NOVARTIS

Clinical Development

QMF149/Indacaterol acetate

CQMF149G2202 / NCT02892019

A multicenter, randomized, double-blind, active-controlled, 2 week treatment, parallel-group study to assess the efficacy and safety of indacaterol acetate delivered via the Concept1 inhalation device in children greater or equal to 6 and less than 12 years of age with asthma

Statistical Analysis Plan (SAP)

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27.3.2019	Before DB lock	Creation of Amendment 1	Added analysis of pre-dose trough FEV1 applying a different time window, excluding measurements outside of the 22 – 30 hour from last dose of the previous day (Day 13).	Section 2.5.4
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3.6.2019	Before DB lock	Creation of Amendment 1	Remove analysis for rescue use at screening.	Section 2.4
3.6.2019	Before DB lock	Creation of Amendment 1	Removed BMI categorization.	Section 2.3
13.8.2019	Before DB lock	Creation of Amendment 1	Added categorical ECG summaries for QTcF	Section 2.8.3

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
CSR	Clinical Study report
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
MedDRA	Medical Dictionary for Drug Regulatory Affairs
o.d.	Once Daily
PD	Protocol Deviation
PDS	Programming Dataset Specification
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
SAP	Statistical Analysis Plan
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 phase IIb clinical trial CQMF149G2202.

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 Appendix 5.

1.1 Study design

This study uses a randomized, multicenter, double-blind, active-controlled study design. The primary endpoint is change from baseline in pre-dose trough FEV1 (mL) after 2 weeks of treatment with indacaterol acetate in children with GINA step 2&3. Study treatment will be administered on top of background asthma ICS controller therapy (fluticasone propionate 100 µg b.i.d. or dose equivalent). This study will consist of 4 epochs: Screening, Run-in, Treatment, and Follow-up (telephone contact for safety).

The study population will consist of approximately 80 male and female children ≥6 years and < 12 years with persistent asthma for at least 1 year and on stable ICS dose (with or without additional controller medication) for at least 4 weeks prior to study start. It is anticipated that approximately 200 patients will need to be screened in order to randomize 80 patients into the treatment epoch. It is intended that approximately 72 patients will complete the study.

At Visit 201, all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients/subjects and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

The randomization scheme for patients/subjects will be reviewed and approved by a member of the Randomization Group.

Randomization will be stratified by region (EU, LA, and other)

No interim analysis is planned for this study.

1.2 Study objectives and endpoints

The study objectives and corresponding endpoints are summarized by the following table from the protocol.

Primary Objectives(s)	To evaluate indacaterol acetate 75 µg o.d and 150 µg o.d. in terms of change from baseline in pre-dose trough FEV1 after 2 weeks of treatment.

Secondary Objectives	• To evaluate the systemic exposure to indacaterol in plasma following sparse pharmacokinetic (PK) sampling on Day 1 and Day 14 after oral inhalation of indacaterol acetate 75 µg and 150 µg.
	• To evaluate the clinical effects and pharmacodynamics of indacaterol acetate (75 µg and 150 µg o.d.) after 2 weeks of treatment in terms of:
	  • Pediatric interviewer-administered Asthma Control Questionnaire (ACQ-IA) score at Week 2
	  • FEV_1 and forced vital capacity (FVC) rate at 30 minutes and 1-hour post dose at Week 2
	  • Rescue medication usage over 2 weeks of treatment as determined by patient diary data
	  • Symptoms as recorded by patient e-diary
	  • Pre-dose morning and evening peak expiratory flow (PEF) over 2 weeks of treatment as determined by electronic peak flow meter data.
	• To evaluate the safety (including labs, vital signs, ECG, adverse events), and tolerability of indacaterol acetate (75 and 150 µg o.d.) over 2 weeks of treatment.

2 Statistical methods

2.1 Data analysis general information

The statistical analysis will be performed by [redacted] (CRO) using SAS Version 9.4..

Since the sample size is limited, no inferential analysis will be performed and all analyses will be descriptive. The stratification is used in randomization mainly to minimize imbalance between treatment groups and will not be used in analysis.

2.1.1 General definitions

Study treatment/drug is indacaterol acetate. There are two treatment groups defined:

- Indacaterol acetate 75 µg capsules for inhalation, delivered via Concept1
- Indaceterol acetate 150 µg capsules for inhalation, delivered via Concept1

Indacaterol acetate will be provided as powder filled capsules with a Concept1 inhalation device.

