organ class (SOC) and preferred term (PT), serious adverse events by system organ class and preferred term, and adverse events leading to permanent discontinuation of study-drug by system organ class and preferred term. The number and percentage of patients with the most frequent AEs will be summarized by treatment group for

- all adverse events
- all adverse events by maximum severity
- adverse events suspected to be related to study drug
- serious adverse events
- adverse events leading to permanent study drug discontinuation
- all adverse events by standardized MedDRA query (SMQ) level
- fatal adverse events, by adjudicated reason for death
- adjudicated serious cardiovascular and cerebrovascular (CCV) events
- adjudicated new onset of atrial fibrillation/ flutter
- adverse events of special interest

Unless otherwise specified, primary system organ classes will be sorted alphabetically and, within each primary system organ class, the preferred terms will be sorted in descending order of frequency in the QVM149 150/50/80 µg treatment. If a patient reported more than one adverse event with the same preferred term, the adverse event will be counted only once. If a patient reported more than one adverse event 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 adverse events will be presented by preferred term in descending order of frequency in the QVM149 150/50/80 µg treatment.

2.7.1.1 Adverse events of special interest / grouping of AEs

Serious CCV events will be adjudicated.

Atrial fibrillation and atrial flutter will be adjudicated according to their onset into: new onset, recurrent/persistent, or unknown.

The Compound Case Retrieval Strategy (CRS) will be used to determine the MedDRA search criteria to be used to identify events of special interest. Selection of appropriate flags in eCRS tool will be mentioned in TFL shells. The most recent list of adverse events of special interest at the time of database lock will be used. Adverse events of special interest will be summarized by risk and preferred term by severity (mild/moderate/severe).

In addition, exposure adjusted analyses of adverse events by preferred term will be performed for each treatment group.

For exposure adjustment, First onset of event will be considered where the exposure is only counted up to the time of the first event. The occurrence rate per 100 patient years will be calculated as 100*(the total number of patients with the event of interest divided by the total number of exposure in patient-years). In the denominator, patients with the event of interest will be counted up to the time of the first event while patients without the event of interest will be counted with their full exposure. Total patient years will be computed as sum of days of exposure over all patients divided by 365.25).

2.7.1.2 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 2% 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.

2.7.2 Deaths

A summary of deaths will be presented by primary system organ class, preferred term, and treatment groups regardless of study drug relationship. In addition, deaths will be summarized by adjudicated primary cause and treatment group.

All the deaths in the clinical database will be listed with both the investigator-reported principal cause and the adjudicated primary cause presented side by side, but only those between the first treatment and (the last dose + 30 days) will be included in summary tables.

2.7.3 Serious asthma outcomes

A composite endpoint of serious asthma outcomes is defined as a) asthma-related hospitalization, b) asthma-related intubation, or c) asthma-related death. All serious asthma outcomes and deaths occurring from the time of randomization until the 30 days after permanent discontinuation of study drug will be adjudicated by an independent external committee to determine their asthma relatedness. The composite endpoint as well as each single component of it will be analyzed for the number of patients with the event, the time to event and the annual rate of events. If a sufficient number of events will occur, similar analyses as described for asthma exacerbations will be performed. Otherwise, a purely descriptive analysis will be done only.

2.7.4 Laboratory data

All laboratory samples will be processed through the central laboratory. Laboratory data consist of hematology, clinical chemistry and urinalysis measurements. All data will be listed with abnormal values flagged. Baseline laboratory data is defined in section 2.1.1.1
Laboratory data measured more than 7 days after last inhalation 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.

The following analyses will be performed by treatment group:

- absolute values and change from baseline summarized for continuous laboratory parameters by visit
- frequency table of results for categorical laboratory parameters by visit
- shift tables relative to the normal reference ranges summarizing the change from baseline to post-baseline by visit for each continuous laboratory parameter
- shift tables from baseline to post-baseline by visit for categorical laboratory parameters

- the number and percentage of patients with newly occurring or worsening laboratory abnormalities meeting the clinically notable criteria (see Section 5.5 for definition of notable values) summarized by laboratory parameter, scheduled post-baseline visit and additionally at any time on treatment considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits.

