

Global Clinical Development - General Medicine

[NVA237/Glycopyrronium bromide]

Clinical Trial Protocol [CQVM149B2204] / NCT03137784

A multicenter, randomized, double-blind, placebo-controlled 3-period complete cross-over study to assess the bronchodilator effects and safety of glycopyrronium bromide (NVA237) (25 µg and 50 µg o.d.) in asthma patients

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Table of contents

Table of contents	2
List of tables	5
List of figures	5
List of abbreviations	6
Glossary of terms.....	8
Protocol summary.....	9
1 Introduction	11
1.1 Background.....	11
1.2 Purpose	12
2 Study objectives and endpoints	12
2.1 Primary objective	12
2.2 Secondary objective(s).....	12
[REDACTED]	12
3 Investigational plan	13
3.1 Study design.....	13
3.2 Rationale for study design	14
3.3 Rationale for dose/regimen, route of administration and duration of treatment....	14
3.4 Rationale for choice of comparator	15
3.5 Purpose and timing of interim analyses/design adaptations	16
3.6 Risks and benefits	16
4 Population.....	17
4.1 Inclusion criteria	18
4.2 Exclusion criteria	18
5 Treatment.....	21
5.1 Study treatment	21
5.1.1 Investigational and control drugs	21
5.1.2 Additional treatment.....	21
5.2 Treatment arms	22
5.3 Treatment assignment and randomization	22
5.4 Treatment blinding.....	23
5.5 Treating the patient	23
5.5.1 Patient numbering	23
5.5.2 Dispensing the study drug	23
5.5.3 Handling of study and additional treatment	24
5.5.4 Instructions for prescribing and taking study treatment.....	25

7.5	Reporting of study treatment errors including misuse/abuse	45
7.6	Pregnancy reporting.....	45
8	Data review and database management.....	46
8.1	Site monitoring	46
8.2	Data collection.....	46
8.3	Database management and quality control	47
8.4	Data Monitoring Committee.....	47
8.5	Adjudication Committee.....	47
9	Data analysis.....	48
9.1	Analysis sets	48
9.2	Patient demographics and other baseline characteristics.....	48
9.3	Treatments	48
9.4	Analysis of the primary variable(s)	49
9.4.1	Variable(s).....	49
9.4.2	Statistical model, hypothesis, and method of analysis	49
9.4.3	Handling of missing values/censoring/discontinuations	50
9.4.4	Sensitivity analyses	50
9.5	Analysis of secondary variables	50
9.5.1	Efficacy variables.....	50
9.5.2	Safety variables	50
9.6	Interim analyses	51
9.7	Sample size calculation.....	51
10	Ethical considerations.....	52
10.1	Regulatory and ethical compliance.....	52
10.2	Informed consent procedures.....	52
10.3	Responsibilities of the investigator and IRB/IEC	53
10.4	Publication of study protocol and results.....	53
10.5	Quality Control and Quality Assurance.....	53
11	Protocol adherence	53
11.1	Protocol amendments.....	54
12	References	55
13	Appendices	56
	Appendix 1: Liver event and Laboratory trigger Definitions and Follow-up Requirements	56
	Appendix 2 Instructions for using inhaler and capsules.....	58
	Appendix 3 Spirometry Guidance	63
	Appendix 4 Patient Asthma Control e-Diary	66

Appendix 5 ICS Dose level	67
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List of tables

Table 5-1	Treatment arms.....	22
Table 5-2	Prohibited asthma related medication	26
Table 5-3	Other Prohibited medication	28
Table 6-1	Assessment schedule	32
Table 6-2	Spirometry timings in relation to study drug administration	36
Table 7-1	Guidance for capturing the study treatment errors including misuse/abuse	45
Table 13-1	Liver Event and Laboratory Trigger Definitions	56
Table 13-2	Follow Up Requirements for Liver Events and Laboratory Triggers ...	56
Table 13-3	Low, medium and high Daily Doses of Inhaled Glucocorticosteroids for Adults and adolescents (12 years and older) (GINA 2015).....	67

List of figures

Figure 3-1	Study design	13
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List of abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATS/ERS	American Thoracic Society / European Respiratory Society
AUC	Area under curve
AV	Atrioventricular
b.i.d.	twice a day
BMI	Body Mass Index
BPH	Benign Prostate Hyperplasia
BTPS	Body Temperature Pressure Saturated
BUN	Blood Urea Nitrogen
CFR	US Code of Federal Regulations
CRA	Clinical Research Associate
COPD	Chronic Obstructive Pulmonary Disease
CPO	Country Pharma Organization
DAR	Drug Administration Record
DALY	Disability-adjusted life years
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
eCRF	Case Report/Record Form (electronic)
ECSC	European Community for Steel and Coal
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOT	Early Treatment Discontinuation
EU	European Union
FAS	Full Analysis Set
FEV1	Forced expiratory volume in 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GLI	Global Lung Function Initiative
γ-GT	Gamma Glutamyl Transferase
GINA	Global Initiative for Asthma
hCG	Human Chorionic Gonadotropin
IB	Investigator Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IN	Investigator Notification
IUD	Intrauterine device
IUS	Intrauterine system

i.v.	intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
LABA	Long Acting Beta-2 Agonist
LAMA	Long acting muscarinic antagonist
LFT	Liver function test
MF	Mometasone furoate
MedDRA	Medical dictionary for regulatory activities
NYHA	New York Heart Association
OC/RDC	Oracle Clinical/Remote Data Capture
o.d.	once a day
PD	Pharmacodynamics
PEF	Peak Expiratory Flow
PPS	Per Protocol Set
p.o.	oral(ly)
QT	QT Interval (measure between Q wave and T wave in the heart's electrical cycle)
QTcF0	QT interval Fridericia's Correction Formula
RBC	Red Blood Cells
SABA	Short Acting beta-2 agonist
SAE	Serious Adverse Event
SAMA	Short acting muscarinic antagonist
SAP	Statistical Analysis Plan
SDDPI	Single Dose Dry Powder Inhaler
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum glutamic-pyruvic transaminase
SmPC	Summary of Product Characteristics
SNRI	Serotonin Noradrenaline Reuptake Inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reactions
TD	Study Treatment Discontinuation
US	United States
WBC	White Blood Cells
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

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

Protocol summary

Protocol number	CQVM149B2204
Title	A multicenter, randomized, double-blind, placebo-controlled 3-period complete cross-over study to assess the bronchodilator effects and safety of glycopyrronium bromide (NVA237) (25 µg and 50 µg o.d.) in asthma patients
Brief title	Bronchodilator effects and safety of glycopyrronium bromide (25 µg and 50 µg o.d.) in asthma
Sponsor and Clinical Phase	Novartis Phase IIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this trial is to characterize the bronchodilator effects and safety of 25 µg and 50 µg o.d. glycopyrronium bromide doses compared to placebo in asthma
Primary Objective(s)	Evaluate the bronchodilator effects of each dose of NVA237 (25 µg and 50 µg o.d.) compared with placebo in terms of trough FEV ₁ after 1 week of treatment
Secondary Objectives	Evaluate the bronchodilator effects of each dose of NVA237 (25 µg and 50 µg o.d.) compared with placebo in terms of: <ul style="list-style-type: none"> • Standardized FEV₁ AUC after 1 week of treatment • Peak FEV₁ after 1 week of treatment • FEV₁, Forced Vital Capacity (FVC) and FEV₁/FVC ratio after 1 week of treatment • Safety and tolerability of each dose of NVA237 (25 µg and 50 µg o.d.) in the respective period To evaluate the effects of each dose of NVA237 (25 µg and 50 µg o.d.) compared with placebo as determined by patient diary data and electronic PEF meter in terms of: <ul style="list-style-type: none"> • Rescue medication usage over 1 week of treatment • Daily morning (pre-medication) and evening peak expiratory flow rate (PEF) over 1 week of treatment
Study design	6 week randomized; double blind; placebo controlled; cross-over
Population	The study population will consist of approximately 144 male and female patients aged between 18 and 65 years with asthma
Key Inclusion criteria	<ul style="list-style-type: none"> • Male and female adult patients aged ≥ 18 to ≤ 65 years • Patients with a diagnosis of asthma for a period of at least 1 year receiving daily treatment of ICS/LABA in a stable regimen for ≥ 4 weeks. • Pre-bronchodilator FEV₁ of $\geq 50\%$ and $\leq 80\%$ of the predicted normal value and an increase in FEV₁ of $\geq 12\%$ and ≥ 200 mLs during reversibility testing.

Key Exclusion criteria	<ul style="list-style-type: none"> • Patients who have had an asthma exacerbation that required either treatment with systemic corticosteroids for at least 3 days, or an emergency room visit, or hospital treatment within 6 weeks prior to screening Visit 1 and patients with a history of life-threatening asthma attacks (e.g. attacks requiring ventilation) • Patients who have had a respiratory tract infection within 4 weeks prior to screening. • Patients who have smoked or inhaled tobacco products within the past 6 month of screening. • Patients with a history of chronic lung diseases other than asthma, including (but not limited to) chronic obstructive pulmonary disease, bronchiectasis, sarcoidosis, interstitial lung disease, cystic fibrosis, and tuberculosis (unless tuberculosis is confirmed as no longer active by imaging). • Patients on Maintenance Immunotherapy (desensitization) for allergies for at least 3 months prior to Run-in who are expected to change therapy throughout the course of the study. • Patients who during the Run-in period are shown to be intolerable to LABA withdrawal. • Patients who have discontinued LAMA therapy in the past (e.g. due to intolerance or perceived lack of efficacy).
Study treatment	Glycopyrronium bromide (NVA237) (25 µg and 50 µg o.d.) and placebo
Efficacy assessments	<p>Spirometry PEF recorded in the electronic diary Rescue medication usage recorded in the electronic diary</p>
Key safety assessments	<p>Vital signs Hematology, Blood chemistry, Urinalysis Electrocardiogram Adverse Events Pregnancy Test (female patients)</p>
Data analysis	<p>The primary endpoint is the trough FEV₁ (mL) after 1 week of treatment defined as the mean of the two FEV₁ values measured at 23 h 15 min and 23 h 45 min post-dose.</p> <p>The following hypotheses will be tested for each of NVA237 doses versus placebo separately:</p> <p>H₁₀: There is no difference between NVA237 50 µg and placebo treatment groups in term of the trough FEV₁ after 1 week of treatment</p> <p>H_{1a}: There is a difference between NVA237 50 µg and placebo treatment groups in term of the trough FEV₁ after 1 week of treatment</p> <p>H₂₀: There is no difference between NVA237 25 µg and placebo treatment groups in term of the trough FEV₁ after 1 week of treatment</p> <p>H_{2a}: There is a difference between NVA237 25 µg and placebo treatment groups in term of the trough FEV₁ after 1 week of treatment</p> <p>The primary endpoint will be analyzed using a linear mixed-effect model. The model will include period, treatment, and sequence as fixed effect factors and baseline trough FEV₁ as a covariate.</p>
Key words	Asthma, NVA237, glycopyrronium bromide

1 Introduction

1.1 Background

Asthma is a chronic inflammatory disorder of the airways associated with hyper-responsiveness of the airways that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction within the lungs that is often reversible, either spontaneously or with treatment. Airflow limitation occurs as a result of obstruction or narrowing of the airways when exposed to precipitating factors. Although exacerbations of asthma are episodic, inflammation is chronic ([GINA 2015](#)).