Study day will be defined as the number of days since the date of first dose of study treatment. The date of first dose of study treatment will be defined as Day 1 and the day before the first dose of study treatment will be defined as Day -1.In general, baseline is defined as the last measurement before or at the randomization visit or prior to first administration of study drug on Day 1. Detailed baseline definitions for certain variable are described in Appendix 5.6.

2.2 Analysis sets

The following analysis sets are defined for data analysis.

- The Randomized Set (RAN) will consist of all patients who were assigned a randomization number; regardless of whether they actually received study medication. Patients in RAN will be analyzed according to the treatment they were randomized to. The RAN will be used for summaries of patient disposition, demographics, and baseline characteristics.
- The Full Analysis Set (FAS) will consist of all patients in the RAN who received at least one dose of study medication. Following the intent-to-treat principle, patients in the FAS will be analyzed according to the treatment they were randomized to.. 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. Rules for complete exclusion of subjects from the PPS will be defined in Appendix 5.4 prior to database lock and the un-blinding of the study. Patients in the PPS will be analyzed according to the treatment they actually received. The PPS will be used for supportive analysis of the primary efficacy analysis.
- The Safety Set (SAF) will consist of all patients who received at least one dose of study medication. Patients in the Safety Set will be analyzed according to treatment received. The Safety Set will be used in the analysis of all safety and pharmacokinetic variables. Note that the safety set allows the inclusion of non-randomized subjects who receive study drug in error.

2.2.1 Subgroup of interest

No subgroup analysis is planned for this study.

2.3 Patient disposition, demographics and other baseline characteristics

Demographic 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 spirometric parameters (FEV1, FVC, FEV1/FVC)
- FEV1 reversibility
- predicted and % of predicted FEV1
- duration of asthma
- history of asthma exacerbations
- prior concurrent medications (non-asthma and asthma-related)
- vital signs (systolic and diastolic blood pressure, pulse rate)
- peripheral blood eosinophil counts
- QTc using Fridericia's correction
- ACQ-IA.

Continuous variables will be summarized using descriptive statistics (number of non-missing data, mean, 25th percentile, median, 75th percentile, standard deviation, 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.

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

- Duration of asthma into < 1 year, 1 - 5 years, and > 5 - 10 years;
- Number of asthma exacerbations in the 12 months prior to the start of the study that required treatment into 0, 1 , >= 2
- pre-bronchodilator FEV1 into 50 - < 70%, 70% - <= 90% of predicted FEV_1
- Eosinophils counts into <300/mcl and >=300/mcl.

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.

2.3.1 Patient disposition

RAN will be used for the summaries and listings of patient disposition.

The number of patients will be summarized by region, country and treatment group.

Further, for each study epoch (i.e., screening, run-in, 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.

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

The number of patients included in each analysis set will be tabulated, as well as the reasons for exclusions from analysis set.

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

2.4.1 Study treatment / compliance

Compliance will be calculated by counting the days where study drug was administered "As per protocol" according to the records on the Dosage Administration Record (DAR) Summary eCRF. The percentage of days divided by the days of exposure will be analyzed. Compliance will be calculated by study treatment.

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

The above compliance analysis will be repeated for Fluticasone propionate.

The SAF set will be used to summarize duration of exposure. The extent of exposure will be examined to determine the degree to which safety can be assessed for the study drug. The extent of exposure to study drug will be characterized according to the duration of exposure and the number of subjects exposed. Duration of exposure to study treatment will be calculated as the number of days starting from the first dose date up to and inclusive of the last dose date. The duration of exposure will be summarized by treatment for the safety set as a continuous variable with the standard descriptive statistics.

2.4.2 Prior, concomitant and post therapies

All summaries will be by treatment group in the SAF Set.

Prior medications are defined as drugs taken and stopped prior to first dose of study medication. Any medication given at least once between the day of first dose of randomized study medication and last day of study visit will be a concomitant medication, including those which were started pre-baseline and continued into the treatment period.

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 they were continued or started after the first dose of study drug).
Asthma medications will be summarized by the route of administration, the recorded pre-specified drug subcategories (including types of combination) and the coded 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.

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.

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

The primary endpoint is change from baseline in pre-dose trough FEV1 after 2 weeks of treatment. The pre-dose trough FEV1 is defined as the mean of the two FEV1 values measured at -45 min and -15 min pre-dose.

