NOVARTIS

Global Clinical Development - General Medicine

QMF149/ Indacaterol acetate

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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

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List of abbreviations

ACQ-IA	Interviewer-administered Asthma Control Questionnaire
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATS	American Thoracic Society
b.i.d.	twice a day
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CFR	US Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
COPD	Chronic Obstructive Pulmonary Disease
CPO	Country Pharma Organization
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
DAR	Dose administration record
DPI	Dry powder inhaler
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
EDC	Electronic Data Capture
e-Diary	Electronic Diary
EOT	End of Treatment
ERS	European Respiratory Society
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GTL	Global Trial Leader
IB	Investigator Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine System
LABA	Long Acting Beta-2 Agonist
LAMA	Long Acting Muscarinic Antagonist

LFT	Liver function test
LTRA	Leukotriene Receptor Antagonist
MAP	Master analysis plan
MDDPI	Multi dose dry powder inhaler
MDI	Metered-dose inhaler
MedDRA	Medical dictionary for regulatory activities
OC/RDC	Oracle Clinical/Remote Data Capture
o.d.	once a day
PDCO	EU Pediatric Committee
PEF	Peak Expiratory Flow
PK	Pharmacokinetic
PPS	Per Protocol Set
PRO	Patient Reported Outcome
QTc	Corrected QT interval
RAN	Randomized Set
SABA	Short Acting Beta-2 Agonist
SAE	Serious Adverse Event
SAMA	Short Acting Anticholinergics
SAP	Statistical Analysis Plan
SCS	Systemic Corticosteroids
SDDPI	Single Dose Dry Powder Inhaler
SGPT	Serum Glutamic Pyruvic Transaminase
SUSAR	Suspected Unexpected Serious Adverse Reactions
TD	Study Treatment Discontinuation
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Cohort	A specific group of patients/subjects fulfilling certain criteria
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and Follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients/subjects with established disease and in those with newly-diagnosed disease.
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug(s), placebo/comparator active drug Run-in or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Protocol summary

Protocol number	**QMF149G2202**
Title	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
Brief title	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
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug and Concept1 Device (Breezhaler®)
Study type	Interventional
Purpose and rationale	This study is designed to explore lung function effects of two doses of indacaterol acetate, 75 µg and 150 µg, in pediatric asthma patients, and to compare the systemic exposure to indacaterol in plasma with historical data in adults, to identify an appropriate dose for Phase III evaluation.
Primary Objective(s)	The primary objective of this study is to evaluate indacaterol acetate 75 µg o.d and 150 µg o.d. in terms of change from baseline in pre-dose trough FEV_1 after 2 weeks of treatment.
Secondary Objectives	One secondary objective is 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. Other secondary objectives include the evaluation of clinical effects and pharmacodynamics of indacaterol acetate (75 µg and 150 µg o.d.) after 2 weeks of treatment in terms of: ACQ-IA score, lung function parameters, rescue medication usage and symptoms as recorded by patient e-diary. Safety (including labs, vital signs, ECG, adverse events), and tolerability of indacaterol acetate (75 and 150 µg o.d.) over 2 weeks of treatment will be evaluated.
Study design	A multicenter, randomized, double-blind, active-controlled, 2 week treatment, parallel-group study
Population	The study population will consist of approximately 80 male and female children ≥ 6 years and < 12 years with persistent asthma
Key Inclusion criteria	1. Male and female children ≥ 6 years and < 12 years with confirmed diagnosis of asthma for at least 1 year prior to study

	enrollment. 2. Written informed consent by parent(s)/legal guardian(s) and depending upon their age and local requirements a consent or assent for the patient. 3. Patients receiving daily treatment with a stable low dose Inhaled Corticosteroid (ICS) (with or without additional controller), or patients receiving daily treatment with a stable mid-dose ICS (monotherapy or together with LTRA) for at least 4 weeks prior to Screening, and able to tolerate fluticasone propionate 100 µg b.i.d. inhaler starting at Visit 1 (or soon after). 4. Patients with a pre-bronchodilator $FEV_1 \geq 50\%$ and $\leq 90\%$ of the predicted normal value for the patient at the start and end of Run-in (Visits 101 and 199). • Withholding period of bronchodilators prior to spirometry at Visit 101: SABA for ≥ 6 hours and FDC or free combinations of ICS/ Long Acting Beta-2 Agonist (LABA) for ≥ 48 hours, o.d. LABA for at ≥ 14 days, SAMA for ≥ 8 hours, LAMA for ≥ 7 days, xanthines ≥ 7 days • One-time re-testing of pre-bronchodilator FEV_1 is allowed only at Visit 101. Re-assessment should be done in an ad-hoc visit before randomization. 5. Patients who demonstrate an increase in FEV1 of ≥ 12% within 30 minutes after administration of 400 µg salbutamol/360 µg albuterol (or equivalent dose) at Visit 101. All patients must perform a reversibility test at Visit 101. Use of spacer devices is mandatory. Reversibility may be repeated once. 6. A single parent/legal guardian must be designated to complete all e-Diary entries and attend all clinic visits with the patient.
Key Exclusion criteria	1. Patients taking a mid-dose ICS (per GINA guidelines) in combination with LABA or any patient taking high-dose ICS. 2. Evidence of unstable disease within 4 weeks prior to Screening (Visit 1). 3. Patients who have had an asthma attack/exacerbation requiring systemic steroids (SCS) or hospitalization or emergency room visit within 3 months prior to Visit 1 (Screening) or more than 3 separate exacerbations in the 12 months preceding Visit 1. If patients experience an asthma attack/exacerbation requiring SCS or hospitalization between Visit 1 and Visit 199 they may be re-screened 3 months after recovery from the exacerbation. 4. 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 Screening (Visit 1). *5.* Prior intubation for asthma

	6. Patients who, in the opinion of the investigator, are not able to be compliant with study treatments, properly use study drug devices (e.g. DPI, MDI, Concept1, peak flow meter), or who have any medical or mental disorder, situation, or diagnosis which could interfere with the proper completion of the protocol requirements.
Study treatment	• Indacaterol acetate 75 µg capsules for inhalation, delivered via Concept1 • Indacaterol acetate 150 µg capsules for inhalation, delivered via Concept1
Efficacy assessments	• Spirometry • Pediatric ACQ-IA • Asthma symptoms based on e-Diary • Peak Expiratory Flow (PEF) • Rescue Medication Use
Key safety assessments	• Medical history and physical examination including oropharyngeal examination • Vital signs • Hematology, blood chemistry, urine dipsticks • Electrocardiogram (ECG) • Adverse events (AEs) including asthma exacerbations, worsening asthma, and serious adverse events (SAEs)
Other assessments	Pharmacokinetic (PK) analysis will be conducted in all patients
Data analysis	The primary endpoint is change from baseline in pre-dose trough FEV_1 (mL) after 2 weeks of treatment. Summary statistics (n, mean, 25^{th} percentile, median, 75^{th} percentile, standard deviation, minimum and maximum) by treatment group will be provided for change from baseline in pre-dose trough FEV_1 as well as pre-dose trough FEV_1 after 2 weeks of treatment. Inferential testing statistics will not be performed since the sample size is small and power is limited. For secondary endpoints (Spirometry, Pediatric ACQ-IA, Asthma symptoms recorded in e-Diary, Peak Expiratory Flow, Rescue Medication Use), summary statistics will be provided by treatment group.
Key words	indacaterol acetate, asthma, GINA 2015, pediatrics

1 Introduction

1.1 Background

Asthma is a chronic inflammatory disorder of the airways associated with hyper-responsiveness of airways that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction within the lung that is often reversible either spontaneously or with treatment. Airflow limitation occurs as a result of obstruction or narrowing of the airways when exposed to precipitating factors. Although exacerbations of asthma are episodic, inflammation is chronic (GINA Global strategy for Asthma management and prevention, 2015). Asthma is defined by its clinical, physiological, and pathobiological characteristics. The wide clinical spectrum of asthma is highly variable, and although different cellular patterns have been observed in asthmatic airways, the presence of airway inflammation remains a consistent feature.

Despite persistent airway inflammation, asthma symptoms are episodic and the relationship between the intensity of inflammation and the severity of asthma is not clearly established. In most patients, the inflammation affects all airways including the upper respiratory tract and nose, but the physiological effects are most pronounced in medium-sized bronchi. Despite the cellular heterogeneity of inflammatory response, the pattern of inflammation in the airways appears to be similar in all clinical forms of asthma at all ages, whether allergic, non-allergic, or aspirin-induced (GINA 2015).

Asthma most often starts early in life and has variable courses and unstable phenotypes which may progress or remit over time. Despite advances in medical management, childhood asthma continues to be a leading cause of emergency department visits, hospitalizations, and school days missed. Children afflicted with uncontrolled asthma have difficulty exercising, sleeping, and participating in the normal activities of childhood (Runge and Hill 2009). Asthma is the most common childhood chronic disease (Bastain et al 2011) and its prevalence has increased especially among children (GINA 2014). Children under 18 years represent one-third of all asthmatics according to the MMWR Surveillance summary - National surveillance for asthma 1980 to 2004 (United States) (Moorman et al 2007), with data showing that the incidence and prevalence of asthma is increasing more rapidly in children than that in adults, particularly in children under 15 years (Masoli et al 2004).

Due to this high impact of asthma on the quality of life of pediatric patients and caregivers, as well as is costs, several guidelines exist to support clinical care of pediatric asthmatics. Two types of medications are used to treat asthma: long-term control (“prevention”) medications and quick-relief medications, which reverse acute airflow obstruction. All children who have persistent asthma should be started on a long-term control (“prevention”) medication. Such anti-inflammatory medications are taken daily to reduce airway inflammation. The recommended type and dose of long-term control medication depends on the level of asthma severity and the age of the child. For persistent asthma, these guidelines recommend step wise intensification of asthma controller medications. Combinations of different controller medications are recommended as preferred treatment options by various guidelines (NIH, GINA, ICON). Especially fixed dose combinations (FDC) products containing a LABA plus

ICS have been shown to be safe and effective in the management of asthma and recommended by GINA as preferred controller therapy ≥ Step 3 for adult and pediatric population. In older children and adults, ICS/LABA combinations have been shown to improve asthma outcomes to a better extent than higher doses of ICS. ICS/LABA combinations are recommended as the preferred add-on treatment in children >5 years (SIGN, GINA), or >12 years (NAEPP), in other studies they are suggested as an option for children >5 years (AAMH, NAEPP) or at any age (JGPA) (Woolcock et al 1996, Greening et al 1994, Ducharme et al 2010). However, most of the currently available FDC products (e.g. salmeterol xinafoate/ fluticasone propionate) require twice a day (b.i.d.) dosing to achieve an optimum therapeutic effect in asthma.

Novartis is developing QMF149 which is a fixed-dose combination (FDC) of indacaterol acetate (inhaled LABA with 24 hour duration of action) and mometasone furoate (MF, ICS) for once-daily maintenance treatment of asthma in both adults and children 6 years of age and above. The mono-components are approved medications: indacaterol as the maleate salt for the treatment of chronic obstructive pulmonary disease (COPD) in adults, and MF for the use in asthma in adult and pediatric patients (Asmanex® Twisthaler®).

QMF149 FDC has been used in clinical trials in healthy volunteers, and adult and adolescent asthma patients. Indacaterol acetate has been investigated in healthy volunteers and adult asthma patients and demonstrated a lower incidence of post-inhalation cough compared to indacaterol maleate in asthma patients, while maintaining bronchodilator efficacy, with a very similar safety profile (study CQAB149D2301).

Studies CQMF149E2203 and CQAB149B2357 evaluated indacaterol acetate and maleate, respectively delivered via the Concept1 (Breezhaler®) inhaler in patients with asthma. These two studies support selection of indacaterol dose 150 µg once daily in the adult and adolescent population.

A dose-ranging study of indacaterol maleate in adult asthmatic patients demonstrated that a dose of 150 µg o.d. was safe and effective (Study CQAB149B2357). The dose of indacaterol acetate was investigated in Study CQMF149E2203 in adult asthma patients, where indacaterol acetate 150 µg and 75 µg was delivered via Concept1 compared to placebo. The study demonstrated that both 150 µg and 75 µg doses were found to be superior to placebo and indacaterol acetate 150 µg showed positive trends in terms of trough forced expiratory volume in 1 second (FEV_1), peak expiratory flow (PEF), and rescue medication use compared with indacaterol acetate 75 µg.

This study is part of the pediatric development plan for QVM149 and is designed based on agreement with EU Pediatric Committee (PDCO). Prior to progressing into Phase III testing of QMF149 in ≥6, <12-year-old children, a dose selection study of indacaterol in this population is needed. The objective of the study is to assess the benefit of two doses of indacaterol when added to baseline ICS therapy to identify an appropriate dose to carry forward for Phase III evaluation. This will be achieved by assessing the totality of lung function data, symptoms and systemic exposure to indacaterol in 6 to 11-year-old children compared with historical PK data collected in adults.

1.2 Purpose

This study is designed to explore lung function effects of two doses of indacaterol acetate, 75 µg and 150 µg, in pediatric asthma patients 6-11 years old, and to compare the systemic exposure to indacaterol in plasma with historical data in adults, to identify an appropriate dose to Phase III evaluation.

2 Study objectives and endpoints

2.1 Primary objective(s)

To evaluate indacaterol acetate 75 µg o.d and 150 µg o.d. in terms of change from baseline in pre-dose trough FEV_1 after 2 weeks of treatment.

2.2 Secondary objective(s)

- 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.

2.3 Exploratory objectives

Not applicable

3 Investigational plan

3.1 Study design

This study uses a randomized, multicenter, double-blind, active-controlled study design. The primary endpoint will be evaluated after 2 weeks of treatment with indacaterol acetate as change from baseline in children ≥6 years and <12 years (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).

Screening (Visit 1)

At an initial Screening visit (Visit 1) informed consent is obtained from the parent(s)/legal guardian(s). Additionally, a patient assent is obtained before any study-related assessments or procedures are performed (according to locally accepted policy/practice). Patients will be screened to determine eligibility (Section 4.1 and 4.2). Where appropriate, concomitant medications are adjusted at this visit and washout begins for any prohibited medications. The window between Visit 1 and 101 (Screening Epoch) is to complete all Screening measures and to washout prohibited medications (Table 5-1, Table 5-2 and Table 5-3). It can be as short as necessary and last up to 30 days.

Patients meeting Screening eligibility will receive the following at the Screening visit (Visit 1):

- Fluticasone propionate 100 µg b.i.d. delivered via Diskus®/ Accuhaler® (if not available in a specific country, fluticasone propionate 125 µg b.i.d. via MDI inhaler; if these formulations are not available, then the closest equivalent to fluticasone propionate 100 µg b.i.d. should be given; MDI can be used with spacer).