Despite existing therapies there is still significant unmet medical need in asthma, with an estimated 300 million people affected worldwide. The Global Burden of Asthma Report estimates that 15 million disability-adjusted life years (DALYs) are lost annually due to asthma, representing 1% of the total global burden. It is estimated that asthma accounts for about one in every 250 deaths worldwide ([Beasley R, 2004](#)).

Recently, tiotropium (Spiriva® Respimat®) has been approved in EU as an add-on maintenance bronchodilator treatment in adult patients (≥ 18 years) with asthma who are currently treated with the maintenance combination of inhaled corticosteroids ($\geq 800\mu\text{g}$ budesonide/day or equivalent) and long-acting beta-2 agonists and who experienced one or more severe exacerbations in the previous year.

Following tiotropium regulatory approval in asthma, the [GINA 2015](#) guideline recommends tiotropium as a new add-on option to the preferred controller choice for steps 4 and 5.

In line with these recommendations, Novartis is developing the fixed-dose combination QVM149 of indacaterol acetate (inhaled long-acting beta-2 agonist (LABA), with 24 hour duration of action), glycopyrronium bromide (inhaled long-acting muscarinic antagonist (LAMA), with 24 hours duration of action), and mometasone furoate (MF, ICS). QVM149 is intended for once daily maintenance treatment of asthma GINA step ≥ 4 .

All three mono-components, indacaterol maleate, glycopyrronium bromide and MF have previously been developed as individual drugs for either COPD or asthma.

Glycopyrronium bromide (NVA237: 50 μg once daily in a lactose-based formulation) has been registered in the EU since 2012 as Seebri® Breezhaler® for the treatment of COPD. The dose is expressed as 44 μg as this is the dose (active moiety) that is delivered by the mouthpiece of the inhaler. Outside the EU, the dose of Seebri® Breezhaler® is generally expressed as the dose of active moiety in the capsule, i.e. 50 μg and will be referred to as such in this protocol.

Glycopyrronium bromide 50 μg once daily has demonstrated a meaningful and statistically significant improvement in lung function in COPD patients which has been sustained over 24 hours and has provided significant symptomatic benefits with a favorable safety and tolerability profile for up to 52 weeks in clinical trials. The fixed dose combination of indacaterol maleate and glycopyrronium bromide is also registered in the EU as Ultibro®,

Breezhaler® (QVA149) with the same and equivalent dose of glycopyrronium and indacaterol, respectively, as proposed for QVM149.

Previous studies with NVA237 were performed in COPD patient population and currently there is no data available on NVA237 efficacy and safety in patients with asthma.

1.2 Purpose

The purpose of this trial is to characterize the bronchodilator effects and safety of two doses (25 µg and 50 µg o.d.) of glycopyrronium bromide (NVA237) compared to placebo in asthma patients.

2 Study objectives and endpoints

2.1 Primary objective

To evaluate the bronchodilator effects of NVA237 delivered by the Concept1 single-dose dry-powder inhaler in patients with asthma in terms of trough FEV₁ (mean of 23 h 15 min and 23 h 45 min post-dose) following 1 week of treatment, by comparing NVA237 at a dose of 25 µg and 50 µg o.d. with placebo.

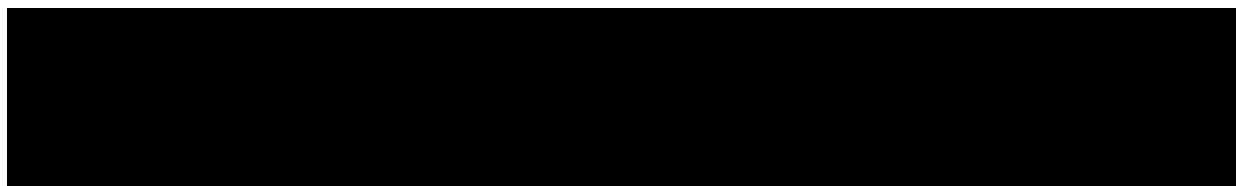
2.2 Secondary objective(s)

To evaluate the bronchodilator effects of each dose of NVA237 (25 µg and 50 µg o.d.) compared with placebo in terms of:

- Standardized FEV₁ AUC (5 min - 1 h), (5 min - 4 h), and (5 min – 23 h 45 min) after 1 week of treatment in the respective period.
- Peak FEV₁ after 1 week of treatment in the respective period during 5 min to 4 h post-dose.
- FEV₁, Forced Vital Capacity (FVC) and FEV₁/FVC ratio at all spirometry time-points after 1 week of treatment in the respective period.
- Safety and tolerability of each dose of NVA237 (25 µg and 50 µg o.d.) in the respective period (laboratory tests, vital signs, ECG and adverse events).

To evaluate the bronchodilator effects of each dose of NVA237 (25 µg and 50 µg o.d.) compared with placebo as determined by patient diary data and electronic PEF meter in the respective period in terms of:

- Rescue medication usage over 1 week of treatment
- Daily morning (pre-medication) and evening peak expiratory flow rate (PEF) over 1 week of treatment.



3 Investigational plan

3.1 Study design

This study uses a randomized, double-blind, placebo controlled, 3-period cross-over clinical trial design. During a screening epoch patient eligibility will be assessed. The screening epoch will be followed by a 21-day Run-in epoch during which patients will continue ICS use but be withdrawn from LABA-treatment and switched to short-acting bronchodilator-rescue medication.

After the Run-in period patients will be randomized to one of the 6 treatment sequences and enter the first 7-day study treatment period.

Treatment period one is followed by a 10-day washout period after which patients begin the second 7-day treatment period which is then followed by a second 10-day washout period followed by the third 7-day treatment period. At the end of each treatment period spirometry will be performed to assess the primary endpoint. Procedures in treatment periods two and three mirror-image the procedures of treatment period one.

Figure 3-1 Study design

Screening	Run In	Treatment Period 1	Wash out Period 1	Treatment Period 2	Wash out Period 2	Treatment Period 3	Study Completion Visit	Treatment Sequences
		A		B		C		Sequence 1
		A		C		B		Sequence 2
		B		A		C		Sequence 3
		B		C		A		Sequence 4
		C		A		B		Sequence 5
		C		B		A		Sequence 6
-28 days to -21 days	-21 to 0 days	7 days	10 days	7 days	10 days	7 days	1 day after last study dose	
ICS background / Rescue Medication								

Each of the six treatment arms consists of three treatment periods:

Sequence 1: A-B-C Sequence 3: B-A-C Sequence 5: C-A-B

Sequence 2: A-C-B Sequence 4: B-C-A Sequence 6: C-B-A

NVA 50 µg = A: NVA 25 µg = B: Placebo = C

3.2 Rationale for study design

The patient population will be described in more detail in the [Section 4](#) below.

This short-term treatment cross-over design is chosen to characterize lung function effects of two doses of once daily NVA237 (50 µg and 25 µg) compared to placebo in patients with asthma. To achieve optimal study adherence in the population of asthma patients there will be a 21-day Run-in period during which patients will be using short-acting rescue medication and ICS, but no LABA. This Run-in period will ensure that patients who cannot tolerate withdrawal from LABA during this period (e.g.: rescue medication use of more than five puffs on average per day) and therefore not expected to tolerate withdrawal for the entire duration of the trial will not be randomized.

The cross-over design (rather than a parallel group design) was chosen because within patient variability is expected to be less than between-subject variability for the assessed parameters. This allows for greater precision to be achieved whilst exposing a smaller number of patients to study treatment and assessments. In addition, the PD characteristics of NVA237, e.g. fast onset of bronchodilatory action and early plateauing of bronchodilatory action, approximately within the first 7 days of dosing, allow for a short study duration which also favors the use of a cross-over study design

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

Glycopyrronium bromide (NVA237: 50 µg once daily in a lactose-based formulation) has been registered in the EU since 2012 as *Seebri® Breezhaler®* for the treatment of COPD.

The glycopyrronium doses that are being evaluated in this trial are based on the experience and dose ranging with glycopyrronium in COPD and the available data of LAMAs, in particular tiotropium, in asthma. The most relevant patient population in this context currently comprises patients with severe asthma.

NVA237 50 µg once daily is supported by Phase II dose-ranging studies in COPD patients. Study NVA237A2205 evaluated NVA237 once daily in doses ranging from 12.5 µg o.d. to 100 µg o.d. (active moiety in the capsule) in COPD patients and demonstrated dose-dependent increases in trough FEV₁ at doses of and above 50 µg o.d. However, there was little difference in efficacy between 50 µg o.d. and 100 µg o.d. doses. Evidence from study NVA237A2208 supported the results of NVA237A2205. In study NVA237A2208, the NVA237 50 µg o.d. dose provided clinically relevant improvements in FEV₁ and was found to be safe and well tolerated in COPD patients. Phase III data from the NVA237 clinical program in COPD demonstrated efficacy of inhaled glycopyrronium bromide 50 µg o.d. which was superior to placebo and comparable to that observed with tiotropium 18 µg administered via the Handihaler®. Tiotropium administered via Handihaler® is considered well-comparable to Tiotropium Respimat® 5 µg which is approved for the asthma indication.