The primary efficacy analysis will be based on the FAS.

2.5.2 Statistical hypothesis, model, and method of analysis

Summary statistics (n, mean, 25th percentile, median, 75th percentile, standard deviation, minimum, and maximum) by treatment will be provided for change from baseline in pre-dose trough FEV1 as well as pre-dose trough FEV1 after 2 weeks of treatment. Inferential testing statistics will not be performed since the sample size is small and power is limited. The data will be presented graphically as well.

2.5.3 Handling of missing values/censoring/discontinuations

If any of the -45 min and -15 min values contributing to the pre-dose trough FEV1 are collected within 7 days of systemic corticosteroid use, 6 h of rescue medication, or actual measurement times are outside the 22 - 30 hour from last dose of the previous day (Day 13) then the individual FEV1 value will be set to missing.

If one of the two values is missing (or set to missing) then the remaining non-missing value will be taken as pre-dose trough FEV1. If both values are missing, or if the patient withdrew from the study, regardless of the reason for discontinuation, then pre-dose trough FEV1 will be regarded as missing in which case the missing value(s) of the patient at the particular visit(s) would not contribute to the summary statistics.

For all spirometry measurements, implausible values will be excluded. If a patient has implausible FEV1 value (defined as > 7 L) at an assessment, all spirometry measurements related to that assessment will be excluded. The threshold of 7 L was chosen because according

to Polgar child predicted values, the maximum normal predicted FEV1 is 5.42 L, we set 7 L as the implausible cutoff to allow for some fluctuation around the maximum mean.

2.5.4 Supportive analyses

As a supportive analysis, summary statistics will be also performed on the PPS.

In addition, the same summary analysis on the FAS will be performed including all spirometric measures irrespective of systemic corticosteroid or rescue medication use but those measures taken outside of the 22 – 30 hour from last dose of the previous day (Day 13) will not be included.

In addition, the same summary analysis on pre-dose trough FEV1 will be performed applying a different time window, excluding measurements outside of the 22 – 25 hour from last dose of the previous day (Day 13).

No subgroup analysis is planned for the primary endpoint.

2.6 Analysis of the key secondary objective

There is no key secondary objective in this study.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

All secondary endpoints are listed as below.

- Pediatric interviewer-administered Asthma Control Questionnaire (ACQ-IA) score at Week 2
- FEV_1 and forced vital capacity (FVC) rate at 30 minutes and 1-hour post dose at Week 2
- Rescue medication usage over 2 weeks of treatment as determined by patient diary data
- Symptoms as recorded by patient e-diary
- Pre-dose morning and evening peak expiratory flow (PEF) over 2 weeks of treatment as determined by electronic peak flow meter data.

2.7.2 Statistical hypothesis, model, and method of analysis

Spirometry

All spirometric efficacy variables will be analyzed for the FAS, unless otherwise specified.

Summary statistics will be provided for post-dose FEV1 (30 min, 1 hr) by treatment. Similar analyses will be performed for pre-dose trough FVC and post-dose FVC and change from baseline in the spirometry values.

Pediatric ACQ-IA

ACQ-IA score at Visit 299 as well as change from baseline will be summarized by treatment using summary statistics. In addition, the proportion of patients who achieve an improvement

of at least 0.5 in ACQ-IA (i.e., a decrease of ACQ-IA score of at least 0.5 from baseline) at Visit 299 will be summarized by treatment.

Rescue medication

The number of puffs of the rescue medication use in the last 12-hour is recorded twice daily (morning/evening) by the patient's parent/caregiver in the e-Diary. The mean daily (morning + evening) number of puffs of rescue medication use over the 2 weeks of treatment will be summarized by treatment. The mean change from Baseline in the daily number of puffs of rescue medication use will be analyzed using summary statistics. No imputation will be done for missing data. This analysis will be performed for morning (night time) and evening (daytime) rescue medication use. Any values > 30 for the number of puffs of rescue medication in a 12 hour period will be set to missing. These high numbers are not realistic and could impact the analyses.

In addition, the percentage of 'rescue medication free days' (defined from diary data as any day where the patient did not use any puffs of rescue medication during daytime and nighttime) will be summarized by treatment.