  The child's parent/ legal guardian will be instructed that their child discontinue their current ICS and be placed on fluticasone propionate. If their child has already taken his/ her ICS prior to arriving at the site, then the child should begin using the provided fluticasone inhaler the next day. Patients will be instructed to take their fluticasone inhaler daily in the morning and evening, in place of their previous ICS.
- The patient's parent/ legal guardian must be instructed that the patient should NOT take fluticasone on the mornings before arriving at the site for their study visits. They will take their morning fluticasone dose at the site on those days. Therefore, it is important that they bring the fluticasone inhaler with them to every study visit. If it is found that a patient did take the fluticasone morning dose prior to arriving at the site, this should be documented in the patient's source and the visit will go on as scheduled.
- Patients will receive the short acting β2-agonist (SABA) salbutamol/albuterol to use as rescue medication throughout the study. Parents/ legal guardians must be instructed that their child NOT take rescue salbutamol/albuterol for at least 6 hours prior to any of their study visits (unless they are experiencing symptoms that mandate salbutamol/albuterol inhalation, in which case the visit would be re-scheduled). Spacers are allowed for the rescue medication use. No other rescue medication is allowed in the study.
- Patients/ patient's parent/legal guardian will be issued an electronic diary (e-Diary) to record asthma symptoms and rescue medication use, which will be completed by the patient's parent/legal guardian. The patient's parent/legal guardian will be instructed to bring the e-Diary with them to every study visit.
  - Patients will also be issued an electronic Peak Flow meter (part of e-Diary) to record their Peak Expiratory Flow (PEF) rate. The patient and his/her parent/legal guardian will be instructed on how to use this device.
- Patients are allowed to use a spacer while taking their inhaled medication and must use a spacer for reversibility testing.

Visit 1 should be conducted up to 30 days before Visit 101. Visit 1 and 101 may occur on the same day, as long as no washout is required (no short-acting rescue medication taken within 6 hours, and appropriate washout of prohibited treatment in Table 5-1, Table 5-2 and Table 5-3).

Patients should bring their ICS (fluticasone propionate) inhaler, rescue salbutamol/albuterol, PEF and e-Diary, and all study medications with them to every study visit.

Run-in epoch (Visit 101-Visit 199)

Once patients' concurrent medications comply with the requirements of the study (Section 5.5.6 and 5.5.8) patients will enter a Run-in epoch.

The Run-in epoch is 2 weeks in duration (Visit 101 and 199) and will be used to further assess eligibility (including meeting reversibility and FEV_1 criteria, collecting baseline patient characteristics, and reviewing fluticasone and rescue salbutamol/albuterol use).

Patients are instructed NOT to take their fluticasone inhaler in the morning of these study visits, and should bring it with them to the site. The patients should take their fluticasone inhaler at the beginning of each study visit, under supervision of the site staff. The patient will take their fluticasone inhaler back home with them and be instructed to take it as directed.

During Visit 101, study staff will administer the pediatric Asthma Control Questionnaire to the child. The Asthma Control Questionnaire – interviewer-administered (ACQ-IA) is further discussed in Section 6.4.2.

Approximately two weeks after the start of the Run-in epoch (Visit 101 + 14 days), the patient will return to the clinic in the morning for Visit 199 (end of Run-in), to have all eligibility criteria reviewed along with their e-Diary and PEF meter and complete another ACQ-IA. If the patient continues to meet eligibility criteria (no salbutamol/albuterol taken within 6 hours of this visit and $FEV_1 \geq 50\%$ and $\leq 90\%$ of the predicted normal value for the patient) the patient will immediately continue to Visit 201 (Randomization/ Day 1).

If the patient's FEV_1 and/or reversibility do not meet criteria at Visit 101, these assessments can be repeated one time, on a different day. For learning purposes, spirometry training can be provided prior to actual measurements.

Table 6-1 displays all Run-in procedures.

For all subsequent study visits, the patient's parent(s)/legal guardian(s) should be instructed that their child does NOT take the morning dose of fluticasone, as they will take this dose at the site and the investigator will observe the inhalation technique of the child. Additionally, patients should NOT take any rescue salbutamol/albuterol for a minimum of 6 hours prior to arriving for their next study visit. If rescue medication is taken within 6 hours of a study visit, the visit must be rescheduled.

NOTE: Since the first spirometry measurement is 45 minutes prior to inhalation of study medication (Visit 199), and study medication is administered in the morning, it is important to schedule the remaining study visits early enough so the patient will have enough time to take their fluticasone on site, have other study assessments done (vital signs and lab) and have the first spirometry 45 minutes prior to inhalation of study medication. Refer to Table 6-2 and Table 6-3 for details.

Treatment epoch (Visit 201-Visit 299)

If the patient continues to meet eligibility criteria, Visit 201 (randomization/ Day 1) occurs on the same day as Visit 199. Qualifying patients will be randomized to one of the two treatment groups below, with an equal (1:1) randomization ratio:

- Indacaterol acetate 75 µg delivered via Concept1 o.d. in the morning
- Indacaterol acetate 150 µg delivered via Concept1 o.d. in the morning

The treatment epoch will last 2 weeks. Patients will receive their first dose of study medication at the site, and the patient's parent/legal guardian should be instructed to give their child study medication at approximately the same time each day. Patients will return to the clinic 2 weeks later for the end of treatment visit (Visit 299).

All patients will be required to attend the clinic visits (Visit 201 and 299) where they will take their morning fluticasone dose, have pre-dose trough measurements of lung function prior to taking the study medication, and post-dose measurements.

Parents/legal guardian(s) will be instructed to record the time of their child's last dose of study medication taken the day prior (~Day 13) to their final treatment visit (Visit 299/Day 14). Additionally, parents/legal guardians should be instructed that their child should not take the last dose of study medication on the day of the last clinic visit (Visit 299/ end of treatment). Rather, the patient (parent/legal guardian) should bring their medication with them to the clinic and this dose will be administered under the supervision of study personnel. If study medication has not been taken in the morning on day 13 (last day before end of treatment Visit 299), the visit has to be rescheduled.

PK sampling (taken ≤ 2 hours pre-dose and at 15 minutes and 1 hour post-dose) will be performed at Visit 199/201 and 299 (Table 6-1 through 6-3). The ACQ-IA will also be done at Visit 299.

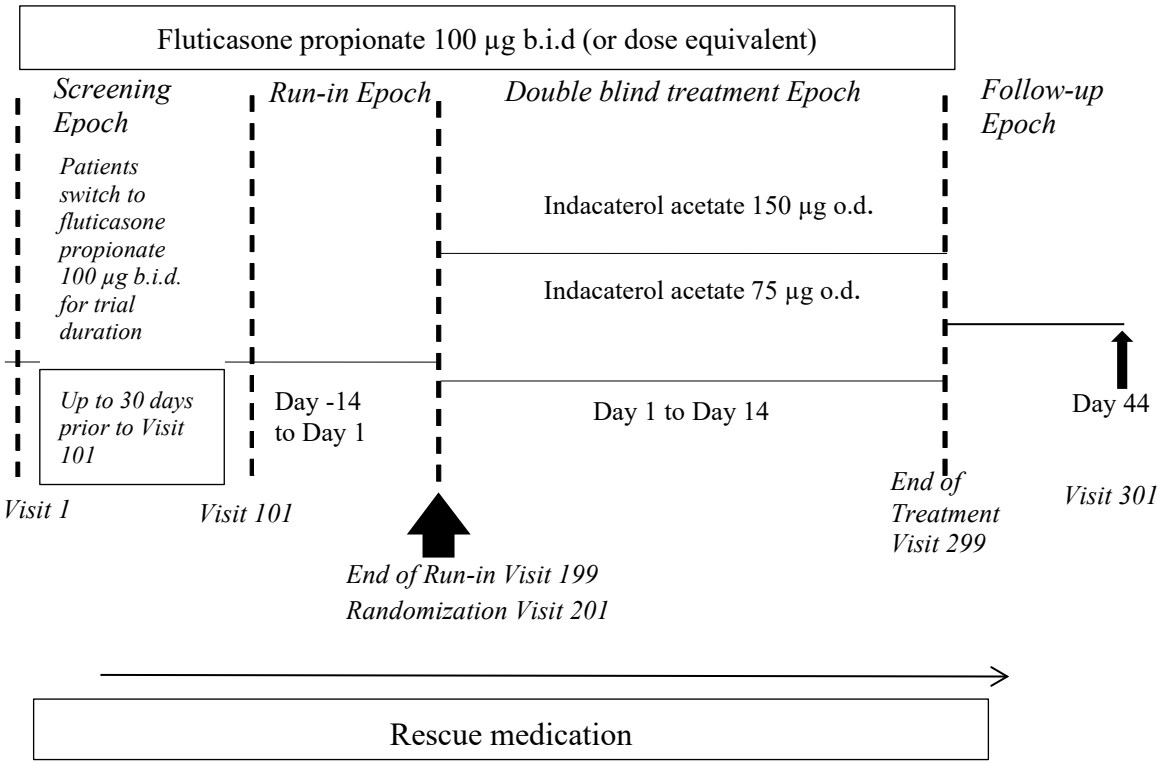
Patients should be seen for all visits on the designated day or as close as possible.

Follow-up epoch

A final telephone contact must be conducted at 30-days after last treatment date (telephone Visit 301). Patients who discontinue their study treatment prematurely will return to the clinic for Visit 299 as a Discontinuation visit and then directly move to Follow-up and disclose with Visit 301.

Figure 3-1 shows the study design.

Figure 3-1 Study design



3.2 Rationale for study design

This study is a randomized, double-blind, parallel-group study, with a 2-week treatment duration to assess 2 different doses of indacaterol acetate. The primary endpoint, trough FEV_1, will be evaluated as change from baseline (randomization) after 2 weeks. This is considered an adequate duration to demonstrate improvements in the primary endpoint of lung function based on the known pharmacodynamic properties of indacaterol.

In order to preserve the integrity of the study, a randomized, double-blind study design is used. This design enables the study treatments to be given for an appropriate and practical length of time to assess the efficacy and safety of the treatments. The study design does not include a placebo control, as this would not be considered ethical in this population of pediatric asthma patients with GINA ≥ Steps 2 and 3 (GINA 2015).

The primary objective of this trial is to evaluate the efficacy of 2 doses of indacaterol in patients with persistent asthma in terms of lung function (measured by pre-dose FEV_1). Other efficacy endpoints include peak expiratory flow, rescue medication, and FEV_1 at 30 minutes and 1 hour post-dose.

Additional secondary endpoints include the evaluation of the systemic exposure to indacaterol in plasma according to a sparse PK sampling (≤ 2 hours pre-dose, and 15 minutes and 1 hour post-dose). This will allow comparison of the systemic exposure to indacaterol after single dose (Day 1) and at steady state (Day 14) observed in these pediatric patients with that collected in adult healthy subjects or patients (historical data). Safety is also evaluated.

The lung function data combined with systemic exposure will be used to identify an appropriate dose of indacaterol which will be carried forward to the Phase 3 pediatric trials. The primary endpoint, change in baseline of pre-dose trough FEV1, will be evaluated descriptively as a function of change from baseline between the two indacaterol doses. Taken together with systemic exposure for each dose, which will be compared with historical PK data collected in adults, an appropriate dose will be selected.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

The dose/regimen, route of administration and duration of treatment are based upon known pharmacokinetic/pharmacodynamics effects of indacaterol as well the clinical data from Phase II studies in asthma in adults.

Indacaterol maleate (Onbrez Breezhaler; QAB149) is a LABA approved globally as a once-daily maintenance bronchodilator treatment of airflow obstruction in adult patients with COPD. The recommended dosage for COPD is 150 µg and 300 µg outside of the US and Canada; US and Canada is approved at 75 µg.

A dose-ranging study of indacaterol maleate in asthmatic patients demonstrated that doses of 75 µg o.d. and 150 µg o.d. were safe and effective with greatest improvements in trough FEV_1 (Study CQAB149B2357).

The acetate salt of indacaterol was found to result in a lower incidence of the post-inhalation cough compared to indacaterol maleate, without impact on efficacy or safety (study CQAB149D2301). For indacaterol, the acetate salt will be used due to lower incidence of post-inhalation cough.

The dose of indacaterol acetate on a mometasone furoate background therapy was investigated in Study CQMF149E2203 in adult asthma patients where indacaterol acetate 150 µg and 75 µg delivered via Concept1 were compared to placebo. The study demonstrated statistically significant improvements compared to placebo for both 150 µg and 75 µg doses. Additionally, indacaterol acetate 150 µg showed positive trends in terms of trough FEV_1, PEF, and rescue medication use compared with indacaterol acetate 75 µg. QMF149 FDC via Twisthaler (indacaterol maleate in a dose equivalent to 150 µg Concept1 with mometasone furoate) demonstrated significant improvement in trough FEV_1 and significant reduction in the risk of exacerbations requiring systemic corticosteroids in adult and adolescent asthma patients (study CQMF149A2210). These data support the evaluation of indacaterol up to 150 µg daily.

There is limited information about pharmacokinetics of indacaterol in the pediatric population. In a previous PK and PD study (Study CQAB149C2101), in asthmatic patients ranging from 4 to 11 years of age, 24 children were randomized to receive doses of 100, 200 or 400 µg indacaterol maleate delivered via a multi dose dry powder inhaler (MDDPI/Certihaler™). During the conduct of the study, as a result of a malfunction with a commercial Foradil® Certihaler™, this study was terminated after the enrolment of only 12 children. Therefore, the pharmacokinetic information was incomplete and firm conclusions could not be drawn. In general; however, the systemic exposure appeared to increase with increasing dose and the data suggested that after 7 days of once-daily dosing systemic exposure was close to steady-state.

On the basis of dose-normalized AUCs the exposure seemed to be similar to that of adults. The limited data set showed no correlations to age or body weight. In the adult COPD population, covariate analysis on age, body weight, and body mass index did not indicate a need for change in dosage regimen. Therefore the selected doses of indacaterol acetate are anticipated to result in systemic exposure in 6-11-year-old children that is similar to the systemic exposure of indacaterol maleate in adults.

Based on the totality of the available data in adults as well as limited PK information in children, the 75 and 150 ug doses of indacaterol are considered appropriate for evaluation to establish appropriate dose for confirmatory Phase III studies.

3.4 Rationale for choice of comparator

It was considered appropriate to explore two doses of indacaterol acetate, 75 µg o.d. and 150 µg o.d. in 6-11-year-olds and to compare the systemic exposure obtained in this trial with that obtained in adults (historical data). Relative differences in lung function between 2 doses will be evaluated descriptively.

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable

3.6 Risks and benefits

The risk to patients in this trial will be minimized by compliance with the eligibility criteria and by close clinical monitoring. Although altering current asthma medication regimens during the trial carries an inherent risk of a decline in lung function and/or a worsening of symptoms, providing patients with rescue medication (salbutamol/ albuterol) and requiring them to take background ICS (fluticasone propionate 100 µg b.i.d.) throughout the trial mitigates this risk.

Patients will be required to perform repetitive lung function measurement maneuvers during the study, and these can lead to cough, shortness of breath, dizziness, or exhaustion. PEF measurements are part of the usual care of most pediatric asthma patient and are not considered an additional burden to patients. Considering the 2-week treatment duration, the number of assessments is relatively small and these are part of the regular medical assessments of this patient population. Other procedural risks are related to blood sampling for safety or PK laboratory analyses: puncturing of the veins can cause discomfort, pain, hematoma, or in rare cases lead to an infection.

