

Novartis Institutes for BioMedical Research

QVM149

Clinical Trial Protocol CQVM149B2203

**A randomized, double-blind, placebo-controlled,  
three-period cross-over study to assess the  
pharmacodynamics, safety, tolerability, and  
pharmacokinetics of two orally inhaled indacaterol salts  
(maleate and acetate) delivered via the Concept1 inhalation  
device in patients with asthma**

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## **Site Operations Manual (SOM)**

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct.

### **Notification of serious adverse events**

Refer to [Section 9.2](#) of the protocol for definitions and reporting requirements for Serious Adverse Events (within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department and notify the Clinical Trial Leader.).

Contact information is listed in the Site Operations Manual.

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## List of abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AV	atrioventricular
b.i.d.	twice a day
BA	bioanalytical
BMI	Body Mass Index
BP	blood pressure
BUN	blood urea nitrogen
CD-ROM	compact disc – read only memory
CFR	Code of Federal Regulation
CK	creatinine kinase
CO <sub>2</sub>	carbon dioxide
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report/Record Form (paper or electronic)
CSR	clinical study report
CV	coefficient of variation
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FDC	fixed-dose combination
FEF <sub>25-75%</sub>	Forced Expiratory Flow (25-75%)
FEV <sub>1</sub>	Forced Expiratory Volume in 1 second
FPM	fine particle mass
FVC	forced vital capacity
GCP	Good Clinical Practice
h	hour
HbA1C	hemoglobin a1c
HBsAG	hepatitis B surface antigen



hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
i.v.	intravenous
IB	Investigator's Brochure
IBD	International birthdate
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	inhaled corticosteroid
IEC	Independent Ethics Committee
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine system
kg	kilogram
LABA	Long-acting $\beta_2$ agonist
LDH	lactate dehydrogenase
LFT	liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
MDDPI	multidose dry powder inhaler
mg	milligram(s)
ml	milliliter(s)
o.d.	once a day
OTC	over-the-counter
p.o.	oral
PD	pharmacodynamic(s)
PEF	peak expiratory flow
PI	post-inhalation
PK	pharmacokinetic(s)
pMDI	pressurized metered-dose inhaler
RBC	red blood cell(s)

REB	Research Ethics Board
SABA	Short acting beta <sub>2</sub> agonist
SAE	serious adverse event
SD	standard deviation
SDDPI	single-dose dry powder inhaler
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
TBL	total bilirubin
ULN	upper limit of normal
ULQ	upper limit of quantification
WBC	white blood cell(s)
γ-GT	gamma-glutamyl transferase
μg	microgram

## Pharmacokinetic definitions and symbols

AUC <sub>0-24h,ss</sub>	The area under the plasma concentration-time curve from time zero to 24 hour post dose [pg.h/mL], at steady state
AUC <sub>tau,ss</sub>	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau at steady state [mass x time / volume]
C <sub>av,ss</sub>	The average steady state plasma (or serum or blood) concentration during multiple dosing
C <sub>max,ss</sub>	The observed maximum plasma (or serum or blood) concentration following drug administration at steady state [mass / volume]
C <sub>min,ss</sub>	The lowest plasma (or serum or blood) concentration observed during a dosing interval at steady state [mass / volume]
F <sub>rel</sub>	Relative bioavailability of indacaterol acetate compared to indacaterol maleate
R <sub>acc</sub>	The accumulation ratio
T <sub>1/2</sub>	The terminal elimination half-life [time]
T <sub>1/2,acc</sub>	The effective half-life based on drug accumulation at steady state [time]
T <sub>max,ss</sub>	The time to reach the maximum concentration after drug administration at steady state [h]

## Glossary of terms

Baseline	Period after screening and prior to the first dose of Treatment period 1
Control drug	A study drug 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.
Enrollment	Point/time of subject entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
Investigational drug	The study 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”.
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.

Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points.

## Protocol synopsis

<b>Protocol number</b>	CQVM149B2203
<b>Title</b>	A randomized, double-blind, placebo-controlled, three-period cross-over study to assess the pharmacodynamics, safety, tolerability, and pharmacokinetics of two orally inhaled indacaterol salts (maleate and acetate) delivered via the Concept1 inhalation device in patients with asthma
<b>Brief title</b>	Pharmacodynamics, safety, tolerability, and pharmacokinetics of two orally inhaled indacaterol salts in adult subjects with asthma.
<b>Sponsor and Clinical Phase</b>	Novartis Phase II
<b>Intervention type</b>	Drug
<b>Study type</b>	Interventional
<b>Purpose and rationale</b>	This study is designed to determine the pharmacodynamics, safety, tolerability, and systemic pharmacokinetics of indacaterol maleate 150 µg (approved product Onbrez® Breezhaler®) and indacaterol acetate 150 µg (development formulation), at steady state, in subjects with asthma.
<b>Primary Objective(s)</b>	To assess the bronchodilator effect of orally inhaled indacaterol salts (maleate and acetate) compared to placebo in subjects with asthma as measured by trough Forced Expiratory Volume in 1 second (FEV <sub>1</sub> ) after 14 days of treatment. Trough is defined as the mean of FEV <sub>1</sub> at 23 h 15 min and 23 h 45 min post-dose.
<b>Secondary Objectives</b>	<p>To assess the steady state pharmacokinetics of orally inhaled indacaterol salts (maleate and acetate) following 14 days of treatment in subjects with asthma</p> <p>To assess the bronchodilator effect of orally inhaled indacaterol salts (maleate and acetate) compared to placebo in subjects with asthma as measured by:</p> <ul style="list-style-type: none"> <li>• Time to peak FEV<sub>1</sub> on Day 14.</li> <li>• FEV<sub>1</sub>, forced vital capacity (FVC), and forced expiratory flow (25-75%) (FEF<sub>25-75%</sub>) at each post-dose time point after 14 days of treatment.</li> <li>• Standardized FEV<sub>1</sub> AUC between baseline (pre-dose) and 4 hr post-dose on Day 14 of treatment.</li> <li>• Morning (pre-dose) and evening peak expiratory flow (PEF) measurements for indacaterol salts (maleate and acetate) in comparison to placebo</li> <li>• To assess day and night rescue medication usage for indacaterol salts (maleate and acetate) in comparison to placebo</li> <li>• To assess the safety and tolerability of indacaterol salts (maleate and acetate) in comparison to placebo in terms of the number and percentage of adverse events, laboratory results, vital signs (blood pressure and pulse rate) and ECGs.</li> </ul>
<b>Study design</b>	This study is a randomized, double-blind, placebo-controlled, three-period complete block cross-over study in approximately 54 subjects (42 completers) with asthma.
<b>Population</b>	The study population will be comprised of male and female patients aged 18 and above with asthma. Approximately 54 adult subjects will be randomized with the intent of having at least 42 subjects complete the study.

<b>Inclusion criteria</b>	<p>Male and female patients with asthma, aged 18 or above, diagnosed according to documented physician diagnosis of asthma and who additionally meet the following criteria:</p> <ul style="list-style-type: none"> <li>• Patients receiving daily treatment with an inhaled corticosteroid up to the maximum dose per day as indicated in the package leaflet and on a stable regimen for at least 4 weeks prior to screening.</li> <li>• Patients with a pre-bronchodilator FEV<sub>1</sub> at screening of <math>\geq 50\%</math> and <math>\leq 90\%</math> of the predicted normal value for the patient. This criterion for FEV<sub>1</sub> will have to be demonstrated after a washout period withholding of bronchodilators.</li> <li>• Patients who demonstrate an increase of <math>\geq 12\%</math> and <math>\geq 200</math> mL in FEV<sub>1</sub> within 30 minutes after inhaling a total of 400 µg of salbutamol/360 µg albuterol or equivalent dose (the reversibility test) as per ATS/ERS Task force: Standardization of Lung Function Testing guidelines (<a href="#">Miller et al 2005a</a>). Reversibility will have to be demonstrated after an appropriate washout period.</li> </ul>
<b>Exclusion criteria</b>	<p>History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.</p> <p>A history of clinically significant ECG abnormalities, (including past medical history of life-threatening arrhythmias or a history, or family history, of long QT syndrome or Torsades de Pointes, and paroxysmal atrial fibrillation)</p> <ul style="list-style-type: none"> <li>• Patients diagnosed with COPD as defined by the (<a href="#">GOLD Guidelines 2017</a>).</li> <li>• Patients with Type I diabetes or uncontrolled Type II diabetes (HbA1c <math>&lt; 9\%</math> at screening).</li> <li>• Patients who have had a severe asthma attack/exacerbation requiring hospital admission in the 6 weeks prior to screening</li> <li>• Patients who have had previous intubation for a severe asthma attack/exacerbation.</li> <li>• Patients with concomitant pulmonary disease, pulmonary tuberculosis (unless confirmed by chest X-ray to be no longer active) or clinically significant bronchiectasis.</li> </ul>
<b>Investigational and reference therapy</b>	<ul style="list-style-type: none"> <li>• Indacaterol Maleate 150 µg</li> <li>• Indacaterol Acetate 150 µg</li> <li>• Placebo</li> </ul>
<b>Efficacy/PD assessments</b>	<ul style="list-style-type: none"> <li>• Spirometry</li> <li>• PEF</li> <li>• Rescue medication use</li> </ul>
<b>Safety assessments</b>	<ul style="list-style-type: none"> <li>• Hematology</li> <li>• Blood chemistry</li> <li>• Urinalysis</li> <li>• Adverse events</li> <li>• Serious adverse events</li> <li>• Vital signs (blood pressure and pulse rate)</li> <li>• ECG</li> </ul>
<b>Other assessments</b>	<p>Pharmacokinetic assessments for indacaterol:</p> <ul style="list-style-type: none"> <li>• Day 14: pre-dose (-15 minutes), 5 min, 10 min, 15 min, 30 min, 1 h, 2 h, 4 h, 8 h, 12 h, and 24 h post-dose.</li> </ul>

<b>Data analysis</b>	<p>The primary endpoint is trough FEV<sub>1</sub> after 14 days of treatment. Trough FEV<sub>1</sub> is defined as the mean of the FEV<sub>1</sub> measurements at 23 h 15 min and 23 h 45 min post dose. The trough FEV<sub>1</sub> will be analyzed using an analysis of variance (ANOVA) with treatment, period and sequence as fixed effects and subject nested within sequence as random effect. Treatment contrasts will be constructed to compare each indacaterol salt (maleate and acetate) with placebo, the results will be expressed as estimates and their two sided 95% confidence intervals and P-value, without adjustment for multiplicity.</p> <p>Additionally as a secondary consideration, an estimate of the differences in trough FEV<sub>1</sub> between indacaterol acetate (test) and indacaterol maleate (reference) will be calculated together with the corresponding two sided 95% confidence intervals.</p> <p>Pharmacokinetic analysis</p> <p>The log transformed pharmacokinetic parameters AUC<sub>0-24h,ss</sub> and C<sub>max,ss</sub> will be compared for indacaterol acetate (test) relative to indacaterol maleate (reference) using a mixed effects model with sequence, treatment and period as fixed effects and subject nested within sequence as random effect. Body weight may be included as a covariate and applied as a fixed effect in the model. Ratios of the geometric means together with their corresponding 90% confidence intervals will be provided for each of the PK parameters above.</p>
<b>Key words</b>	Asthma, indacaterol, bronchodilator, pharmacokinetics, pharmacodynamics, tolerability



## 1 Introduction

### 1.1 Background

Asthma is a chronic inflammatory disorder of the lungs characterized by variable airflow limitation and hyper-responsiveness. It is a common disorder with an estimated worldwide prevalence of 300 million. It impacts morbidity, with a substantial socioeconomic burden.

QVM149 is a fixed dose combination (FDC) of an inhaled long-acting  $\beta_2$ -agonist (indacaterol acetate), an inhaled long-acting antimuscarinic (glycopyrronium bromide) and an inhaled corticosteroid (mometasone furoate) that is currently being developed as a lactose-blended dry powder for the once-daily maintenance treatment of asthma GINA step  $\geq 4$  and administered via the Concept1 single-dose dry powder inhaler (SDDPI). All three mono-components, indacaterol (as the maleate salt), glycopyrronium bromide, and mometasone furoate have previously been developed and approved as individual drugs for either chronic obstructive pulmonary disease (COPD) or asthma. Indacaterol maleate, delivered via Concept1, a SDDPI (Onbrez<sup>®</sup> Breezhaler<sup>®</sup>), is approved in over 110 countries worldwide for the once daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD.

During the clinical development of indacaterol maleate, a small proportion of subjects (including healthy volunteers and patients with asthma, and COPD) developed a postinhalation (PI) cough. This was of rapid onset, short-lived, and with no adverse impact on safety, efficacy or tolerability. This PI cough was not dose dependent. In Study CQAB149D2301, an early proof-of-concept type formulation was used and post-inhalation cough was observed in 45% to 59% of subjects receiving indacaterol maleate whereas only 7% to 14% of subjects receiving indacaterol acetate experienced post-inhalation cough. Hence, the acetate salt of indacaterol reduced the incidence of post-inhalation cough compared to the maleate salt whilst demonstrating similar efficacy, safety, and systemic exposure. Due to likely patient preference of a product which does not cause PI cough, all ongoing and future QVM149 studies will be performed using the indacaterol acetate salt.

This study is designed to determine the pharmacodynamics, safety, tolerability, and systemic pharmacokinetics of indacaterol maleate 150  $\mu\text{g}$  (the salt form of the approved product Onbrez<sup>®</sup> Breezhaler<sup>®</sup>) and indacaterol acetate 150  $\mu\text{g}$  at steady state, in subjects with asthma.

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## **1.3 Clinical data**

### **1.3.1 Human safety and tolerability data**

#### **Indacaterol maleate**

Indacaterol has been studied in healthy subjects, adult subjects with COPD, and adult, adolescent, and pediatric subjects with asthma. In total, over 28,000 subjects were included in the indacaterol clinical development program.

Indacaterol, at doses from 75 µg to 300 µg once daily, has been approved for the treatment of COPD in over 110 countries worldwide including those of European Economic Area, USA and Japan. The lowest dose approved for the maintenance therapy for COPD outside of the US and Canada is 150 µg given once daily.

The cumulative patient exposure since the International Birth Date until 30 Nov 2015 of the product is estimated to be approximately 2,236,431.77 patient years. About 76.2% of the cumulative exposure to indacaterol maleate was related to the 150 µg dose strength.

Overall, the safety profile of indacaterol is similar to that of other LABAs at therapeutic doses, with the added benefit that the drug is administered once daily. The most common adverse reactions at the recommended doses were nasopharyngitis, upper respiratory tract infection, cough, headache, and muscle spasms. These were in the vast majority mild or moderate and became less frequent if treatment was continued.

At recommended doses, the adverse reaction profile of Onbrez<sup>®</sup> Breezhaler<sup>®</sup> in patients with COPD shows clinically insignificant systemic effects of  $\beta_2$ -adrenergic stimulation. Mean heart rate changes were less than one beat per minute, and tachycardia was infrequent and reported at a similar rate as under placebo treatment. Relevant prolongations of QTcF were not detectable in comparison to placebo. The frequency of notable QTcF intervals (i.e. >450 ms (males) and >470 ms (females)) and reports of hypokalemia were similar to placebo. The mean of the maximum changes in blood glucose were similar between Onbrez<sup>®</sup> Breezhaler<sup>®</sup> and placebo.

The effects of indacaterol on QT intervals were assessed in healthy subjects, COPD subjects, and asthma subjects. In a thorough QT study (CQAB149B2339) conducted in compliance with current ICH guidance, indacaterol treatment with multiple daily doses (150, 300, and 600  $\mu$ g) was assessed as safe and well tolerated. Maximum mean prolongations of QTcF intervals were <5 msec (the regulatory threshold of concern) and the upper limit of the 90% confidence interval was below 10 msec for all time matched comparisons versus placebo at the investigated doses. This shows that there is no concern for QTcF prolongation in the investigated dose range.

Administration of indacaterol at daily doses of up to 600  $\mu$ g for up to one year of exposure was safe and well tolerated. There were no notable differences between the safety profiles of indacaterol once daily and other LABAs given twice daily. Post-marketing data from countries where indacaterol is approved for the treatment of COPD do not reveal any new safety concerns and have not led to any regulatory or manufacturer actions being taken for safety reasons.

For further detailed information on the pharmacodynamic profile of indacaterol, please refer to the (Indacaterol (QAB149) Investigator's Brochure (IB)) and Onbrez<sup>®</sup> SmPC.

### **Indacaterol acetate**

To date, three studies (CQAB149B2102, CQAB149D2301, and CQMF149E2203 (as part of the development program for the FDC of indacaterol acetate with mometasone furoate)), in a total of 463 subjects with asthma have been completed using indacaterol acetate. So far, one study with indacaterol acetate as one of the study arms has been concluded in a total of 64 healthy subjects (CQMF149E2102, as part of the development program for the FDC of indacaterol acetate with mometasone furoate).