Peak Expiratory Flow (PEF) Rate

All the patients are instructed to record PEF twice daily using an electronic Peak Flow Meter device, once in the morning and once approximately 12 hours later in the evening, from Run in visit 101 and throughout the study. PEF (liters/min) will be analyzed separately for morning and evening values. Mean values will be calculated over the 2 weeks treatment phase. Morning and evening PEF data averaged over the days of run-in period will be used as baseline values.

Mean morning/evening PEF will be summarized by treatment. In addition, change from baseline in mean morning/evening PEF during the 2 weeks treatment will be summarized.

Asthma symptoms based on e-Diary

Daily e-Diary recordings will be used to derive

- the mean daytime asthma symptom score i.e., the mean score over the 5 evening questions with respect to shortness of breath, wheeze, cough, chest tightness, and 'Did your respiratory symptoms stop you from performing your usual daily activities?', each with scores from 0 (no problems) to 4 (very severe problems)
- the total daily symptom score, defined as the sum of the nighttime score ('How often were you woken up by your asthma during the night?' with scores from 0 - 4), the morning awakening score ('Did you have asthma symptoms upon awakening in the morning?' with scores from 0 - 4) and the mean daytime asthma symptom score. The sum will be in the range of 0 – 12.
- day with no daytime symptoms, i.e., all 5 evening questions must have a score = 0. However, a patient will not be considered symptom free if they have used rescue medication that day even if his/her total daytime symptoms score is zero.
- night with no night-time awakenings, i.e., the question How often were you woken up by your asthma during the night?' must be answered with 'I did not wake up because of any breathing problems'

- morning with no symptoms on awakening, i.e., the question 'Did you have asthma symptoms upon awakening in the morning?' to be answered with 'None'
- asthma symptoms free days, i.e., days with no daytime symptoms and no night-time awakenings and no symptoms on awakening

Daily scores will be averaged for each patient over the days of the run-in period (which will be used as the baseline value) and the 2 weeks double-blind period. Specifically, the average score is defined as the sum of daily scores divided by the number of days where e-Diary records have been made on night time/morning/daytime score for the time period of interest. Days with no daytime symptoms, nights with no night-time awakenings, mornings with no symptoms on awakening, and days with no asthma symptoms will be expressed in percentage of days with data during the respective periods where diary recordings have been made. The same periods as for average scores will be analyzed for percentage of days. For post-baseline periods only the days on double-blind treatment will be considered. In addition, changes from baseline will be summarized as well.

2.7.3 Handling of missing values/censoring/discontinuations

Spirometry

Spirometry measurements taken within 7 days of systemic corticosteroid use, within 6 hours of rescue medication use or if the actual measurement times are outside the 22-30 hour post morning dose time window, then the individual FEV1 value will be set to missing and not be imputed, unless specified otherwise. For all spirometry measurements, implausible values will be excluded. If a patient has implausible FEV1 value (defined as > 7 L) at an assessment, all spirometry measurements related to that assessment will be excluded. The threshold of 7 L was chosen because according to Polgar child predicted values, the maximum normal predicted FEV1 is 5.42 L, we set 7 L as the implausible cutoff to allow for some fluctuation around the maximum mean.

Rescue Medication

No explicit imputation will be done for missing data.

Each night time use will be based on the data recorded in the 12h prior to the morning assessment and each daytime use will be based on the data recorded the 12h prior to the evening assessment. Where the number of puffs of rescue medication is missing but the rest of the e-Diary has non-missing data, the number of puffs will be assumed to be zero.

The daily total number of puffs of rescue medication will be divided by the total number of days with non-missing rescue data to derive the mean daily number of puffs of rescue medication taken for the patient for each given time interval. If the number of puffs is missing for part of the day (either morning or evening) then a half day will be used in the denominator. The non-missing data within the time period of interest will be used to calculate the mean value, as long as there are at least 7 days with non-missing data within a the time period.

Asthma symptoms based on e-Diary

Unless otherwise specified, no daily value for diary symptom score will be explicitly imputed.

The non-missing data within the time period of interest will be used to calculate the mean value, as long as there are at least 7 days with non-missing e-diary data within the time period.

E-Diary data recorded during the run-in period (visits 101-199) will be used to calculate the baseline values, as long as there is at least 7 days (e.g. 7 days) of non-missing data available. Otherwise, the baseline will be set as missing.

Peak Expiratory Flow (PEF) Rate

No explicit imputation will be done for missing data. The non-missing data within the time period of interest will be used to calculate the mean value, as long as there are at least 7 days with non-missing data within a the time period.