The risk to the patients in participating in the study is that QMF149 is under development and there is limited safety data in children 6-11 years old for indacaterol. Data to support the efficacy and safety of indacaterol in adolescents was demonstrated in one large Phase II event driven trial with a duration up to 68 weeks in over 1500 moderate to severe asthma patients including 66 adolescents (12-17 years old). Patients treated with QMF149 (indacaterol/mometasone delivered by Concept1) compared with patients treated with MF delivered by Twisthaler showed a favorable efficacy and safety profile over MF (Beasley et al 2015).

It is possible that unexpected safety issues may be identified; this will be minimized by compliance with the eligibility criteria and close clinical monitoring. The risks of side effects are well characterized in adult population in COPD as well from the early QMF149 asthma

development in the Twisthaler® device (see Section 1.1 Background and QMF149 Investigator Brochure (IB)).

There are concerns that LABA treatment used alone in asthma might cause severe asthma exacerbations. To address this safety concern, all patients are treated with background ICS in this study so LABA alone will not be allowed.

During the trial, additional treatment options for the patients are limited as the protocol does not allow administration of other asthma medications except ICS, previously initiated Leukotriene Receptor Antagonist (LTRA), and short acting β2-adrenergic receptor agonist (SABA) for rescue use. Furthermore, patients will have to discontinue their pre-study ICS controller medication and begin taking fluticasone propionate. Change of the device and controller medication may introduce a risk for worsening of asthma symptoms and lung function for these patients due to reduced adherence. ICS therapy as controller treatment for asthma is aligned with GINA guidelines at all times. In order to minimize the risk to patients, extensive safety monitoring (e.g. electronic daily patient dairy assessment of rescue medication use, PEF measurements, and adverse event monitoring) will be carried out throughout the study. E-Diary data will be transmitted electronically from the device to the investigator regularly.

Investigators should withdraw a patient if they feel, based on their medical judgment, that this would be best for the patient, or after occurrence of any of the discontinuation criteria listed in Section 5.6.2. Parents/legal guardians are also instructed that their child can withdraw from the trial at any time, and for whatever reason.

The potential individual benefit for the patient lies in a thorough medical evaluation of the patient's disease and close clinical monitoring for the duration of the study. The potential benefit also includes an improvement in lung function, and symptoms (during treatment periods). All patients in the study will be receiving active treatment with indacaterol acetate on ICS background, which is consistent with GINA treatment guidelines. There ***is no placebo arm***, which mitigates risk of under-treatment.

4 Population

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, GINA step 2 & 3) 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. Dropouts may be replaced if dropout rate is higher than expected (>10%).

4.1 Inclusion criteria

Patients/subjects eligible for inclusion in this study must fulfill all of the following criteria:

1. Male and female children ≥ 6 years and <12 years.
2. Written informed consent by parent(s)/legal guardian(s) for the pediatric patient and assent by the pediatric patient (depending on local requirements) must be obtained before any study-specific assessment is performed.

3. Confirmed diagnosis of asthma, as defined by national and international asthma guidelines (GINA 2015) for at least 1 year prior to study enrollment.
4. Patients receiving daily treatment with a stable low dose ICS (with or without additional controller), or patients receiving daily treatment with a stable mid-dose ICS (monotherapy or together with LTRA) for at least 4 weeks prior to Screening, and able to tolerate fluticasone propionate 100 µg b.i.d. inhaler starting at Visit 1 (or soon after).
5. Patients with a pre-bronchodilator FEV_1 ≥50% and ≤ 90% of the predicted normal value for the patient at the start and end of Run-in (Visits 101 and 199) (performed according to ATS/ERS guidelines).
   - Withholding period of bronchodilators prior to spirometry at Visit 101: SABA for ≥ 6 hours and FDC or free combinations of ICS/LABA for ≥ 48 hours, o.d. LABA for at ≥ 14 days, SAMA for ≥ 8 hours, LAMA for ≥ 7 days, xanthines ≥ 7 days
   - A one-time re-testing of pre-bronchodilator FEV_1 is allowed only at Visit 101. Re-assessment should be done in an ad-hoc visit to be scheduled on a date that would provide sufficient time to receive confirmation from the spirometry data central reviewer of the validity of the assessment before randomization.*
6. Patients who demonstrate an increase in FEV_1 of ≥ 12% within 30 minutes after administration of 400 µg salbutamol/360 µg albuterol (or equivalent dose) at Visit 101 (performed according to ATS/ERS guidelines, use of spacer mandatory). All patients must perform a reversibility test at Visit 101. If reversibility is not demonstrated at Visit 101, it may be repeated once. If reversibility is still not demonstrated at Visit 101 (or after repeated assessment) patients must be screen failed.*

   *If patients do not meet FEV_1, reversibility or ATS/ERS criteria after re-testing, patients may be re-screened once.
7. A single parent/legal guardian must be designated to complete all e-Diary entries and attend all clinic visits with the patient.
8. Parents/ legal guardian must be willing and able to assist the child with the procedures outlined in the protocol, e.g. compliance with study medication, completion of electronic patient diary.
9. Patient must be able to use Concept1 dry powder inhaler and also be proficient in use of other study devices (including those used during Run-in), and complete spirometry procedures.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Patients taking a mid-dose ICS (per GINA guidelines) in combination with LABA or any patient taking high-dose ICS.
2. Evidence of unstable disease within 4 weeks prior to Screening (Visit 1) that in the opinion of the investigator would put the safety of the subject at risk through study participation or would confound the interpretation of the results if the condition/disease exacerbated during the study.

3. Patients who have had an asthma attack/exacerbation requiring SCS or hospitalization or emergency room visit within 3 months prior to Visit 1 (Screening) or more than 3 separate exacerbations in the 12 months preceding Visit 1. If patients experience an asthma attack/exacerbation requiring SCS or hospitalization between Visit 1 and Visit 199 they may be re-screened 3 months after recovery from the exacerbation.
4. 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 Screening (Visit 1).
5. Prior intubation for asthma
6. Patients who, in the opinion of the investigator, are not able to be compliant with study treatments, properly use study drug devices (e.g. Dry powder inhaler (DPI), MDI, Concept1, peak flow meter), or who have any medical or mental disorder, situation, or diagnosis which could interfere with the proper completion of the protocol requirements.
7. History of hypersensitivity to any ingredients of the study drugs including indacaterol, rescue medication, or fluticasone. This includes any known hypersensitivity or intolerance to the excipients, including lactose.
8. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption or diagnosed intolerance to lactose or milk products.
9. Parent/guardian has a history of psychiatric disease, intellectual deficiency, substance abuse, or other condition (e.g. inability to read, comprehend and write) which will limit the validity of consent for their child to participate in this study.
10. Patients with a history of long QT syndrome or whose corrected QT interval (QTc) measured at Visit 101 and 199 (Fridericia method) is prolonged (≥ 450 msec for boys and girls) and confirmed by a central assessor (these patients should not be rescreened).
11. Patients who have a clinically significant ECG abnormality at Visit 101 (start of Run-in) and prior to randomization (Visit 199).
12. Patient who is a ward of the state or government.
13. Patient is an immediate family member of the participating investigator, sub-investigator, study coordinator, or employee of the participating investigator
14. History of malignancy of any organ, treated or untreated within the past 5 years, whether or not there is evidence of local recurrence of metastases
15. 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
16. History of chronic lung disease other than asthma within 3 months of Visit 101, sarcoidosis interstitial lung disease, cystic fibrosis, and known active bacterial, viral, fungal, mycobacterial or other infection (including active tuberculosis or atypical mycobacterial disease).
17. Patients with Type I diabetes or uncontrolled Type II diabetes.
18. Patients who have any clinically significant abnormal lab values reported at Visit 101.
19. History or presence of impaired renal function as indicated by clinically significantly abnormal creatinine or blood urea nitrogen (BUN) and/or urea values, or abnormal urinary constituents (e.g., albuminuria).

20. History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result.
21. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study.
22. Patients receiving any asthma-related medications in the classes specified in Table 5-1 unless they undergo the required washout period prior to Visit 101 and follow the adjustment to treatment program.
23. Patients receiving medications in the classes listed in Table 5-2 should be excluded unless the medication has been stabilized for the specified period and the stated conditions have been met.
24. Patients receiving any of the prohibited medications in the classes listed in Table 5-3 should be excluded.
25. Immunotherapy or desensitization for allergies started within 3 months prior to Visit 101, or where the maintenance dose is expected to change during the study.
26. Parent or legal guardian unable or unwilling to complete an electronic patient diary.
27. Treatment with any investigational agent within 30 days of Screening.
28. Pregnant or nursing (lactating) females

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

The Investigational treatments are as follows:

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

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

Under no circumstances is an alternative inhalation device to be used for the administration of indacaterol acetate capsules during the treatment period.

Both doses of indacaterol acetate will be supplied by Novartis Drug Supply Management in blister packs, providing sufficient quantity of medication to last each patient between visits.

Patients will be instructed by study personnel on the correct technique and dosing instructions for the device. Dosing will be supervised by the site personnel. Dispensation instructions are provided in Sections 5.5.2, 5.5.3, and 5.5.4. Instructions for use of the Concept1 device are provided in Appendix 1.

5.1.2 Additional treatment

At Visit 1 (Screening visit), patients will be provided with a salbutamol/albuterol inhaler to use as rescue medication on an "as needed" basis throughout the study (Section 5.5.6). Additionally, patients will be supplied with a fluticasone propionate inhaler (Diskus®/ Accuhaler®) and will be instructed to take 100 µg b.i.d for the trial duration (if not available in

a specific country, MDI dosed 125 µg should be used; in case these formulations are not available, then the closest equivalent to fluticasone propionate 100 µg b.i.d. should be given; MDI can be used with spacer). Patients taking another ICS (with our without controller medication) must be discontinued from that medication and begin the fluticasone propionate provided. Patients taking background LTRA may continue this throughout the study, if all other entry criteria are met.

5.2 Treatment arms

Patients/subjects will be randomized at Visit 201 to one of the following two treatment arms in a ratio of 1:1

- Indacaterol acetate 75 µg o.d. delivered via Concept1 inhaler (in the morning)
- Indacaterol acetate 150 µg o.d. delivered via Concept1 inhaler (in the morning)

5.3 Treatment assignment and randomization

At Visit 201, all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms above. 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).

Randomization will be stratified by region.

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

5.4 Treatment blinding

Patients, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods:

- Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone involved in the study
- The identity of the treatment will be concealed by the use of study drugs that are all identical in packaging, labeling, and schedule of administration, appearance, taste, and odor.

The randomization codes associated with patients/subjects from whom PK samples are taken will be disclosed to PK bioanalysts who will keep PK results confidential until data base lock.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.9) and at the conclusion of the study.

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number by the investigator. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site must select the Case Report/Record Form (CRF) book with a matching Subject Number from the electronic data capture (EDC) system to enter data.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the CRF.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in packaging of identical appearance.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the investigational drugs. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Pharma Organization (CPO) Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients/subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of additional treatment

The following non-study drug will be monitored as follows:

The non-study drug must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Clinical supplies are to be dispensed only in accordance with the protocol.

The investigator must maintain an accurate record of the shipment and dispensing of the non-study drug in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all unused non-study drug and packaging at the end of the Run-in for the Run-in medication and at the end of the study or at the time of discontinuation of study drug for the rescue medication.

These medications are:

- Salbutamol (100 µg) or albuterol (90 µg) used as rescue medication from Visit 1 to Visit 299
- Fluticasone propionate (100 µg b.i.d. or acceptable dose equivalent as outlined in Section 3.1 used as Background medication from Visit 1 to Visit 299

5.5.4 Instructions for prescribing and taking study treatment

Patients will be provided with medication as described in Section 5.1.

Study medication prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF (e-CRF).

At Visit 1 all patients (and parent/legal guardian) will be instructed how to use the inhalers to administer rescue salbutamol/albuterol and the fluticasone propionate correctly. Patients and parent/legal guardian will be trained to use the peak flow meter and e-Diary as well. Beginning at Visit 101, patients will be fully trained in the correct use of the Concept1 inhaler device used to administer study medication. Patients/parents who are unable to use the device correctly will not be eligible to enter the treatment epoch. Additional training devices will be supplied for demonstration purposes. At clinic visits the investigator should check the patient's use of the inhalational device to ensure that the child is using the device correctly. Additional device training may be provided if required.

At randomization, the patient will take a single inhalation, from the Concept1 device, while at the site.

Patients, along with their parent/ legal guardian will be instructed to take one inhalation from the Concept1 device once daily, at approximately the same time each day during the two-week timeframe. Dosing should be done in the morning, following the patient's morning dose of fluticasone propionate. Parents/legal guardian should be instructed to rinse the child's mouth after inhalation of study drug. Water used for mouth rinsing should be

spat out and should NOT be swallowed. Patients should take their 2nd dose of fluticasone propionate in the evenings.

The time of study medication taken on morning of Day 13 (or one day prior to Day 14/Visit 299/End of Treatment) should be recorded by the parent and brought to the clinic at Visit 299. The child should not take study medication at home on the morning of Visit 299 (end of treatment visit). Study medication will be taken at the site on this day, under staff supervision.

All kits of study treatment assigned by the IRT will be recorded/databased in the IRT. All used and unused study medication/packaging must be returned at each study visit and/or at the time of discontinuation.

The investigator must promote compliance by instructing the parent/legal guardian that their child needs to take the study treatment exactly as prescribed and by stating that compliance is necessary for the child's safety and the validity of the study. The parent/legal guardian must also be instructed to contact the investigator if their child is unable for any reason to take the study treatment as prescribed.

Instructions for use of the Concept1 device are provided in Appendix 1.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Investigational treatment dose adjustments and/or interruptions are not permitted unless the investigator considers an interruption is necessary for the treatment of an adverse event.

These changes must be recorded on the Dosage Administration Record CRF.

In case of blind broken, the study medication is to be permanently discontinued.

5.5.6 Rescue medication

At Visit 1 (Screening), all patients will be provided with a short acting β_2-agonist (100 µg salbutamol/90 µg albuterol via inhaler) which they will be instructed to use throughout the study as rescue medication. Nebulized salbutamol is not allowed as rescue medication throughout the entire trial. No other rescue treatment is permitted.

In order to standardize measurements, patients will be instructed to abstain from taking rescue medication (salbutamol) within 6 hours of the start of each visit where spirometry is being performed unless absolutely necessary. If rescue medication is taken within 6 hours prior to spirometry assessments, then the visit should be rescheduled to the next day if possible and the number of puffs of rescue medication taken recorded in the patient e-Diary.