Based on recent literature ([Kerstjens et al, 2012](#), [Kerstjens et al, 2015](#), [Peters SP et al 2010](#)) supporting the efficacy of tiotropium in patients with severe asthma at the same doses used in COPD, it is expected that glycopyrronium bromide 50 µg once daily will provide similar bronchodilator effects in an asthma population that are comparable to those observed in

patients with COPD. Data with tiotropium Respimat® in patients with mild to moderate asthma may suggest that a lower dose (2.5 µg) of tiotropium can elicit bronchodilation in this milder patient population that is at least as good as a higher dose (5µg) ([Chin et al,2016](#)). In this study in asthma patients on low, mid and high dose ICS/LABA combination, glycopyrronium bromide at doses of 50 µg once daily and 25 µg once daily will be evaluated in comparison to placebo (on top of background ICS therapy). Since patients with asthma are typically younger and usually do not have co-morbid conditions than those observed with COPD, it is expected that NVA237 will also have an acceptable safety profile in asthmatic patients.

In conclusion, 50 µg o.d. was selected as the high dose to be explored in the present study with the 25 µg o.d. dose also to be assessed to characterize the respective bronchodilator effects of these doses compared to placebo (on top of background ICS therapy) in moderate to severe asthma patients.

Budesonide is the selected background ICS therapy to ensure a standardization of patient treatment during the conduct of the study.

A one-week study duration is considered sufficient to investigate lung-function effects of NVA237 based on data from study NVA237A2205 in which there were clinically meaningful improvements in spirometric measurements after one-week of treatment. In study NVA237A2208 which investigated lung function over 28 days, FEV₁ was improved on all assessment days compared to placebo (Day 1, Day 14, Day 28; no assessments on Day 7). As the totality of data in COPD patients suggests that no substantial further increase in lung function is observed after 7 days of treatment, a 7 day treatment duration is also considered appropriate for the asthma indication.

The washout period between the two treatment periods is 10 days (but may be extended to a maximum of 14 days to allow for some flexibility for visit attendance). Based on 24 hour spirometry data, the half-life of the bronchodilatory effect of NVA237 is estimated to be \leq 80 hours. Therefore the bronchodilatory effect is expected to be washed-out following 17 days after last dose administration. Consequently, the proposed minimum 10 days of washout plus 1 week of treatment in the next following treatment period are sufficient to avoid a carry-over pharmacodynamic effect between treatment periods.

3.4 Rationale for choice of comparator

To characterize the bronchodilator effects of 50 µg and 25 µg doses of NVA237 once daily, a comparison will be made between the different NVA237 doses vs. placebo, when added to background ICS therapy. A placebo arm will add rigor and reduce bias in assessing the study endpoints. It should be noted that at no point in the study will patients be receiving placebo only, it will always be administered in addition to background ICS, and patients will always be provided with rescue medication (short-acting beta-2 agonists, (SABA), such as salbutamol/albuterol) to control symptoms. Patients will be required to abstain from using SABA rescue medication within the 6 hours of spirometric assessments to maintain the scientific integrity related to the determination of the primary endpoint.



3.5 Purpose and timing of interim analyses/design adaptations

Not applicable

3.6 Risks and benefits

The risks to which patients 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 treatment, NVA237.

Patients 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 patients 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 1 week treatment duration, 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 safety laboratory. Puncturing of the veins can cause discomfort, pain, hematoma, or in rare cases lead to an infection.

NVA237 50 µg dose is registered in EU since 2012 as Seebri® Breezhaler® for the treatment of COPD.

The risks of side effects from NVA237 are similar to other anticholinergics such as tiotropium. The most common ($\geq 1/100$ to $< 1/10$) anticholinergic side effect for NVA237 is dry mouth. Other common adverse drug reactions reported with NVA237 in COPD patients include insomnia and gastroenteritis. Atrial fibrillation was an uncommon ($\geq 1/1,000$ to $< 1/100$), but potentially serious adverse drug reaction reported with NVA237 in patients with COPD (also please compare exclusion criteria in [Section 4.2](#)). Please refer to the current NVA237 Investigator's Brochure for more information. Adverse drug reactions reported in individual patients taking other anticholinergic agents include: constipation, increased heart rate, blurred vision, glaucoma, urinary difficulty, and urinary retention. Clinical studies in COPD patients so far conducted with NVA237 have not demonstrated any unexpected safety/tolerability issues beyond those expected for an anticholinergic medication.

NVA237 50 µg in COPD is contraindicated in patients with a hypersensitivity to the active substance or to any of its excipients. Therefore, patients with a history of hypersensitivity to muscarinic antagonist agents, sympathomimetic amines, adrenoreceptor agonist agents, lactose or any of the other excipients of the study drug, or corticosteroids are excluded from participation in this study.

Other "Special warnings and precautions" listed in the Seebri® Breezhaler® EU SmPC are also accounted for in the protocol. Patients with conditions that may be worsened by anticholinergic agents, including narrow-angle glaucoma, urinary retention, or severe renal impairment are excluded from the study along with patients with a history of cardiovascular diseases, history of paradoxical bronchospasm, galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

The co-administration of NVA237 with other anticholinergic-containing medicinal products is not recommended in the EU SmPC and therefore not allowed in the study. In addition, there

are no clinically relevant interactions expected between glycopyrronium and other medicinal products.

Sections 4.3, 4.4, and 4.5 of the current Seebri® Breezhaler® EU SmPC can be referred to for additional information.

There are, however, potentially unknown risks to NVA237, which may be serious and unforeseen.

Altering the current asthma medication regimen of enrolled asthma patients carries a potential risk of de-stabilizing the patient. Patients who cannot tolerate the change in medication regimen are expected to be identified during the Run-in period and if deemed intolerable of the change in medication will not be randomized. In randomized patients the continuous background treatment with ICS throughout the study, the short duration of the trial and the provision of short-acting bronchodilator rescue medication for the entire study duration is considered to provide sufficient risk mitigation for the patients. Regular contacts will occur in terms of clinic visits and telephone contacts to each patient. In addition, safety monitoring (e.g. rescue medication use via electronic diary), assessment of compliance with the study medication regimen and daily PEF measurements throughout the study will help to assess the status of the patient's asthma symptom control. Therefore, investigators may have an early indication of worsening symptoms and will be able to monitor the patient closely throughout the study.

During the study, patients will continue using inhaled corticosteroids and may use their provided rescue medication (short-acting beta-2agonists, provided at the end of Visit 1) until a window of 6 hours before any spirometric assessment.

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria (inclusion/exclusion criteria, see [Sections 4.1](#) and [4.2](#)) and close clinical monitoring. In addition, investigators can withdraw a patient if they feel, based on their medical judgment, that this would be in the best interest of the patient. Patients are also instructed that they can withdraw from the trial at any time, and for any reason.

The potential individual benefit for the patient lies in a thorough medical evaluation of the patient's disease and close clinical monitoring for the duration of the study. This is a research study and although lung function may improve compared to ICS treatment alone it is not expected to provide a significant medical benefit in this short-term study

4 Population

The study population will consist of approximately 144 male and female patients aged between 18 and 65 years with asthma who have been treated in a stable regimen of ICS/LABA for at least 4 weeks prior to screening.

It is anticipated that at least 215 patients will need to be screened (assuming a screening failure rate of 33%) in order to randomize approximately 144 patients. It is intended that approximately 115 patients will complete the study. Dropouts will not be replaced. The study will be a multinational multi-center study.



4.1 Inclusion criteria

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 adult patients aged ≥ 18 to ≤ 65 years
3. Patients with a documented physician diagnosis of asthma for a period of at least 1 year prior to screening, receiving daily treatment of ICS/LABA in a stable regimen for ≥ 4 weeks prior to screening.
4. Pre-bronchodilator FEV₁ of $\geq 50\%$ and $\leq 80\%$ of the predicted normal value for the patient after withholding bronchodilators in accordance with [Table 5-2](#) at Visit 101 and confirmed after Run-in period at Visit 102.
 - Withholding period of bronchodilators prior to spirometry: SABA for ≥ 6 hours and fixed-dose or free combinations of ICS*/LABA for ≥ 48 hours if with b.i.d. LABAs and ≥ 7 days if with o.d. LABAs, SAMA for ≥ 8 hours, LAMA for ≥ 7 days, theophylline for ≥ 7 days

* ICS must be continued.

- A one-time re-testing is allowed only at Visit 101. Re-assessment of percentage predicted FEV₁ 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 FEV₁ of $\geq 12\%$ and ≥ 200 mLs within 30 minutes after inhalation of 400 μg salbutamol/360 μg albuterol during reversibility testing at Visit 101 before entering the Run-in period. Spacer devices are not permitted during reversibility testing.
 - A one-time re-testing is allowed. Re-assessment of reversibility 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.

4.2 Exclusion criteria

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

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.
 - Muscarinic antagonist agents
 - Sympathomimetic amines/adrenoreceptor 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)

- Corticosteroids

2. 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., selective 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 Visit 101 with a resting ventricular rate < 100/min.

3. Resting QTcF \geq 450 ms (male) or \geq 460 ms (female) at Visit 101.

4. 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.

5. 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.

6. 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 30 days after stopping of study medication. 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, (estrogen and progesterone), 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 have been 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) 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.

7. Patients with uncontrolled Type 1 or Type 2 diabetes.
8. Patients who, either in the judgment of the investigator or the responsible Novartis personnel, have a clinically significant condition such as (but not limited to) unstable ischemic heart disease, NYHA Class III/IV heart failure, clinically relevant arrhythmia with exception of rate-controlled persistent atrial fibrillation, uncontrolled hypertension, cerebrovascular 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.
9. Patients with a history of myocardial infarction within the previous 12 months.
10. Patients with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia or bladder-neck obstruction or moderate to severe renal impairment or urinary retention (BPH patients who are stable on treatment can be considered).
11. Patients who have had an asthma exacerbation that required either treatment with systemic corticosteroids for at least 3 days, or an emergency room visit, or hospital treatment within 6 weeks prior to screening Visit 1 and patients with a history of life-threatening asthma attacks (e.g. attacks requiring ventilation)
12. Patients who develop an asthma attack/exacerbation between screening and prior to study drug treatment will not be eligible but may be permitted to be re-screened after a minimum of 6 weeks after the resolution of the asthma exacerbation.
13. Patients who have had a respiratory tract infection within 4 weeks prior to screening.
14. Patients who develop a respiratory tract infection between screening and prior to study drug treatment will not be eligible, but may be permitted to be re-screened 4 weeks after the resolution of the respiratory tract infection.
15. Patients who have smoked or inhaled tobacco products (including electronic cigarettes) within the 6 month period prior to screening, or who have a smoking history of greater than 10 pack years (Note: 10 pack years = 1 pack /day x 10 yrs., or one-half pack/day x 20 yrs.).
16. Patients with any chronic conditions affecting the upper respiratory tract (eg. chronic sinusitis) which in the opinion of the investigator may interfere with the study evaluation or optimal participation in the study.
17. Patients with a history of chronic lung diseases other than asthma, including (but not limited to) chronic obstructive pulmonary disease, bronchiectasis, sarcoidosis, interstitial lung disease, cystic fibrosis, and tuberculosis (unless tuberculosis is confirmed as no longer active by imaging).
18. Patients who have not achieved acceptable spirometry results at Run-in in accordance with ATS/ERS criteria for acceptability and repeatability.
19. Patients receiving any medications in the classes listed in [Table 5-3](#) unless the medication has been stabilized for the specified period and the stated conditions have been met.
20. Patients receiving any asthma related medications in the classes specified in [Table 5-2](#) unless they undergo the required washout period prior to Visit 101 and follow the adjustment to treatment program.