Study CQAB149B2102 was a multi-center, randomized, single-dose, double-blind, 4-way cross-over study to evaluate tolerability following treatment with indacaterol salts (maleate, xinafoate, and acetate using the Aerolizer<sup>™</sup> device, a SDDPI) in comparison to placebo in 98 subjects with mild to moderate persistent asthma.

All three indacaterol salts were generally safe and well tolerated. There were no deaths or serious adverse events. Two subjects withdrew due to adverse events. These were not suspected to be study drug related. The most common adverse event was cough. This was predominantly mild or moderate. There were no cough-related study withdrawals.

There was a marked increase in the incidence of cough 5 minutes after inhalation (as evaluated by direct and targeted observation by the investigator) of each of the indacaterol salts compared to placebo; the incidence rates following inhalation of indacaterol maleate, indacaterol acetate, indacaterol xinafoate, and placebo were 69%, 28%, 20%, and 7%, respectively. There was a significantly lower incidence of PI cough with the xinafoate and acetate salts in comparison to the maleate salt. The cough was characterized by a rapid onset, short duration and was predominantly mild to moderate in severity.

Study CQAB149D2301 was a multi-center, randomized, double-blind, placebo-controlled, multiple-dose, 4-way cross-over study consisting of four treatments namely indacaterol maleate, indacaterol xinafoate, indacaterol acetate (each at 400 µg) and matching placebo inhaled via the Concept1 device in 30 subjects with persistent asthma. Indacaterol, in all three salt forms, was well tolerated by subjects with no unexpected events observed and no subject having a serious adverse event. Only one subject was withdrawn from the study for severe adverse events that were not considered to be related to study drug. There were no clinically relevant changes in laboratory values or in ECG and vital signs. Cough within 5 minutes of dosing affected up to 59% subjects in the indacaterol maleate group. These coughs were mainly of moderate severity on day 1 but mainly mild thereafter. The incidence of cough was lower with the other two salts (14% patients in each group on Day 7).

Study CQMF149E2203 was a multicenter, randomized, double-blind, placebo-controlled, 12-week treatment, parallel-group study to assess the efficacy, safety, and pharmacokinetics of indacaterol acetate (75 and 150 µg o.d.) inhaled via the Concept1 device in patients with persistent asthma. Both indacaterol acetate treatment groups were safe and well tolerated. There were no deaths in this study. Besides one subject who discontinued the study due to an AE (asthma), there were no SAEs or discontinuations due to SAEs in the indacaterol acetate 150 µg group. The frequency of SAEs and discontinuations to AEs or SAEs was similar across the indacaterol acetate 75 µg and the placebo groups. The incidence of AEs and discontinuations from study was lower in indacaterol acetate 150 µg treatment group compared with the indacaterol acetate 75 µg and placebo groups.

### **1.3.2 Human pharmacokinetic data**

#### **1.3.2.1 Indacaterol Maleate**

##### **Absorption**

The median time to reach peak serum concentrations of indacaterol delivered as lactose dry powder formulation in the Concept1 device was approximately 15 minutes after single or repeated inhaled doses. Systemic exposure increased with increasing dose (from 150 µg to 600 µg) in a dose proportional manner on repeated once-daily dosing via Concept1 and was about dose-proportional in the dose range of 75 µg to 150 µg. Accumulation factors ( $R_{acc}$ ; i.e. Day 14/Day 1 or Day 15/Day 1 ratios) for AUC and  $C_{max}$  were in the range of 2.9 to 3.8 and

1.6 to 2.8, respectively at steady-state of once-daily doses between 75 µg and 600 µg. Apparent systemic clearance (CL/F) did not appear to change on repeated dosing. Absolute bioavailability of an inhaled dose was on average 43%-45%.

## **Distribution**

The high apparent volumes of distribution ( $V_z/F$ ) seen in all studies indicated that inhaled indacaterol once absorbed into systemic circulation was distributed extensively throughout the body. After intravenous infusion the volume of distribution ( $V_z$ ) was 2,557 L thus confirming extensive distribution of indacaterol throughout the body. The in vitro human serum and plasma protein binding was 94.1-95.3% and 95.1-96.2%, respectively, consistent with ex vivo protein binding measurements. Mild-to-moderate hepatic impairment did not alter the protein binding of indacaterol. Indacaterol had an in vitro blood-to-plasma concentration ratio of 1.2.

## **Biotransformation/Metabolism**

After oral administration of radiolabeled indacaterol in a human ADME study, indacaterol itself was the main component in serum, accounting for over one-third of the total drug related AUC<sub>0-24h</sub>. A hydroxylated derivative was the most prominent metabolite in serum. A direct phenyl-O-glucuronide and hydroxylated glucuronide were also prominent metabolites. A diastereoisomer of the hydroxylated derivative, an N-glucuronide of indacaterol and C- and N-dealkylated products were further metabolites identified.

The key enzymes responsible for metabolic clearance of indacaterol are UGT1A1 and CYP3A4. In vitro investigations indicated that UGT1A1 was the only UGT isoform that metabolized indacaterol to the phenolic-O-glucuronide. The oxidative metabolites were found in incubations with recombinant CYP1A1, CYP2D6, and CYP3A4. It was concluded that CYP3A4 is the predominant isoenzyme responsible for hydroxylation of indacaterol. In vitro investigations further indicated that indacaterol is a low affinity substrate for the efflux pump P-glycoprotein (P-gp).

Clinical drug interaction studies were carried out using potent and specific inhibitors of CYP3A4 and P-gp (i.e. ketoconazole (Study QAB149A2311), erythromycin (Study QAB149B2220), ritonavir (Study QAB149B2107) and verapamil (Study QAB149B2216)). Verapamil was used as the prototypic inhibitor of P-gp and resulted in 1.4- to 2-fold increase in AUC and 1.5-fold increase in C<sub>max</sub>. Co-administration of erythromycin resulted in an increase of 1.4- to 1.6-fold for AUC and 1.2-fold for C<sub>max</sub>. Combined inhibition of P-gp and CYP3A4 by the very strong dual inhibitor ketoconazole caused a 1.9-fold and 1.3-fold increase in AUC and C<sub>max</sub> respectively. Concomitant treatment with another dual inhibitor of CYP3A4 and P-gp, ritonavir, resulted in a 1.7-fold increase in AUC, whereas C<sub>max</sub> was virtually unaffected. Given the safety data of study QAB1492339 and of the pivotal studies (which both confirmed safe use of a 600 µg o.d. dosage regimen), the magnitude of exposure increases due to drug-interactions do not raise any safety concerns for therapeutic doses of 75 µg o.d. or 150 µg o.d.

In-vitro investigations have indicated that indacaterol is devoid of any potential to cause metabolic drug interactions (by inhibition or induction of cytochrome P450 enzymes, or induction of UGT1A1) with medications at the systemic exposure levels achieved in clinical practice.

## Elimination

The available data suggest that elimination of systemically available indacaterol is due to a variety of processes, including 1) P-gp transport of indacaterol, 2) O- and N-glucuronidation of indacaterol (UGT1A1), 3) oxidative metabolism by CYP3A4, possibly followed by glucuronidation, 4) biliary excretion of glucuronides into the gut, where indacaterol and hydroxylated metabolites are liberated and excreted with the feces, and 5) renal excretion. The quantitative contribution of each hepatobiliary elimination process cannot be assessed. However, the clinical drug interaction studies suggest that P-gp mediated transport and CYP3A4-metabolism are major processes. Mild and moderate hepatic impairment did not change systemic clearance to a clinically meaningful extent.

Indacaterol serum concentrations declined in a multiphasic manner. The apparent terminal half-life determined in individual studies, depending on the sampling time interval and the assay sensitivity, ranged from 45.5 to 126 h. The effective half-life for accumulation was calculated according to a method ([Boxenbaum and Battle 1995](#)) based on the actually observed accumulation of indacaterol after repeated dosing. The results indicated that the effective half-life ranged from 40 to 56 hours for once-daily doses between 75 µg and 600 µg. This is consistent with the observed time to steady state of approximately 12 to 15 days.

### 1.3.2.2 Indacaterol acetate

Study CQAB149D2301 was conducted with an early proof-of-concept type formulation (see [Section 1.3.1](#)). Following oral inhalation of 400 µg indacaterol via the Concept1, the pharmacokinetic profiles and systemic exposures of indacaterol acetate and indacaterol maleate in plasma were similar. The ratio of geometric means on Day 7 for AUC<sub>0-24h</sub> (acetate vs. maleate) was 0.975 [90% CI: (0.908, 1.046)] and for C<sub>max</sub> 0.976 [90% CI: (0.885, 1.077)]. This result showed that the PK profile for indacaterol was similar following oral inhalation as acetate or maleate via the Concept 1 device, which allowed for bridging to the existing human PK data for indacaterol maleate.

## 1.3.3 Human pharmacodynamic data

### 1.3.3.1 Indacaterol maleate

A number of clinical trials have investigated the efficacy of inhaled indacaterol maleate in subjects with obstructive airway diseases, specifically asthma and COPD. A number of single and multiple dose dry powder and pressurized metered dose inhaler (pMDI) devices have been employed and doses of up to 3000 µg (single dose) and 800 µg (multiple dose for 28 days)/600 µg (multiple dose for 52-weeks) have been evaluated.

Data from an extensive clinical development program demonstrate that indacaterol maleate is an effective bronchodilator with a rapid onset and full 24 h duration of action in both asthma and COPD (approved indication for Onbrez® Breezhaler® (indacaterol maleate)). The bronchodilator effect data in subjects with asthma are also summarized below as this reflects the target population in this current study.

## **Indacaterol maleate in patients with COPD**

### ***Lung function***

Onbrez<sup>®</sup> Breezhaler<sup>®</sup>, administered once a day at doses of 150 µg and 300 µg, demonstrated clinically meaningful improvements in lung function. At the 12-week primary endpoint (24-hour trough FEV<sub>1</sub>), the 150 µg dose resulted in a 130-180 mL increase compared to placebo (p<0.001) and a 60 mL increase compared to salmeterol 50 µg twice a day (p<0.001). The 300 µg dose resulted in a 170-180mL increase compared to placebo (p<0.001) and a 100 mL increase compared to formoterol 12 µg twice a day (p<0.001). Both doses resulted in an increase of 40-50mL over open-label tiotropium 18 µg once a day (150 µg, p=0.004; 300 µg, p=0.01). The 24-hour bronchodilator effect of Onbrez<sup>®</sup> Breezhaler<sup>®</sup> was maintained from the first dose throughout a one-year treatment period with no evidence of loss in efficacy (tachyphylaxis) (Indacaterol (QAB149) IB).

### ***Symptomatic benefits***

Both doses demonstrated statistically significant improvements in symptom relief over placebo for dyspnea and health status (as evaluated by Transitional Dyspnea Index [TDI] and St. George's Respiratory Questionnaire [SGRQ], respectively). The magnitude of response was generally greater than seen with active comparators (salmeterol and tiotropium). In addition, patients treated with Onbrez<sup>®</sup> Breezhaler<sup>®</sup> required significantly less rescue medication, had more days when no rescue medication was needed compared to placebo and had a significantly improved percentage of days with no daytime symptoms.

Pooled efficacy analysis over 6 months treatment demonstrated that the rate of COPD exacerbations was statistically significantly lower than the placebo rate. Treatment comparison compared to placebo showed a ratio of rates of 0.68 (95% CI [0.47, 0.98]; p-value 0.036) and 0.74 (95% CI [0.56, 0.96]; p-value 0.026) for 150 µg and 300 µg, respectively (Indacaterol (QAB149) IB) (Onbrez<sup>®</sup> Breezhaler<sup>®</sup> SmPC).

## **Indacaterol maleate in subjects with asthma**

The completed clinical studies have demonstrated the efficacy of indacaterol in subjects with asthma. Collectively, these studies show that indacaterol provides efficacious bronchodilation in subjects with asthma similar to that achieved in subjects with COPD.

The efficacy of indacaterol in subjects with asthma has been investigated across a broad range of variables including trough FEV<sub>1</sub>, peak FEV<sub>1</sub>, time to onset of action, and AUC at specified time points.

Randomized trials in subjects with asthma compared the impact of indacaterol on lung function in terms of FEV<sub>1</sub>. Clinically significant improvements in trough FEV<sub>1</sub>, FEV<sub>1</sub>(AUC<sub>22-24h</sub>), FEV<sub>1</sub>(AUC<sub>0-4h</sub>), and peak FEV<sub>1</sub> were observed with once-daily indacaterol 100, 200, 300, 400 and 600 µg vs. placebo. Indacaterol 300 and 600 µg q.d. showed significantly greater improvements in trough FEV<sub>1</sub> than formoterol 12 µg b.i.d. (p<0.01).

A rapid onset of action has been demonstrated for indacaterol compared with placebo. Significant improvements in FEV<sub>1</sub> were observed with indacaterol 200 and 400 µg within 5 min post-dose vs. placebo ( $p < 0.05$ ). Indacaterol has also been shown to have a more rapid onset of action compared with salmeterol and a comparable onset versus the short-acting  $\beta_2$ -agonist, salbutamol. A clinically relevant increase in mean FEV<sub>1</sub> was seen at 5 min post-dose for salbutamol 200 µg, between 15 and 30 min post-dose for indacaterol 200 µg and between 1 and 2 h post-dose for salmeterol 50 µg.

Clinically significant improvements in FEV<sub>1</sub> achieved with indacaterol therapy post-dose were maintained for at least 24-h compared with placebo. A single 200 µg dose of indacaterol demonstrated a prolonged duration of action (FEV<sub>1</sub>) when compared to a single 50 µg dose of salmeterol and a single 200 µg dose of salbutamol.

### **Indacaterol acetate in subjects with asthma**

Studies conducted with indacaterol acetate show similar improvements in lung function and therefore suggest that the efficacy of indacaterol is independent from the used salt form.

Study CQAB149D2301, is a randomized, double-blind, placebo-controlled, multiple-dose, 4-way cross-over study consisting of four treatments namely indacaterol maleate, indacaterol xinafoate, indacaterol acetate (each at 400 µg) and matching placebo inhaled via the Concept1 device in 30 subjects with persistent asthma. The acetate salt, in this population, resulted in a change in FEV<sub>1</sub> similar to that of the maleate salt with no differences in systemic exposure or safety parameters.

In Study CQMF149E2203, a randomized, double-blind, placebo-controlled, 12-week treatment, parallel-group study to assess the efficacy, safety and pharmacokinetics of indacaterol acetate (75 and 150 µg o.d.) in 335 subjects with persistent asthma, indacaterol acetate 150 µg and 75 µg both showed statistically significant superiority of trough FEV<sub>1</sub> to placebo at Week 12. The increase in LS mean of trough FEV<sub>1</sub> at Week 12 in the indacaterol acetate 150 µg group was 106 ml and 80 ml in the indacaterol acetate 75 µg group compared with placebo.

## **1.4 Study purpose**

This study is designed to determine the steady-state pharmacodynamics, safety, tolerability, and systemic pharmacokinetics of indacaterol maleate 150 µg (the salt form used in the approved product Onbrez<sup>®</sup> Breezhaler<sup>®</sup>) and indacaterol acetate 150 µg (the salt form used in clinical development of QVM149 and QMF149 as a FDC with mometasone furoate) in subjects with asthma. The data from this study will support clinical development and registration of QMF149 and QVM149 by enabling bridging to the safety database of the approved monotherapy product, indacaterol maleate.