Additionally, patients will be provided with fluticasone propionate 100 µg (or dose equivalent see Section 5.1.2) via an inhaler, which should be taken b.i.d. beginning at Visit 1, or the next day if patient already took their daily ICS, and continue through the duration of the trial. If the patient is currently taking an ICS (with or without additional controller medication) the patient must switch to fluticasone provided at this visit. Fluticasone should be taken in the morning, prior to study drug, and in the evening. On days of study visits, patients should bring their fluticasone inhaler with them and take the dose at the site under supervision of study staff. Fluticasone use should also be captured in the eCRF.

The rescue salbutamol/albuterol and fluticasone will be provided to the patients by the study center and reimbursed locally by Novartis.

5.5.7 Concomitant medication

The investigator must instruct the patient to notify the study staff about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the concomitant medications / significant non-drug therapies e-CRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started.

5.5.8 Prohibited medication

Prohibited asthma-related medications, as listed in Table 5-1, must not be taken during the study. The specified minimum washout periods are described in Table 5-1. The classes of medication listed in Table 5-3 are not permitted to be taken during the study. The medications in Table 5-2 are only permitted under the circumstances given. Each concomitant drug must be individually assessed against all exclusion criteria and the tables below to see if it is allowed. If in doubt, the investigator should contact the medical monitor before randomizing a patient or allowing a new medication to be started.

Table 5-1 Prohibited asthma-related medications

Class of medication	Minimum washout period starting at Visit 101[1,2]
Long-acting β2 agonists (LABA)	*LABAs used b.i.d. must be discontinued 48 hours prior to Visit 101. LABAs used o.d. must be discontinued at least 14 days prior to Visit 101).*
Long Acting Muscarinic Antagonist (LAMA)	Must be discontinued 7 days prior to Visit 101.
Short acting anticholinergics (SAMA)	Must be discontinued 8 hours prior to Visit 101.
Fixed combinations of short-acting β2-agonist and short-acting anticholinergics	Must be discontinued 8 hours prior to Visit 101.
Salbutamol/albuterol (SABA) provided at Visit 1 and throughout study as required for rescue medication	Must be withheld 6 hours prior to study visits beginning at Visit 101.
Short acting β2-agonists (SABAs) (other than Salbutamol/albuterol provided at Visit 1 for rescue medication)	Must be discontinued at Visit 1 and are not permitted during the study [3]
Intra-muscular depot corticosteroids	Must be discontinued 3 months prior to Run-in (Visit 101)
Systemic corticosteroids (Parenteral or oral)	Must be discontinued 3 months prior to Run-in (Visit 101)
Immunoglobin E inhibitors (e.g. omalizumab)	Must be discontinued 6 months prior to Run-in (Visit 101)
Xanthines	Must be discontinued 7 days prior to Run-in (Visit 101)
Systemic mast cell stabilizers (e.g. cromoglycate, nedocromil, ketotifen)	Must be discontinued 7 days prior to Run-in (Visit 101)

[1] This table is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria.

[2] These medications are also prohibited if administered for other indications.

[3] SABA (salbutamol/albuterol rescue medication) should be withheld for at least 6 hours prior to spirometry measurements at clinic visits if possible. Clinic visits may be rescheduled if rescue medication were taken less than 6 hours prior to the spirometry assessments.

Table 5-2 Medications allowed under certain conditions

Class of medication	Condition under which medication is permitted
Topical Corticosteroids for treatment of eczema	Recommended doses and dosage regimens
Leukotriene antagonists and leukotriene synthesis inhibitors	Stable dose for at least 4 weeks prior to Visit 101.
Maintenance Immunotherapy for allergies	Stable dose for at least 3 months prior to Visit 101 and must continue unchanged for the duration of the study
Mucolytic agents not containing bronchodilators	If stabilized for at least 4 weeks prior to Visit 101 and throughout the trial.
Inactivated influenza vaccination, pneumococcal vaccination or any other inactivated vaccine	Not administered within 48 hours prior to a study visit
Intra-nasal corticosteroids	If an established pattern of use has been documented prior to Visit 101.

Table 5-3 Other prohibited medications

Class of medication	Minimum cessation period prior to Run-in (Visit 101)
Any drug with the potential to prolong QT interval	14 days or 5 half-lives, whichever is longer
Non-potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug	7 days
Strong inhibitors of cytochrome P4503A	7 days
Other investigational drugs	30 days or 5 half-lives, whichever is longer
Noradrenaline reuptake inhibitors	7 days
Live attenuated vaccines	30 days

5.5.9 Emergency breaking of assigned treatment code

Emergency treatment code breaks should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study treatment discontinuation (TD) and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Global Trial Leader (GTL) that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- patient number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

Completion of the study will be when the last patient has completed Visit 301 and as close as possible to serious adverse event (SAE) Follow-up at Day 44.

The investigator must provide Follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by the patient, patient's parent/ legal guardian, or the investigator.

The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Study treatment *must* be discontinued under the following circumstances:

- Patient`s or parent/ legal guardian's wish
- Administration of a prohibited medication (Table 5-1 and Table 5-3)
- Worsening asthma as defined in Section 6.5.6, as well as the following.
  - Excessive use of rescue medication (more than 200 µg salbutamol/ 180 µg albuterol four times per day for three consecutive days)
  - Abnormal test procedure results indicating risk for the patient on continued inhalation of the study drug including:
- Decline in PEF from the baseline PEF of ≥ 20% for one day or ≥ 15% for 3 consecutive days. The baseline PEF for the Run-in epoch would be the PEF taken at Visit 101. The baseline PEF (morning and evening) for the treatment epoch is calculated at visit 199 and is the mean of the best of the three daily PEF measurements over the past 14 days.
- Patients who experience moderate or severe asthma exacerbations (Section 6.5.7)
- ECGs:
  - If the absolute QTcF ≥450 msec or an increase from baseline of > 60 msec on 2 adequate ECGs at least a minute apart
  - 2nd or 3rd degree AV block
  - Atrial or ventricular arrhythmias (as judged clinically significant by the investigator)

- Any severe or serious adverse event considered possibly related to the study medication
- Patients who experience paradoxical bronchospasm: dyspnea and wheezing significantly increasing shortly after the administration of bronchodilator (*see Investigator's Brochure for more details*)
- Adverse events for which continued inhalation of the study drug would be detrimental
- If a patient develops a medical condition that requires use of prohibited treatment as per Section 5.5.8, or if patient exhibits a behavior of non-compliance regarding prohibited medications.
- Pregnancy (see Section 7.5)
- Any situation in which study participation might result in a safety risk to the patient
- Clinically significant abnormal laboratory value(s) (e.g., potassium below 3.0 mmol/L, LFT >3 x ULN)
- Any other protocol deviation that results in a significant risk to the patient's safety

If discontinuation of study treatment occurs, the patient should NOT be considered withdrawn from the study. The patient should return to the clinic as soon as possible, after discontinuation of study drug, for a study treatment discontinuation visit (Visit 299 will act as an early discontinuation visit in this case) and directly move into the Follow-up epoch. Treatment discontinuation visit assessments detailed in the Table 6-1 should be completed and recorded in the eCRF. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this in the End of treatment disposition page in the eCRF.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

The data which must continue to be collected for all patients (including the patients discontinuing study treatment) are adverse event and serious adverse events for up to 30 days after drug discontinuation until the end of the study Follow-up visit (Visit 301). Documentation of attempts to contact the patient should be recorded in the source documentation.

If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.9.

If the patient fails to return for an end of study visit for unknown reasons, every effort should be made to contact them as specified in Section 5.6.4.

5.6.3 Withdrawal of informed consent

Patients themselves or parents/ legal guardians may voluntarily withdraw consent for their child to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when a patient does not want to or the patient's parent/ legal guardian does not want their child to:

- Participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- Does not allow analysis of already obtained biologic material

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient`s or parent's/ legal guardian's decision to withdraw their consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the parent/legal guardian are not allowed unless safety findings require communicating or Follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in Table 6-1.

5.6.4 Lost to Follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. If contact has not been re-established, all efforts should still be made to locate the patient and obtain information regarding concomitant medications, serious adverse events, and survival status at the end of the 2 weeks intended treatment epoch (Visit 299). This information should also be obtained at the safety Follow-up visit (Visit 301). A patient cannot be considered as lost to Follow-up until the time point of his/her scheduled end of study visit has passed.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

The study will consist of a Screening epoch, a Run-in epoch, a 2-week blinded treatment epoch and a Follow-up epoch of 30 days after the last treatment.

Table 6-1 lists all the assessments to be performed for the study and indicates with an "X" the visits at which they will be performed. Patients should be seen for all visits on the designated day or as close as possible to that date. All data obtained for these assessments must be supported in the patients' source documentation.

Study assessments should be performed in a manner that the spirometry measurements occur at the scheduled time point (See Table 6-2 and 6-3 for Timed Assessments).

Whenever other assessments are scheduled at the same time-point, spirometry should occur at the scheduled time point or as near as possible.

Patients must be seen for all visits on the designated day, or as close to it as possible. Visit 199/201 (Randomization) and 299 (End of treatment) must occur in the morning, since patients will be taking their study medication in the morning. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time assessments listed for early discontinuation will be performed.

Since the first spirometry measurement is 45 minutes prior to inhalation of study medication, and study medication is adminstered in the morning, it is important to schedule study visits early enough so the patient will have enough time to take their fluticasone on site, have other study assessments done (questionnaire, vital signs, ECG, labs), have the first spirometry 45 minutes prior to study medication, and be dosed with study medication in the morning.

Patients who discontinue early are not required to undergo the spirometry measurements. However, at least one spirometry measurement should be measured if the patient can tolerate it. Study drug is not administered following early discontinuations.

If a patient's parent/legal guardian refuses to bring their child to the clinic for a discontinuation visit, or is unable to do so, every effort should be made to contact the parent/legal guardian, by telephone, to determine the reason for their child's study discontinuation.

Study medication should be reconciled and the adverse event and concomitant medications reconciled on the CRF. Patients must return the indacaterol at the end of the study.

Thirty days after the End of treatment epoch (Visit 299), the patient's parent/ legal guardian will be contacted for safety evaluations following the last administration of study treatment. This information should be captured in the patient's source documents and SAEs/ AEs will be captured in the eCRF (Visit 301).

Table 6-1 Assessment schedule

Epoch	Screening*	Run-in		Treatment		Follow-up
					End of study treatment/ Early termination**	
Visit	1	101	199	201	299	301[6]
Day *Note: V199 and 201 will occur on the same day if the patient is randomized.*	*Up to 30 days prior to Visit 101*	*-14*	*1*	*1*	*14*	*44*
Obtain parental Informed Consent / patient assent (if applicable)	X					
Current medication review/ adjust	X					
Contact IRT	S	S	S	S	S**	S**
Randomization via IRT				S		
Inclusion/Exclusion criteria	X	X	X			
Demographics, Medical History	X					
Pulmonary history: - protocol solicited events for asthma	X					
Asthma exacerbation history	X					
Smoking exposure	X					
Prior/ concomitant medication review	X	X	X	X	X**	
Urine pregnancy test[1] (if applicable)	X	X	X		X**	

Epoch	Screening*	Run-in		Treatment		Follow-up
					End of study treatment/ Early termination**	
Visit	1	101	199	201	299	301[6]
Day *Note: V199 and 201 will occur on the same day if the patient is randomized.*	*Up to 30 days prior to Visit 101*	*-14*	*1*	*1*	*14*	*44*
Evaluation of sexual development status[8]	X					
Device training[4]	S	S	S			
Height and weight		X	X		X**	
Physical examination complete		S				
Physical examination short			S		S**	
Oropharyngeal examination		S	S		S**	
ECG[3]		X	X	X	X**	
Vital signs[3]		X	X	X	X**	
Issue rescue medication as necessary	S	S	S	S		
Review rescue medication use		X	X	X	X**	
Issue fluticasone propionate	X					
Review daily fluticasone use		X	X	X	X**	
Spirometry Practice	S					

Epoch	Screening*	Run-in		Treatment		Follow-up
					End of study treatment/ Early termination**	
Visit	1	101	199	201	299	301[6]
Day *Note: V199 and 201 will occur on the same day if the patient is randomized.*	*Up to 30 days prior to Visit 101*	*-14*	*1*	*1*	*14*	*44*
(Optional)						
Screening spirometry (FEV_1)[7]		X	X			
Screening reversibility (SABA)[7]		X				
Spirometry[3]			X	X	X**	
Issue e-Diary	S					
Issue Peak Flow meter	S					
Review and upload e-Diary recordings		S	S	S	S**	
Dispense study medication via IRT				S		
Administer study drug at visit				X	X	
Provide parent/ legal guardian and patient with instructions to record time of last dose of study medication taken on Day 13 (or one day prior to Visit 299/Day 14).				S		

Epoch	Screening*	Run-in		Treatment		Follow-up
					End of study treatment/ Early termination**	
Visit	1	101	199	201	299	301[6]
Day *Note: V199 and 201 will occur on the same day if the patient is randomized.*	*Up to 30 days prior to Visit 101*	*-14*	*1*	*1*	*14*	*44*
Record time of study drug taken one day prior (Day 13) to Visit 299/Day 14					X**	
Collect unused study medication					S**	
Record interruption/ changes in study drug administration to assess compliance				X	X**	
AE recording		X	X	X	X**	X
SAE recording	X	X	X	X	X**	X
Review and record surgeries and procedures		X	X	X	X**	X
Study disposition (Screening)	X					
Study disposition (Run-in)			X			
Study disposition (End of Treatment)					X**	
Study disposition (Follow-up)						X
Safety Lab assessments[1]		X	X		X**	

Epoch	Screening*	Run-in		Treatment		Follow-up
					End of study treatment/ Early termination**	
Visit	1	101	199	201	299	301[6]
Day *Note: V199 and 201 will occur on the same day if the patient is randomized.*	*Up to 30 days prior to Visit 101*	*-14*	*1*	*1*	*14*	*44*
(hematology, chemistry, urine dipstick)						
PK sampling[3]			X	X	X**	
ACQ-IA[5]		X	X		X**	
Telephone parent/ legal guardian in advance of study visit, with reminder to not take rescue medication within 6 hours of study visit, and bring in all study medication and e-Diary		S	S	S	S	

*Screening Visit 1 and Run-in Visit 101 can occur on the same day if patient did not take any salbutamol/albuterol within 6 hours of the study visit.

**These assessments should be conducted for patients who discontinue.

S These assessments are source documentation only and will not be entered into the CRF.

X Assessment to be reported in the clinical database.

[1]For females of child-bearing potential only.

[2]Labs and urine dipstick are done pre-dose.

[3]Details of timed assessments are provided in Table 6-2 and 6-3.

[4]Device training at Visit 1 is for e-diary/peak flow meter, salbutamol/albuterol and fluticasone propionate inhaler. Device training at Visits 101 and 199 is for Concept1.

[5]The ACQ-IA is completed at the clinic, before any other assessment.

[6]Information about any AEs/ SAEs occurring within 30 days of the patients' last study treatment will be obtained by a telephone call 30 days after the patient's last dose of study drug for completed patients. For patients who withdraw early, please refer to discontinuation of study treatment and premature patient withdrawal Section.