For a patient to meet the criterion of a newly occurring clinically notable value, the patient needs to have a baseline value that 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 that is clinically notable and also have a worse post-baseline value. For patients with missing baseline value, any post-baseline notable value will be considered as newly occurring. A listing of all patients with notable laboratory values will be provided.
Furthermore, the number and percentage of patients with newly occurring or worsening abnormalities in liver function tests (LFT) will be summarized by treatment and scheduled post-baseline visit and additionally at any time on treatment considering all post-baseline data from scheduled, unscheduled and premature discontinuation visit (if not measured more than 7 days after last dose) based on the criteria mentioned in the section 5.4.
When a criterion contains multiple laboratory parameters, the criterion will only be considered to have been met when all conditions occur at the same time (i.e., within the same sample). A case where all criteria are met at a post-baseline time point will be considered as newly occurring if the criteria are not met at baseline and will be considered as worsening if the criteria are met at baseline and at least one component is worsening from baseline irrespective of whether the other(s) are better.

Listings of patients with clinically notable LFT values will be provided.

2.7.5 Other safety data

2.7.5.1 ECG

ECG measurements include ventricular rate, QT interval, RR interval, PR interval, QRS duration, and Fridericia's QTc (calculated as QTcF = QT / 3√ RR (in seconds), where 3√ 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 inhalation 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.
The following analyses will be performed by treatment group:

- absolute values and change from baseline summarized by parameter, and visit
- the number and percentage of patients with newly occurring or worsening notable QTcF values (see Section 5.5 for definition of notable values) 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
- frequency table of results for overall ECG interpretation (normal, abnormal) by visit and with shift tables from baseline to the worst interpretation during treatment
- the number and percentage of patients with ECG abnormalities summarized by evaluation type, abnormality finding, and visit. In addition, the number and percentage of patients with

newly occurring or persistent/recurrent ECG abnormalities at any time point over the treatment period (considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits) will be summarized by evaluation type and abnormality finding

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

A listing of all patients with notable QTc values and changes will be provided.

2.7.5.2 Vital signs

Vital signs measurements include systolic and diastolic blood pressure (SBP and DBP), pulse rate, height and body weight.

Vital signs data measured more than 7 days after last inhalation 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.

The following analyses will be performed by treatment group:

- absolute values and change from baseline summarized by parameter, and visit
- the number and percentage of patients with newly occurring or worsening notable vital signs values (see Section 5.6 for definition of notable values) summarized by parameter (except height), scheduled post-baseline visit and additionally at any time on treatment considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits

The by-visit summaries will include the post-baseline SBP, DBP, and pulse rate values (even if from post-baseline unscheduled and premature discontinuation visits, if not measured more than 7 days after last dose).

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.