## 2 Study objectives and endpoints

### 2.1 Primary objective(s)

<b>Primary objective(s)</b>	<b>Endpoints related to primary objective(s)</b>
<ul style="list-style-type: none"> <li>To assess the bronchodilator effect of orally inhaled indacaterol salts (maleate and acetate) in subjects with asthma compared to placebo as measured by trough FEV<sub>1</sub> after 14 days of treatment.</li> </ul>	<ul style="list-style-type: none"> <li>Trough FEV<sub>1</sub> (mean of FEV<sub>1</sub> at 23 h 15 min and 23 h 45 min post-dose) after 14 days of treatment</li> </ul>

### 2.2 Secondary objective(s)

<b>Secondary objective(s)</b>	<b>Endpoints related to secondary objective(s)</b>
<ul style="list-style-type: none"> <li>To assess the steady state pharmacokinetics of indacaterol after 14 days of treatment of orally inhaled indacaterol salts (maleate and acetate) in subjects with asthma.</li> </ul>	<ul style="list-style-type: none"> <li>AUC<sub>0-24h,ss</sub> and C<sub>max,ss</sub>, T<sub>max,ss</sub>, C<sub>min,ss</sub>, C<sub>av,ss</sub> and F<sub>rel</sub></li> </ul>
<ul style="list-style-type: none"> <li>To assess the bronchodilator effect of orally inhaled indacaterol salts (maleate and acetate) in subjects with asthma compared to placebo as measured by: <ul style="list-style-type: none"> <li>Time to peak FEV<sub>1</sub> on Day 14</li> <li>FEV<sub>1</sub>, FEV<sub>1</sub> (% predicted), FVC, FVC (% predicted), FEV<sub>1</sub>/FVC, and FEF<sub>25-75%</sub> at each post-dose time point after 14 days of treatment</li> <li>Standardized FEV<sub>1</sub> AUC from pre-dose to 4 h post-dose on Day 14 of treatment</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>FEV<sub>1</sub>, FVC, and FEF<sub>25-75%</sub> after 14 days of each treatment period</li> </ul>
<ul style="list-style-type: none"> <li>To assess the bronchodilator effect of indacaterol acetate, indacaterol maleate, and placebo by comparing the pre-medication (morning (pre-dose) and evening) peak expiratory flow (PEF) rate collected between days 8 and 14 of each treatment.</li> </ul>	<ul style="list-style-type: none"> <li>Peak expiratory flow rate collected daily between days 8 and 14 during all three treatment periods (indacaterol acetate, indacaterol maleate, and placebo)</li> </ul>
<ul style="list-style-type: none"> <li>To assess rescue medication usage for indacaterol salts (maleate and acetate) in comparison to placebo.</li> </ul>	<ul style="list-style-type: none"> <li>Usage of rescue medications as reported by subjects via diary during each treatment arm</li> </ul>

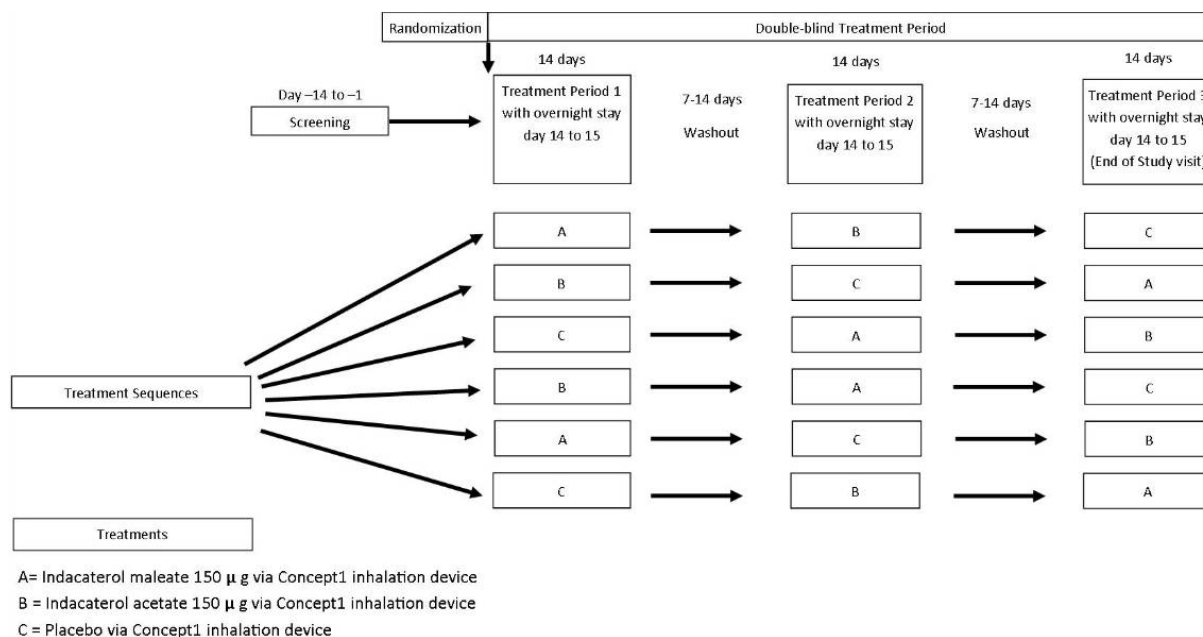
<b><i>Secondary objective(s)</i></b>	<b><i>Endpoints related to secondary objective(s)</i></b>
<ul style="list-style-type: none"><li>• To assess the safety and tolerability of indacaterol salts (maleate and acetate) in comparison to placebo of 14 days of treatment in each treatment period.</li></ul>	<ul style="list-style-type: none"><li>• Safety assessments during each treatment period including:<ul style="list-style-type: none"><li>• Adverse Events and Serious Adverse Events</li><li>• Vital signs</li><li>• Hematology</li><li>• Blood Chemistry</li><li>• Urinalysis</li><li>• ECG evaluation</li></ul></li></ul>

Corporate Confidential Information

## 3 Investigational plan

### 3.1 Study design

**Figure 3-1 Study Design**



This is a confirmatory, randomized, double-blind, placebo-controlled, three-period complete block, cross-over study in approximately 54 subjects with asthma.

Once informed consent is obtained, subjects will be assessed for study eligibility during the 14 day screening epoch. Subjects are only eligible to participate in the study if their inhaled corticosteroid (ICS) dose has been stable for at least 4 weeks prior to screening. During this time, subjects will continue their ICS regimen but will be required to abstain from using any other asthma medication as well as lung function assessments following the cessation periods as detailed in [Section 5.3](#) and [Table 5-2](#).

Short-acting  $\beta_2$ -agonist bronchodilators will be provided to be used as rescue medication throughout the trial, as detailed in [Section 5.3](#) and [Table 5-1](#). Rescue medication use will be recorded in the patient diary.

The 2-week screening epoch may be divided into more than one visit for logistical reasons.

Eligible subjects may be re-screened in case they are not included in the study within the allowed 2-week screening epoch. Subjects may also be re-screened at the discretion of the investigator, and following discussion with the Medical Monitor and/or Sponsor, if the reason for screen failure was considered temporary in nature. All screening data must be obtained within 2 weeks prior to administration of study medication. Subjects who are re-screened will re-consent and be allocated a new screening number.

During screening, subjects will be provided with an electronic device to collect information on rescue medication use, mouth rinsing, ICS use compliance, and will collect and store PEF meter measurements. All subjects will be trained on the use of this device. Diary entries will be made daily throughout the entire study duration (including washout periods). Stopping rules with regard to rescue medication and PEF rate should be adhered to by the investigator to ensure the patient remains stable. Training of the Concept1 inhalation device will occur at screening and then will be reinforced at each onsite study visit. Subjects who are unable to demonstrate correct use of the Concept1 device will not be eligible to enter the treatment epoch.

Subjects who meet all of the eligibility criteria will be randomized to one of six treatment sequences as described in [Figure 3-1](#). They will receive their first dose on the morning of Day 1. Subjects will be dosed between 06:00 a.m. and 10:00 a.m. under the guidance and supervision of the investigator or designee after an additional training for correct use of the Concept1 inhalation device. Dosing of investigational product and background ICS medication should occur at approximately the same time of the day throughout the study. For details of administration of investigational product please refer to [Section 6.5](#). PEF measurements (if not already performed at home on the morning of Day 1 or Day 14) should be taken prior to pre-dose spirometry and safety assessments

For further details, refer to the [Assessment schedule](#).

On Day 1, subjects will leave the clinic after the completion of the required assessments and will dose at home once daily in the morning on Days 2 to 13. During days 2-13, subjects will record drug administration, PEF measurements, mouth rinsing, and rescue medication use in their diary. Subjects will be domiciled at the clinic on the morning of Day 14, for drug administration and Day 14 visit assessments. For details, refer to the [Assessment schedule](#). Subjects will be discharged on Day 15 following the final PK and safety blood sample draw and completion of Day 15 assessments.

A washout period of 7 - 14 days will separate each treatment period. Apart from the pre-dose spirometry and safety assessments on Day 1 which will only be done before Treatment period 1, the assessments for Treatment Periods 2 and 3 will be identical to Treatment period 1 (refer to the [Assessment schedule](#) for Treatment periods 2 and 3 assessments).

Epoch Completion assessments must be conducted for subjects who complete all three treatment periods or at any time a subject early terminates from the trial. The last visit (Day 65) of Treatment period 3 will also be the end of study visit. For assessments that are listed in both Day 65 and in Epoch completion, the assessment is to be completed once. Subjects should be discharged from the site after the completion of Day 15 assessments for all 3 periods. Serious Adverse Event (SAE) reporting after the End of Study visit is described in [Section 9.2.2](#) (SAE reporting).

### **3.2 Rationale of study design**

Long action  $\beta_2$  agonists are recommended in asthmatics not adequately controlled with ICS alone. In addition, long-acting  $\beta_2$  agonists are not recommended in asthmatics without ICS background therapy. Therefore subjects with asthma requiring daily treatment with an ICS (i.e. maintenance treatment) to achieve control have been specifically selected for this study.

A 14-day treatment crossover design is chosen to characterize lung function effects of once daily indacaterol maleate and indacaterol acetate compared to placebo in subjects with asthma. Bronchodilator effects of indacaterol are expected to reach steady state with no additional improvements in lung function after 14 days of treatment. For further details please refer to [Section 3.3](#).

The crossover design has been selected for this study as the intra-subject variability of the primary endpoint (FEV<sub>1</sub>) is lower than the inter-subject variability in this patient population thereby allowing the total number of subjects studied to be minimized without impacting statistical power. The utilization of a Williams design is efficient with the use of six sequences of seven subjects/sequence allowing balance for first order carryover. For once daily dosing regimens of indacaterol, the effective half-life of accumulation (T<sub>1/2,acc</sub>), of indacaterol ranges from 40 to 56 hours. Therefore, the maximum expected washout period based on T<sub>1/2,acc</sub> would need to be approximately 12 days [(5 x T<sub>1/2</sub>)/24]. As pharmacokinetic assessments will only be completed at steady state i.e. at the end of each treatment period, the duration between PK assessments in successive treatment periods in this study will be effectively 21 to 28-days (14 days treatment periods separated by 7-14 day washout periods). In addition, this washout is considered appropriate with regards to the measured primary PD effect (trough FEV<sub>1</sub>), with the effect of indacaterol on FEV<sub>1</sub> lasting for approximately 48-hours after the last dose (Study CQAB149B2223).

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

The lowest dose of indacaterol approved for the maintenance therapy for COPD in the EU, Japan, and other countries worldwide (outside of the US and Canada) is 150 µg given once daily. This dose is proposed to be used as part of the FDC in both asthma and COPD. This dose has been discussed and agreed for evaluation in Phase III studies with competent authorities. Therefore, this dose and regimen are considered appropriate and relevant for evaluating the comparability of indacaterol maleate and indacaterol acetate in this study.

The duration of treatment per treatment period is 14 days. Indacaterol maleate achieves PD (Studies CQAB149B2357 and CQAB149B2235S) and PK steady state (Study CQAB149B2339) within 14 days. The PD and PK steady state were confirmed in a 12 week, lung function study (CQMF149E2203) with indacaterol acetate in subjects with asthma. In this study, a near maximal FEV<sub>1</sub> effect was observed on Day 2 of treatment. While there are no further primary data establishing the PD and PK steady states for indacaterol acetate, based on the comparability of the two salts from the 7-day PD and systemic exposure data from Study CQAB149D2301 indacaterol maleate and acetate are not expected to differ with regards to PD and PK following administration of an identical nominal dose.

### **3.4 Rationale for choice of comparator**

A placebo control is included to allow calibration of the overall bronchodilator response for indacaterol when formulated as either salt delivered via the Concept1 in subjects with asthma. Indacaterol maleate is considered an active calibrator rather than a comparator in this study because the study is not adequately powered for a direct comparison of the two salts.

### **3.5 Rationale for choice of background therapy**

Subjects will continue on stable background ICS therapy as established prior to study entry, thereby justifying treatment with placebo. Subjects will maintain their preexisting, stable medical regimen for treatment of preexisting medical conditions throughout the study.

### **3.6 Purpose and timing of interim analyses/design adaptations**

No interim analysis has been planned.

### **3.7 Risks and benefits**

The risks to which subjects participating in this study will be exposed may be divided into those associated with the conduct of the study itself, and those associated with the investigational treatments indacaterol acetate and maleate.

Subjects will be required to perform repetitive lung function measurements during the study, and these can lead to cough, shortness of breath, dizziness, or exhaustion. Since subjects only carry out full forced maneuvers during clinic visits (not at home), these will be performed under medical supervision to ensure availability of immediate aid if required. Considering the 2 week treatment duration per period, the number of assessments is small and these are part of the regular medical assessments of this patient population. Other procedural risks are related to blood sampling for PK assessments and safety laboratory. Puncturing of the veins can cause discomfort, pain, hematoma, or in rare cases lead to an infection.

Indacaterol acetate, administered at doses of up to 400 µg (and for up to 12 weeks) via the Concept1 inhalation device has been shown to be safe and well tolerated in previous studies conducted in subjects with asthma (QAB149B2102 - single dose; QAB149D2301 – 1 week; QMF149E2203 – 12 weeks). This is substantiated with studies using indacaterol maleate, which, administered at doses of up to 600 µg (and for up to 6-months) via the Concept1 have been shown to be safe and well tolerated in previous studies conducted in subjects with asthma (QAB149B2102 - single dose; QAB149D2301 – 1 week; QAB149B2357 – 2 weeks; QAB149B2223 – 2 weeks; QAB149B2338 – 6 months). Overall, the safety and tolerability profile of indacaterol is consistent with the known profile of the class of  $\beta_2$  agonist agents.

In principle, the characteristic adverse effects of inhaled  $\beta_2$ -adrenergic agonists can occur as a result of activation of systemic  $\beta$ -adrenergic receptors after inhalation of indacaterol. The most common adverse effects include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in serum potassium, and increases in plasma glucose. Detailed information is available in the IB and in the SmPC for Onbrez<sup>®</sup> Breezhaler<sup>®</sup>. The most common adverse reactions of indacaterol observed in clinical trials at the recommended doses were nasopharyngitis, upper respiratory tract infection, cough, headache,



and muscle spasms. The vast majority of these cases was mild or moderate and became less frequent if treatment was continued.

There may be a potential risk related to changing patient treatment as they need to comply with allowed concomitant medication and bronchodilator washouts. The risk of clinical deterioration will be minimized by the following eligibility criteria and assessments completed from screening and throughout the study including washout periods:

- For this study, only subjects who have been on a stable dose of ICS for at least 4 weeks prior to screening are eligible for participation. Subjects will be required to continue their stable steroid dose throughout the study.
- Subjects who were previously intubated for severe asthma, recently hospitalized for asthma exacerbation, or treated for a lower respiratory tract infection, will not be allowed to participate in the study.
- The PEF rate will be assessed throughout the study (including washout periods). Withdrawal criteria related to this assessment will mitigate risk of clinical deterioration.
- The dose and frequency of Short Acting Beta Agonists (SABAs) administered will be monitored throughout the study. Subjects who note excessive use of SABAs will be withdrawn from the study.

There may be a small potential risk of a hypersensitivity reaction (including anaphylactoid reactions and anaphylaxis) to either indacaterol maleate, indacaterol acetate, or one of the excipients of the formulations. The risk will be limited by the exclusion of individuals with prior hypersensitivity to indacaterol, drugs of the same class or with similar chemical structure or its excipients.

Reflex bronchoconstriction can occur as an unspecific intolerance reaction to inhaled drugs. Subjects are under clinical observation at the site when inhaling the drugs for the first time so an intolerance reaction can be detected. When indacaterol is inhaled, subjects may react with short-lasting cough immediately after inhalation; this post-inhalational cough was not associated with other symptoms or bronchial obstruction in previous studies.

There may be unknown risks of indacaterol which may be serious.

The risk to subjects in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, and following study discontinuation criteria.

### **3.7.1 Blood sample volumes**

A maximum of approximately 250 mL of blood is planned to be collected over a period of approximately 90 days, from each subject as part of the study. Additional samples for monitoring of any safety findings would be in addition to this. This is not considered to be a risk for this population.

Timing of blood sample collection is outlined in [Section 8.1](#) (Assessment schedule).

A summary blood log is provided in the Site Operations Manual, together with instructions for all sample collection, processing, storage, and shipment information.

See [Section 8.9](#) regarding the potential use of residual samples.

## 4 Population

### Asthma patients

The study population will be comprised of male and female patients aged 18 and above with asthma. Approximately 54 adult patients will be randomized with the intention that at least 42 subjects complete the study.

The investigator must ensure that all subjects being considered for the study meet eligibility criteria. No additional exclusions should be applied by the investigator.

Subject selection is to be established by checking through all inclusion and exclusion criteria throughout the screening epoch and prior to the first dose in Treatment period 1. Source documentation relating to eligibility must be stored at the study site.