21. Patients on Maintenance Immunotherapy (desensitization) for allergies for at least 3 months prior to Run-in who are expected to change therapy throughout the course of the study.
22. Patients unable to use a dry powder inhaler device.
23. Patients with a known history of non-compliance to medication or who are unable or unwilling to complete a patient diary or who are unable or unwilling to use the Electronic Peak Flow meter.
24. Use of other investigational drugs within 30 days of Visit 101 or 5 half-lives whichever is longer.
25. Patients who during the Run-in period are shown to be intolerable to LABA withdrawal as assessed by investigator (based on patient diary data, PEF during the Run-in period; clinical judgement) or by patient self-assessment
26. History of paradoxical bronchospasm in response to inhaled medicines.
27. Patients who have discontinued LAMA therapy in the past (e.g. due to intolerance or perceived lack of efficacy).
28. Patients in whom the absolute variability in pre-bronchodilator FEV₁ between Visits 101 and 102 is > 20%.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

- NVA237 50 µg capsules for inhalation, delivered via Concept1
- NVA237 25 µg capsules for inhalation, delivered via Concept1
- Placebo capsules for inhalation, delivered via Concept1

NVA237 and matching placebo will be provided as powder filled capsules with a Concept1 inhalation device.

Under no circumstances is an alternative inhalation device to be used for the administration of NVA237 or placebo capsules during the treatment period.

Both NVA237 and placebo will be supplied by Novartis Drug Supply Management in blister packs, providing sufficient quantity of medication to last each patient between visits.

5.1.2 Additional treatment

All patients will be required to have been on a stable ICS/LABA treatment regimen for at least 4 weeks prior to screening. Patients will be switched prior to the start of the Run-in period to the following ICS mono treatment regimen:

- Patients on a low dose of ICS at screening will be switched to an equivalent low dose of budesonide
- Patients on a mid dose of ICS at screening will be switched to an equivalent mid dose of budesonide

- Patients on a high dose of ICS at screening will be switched to an equivalent high dose of budesonide

Any long-acting bronchodilators will be withdrawn during the screening period and patients will receive SABA as rescue medication throughout the trial.

Patients will be instructed not to take any rescue medication within 6 hours prior to any spirometric assessment if possible. If a patient has to use rescue medication within 6 hours prior to any spirometric assessment, the visit has to be rescheduled.

5.2 Treatment arms

Patients will be assigned to one of the following six treatment arms in a ratio of 1:1:1:1:1:1, expecting 24 patients allocated to each of the treatment arms. Each treatment arm consists of 3 treatment periods during which study drug will be administered in the sequence as laid forth in [Table 5-1](#)

Table 5-1 Treatment arms

Treatment arms	Treatment sequence description		
	Period 1	Period 2	Period 3
1	A	B	C
2	A	C	B
3	B	A	C
4	B	C	A
5	C	A	B
6	C	B	A

NVA237 50 µg o.d. is denoted as treatment A
NVA237 25 µg o.d. is denoted as treatment B
Placebo is denoted as treatment C

In this cross-over trial all patients will receive the three study medications in one of the given arms.

All study treatments will be assigned according to the corresponding treatment sequence whilst the patient receives ICS background therapy.

5.3 Treatment assignment and randomization

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

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients/subjects and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system

that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

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

5.4 Treatment blinding

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

- Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study.
- The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration and appearance.
- Unblinding will only occur in the case of patient emergencies (see [Section 5.5.9](#)) and at the conclusion of the study.

Any patient whose treatment code has been broken inadvertently or for any emergency-related or non-emergency reason will be discontinued from the study

5.5 Treating the patient

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

5.5.1 Patient numbering

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

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

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

5.5.2 Dispensing the study drug

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

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to the specific drug contained in that study drug



packaging. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

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

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

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

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

5.5.3.2 Handling of additional treatment

The following non-investigational treatment will be monitored as follows:

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

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

These medications are:

- Salbutamol (100 µg) or albuterol (90 µg) used as rescue medication from Visit 1 to Visit 403
- Budesonide for ICS dose standardization if needed from Visit 1 to Visit 403

Details will be described in the CRF completion guidelines.

5.5.4 Instructions for prescribing and taking study treatment

Patients will be provided with medication as described in [Section 5.1](#).

At Visit 1 all patients will be instructed how to use an inhaler to administer rescue salbutamol/albuterol and ICS (if applicable) correctly. Patients will also be trained how to use the e-diary at Visit 1 and the peak flow meter at Visit 101. At Visit 102 all patients will be fully trained in the correct use of the Concept1 inhaler devices used to administer study medication. Patients who are unable to use either device correctly at Visit 102 will not be eligible to enter the treatment epoch. Additional training devices will be supplied for demonstration purposes. At clinic visits the investigator should check the patient's use of the inhalational devices to ensure correct use of each device. If required, further device training should be provided. Patients will be instructed to contact the site if the device is not functioning properly.

It is important that patients be instructed to take their dose of study medication at approximately the same time every morning.

Instructions for use of the Concept1 inhaler are provided in [Appendix 2](#).

All kits of study treatment assigned by the IRT will be recorded/databased in the IRT.

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

5.5.5 Permitted dose adjustments and interruptions of study treatment

Investigational or other treatment dose adjustments and/or interruptions are not permitted

However if a dose interruption occurs the patient will not be discontinued from the study.

5.5.6 Rescue medication

At Visit 1, all patients will be provided with a short-acting beta-2 agonist (100 µg salbutamol/90 µg albuterol) and they will be instructed to use it throughout the study as rescue medication on an 'as needed basis'. Patients will be advised that between visits they can take their rescue medication for symptoms of intercurrent bronchospasm. Nebulized salbutamol is not allowed as rescue medication throughout the entire trial. No other rescue treatment is permitted.

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

Bronchodilator medications that the patients used prior to Visit 1 must be recorded in the asthma-related prior/concurrent medication page of the eCRF, with the stop date for these bronchodilators recorded as the date of Visit 1. The rescue salbutamol/albuterol provided at Visit 1 for use during the study should NOT be recorded on the asthma-related prior/concurrent medication page of the eCRF. From Visit 1, daily use of rescue medication will be recorded by the patient in their electronic diary.

The rescue salbutamol/albuterol will be provided to the patients by the study center and reimbursed locally by Novartis or supplied to the investigator sites locally by Novartis

5.5.7 Concomitant medication

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

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

5.5.8 Prohibited medication

Use of the treatments displayed in [Table 5-2](#) and [Table 5-3](#) is NOT allowed after screening (unless for the treatment of asthma exacerbations). The specified minimum washout periods prior to the Run-in epoch (Visit 101) or visit 1 are described. Each concomitant drug must be individually assessed against all exclusion criteria and the tables below to see if it is allowed. If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started.

Table 5-2 Prohibited asthma related medication

Medication²	Minimum cessation period prior to Visit 1 or Run in (Visit 101)
Long-acting anticholinergics (LAMA)	7 days prior to Run-in (Visit 101). All patients will be provided with SABA at Visit 1 for use throughout the study.
Short acting anticholinergics (SAMA)	8 hours prior to Run-in (Visit 101).
Fixed combinations of β_2 -agonists and inhaled corticosteroids	Must be discontinued ≥ 48 hours prior to Run-in (Visit 101) if with LABAs b.i.d. and for 7 days if with LABAs o.d. Patients can continue with an ICS until Visit 101 when patients will be switched to their corresponding ICS dose for run-in.
Inhaled corticosteroids	All patients must be treated for asthma with a corresponding dose of budesonide throughout the trial. Any other ICS must be discontinued prior to Run-In (Visit 101)
Fixed combinations of short-acting β_2 -agonist and short-acting anticholinergic	Must be discontinued 8 hours prior to Run-in (Visit 101).

Medication ²	Minimum cessation period prior to Visit 1 or Run in (Visit 101)
Leukotriene Antagonist and leukotriene synthesis inhibitors	7 days prior to Run-in (Visit 101)
Long-acting β_2 -agonists (LABAs)	LABAs b.i.d. must be discontinued 48 hours prior to Run-in (Visit 101). LABAs o.d. must be discontinued ≥ 7 days prior to reversibility testing. All patients will be provided with SABA at Visit 1 for use throughout the study.
Salbutamol/albuterol (SABA) provided at Visit 1 and throughout study as required for rescue medication prn ¹	Must be withheld 6 hours prior to any visit with a spirometric assessment
Short acting β_2 -agonists (SABAs) (other than Salbutamol/albuterol provided at Visit 1 for rescue medication)	Must be discontinued at Visit 1 and are not permitted during the study
Parenteral or oral corticosteroids (systemic corticosteroids are permitted for the treatment of asthma exacerbations)	4 weeks prior to Run-in (Visit 101)
Intra-muscular depot corticosteroids	3 months prior to Run-in (Visit 101)
IgE inhibitors (e.g., omalizumab)	4 months prior to Run-in (Visit 101)
Monoclonal antibodies /other biologics for treatment of asthma	4 months prior to Run-in (Visit 101)
Xanthines (e.g Theophylline)	7 days prior to Run-in (Visit 101)
Systemic mast cell stabilizers e.g cromoglycate, nedocromil, ketotifen	7 days prior to Run-in (Visit 101)
Mucolytic agents not containing bronchodilators	Prohibited unless has been stabilized for at least 4 weeks prior to Visit 1 and will be continued at a stable dose throughout the trial
Intranasal corticosteroids	Prohibited unless taken at a Stable dose for at least 30 days prior to Visit 101 In the case of prn, use is permitted providing an established pattern of use has been documented.
Antihistamines	Prohibited unless has been stabilized for at least 4 weeks prior to Visit 1 and will be continued at a stable dose throughout the trial ¹

¹ SABA (salbutamol/albuterol rescue medication) should be withheld for at least 6 hours prior to spirometry measurements at clinic visits. Clinic visits may be rescheduled to the next day if rescue medication were taken less than 6 hours prior to the spirometry assessments

² This table is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria.