Epoch	Screening*	Run-in		Treatment		Follow-up
					End of study treatment/ Early termination**	
Visit	1	101	199	201	299	301[6]
Day *Note: V199 and 201 will occur on the same day if the patient is randomized.*	*Up to 30 days prior to Visit 101*	*-14*	*1*	*1*	*14*	*44*

[7]If reversibility fails on the first attempt, it can be repeated once.

[8]For girls the sexual development status has to be evaluated to identify females who have reached menarche, and thus, with child bearing potential.

Table 6-2 Timed assessment schedule (Visit 199)

	Time point vs. 0 (dose time)***	ACQ-IA	ECG	Vitals (Systolic/ diastolic BP /radial pulse)	PK	Hematology/ chemistry/ urine dipstick	Spiro-metry	Call IRT**
Visit 199	≤ - 2 hr	Administer fluticasone dose and ancillary study assessments						
	≤ - 2 hr	X	X	X	X	X		
	-45 min						X*	X
	-15 min						X	

*At Visit 199, patients are required to meet FEV_1 criteria of ≥50% and ≤ 90% of the predicted normal value for the patient. If criteria are met at this visit, the patient will be immediately randomized.
**IRT can be called for randomization information after the -45 minute spirometry assessment, assuming the patient meets the FEV_1 criteria at -45 min. Study medication should not be dispensed until appropriate time in Visit 201.
***All time points are approximate time points, and fluctuations are allowed.

Table 6-3 Timing of key visit procedures during treatment

	Time point vs. 0 (dosing time)***	ACQ-IA	Vitals (Systolic/ diastolic BP and radial pulse)	PK	Hematology/ chemistry/ urine dipstick	ECG	Spirometry
Visit 201	0 min	Morning dose of study medication					
	15 min		X	X			
	20 min					X	
	30 min						X
	50 min					X	
	1 hour		X**	X			X
Visit 299	≤ - 2 hr	Administer fluticasone dose and ancillary study assessments					
	≤ - 2 hr	X*	X	X	X	X**	
	-45 min						X
	-15 min						X
	0 min	Morning dose of study medication					
	15 min		X	X			
	20 min					X	
	30 min						X
	50 min					X**	
	1 hour		X**	X			X

*ACQ-IA should be given prior to any other assessment.
** Vitals done 1 hour post-dose should be taken *before* the 1-hour post-dose spirometry measurement.
*** All time points are approximate time points, and fluctuations are allowed.

6.1 Information to be collected on screening failures

All patients/subjects who have signed informed consent but not entered into the next epoch will have the study completion page for the Screening epoch, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include:

- Year of birth
- Age (calculated)
- Gender
- Race & Ethnicity
- Height & Weight
- Body Mass Index (BMI) (calculated)
- Baseline physical examination (not databased other than in the context of relevant medical history)
- Vital signs
- ECG
- Date of diagnosis of asthma
- Relevant medical history/current medical condition present before signing the informed consent
- Smoking exposure
- Health status
- Prior/ concomitant medication (asthma and non-asthma related)
- Pre and post-bronchodilator spirometry (Screening spirometry and reversibility testing).

6.3 Treatment exposure and compliance

The time of study treatment dosing, at Visit 201 and 299/End of treatment, will be collected on the e-CRF as well as any dosing interruptions. For assessments where spirometry is performed, the time of dosing is to be taken from the spirometer.

Study treatment compliance should be assessed by the investigator and/or center personnel at all visits. Where necessary, the Investigator will discuss compliance/documentation issues with the patient's parent/legal guardian. The Investigator or designee will collect, from the patient's parent/legal guardian, the used/unused investigational medication and packaging (unused capsules/blister strips SDDPIs) at Visits 299/End of Treatment/ Early Treatment Discontinuation. Study treatment compliance will be assessed from the capsule count from previously dispensed blister strips for the Concept1®.

The number of puffs of rescue medication (salbutamol/albuterol) between study visits will be recorded by the patient's parent/ legal guardian in the e-Diary.

Fluticasone use should be assessed by the investigator and/or center personnel at all visits. The investigator or designee should ask the patient and parent about their daily fluticasone use and should document this in the patient's source document as well as in the eCRF.

6.4 Efficacy

The following assessments of efficacy will be performed:

- Spirometry
- Pediatric ACQ-IA
- Asthma symptoms recorded in e-Diary
- Peak Expiratory Flow
- Rescue Medication Use

6.4.1 Spirometry assessments

The following spirometry assessments will be made:

- Forced expiratory volume in 1 second (FEV_1)
- Forced Vital Capacity (FVC)
- Spirometric assessments will be measured at Visits 199, 201 and 299/EOT as indicated in Table 6-1 through Table 6-3.
- Pre-dose FEV_1 is defined as the mean of the two FEV_1 values measures at -45 min and -15 min prior to morning dose.

Please refer to the Spirometry Guidance in Appendix 3 and Table 6-2 and Table 6-3 for full details on scheduling and performing spirometry.

6.4.2 Patient reported outcomes (PRO)

Asthma Control Questionnaire-Interviewer administered, for children

In this study, the Asthma Control Questionnaire Interviewer - Administered (ACQ-IA) will be used to assess improvements in asthma symptom control. The ACQ-IA is a seven-item disease-specific instrument developed and validated to assess asthma control in patients in clinical trials as well as in individuals in clinical practice. The ACQ is valid for use in children 6-16 years old, and has strong measurement properties in this age group. Initial cognitive debriefing studies provided evidence that children 11 years and older could understand the instructions, questions and response options of the self-administered version of the adult ACQ accurately and unaided; however, children 10 years and younger needed help. Therefore, the interviewer-administered version of the adult ACQ was developed for children 6-10 years old, and must be administered by a trained interviewer (Juniper et al 2010). Given the fact that this trial includes 11-year-old, and to make it consistent, all patients will have the ACQ given to them by a trained interviewer.

The ACQ-IA will be provided to the site. All seven items are then scored on a 7-point Likert scale, with 0 indicating total control and 6 indicating no control. The questions are equally weighted and the total score is the mean of the seven items.

The interviewer must ask the child the first 6 questions of the ACQ-IA and the child should be encouraged to respond directly (parent/ legal guardians should only help if the child is having

difficulties responding). The investigator should complete the last question (for the last ACQ question – airway caliber FEV_1% predicted based on the masterscope at site) at the investigator's site at Visits 101, 199, and 299/End of treatment (EOT).

The ACQ-IA will be asked in the language most familiar to the patient, at the scheduled study visit prior to the patient seeing the investigator for any clinical assessment or evaluation. The patient's parent/ legal guardian can be present during the interview. The interviewer should make the child comfortable and should reassure the child that there are no right or wrong answers. The interviewer can have the child read aloud each of the questions and responses, if the child is able to read. The interviewer will complete the questionnaire with the patient's responses. All questionnaires should be complete.

For paper CRFs the original questionnaire will be kept with the patient's file as the source document.

Completed questionnaires will be reviewed and examined by the investigator, before the clinical examination, for responses that may indicate potential adverse events (AEs) or serious adverse events (SAEs). The investigator should review not only the responses to the questions in the questionnaires but also for any unsolicited comments written by the patient. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Section 7.1 and Section 7.2 of the protocol.

6.4.3 Electronic Diary

At Visit 1, parents/ legal guardians will be provided with an e-Diary to record their child's rescue medication (salbutamol/albuterol) use. From Visit 101 on, they will record their child's clinical symptoms and PEF in the e-diary. The patient's parent/ legal guardian will be instructed to routinely complete the e-Diary twice daily – at the same time each morning and again approximately 12 hours later in the evening. The e-Diary is to be reviewed at each clinic visit until study completion. Sites and the patient's parent/ legal guardian will receive appropriate training and guidance on the use of the e-Diary device. A list of the Patient asthma control e-Diary questions is provided in Appendix 4.

6.4.4 Peak expiratory flow

An electronic Peak Flow Meter part of the e-Diary device will be provided to the patient's parent/ guardian at Visit 1 for the measurement of morning and evening PEF during the study (Appendix 4).

PEF will be measured at consistent times for a patient, in the morning and evening each day during the study from Visit 1 to 299/End of study. PEF will be measured twice a day; in the morning just prior to taking study medication and again 12 hours later. Patients should be encouraged to perform morning and evening PEF measurements BEFORE taking study medication. At each time point, the parent/guardian should instruct their child to perform 3 consecutive maneuvers within 10 minutes. These PEF values are captured in the e-PEF/diary. The best of 3 values will be used. The PEF/ e-Diary is to be reviewed at each clinic visit until study completion.

6.4.5 Rescue medication usage

The use of rescue salbutamol/albuterol should be recorded by the patient's parent/ legal guardian in the e-Diary twice each day in the morning and evening. In the morning the

number of puffs of rescue medication their child has taken during the night and since the last diary entry, and in the evening the number of puffs of rescue medication the child has taken during the day since the morning diary entry should be recorded.

6.4.6 Appropriateness of efficacy assessments

The efficacy assessments selected are standard for this indication/patient population.

6.5 Safety

The following safety assessments will be performed:

- Medical history and physical examination including oropharyngeal examination
- Vital signs
- Hematology, blood chemistry, urine dipsticks
- ECG
- Adverse events including asthma exacerbations, worsening asthma, and serious adverse events

ECG and Laboratory assessments, excluding urine dipsticks, will be centralized.

6.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities, vascular and neurological. An oropharyngeal examination will be performed at each clinic visit. A short physical examination will include the examination of vital signs, heart, lungs, abdomen, extremities and any other evaluation the Investigator considers appropriate based on the patient's clinical status at the time of the visit.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to informed consent being granted must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's e-CRF. Significant findings made after informed consent (Visit 1) is given which meet the definition of an Adverse Event must be recorded on the Adverse Event screen of the patient's e-CRF.

6.5.2 Vital signs

Systolic and diastolic blood pressure and radial pulse rate (over a 30 sec interval), performed in the sitting position, will be recorded at each scheduled clinic visit as detailed in Table 6-1 through Table 6-3. Vitals are taken pre-dose and 15 minutes and 1 hour post-dose. The vitals taken 1-hour post-dose should be done *before* the 1-hour post-dose spirometry measurement.

6.5.3 Height and weight

Height in centimeters (cm) and weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at Visit 101, 199, and 299. BMI will be calculated based on height and weight.

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

All patients with laboratory tests containing clinically significant abnormalities should be followed regularly until the values return to within the normal ranges or until a valid reason other than drug-related adverse experiences is identified, even after the medication has discontinued.

Safety Laboratory assessments (hematology, clinical chemistry, blood eosinophil counts) will be performed at Visits 101, 199 and 299/EOT if applicable.

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured.

Peripheral blood eosinophil counts will be captured with a unit of cells/ mcL.

6.5.4.2 Clinical chemistry

Albumin, alkaline phosphatase, aspartate aminotransferase (AST) or Serum Glutamic-Oxaloacetic Transaminase (SGOT), alanine aminotransferase (ALT) or Serum Glutamic Pyruvic Transaminase (SGPT), bilirubin, creatinine, γ-GT, glucose, potassium, magnesium, BUN and uric acid will be measured.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal range, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.

6.5.4.3 Urinalysis

In this trial, urine dipsticks will be collected at Visits 101, 199, and 299/EOT.

6.5.4.4 Hepatotoxicity

Any liver event which meets the criteria for "**medically significant**" event as outlined in Table 13-1 of Appendix 7 should follow the **standard procedures for SAE reporting** as described in Section 7.2.

6.5.5 Electrocardiogram (ECG)

ECGs must be recorded after the patient rests (10 minutes if possible) in the supine position to ensure a stable baseline.

When the ECG recording time coincides with vital signs, spirometry, and blood draws, the ECG should be performed first, followed by vital signs and the blood draws but with enough time planned to ensure the spirometry is performed at the planned time point outlined in Table 6-2 and 6-3. Spirometry must be performed as close to the scheduled time point as possible.

Centralized ECG equipment

At Visit 101, a screening ECG will be measured to test for eligibility for trial inclusion. Patients with an abnormal ECG at Visit 101, due to technical/mechanical faults, may be rescreened.

At Visits 199/201 and 299/End of study, ECGs will be measured at pre-dose (prior to spirometry) and 20 minutes and 50 minutes post-dose of study medication as indicated in Table 6-2 and 6-3. All ECGs should include 12 standard leads. An ECG tracing should be taken for those patients who prematurely discontinue from the study treatment.

For each ECG performed original traces and identical duplicate traces should be printed. Each ECG will be sent electronically for central review directly from the ECG machine. Two 'identical' duplicate print-outs will be generated and kept at the investigator site as source documentation and as back-up for submission to the central laboratory in case of problems with the electronic transmission. Each print out will be kept at the investigator site and will be dated and signed. The subject's number, the date, actual time of the tracing, and Study Code must appear on each page of the tracing.

Full details of all procedures relating to the ECG collection and reporting will be contained in an investigator manual to be provided by the central ECG group to each investigator site. In the event that the central cardiologist reports that an ECG is abnormal, the investigator must assess whether the ECG abnormality is clinically significant or not. A clinically significant abnormality should be reported as an AE. If necessary a pediatric cardiologist may be consulted.

Clinically significant ECG findings at baseline must be discussed with the sponsor before administration with investigational treatment.

If a patient experiences a clinically significant change in cardiac rhythm or other clinically significant cardiovascular abnormality, the investigator should consider withdrawing the patient from the study.

Clinically significant abnormalities should be recorded on the relevant Section of the medical history/Current medical conditions/AE CRF/e-CRF page as appropriate.

6.5.6 Worsening of asthma

Investigators and patients will be instructed how to deal with worsening of asthma symptoms. The data captured in the patient diary will also be used to alert the patient and/or investigator to possible signs of worsening asthma. Worsening asthma should be recorded as an Adverse Event. The investigator must provide the patient's parent/ legal guardian with written instructions to contact the investigator if at any time during the trial from the Run-in onwards one or more of the following criteria of worsening asthma develops:

Asthma Worsening Criteria

- Excessive use of rescue medication (more than 200 µg salbutamol/ 180 µg albuterol four times per day for three consecutive days)
- Decline in PEF from the baseline PEF of ≥ 20% for one day or ≥ 15% for 3 consecutive days.
- 20% decrease in FEV_1 from baseline value (this criterion applies to Investigator review at the time of a study visit and an alert setting in the Masterscope)
- < 60% of PEF compared to baseline
- Night time awakenings requiring SABA use on at least 2 out of any 3 consecutive nights (patients may be continued in the study based on their general pattern of night time symptoms as per investigators judgement)

- Urgent unscheduled clinic visit due to asthma related deterioration

Note: The baseline FEV_1 and PEF for the Run-in epoch would be the FEV_1 and PEF taken at Visit 101. The baseline FEV_1 for the treatment epoch is the mean of the 45 min and 15 min pre-dose FEV_1 measurements at Day 1. The baseline PEF (morning and evening) for the treatment epoch is calculated at visit 199 and is the mean of the best of the three daily PEF measurements over the past 14 days.