2.8 Pharmacokinetic endpoints

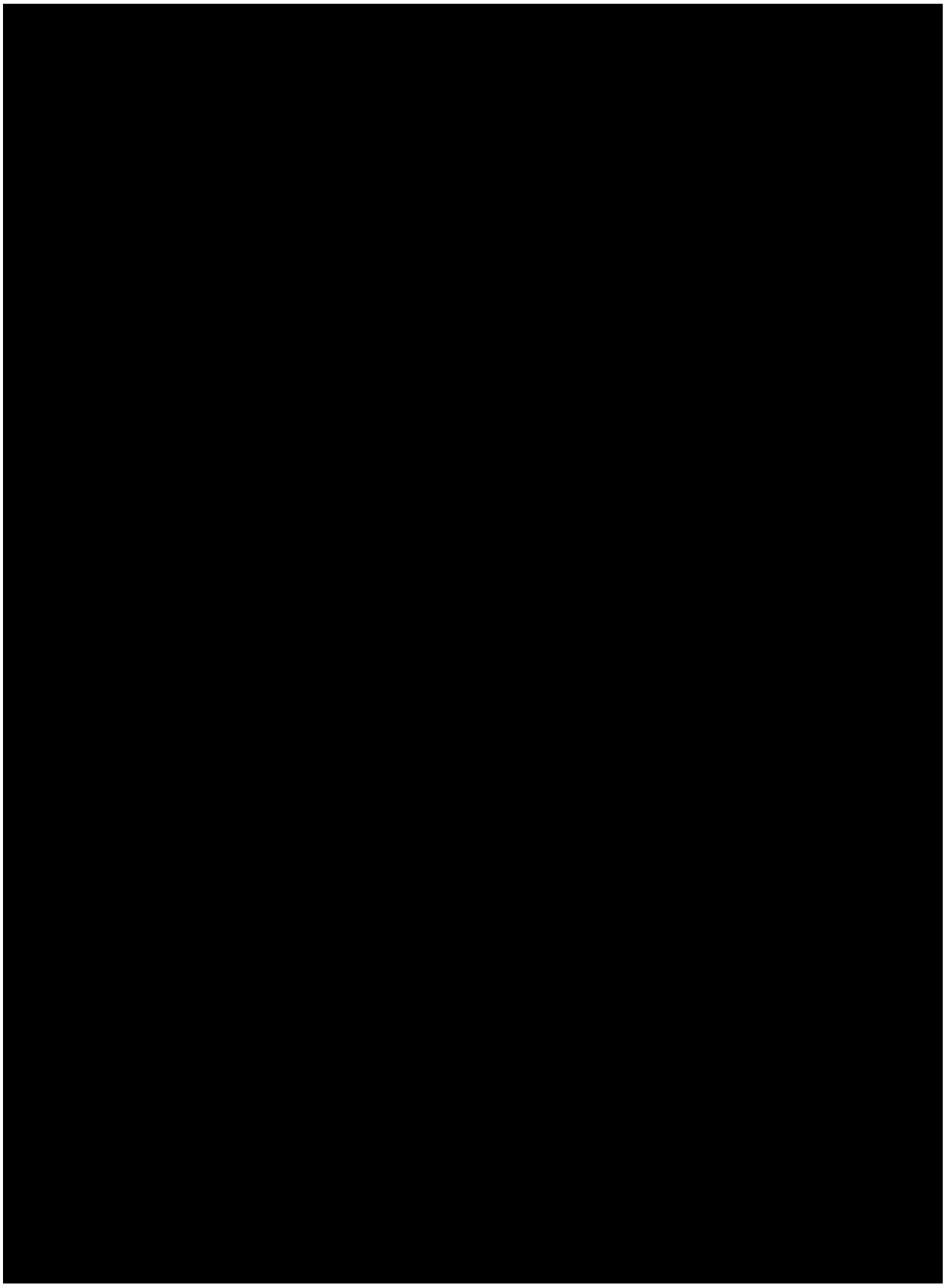
Not Applicable

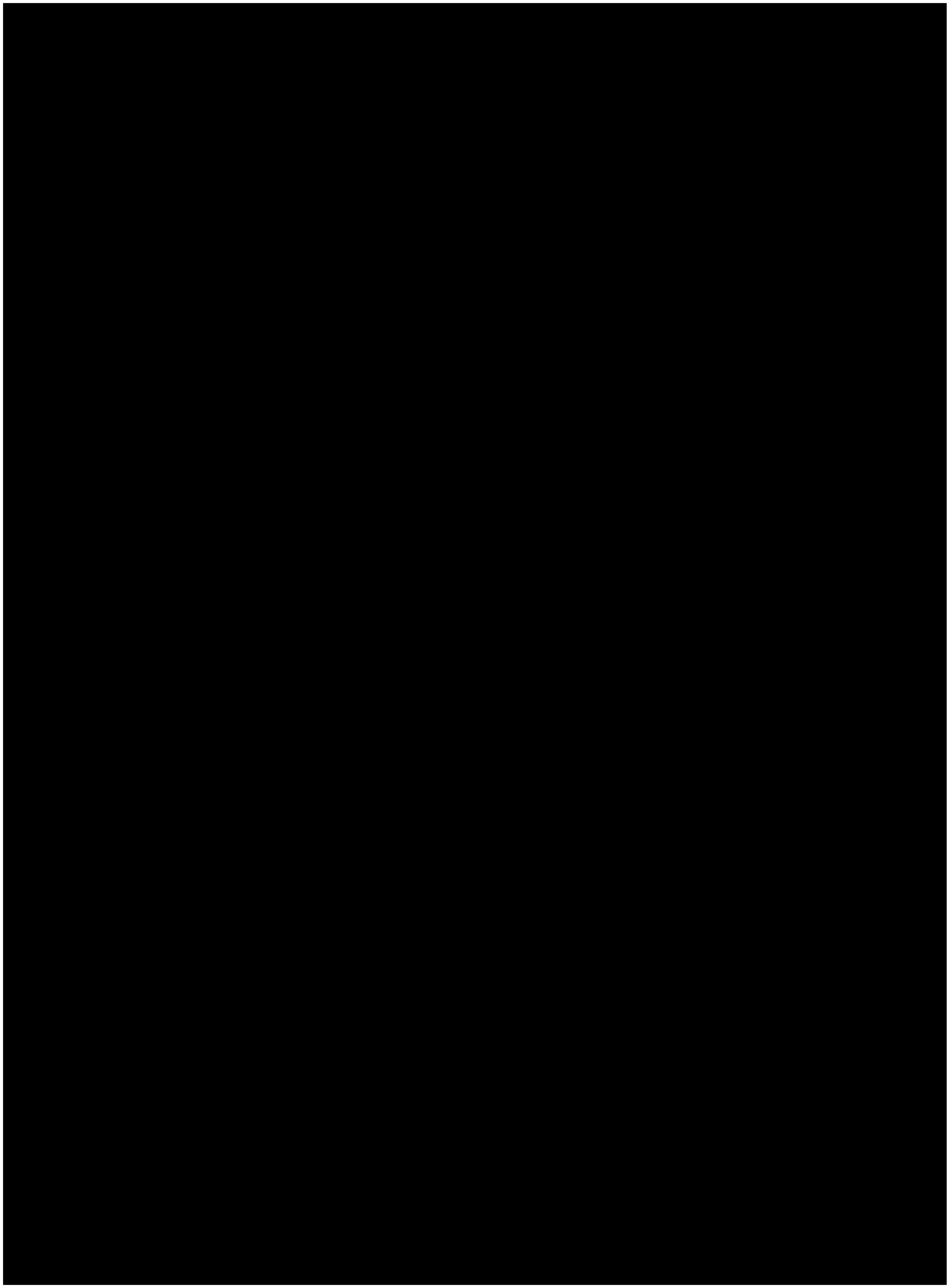
2.9 PD and PK/PD analyses

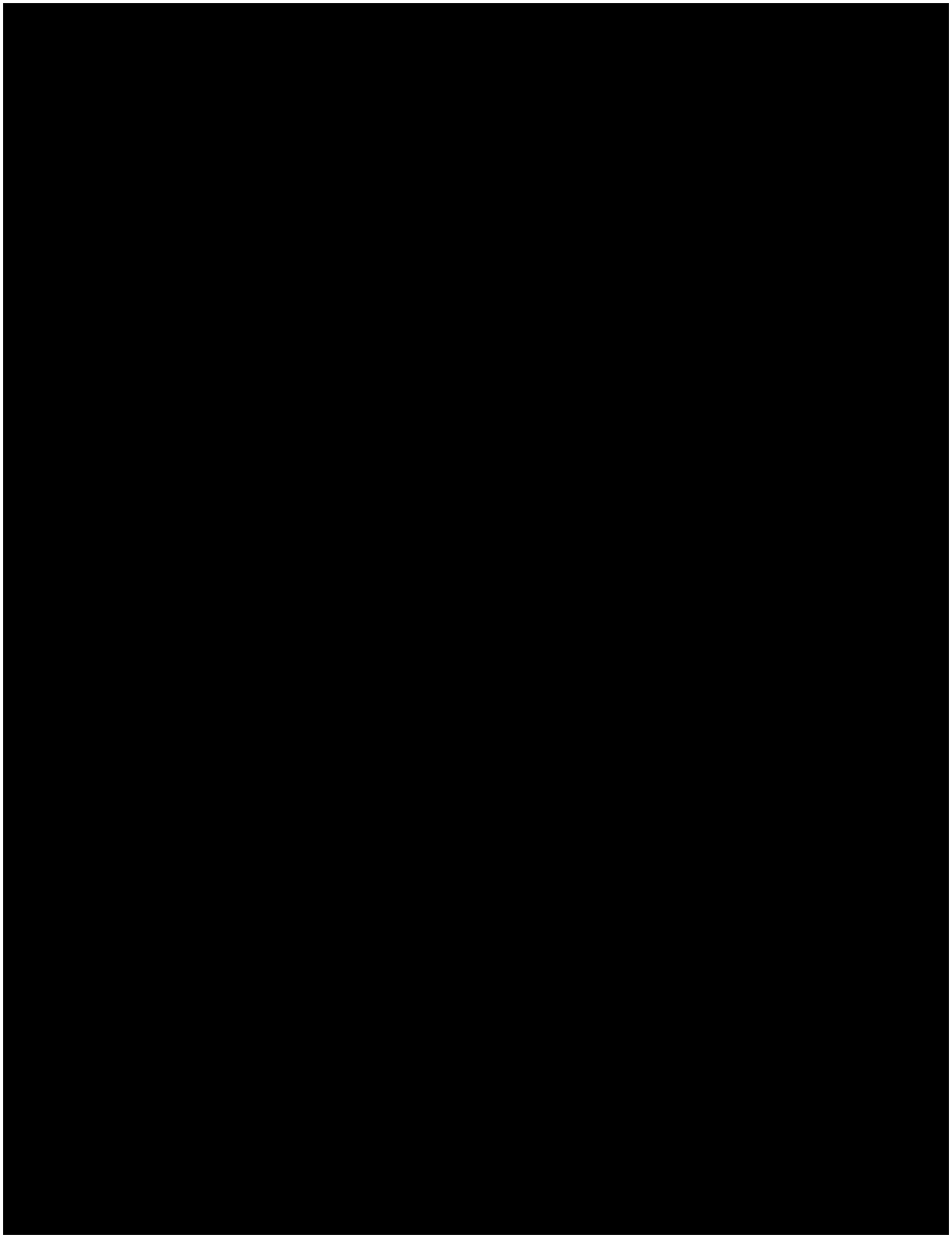
Not Applicable

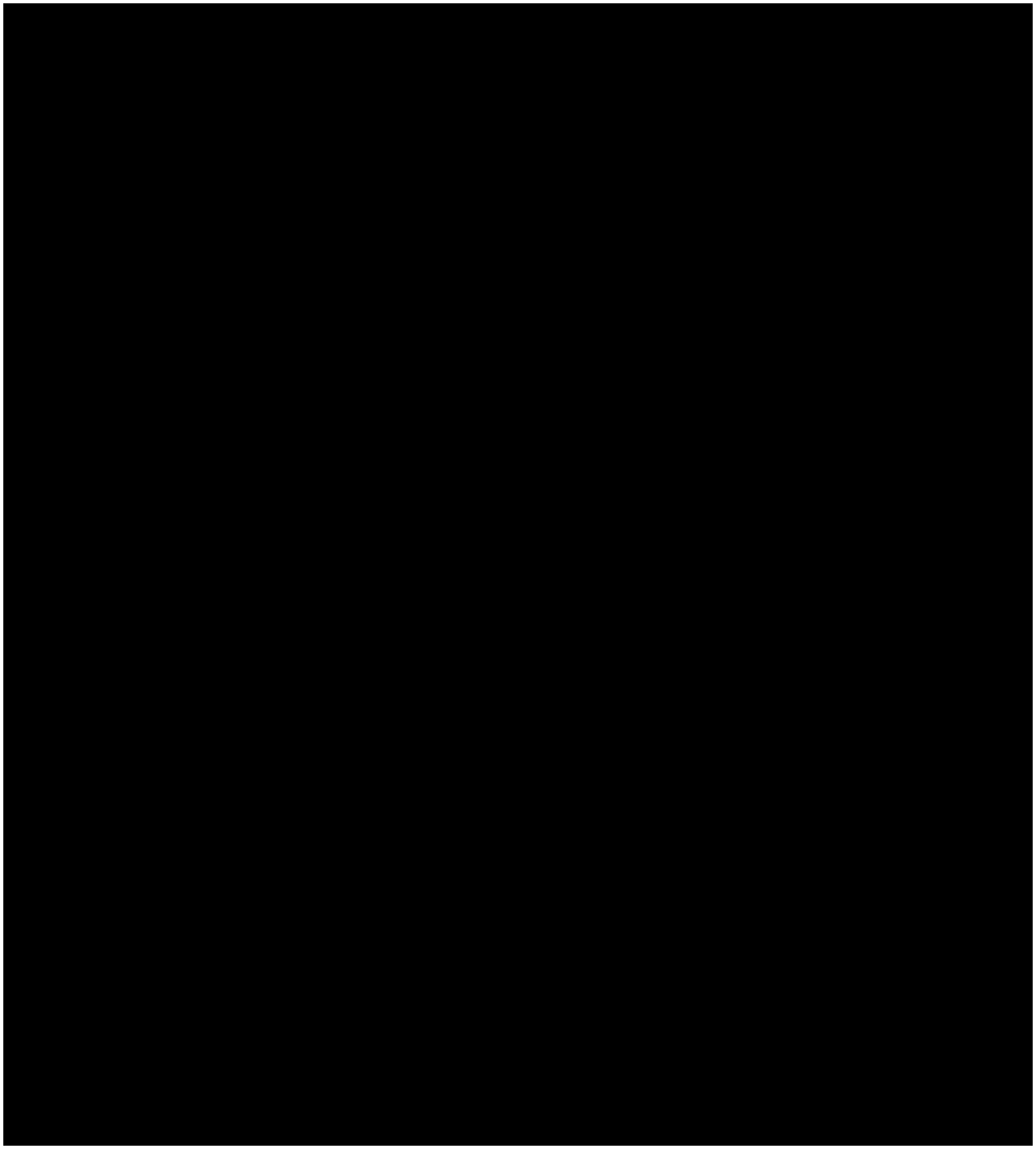
2.10 Biomarkers

Not applicable









2.12 Additional analysis

Apart from the above mentioned primary, secondary, safety [redacted] analyses, further analysis may be performed on a local level for HTA purposes, such as, but not limited to responder analysis for patient reported outcomes and subgroup analysis.

2.13 Interim analysis

No interim analysis is performed for this study.

3 Sample size calculation

The sample size calculation takes into account the following consideration:

To achieve at least 90% power (with multiplicity adjustment) for primary endpoint, to demonstrate the non-inferiority of either of QVM149 dose vs. the free triple combination of salmeterol/fluticasone + tiotropium in patients with uncontrolled asthma for AQLQ at the week 24. With the assumption of 0.25 for the NI margin, zero as the point estimation of the treatment difference, one-sided alpha level of 0.025, and 0.8 of the standard deviation based on studies QMF149E2203 and Kerstjens (2012).