Deviation from any entry criterion excludes a subject from enrollment into the study.

### 4.1 Inclusion criteria

Asthma patients eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female patients aged  $\geq 18$  and above
3. Patients with a documented physician diagnosis of asthma for a period of at least 1 year prior to screening and who additionally meet the following criteria:
  - Patients receiving daily treatment with an inhaled corticosteroid up to the maximum dose per day (as indicated in the package leaflet), on a stable regimen (dose cannot have changed within 4 weeks prior to screening) for at least 4 weeks prior to screening.
4. Pre-bronchodilator  $FEV_1 \geq 50\%$  and  $\leq 90\%$  of the predicted normal value for the patient (after withholding bronchodilators) during screening.
  - Withholding period of bronchodilators prior to spirometry (also applicable for Reversibility testing) are given in [Table 5-1](#)
  - Re-testing is allowed once. Re-assessment of percentage predicted  $FEV_1$  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
5. Patients who demonstrate an increase in  $FEV_1$  of  $\geq 12\%$  and  $\geq 200$  mL within 30 minutes after administration of 400 µg salbutamol/360 µg albuterol (or equivalent dose) at screening. All patients must perform a reversibility test at Visit 1 (screening).

If reversibility is not demonstrated at screening, then reversibility testing may be repeated once during the screening epoch 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.

If reversibility is not demonstrated after repeated assessment, patients must be screen failed.

Spacer devices are not permitted during reversibility testing.



At screening, and prior to the first dose of Treatment period 1, vital signs (systolic and diastolic blood pressure and pulse rate) will be assessed in the sitting position and again (when required) in the standing position as outlined in the SOM.

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Hypertensive subjects should have been on stable antihypertensive therapy for at least 4 weeks prior to screening to be included in the trial.

6. Subjects must weigh at least 50 kg at screening to participate in the study, and must have a body mass index (BMI) within the range of 18 to 40 kg/m<sup>2</sup>.
7. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

## 4.2 Exclusion criteria

Asthma patients fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Contraindicated for treatment with, or having a history of reactions/ hypersensitivity to any of the following inhaled drugs, drugs of a similar class, or any component thereof.
  - Sympathomimetic amines / adrenoceptor agonist agents
  - Lactose or any of the other excipients of the study drug (including patients with history of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption)
2. Patients who have had an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit within 6 weeks of screening. If patients experience an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit during the screening epoch, they may be re-screened 6 weeks after recovery (in the investigator's judgment) from the exacerbation.
3. Patients who have had previous intubation for a severe asthma attack/exacerbation.
4. Patients who have had a respiratory tract infection or asthma worsening within 4 weeks prior to screening. Patients may be re-screened 4 weeks after recovery from their respiratory tract infection or asthma worsening.
5. Patients with a history of chronic lung diseases other than asthma, including (but not limited to) COPD, sarcoidosis, interstitial lung disease, cystic fibrosis, clinically significant bronchiectasis, and active tuberculosis.

6. Patients with any chronic conditions affecting the upper respiratory tract (e.g. chronic sinusitis) which in the opinion of the investigator may interfere with the study evaluation or optimal participation in the study.
7. Patients who have a decline in PEF from the reference PEF (taken at screening) of  $\geq 30\%$  for 5 of 6 consecutive scheduled PEF readings (readings taken at morning and evening) during at least 3 days of screening epoch prior to randomization.
8. Patients who require the use of  $\geq 12$  puffs / 24 hours of rescue medication for 48 hours (over two consecutive days) during screening prior to randomization.
9. Patients with a history of clinically relevant bronchoconstriction upon repeated forced expiratory maneuvers.
10. History of paradoxical bronchospasm in response to inhaled medicines.
11. History or current diagnosis of the following ECG abnormalities:
  - Clinically significant cardiac arrhythmias (for example sustained ventricular tachycardia, and second or third degree AV block)
  - History of familial long QT syndrome or known family history of Torsades de Pointes
  - Paroxysmal (e.g., intermittent) atrial fibrillation.
  - Patients with persistent atrial fibrillation as defined by continuous atrial fibrillation for at least 6 months and controlled with a rate control strategy (i.e., cardioselective beta blockers, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) for at least 6 months may be considered for inclusion. In such patients, atrial fibrillation must be present at screening with a resting ventricular rate  $< 100/\text{min}$ .
12. Patients with a history of myocardial infarction within the previous 12 months.
13. Patients who have a clinically significant ECG abnormality (as determined by the investigator) at screening and prior to randomization.
14. Patients with a history of long QT syndrome or whose QTc measured at screening (Fridericia method) is prolonged ( $> 450$  msec for males and  $> 460$  msec for females).
15. Patients who, either in the judgment of the investigator, have a clinically significant condition such as (but not limited to) unstable ischemic heart disease, New York Heart Association (NYHA) Class III/IV left ventricular failure arrhythmia, uncontrolled hypertension, cerebrovascular disease, psychiatric disease, neurodegenerative diseases, or other neurological disease, uncontrolled hypo- and hyperthyroidism and other autoimmune diseases, hypokalemia, hyperadrenergic state, or ophthalmologic disorder or patients with a medical condition that might compromise patient safety or compliance, interfere with evaluation, or preclude completion of the study.
16. Concomitant use of an agent known to prolong the QT interval unless it can be discontinued for the duration of study.
17. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in-situ* cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.

18. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.

- In this study, ICS background therapy is required throughout the study. Therefore, women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 2 weeks after stopping of investigational drug. ***Highly effective contraception methods include:***
  - Total abstinence: when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
  - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
  - Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
  - 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 of use of oral contraception, women should be stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

A pregnancy test will be done on all female patients regardless of reported reproductive status at specified time points throughout the study.

If requested by local authorities, additional and more frequent pregnancy testing may be performed.

19. Patients with Type I diabetes or uncontrolled Type II diabetes (HbA1c > 9%) at screening.
20. Plasma donation > 150 mL within 7 days prior to first dosing.
21. Donation or loss of 400 mL or more of blood within eight (8) weeks prior to initial dosing, or longer if required by local regulation.
22. Hemoglobin levels below the laboratory lower limit of normal and considered clinically significant at screening.
23. Significant illness which has not resolved within two (2) weeks prior to initial dosing.
24. Recent (within the last three years) and/or recurrent history of autonomic dysfunction (e.g., recurrent episodes of fainting, palpitations, etc.).

25. Patients receiving medications in the classes listed in [Section 5.2](#) (Prohibited treatment) should be excluded.
26. Use of other investigational drugs at screening, or within 30 days or 5 half-lives of enrollment, whichever is longer; or longer if required by local regulations, and for any other limitation of participation in an investigational trial based on local regulations.
27. Current smokers (urine cotinine > than the laboratory's lowest level of quantification (LoQ of 500 ng/mL or lower)) and patients who have smoked or inhaled tobacco products within the 6 month period prior to screening, or who have a smoking history of greater than 10 pack years (*Note: 1 pack is equivalent to 20 cigarettes. 10 pack years = 1 pack /day x 10 yrs., or ½ pack/day x 20 yrs.*).
28. Any surgical or medical condition that might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study. The investigator should make this determination in consideration of the subject's medical history and/or clinical or laboratory evidence of any of the following:
  - Inflammatory bowel disease, peptic ulcers, gastrointestinal (including rectal) bleeding;
  - Major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection;
  - Pancreatic injury or pancreatitis;
  - Liver disease or liver injury as indicated by abnormal liver function tests. ALT (SGPT), AST (SGOT),  $\gamma$ -GT, alkaline phosphatase and serum bilirubin will be tested at screening.
29. Patients who have a clinically significant laboratory abnormality at screening in the opinion of the investigator (one re-test is allowed before the randomization). If the retest is outside the reference range but is not clinically significant in the opinion of the investigator, the patient can be enrolled.
30. Patients with a serum potassium or magnesium level below the laboratory limit of normal at screening.
31. History of being immunocompromised; immunodeficiency diseases, including a positive HIV (refer to [Section 6.2](#)) test result at screening.
32. A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result at screening.
33. Patients with evidence upon visual inspection (laboratory culture is not required) of clinically significant (in the opinion of investigator) oropharyngeal candidiasis during screening, with or without treatment. Patients may be re-screened once their candidiasis has been treated and has resolved.
34. History of drug or alcohol abuse within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during screening.
35. Patients with seasonal allergy whose asthma is likely to deteriorate during the study period in the investigator's judgment.
36. No person who is considered vulnerable or person who is in detention may participate in this study.

37. Patients with a known history of non-compliance to medication or who were unable or unwilling to complete a patient diary or who are unable or unwilling to use Electronic Peak Flow with e-diary device.
38. Patients unable to use the Concept1 dry powder inhaler or a metered dose inhaler.
39. Patients on Maintenance Immunotherapy (desensitization) for allergies for less than 3 months prior to randomization or patients on Maintenance Immunotherapy for more than 3 months prior to randomization but expected to change throughout the course of the study.
40. Patients with narcolepsy and/or insomnia.
41. Patients who are directly associated with any members of the study team or their family members
42. Patients who do not maintain regular day/night, waking/sleeping cycles (e.g., night shift workers).
43. Subjects incapable of understanding the nature, significance and implications of the clinical trial and therefore incapable of giving consent personally
44. No additional exclusions may be applied by the investigator, to ensure that the study population will be representative of all eligible patients.

## **5 Restrictions for Study Subjects**

During recruitment, screening, and informed consent review, subjects must be informed and reminded of the restrictions outlined in this section.

### **5.1 Contraception requirements**

Women 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 to participate in the study they must adhere to the contraception requirement for the duration of the study.

As ICS background therapy is required throughout this study, women of childbearing potential cannot participate unless they agree to use highly effective measures of contraception. Please refer to [Section 4.2](#) (Exclusion criteria) for details of contraception requirements for the study.

## 5.2 Prohibited treatment

Restrictions for medications other than study drug and background ICS therapy apply according to below tables:

**Table 5-1 Withholding period of bronchodilators prior to spirometry**

<b>Class of Medication</b>	<b>Minimum cessation prior spirometry</b>
SABA	≥ 6 hrs
SAMA	≥ 8 hrs.
LABA or fixed dose combination of ICS/LABA b.i.d.	≥ 24 hrs.
LABA or fixed dose combination of ICS/LABA o.d. or tiotropium	≥ 48 hrs.
xanthines	≥ 7 days

**Table 5-2 Prohibited asthma medication during treatment period**

<b>Medication</b>	<b>Action to be taken</b>
Long-acting anti-cholinergic agents (e.g. tiotropium bromide)	<i>subject to be withdrawn</i>
Short-acting anti-cholinergics	<i>subject to be withdrawn</i>
Fixed-combinations of long-acting $\beta_2$ -agonists and inhaled corticosteroids	<i>subject to be withdrawn</i>
Long-acting $\beta_2$ -agonists (other than study drug)	<i>subject to be withdrawn</i>
Short acting $\beta_2$ -agonists (other than those prescribed in the study)	<i>subject to be withdrawn</i>
Theophylline and other xanthines	<i>subject to be withdrawn</i>
Parenteral or oral corticosteroids	<i>subject to be withdrawn</i>
Newly introduced or increased dose leukotriene antagonists, ketotifen, inhaled nasal cromolyn, nedocromil, inhaled nasal corticosteroid	<i>subject to be withdrawn *</i>

\* Leukotriene antagonists, ketotifen, inhaled nasal cromolyn, nedocromil and inhaled nasal corticosteroids are allowed for the treatment of asthma or allergic conditions during the study if taken regularly every day as part of the patient's treatment regime and if treatment has been stable for 4 weeks prior to screening.

**Table 5-3 Prohibited treatments, cessation periods**

<b>Medication</b>	<b>Minimum cessation period prior to Baseline or as indicated</b>
Non-potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug)	7 days prior to Baseline
Non-selective systemic $\beta$ -blocking agents	7 days prior to Baseline
Cardiac anti-arrhythmics Class Ia	7 days prior to Baseline
Cardiac anti-arrhythmics Class III	7 days, amiodarone 3 months prior to Baseline
All antipsychotic agents (first, second, and third generation, inclusive of atypical antipsychotics). Combinations of antipsychotic agents with antidepressants are prohibited	14 days prior to Baseline
Serotonin Noradrenaline Reuptake Inhibitors (SNRIs)	14 days prior to Baseline
Monoamine-oxidase inhibitors	14 days prior to Baseline
Systemic anticholinergics	7 days prior to Baseline
Mizolastin or terfenadine (H1 antagonists)	5 days prior to Baseline
Strong inhibitors of cytochrome P4503A e.g. ketoconazole	7 days prior to Baseline
Tricyclic antidepressants (Note that tetracyclics that are similar in class with regards to drug interaction are also to be excluded)	14 days prior to Baseline
Other investigational drugs	30 days or 5 half-lives, whichever is longer prior to Baseline
Parenteral or oral corticosteroids	Within 30 days prior to baseline
Noradrenaline reuptake inhibitors	7 days prior to Baseline
Live attenuated vaccine	Must not administered within 30 days prior to 1st dose and anytime thereafter during the trial.

### 5.3 Dietary restrictions and smoking

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

- Alcohol for 4 hours prior to spirometry
- Smoking within at least 4 hours of spirometry
- Exposure to environmental smoke, dust or areas with strong odors within, at least, 4 hours of spirometry
- Strenuous activity for 12 hours prior to spirometry
- Intake of xanthine (e.g. caffeine) containing food or beverages (i.e. coffee, tea, soda, chocolate) is not permitted at any time while the subjects are domiciled. During the out-patient phase of the study (Days 2-13), caffeinated beverages will be restricted to no more than 4 cups/day until after all assessments on Day 15 (for each Treatment period) are complete.
- No grapefruit or grapefruit juice can be consumed for 14 days prior to the first dose of Treatment period 1 until 24 hours following the last dose of Treatment period 3.

- All subjects will fast overnight from midnight on Day 13 (water allowed). Dosing will occur in the morning of Day 14, between the hours of 06:00 and 10:00. On day 14, a standard lunch will be served at approximately 4 hours post-dose (i.e. between the hours of 10:00 and 14:00) and dinner will be provided at approximately 9 hours post-dose (i.e. between the hours of 16:00 and 19:00). When meal and blood draw times coincide, blood should be drawn before the meal is provided. On Day 14, no fluids are permitted for 1 hour before and 1 hour after study drug administration, with the exception of fluid given for mouth rinsing following the inhalations. Otherwise, subjects should have a fluid intake of approximately 200 mL every 4 hours during waking hours on day 14 in addition to fluid taken with meals and medication. There are no fluid restrictions at any other times.

If a deviation occurs for any of the restrictions above, it must be noted in the CRF.

## **5.4 Other restrictions**

No unusual (for individual patients) strenuous physical exercise for 7 days before first dosing of Treatment period 1 until after Study Completion evaluation.

# **6 Treatment**

## **6.1 Study treatment**

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment are outlined in the Site Operations Manual.

### **6.1.1 Investigational treatment and control drugs**

Indacaterol maleate 150 µg, indacaterol acetate 150 µg, and matching placebo capsules will be prepared by Novartis and supplied to the investigator as single-blind patient kits with a tear off label along with the Concept1 devices.

Additional placebo capsules and Concept1 inhalation devices will also be supplied to train site staff and to allow the study subjects to 'practice' inhalation.

All patients must be trained on the use of the Concept1 during the screening epoch, with additional training provided throughout the study in accordance with the [Assessment schedule](#).

A separate manual will be provided detailing instructions for use of the Concept1 inhalation device.



**Table 6-1 Overview of study medication**

Study drug name	Formulation	Unit dose	Packaging	Provided by
Indacaterol maleate	Capsules with powder for inhalation	150 mcg	Supplied in single-blind patient pack including Concept1 devices	Novartis Drug Supply Management
Indacaterol acetate	Capsules with powder for inhalation	150 mcg	Supplied in single-blind patient pack including Concept1 devices	Novartis Drug Supply Management
Placebo	Capsules with powder for inhalation	0 mcg	Supplied in single-blind patient pack including Concept1 devices	Novartis Drug Supply Management
Concept1 device	N/A	N/A	Supplied with IP	Novartis Drug Supply Management

### Additional study treatment

All subjects participating in the study will continue to use an inhaled corticosteroid and remain on a stable dose and regimen throughout the study including the washout between treatment periods. These corticosteroids will be used according to their approved labels. The subjects' ICS compliance will be reviewed by the site in the medication diary.