2.8 Safety analyses

All safety parameters will be summarized on the safety set.

2.8.1 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 summarized and listed. In general, summaries will include treatment-emergent adverse events only, i.e., those starting on or after the time of the first administration of study drug but not later than 7 days (30 days in the case of a SAE) after the last study drug administration. Any adverse events that started during the study before the time of the first inhalation of study drug of the first period will be classified as a prior adverse event.

The number and percentage of patients who reported treatment-emergent adverse events will be summarized by primary system organ class, preferred term, and treatment for

- all adverse events
- all adverse events by maximum severity
- adverse events suspected to be related to study drug
- adverse events leading to permanent study drug discontinuation
- serious adverse events
- fatal adverse events
- 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 indacaterol acetate 75 µg treatment group. If a patient reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. 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, where applicable.

In addition, the number and percentage of patients with the most frequent AEs will be summarized by treatment, in descending order of frequency in the indacaterol acetate 75 µg treatment group.

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.

2.8.1.1 Adverse events of special interest

The Compound Case Retrieval Strategy (CRS) will be used to determine the MedDRA search criteria to be used to identify events of special interest. The most recent list of adverse events of special interest at the time of database lock will be used.

2.8.2 Laboratory data

All laboratory samples will be processed through the central laboratory. Laboratory data consist of hematology, biochemistry and urinalysis measurements. All data will be listed with abnormal values being flagged.

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:

- 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 Appendix 5.7 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

Serum potassium and blood glucose at all visits will be summarized. All data will be included in the analysis regardless of rescue medication usage.

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) at any time post-baseline will be summarized by treatment based on the following criteria:

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.

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.

2.8.3 Other safety data

2.8.3.1 ECG and cardiac imaging data

ECG measurements include heart rate, QT interval, RR interval, PR interval, QRS duration, and QTc (calculated using Fridericia's formula as QTcF = QT / $3\sqrt{}$ RR (in seconds), where $3\sqrt{}$ denotes the cube root). Furthermore, an overall interpretation of the central cardiologist will be provided as well as a specification of abnormal findings.

ECG data measured more than 7 days after last inhalation of study drug are regarded as posttreatment 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:

- absolute values and change from baseline summarized by parameter, visit and time point. The by-visit/time point summaries will include the maximum QTcF and maximum heart rate (even if from post-baseline unscheduled and premature discontinuation visits, if not measured more than 7 days after last dose).
- the number and percentage of patients with newly occurring or worsening notable QTcF values (see Appendix 5.8 for definition of notable values) summarized by scheduled post-baseline visit and time point and additionally at any time on treatment considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits
- In addition to notable QTcF values, the number and percentage of patients with newly occurring or worsening QTcF values > 450 msec and >480 msec and change from baseline 0-30, >30 msec will be summarized by scheduled post-baseline visit and time point 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 time point 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, visit and time point. 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.

2.8.3.2 Vital signs

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

Weight will be summarized by visit and treatment group. Changes from baseline will also be summarized by treatment. The baseline measurement will be the measurement at Visit 101.

The following analyses will be performed by treatment:

- absolute values and change from baseline summarized by parameter, visit and time point. The by-visit/time point summaries will include the maximum and minimum 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 number and percentage of patients by parameter, visit and time point with
    - pulse rate < 40 bpm, 40 – 90 bpm, and > 90 bpm
    - SBP < 90 mm Hg, 90 – 140 mm Hg, and > 140 mm Hg
    - DBP < 50 mm Hg, 50 – 90 mm Hg, and > 90 mm Hg
- the number and percentage of patients with newly occurring or worsening notable vital signs values (see Appendix 5.8 for definition of notable values) summarized by parameter, scheduled post-baseline visit and time point and additionally at any time on treatment considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits

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.

2.9 Pharmacokinetic endpoints

For PK concentration data, listings and descriptive statistics will be provided. The descriptive statistics will comprise arithmetic and geometric means, SD, geometric CV, median, minimum

and maximum for plasma indacaterol concentrations at pre-dose (<2 hours) and at 15 min and 1 hour post-dose at Visit 199/201 and 299. Plasma concentrations will be expressed in pg/mL units. All concentrations below the lower limit of quantification or missing data will be labeled as such in the concentration data listings. Concentrations below the lower limit of quantification will be treated as zero in summary statistics of concentration data..

2.10 PD and PK/PD analyses

Not applicable.