If 10% dropout rate is assumed, then the calculation shows that the sample size of 1251 patients (i.e. 417/arm) will provide 99% power with multiplicity adjustment as given in section 2.5.5..

The sample size and power calculations are performed in R 3.1.2 with package gMCP.

4 Change to protocol specified analyses

- Analysis for percentage of patients achieving thedifference) change from baseline ACQ-7≥ 0.75 decrease over 24 weeks of treatment will be done. Analysis for percentage of patients achieving the difference) [redacted] All analyses mentioned for ACQ-7 will be repeated [redacted] RR of treatment comparisons will also be shown.
- [redacted]

5 Appendix

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

5.1 Imputation rules

5.1.1 Study drug

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

5.1.2 AE date imputation

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

5.1.3 Concomitant medication date imputation

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

5.1.3.1 Prior therapies date imputation

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

5.1.3.2 Post therapies date imputation

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

5.2 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.

5.3 Data pooling and assessment windows

Data from unplanned or unscheduled visits or the early treatment/study discontinuation visits will be listed. For patients who do not complete the study treatment, the treatment discontinuation visit will be an unscheduled visit.

Clinical laboratory measurements, vital signs and ECG data from unplanned or unscheduled visits will only be included in the summaries of the notable values and extreme values. All efficacy data from these visits will not be used for missing data imputation unless specified otherwise.

Laboratory, vital signs, and ECG values that have complete data and time values will be slotted into pre- or post-dose assessment based on the actual date/time. For values with missing date/time, scheduled visit date and time will be used. This rule will be applied to data from scheduled visits only. If a measurement scheduled as pre-dose is actually performed post-dose, or vice versa, the data will not be used for by time point assessments.

5.4 Time Windows

Below mentioned time windows will be used for week 24 visit (visit corresponding to day 169).