If patients develop any of the above criteria, the patient should notify the investigator and be evaluated by the investigator and treated as clinically appropriate.

If any of the above criteria are met while a patient is in the Run-in epoch of the study, they may be withdrawn if, in the opinion the investigator, it is appropriate to do so.

Patients should also be withdrawn for safety reasons if, in the opinion of the investigators, it is appropriate to do so.

Worsening of asthma symptoms may require unscheduled evaluation between visits. Study site personnel must be available to monitor and document patient's progress until asthma control is regained.

6.5.7 Asthma Exacerbation

In this trial, any patient who suffers from a moderate or severe asthma exacerbation will be discontinued from this trial.

Asthma exacerbations will be recorded as Adverse Events.

A **severe asthma** exacerbation (Draft note for guidance on clinical investigation of medicinal products for treatment of asthma CHMP/EWP/2922/01 Rev.1) is defined as an aggravation of asthma symptoms (like shortness of breath, cough, wheezing, or chest tightness) that requires systemic corticosteroids (SCS) for at least three consecutive days and/or a need for an ER visit (or local equivalent structure), or hospitalization due to asthma or death due to asthma.

- Start date and end date:
- In case of the use of SCSs for at least three days, the first day of treatment will determine the onset date of the event while the last day of treatment will define the stop date.
- In the event that an ER visit and/or hospitalization due to asthma exacerbation were not associated with a course of SCSs as described above, start and end dates would be defined by the corresponding dates entered by the Investigator in the CRF.

A **moderate asthma** exacerbation in this protocol is defined as the occurrence of two or more of the following:

1. Progressive increase of at least one of the asthma symptoms like shortness of breath, cough, wheezing, or chest tightness. The symptoms should be outside the patient's usual range of day-to-day asthma and should last at least two consecutive days
2. Increased use of "rescue" inhaled bronchodilators defined by:
   a. 50% increase in SABA use and >8 puffs on 2 out of any 3 consecutive days compared to baseline captured

      OR

   b. Night time awakenings requiring SABA use on at least 2 out of any 3 consecutive nights

3. Deterioration in lung function, which last for two days or more but usually not severe enough to warrant SCSs for more than 2 days or hospitalization. This deterioration would be defined by:

a. 20% decrease in FEV_1 from baseline value
   OR
b. ≥ 20% decrease in am or pm PEF from baseline on 2 out of any 3 consecutive days compared to baseline
   OR
c. < 60% of PEF compared to baseline

At no time may patients self-medicate (other than rescue medication use) for treatment of asthma exacerbation or worsening of symptoms.

6.5.8 Pregnancy and assessments of fertility

Girls who begin menstruating (reached menarche) will have urine pregnancy tests at study visits 1, 101, 199, and 299/EOT. A positive pregnancy test will result in study discontinuation. Refer to Sections 5.6.2 and 7.5 for more details.

6.5.9 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

6.6 Other assessments

6.6.1 Pharmacokinetics

Blood samples for PK analysis will be collected in all patients at the following time points below, with the aim to collect indacaterol exposure data in asthma patients.

Visit 199/201 (End of Run-in/Randomization)

- Pre-dose: ≤ 2 hours Post-dose: 15 minutes and 1 hour

Visit 299/End of treatment

- Pre-dose: ≤ 2 hours
- Post-dose: 15 minutes and 1 hour

All blood samples will be taken by either direct venipuncture or indwelling cannula inserted in a forearm or vein at time points specified in Table 6-2 and Table 6-3.

All time points listed are relative to the time of dose administration. The time of the dosing, as well as actual sample collection date and time will be entered on the PK blood collection summary page of the e-CRF. Sampling problems will be noted in the Notes field of the e-CRF. Details of the blood collection methods and the analytical methods will be provided in the Laboratory Manual.

7 Safety monitoring

7.1 Adverse events (AEs)

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease) in a subject or

clinical investigation subject *after providing written informed consent* for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an AE irrespective if a clinical event has occurred.

The occurrence of AEs must be sought by non-directive questioning of the patient at each visit during the study. AEs also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying AEs. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

AEs must be recorded in the AEs CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information.

- The severity grade -
  Mild: usually transient in nature and generally not interfering with normal activities
  Moderate: sufficiently discomforting to interfere with normal activities
  Severe: prevents normal activities
- its relationship to the study treatment (Yes or No):
  "No Relationship to study treatment or other investigational treatment" or
  "Relationship to study treatment" or
  "Relationship to other investigational treatment or
  "Relationship to both study treatment and other investigational treatment or indistinguishable".
- Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved should be reported.
- Whether it constitutes a SAE, as defined in Section 7.2 and which seriousness criteria have been met.
- Action taken regarding the study treatment
  All AEs should be treated appropriately. Treatment may include one or more of the following:
  - no action taken (e.g. further observation only)
  - study treatment dosage increased/reduced

- study treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient. Investigators should be familiar with known potential AEs outlined in the IB as well as local labelling. If patients experience such AEs (or any AE), they should be treated as considered clinically appropriate. This may include discontinuation from treatment medication.

The investigator must also instruct each patient to report any new AE (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events (SAEs)

7.2.1 Definition of SAE

An SAE is defined as any AE [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (see Annex IV, ICH-E12D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E12D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the eCRF. SAEs are also required for individual reporting to Drug Safety & Epidemiology (DS&E) as per Section 7.2.2.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day period following the last administration of study treatment should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All Follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as Follow-up to the original episode within 24 hours of the investigator receiving the Follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to *each specific component of study treatment, (if study treatment consists of several components)* complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a Follow-up to that event regardless of when it occurs. The Follow-up information should describe

whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.2.3 Pneumonia reporting

Pneumonia will be defined as an event characterized by increased respiratory symptoms (e.g. increased cough, dyspnea, wheezing, purulent sputum), fever (i.e. body temperature greater than 38 °C) or pleuritic chest pain or leukocytosis or other clinical signs consistent with pneumonia considered relevant in the opinion of the investigator and confirmed by X-ray. Any reported pneumonia will have to be confirmed by either X-ray or radiologist reading report of the X-ray (to be kept in the source documents). If not confirmed by X-ray, it should be reported as lower respiratory tract infection.

7.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as (S)AE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, Follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Table 13-1 in Appendix 7 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 13-1 of Appendix 7 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 13-2 in Appendix 7.

For the liver laboratory trigger:

- Repeating the liver function test (LFT) within the next week to confirm elevation.

These LFT repeats must be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory must then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event must be reported on the Liver CRF pages.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All Follow-up information, and the procedures performed must be recorded on appropriate CRF pages, including the liver event overview CRF pages.

7.4 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) e-CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Treatment error type	Document in Dose Administration (DAR) e-CRF (Yes/No)	Document in AE e-CRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes,	Yes, even if not associated with a SAE

7.5 Pregnancy reporting

Given the age of this patient population, there may be female patients who have reached menarche (and therefore of child-bearing potential). Female patients who fall in this category will have routine urine pregnancy tests as noted in Table 6-1.

If there is evidence of sexual activity in female patients of child-bearing potential, appropriate moral and legal actions for reporting should be taken by the investigator to ensure the safety of the child and minimize the risk of becoming pregnant.

Abstinence from sexual activity while participating in a clinical trial should be encouraged in this category of patients. Otherwise, contraceptive methods should be discussed and may be provided as appropriate to sexually active pediatric patients after careful consideration of any medical conditions, the individual situation, and cultural and legal aspects.

The basic contraception methods are (if allowed by local regulations):

- Barrier method: Condom or Occlusive cap (diaphragm or cervical/vault caps).
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

In case local regulations deviate from the methods listed, local regulations apply and will be described in the ICF.

In the event the patient become pregnant, and to ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy Follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All

information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient/parent or guardian (a signed copy is given to the patient/parent or guardian).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients/subjects will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff (or a designated Contract Research Organization (CRO) will review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

ECG readings will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Spirometry readings will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Diary data will be entered into an electronic diary by the patient`s parent/legal guardian. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis.

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be

supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

9.1 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 they actually received study medication. Several tables will summarize all screened subjects (e.g. “Screening Phase subject disposition, All screened subjects” and “Analysis sets by treatment, All subjects”). In consistency with the master analysis plan (MAP), there will not be a definition of a screened set.
- 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 in the assigned treatment sequence. 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 exclusion of subjects from the PPS will be defined in the Statistical Analysis Plan (SAP) 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 analysis.
- The Safety Set 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 variables.

9.2 Patient demographics and other baseline characteristics

Demographic and baseline characteristics measured before randomization age, gender, race, ethnicity, height, weight, body mass index (BMI), relevant medical history, screening spirometric parameters (FEV_1, FVC, FEV_1/FVC), FEV_1 reversibility, predicted and percentage of predicted FEV_1, duration of asthma, history of asthma exacerbations, smoking exposure, 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 and baseline ACQ-IA will be summarized by treatment group.

Continuous variables will be summarized using descriptive statistics (n, 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.

Baseline is defined as the last measurement before first dose of study drug.

No statistical analyses will be provided for baseline comparability among the treatment groups.

9.3 Treatments

Study drug administration and concomitant medication data will be listed and summarized using the Safety set. The duration of exposure, the number of patients randomized who completed the treatment period, and who discontinued from study medication will be summarized.

Medications started and stopped prior to study drug and taken concomitantly, will be summarized by treatment group in separate tables in the Safety Set.

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

SABA usage (number of puffs) during the Screening epoch will be summarized.

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

Treatment compliance with study medication over the study period will be summarized.

9.4 Analysis of the primary variable(s)

9.4.1 Variable(s)

The primary endpoint is change from baseline in pre-dose trough FEV_1 (mL) after 2 weeks of treatment. The pre-dose trough FEV_1 (mL) is defined as the mean of the two FEV_1 (mL), values measured at -45 min and -15 min pre-dose.

9.4.2 Statistical model, hypothesis, and method of analysis

The dose selection will be based on the totality of clinical, physiological and PK data in pediatric patients ≥ 6 years and < 12 years years old. Summary statistics (n, mean, 25th percentile, median, 75th percentile, standard deviation, minimum and maximum) by treatment

group will be provided for change from baseline in pre-dose trough FEV_1 as well as pre-dose trough FEV_1 after 2 weeks of treatment. Inferential testing statistics will not be performed since the sample size is small and power is limited.

9.4.3 Handling of missing values/censoring/discontinuations

If any of the -45 min and -15 min values contributing to the pre-dose trough FEV_1 are collected within 7 days of systemic corticosteroid use, 6 hours of rescue medication, or actual measurement times are outside the 22 - 25 hour from last dose of the previous day (Day 13) then the individual FEV_1 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 FEV_1. If both values are missing, or if the patient withdrew from the study, regardless of the reason for discontinuation, then pre-dose trough FEV_1 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.

9.4.4 Sensitivity analyses

As a supportive analysis, summary statistics will be provided for the PPS.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

9.5.1.1 Spirometry

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

Spirometry measurements taken within 7 days of systemic corticosteroid use and/or within 6 hours of rescue medication use will be set to missing and not be imputed, unless specified otherwise.

Summary statistics will be provided for pre-dose trough FEV_1 and post-dose FEV_1 (30 min, 1 hr) by visit and by treatment. Similar analyses will be performed for pre- and post-dose FVC and change from baseline in the spirometry values.

9.5.1.2 ACQ-IA

ACQ-IA score at each visit will be summarized by treatment groups. The proportion of patients who achieve an improvement of at least 0.5 in ACQ-IA (i.e. decrease of ACQ-IA score of at least 0.5 from baseline) at visit 299 will be summarized by treatment groups.

9.5.1.3 Exposure to indacaterol in plasma following sparse pharmacokinetic (PK)

Blood samples for PK analysis will be collected in all patients.

9.5.1.4 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/legal guardian in the e-Diary. The mean daily number of puffs (morning + evening) 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 summarized by treatment. No imputation will be done for missing data. This analysis will be repeated for morning (nighttime) and evening (daytime) rescue medication use.

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) will be summarized by treatment.

9.5.1.5 Peak expiratory flow 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.

9.5.1.6 Asthma symptoms based on e-Diary

The e-Diary data on asthma symptoms will be summarized for:

- the mean daytime asthma symptom score
- the total daily symptom score
- percentage of days with no daytime symptoms
- percentage of nights with no nighttime awakenings
- percentage of mornings with no symptoms on rising
- percentage of asthma symptoms free days, i.e., days with no daytime symptoms and no nighttime awakenings and no mornings with symptoms on rising

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 treatment period. 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. 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, summary statistics will be provided for changes from baseline.

9.5.2 Safety variables

All safety parameters will be summarized on the safety set.

Adverse events

All treatment emergent AEs including asthma exacerbations will be summarized and listed. AEs 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 a SAE) after the last inhalation will be classified as a treatment emergent AE. Any AEs that started during the study before the time of the first inhalation of study drug will be classified as a prior AE.

The following treatment emergent AE summaries will be produced, overall by system organ class and preferred term, overall by system organ class, preferred term and maximum severity, suspected drug-related AEs by system organ class and preferred term, SAEs by system organ class and preferred term, and AEs 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.
In addition, AEs will be summarized by standardized MedDRA query (SMQ) level. The Compound Case Retrieval Strategy (CRS) will be used to determine the MedDRA search criteria to be used to identify AEs of special interest which will be summarized too.

Electrocardiogram (ECG) and vital signs

Data from the electrocardiogram will be summarized by treatment and visit.

Vital signs (blood pressure and radial pulse rate) data will be summarized by treatment and visit.

The maximum (QTc, systolic blood pressure, pulse rate and heart rate) or minimum (diastolic blood pressure) post first dosing (i.e. post baseline) value will also be summarized. Changes from baseline will also be summarized by treatment.

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.

All data will be included in the analysis regardless of rescue medication usage.
The number (%) of patients with treatment emergent pulse rate, systolic blood pressure and diastolic blood pressure outside the ranges of below defined notable values will be summarized by treatment group.
Notable values for vital signs and change from baseline will be summarized. A notable value is defined per age group as follows:

Systolic blood pressure:
“Low” criterion: ≤ 80 mmHg (6-8 years) or ≤ 85 mmHg (9-11 years) and decrease from baseline ≥ 20 mmHg (Haque et al 2007)
“High” criterion: ≥ 115 mmHg (6-8 years) or ≥ 120 mmHg (9-11 years) and increase from baseline ≥ 20 mmHg (Fourth Report 2004)

Diastolic blood pressure:
“Low” criterion: ≤ 40 mmHg (6-8 years) or ≤ 45 mmHg (9-11 years) and decrease from baseline ≥ 20 mmHg (Horan et al 1987
“High” criterion: ≥ 75 mmHg (6-8 years) or ≥ 80 mmHg (9-11 years) and increase from baseline ≥ 20 mmHg (Fourth Report 2004)

Pulse rate:
”Low” criterion: decrease from baseline ≥ 25% to a value < 70 bpm (6-8 years) or < 60 bpm (9-11 years)

"High" criterion: 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)

Categorical QTc values and changes from baseline will be summarized as the number (%) of patients with new (treatment-emergent) QTc >450, >480 and >500 ms.