2.11 Interim analysis

No interim analyses are planned for this study.

3 Sample size calculation

The sample size of 72 patients evaluable for the primary endpoint in the study is based on pragmatic considerations and per agreement with EU Pediatric Committee (PDCO), not based on statistical considerations. It is assumed that approximately 10% of patients will not complete the trial so that 80 patients need to be randomized to ensure 72 patients will be evaluable for the primary endpoint.

4 Change to protocol specified analyses

The study protocol planned a summary analysis on plasma cortisol and smoking exposure. As plasma cortisol and smoking exposure data will not be collected, this analysis will not be conducted.

The study protocol planned to summarize concomitant asthma related medications by pharmacological (ATC) class and preferred term and concomitant medications not related to asthma by ATC class. To be consistent with other studies under QVM program, which the study CQMF149G2202 is part of, asthma medications will be summarized by the route of administration, the recorded pre-specified drug subcategories (including types of combination) and the coded 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.

For primary endpoint it is described in the protocol that trough measurements outside the 22 - 25 hour window will not be considered for the analysis. This time window will be extended to a time window of 22 - 30 hours. A broader time window is considered appropriate given the known half-life of Indacaterol, which ranges from 40-56 hours and supports once daily administration. This also provides a reasonable time window for parents of school age children to schedule visits in which spirometry is assessed. A supportive analysis will be performed using the initial time window of 22 - 25 hours.

For consistency with QVM pivotal trials QTc time will be analyzed using Fridericia's formula and not Bazett.

5 Appendix

5.1 Imputation rules

The general approach to handling missing dates is shown below for dates of AEs, medical history diagnosis, and concomitant treatment. The imputation of missing dates for surgery or procedures will use the same rules as for concomitant treatment.

The detailed algorithms will appear in Programming Dataset Specifications (PDS).

5.1.1 Study drug

Missing date and time of study treatment will not be imputed for this study.

5.1.2 AE date imputation

Rules for imputing AE end date or start date will be provided in 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 PDS document in details.

5.2 AEs coding/grading

The MedDRA version which will be available at the time of database lock, will be used for the coding purpose of the adverse events.

5.3 Statistical models

Not applicable as no inferential analyses will be conducted.

5.4 Rule of exclusion criteria of analysis sets

The following table provides the protocol deviations (PD) and other criteria leading to partial or complete exclusion from analyses sets

Deviation ID	Description of Deviation
Deviations leading to exclusion from all analyses sets	
INCL02	Patient entered the study without signing the informed consent.
EXCL09	Parent/guardian has a history of psychiatric disease/intellectual deficiency, substance abuse, or other condition which limits the validity of consent for their child to participate.
Deviations leading to exclusion from RAN, FAS and PPS	
OTH05	Patient received study drug before or without randomization.
Deviations leading to exclusion from FAS, PPS and Safety	
OTH04	Patient randomized but did not receive study drug.
Deviations leading to exclusion from FAS and PPS	

Deviation ID	Description of Deviation
OTH03	Patient randomized in error, randomized more than once in this study, randomized in another study, randomized in wrong study.
Deviations leading to exclusion from PPS	
INCL01	Age < 6 years or greater than equal to 12 years or missing
INCL03	No documented diagnosis of Asthma for at least 1 year prior to study enrollment
INCL04	Patient not receiving daily treatment with ICS or ICS/LABA according to study requirements.
INCL05	Patient with a pre-bronchodilator FEV1 < 50% or > 90% of the predicted normal value, or spirometry not performed as per protocol or missing at the start and/or end of Run-in (Visits 101 and 199).
INCL06	Reversibility test is negative or missing or not performed as per protocol.
INCL08	Parents/ legal guardian not willing or able to assist the child with the procedures outlined in the protocol, eg. completion of electronic patient diary.
INCL09	Patient not able to use Concept1 dry powder inhaler or be proficient in use of other study devices (including those used during Run-in), or complete spirometry procedures.
EXCL01	Patient taking a mid-dose ICS (per GINA guidelines) in combination with LABA or high dose ICS.
EXCL03a	Patient who had more than 3 separate asthma attack/exacerbation in the 12 months prior to visit 1 or 1 asthma attack/exacerbation within 3 months prior to Visit 1
EXCL03b	Patient had an exacerbation requiring SCS/hospitalization or emergency room visit within 3 months prior to Visit 1 or > than 3 separate exacerbations in the 12 months prior to Visit 1.
EXCL04	Patient who had suspected or documented bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear that is not resolved within 4 weeks of Visit 1.
EXCL05	Patients who has prior intubation for asthma.
EXCL06	Patient not able to be compliant with study requirements or has any medical or mental disorder, situation, or diagnosis which could interfere with the proper completion of the study.
EXCL13	Patient is an immediate family member of the participating investigator, sub-investigator, study coordinator or employee of the participating investigator.
EXCL15	Any chronic condition of the respiratory tract which in the opinion of the investigator may interfere with study evaluation or optimal participation in the study.
EXCL16	History of chronic lung disease other than asthma within 3 months of V101 or other infection listed on.
EXCL25	Patients that receive immunotherapy or desensitization for allergies that started within 3 months prior to Visit 101 or where the maintenance dose is expected to change during the study.