All subjects participating in the study will be provided (locally sourced by the site) with an inhaled, short-acting  $\beta_2$ -agonist (salbutamol or any other short-acting  $\beta_2$ -agonist at matching dose-strength) and allowed to use this throughout the study as needed. Use of salbutamol (or any other short-acting  $\beta_2$ -agonist at matching dose-strength) will be recorded in a daily diary and if any patient meets stopping criteria ([Section 7.5](#) (Study Stopping rules)) related to excessive use of salbutamol or any other short-acting  $\beta_2$ -agonist at matching dose-strength, they will be withdrawn.

## 6.2 Treatment arms

Study treatments are defined as:

- A: indacaterol maleate 150  $\mu$ g via Concept1 device
- B: indacaterol acetate 150  $\mu$ g via Concept1 device
- C: matching placebo capsules to indacaterol via Concept1 device

Subjects will be randomized to one of the following six treatment sequences (defined according to a Williams design for 3 treatments and 3 periods) in the ratio of 1:1:1:1:1:1.

**Table 6-2 Definition of treatment sequences**

Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	B	C	A
3	C	A	B
4	A	C	B
5	B	A	C
6	C	B	A

### 6.3 Treatment assignment and randomization

At the randomization visit, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or delegate will contact IRT after confirming that the subject fulfills all eligibility criteria. IRT will assign a randomization number to the subject, that will be used to specify a treatment arm and the unblinded pharmacist will provide the correct medication. The medication will be provided as a single label tear off to maintain the blind outside of the pharmacy. 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 subjects and investigative staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

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

Follow the details outlined in the Site Operations Manual regarding the process and timing of treatment assignment and randomization of patients.

The investigator will enter the screening number which will be kept throughout the study in the eCRF.

**Table 6-3 Treatment Assignment Numbering**

Randomization numbers	Replacement randomization numbers
5101 – 5166	6101 – 6166

### 6.4 Treatment blinding

This is a subject, investigator, and sponsor-blinded study. Subjects, investigators and sponsor will remain blinded to study treatment throughout the study, except where indicated below. At database lock, all roles can be unblinded.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

#### Site staff

With the exception of any unblinded site staff identified below, all site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study.

Unblinding a single subject at a site for safety reasons (necessary for subject management) will occur via the process defined in ([Section 6.7](#) (Emergency breaking of assigned treatment code)).

**Table 6-4 Blinding levels**

Role	Time or Event		
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)
Subjects/Patients	B	B	UI
Site staff	B	B	UI
Unblinded site staff (see text for details)	B	UI	UI
Drug Supply and Randomization Office	UI	UI	UI
Unblinded sponsor staff (see text for details)	B	UI	UI
Statistician/statistical programmer/data analysts	B	B	UI
Independent committees used for assessing interim results	B	B	UI
All other sponsor staff not identified above	B	B	UI

B Remains blinded

UI Allowed to be unblinded on individual patient level

## 6.5 Treating the subject

Indacaterol maleate, indacaterol acetate, and placebo will be administered via the Concept1 inhalation device. IP administration will occur at the site by the subject on Day 1 and Day 14 under the guidance and supervision of site staff and will be administered by the subject at the subject's home on study days 2-13 for each treatment period.

Investigational product should be administered approximately between 6:00 a.m. and 10:00 a.m. every day of each treatment period.

On Day 1 and 14 of Treatment period 1, investigational product (and background ICS medication) should be administered between 06:00 a.m. and 10:00 a.m and within  $\pm$  1h of each other. This means that time of dosing between Day 1 and Day 14 should not differ by more than one hour. On Day 1 and Day 14 of Treatment periods 2 and 3, investigational product (and background ICS medication) should be administered within  $\pm$  1h of the time of study medication administration of Day 1 and Day 14 of Treatment period 1 respectively. This will ensure that assessments are done at approximately the same time of the day in each treatment period.

After each dose inhalation, subjects should rinse their mouths with water. Water used for mouth rinsing should be spat out and should not be swallowed.

One Concept1 inhalation device will be provided for each treatment period for a total of 3 devices dispensed for the duration of the study. Subjects should re-use the Concept1 device for 14 sequential doses for each treatment period.

The last dose on Day 14 should be taken at the site. An extra medication kit (in addition to the one dispensed to the subject) will be assigned for the Day 14 dosing, which will not be dispensed to the subject but kept at the site. On Day 14, one capsule should be taken from the kit kept at the site, and the subject should administer the capsule using the same Concept1 device used during Days 1-13. No new device should be provided for the Day 14 dose.

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

See the Site Operations Manual for further details.

## **6.6 Permitted dose adjustments and interruptions of study treatment**

Study drug dose adjustments and/or interruptions are not permitted.

## **6.7 Emergency breaking of assigned treatment code**

Emergency code breaks must occur only when it is required to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the study monitor for the site and the Study Team 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 IRT in case of an emergency. The investigator will need to provide:

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

In addition, the investigator must provide oral and written information to inform the subject how to contact the investigator's backup in case of emergency when he/she is unavailable to ensure that un-blinding can be performed at any time.

An assessment will be done by the appropriate site personnel and sponsor after an emergency unblinding to assess whether or not study treatment should be discontinued for a given subject.

## **6.8 Treatment exposure and compliance**

For all study drug treatment administered in the clinic, compliance will be adhered to by administration under the guidance and direct supervision of the investigator/designee. The investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study.

For doses administered at the site, after inhalation in each treatment period, the capsule shell will be checked for residual powder. If residual powder is found, the inhalation procedure will be repeated up to a maximum of 3 times provided that total inhalation time does not exceed 2 minutes. The finding will be recorded in the drug administration section of the (e)CRF. Compliance will be assessed by the investigator and/or designee at each visit. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded on the Drug Accountability Log.

Furthermore, compliance with the intake of inhaled corticosteroid and study drug treatment at home will be monitored closely by a review of a patient diary in which all subjects will record administration each day (washout periods). The subject must also be instructed to contact the investigator if he/she is unable to take the study treatment as prescribed at home.

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects on Day 14 of each treatment period during which they were treated with indacaterol acetate and indacaterol maleate, as detailed in [Section 8.7](#) (Pharmacokinetics).

## **6.9 Recommended treatment of adverse events**

Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies eCRF.

## **6.10 Rescue medication**

At screening, all patients will be supplied with an inhaled short-acting  $\beta_2$ -agonist (100  $\mu\text{g}/\text{puff}$  salbutamol or other short-acting  $\beta_2$ -agonist at matching dose strength) which they will be instructed to use throughout the study as rescue medication. Rescue medication will be procured by the investigative site. Subjects should be instructed to abstain from taking rescue medication within 6 hours of the start of each site visit unless absolutely necessary. If a subject does use their rescue medication within 6 hours of the spirometry assessments on Day 14 in either of the three treatment periods, the spirometry assessments should continue as planned, with the rescue medication usage recorded in the CRF and the data will be excluded from the PD analysis set.

During the study, subjects will record use of rescue medication in a patient diary. Patients should monitor this use carefully and if they use more than  $\geq 12$  puffs (100  $\mu\text{g}/\text{puff}$ ) over 24 hours then they should call the site and inform the site personnel. If rescue medication use continues at this level for another 48 hours on two consecutive days then the patient will meet withdrawal criteria ([Section 7.5](#) Study Stopping rules).

Use of rescue medication must be recorded in the patient diary from screening until Day 15 of the Treatment period 3. Concomitant medications and significant non-drug therapies will be collected in the eCRF from screening through completion of the study.

### **6.10.1 Salbutamol usage**

Rescue medication allowed during the conduct of the study is salbutamol (100  $\mu\text{g}/\text{puff}$ ) or any other short-acting  $\beta_2$ -agonist at matching dose strength. Daily use of rescue medication will be recorded in the patient diary and this should be recorded in the rescue medication eCRF from screening until discharge of patients from the site on Day 15 of Treatment period 3.

## 6.11 Concomitant treatment

The investigator must instruct the subject to notify the study site about any new medications he/she takes after the subject was enrolled into the study.

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact Novartis before randomizing a subject or, if the subject is already enrolled, to determine if the subject should continue participation in the study.

### Regular asthma treatment

To be eligible patients must have received inhaled corticosteroids (ICS) at a regimen that has remained stable for at least 4 weeks prior to screening. Patients must continue their individual ICS dosing regimen and it must remain unchanged throughout the study.

The only exception allowed is:

- When, in the medical opinion of the investigator, the patient experiences an asthma exacerbation requiring the use of additional anti-inflammatory therapy. If an exacerbation occurs during the screening epoch, the patient may be re-screened 6 weeks after resolution of the exacerbation. If the patient experiences an asthma exacerbation after randomization that requires the use of additional anti-inflammatory therapy, the patient must be withdrawn from the study and treated as clinically indicated.

In addition, SABA rescue medication supplied to the patient at screening may be used, as needed, for any asthma symptoms that may occur.

The following medications are allowed for the treatment of asthma or allergic conditions during the study if taken regularly every day as part of the patient's treatment regime, and if treatment has been stabilized (stable dose regimen for 4 weeks) prior to screening:

- Topical corticosteroids in recommended doses and dosage regimens will be allowed for the treatment of eczema.
- Antihistamines, inhaled nasal cromolyn, nedocromil, and inhaled nasal corticosteroids

In addition these are allowed concomitant medications:

- Maintenance immunotherapy (desensitization) for allergies is allowed if treatment has been stabilized for at least 3 months prior to screening, and remains unchanged throughout the course of the study.
- Influenza and pneumonia vaccination is acceptable provided it is administered >48 hours prior to the first dose of Treatment period 1. Vaccinations within 48 hours and after are not allowed for this study.

- Selective Serotonin Reuptake Inhibitors at stable dose for at least 30 days prior to screening and during the trial.
- Topical corticosteroids for skin disease at stable dose for at least 30 days prior to screening.
- H1-antagonists except mizolastin or terfenadine at stable dose/regimen for at least 5 days prior to screening.

### **Adjustments to long acting $\beta_2$ -agonist**

The use of any long-acting  $\beta_2$ -agonist must be stopped during the screening epoch in accordance with [Table 5-1](#).

Subjects using long-acting  $\beta_2$ -agonists and combination medicines containing LABA must be switched to the as-needed use of short acting  $\beta_2$ -agonist (i.e. salbutamol MDI) with cessation periods prior to lung function testing in accordance with [Table 5-1](#).

The steroid component of any fixed combination (ICS and  $\beta_2$ -agonist) therapy must be replaced with the equivalent monotherapy ICS plus the as needed use of a short-acting  $\beta_2$ -agonist that is provided to the patient at screening.

## **7 Study completion and discontinuation**

### **7.1 Study completion and post-study treatment**

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

Study completion is defined as when the last subject completes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the investigator, or in the event of an early study termination decision, the date of that decision.

All subjects should have a safety follow-up call conducted 30 days after last visit. The information collected is kept as source documentation. All SAEs reported during this period must be reported as described in [Section 9.2](#) and the Site Operations Manual. Documentation of attempts to contact the subject should be recorded in the source documentation.

### **7.2 Discontinuation of study treatment**

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration. Discontinuation of study treatment can be decided by either the subject or the investigator.

Study treatment must be discontinued and the subject withdrawn from the trial under the following circumstances:

- Any severe or serious adverse event considered at least possibly related to the study medications.
- Any other protocol deviation that results in a significant risk to the subject's safety

- Subject decision - subjects may choose to discontinue study treatment or withdraw informed consent for any reason at any time.
- The investigator believes that continuation would negatively impact the safety of the subject or the risk/benefit ratio of trial participation.
- Pregnancy (see [Section 8.6](#)) and [Section 9.6](#) (Pregnancy reporting)
- Use of prohibited treatment as per recommendations in [Section 5.2](#)
- For liver events, refer to [Section 15-Appendix 1: Liver Event Definitions and Follow-up Requirements](#)).
- Patients who have a decline in PEF from the reference PEF (taken at screening) of  $\geq 30\%$  for 5 of 6 consecutive scheduled PEF readings (includes readings taken at morning and evening) at any point during the study ([Section 4.2](#)).
- $\geq 3$  consecutive days in any one treatment period in which  $\geq 12$  inhalations/day of SABA rescue medication were used
- Emergency department therapy resulting in the use of oral, parenteral, or non-study related inhaled corticosteroids therapy related to the treatment of worsened asthma.
- Use of prohibited treatment as per [Section 5.2](#) (Prohibited treatment).

Emergence of the following adverse events:

- Paradoxical bronchospasm as evidenced either by a significant increase in wheeze and dyspnea shortly after the administration of study drug or a fall in FEV<sub>1</sub> of  $>20\%$  within 30 minutes of administration of study drug
- Reflex bronchoconstriction or other severe intolerance reaction to study drug inhalation
- If the absolute QTcF is  $>500$  msec or an increase from pre-dose Treatment period 1 of  $>60$  msec on two adequate ECGs at least a minute apart, second (if Mobitz Type 2) or third degree AV block, atrial or ventricular arrhythmias (as judged clinically significant by the investigator).
- Clinical asthma worsening which required additional asthma treatment other than study medication or study-defined rescue medication in any one treatment period.

If a liver event occurs, follow guidelines outlined in [Appendix 1](#) regarding discontinuation of study treatment.

Any of the following laboratory abnormalities:

- Random (non-fasting) plasma glucose greater than 15 mmol/L
- Serum potassium below the lower limit of the laboratory reference range if confirmed by a repeat test to exclude laboratory error
- Urine cotinine  $>$  than the laboratory's lowest level of quantification (LoQ of 500 ng/mL or lower) after randomization ( a positive test at screening would preclude inclusion into the study)

Discontinuation of study treatment and subject withdrawal will be at the discretion of the investigator, under the following circumstances:

- Clinically significant abnormal laboratory value(s) (as judged clinically significant by the investigator).
- The investigator deems discontinuation is necessary for the safety of the patient.



The appropriate personnel from the site and Novartis will assess whether study treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

If discontinuation of study treatment occurs, investigator must determine the primary reason for the subject's premature discontinuation of study treatment and record this information on the Dosage Administration eCRF.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should not be considered withdrawn from the study unless they withdraw their consent (see [Section 7.3](#)). Where possible, they should return for the assessments conducted on Day 15/End of Study Visit. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in [Section 7.4](#). (Lost to follow-up). This contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact until the subject's end of study visit:

- new /change in concomitant treatments
- adverse events/serious adverse events

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

Subjects who are prematurely withdrawn from the study for reasons other than safety may be replaced on a case by case basis.

### **7.3 Withdrawal of informed consent**

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent from the study is defined as when a subject:

- Does not want 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 subject's decision to withdraw his/her 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 subject are not allowed unless safety findings require communicating or follow-up.

#### **7.4 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. A subject should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

#### **7.5 Study stopping rules**

The study will be halted with no further recruitment and dosing suspended for all study participants pending a safety review if two or more study-drug related SAEs are reported or if the aggregate of severity, frequency, and/or drug relatedness of AEs, in the opinion of the investigator or Novartis, merit halting the study. Further dosing may only commence if deemed safe after a full safety review by the Novartis Translational Medical Expert (TME) and investigator.