Table 5-3 Other Prohibited medication

Medication	Minimum cessation period prior to Run-in (Visit 101) or as indicated
Non-potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug)	7 days prior to Run-in (Visit 101)
Non-selective systemic β -blocking agents	7 days prior to Run-in (Visit 101)
Cardiac anti-arrhythmics Class Ia	7 days prior to Run-in (Visit 101)
Cardiac anti-arrhythmics Class III	7 days, amiodarone 3 months prior to Run-in (Visit 101)
All antipsychotic agents (first, second and third generation, inclusive of atypical antipsychotics). Combinations of antipsychotic agents with antidepressants are prohibited	14 days prior to Run-in (Visit 101)
Serotonin Noradrenaline Reuptake Inhibitors (SNRIs)	14 days prior to Run-in (Visit 101)
Monoamine-oxidase inhibitors	14 days prior to Run-in (Visit 101)
Systemic anticholinergics	7 days prior to Run-in (Visit 101)
Strong inhibitors of cytochrome P4503A e.g. ketoconazole	7 days prior to Run-in (Visit 101)
Tricyclic antidepressants (Please note that tetracyclics which are similar in class with regards to drug interaction are also to be excluded)	14 days prior to Run-in (Visit 101)
Other investigational drugs	30 days or 5 half-lives, whichever is longer prior to Run-In (Visit 101)
Noradrenaline reuptake inhibitors	7 days prior to Run-in (Visit 101)
Live attenuated vaccine	30 days prior to Run-in (Visit 101)
Topical corticosteroids for treatment of eczema	Prohibited unless used at recommended doses and dosage regimens
Inactivated influenza vaccination, pneumococcal vaccination or any other inactivated vaccine	Not administered within 48 hours prior to a study visit
Pure selective Serotonin Reuptake Inhibitors	Prohibited unless has been stabilized for at least 4 weeks prior to Visit 1 and will be continued at a stable dose throughout the trial

5.5.9 Emergency breaking of assigned treatment code

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

will automatically inform the Novartis monitor for the site and the 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 the IRT code break at any time in case of emergency. The investigator will provide:

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

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

After an emergency break the patient will not continue in the study.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol (Visit 403)

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

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the patient or the investigator.

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

Study treatment must be discontinued under the following circumstances:

- Patient wish
- Pregnancy (see [Section 6.5.6](#) and [7.6](#))
- Use of prohibited treatment as per recommendations in [Table 5-2](#) and [Table 5-3](#)
- Any situation in which study participation might result in a safety risk to the patient
- Patient experiences at least one asthma exacerbation that required treatment with systemic corticosteroids
- Any laboratory abnormalities that, in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study
- Unblinding of study treatment for any reason

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should to be collected at clinic visits or via telephone visits:

- new/concomitant treatments

- Adverse Events/Serious Adverse Events

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule.

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

If a patient/investigator interrupts the treatment during a specific treatment period for other reasons than safety the patient can return for the next treatment period if it is considered adequate by the investigator.

If study drug discontinuation occurs because treatment code has been broken, please refer to [Section 5.5.9](#).

5.6.3 Withdrawal of informed consent

Patients/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 patient:

- 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 patient'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 patient are not allowed unless safety findings require communicating or follow-up.

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

5.6.4 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.



5.6.5 Early study termination by the sponsor

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

6 Visit schedule and assessments

[Table 6-1](#) lists all of the assessments and indicates with an “x” when the visits are performed.

Patients/subjects must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients/subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

When the following assessments are scheduled to be performed at the same timepoint, the order of priority will be as follows:ECG, spirometry, vital signs and samples for urine/hematology/blood chemistry. Spirometry assessments will be performed such that the spirometry measurements occur at the scheduled timepoint and other tests subsequently as close as possible to scheduled timepoints. When an ECG is needed to be taken after spirometry, a 10 minute rest from the end of spirometry to start of ECG assessments should be considered.

Table 6-1 Assessment schedule

Epoch	Screen	Run-in		Treatment (Period 1)						Treatment (Period 2)					Treatment (Period 3)				PSD**		
Visit	1	101	102*	201			202	203		301			302	303		401			402	403	
Day ³	-28 to -21 to 0	1 to 0	1	1	2 to 5	6	7	8	9 to 17	18	19 to 22	23	24	25	26 to 34	35	36 to 39	40	41	42	
Obtain informed consent	x																				
Inclusion/Exclusion Criteria	x	x	x																		
Current Medication review /Adjustment	x																				
Medical History	x																				
Demography	x																				
Smoking History	x																				
Physical Exam	S			S			S		S				S		S			S	S		
Height	x																				
Weight	x																	x	x		
Vital Signs	x			x			x		x				x		x			x	x		
ECG		x		x					x						x				x		
Safety Laboratory assessments (Hematology, Chemistry)		x		x					x						x					x	
Pregnancy test (serum) ¹		x																			
Pregnancy test (urine) ¹	x			x					x						x				x		
Urine analysis (dipstick)		S		S					S						S				S		

Epoch	Screen	Run-in		Treatment (Period 1)						Treatment (Period 2)						Treatment (Period 3)				PSD**	
Visit	1	101	102*	201			202	203		301			302	303		401		402	403		
Day ³	-28 to -21	-21 to 0	1	1	2 to 5	6	7	8	9 to 17	18	19 to 22	23	24	25	26 to 34	35	36 to 39	40	41	42	
Spirometry for eligibility		x	x																		
Spirometry (efficacy and safety assessments)				x			x	x		x			x	x		x	x	x	x		
Randomization				s																	
Device training ²	s	s		s						s						s					
Provide e-Diary	x																				
Provide Peak Flow Meter		x																			
Provide rescue medication	x	x		x			x		x				x		x			x			
Study Drug Administration at site				x			x			x			x			x		x			
Study Drug Administration by patient at home					x	x					x	x				x	x				
Collect unused medication							s						s				s		s	s	
Overnight stay							x						x					x			
Telephone patient 1 day in advance of visit						s							s					s			
Review and upload e-diary recordings			s				s			s			s			s		s		s	

Epoch	Screen	Run-in		Treatment (Period 1)					Treatment (Period 2)					Treatment (Period 3)				PSD**		
Visit	1	101	102*	201		202	203		301		302	303		401		402	403			
Day ³	-28 to -21	-21 to 0	1	1	2 to 5	6	7	8	9 to 17	18	19 to 22	23	24	25	26 to 34	35	36 to 39	40	41	42
AE recordings	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
SAE recordings	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Concomitant Medication recordings	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Study Disposition (Screening)	x																			
Study Disposition (Run-in)			x																	
Study Disposition (Treatment Phase)								x						x			x			

* Visit 102 and Visit 201 will be performed on the same day. Patients are required to repeat the Spirometry for eligibility prior to moving into Visit 201 Treatment.

**, PSD = Premature patient discontinuation to be performed on the same day as discontinuation/withdrawal.

S: these assessments are source documentation only and will not be entered into the eCRF.

X: these assessments are to be reported in the clinical database.

¹ For females of child-bearing potential only. Additional pregnancy testing might be performed if requested by local requirements.

² Device training at Visit 1 and/or Visit 101 is for e-diary/peak flow meter and rescue medication /ICS (if required) inhaler. Device training at Visit 102/201 is for Concept1. The diary is an electronic device to collect information on rescue medication use and to store PEF meter measurements.

³ Day numbering described in the table of assessments is based on the minimum washout period of 10 days at each treatment period.

■

6.1 Information to be collected on screening failures

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

6.2 Patient demographics/other baseline characteristics

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

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

6.3 Treatment exposure and compliance

The time of study treatment administration at each clinic dosing visit (Day 1 and Day 7 of each treatment period) will be collected on the eCRF as well as any dosing interruptions. For assessments where spirometry is performed, the time of dosing is to be taken from the spirometer.

Study treatment compliance should be assessed by the investigator and/or center personnel at all clinic visits. Where necessary, the Investigator will discuss compliance/documentation issues with the patient. The Investigator or designee will collect, from the patient, the used/unused investigational medication and packaging (unused capsules/blister strips and SDDPIs) at Visits 202, 302 and 402 and/or at Premature Patient Discontinuation visit if applicable. Study treatment compliance will be assessed from the capsule count from previously dispensed blister strips for the Concept1. All study treatment dispensed and returned must be recorded in the drug accountability log

6.4 Efficacy

The following efficacy assessments will be performed:

- Spirometry
- PEF recorded in the electronic diary
- Rescue Medication usage recorded in the electronic diary

6.4.1 Spirometry

The following spirometric assessments will be performed:

- Forced expiratory volume in one second (FEV₁)
- Forced Vital Capacity (FVC)

Patients will be admitted to the center in the morning of the last treatment day of each treatment period and stay overnight until the next day to perform the spirometric assessments indicated in [Table 6-2](#).

Site staff will ensure that for each individual patient the last dose of study medication and lung function assessments are done at the same hour of the respective day (+/- one hour) during each treatment period.