Deviation ID	Description of Deviation
EXCL27	Patients that received treatment with any investigational agent within 30 days of Screening.
COMD01	LABA b.i.d taken within 48 hours prior to visit 101
COMD02	LABA o.d continuing at visit 1
COMD03	LAMA taken less than 7 days prior to Visit 101
COMD04	SAMA taken less than 8 hours prior to visit 101
COMD05	Fixed combinations of short-acting β2-agonist and short-acting anticholinergic taken within 8 hours prior to Visit 101.
COMD07	Short Acting B2 Agonist, other than Salbutamol / Albuterol is not discontinued after visit 1.
COMD08	Intra-muscular depot corticosteroids taken within 3 months prior to Run in 101
COMD09	Systemic (Parenteral or oral) corticosteroids taken within 3 months prior to run in 101
COMD10	Immunoglobin E inhibitors taken 6 months prior to visit 101
COMD11	Xanthines taken within 7 days prior to Run In 101
COMD12	Systemic mast cell stabilizers taken within 7 days prior to Run in visit 101
OTH01	Patient not having correct run in medication (i.e. 100mcg accuhaler or 125 mcg via MDI inhaler).
OTH02	Patient not taking run in medication as per protocol. (At least one dose less or more is missed by the subject)
OTH07	Patient took study drug not as per protocol.
OTH08	Patient received wrong treatment or expired drug.
WTH01	Patient remains on study treatment even after discontinuation and/or withdrawal on patient's or parent/legal guardian's wish.
WTH05	Patient experienced moderate or severe exacerbation according to Section 6.5.7 of study protocol, and not discontinued from study
WTH15	Blind broken and study treatment not permanently discontinued.
Deviations leading to exclusion of data collected after occurence of that event, from all analyses set	
WTH16	Study procedures performed after withdrawing of informed consent.

5.5 Baseline definitions

In general, baseline is defined as the last measurement before the first dose of study drug at Day 1. Detailed baseline definitions for diary data, vital signs, height and weight, ECG, laboratory data, ACQ-IA, FEV1, and FVC are provided below.