- For Treatment Emergent Flag: +7 days , SAE + 30 days
- For EG, LB, VS : +7days
- ACQ7, AQLQ: +1 day
- [redacted]
- ADRESPI (Respiratory): +1
- [redacted]
- Time to event: +1 days except for adjudicated events(+30)

5.5 Laboratory parameters derivations

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

Laboratory parameter (unit)	Lower bound of clinically notable range	Upper bound of clinically notable range
Hematology		
Hematocrit (v/v)		
Male	*0.37*	
Female	*0.32*	
Hemoglobin (g/L)		
Male	*115*	
Female	*95*	
Platelets (x10E^9/L)	*75*	*700*
WBC (x10^9/L)	*2.8*	*16.0*
Chemistry		
Albumin (g/L)	*25*	-
Alkaline Phosphatase (U/L)	-	*3xULN*
ALT/SGPT (U/L)	-	*3xULN*
AST/SGOT (U/L)	-	*3xULN*
Bilirubin Total (mcmol/L)	-	*34.2*
BUN (mmol/L)	-	*9.99*
Creatinine (mcmol/L)	-	*176.8*
Glucose (mmol/L)	*2.78*	*9.99*
Gamma GT (U/L)	-	*3 x ULN*
Potassium (mmol/L)	*3*	*6*

v = volume, ULN = upper limit of normal

Notable liver function test values

Criterion
ALT > 3 x the upper limit of normal range (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
* Based on the signs/symptoms information as recorded on the liver events eCRF, not the adverse events eCRF.