Table 6-2 Spirometry timings in relation to study drug administration

Visit (Day)	Spirometry (timing in relation to study drug administration)
Visit 201 (Day 1)	At 45 and 15 min prior to dosing At 30 min -1 h (post dosing)
Visit 202 (Day 7)	15 min prior to dosing 5 min (post dosing) 15 min (post dosing) 30 min (post dosing) 1 h (post dosing) 2 h (post dosing) 4 h (post dosing) 8 h (post dosing)
Visit 203 (Day 8)	23 h 15 min (post dosing) 23 h 45 min (post dosing)
Visit 301 (Day 18)	At 30 min -1 h (post dosing)
Visit 302 (Day 24)	15 min prior to dosing 5 min (post dosing) 15 min (post dosing) 30 min (post dosing) 1 h (post dosing) 2 h (post dosing) 4 h (post dosing) 8 h (post dosing)

Visit (Day)	Spirometry (timing in relation to study drug administration)
Visit 303 (Day 25)	23 h 15 min (post dosing) 23 h 45 min (post dosing)
Visit 401 (Day 35)	At 30 min -1 h (post dosing)
Visit 402 (Day 41)	15 min prior to dosing 5 min (post dosing) 15 min (post dosing) 30 min (post dosing) 1 h (post dosing) 2 h (post dosing) 4 h (post dosing) 8 h (post dosing)
Visit 403 (Day 42)	23 h 15 min (post dosing) 23 h 45 min (post dosing)

Assessments in Table 6-2 are to be performed as close as possible to designated timeframes; however a \pm 5 min window is permitted.

Trough FEV₁ is defined as the mean of the two FEV measurements at 23 hr 15 min and 23 hrs 45 min after the last dose of each treatment period.

6.4.2 Assessments in electronic diary

At visit 1 all patients will be provided with an electronic diary to record rescue medication (salbutamol/albuterol) use and PEF. The patients will be instructed to routinely complete the e-Diary twice daily at the same time in the morning (before taking the study drug) and evening, approximately 12 hours apart. The e-Diary is to be reviewed at each clinic visit until study completion. Sites and patients will receive appropriate training and guidance on the use of the e-Diary device. A list of e-Diary questions is provided in [Appendix 4](#).

6.4.2.1 Peak Expiratory Flow (PEF)

An electronic Peak Flow Meter will be given to each patient at Visit 101 for the measurement of the morning and the evening PEF during the screening and treatment periods.

PEF will be measured at consistent times for a patient: in the morning prior to taking study medication and in the evening. Patients should be encouraged to perform the measurements before the use of any rescue medication. At each timepoint the patient should be instructed to perform 3 consecutive maneuvers within 10 minutes. These PEF values are captured in the e-Diary. The best of 3 values will be used for analysis.

6.4.2.2 Rescue medication usage

The use of rescue salbutamol/albuterol should be recorded by patients in their e-Diary twice a day. In the morning the patients should record the number of puffs of rescue medication they have taken during the night and since the last diary entry, and in the evening patients should record the number of puffs of rescue medication they have taken during the day since the morning diary entry.

6.4.3 Appropriateness of efficacy assessments

The efficacy assessments selected (spirometry, PEF, and recording of rescue medication usage) are standard for this indication/patient population.

6.5 Safety

The following safety assessments will be performed:

- Medical History and physical examination
- Vital signs
- Hematology, blood chemistry and urinalysis
- ECG
- Adverse events including serious adverse events
- Pregnancy test (female patients)

Additional pregnancy testing might be performed if requested by local requirements.

6.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Assessments will be performed as indicated in [Table 6-1](#).

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

6.5.2 Vital signs

Systolic and diastolic blood pressure and radial pulse rate (over a 30 seconds interval), performed in the sitting position will be recorded at each scheduled visits as indicated in [Table 6-1](#). Vital signs should be measured after ECG assessments.

6.5.3 Height and weight

Height and weight will be measured as indicated in [Table 6-1](#). Body weight will be measured in indoor clothing, but without shoes

6.5.4 Laboratory evaluations

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



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

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential counts (neutrophils including bands, lymphocytes, monocytes, eosinophils, basophils), and platelet count will be measured

6.5.4.2 Clinical chemistry

Albumin, alkaline phosphatase, AST (SGOT), ALT (SGPT), bilirubin, creatinine, γ -GT, glucose, potassium, magnesium, BUN and uric acid will be measured.

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

6.5.4.3 Urinalysis

Urine dipsticks will be provided by the central laboratory to the sites for local urinalysis assessments. Dipstick measurements for specific gravity, pH, protein, glucose and blood will be performed.

If the urine dipstick is abnormal, the sample will be sent to central laboratory for additional testing, including assessment of WBC and RBC sediments

6.5.5 Electrocardiogram (ECG)

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. When the ECG recording time coincides with vital signs, spirometry and blood draws the ECG must be performed first, followed by vital signs and blood draws but with enough time planned to ensure the spirometry is performed at the planned timepoint.

A screening ECG will be obtained to confirm eligibility for trial inclusion. At Day 1 of every Treatment period or early discontinuation visit, an ECG will be measured.

Single 12 lead ECGs are collected.

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

Full details of all procedures relating to the ECG collection and reporting will be contained in an investigator manual to be provided by the central laboratory to each investigator site. In the

event that the central cardiologist reports that an ECG is abnormal, the investigator must assess whether the ECG abnormality is clinically significant or not.

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

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

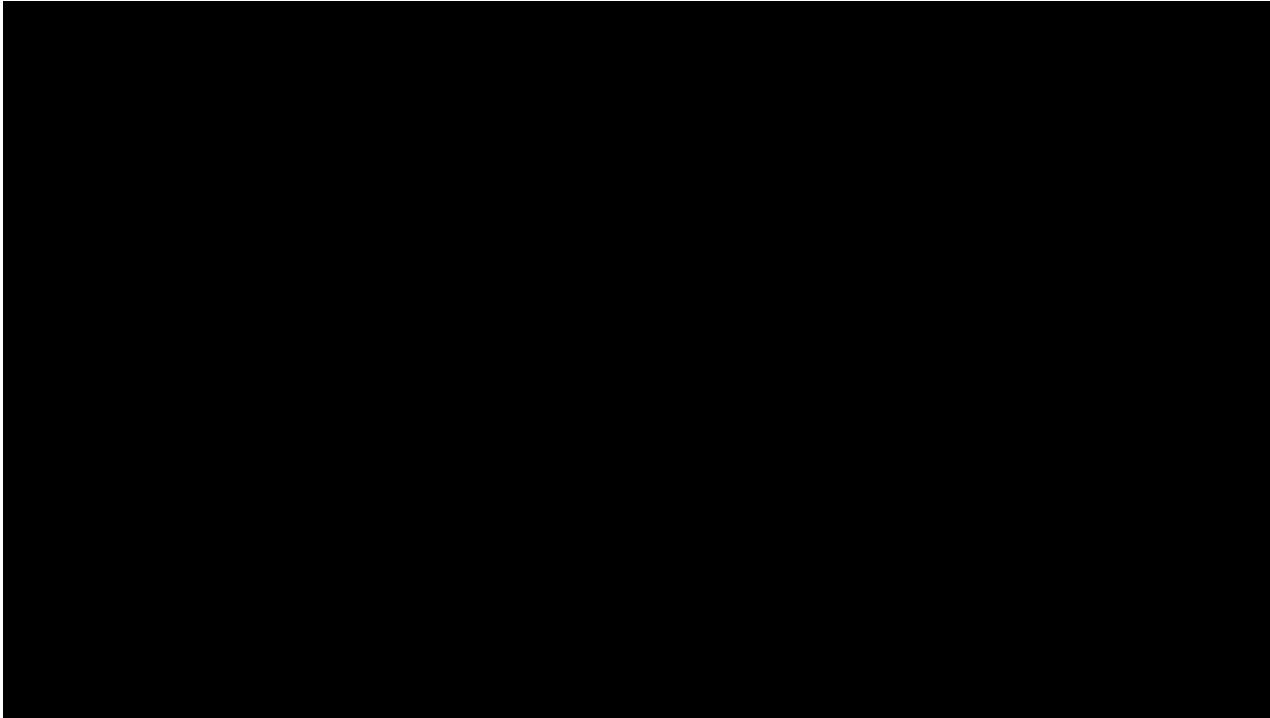
6.5.6 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. A serum and urine pregnancy test will be performed (tests provided by the Central Laboratory) per Assessment schedule [Table 6-1](#). A positive pregnancy test at any time during the study requires the patient to be discontinued from the study treatment. Refer to [Section 7.6](#) for more details.

Additional pregnancy testing can be performed if required by local authorities

6.5.7 Appropriateness of safety measurements

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



7 Safety monitoring

7.1 Adverse events

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



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

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

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

Abnormal laboratory values or test results constitute 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 must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity grade
 - mild: usually transient in nature and generally not interfering with normal activities
 - moderate: sufficiently discomforting to interfere with normal activities
 - severe: prevents normal activities
- its relationship to the study treatment
 - Yes
 - No
- 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 (SAE - See [Section 7.2](#) for 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 increased/reduced
- [investigational] treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given

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

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

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

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

7.2 Serious adverse events

7.2.1 Definition of SAE

An 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 signing the informed consent
 - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
 - social reasons and respite care in the absence of any deterioration in the patient's general condition

- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

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

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to [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 patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to [Annex IV, ICH-E2D Guideline](#)).

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

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

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

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

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the

investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

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

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

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

Please refer to [Appendix 1](#) for complete definitions of liver laboratory triggers and liver events.

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

For the liver laboratory trigger:

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

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

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

For the liver events:

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

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

7.4 Renal safety monitoring

Not required

7.5 Reporting of study treatment errors including misuse/abuse

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

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

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

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

Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse

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

7.6 Pregnancy reporting

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

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

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

8 Data review and database management

8.1 Site monitoring

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

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

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

8.2 Data collection

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

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

database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

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

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

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis.

ECG readings will be processed centrally and the results will be sent electronically to Novartis.

Spirometry readings will be processed centrally and the results will be sent electronically to Novartis.

Diary data will be entered into an electronic diary by the patient. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis personnel.

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

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

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

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

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

9.1 Analysis sets

The following analysis sets are defined for data analysis.