#### **7.6 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 (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. 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 subject's interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

[illegible]

Epoch	Screening <sup>2</sup>	Treatment period 1/ Treatment period 2/ Treatment period 3											
Visit name	Screening	Treatment period 1/ Treatment period 2/ Treatment period 3											Early discontinuation or Epoch completion <sup>20</sup>
Visit Numbers <sup>1</sup>													
Period 1		101	At home dosing		102	103	Washout <sup>3</sup>						199
Period 2	1	201			202	203							299
Period 3		301			302	303							399
Study Day(s)	-15 to -1	1 26 51	2 to 13 27 to 38 52 to 63		14 39 64	15 40 65 <sup>22</sup>	15 to 25 40 to 50 None required						26 <sup>3,4</sup> 51 <sup>3,4</sup> 65 <sup>3,4</sup>
Time	-	-1h <sup>5</sup>	0h	30min	1h	-	-1h <sup>6</sup>	0h	30min	1h	24h	-	-
Physical examination	X	X									X		X
Hepatitis and HIV Screen	S												

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Alcohol Test, Drug Screen, and Cotinine Test	S												
Smoking history	X												
Pregnancy test <sup>9</sup>	X <sup>10</sup>	X <sup>11</sup>					X <sup>11</sup>						X <sup>11</sup>
Study drug administration			X <sup>12</sup>				X <sup>14</sup>		X <sup>13</sup>				
Device training	S	X					X						
Reversibility	X <sup>15</sup>												
Body height	X												
Body weight	X	X									X		X
Body temperature	X	X					X						X

Epoch	Screening <sup>2</sup>	Treatment period 1/ Treatment period 2/ Treatment period 3											
Visit name	Screening	Treatment period 1/ Treatment period 2/ Treatment period 3											Early discontinuation or Epoch completion <sup>20</sup>
Visit Numbers <sup>1</sup>						At home dosing						Washout <sup>3</sup>	
Period 1	1	101					102				103		199
Period 2		201					202				203		299
Period 3		301					302				303		399
Study Day(s)	-15 to -1	1 26 51				2 to 13 27 to 38 52 to 63	14 39 64				15 40 65 <sup>22</sup>	15 to 25 40 to 50 None required	26 <sup>3,4</sup> 51 <sup>3,4</sup> 65 <sup>3,4</sup>
Time	-	-1h <sup>5</sup>	0h	30min	1h	-	-1h <sup>6</sup>	0h	30min	1h	24h	-	-
Blood pressure	X <sup>16</sup>	X <sup>16</sup>		X	X		X		X	X	X		X
Pulse rate	X	X		X	X		X		X	X	X		X
ECG evaluation	X	X		X	X		X		X	X			X
Hematology	X										X <sup>17</sup>		X
Blood chemistry	X										X <sup>17</sup>		X
Urinalysis	X										X		X
Serum potassium <sup>18</sup>		See table below											X
Glucose <sup>18</sup>		See table below											X
PK blood collection		See table below											X
Spirometry	See table below												X
Peak expiratory flow	X including home dosing days												X
Patient diary	X including home dosing days												X
Adverse events	X												

Epoch	Screening <sup>2</sup>	Treatment period 1/ Treatment period 2/ Treatment period 3											
Visit name	Screening	Treatment period 1/ Treatment period 2/ Treatment period 3											Early discontinuation or Epoch completion <sup>20</sup>
Visit Numbers <sup>1</sup>	1					At home dosing				103	Washout <sup>3</sup>		
Period 1		101					102			203		199	
Period 2		201					202			303		299	
Period 3		301					302					399	
Study Day(s)	-15 to -1	1				2 to 13	14			15	15 to 25	26 <sup>3,4</sup>	
		26				27 to 38	39			40	40 to 50	51 <sup>3,4</sup>	
		51				52 to 63	64			65 <sup>22</sup>	None required	65 <sup>3,4</sup>	
Time	-	-1h <sup>5</sup>	0h	30min	1h	-	-1h <sup>6</sup>	0h	30min	1h	24h	-	-
Serious adverse events <sup>21</sup>	X												
Comments	As required												
Epoch completion information <sup>19</sup>												X	

<sup>1</sup> Visit structure given for internal programming purpose only

<sup>2</sup> After informed consent, screening procedures may be performed over more than 1 day/visit as long as it is completed during the defined screening epoch.

<sup>3</sup> A washout (minimum of 7 days and maximum of 14 days from last dose on Day 14) must occur after completion of Treatment period 1 prior to beginning Treatment period 2 and after completion of Treatment period 2 prior to beginning Treatment period 3. There is no washout after Day 15 of Treatment period 3. A + 2 days washout window is allowed for each treatment. Study days are based on a 10 days washout period, Visit days may be adapted as per the actual washout period; 7-14 days allowed per protocol.

<sup>4</sup> Assessments to be performed if subject terminates early or at V399 Study completion.

<sup>5</sup> Pre-dose assessments on Day 1 may be completed any time on Day 1 prior to first dose. For Treatment period 1 only: Pre-dose, Day 1 assessments (with the exception of blood pressure, pulse, spirometry, PEF, diary entry, and device training) do not need to be repeated if screening assessments were completed within 7 days of Day 1 in Treatment period 1. All Day 1, pre-dose assessments must be completed for Treatment period 2 and 3.

<sup>6</sup> Pre-dose assessments with the exception of spirometry may be completed any time on Day 14 prior to dosing

<sup>7</sup>

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<sup>9</sup> Pregnancy assessments may be performed at a greater frequency if required by local regulations.

<sup>10</sup> Serum pregnancy test

<sup>11</sup> Urine pregnancy test.

<sup>12</sup> For Treatment periods 2 and 3, dosing on site on Day 1 should be between 06:00am and 10:00am and +/-1h of the time on dosing on Day 1 of Treatment period 1.

<sup>13</sup> For Treatment periods 1, 2 and 3 dosing on site on Day 14 should be between 06:00am and 10:00am and +/-1h of the time of dosing on Day 1 of the current Treatment Period.

<sup>14</sup> At home study drug administration should be between 06:00am and 10:00am and +/-1h of the time on dosing on Day 1 of Treatment period 1.

<sup>15</sup> Can be repeated once during screening if necessary

<sup>16</sup> Both standing and supine/sitting blood pressure measurements are required at screening and at pre-dose Treatment period 1 only. Only sitting or supine blood pressure measurements are required for other visits. Subjects' positions during blood pressure collections should remain consistent between visits (sitting or supine throughout the study).

<sup>17</sup> This assessment is completed on Day 65 of Treatment period 3 only

<sup>18</sup> If value is outside the acceptable reference range, this assessment may be retested

<sup>19</sup> Subject status information will be collected at the end of each epoch (screening, after each treatment period and at early discontinuation or study completion), in the Summary eCRF page.

<sup>20</sup> Subjects will complete these assessments when a subject early terminates or after the subject has completed Treatment periods 1, 2, and 3. These assessments are completed one time only.

<sup>21</sup> SAE monitoring is to be conducted from informed consent signature to 30 days after the last IP administration.

<sup>22</sup> For Treatment period 3 only, assessments listed in Epoch completion will be completed in addition to assessments listed for Day 65. For assessments that are listed in both Day 65 and in Epoch completion, the assessment is to be completed once.

### Details for highly repetitive assessments

Epoch	Periods 1/2/3 Visit numbers	Study Day(s)	Time	Subjects domiciled	Pharmaco- genetic	Hematology Biochemistry	Serum potassium <sup>1</sup>	Glucose <sup>1</sup>	PK blood collection	Spirometry
Screening <sup>2</sup>	1	-15 to -1				X				X
Treatment period 1/2/3 <sup>3</sup>	101	1	-1h <sup>4</sup>		X <sup>5</sup>		X	X		X
	201	26	30min				X	X		
	301	51	1h				X	X		
	Dosing at home	2 to 13 27 to 38 52 to 63								
	102 <sup>6</sup> 202 <sup>6</sup> 302 <sup>6</sup>	14 39 64	-1h	X			X	X		
			-45min	X						X
			-15min	X					X	X
			0h	X						
			5min	X					X	X
			10min	X					X	
			15min	X					X	X
			30min	X			X	X	X	X
			1h	X			X	X	X	X
			2h	X					X	X
			4h	X					X	X
			8h	X					X	X
			12h	X					X	X
	103 <sup>7</sup> 203 <sup>7</sup> 303 <sup>7</sup>	15 40 65	23h15	X						X
			23h45	X						X
			24h00	X		X			X	



<sup>1</sup> If value is outside the acceptable reference range, this assessment may be retested

<sup>2</sup> After informed consent, screening procedures may be performed over more than 1 day/visit as long as it is completed during the defined screening epoch.

<sup>3</sup> A washout (minimum of 7 days and maximum of 14 days from last dose on Day 14) must occur after completion of Treatment period 1 prior to beginning Treatment period 2 and after completion of Treatment period 2 prior to beginning Treatment period 3. There is no washout period after Day 65 of Treatment period 3. A + 2 days washout window is allowed for each treatment. Study days are based on a 10 days washout period, Visit days may be adapted as per the actual washout period; 7-14 days allowed per protocol.

<sup>4</sup> Pre-dose assessments on Day 1 may be completed any time on Day 1 prior to first dose. For Treatment period 1 only: Pre-dose, Day 1 assessments (with the exception of blood pressure, pulse, spirometry, PEF, diary entry, and device training) do not need to be repeated if screening assessments were completed within 7 days of Day 1 in Treatment period 1. All Day 1, pre-dose assessments must be completed for Treatment period 2 and 3.

<sup>5</sup> Collected on Day 1 of Treatment period 1 only

<sup>6</sup> Pre-dose assessments with the exception of spirometry may be completed any time on Day 14 prior to dosing

<sup>7</sup> Early discontinuation or Epoch completion assessments should be completed after completion of each treatment period or at any time a subject early terminates from the study (does not complete Treatment period 1, 2, or 3 per protocol). Day 65 of Treatment period 3 will also be the end of study visit. Subjects should be discharged from site after completing Day 65/Epoch completion visit.

## 8.2 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents.

The date of signing of informed consent (and withdrawal, if later withdrawn) should be documented in the CRF.

Novartis will provide investigators a proposed informed consent form that complies with the ICH E6 GCP guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the subject agrees to future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug 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 then must be discussed with the subject.

Ensure subjects are informed of the contraception requirements outlined in the [Section 4.2](#) (Exclusion criteria) and in [Section 5.1](#) (Contraception requirements).

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A copy of the approved version of all consent forms must be provided to Novartis or designee after IRB/IEC approval.

## 8.3 Subject screening

See [Section 3.1](#)

## **8.4 Subject demographics/other baseline characteristics**

### **Demographics**

Subject demographic and baseline characteristic data will be collected on all subjects. Details are outlined in the Site Operations Manual.

### **Relevant medical history / Current medical conditions**

Relevant medical history and current medical conditions will be recorded in the CRF until informed consent. Where possible, diagnoses instead of symptoms should be recorded. Any event or change in the subject's condition or health status occurring prior to informed consent will be reported in the Relevant medical history / Current medical conditions section of the CRF.

### **Alcohol test, Drug screen, Smoking History, Urine Cotinine**

Subjects will be tested for substance abuse (e.g., alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates).

Results will be available as Source data and will not be recorded within the CRF.

Each subject will also be tested for urine cotinine levels. Cotinine levels will be checked at screening. Subjects with levels greater than the level indicated in the exclusion criteria will be considered smokers and thereby not included. A cotinine level exceeding this value after randomization will result in withdrawal of the subject (see [Section 7.2](#) (Discontinuation of study treatment)). Unscheduled urine cotinine testing may be done at the discretion of the investigator at any time during the study.

Smoking history, including number of pack years will be completed in the CRF. Pack years is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. (e.g. 1 pack year is equal to smoking 1 pack per day for 1 year, or 2 packs per day for half a year).

#### **8.4.1 Hepatitis and HIV Screen**

All subjects will be tested for Hepatitis B, Hepatitis C, and HIV seropositivity during the screening epoch. Hepatitis B will be evaluated using the Hepatitis B surface antigen (HBsAg). Screening for Hepatitis C will be based on HCV antibodies. Evaluation for HIV seropositivity will be performed, and if positive, confirmation by a second technique available at the laboratory site, e.g., Western blot or as specified by local regulation.

Appropriate counseling will be made available by the investigator in the event of a positive finding. Notification of state and federal authorities, as required by law in the US, will be the responsibility of the investigator.

Results will be available as source data and will not be recorded within the clinical database.

### 8.4.2 Reversibility

To be measured during screening. If reversibility is not achieved then the reversibility assessment may be repeated **once** prior the randomization.

All reversibility evaluations should follow the recommendations of the [Miller et al 2005b](#) unless otherwise indicated by inclusion/exclusion criteria of the study.

A spirometry assessment should be performed at screening after a washout period of at least (see [Table 5-1](#) Withholding period of bronchodilators prior to spirometry for more details):

- 6 hours for short-acting bronchodilators
- 24 hours for long-acting  $\beta_2$ -agonist containing medications administered b.i.d. (e.g. salmeterol, formoterol and combinations using these, e.g. LABA/ICS)
- 48 hours for long-acting  $\beta_2$ -agonist containing medications administered o.d. (e.g. indacaterol, vilanterol, and combinations using these, e.g. LABA/ICS) and for tiotropium.

400  $\mu$ g (4 x 100  $\mu$ g) of salbutamol is then administered following completion of the baseline assessment. A second spirometry assessment is then performed starting within 30 minutes of the administration of salbutamol.

Reversibility (%) is calculated as:

$(FEV_1 \text{ (post-bronchodilator)} - FEV_1 \text{ (pre-bronchodilator)} \times 100) / FEV_1 \text{ (pre-bronchodilator)}$

The findings of the reversibility evaluations will be recorded in the CRF.

## 8.5 Efficacy / Pharmacodynamics

Pharmacodynamic samples will be collected at the timepoints defined in the Assessment schedule, [Section 8.1](#). Follow instructions outlined in the Site Operations Manual regarding sample collection, numbering, processing, and shipment.

To better define the PD profile, the timing of the sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected should not exceed those stated in the protocol.

Pharmacodynamic (PD) samples will be obtained and evaluated in all subjects at all dose levels.

### 8.5.1 Spirometry

Forced Expiratory Volume in 1 second ( $FEV_1$ ), 3 seconds ( $FEV_3$ ), 6 seconds ( $FEV_6$ ), Forced Vital Capacity (FVC), and Forced Expiratory Flow 25-75% ( $FEF_{25-75\%}$ ) will be measured at screening, pre-dose, and specific time points for approximately 24 hours post dose (on Days 14 and 15) in each treatment period. Additional lung function parameters will be derived mathematically from the listed measurements (e.g.  $FEV_1/FVC$ ,  $FEV_1/FEV_6$ ,  $FEV_3/FVC$ ,  $FEV_3/FEV_6$ ,  $1-FEV_3/FVC$ ,  $1-FEV_6/FVC$ ).

For each patient, *the spirometric measurements* must be taken at approximately the same *corresponding* time of day *in each treatment period* as closely as practically possible.

Pre-bronchodilator  $FEV_1$ ,  $FEV_3$ ,  $FEV_6$ , FVC, and  $FEF_{25-75}$  assessments will be conducted at screening.

Spirometry timepoints following the last dose of study medication in each treatment period are as follows:

- Day 14 predose: - 45 min and -15 min
- Day 14/15 post-dose: 5 min, 15 min, 30 min, 1 h, 2 h, 3h, 4 h, 8 h, 12 h, 23 h 15 min, 23 h 45 min

All spirometry evaluations should follow the recommendations of the ATS/ERS 2005 Task force: Standardization of Lung Function Testing ([Miller et al 2005a](#)).

The spirometry equipment used during the trial must meet or exceed the minimal ATS/ERS recommendations for diagnostic spirometry equipment as defined in the guideline ([Miller et al 2005b](#)). Calibration of the spirometry equipment is mandatory on all visit days and must be performed before the first study measurement. All calibration reports and patient spirometry reports should be stored as source data.

The same spirometry equipment should be used for all assessments performed by a subject. A limited number of staff, as designated by the investigator, will evaluate all patients at all visits throughout the entire trial. Where possible the same technician should perform all maneuvers for an individual subject. All staff conducting the spirometry tests must have received appropriate training which must be documented.

Results for *sprimetry assessments* are highly dependent on effort and cooperation from the subject. Thus, throughout the maneuver, enthusiastic coaching of the subject is required.

All spirometry maneuvers should be performed in sitting position whilst wearing nose-clips. At least three acceptable maneuvers should be performed for each time point, and the results must meet within-test and between-test criteria for acceptability. A maximum of eight maneuvers should be performed at any time point.

The highest value obtained of FEV<sub>1</sub> and FVC from any of the three maneuvers that meet acceptability criteria (can be from different curves) will be recorded on the CRF. All displaceable volumes will be reported in liters (L) at body conditions: normal body temperature (37°C), ambient pressure, saturated with water vapor (BTPS).

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### **8.5.2 Peak expiratory flow**

PEF will be measured on **all** days from screening through the end of study visit. The PEF will be measured twice daily, once in the morning (between 06:00 am and 10:00 am) prior to ICS treatment and prior to study drug during treatment periods) and once in the evening, approximately 12 hours later (between 6:00 pm and 10:00 pm) and prior to ICS treatment. Each subject will be provided with a PEF meter and diary into which they will record their results and the use of rescue medication. PEF meter training should occur at screening. PEF measurements should be taken prior to pre-dose assessments.

Patients should measure PEF in triplicate and record the best value. The diary data will be available to the investigator for review to monitor subject safety and compliance (to verify that subjects are performing the assessments twice daily as instructed). The investigator must make all efforts to achieve compliance from their subjects.

The PEF value recorded at the first screening visit will become the reference value for PEF safety monitoring. This value should be recorded on the patient diary and the patients should monitor their PEF readings using this value to detect a decline. The investigator should instruct the patient to call the site if the PEF drops below the limit required for discontinuation (see [Section 7.1](#)) and this should be tracked by the site to track when the patient meets stopping criteria.

## **8.6 Safety**

Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the Assessment Schedule, [Section 8.1](#) detailing when each assessment is to be performed.

### **8.6.1 Physical examination**

See the Site Operations Manual for details.

### **8.6.2 Vital signs**

- Body temperature (oral or tympanic) 35.0-37.5°C.
- Blood pressure (BP)
- Pulse

### **8.6.3 Height and weight**

- Height
- Body weight
- Body mass index (BMI) will be calculated as  $(\text{Body weight (kg)} / [\text{Height (m)}]^2)$

### **8.6.4 Laboratory evaluations**

In the case where a laboratory assessment that is listed in the inclusion/exclusion criteria is outside of a protocol-specified range at screening, the assessment may be repeated once (for the purpose of inclusion), and in any case, prior to enrollment/randomization, to rule out laboratory error. If the repeat value remains outside of protocol-specified ranges, the subject should be excluded from the study.