- For patient **diary data (PEF, symptoms, and rescue medication use**), the baseline values are defined as the average from all non-missing records taken in the run-in period over 14 days from Visit 101 up to the morning assessment at date of first dose of study drug (i.e., from Day -14 to Day 1 morning assessment inclusively). Missing diary data will not be imputed. If a patient has less than 7 days with non-missing data, then the respective baseline value will be set to missing.
- **Vital signs** include pulse rate (measured as radial pulse for 60 seconds) and systolic and diastolic blood pressures. Baseline vital signs are defined as the last scheduled assessment taken pre-dose on Day 1. Checks may be performed to ensure the assessments were indeed taken prior to the first dose of study drug on Day 1. If this assessment is missing or not confirmed to be pre-dose, the last value prior to the first dose will be used for baseline. Otherwise, the vital sign baseline will be set to missing without imputation.
- **Height and weight** are defined as the measurements taken at Visit 199. If the value is missing, then the value from Visit 101 will be used.
- **ECG** is defined as the last scheduled assessment (≤ -2 hr) taken prior to the first dose of study drug on Day 1. Checks will be performed to ensure the ECG was indeed assessed prior to the first dose of study drug. If the value on Day 1 is missing (or not confirmed to be pre-dose) then the last value prior to the first dose will be used for baseline. Otherwise, the ECG baseline will be set to missing without imputation. For baseline ECG interpretation there will only be one assessment at each time-point, and hence this will be used as the baseline ECG interpretation (pre-dose Day 1 value if present and confirmed to be pre-dose, otherwise the last value prior to the first dose).
- **Laboratory data** include hematology, clinical chemistry, urinalysis and hepatotoxicity. Baseline is defined as the last scheduled assessment taken prior to first dose of study drug on Day 1. Checks will be performed to ensure baseline laboratory values were indeed assessed pre-dose. If the pre-dose measurement on Day 1 is missing (or was not confirmed to be pre-dose), then the last value prior to the first dose may be used. Otherwise, the baseline laboratory data will be set to missing.
- **ACQ-IA** score is defined as ACQ-IA scores obtained on Day 1 (Visit 199). If the ACQ-IA score on Day 1 is missing then the last available ACQ-IA score prior to Day 1 will be used.
- **FEV1** is defined as average of the last FEV1 assessments taken at 45 minutes and 15 minutes prior to the first dose of study drug (Day 1, Visit 201). If any one of these assessments is missing (or is not confirmed to be pre-dose), then the remaining non-missing observation will be considered as baseline. If both assessments are missing (or are not confirmed to be pre-dose) then the last available average of the FEV1 assessments prior to Day 1 will be used for baseline. If the FEV1 measurements are missing on Day 1 and at the run-in visit, the respective baseline values will be set to missing. Measurements taken within 6 hours of rescue use or within 7 days of systemic corticosteroid use will be set to missing. For all spirometry measurements, implausible values will be excluded. If a patient has implausible FEV1 value (defined as > 7 L) at an assessment, all spirometry measurements related to that assessment will be excluded.

The threshold of 7 L was chosen because according to Polgar child predicted values, the maximum normal predicted FEV1 is 5.42 L, we set 7 L as the implausible cutoff to allow for some fluctuation around the maximum mean.

- **FVC** is derived in a similar way as baseline FEV1.

5.6 Laboratory parameters – definition of clinically notable values

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

Clinical notable criteria for selected laboratory tests

Laboratory parameter (unit)	Lower bound of clinically notable range	Upper bound of clinically notable range
Hematology		
Hematocrit (v/v))		
Male	*0.34*	
Female	*0.31*	
Hemoglobin (g/L)		
Male	*108*	
Female	*90*	
Thrombocytes (x10E^9/L	*75*	*700*
WBC's (x10E^9/L)	*2.4*	*16.0*
Chemistry		
Alkaline Phosphatase (U/L)	-	*2xULN*
Total Bilirubin (umol/L)	-	*35.9*
Creatinine (umol/L)		*132.6*
Potassium (mmol/L)	*3*	*6*
Glucose (mmol/L)	*2.78*	*11.10*
SGOT (U/L)	-	*3 x ULN*
SGPT (U/L)	-	*3 x ULN*
BUN/Serum Urea (mmol/L)		*10.71*
Albumin (g/L)	*10*	*70*
Gamma GT (U/L)		*3 x ULN*
Magnesium (mmol/L)	0.51	1.07

v = volume, ULN = upper limit of normal

5.7 Vital signs and ECG – definition of clinically notable values

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

Clinical notable criteria for vital signs

Vital sign parameter (unit)	Lower bound of clinically notable range	Upper bound of clinically notable range
Notable Value		
Systolic blood pressure (mmHg)	≤ 80 mmHg (6-8 years) or ≤ 85 mmHg (9-11 years) and decrease from baseline ≥ 20 mmHg	≥ 115 mmHg (6-8 years) or ≥ 120 mmHg (9-11 years) and increase from baseline ≥ 20 mmHg
Diastolic blood pressure (mmHg)	≤ 40 mmHg (6-8 years) or ≤ 45 mmHg (9-11 years) and decrease from baseline ≥ 20 mmHg	≥ 75 mmHg (6-8 years) or ≥ 80 mmHg (9-11 years) and increase from baseline ≥ 20 mmHg
Pulse rate (bpm)	Low" criterion: decrease from baseline ≥ 25% to a value < 70 bpm (6-8 years) or < 60 bpm (9-11 years)	increase from baseline ≥ 25% to a value > 115 bpm (6-8 years) or > 110 bpm (9-11 years) (according to internal draft ECQ_QT Guidelines)

Notable QT values are defined as QTc increases of 30-60 and >60 ms, and QTc >500 ms.

6 Reference

Polgar child predicted values for FEV1 (https://vitalograph.com/resources/ers-normal-values)