5.6 Vital signs and ECG – definition of clinically notable values

The following table shows the 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

The following table shows the clinical notable criteria for QTcF.

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	

ECG parameter (unit)	Clinically notable range
QTc	>=30 – 60
QTc	> 60

5.7 Statistical methodology and assumptions

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

5.7.1 Mixed Model Repeated Measures (MMRM)

The following MMRM model will be used for AQLQ, Trough FEV1, Spirometry data, ACQ-7, [redacted]:

Dependent variable = intercept + treatment + region + visit + background ICS/LABA(medium or high dose) +treatment*visit + baseline*visit + baseline value + random effect of center nested within region + error.

The SAS procedure PROC MIXED will be used for analysis. Results will be presented with least squares mean (LSM) and standard error (SE) for treatment effects and LSM, SE, associated 95% or 97.5% confidence interval, and p-value for the treatment contrast.

5.7.2 Logistic Regression Model via GEE

The following logistic regression model via GEE will be used for Response rate analysis for AQLQ, ACQ-7 [redacted] endpoints, and other data:
Dependent variable = intercept + treatment + region + visit + background ICS/LABA (medium or high dose) + treatment*visit + baseline *visit + baseline value + error.

[redacted]

The SAS procedure PROC GENMOD will be used for both scenarios. The estimated adjusted odds ratios of the treatment comparisons will be displayed along with the associated 95% (two-sided) confidence intervals and superiority p-values. For odds ratio, binomial distribution with logit link will be used and correlation structure will be "Unstructured". For AQLQ, ACQ-7 [redacted], the estimated risk ratios between the treatments will be displayed along with the associated 95% (two-sided) confidence intervals and superiority p-values.For risk ratios, poisson link will be used in model with correlation structure as "unstructured".

Percentage of patients achieving the change from baseline ACQ-7 $\geq$ 0.75 decrease over 24 weeks of treatment (responder rate) (i.e. decrease of ACQ-7 score of at least 0.75 from baseline) at post-baseline visits will be analyzed using the same logistic regression model via GEE specified for the AQLQ analysis except that baseline ACQ-7 score will be used as the covariate in the model, instead of the baseline AQLQ total score. The estimated adjusted odds ratios of the treatment comparisons will be displayed along with the associated 95% (two- sided) confidence intervals and p-values as mentioned above. The estimated risk ratios of the treatment

comparisons will be displayed along with the associated 95% (two-sided) confidence intervals and superiority p-values as mentioned above.

5.7.3 ANCOVA Model

[redacted]

Dependent variable = intercept + treatment + region + background ICS/LABA (medium or high dose) + baseline value + random effect of center nested within region + error.

The SAS procedure PROC MIXED will be used for analysis. Results will be presented with least squares mean (LSM) and standard error (SE) for treatment effects and LSM, SE, associated two-sided 95% confidence interval, and two-sided p-value for the treatment contrast.

5.7.4 Cox Regression Model

The following ANCOVA model will be used for Time-to-event variables.

Dependent variable = intercept + treatment + region + history of asthma exacerbation in the 12 months prior to screening (Yes, No) + FEV1 prior to inhalation + FEV1 within 15 to 30 min post inhalation of salbutamol/albuterol + error.

The SAS procedure PROC PHREG will be used for analysis.

The estimated adjusted hazard ratio for either of QVM149 doses over the free triple combination group will be displayed along with the associated two-sided 95% confidence interval and corresponding p-value.

5.7.5 Generalized Linear Model assuming a Negative Binomial Distribution

The number of the asthma exacerbations and their annualized event rates will be analyzed using a generalized linear model assuming a negative binomial distribution including treatment, region, background ICS/LABA (medium or high dose) and history of asthma exacerbation in the 12 months prior to screening (Yes, No) as fixed-effect factors,. The log exposure in years will be included as an offset variable in the model.