- The Randomized Set (RAN) will consist of all patients who were assigned a randomization number; regardless they actually received study medication. The RAN set will be used for a summary of patient disposition, demographics and baseline characteristics.
- The Full Analysis Set (FAS) will consist of all patients in the RAN who received at least one dose of study medication. Following the intent-to-treat principle, patients in the FAS will be analyzed according to the treatment they were randomized to in the assigned treatment sequence. The FAS will be used in the analysis of all efficacy variables.
- The Per Protocol Set (PPS) will include all patients in the FAS who did not have any protocol deviations that could affect the primary analysis. Rules for complete exclusion of subjects from the PPS, respectively exclusion of subjects' data from single periods will be defined in the Statistical Analysis Plan (SAP) prior to database lock and the un-blinding of the study. Patients in the PPS will be analyzed according to the treatment they actually received. The PPS will be used for supportive analysis and sensitivity analysis to assess robustness of the primary efficacy analysis.
- The Safety Set will consist of all patients who received at least one dose of study medication. Patients in the Safety Set will be analyzed according to treatment received. The Safety Set will be used in the analysis of all safety variables

9.2 Patient demographics and other baseline characteristics

Demographic and baseline characteristics measured before randomization including age, gender, race, ethnicity, height, weight, body mass index (BMI), relevant medical history, screening spirometric parameters (FEV₁, FVC, FEV₁/FVC), FEV₁ reversibility, predicted and percentage of predicted FEV₁, duration of asthma, history of asthma exacerbations, smoking history, prior concurrent medications (non-asthma and asthma-related), vital signs (systolic and diastolic blood pressure, pulse rate) and QTc using Fridericia's correction will be summarized using the Randomized set.

Continuous variables will be summarized using descriptive statistics (n, mean, 25th percentile, median, 75th percentile, standard deviation, minimum and maximum) and categorical variables will be summarized in terms of the number and percentage of patients in each category.

9.3 Treatments

Study drug administration and concomitant medication data will be listed and summarized using the Safety set.

The duration of exposure, the number of patients randomized who completed the treatment period, and who discontinued from study medication will be summarized.

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

Concomitant therapies will be recorded, listed and summarized separately for asthma related medications/non-drug therapies and other medications. Concomitant medications will be tabulated by pre-specified categories, route of administration, and preferred term.

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

9.4 Analysis of the primary variable(s)

9.4.1 Variable(s)

The primary endpoint is the trough FEV₁ (mL) after 1 week of treatment. The trough FEV₁ is defined as the mean of the two FEV₁ values measured at 23 h 15 min and 23 h 45 min post-dose of the last study treatment in a given period. The mean baseline measurement is defined as the average of the FEV₁ values taken in the clinic at 45 and 15 min prior to dosing at Visit 201 (Day 1).

9.4.2 Statistical model, hypothesis, and method of analysis

The following hypotheses will be tested for each of NVA237 doses versus placebo separately:

H₀: There is no difference between NVA237 50 µg and placebo treatment groups in term of the trough FEV₁ after 1 week of treatment

H_{1a}: There is a difference between NVA237 50 µg and placebo treatment groups in term of the trough FEV₁ after 1 week of treatment

H₂₀: There is no difference between NVA237 25 µg and placebo treatment groups in term of the trough FEV₁ after 1 week of treatment

H_{2a}: There is a difference between NVA237 25 µg and placebo treatment groups in term of the trough FEV₁ after 1 week of treatment

The primary endpoint will be analyzed using a linear mixed-effect model. The model will include period, treatment, and sequence as fixed effect factors and baseline trough FEV₁ as a covariate. The within-patient correlation will be modeled using the unstructured covariance matrix. Restricted maximum likelihood method will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. In case of the analysis failing to converge, compound symmetric covariance structure will be used.

The treatment differences of each NVA237 dose versus placebo along with the corresponding 2-sided 95% confidence intervals will be presented.

Each of the primary analyses is performed at the nominal 2-sided 5% level without multiplicity adjustment.

9.4.3 Handling of missing values/censoring/discontinuations

If any of the 23 h 15 min and 23 h 45 min values contributing to the trough FEV₁ are collected within 6 h of rescue medication, or actual measurement times are outside the 22 - 25 hour post-dose time window then the individual FEV₁ value will be set to missing.

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

The model used for the primary variable is based on missing at random mechanism for the missing values and assesses the treatment effects of trough FEV₁ without explicit imputation.

9.4.4 Sensitivity analyses

As a sensitivity analysis a model adding a factor for carry-over could be run to investigate whether relevant carry-over effects were observed

As a sensitivity analysis, the same model used in the primary analysis will be also performed on the PPS to assess the robustness of the results from the primary analyses.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The secondary endpoints obtained from spirometry data are

- Standardized AUC in FEV₁ across different time intervals (5 min – 1 h, 5 min – 4 h, 5 min – 23 h 45 min)
- Peak FEV₁ during 5 min – 4 h.
- FVC and FEV₁/FVC at day 7

Further secondary endpoints obtained from the e-diary data are:

- PEF pre-dose morning and evening
- Number of rescue puffs during the previous night and during the day

The same model used in the primary analysis will be used for the above secondary endpoints from spirometry data and from the e-Diary data except to include the appropriate baseline covariate

9.5.2 Safety variables

All safety parameters will be summarized on the safety set.

Adverse events

All study emergent adverse events will be summarized and listed. 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 a treatment 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 following 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.

The number and percentage of patients with the most frequent AEs will be summarized by treatment.

Electrocardiogram (ECG) and vital signs

Data from the electrocardiogram will be listed by treatment.

Vital signs (blood pressure and radial pulse rate) will be listed.

QTc will be calculated from the QT interval and RR (in seconds) using Fridericia's formula: $QTc = QT / 3\sqrt[3]{RR}$, where $3\sqrt[3]{}$ denotes the cube root.

Laboratory data

All laboratory data will be listed with abnormal values being flagged.

9.6 Interim analyses

No interim analyses are planned for this study.

9.7 Sample size calculation

The assumptions to support the sample size calculations were based on 7 historical cross-over studies: NVA237A2205, NVA237A2208, QVA149A2210, QMF149A2202, GSK study HZA113310 (clinicaltrials.gov nr. NCT00980200) and the dose ranging studies with Tiotropium ([Beeh et al., 2014](#)) and Umeclidinium ([Lee et al., 2015](#)).

The two doses of interest were investigated in studies NVA237A2205 and NVA237A2208. The mean treatment estimates observed in these studies suggest that a treatment difference to Placebo of at least 100 mL in trough FEV₁ could be expected after treatment with glycopyrronium bromide 50 µg o.d. and a treatment difference to Placebo of around 70 mL and up to 90 mL could be expected after treatment with glycopyrronium bromide 25 µg o.d. This is considered conservative estimates as both studies were conducted in COPD patients and asthma patients may be expected to show larger treatment effects.

The within subject standard deviations observed in the above mentioned 7 studies varied substantially between 102 mL and 237 mL. Only those historical studies with a similar patient population were considered (i.e. excluding the Umeclidinium study which enrolled mild asthmatics). This resulted in a standard deviation of 209 mL being used for powering the current study.



Randomizing 144 subjects and assuming a drop-out rate of up to 20% (i.e. 115 subjects completing the study) the power for the comparison of glycopyrronium bromide 50 µg o.d. with Placebo on a 2-sided 5% level would be 95%. For the comparison of glycopyrronium bromide 25 µg o.d. with Placebo the power would be 71% assuming a true underlying treatment difference of 70mL and 90% for an underlying difference of 90 mL. The sample size was calculated via simulation in a program written in R3.2.2.

No adjustment for multiple comparisons is made.

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

Eligible patients/subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

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

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 in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.



10.3 Responsibilities of the investigator and IRB/IEC

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

10.4 Publication of study protocol and results

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

10.5 Quality Control and Quality Assurance

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

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

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

11 Protocol adherence

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

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis

and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

11.1 Protocol amendments

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



12 References

References are available upon request

Annex IV, ICH-E2D Guideline. Available from www.ich.org

[[Beasley R \(2004\)](#)] The Global Burden of Asthma Report, Global Initiative for Asthma (GINA). Available from www.ginasthma.org

[[Beeh KM et al \(2014\)](#)] Tiotropium Respimat® in asthma: a double-blind randomized, dose-ranging study in adult patients with moderate asthma. *Respiratory Research*; 15:61

[[Chin SJ et al \(2016\)](#)] Tiotropium Respimat Is Effective for the Treatment of Asthma at a Dose Lower Than That for Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc*. 13(2):173-9.

[[European Medicines Agency \(2013\)](#)] Note for guidance on clinical investigation of medicinal products for treatment of asthma. CHMP/EWP/2922/01-rev.1.

[[Global Initiative for Asthma \(GINA\) \(2015\)](#)] Global Strategy for Asthma Management and Prevention. Available from <http://ginasthma.org>

[[Kerstjens HAM et al \(2012\)](#)] Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med*; 367:1198-207.

[[Kerstjens HAM et al \(2015\)](#)] Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials. *Lancet Respir Med*. 2015 May;3(5):367-76.

[[Lee LA et al \(2015\)](#)] A randomized, three-period cross-over study of umeclidinium as monotherapy in adult patients with asthma. *Respiratory Med*;109:63-73.

[[Peters SP et al \(2010\)](#)] Tiotropium bromide as step-up therapy for adults with uncontrolled asthma. *N Engl J Med*; 363(18): 1715-26.

[[Quanjer PH et al \(1993\)](#)] Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J*; 6 suppl. 16: 5-40.

13 Appendices

Appendix 1: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 13-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	<ul style="list-style-type: none"> • $3 \times \text{ULN} < \text{ALT} / \text{AST} \leq 5 \times \text{ULN}$ • $1.5 \times \text{ULN} < \text{TBL} \leq 2 \times \text{ULN}$
LIVER EVENTS	<ul style="list-style-type: none"> • ALT or AST $> 5 \times \text{ULN}$ • ALP $> 2 \times \text{ULN}$ (in the absence of known bone pathology) • TBL $> 2 \times \text{ULN}$ (in the absence of known Gilbert syndrome) • ALT or AST $> 3 \times \text{ULN}$ and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST $> 3 \times \text{ULN}$ and TBL $> 2 \times \text{ULN}$ [mainly conjugated fraction] without notable increase in ALP to $> 2 \times \text{ULN}$) • Any clinical event of jaundice (or equivalent term) • ALT or AST $> 3 \times \text{ULN}$ accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