QTc change from baseline will be presented as QTc changes, both positive and negative, or 0-30 ms, >30ms, and >60 ms.

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

QTc will be calculated from the QT interval and RR (in seconds) using the Fridericia formula or dependent on the age Bazett formula, respectively.

Vital signs and ECG data measured more than 7 days after last inhalation of study drug is regarded as post-treatment data and will not be summarized, only listed.

Laboratory data

The laboratory parameters (hematology, blood chemistry including glucose and potassium, urinalysis and evening plasma cortisol, eosinophil counts) will be summarized by treatment, visit and time point, including changes from baseline.

All laboratory data will be listed with abnormal values flagged. The laboratory values and the change from baseline for continuous laboratory parameters will be summarized at each visit. A frequency table of results for categorical laboratory parameters will be produced by visit. Shift tables relative to the normal reference ranges will be used to summarize the change from baseline to post-baseline by visit for each laboratory parameter.

The number and percentage of patients with newly occurring or worsening laboratory abnormalities meeting the clinically notable criteria will be summarized by laboratory 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. Similar analysis will be done for newly occurring or worsening abnormalities in liver function tests (LFT).

Laboratory data measured more than 7 days after last inhalation of study drug is regarded as post-treatment data and will not be summarized, only listed.

9.5.3 Pharmacokinetics

For PK concentration data, listings and descriptive statistics will be provided. The descriptive statistics will comprise arithmetic and geometric means, SD, 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. In addition, the plasma concentration data from this study may be combined with data from other studies to perform a population PK analysis, which will follow the principles outlined in the FDA Guidance for Industry 1999.

9.5.4 PK/PD

Not applicable.

9.6 Interim analyses

No interim analyses are planned for this study.

9.7 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.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

Participation of patients in this study will be based on the local regulations and ethics committee requirements in various participating countries.

10.2 Informed consent procedures

Eligible patients/subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient. Patients below the legal age of consent are required to have the Parental Informed Consent signed by the patient's parent/guardian; children are required to sign the Assent Form (according to locally accepted policy/practice).

In cases where the patient's representative gives consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Girls of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, written assent form (according to local policy/practice), consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients/subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance (CQA), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients/subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented. All significant protocol deviations will be recorded and reported in the clinical study report (CSR).

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients/subjects may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

12 References

References are available upon request

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Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. Am J RespirCrit Care Med 1996;153:1481–1488.

13 Appendices

Appendix 1: Instruction for Use of Concept1

Instructions for using inhaler and capsules.

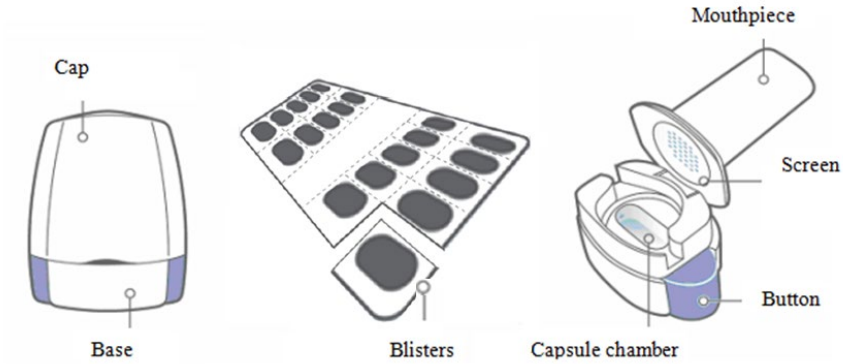
Do not swallow capsules.

Follow the instructions below for using your inhaler. You will take the study drug contained within the capsules by inhalation using the inhaler. If you have any questions, please ask the doctor or nurse at the study center.

Your inhaler and capsules

The study drug package consists of both the inhaler and one or more blister-packaged capsules.

- Capsules are supplied in blisters.
- Inhaler consists of a cap, mouthpiece and a base.



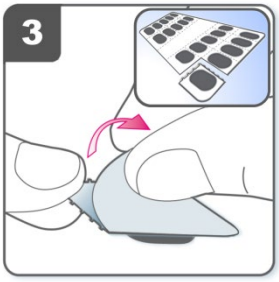
Your inhaler is designed to deliver the medicine contained within the capsules.

Do not use the study medication capsules with any other capsule inhaler, and do not use the inhaler to take any other capsule medicine.

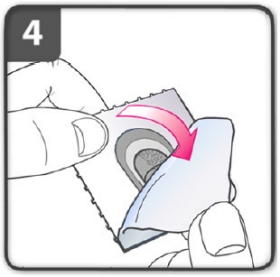
How to use your inhaler

Pull off cap.

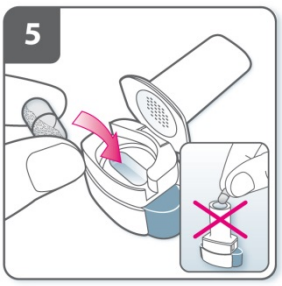
Open inhaler:
Hold the base of the inhaler firmly and tilt back the mouthpiece. This opens the inhaler.



Prepare capsule:
Immediately before use, with dry hands, separate one of the blisters from the blister card by tearing along the perforations and lift the corner of the foil.

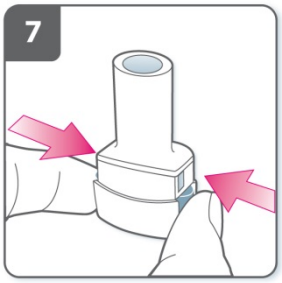


Remove a capsule:
Peel away the foil and remove the capsule from the blister.



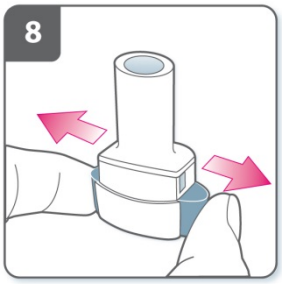
Insert capsule:
Place the capsule into the capsule chamber.
Never place a capsule directly into the mouthpiece.

Close the inhaler:
You should hear a “click” as the mouthpiece closes onto the inhaler base.

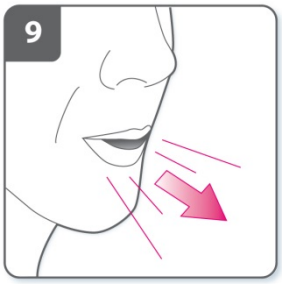


Pierce the capsule:

- Hold the inhaler upright with the mouthpiece pointing up.
- Pierce the capsule by firmly pressing together both side buttons at the same time. **Do this only once.**
- You should hear a “click” as the capsule is being pierced.



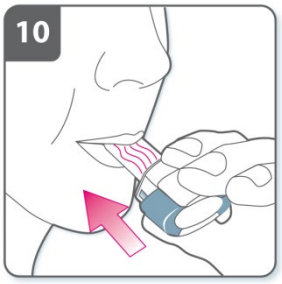
Release the side buttons fully.



Breathe out:

Before placing the mouthpiece in your mouth, breathe out fully.

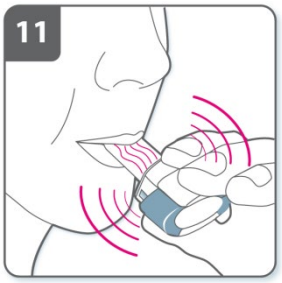
Do not blow into the mouthpiece.



Inhale the medicine

To breathe the medicine deeply into your airways:

- Hold the inhaler as shown in the picture. The side buttons should be facing left and right. Do not press the side buttons.
- Place the mouthpiece in your mouth and close your lips firmly around it.
- Breathe in rapidly but steadily and as deeply as you can.



Note:

As you breathe in through the inhaler, the capsule spins around in the chamber and you should hear a whirring noise. You will experience a sweet flavor as the medicine goes into your lungs.

Additional information

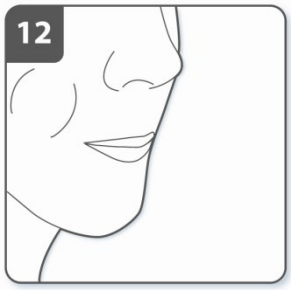
Occasionally, very small pieces of the capsule can get past the screen and enter your mouth. If this happens, you may be able to feel these pieces on your tongue. It is not harmful if these pieces are swallowed. The chances of the capsule breakage will be increased if the capsule is accidentally pierced more than once (step 7). Therefore it is recommended that you

follow the storage directions, remove the capsule from the blister immediately before use and pierce each capsule only once.

If you do not hear a whirring noise:

The capsule may be stuck in the capsule chamber. If this happens:

- Open the inhaler and carefully loosen the capsule by tapping the base of the inhaler. Do not press the side buttons.
- Inhale the medicine again by repeating steps 9 to 11.



Hold breath:

After you have inhaled the medicine:

- Hold your breath for at least 5-10 seconds or as long as you comfortably can while taking the inhaler out of your mouth.
- Then breathe out.
- Open the inhaler to see if any powder is left in the capsule.

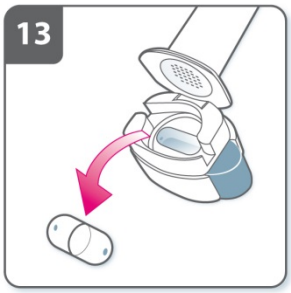
If there is powder left in the capsule:

- Close the inhaler.
- Repeat steps 9, 10, 11 and 12.

Most people are able to empty the capsule with one or two inhalations.

Additional information

Some people may occasionally cough briefly soon after inhaling the medicine. If you do, don't worry. As long as the capsule is empty, you have received your medicine.



After you have finished taking your medicine:

- You may be directed by your physician to rinse mouth with water and spit it out; do not swallow the water.
- Open the mouthpiece again, and remove the empty capsule by tipping it out of the capsule chamber. Put the empty capsule in your household waste.
- Close the inhaler and replace the cap.

Do not store the capsules in the inhaler.

REMEMBER:

- Do not swallow capsules.
- Only use the inhaler contained in this pack.
- Capsules must always be stored in the blister, and only removed immediately before use.

- Never place a capsule directly into the mouthpiece of the inhaler.
- Do not press the side buttons more than once.
- Never blow into the mouthpiece of the inhaler.
- Always release the push buttons before inhalation.
- Never wash the inhaler with water. Keep it dry. See “How to clean your inhaler”.
- Never take the inhaler apart.
- Always use the new inhaler that comes with your new medication pack.
- Do not store the capsules in the inhaler.
- Always keep the inhaler and capsules in a dry place, and avoid very hot or cold temperatures.

How to clean your inhaler

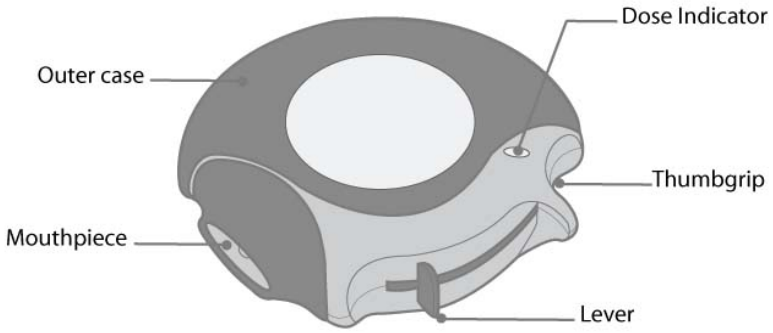
- Clean your inhaler once a week.
- Wipe the mouthpiece inside and outside to remove any powder with a clean, dry lint-free cloth.
- Do not wash your inhaler with water. Keep it dry.
- Do not take the inhaler apart.

Appendix 2: How to Use an Accuhaler®/ Diskus®

Instructions for use

Follow the instructions below for using your Diskus® inhalation device. You will breathe in (inhale) the medicine from the Diskus. Do not use the Diskus unless your healthcare provider has taught you, and you understand everything. If you have any questions, ask the doctor, nurse or pharmacist personnel at the study site.

Figure 1 Parts of the Diskus



Take the Diskus out of the medication pack given to you. The Diskus will be in the closed position. The dose indicator on the top of the Diskus tells you how many doses are left. The dose indicator number will decrease each time you use the Diskus. After you have used 55 doses from the Diskus, the numbers 5 to 0 will appear in red to warn you that there are only a few doses left (see Figure 2).

Figure 2 Dose Indicator for the Diskus®

Taking a dose from the Diskus® requires the following 3 steps: Open, Click, Inhale.

1. OPEN

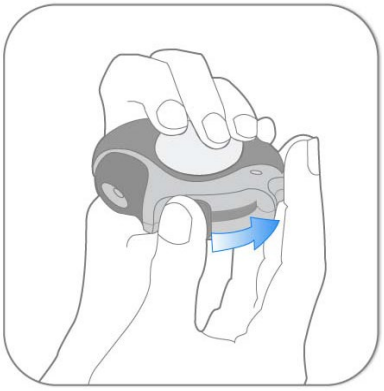
Hold the Diskus® in one hand and put the thumb of your other hand on the thumbgrip. Push your thumb away from you as far as it will go until the mouthpiece appears and snaps into position (see Figure 3).

Figure 3 Opening the Mouthpiece Cover

2. CLICK

Hold the Diskus® in a level, flat position with the mouthpiece towards you. Slide the lever away from you as far as it will go until it clicks (see Figure 4). The Diskus® is now ready to use.

Figure 4 Sliding the Lever Until It Clicks



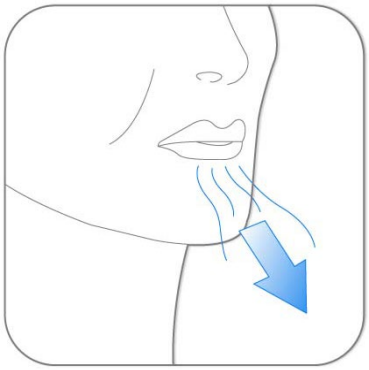
Every time the **lever** is pushed back, a dose is ready to be inhaled. This is shown by a decrease in numbers on the dose counter. **To avoid releasing or wasting doses once the** Diskus® **is ready:**

- Do not close the Diskus.
- Do not tilt the Diskus.
- Do not play with the lever.
- Do not move the lever more than once.

3. INHALE

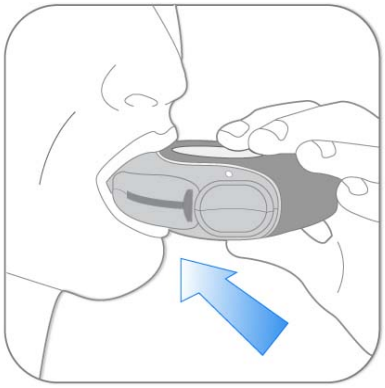
Before inhaling your dose from the Diskus®, breathe out (exhale) fully while holding the Diskus® level and away from your mouth (see Figure 5). **Remember, never breathe out into the Diskus® mouthpiece.**

Figure 5 Exhaling



Put the mouthpiece to your lips (see Figure 6). Breathe in quickly and deeply through the Diskus®. Do not breathe in through your nose.