The SAS procedure GENMOD will be used for analysis. Treatment group ratio of exacerbation rate will be presented together with 95% confidence interval and two-sided p-value.

log (exacerbation rate) = treatment + background ICS/LABA use (medium/high) + baseline number of asthma exacerbations + region

5.8 Rule of exclusion criteria of analysis sets

5.8.1 Major protocol deviations and other exclusion criteria

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

Exclusions from Full Analysis Set:

- INCL01: Informed consent not obtained.

- OTH 02: Patient was Randomized but no study drug was taken.
- OTH 05: Patient randomized more than once in the trial.
- OTH 12: Patient who received study medication before or without randomization

Exclusions from Safety Set:

- INCL01: Informed consent not obtained.
- EXCL14: Clinical significant condition compromising patient safety or compliance
- OTH 02: Patient was Randomized but no study drug was taken.
- OTH 04: Patient receiving investigational drug other than study drug during the course of the study.

Exclusion from Randomized Set:

- INCL01: Informed consent not obtained.
- OTH 02: Patient was Randomized but no study drug was taken.
- OTH 12: Patient who received study medication before or without randomization

Exclusions from per-protocol set:

- INCL01: Informed consent not obtained.
- INCL02: Male and female adult patient ≥ 18 years old.
- INCL03: No current diagnosis of persistent Asthma of at least 6 months prior to Visit 1.
- INCL04: Patients are not treated with medium or high dose of ICS/LABA combination for at least 3 months and/or not at stable dose 1 month prior to Visit 1.
- INCL05: Lack of ACQ questionnaire and ACQ score < 1.5 at V101 and/or V201.
- INCL08: Patient has not demonstrated reversiblity via spirometry test at Visit 101 and does not have historical reversibility or bronchoprovocation.
- INCL08A: Patients without Historical reversibility OR bronchoprovocation according to ATS/ERS as per source documentation.
- EXCL01: Patient has a smoking history of > 20 pack years or missing.
- EXCL03: Asthma exacerbation within 6 weeks prior to Visit 1 or between Visit 1 and Visit 201 prior to randomization.
- EXCL03A: Asthma attack/exacerbation requiring SCS or hospitalization or ER visits within 6 weeks prior to Visit 1.

- EXCL08: Respiratory Tract Infection or asthma worsening between screening and 201 visits.
- EXCL08A: Respiratory Tract Infection within 4 weeks prior to V1.
- EXCL09: Chronic condition affecting the upper respiratory tract.
- EXCL10: Patient has a history of chronic lung diseases other than asthma.
- EXCL13: Investigational drugs used within 5 half-lives of enrollment, until the expected pharmacodynamics effect has returned to baseline, whichever is longer.
- EXCL 26: Patient is not on maintenance immunotherapy for allergies for at least 3 months prior to V101.
- EXCL 29: Unable to use dry powder inhaler device at V101 and/or V201.
- EXCL 30: Patient has history of alcohol or other substance abuse that would interfere with study conduct.
- COMD01: Banned asthma related Concomitant medication
- COMD06: Use of SABA other than rescue medication, not discontinued at visit 1
- COMD07: Use of parenteral corticosteroids less or unstable OCS dose than 4 weeks prior to visit 101
- COMD08: Intra muscular corticosteroid less than 3 months prior to visit 101
- COMD09: Use of biologic less than 3 months prior to visit 1 not in stable dose
- COMD12: ICS and LABA, not discontinued before required washout period to visit 101.
- OTH 02: Patient was Randomized but no study drug was taken.
- OTH 03: Patient received wrong treatment or expired drug.
- OTH 04: Patient receiving investigational drug other than study drug during the course of the study.
- OTH 05: Patient randomized more than once in the trial.
- OTH 06: Compliance failure of the Patient influencing the safety and efficacy date as per investigator judgment
- OTH 12: Patient who received study medication before or without randomization
- OTH 18: Prohibited asthma related medications started in periods different from the once stablish in the protocol

5.9 Rules to exclude patients using single depot corticosteriod injections:

Patients using below listed single depot corticosteriod injections will be excluded from efficacy analysis.

Reported Name of Drug, Med, or Therapy	Standardized Medication Name
CELESTONE CHRONODOSE	CELESTONA BIFAS
celestone(betamethasone acetate +sodium phosphate)	BETAMETHASONE SODIUM PHOSPHATE
CORTEROID RETARD (BETAMETHASONE ACETATO)	BETAMETHASONE ACETATE
Corteroid retard.	BETAMETHASONE
Diprospan	BETAMETHASONE
Methylprednisolone Acetate or Depo-Medrol	

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