In the case where a laboratory range is not specified by the protocol, but is outside the reference range for the center at screening, a decision regarding whether the result is of clinical significance or not shall be made by the investigator and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once (for the purpose of inclusion) and in any case, prior to enrollment/randomization, to rule out laboratory error.

In all cases, the investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the subject to continue in the study.

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. When in doubt, Novartis personnel should again be contacted.

## **Hematology**

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (i.e., neutrophils, basophils, eosinophils, monocytes, and lymphocytes) platelet, aPTT, PT/INR, count will be measured.

## **Clinical chemistry**

Sodium, potassium, creatinine, BUN/urea, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, bicarbonate/HCO<sub>3</sub>, LDH, GGT, AST, ALT, amylase, lipase, CK, glucose, total cholesterol, triglycerides. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated. HbA1c will be included in the panel at *screening only*.

## **Urinalysis**

A midstream urine sample (approx. 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

A semi-quantitative 'dipstick' evaluation for the following parameters will be performed: specific gravity, pH, glucose, protein, bilirubin, ketones, leukocytes, and blood.

If the dipstick result is positive for protein, leucocytes and/or blood, the sample will be sent for microscopic analysis of WBC, RBC, and casts.

Dipstick measurements for specific gravity, albumin, protein, glucose and blood will be performed. Microscopy, WBC, RBC and sediments will also be assessed in case of an abnormal dipstick test.



### 8.6.5 Electrocardiogram (ECG)

Full details of all procedures relating to the ECG collection and reporting are contained in the Site Operations Manual.

The following ECG parameters will be captured in the CRF: heart rate, PR interval, QRS duration, QT interval, RR interval, and QTc.

The Fridericia QT correct formula (QTcF) should be used for clinical decisions. Clinically significant abnormalities must be reported in the AE CRF.

### 8.6.6 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. See the Assessment Schedule, [Section 8.1](#), for timing of the protocol required pregnancy testing; additional pregnancy testing may be performed to meet local requirements\*. A positive urine pregnancy test requires immediate interruption of study treatment until serum  $\beta$ -hCG is performed and found to be negative.

\*If additional pregnancy testing is needed per local requirements, those additional results will be kept as source documentation only.

## 8.7 Pharmacokinetics

Timing of pharmacokinetic blood sample collection is outlined in the Assessment Schedule, [Section 8.1](#).

Pharmacokinetic (PK) samples will be obtained and evaluated in all subjects administered all forms of indacaterol.

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Untreated samples (placebo) will not be analyzed.

Concentrations will be expressed in mass per volume units and will refer to the free base of indacaterol.

Details of the analytical methods, the validation method, and the analytical within-study quality control procedures, together with the data, will be provided in the Bioanalytical Data Report. Concentrations below the LLOQ will be reported as “zero” in summary statistics of concentration data as well as PK parameter calculations and missing data will be labeled as such in the Bioanalytical Data Report.

PK samples remaining after completion of the determination of parent may be used for exploratory assessment of metabolites or other bioanalytical purposes (e.g. cross check between different sites, stability assessment). Given the exploratory nature of the work, the analytical method used for those assessments will not be validated.

For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol.



Other pharmacokinetic parameters may be determined as appropriate. Pharmacokinetic parameters will be determined by non-compartmental methods using Phoenix WinNonlin (Version 6.4 or higher).

## **8.8 Other assessments**

### **8.8.1 Patient diary**

Each subject will be provided with a diary to record study assessments while at home (from screening, through all treatment periods including washout periods).

Subjects will record:

- Use of ICS
- Rescue medication use
- PEF measurements: am and pm
- Mouth rinsing

The diary will contain instructions for the subjects to perform PEF measurements prior to the intake of ICS. Whilst it is preferred that PEF measurements are made prior to (6-hours) the administration of salbutamol (as rescue medication), subjects should not withhold their rescue medication in the event that their clinical condition deems the immediate use of medication.

Subjects will be informed of their alert values for PEF at screening and after randomization so that if they meet stopping criteria related to PEF measurements whilst at home, they can contact the clinic immediately and appropriate action taken for review and withdrawal/ongoing management of their asthma.

### **8.8.2 Device training**

Subjects will be provided with device training for the e-diary/peak flow meter device. The electronic device will be used to collect information on rescue medication use and to store PEF meter measurements.

## 9 Safety monitoring

### 9.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., 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 study treatment are also considered an adverse event irrespective if a clinical event has occurred. See [Section 9.5](#) (Reporting Medication errors including misuse/abuse) for an overview of the reporting requirements.

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

Abnormal laboratory values or test results constitute adverse events 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 should 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 subjects with underlying disease. Investigators have the responsibility for managing the safety of individual subjects and identifying adverse events. Alert ranges for liver related events are included in [Section 15-Appendix 1: Liver Event Definitions and Follow-up Requirements](#)). Adverse events must be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, and 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
  - study treatment (no/yes), or
  - other treatment (no/yes), or
  - both or indistinguishable
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event ([Section 9.2.1 \(Definition of SAE\)](#)) and which seriousness criteria have been met
- action taken regarding investigational treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- investigational treatment dosage adjusted/temporarily interrupted
- investigational treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- subject hospitalized/subject's hospitalization prolonged ([Section 9.2.1 \(Definition of SAE\)](#))
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Information about common side effects already known about the investigational drug can be found in the IB. Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational drug, the interventions required to treat it, and the outcome.

The investigator must also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject'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.

## 9.2 Serious adverse event reporting

### 9.2.1 Definition of SAE

A SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical condition(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
  - elective or pre-planned treatment for a pre-existing condition (that is unrelated to the indication under study and has not worsened since the start of study drug
  - 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 subject's general condition
- is medically significant, e.g. defined as an event that jeopardizes the subject 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 subject 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-E2D 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 subject 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-E2D 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 CRF; SAEs also require individual reporting to Novartis Drug Safety & Epidemiology (DS&E) as per [Section 9.2.2](#) (SAE reporting).

### 9.2.2 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last IP administration, must be reported to Novartis **within 24 hours of learning of its occurrence** as described below. Any SAEs experienced after this period 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.

Follow-up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the subject continued or withdrew from study participation. 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.

If the SAE is not previously documented in the IB 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 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.

Follow the detailed instructions outlined in the Site Operations Manual regarding the submission process for reporting SAEs to Novartis. **SAEs must be reported to Novartis within 24 hours** of the investigator learning of its occurrence/receiving follow-up information.

### 9.3 Liver safety monitoring

To ensure subject 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

Refer to [Table 15-1-Appendix 1](#) for complete definitions of liver events.

Every liver event defined in [Table 15-1-Appendix 1](#) should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in [Table 15-2-Appendix 1](#).

- Repeating liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and  $\gamma$ GT) to confirm elevation within 48-72 hours.

These liver chemistry repeats should always be performed using the central laboratory, with the results provided via the standard electronic transfer. If results will not be available from the central laboratory within 24 hours, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unscheduled local laboratory CRF.

If the initial elevation is confirmed, close observation of the subject will be initiated, including:

- Consideration of treatment interruption if deemed appropriate
- Discontinuation of the investigational drug (refer to [Section 7.2](#) (Discontinuation of study treatment)), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include:
  - Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and  $\gamma$ GT. If total bilirubin is elevated  $> 2 \times$  ULN, fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. Retesting should be continued up to resolution.
  - Obtaining a more detailed history of symptoms and prior or concurrent diseases.
  - Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
  - Exclusion of underlying liver disease, as specified in [Table 5-3](#).
  - Imaging such as abdominal US, CT, or MRI, as appropriate
  - Obtaining a history of exposure to environmental chemical agents.
  - Considering gastroenterology or hepatology consultations.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF.

## 9.4 Reporting Medication 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/subject 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.

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) CRF. Study treatment errors are only to be reported to Novartis Drug Safety and Epidemiology department if the treatment error is associated with a SAE.

All instances of misuse or abuse must be documented in the adverse event (AE) CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis Drug Safety and Epidemiology. As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. [Table 9-1](#) summarizes the reporting requirements.

**Table 9-1 Summary of reporting requirements for medication errors**

Treatment error type	Document in Dose Administration (DAR) CRF	Document in AE CRF	Complete SAE form/CRF
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

For more information on AE and SAE definition and reporting requirements, please see [Section 9.1](#) and [Section 9.2](#), respectively.

## 9.5 Pregnancy reporting

To ensure subject 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.



The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

## **9.6 Prospective suicidality assessment**

Not Applicable.

## **9.7 Early phase safety monitoring**

The investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

# **10 Data review and database management**

## **10.1 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 GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRF's must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).



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 eligibility criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRF's are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

## **10.2 Data collection**

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to Novartis. 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 a CD-ROM or paper copies of the subject data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Site Operations Manual and [Assessment schedule](#) and can be recorded directly on the CRF's. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

## **10.3 Database management and quality control**

Novartis staff or designee 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. Medical history/current medical conditions 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 designee.

Diary data will be entered into an electronic diary by the subject. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis or designee.

Randomization codes and data about all study drug(s) dispensed to the subject and all dosage changes will be tracked using the Novartis IRT system. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis or designee.

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 any 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.

Data quality processes and query generation and resolution procedures will be provided in vendors' manuals.

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## **10.4 Data Monitoring Committee**

Not required

## **10.5 Adjudication Committee**

Not required

## **11 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.

### **11.1 Analysis sets**

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The safety analysis set will include all subjects that received any study drug.

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who receive any study drug and no major protocol deviations with relevant impact on PK data.

The PD analysis set will include all subjects with available PD parameter data who received any study drug and experienced no major protocol deviations with relevant impact on PD data. Any PD data for the primary endpoint obtained within 6 hours after rescue medication use or within 7 days of systemic corticosteroid will be set to missing.

## **11.2 Subject demographics and other baseline characteristics**

All data for background and demographic variables will be listed by treatment sequence and subject. Summary statistics will be provided for all subjects, as well as for each treatment sequence.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment sequence and subject.

## **11.3 Treatments**

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment sequence and subject.

## **11.4 Analysis of the primary variable(s)**

### **11.4.1 Variable(s)**

The primary variable is trough FEV<sub>1</sub> to assess the bronchodilator effect of orally inhaled indacaterol salts (maleate and acetate) in subjects with asthma compared with placebo. Trough FEV<sub>1</sub> is defined as the average of the FEV<sub>1</sub> measurements at 23 h 15 min and 23 h 45 min post dose.

### **11.4.2 Statistical model, hypothesis, and method of analysis**

The following hypothesis will be tested for each of indacaterol salts (acetate and maleate) versus placebo separately:

- HA<sub>1</sub>: Indacaterol acetate is different to placebo in terms of the trough FEV<sub>1</sub> after 14 days of treatment
- HA<sub>2</sub>: Indacaterol maleate is different to placebo in terms of the trough FEV<sub>1</sub> after 14 days of treatment

The trough FEV<sub>1</sub> after 14 days of treatment will be analyzed using an analysis of variance (ANOVA) with treatment, period and sequence as fixed effects and subject nested within sequence will be included as a random effect. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

The final model estimates will include the LS mean for each treatment (indacaterol acetate, maleate and placebo) together with standard error (SE), the adjusted mean difference between indacaterol salts (acetate and maleate) and placebo, and corresponding two-sided 95% confidence intervals and P-value for the differences (acetate vs placebo and maleate vs placebo) using placebo as reference treatment. Additionally as a secondary consideration, an estimate of the differences in trough FEV<sub>1</sub> between indacaterol acetate (test) and indacaterol maleate (reference) will be calculated together with the corresponding two sided 95% confidence intervals.

Trough FEV<sub>1</sub> will be listed by treatment sequence, subject and visit/time and descriptive summary statistics will be provided by treatment and visit/time. Summary statistics will include arithmetic mean, SD, CV (arithmetic), median, minimum and maximum.

Graphical methods will be employed to show mean and individual figures for trough FEV<sub>1</sub>

No adjustments will be made for multiplicity because the objective is to prove that both formulations must be statistically significantly different from placebo each at 2 sided 5% level of significance.

#### **11.4.3 Handling of missing values/censoring/discontinuations**

Subjects withdrawn for any reasons other than safety and tolerability may be replaced on a case by case basis.

If one of the 23h 15 min and 23h 45 min values are missing (or set to missing) then the remaining non-missing value will be taken as trough FEV<sub>1</sub>. If both values are missing, or if the subject withdrew from the study, regardless of the reason for discontinuation, then trough FEV<sub>1</sub> will be regarded as missing.

If any of the values used in the trough FEV<sub>1</sub> are collected within six hours of rescue medication then the individual FEV<sub>1</sub> value will be set to missing and the imputation rules stated above will then be applied.

#### **11.4.4 Summary statistics of safety**

Not applicable

#### **11.4.5 Summary statistics of pharmacokinetics**

Not Applicable

#### **11.4.6 Sensitivity analyses**

Not Applicable

### **11.5 Analysis of secondary variable(s)**

#### **11.5.1 Efficacy / Pharmacodynamics**

FEV<sub>1</sub>, FEV<sub>1</sub>% predicted, FVC, FVC% predicted, FEF<sub>25-75%</sub> after 14 days of treatment will be analyzed using the same model as for the primary analysis with the additional fixed effects for time and treatment by time interaction term. Time will be repeated within each subject\*period interaction term. An unstructured covariance matrix will be applied.

Peak FEV<sub>1</sub> (maximum FEV<sub>1</sub> post treatment) and Standardized FEV<sub>1</sub> AUC<sub>0-4h</sub> between screening (pre dose) and 4h post dose on Day 14 of treatment will be analyzed using the same model as for the primary analysis.

All subjects will be instructed to record PEF twice daily using a Peak Flow Meter device, once in the morning and once approximately 12 h later in the evening from screening and throughout the study. The morning/evening and the overall PEF (L/min) will be averaged between days 8 to 14 of each treatment period for each subject. Mean morning/evening and overall PEF will be analyzed using the same model as for the primary analysis and summarized by treatment.

Time to peak FEV<sub>1</sub> on Day 14 will be analyzed using non-parametric methods. The median difference and the two sided 95% confidence interval of the median difference in time to peak FEV<sub>1</sub> will be estimated using Hodges-Lehmann estimation procedure.

The number of puffs of the rescue medication use is recorded twice (morning/evening) by subjects in the eDairy. The average number of puffs of rescue medication use will be calculated as the number of puff >0 divided by days (14-8) for morning/evening and overall number of puffs of each treatment period for each subject and will be used for statistical analysis. The mean morning/evening and overall number of puffs of rescue medication use will be analyzed using the same model as for the primary analysis and summarized by treatment. The number and percentage of subjects with rescue medications, together with the number of events, were tabulated by treatment.

All the above secondary variables will be listed by treatment sequence, subject and visit/time and descriptive summary statistics will be provided by treatment and visit/time. Summary statistics will include arithmetic mean, SD, CV (arithmetic), median, minimum and maximum.

Graphical methods will be employed to show mean and individual figures for all parameters.

## **11.5.2 Safety**

### **Vital signs**

All vital signs data will be listed by treatment sequence, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

### **ECG evaluations**

All ECG data will be listed by treatment sequence, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. Summary table for percentage and number of subjects with abnormal values <40 /40-90 />90 bpm in heart rate and summary table for percentage and number of subjects with notable values increase >30 / increase >60 / >450 />480/>500 msec in QTcF interval will be provided.

### **Clinical laboratory evaluations**

All laboratory data will be listed by treatment sequence, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Summary table for percentage and number of subjects with notable values for serum potassium (<3 /3-<3.5 />5.5 mmol/L) and plasma glucose (>10-15 />15 mmol/L) will be provided.

## **Adverse events**

All information obtained on adverse events will be displayed by treatment and subject.

All study emergent adverse events will be summarized. Adverse events starting on or after the time of the first inhalation of study drug will be classified as a treatment emergent adverse event. Any adverse events that started during a washout period will be assigned to the treatment period just prior to that washout period. Any adverse events that started during the study before the time of the first inhalation of study drug of the first period will be classified as a prior adverse event.

The number and percentage of subjects with treatment emergent adverse event 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 adverse events by system organ class and preferred term, serious adverse events by system organ class and preferred term, and adverse events leading to permanent discontinuation of study drug by system organ class and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system and treatment period is only counted once towards the total of this body system and treatment.

## **Concomitant medications / Significant non-drug therapies**

All concomitant therapies will be listed by treatment sequence and subject.