Figure 6 Inhaling

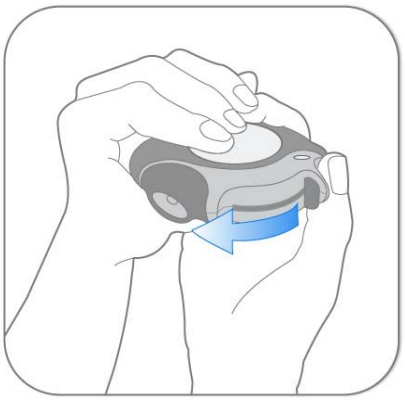


Remove the Diskus® from your mouth. Hold your breath for about 10 seconds, or for as long as is comfortable. Breathe out slowly. The Diskus® delivers your dose of medicine as a very fine powder. Most patients can taste or feel the powder. Do not use another dose from the Diskus® if you do not feel or taste the medicine.

4. CLOSE

Close the Diskus® when you are finished taking a dose so that the Diskus® will be ready for you to take your next dose. Put your thumb on the thumbgrip and slide the thumbgrip back towards you as far as it will go (see Figure 7). The Diskus® will click shut. The lever will automatically return to its original position. The Diskus® is now ready for you to take your next scheduled dose, due in about 12 hours. (Repeat steps 1 to 4 at that time).

Figure 7 Closing the Mouthpiece Cover



Remember:

- Never breathe into the Diskus®.
- Never take the Diskus® apart.
- Always ready and use the Diskus® in a level, flat position.
- Do not use the Diskus® with a spacer device.
- Never wash the mouthpiece or any part of the Diskus®. **Keep it dry.**
- Always keep the Diskus® in a dry place.

Never take an extra dose, even if you did not taste or feel the medicine

Appendix 3: Spirometry Guidance

Equipment

Spirometers must meet the specifications and performance criteria recommended in the American Thoracic Society (ATS)/European Respiratory Society (ERS) Standardization of Spirometry[1]. Spirometers must have the capacity to print FVC tracings. All spirometry values should be reported at BTPS by the method established by the manufacturer.

Calibration

The spirometer should be calibrated every morning before any spirometric measurements for the study are performed. Calibration reports should be printed and stored as source data at the site.

Preparing the test subject

On study days when spirometry will be performed, patients should refrain from the following:

- Coffee, tea, chocolate, cola and other caffeine-containing beverages and foods and ice-cold beverages for 4 hours prior to spirometry
- Strenuous activity for 12 hours prior to spirometry
- Exposure to environmental smoke, dust or areas with strong odors

Every effort should be made to assure consistent testing conditions throughout the study. A seated position with nose clips is recommended to reduce risks related to dizziness or syncope. When possible, spirometry should be conducted by the same technician using the same spirometer. To minimize the effects of diurnal variation on lung function, spirometry visits should start at approximately the same time of day at each visit.

Performing Spirometry

The subject's age, height and gender will be entered into the spirometer. It is important that the height is measured accurately at the study site. Spirometry, an effort-dependent test, requires careful instruction and cooperation of the subject. The technician should ensure a good seal around the mouthpiece, and confirm that the subject's posture is correct. The subject should be instructed to perform a maximal inspiration, followed by maximum forced expiration until no more air can be exhaled or for at least 6 seconds. Expiration must be rapid with exertion of maximal effort. The results of spirometry should meet the ATS/ERS criteria for acceptability and repeatability. Acceptability criteria should be applied before repeatability is determined.

Number of trials

A minimum of 3 acceptable forced vital capacity (FVC) maneuvers should be performed. If a subject is unable to perform a single acceptable maneuver after 8 attempts, testing may be discontinued.

Acceptability

An acceptable maneuver has the following characteristics:

- No hesitation or false start;
- A rapid start;
- No cough, especially during the first second of the maneuver;
- No glottic closure or obstruction by tongue or dentures

- No early termination of exhalation (minimum exhalation time of 6 seconds is recommended, or no volume change for at least 1 second) or the subject cannot continue to exhale further

Repeatability

The 2 largest FVC and FEV_1 values from 3 acceptable maneuvers should not vary by more than 0.150 L.

Recording of data

The highest FEV_1 and FVC from any of the acceptable curves are recorded. (The highest FEV_1 and FVC may not necessarily result from the same acceptable curve).

Predicted normal

This study will utilize the spirometric predication equation standards for the European Community for Coal and Steel[2], Nhanes[3], ERS Global Lung Function Initiative (GLI)[2] or Japanese Respiratory Society[3].

Reversibility

All reversibility evaluations should follow the recommendations of the ATS/ERS Task force: Standardization of Lung Function Testing

Administer 400 μg of salbutamol/albuterol following the completion of the baseline assessment. A second spirometry assessment is then performed within 30 minutes after administration of the salbutamol/albuterol.

Reversibility is calculated as:

$$100 \times \frac{FEV_1 \text{ (post } \beta_2\text{-agonists)} - FEV_1 \text{ (baseline)}}{FEV_1 \text{ (baseline)}}$$

Subjects will be considered reversible if an increase of at least 12% is demonstrated after administration of the bronchodilator.

Predicted normal values will be calculated according to ECSC

For height measured in meters

Males: FEV_1 predicted (L)=4.30x(height(meters))-0.029xage(years)-2.49

Females: FEV_1 predicted (L)=3.95x(height(meters))-0.025xage(years)-2.60

References

[1] Miller MR et al, Standardization of Lung Function Testing. Eur Resp J 2005;26:153-161.

[2] Quanjer PH, et al. ERS Global Lung Function Initiative, Multi ethnic reference values for spirometry for the 3-95 year age range: the global lung function 2012 equations. Report of the Global Lung Function Initiative (GLI). ERS Task Force to establish improved Lung Function Reference Values.

[3] Kubota, Kobayashi, Quanjer PH, et al. Reference values for spirometry, including vital capacity, in Japanese adults calculated with the LMS method and compared with previous values. Clinical Pulmonary Functions Committee of the Japanese Respiratory Society. Respiratory Investigations 2014, 242-250.

Appendix 4: Patient Asthma Control e-Diary

For illustrative purposes only

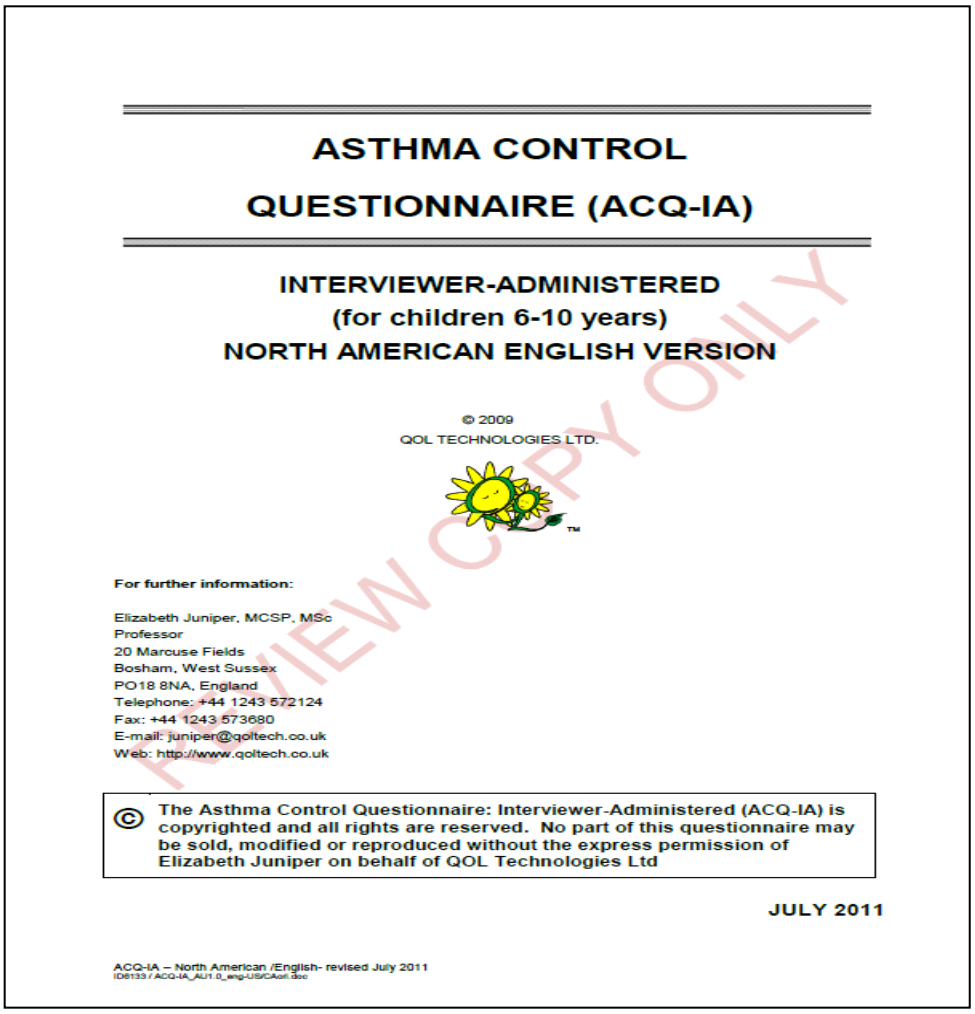
The patient's parent/ legal guardian should assist the patient in completing the e-Diary.

The following information will be captured:

In the Morning	In the Evening
Peak expiratory flow rate	
How often were you woken up by your asthma during the night?	
Did you have asthma symptoms upon awakening in the morning?	
Number of puffs of rescue medication during the past 12 hours	
	Peak expiratory flow rate
	Did your symptoms stop you from performing your usual daily activities?
	How severe was your shortness of breath today?
	How much did you wheeze today?
	How was your cough today?
	Did you have chest tightness today?
	Number of puffs of rescue medication during the past 12 hours.

Appendix 5: ACQ-IA

For illustrative purposes only



ASTHMA CONTROL

QUESTIONNAIRE (ACQ-IA)

INTERVIEWER-ADMINISTERED
(for children 6-10 years)
NORTH AMERICAN ENGLISH VERSION

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QOL TECHNOLOGIES LTD.

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ACQ-IA – North American /English- revised July 2011
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ASTHMA CONTROL QUESTIONNAIRE©
(NORTH AMERICAN ENGLISH VERSION)
INTERVIEWER-ADMINISTERED

PATIENT ID: _____

DATE: _____

ASTHMA CONTROL QUESTIONNAIRE (for children 6-10 years)

Please read these instructions carefully before administering the questionnaire

Parents may be present during the interview but you should encourage the child to respond and only ask the parent to help if the child is having difficulties.

Some younger children may have difficulty understanding the meaning of some questions. First, you should read each question to the child exactly as written in the text. If the child doesn't understand, read the question again using the secondary wording (marked with 'a'). Try not to place your own interpretation on the question.

The questionnaire will ask how the child's asthma has been during the last week (7 days). Check that the child understands this time frame. If in doubt, ask the parent to identify an event that occurred a week previously (e.g. a football match) and then ask the child to tell you how she/he has been since that event. Make sure that the child understands that we want to know how their asthma has been **on average** during the week, not about one specific asthma event.

Show the child the response card and explain the options. Explain the concept of the 7 responses. Explain that 0 means that they have not had any asthma symptoms and have not been limited at all in their daily activities and that 6 means that their symptoms and activity limitations have been really, really bad. Explain that the other numbers (1-5) represent levels in between. For children who can read, we suggest that you ask them to read aloud each of the responses. For younger children, start by reading to them just the 7 responses to question one (both number and words) and check that they understand the meaning of the words (then repeat at the beginning of each question).

Reassure the child that there are no right or wrong answers.

ASTHMA CONTROL QUESTIONNAIRE©
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PATIENT ID: _____

DATE: _____

First, read each question to the child using the primary wording. If the child does not fully understand the question, read it again using the secondary wording marked with 'a' (e.g. 2a, 3a etc.).

1. During the past week, how often were you **woken by your asthma** during the night?

2. During the past week, how **bad were your asthma symptoms when you woke up** in the morning?

2a During the past week, how **bad were your asthma symptoms (for instance, hard to breathe, wheeze, cough) when you woke up** in the morning?

3. During the past week, how **limited were you in your activities** because of your asthma?

3a During the past week, how **bothered were you in the things you do every day** because of your asthma?

4. During the past week, how much **shortness of breath** did you experience because of your asthma?

4a During the past week, how much **shortness of breath (hard or difficult to breathe, breathless)** did you have because of your asthma?

5. During the past week, how much time did you **wheeze?**

6. During the past week, how many **puffs/inhalations of short-acting bronchodilator** (e.g. Ventolin/Bricanyl) have you used each day?

6a During the past week, how many **puffs of your Reliever (quick relief, rescue)** have you used each day?

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INTERVIEWER-ADMINISTERED

PATIENT ID: _____

DATE: _____

RESPONSE SHEET

Question	Response (0-6)
1. Woken by asthma	.....
2. Asthma symptoms on waking	.....
3. Activity limitation	.....
4. Short of breath	.....
5. Wheeze	.....
6. Bronchodilator	.....

Please circle the response (0-6) for the child's FEV_1% predicted

7. FEV_1pre-bronchodilator: .....
FEV_1predicted:.....
FEV_1%predicted:.....
(Record actual values on the dotted lines and score the FEV_1 % predicted in the next column)

0	> 95% predicted
1	95 - 90%
2	89 - 80%
3	79 - 70%
4	69 - 60%
5	59 - 50%
6	< 50% predicted

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DATE: _____

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RESPONSE CARD

QUESTION 1
0 Never
1 Hardly ever
2 A few times
3 Several times
4 Many times
5 A great many times
6 Unable to sleep because of asthma

QUESTION 2
0 No symptoms
1 Very mild symptoms
2 Mild symptoms
3 Moderate symptoms
4 Quite severe symptoms
5 Severe symptoms
6 Very severe symptoms

QUESTION 3
0 Not limited at all
1 Very slightly limited
2 Slightly limited
3 Moderately limited
4 Very limited
5 Extremely limited
6 Totally limited

QUESTION 4
0 None
1 A very little
2 A little
3 A moderate amount
4 Quite a lot
5 A great deal
6 A very great deal

QUESTION 5
0 Never
1 Hardly any of the time
2 A little of the time
3 A moderate amount of the time
4 A lot of the time
5 Most of the time
6 All the time

QUESTION 6
0 None
1 1 - 2 puffs/inhalations most days
2 3 - 4 puffs/inhalations most days
3 5 - 8 puffs/inhalations most days
4 9 - 12 puffs/inhalations most days
5 13 - 16 puffs/inhalations most days
6 More than 16 puffs/inhalations most days

Appendix 6: Clinically notable laboratory values and vital signs

There are no specific criteria for this study; however, the Central Laboratory will flag laboratory values falling outside of the normal range on the Central Laboratory Report (which the investigator should sign off) and the investigator will report any values considered clinically significant in the eCRF.

Appendix 7: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 13-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

Table 13-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue Follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.