TBL: total bilirubin; ULN: upper limit of normal

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

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case ^a	<ul style="list-style-type: none"> • Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF 	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution ^c (frequency at investigator discretion)
ALT or AST		
$> 8 \times \text{ULN}$	<ul style="list-style-type: none"> • Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF 	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution ^c (frequency at investigator discretion)
$> 3 \times \text{ULN}$ and INR > 1.5	<ul style="list-style-type: none"> • Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF 	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution ^c (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 5 to \leq 8 \times ULN	<ul style="list-style-type: none"> Repeat LFT within 48 hours If elevation persists, continue follow-up monitoring If elevation persists for more than 2 weeks, discontinue the study drug Establish causality Complete liver CRF 	ALT, AST, TBL, Alb, PT/INR, ALP and γ GT until resolution ^c (frequency at investigator discretion)
> 3 \times ULN accompanied by symptoms ^b	<ul style="list-style-type: none"> Discontinue the study treatment immediately Hospitalize if clinically appropriate Establish causality Complete liver CRF 	ALT, AST, TBL, Alb, PT/INR, ALP and γ GT until resolution ^c (frequency at investigator discretion)
> 3 to \leq 5 \times ULN (patient is asymptomatic)	<ul style="list-style-type: none"> Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient 	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 \times ULN (in the absence of known bone pathology)	<ul style="list-style-type: none"> Repeat LFT within 48 hours If elevation persists, establish causality Complete liver CRF 	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 \times ULN (in the absence of known Gilbert syndrome)	<ul style="list-style-type: none"> Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver CRF 	ALT, AST, TBL, Alb, PT/INR, ALP and γ GT until resolution ^c (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to \leq 2 \times ULN (patient is asymptomatic)	<ul style="list-style-type: none"> Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient 	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	<ul style="list-style-type: none"> Discontinue the study treatment immediately Hospitalize the patient Establish causality Complete liver CRF 	ALT, AST, TBL, Alb, PT/INR, ALP and γ GT until resolution ^c (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	<ul style="list-style-type: none"> Consider study treatment interruption or discontinuation Hospitalization if clinically appropriate Establish causality Complete liver CRF 	Investigator discretion

^aElevated ALT/AST > 3 \times ULN and TBL > 2 \times ULN but without notable increase in ALP to > 2 \times ULN

^b(General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

^cResolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

Appendix 2 Instructions for using inhaler and capsules.

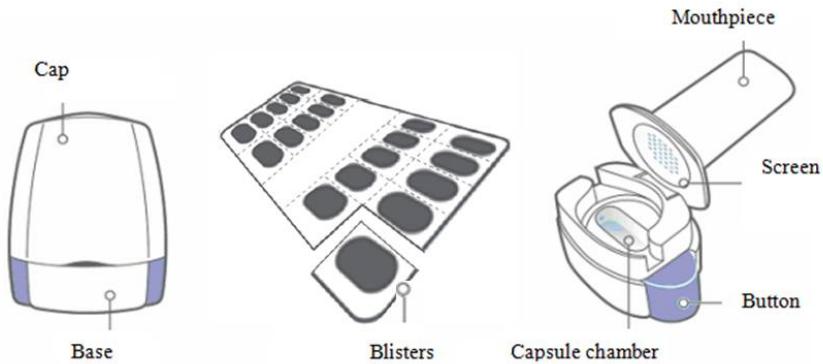
Do not swallow capsules.

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

Your inhaler and capsules

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

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



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

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

How to use your inhaler

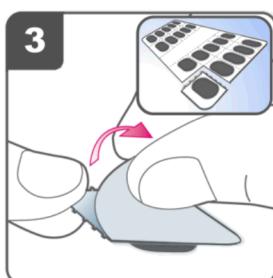


Pull off cap.



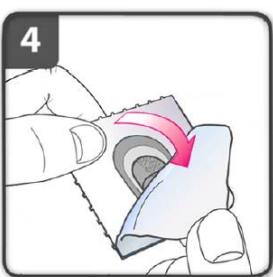
Open inhaler:

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



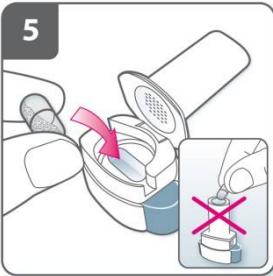
Prepare capsule:

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



Remove a capsule:

Peel away the foil and remove the capsule from the blister.



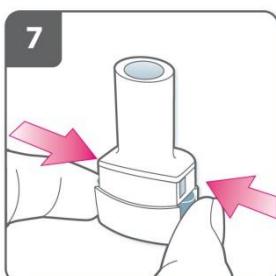
Insert capsule:

Place the capsule into the capsule chamber.

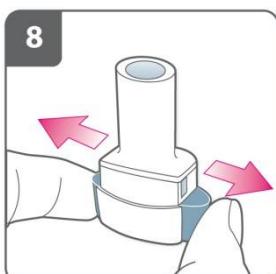
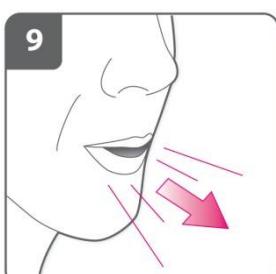
Never place a capsule directly into the mouthpiece.

**Close the inhaler:**

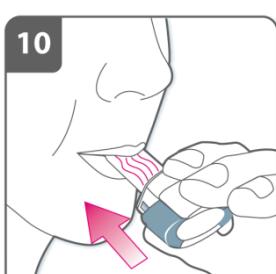
You should hear a “click” as the mouthpiece closes onto the inhaler base.

**Pierce the capsule:**

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

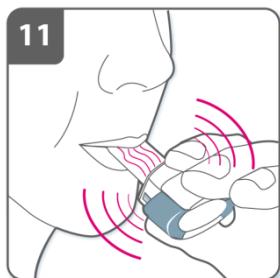
**Release the side buttons fully.****Breathe out:**

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

Do not blow into the mouthpiece.**Inhale the medicine**

To breathe the medicine deeply into your airways:

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

**Note:**

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

Additional information

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

If you do not hear a whirring noise:

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

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

Hold breath:

After you have inhaled the medicine:

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

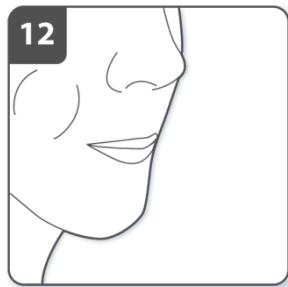
If there is powder left in the capsule:

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

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

Additional information

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



**After you have finished taking your medicine:**

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

Do not store the capsules in the inhaler.

REMEMBER:

- Do not swallow capsules.
- Only use the inhaler contained in this pack.
- Capsules must always be stored in the blister, and only removed immediately before use.
- Never place a capsule directly into the mouthpiece of the inhaler.
- Do not press the side buttons more than once.
- Never blow into the mouthpiece of the inhaler.
- Always release the push buttons before inhalation.
- Never wash the inhaler with water. Keep it dry. See "How to clean your inhaler".
- Never take the inhaler apart.
- Always use the new inhaler that comes with your new medication pack.
- Do not store the capsules in the inhaler.
- Always keep the inhaler and capsules in a dry place, and avoid very hot or cold temperatures.

How to clean your inhaler

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

Appendix 3 Spirometry Guidance

Equipment

Spirometers must meet the specifications and performance criteria recommended in the American Thoracic Society (ATS)/European Respiratory Society (ERS) Standardization of Spirometry¹. Spirometers must have the capacity to print FVC tracings. All spirometry values should be reported at BTPS by the method established by the manufacturer.

Calibration

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

Preparing the test subject

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

- Coffee, tea, chocolate, cola and other caffeine-containing beverages and foods and ice-cold beverages for 4 hours prior to spirometry
- Alcohol for 4 hours prior to spirometry
- Strenuous activity for 12 hours prior to spirometry
- Smoking within at least 1 hour of testing
- Exposure to environmental smoke, dust or areas with strong odors

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

Performing Spirometry

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

Number of trials

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

Acceptability

An acceptable maneuver has the following characteristics:

- No hesitation or false start;
- A rapid start;
- No cough, especially during the first second of the maneuver;
- No glottic closure or obstruction by tongue or dentures
- No early termination of exhalation (minimum exhalation time of 6 seconds is recommended, or no volume change for at least 1 second) or the subject cannot continue to exhale further

Repeatability

The 2 largest FVC and FEV₁ values from 3 acceptable maneuvers should not vary by more than 0.150 L.

Recording of data

The highest FEV₁ and FVC from any of the acceptable curves are recorded. (The highest FEV₁ and FVC may not necessarily result from the same acceptable curve).

Predicted normal

This study will utilize the spirometric predication equation standards as described by the ERS Global Lung Function Initiative (GLI)² or Japanese Respiratory Society³. Further details will be provided in a specification document for the central spirometry assessments.

Reversibility

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

Administer 400 µg of salbutamol/360 µg albuterol following the completion of the baseline assessment. A second spirometry assessment is then performed within 30 minutes after administration of the salbutamol/albuterol.

Reversibility is calculated as:

$$100 \times \frac{\text{FEV}_1(\text{post } \beta_2\text{-agonists}) - \text{FEV}_1(\text{baseline})}{\text{FEV}_1(\text{baseline})}$$

Subjects will be considered reversible if an increase of at least 12% (and 200 mL) is demonstrated after administration of the bronchodilator.

References

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

² Quanjer PH, et al. ERS Global Lung Function Initiative, Multi ethnic reference values for spirometry for the 3-95 year age range: the global lung function 2012 equations. Report of the Global Lung Function Initiative (GLI). ERS Task Force to establish improved Lung Function Reference Values. Eur Respir J 2012; 40: 1324-1343.

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

Appendix 4 Patient Asthma Control e-Diary

(For illustrative purposes only)

The following information will be captured:

In the MORNING	In the EVENING
Peak expiratory flow rate	
Number of puffs of rescue medication during the past 12 hours	
	Peak expiratory flow rate
	Number of puffs of rescue medication during the past 12 hours

Appendix 5 ICS Dose level

Table 13-3 Low, medium and high Daily Doses of Inhaled Glucocorticosteroids for Adults and adolescents (12 years and older) (GINA 2015)

Drug	Total Daily Dose (µg/day)		
	Low	Medium	High
Beclomethasone dipropionate – CFC*	200-500	> 500 -- 1000	> 1000
Beclomethasone dipropionate – HFA	100-200	> 200 -- 400	> 400
Budesonide- DPI	200-400	> 400 – 800	> 800
Ciclesonide – HFA	80-160	> 160 – 320	> 320
Fluticasone propionate – DPI	100-250	> 250 – 500	> 500
Fluticasone propionate – HFA	100-250	> 250 – 500	> 500
Mometasone furoate	110-220	> 220-440	≥ 440
Triamcinolone acetonide	400-1000	> 1000 -- 2000	> 2000

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant.

* Beclomethasone dipropionate CHF is included for comparison with older literature.