### **11.5.3 Pharmacokinetics**

#### **Statistical methods for pharmacokinetic analysis**

The log transformed pharmacokinetic parameters AUC<sub>0-24h,ss</sub> and C<sub>max,ss</sub> on day 14 will be compared for indacaterol acetate (test) relative to indacaterol maleate (reference) using a mixed effects model with sequence, treatment and period as fixed effects and subject nested within sequence as random effect. Body weight assessed in period 1 may be included as a covariate and applied as a fixed effect in the model. The estimates of the treatment differences (indacaterol acetate (test) vs. maleate (reference); Frel) along with their 90% confidence intervals will be obtained. The estimates and confidence intervals will be transformed back to the original scale to provide ratios of the geometric means together with their corresponding 90% confidence intervals.

T<sub>max,ss</sub> will be analyzed using non-parametric methods. The median difference and the 90% confidence interval of the median difference in T<sub>max,ss</sub> will be estimated using Hodges-Lehmann estimation procedure.

#### **Handling of missing values/censoring/discontinuations**

All subjects with evaluable PK parameters data for at least one study treatment will be included for this analysis

## **Summary statistics for pharmacokinetic data**

Indacaterol plasma concentrations will be listed by treatment sequence, subject, profile day, and sampling time point. Descriptive summary statistics will be provided by treatment, profile day, and sampling time point. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics. A geometric mean will not be reported if the dataset includes zero values.

Pharmacokinetic parameters will be calculated as described in [Section 8.7](#) (Pharmacokinetics) and will be listed by treatment sequence, profile day, and subject. Descriptive summary statistics will be provided by treatment and profile day. Summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum. An exception to this is T<sub>max</sub> where median, minimum and maximum will be presented.

Graphical methods will be employed to show mean and individual time-concentration profiles.

Pharmacokinetic parameters will be determined using WinNonlin Phoenix (version 6.4 or higher).

### **11.5.4 Pharmacokinetic / pharmacodynamic interactions**

Not Applicable.

### **11.5.5 Other assessments**

Not Applicable.

Corporate Confidential Information

## 11.7 Sample size calculation

Sample size calculations are based on the primary endpoint of trough FEV<sub>1</sub>. Trough FEV<sub>1</sub> is defined as the average of the FEV<sub>1</sub> measurements at 23 h 15 min and 23 h 45 min post-dose.

The primary objective is to prove that the test formulation (the one included in the combination therapy which is acetate and maleate salt) must be better than placebo. Using an estimate of within subject standard deviation of 230 mL from Study QAB149D2301 and assuming the data are normally distributed, 42 (7 per sequence) subjects are required to detect the difference of 170 mL in trough FEV<sub>1</sub> with 90% power in each test (acetate vs placebo and maleate vs placebo).

No adjustment will be made for multiplicity because the objective is to obtain a statistical separation from placebo for both the comparisons.

The power where both tests are required to meet the overall objective is >81% power, with a two-sided test at a significance level of 5%.

Allowing for a 20% drop out rate, a total sample size of 54 (9 per sequence) subjects will be randomized to six treatment sequences.

## 11.8 Power for analysis of key secondary variables

The sample size was estimated based on the primary endpoint of trough FEV<sub>1</sub> is also adequate from a pharmacokinetic bioequivalence perspective. The intra-subject CV (coefficient of variation) of C<sub>max</sub> and AUC<sub>0-24h</sub> in Study CQAB149D2301 was 14% and 20%, respectively. Assuming a maximum intra-subject CV of 20% for AUC<sub>0-24h</sub> (based on 7-day dosing in asthma subjects in Study CQAB149D2301), a sample size of 42 completers will provide at least 95% power to achieve [90% CI for geometric mean ratio (test/reference) within the interval of 0.80-1.25] with respect to the AUC<sub>0-24h,ss</sub> of indacaterol, if the true geometric mean ratio is 1.



## **12 Ethical considerations**

### **12.1 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 Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

### **12.2 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, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to 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.

For multi-center trials, a Coordinating investigator will be selected by Novartis around the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

### **12.3 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.

## **13 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 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.

### **13.1 Protocol Amendments**

Any change 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.

Amendments that are intended to eliminate an apparent immediate hazard to 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 subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in [Section 9](#) (Safety monitoring) must be followed and the Study Lead informed.

## 14 References

Boxenbaum H, Battle M (1995) Effective half-life in clinical pharmacology. *J Clin Pharmacol* Aug;35(8): 763-6.

Global Initiative for Chronic Obstructive Lung Disease (GOLD); Global Initiative for Chronic Obstructive Lung Disease (2017 report).

Miller MR, Crapo R, Hankinson J, et al (2005a) General considerations for lung function testing. *Eur. Respir. J.* Jul;26(1): 153-61.

Miller MR, Hankinson J, Brusasco V, et al (2005b) Standardisation of spirometry. *Eur. Respir. J.* Aug;26(2): 319-38.

## 15 Appendix 1: Liver Event Definitions and Follow-up Requirements

**Table 15-1 Liver Event and Laboratory Trigger Definitions**

Definition	Thresholds
Potential Hy's law cases	<ul style="list-style-type: none"> <li>ALT or AST &gt; 3 × ULN and TBL &gt; 2 × ULN without initial increase in ALP to &gt; 2 × ULN</li> </ul>
ALT or AST elevation with coagulopathy	<ul style="list-style-type: none"> <li>ALT or AST &gt; 3 × ULN and INR &gt; 1.5 (in the absence of anticoagulation)</li> </ul>
ALT or AST elevation accompanied by symptoms	<ul style="list-style-type: none"> <li>ALT or AST &gt; 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia</li> </ul>
Isolated ALT or AST elevation	<ul style="list-style-type: none"> <li>ALT or AST &gt; 8 × ULN</li> </ul>
Isolated ALP elevation	<ul style="list-style-type: none"> <li>5 × ULN &lt; ALT/AST ≤ 8 × ULN</li> <li>3 × ULN &lt; ALT/AST ≤ 5 × ULN</li> </ul>
Others	<ul style="list-style-type: none"> <li>ALP &gt; 2 × ULN (in the absence of known bone pathology)</li> <li>Any clinical event of jaundice (or equivalent term)</li> <li>Any adverse event potentially indicative of liver toxicity</li> </ul>

**Table 15-2 Actions required for Liver Events**

Criteria	Actions required
Potential Hy's Law case	
ALT or AST elevation with coagulopathy	<ul style="list-style-type: none"> <li>Discontinue the study treatment immediately</li> </ul>
ALT or AST elevation accompanied by symptoms	<ul style="list-style-type: none"> <li>Hospitalize, if clinically appropriate</li> <li>Establish causality</li> </ul>
Isolated ALT or AST elevation > 8 × ULN	<ul style="list-style-type: none"> <li>Complete CRFs per liver event guidance</li> </ul>
Jaundice	
Isolated ALT or AST elevation > 5 to ≤ 8 × ULN	<ul style="list-style-type: none"> <li>If confirmed, consider interruption or discontinuation of study drug</li> <li>If elevation persists for more than 2 weeks, discontinue the study drug</li> <li>Establish causality</li> <li>Complete CRFs per liver event guidance</li> </ul>
Isolated ALT or AST elevation > 3 to ≤ 5 × ULN (patient is asymptomatic)	<ul style="list-style-type: none"> <li>Monitor liver chemistry tests two or three times weekly</li> </ul>
Isolated ALP elevation	<ul style="list-style-type: none"> <li>Repeat liver chemistry tests within 48-72 hours</li> <li>If elevation is confirmed, measure fractionated ALP; if &gt;50% is of liver origin, establish hepatic causality</li> <li>Complete CRFs per liver event guidance</li> </ul>
Any AE potentially indicative of liver toxicity	<ul style="list-style-type: none"> <li>Consider study treatment interruption or discontinuation</li> <li>Hospitalize if clinically appropriate</li> <li>Complete CRFs per liver event guidance</li> </ul>

**Table 15-3 Exclusion of underlying liver disease**

<b>Disease</b>	<b>Assessment</b>
Hepatitis A, B, C, E	<ul style="list-style-type: none"> <li>IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM &amp; IgG anti-HEV, HEV RNA</li> </ul>
CMV, HSV, EBV infection	<ul style="list-style-type: none"> <li>IgM &amp; IgG anti-CMV, IgM &amp; IgG anti-HSV; IgM &amp; IgG anti-EBV</li> </ul>
Autoimmune hepatitis	<ul style="list-style-type: none"> <li>ANA &amp; ASMA titers, total IgM, IgG, IgE, IgA</li> </ul>
Alcoholic hepatitis	<ul style="list-style-type: none"> <li>Ethanol history, <math>\gamma</math>GT, MCV, CD-transferrin</li> </ul>
Nonalcoholic steatohepatitis	<ul style="list-style-type: none"> <li>Ultrasound or MRI</li> </ul>
Hypoxic/ischemic hepatopathy	<ul style="list-style-type: none"> <li>Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.</li> </ul>
Biliary tract disease	<ul style="list-style-type: none"> <li>Ultrasound or MRI, ERCP as appropriate.</li> </ul>
Wilson disease	<ul style="list-style-type: none"> <li>Caeruloplasmin</li> </ul>
Hemochromatosis	<ul style="list-style-type: none"> <li>Ferritin, transferrin</li> </ul>
Alpha-1-antitrypsin deficiency	<ul style="list-style-type: none"> <li>Alpha-1-antitrypsin</li> </ul>

## 16 Appendix 2: Concept1 Platform Inhaler: Instructions for use of medical devices for investigational human use

### Instructions for using inhaler and capsules

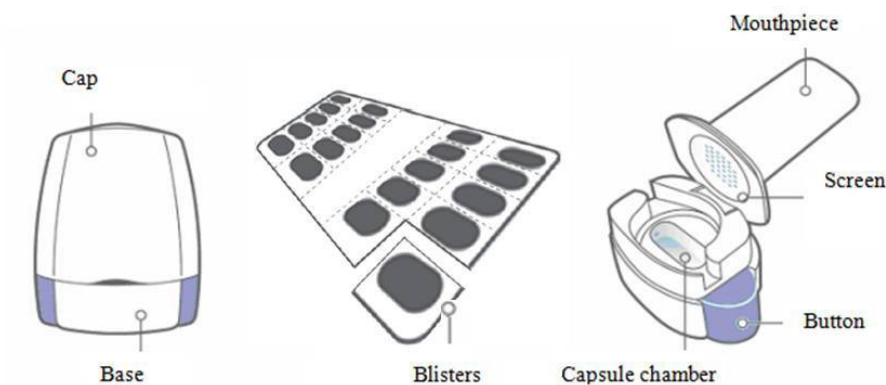
**Do not swallow capsules.**

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.




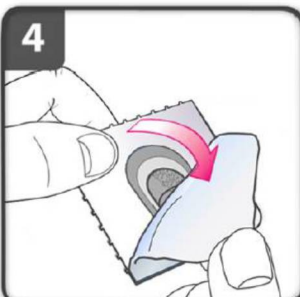
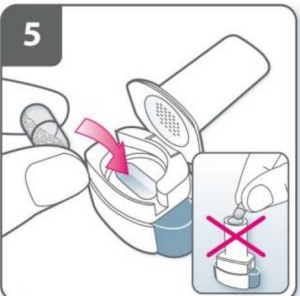
- Capsules are supplied in blisters.
- Inhaler consists of a cap, mouthpiece, and a base


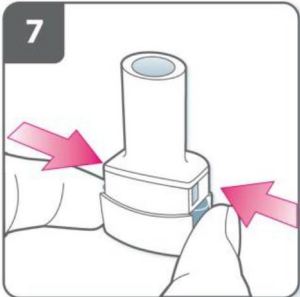
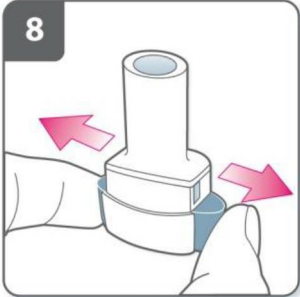
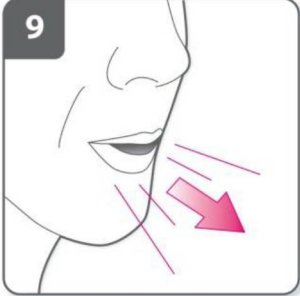
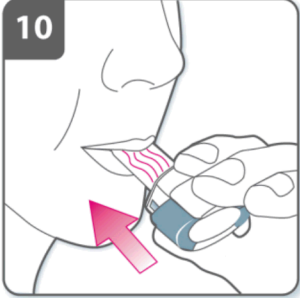


Your inhaler is designed to deliver the medicine contained within the capsules.

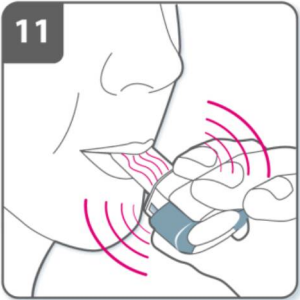
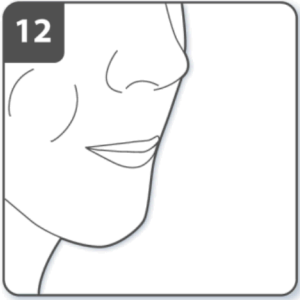
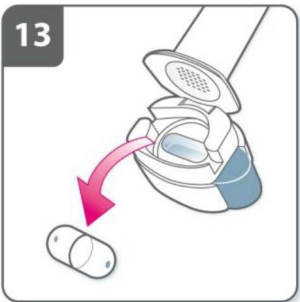
Do not use study medication capsules with any other capsule inhaler and do not use the inhaler to take any other capsule medicine.

## How to use your inhaler

	<p><b>Pull off cap.</b></p>
	<p><b>Open inhaler:</b> Hold the base of the inhaler firmly and tilt back the mouthpiece. This opens the inhaler.</p>
	<p><b>Prepare capsule:</b> 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.</p>
	<p><b>Remove a capsule:</b> Peel away the foil and remove the capsule from the blister.</p>
	<p><b>Insert capsule:</b> Place the capsule into the capsule chamber. <b>Never place a capsule directly into the mouthpiece.</b></p>

	<p><b>Close the inhaler:</b> You should hear a “click” as the mouthpiece closes onto the inhaler base.</p>
	<p><b>Pierce the capsule:</b></p> <ul style="list-style-type: none"><li>• Hold the inhaler upright with the mouthpiece pointing up.</li><li>• Pierce the capsule by firmly pressing together both side buttons at the same time. <b>Do this only once.</b></li><li>• You should hear a “click” as the capsule is being pierced.</li></ul>
	<p><b>Release the side buttons fully.</b></p>
	<p><b>Breathe out:</b> Before placing the mouthpiece in your mouth, breathe out fully. <b>Do not blow into the mouthpiece.</b></p>
	<p><b>Inhale the medicine</b> To breathe the medicine deeply into your airways:</p> <ul style="list-style-type: none"><li>• Hold the inhaler as shown in the picture. The side buttons should be facing left and right. Do not press the side buttons.</li><li>• Place the mouthpiece in your mouth and close your lips firmly around it.</li><li>• Breathe in rapidly but steadily and as deeply as you can.</li></ul>



 <p>11</p>	<p><b>Note:</b></p> <p>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.</p> <p><b>Additional information</b></p> <p>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.</p> <p><b>If you do not hear a whirring noise:</b></p> <p>The capsule may be stuck in the capsule chamber. If this happens:</p> <ul style="list-style-type: none"><li>• Open the inhaler and carefully loosen the capsule by tapping the base of the inhaler. Do not press the side buttons.</li><li>• Inhale the medicine again by repeating steps 9 to 11.</li></ul>
 <p>12</p>	<p><b>Hold breath:</b></p> <p>After you have inhaled the medicine:</p> <ul style="list-style-type: none"><li>• Hold your breath for at least 5-10 seconds or as long as you comfortably can while taking the inhaler out of your mouth.</li><li>• Then breathe out.</li><li>• Open the inhaler to see if any powder is left in the capsule.</li></ul> <p><b>If there is powder left in the capsule:</b></p> <ul style="list-style-type: none"><li>• Close the inhaler.</li><li>• Repeat steps 9, 10, 11, and 12.</li></ul> <p>Most people are able to empty the capsule with one or two inhalations.</p> <p><b>Additional information</b></p> <p>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.</p>
 <p>13</p>	<p><b>After you have finished taking your medicine:</b></p> <ul style="list-style-type: none"><li>• You may be directed by your physician to rinse mouth with water and spit it out; do not swallow the water.</li><li>• 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.</li><li>• Close the inhaler and replace the cap.</li></ul> <p><b>Do not store the capsules in the inhaler.</b></p>

**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. Dispose of each inhaler after the number of uses identified by your physician.
- 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.

Manufactured by:

Novartis Pharma AG, Switzerland

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