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QMF149

Clinical Trial Protocol CQMF149G2203 / NCT04589663

An open-label, two-period, single-sequence, crossover study to compare the systemic exposure of a single inhaled dose of mometasone furoate (MF) when administered alone via the MF Twisthaler® (TH) to a single inhaled dose of QMF149 indacaterol acetate/MF fixed dose combination when administered via the Concept 1 (Breezhaler®) device in ≥ 6 to <12 year old asthma patients

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List of abbreviations

AAMH	Australian Asthma Management Handbook
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Antinuclear antibody
ASMA	Anti-smooth muscle antibodies
AST	Aspartate Aminotransferase
AV	atrioventricular
b.i.d.	bis in die/twice a day
BUN	Blood Urea Nitrogen
C1	Concept 1 (Breezhaler®)
CD	Carbohydrate-deficient
CDS	Core Data Sheet
CFR	US Code of Federal Regulations
CHF	Congestive heart failure
CK	Creatinine Kinase
CMV	Cytomegalovirus
CO	Country Organization
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTT	Clinical Trial Team
CV	coefficient of variation
CVD	Cardiovascular disease
CYP3A	Cytochrome P450 3A
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
DOB	Date of Birth
DRF	Dose Range Finding
EBV	Epstein-Barr virus
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDD	Expected Delivery Date
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
ERCP	Endoscopic Retrograde Cholangiopancreatography
eSource	Electronic Source
FDC	Fixed dose combinations
FPF	fine particle fraction
FPM	fine particle mass

[redacted]

GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GINA	Global Initiative for Asthma
GLDH	Glutamate dehydrogenase
h	Hour
HAV	Hepatitis A virus
HBc	Hepatitis B core
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HEV	Hepatitis E virus
HSV	Herpes simplex virus
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICON	International Consensus On pediatric asthma
ICS	Inhaled corticosteroid
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
LABA	Long Acting ß-Agonist
LAMA	Long Acting Muscarinic Antagonist
LC-MS/MS	Liquid Chromatography-Mass Spectrometry/Mass Spectrometry
LFT	Liver function test
LLOQ	lower limit of quantification
LTRA	Leukotriene Receptor Antagonist
MCV	Mean Corpuscular Volume
MDDPI	multi-dose dry powder inhaler
MedDRA	Medical dictionary for regulatory activities
MF	Mometasone furoate
mg	milligram(s)
mL	milliliter(s)
MMWR	Morbidity and Mortality Weekly Report
MRI	Magnetic resonance imaging

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NAEPP	National Asthma Education and Prevention Program
NIH	National Institutes of Health
OTC	Over-the-counter
PK	Pharmacokinetic(s)
PT	prothrombin time
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
R Value	ALT/ALP x ULN
RBC	red blood cell(s)
RNA	Ribonucleic acid
SABA	short-acting ß-agonist
SAE	Serious Adverse Event
SAMA	Short-acting anti-muscarinic
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	standard deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SIGN	Scottish Intercollegiate Guidelines Network
SoC	Standard of care
SUSAR	Suspected Unexpected Serious Adverse Reaction
T3	Triiodothyronine
T4	Thyroxine
TBL	Total bilirubin
TH	Twisthaler®
TSH	Thyroid stimulating hormone
UDDPI	Unit dose dry powder inhaler
ULN	upper limit of normal
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent
γ-GT	Gamma-glutamyl transferase
COVID-19	Coronavirus Disease
IND	Indacaterol

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Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) 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
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)

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Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Run-in Failure	A participant who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to participant's intervention or other treatment)
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

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Amendment 1

Amendment rationale

The protocol is being amended to correct the details regarding the Lab assessments, blood sampling and to include the early termination visit assessment details.

Changes to the protocol

The following changes will be implemented in the protocol:

- Section 8: The details have been modified to specify the reference to early termination visit column in assessment table.
- Table 8-1: Additional column for early termination visit included to maintain consistency with Section 9.1.1 of protocol which states early termination visit would be performed in case of discontinuation.
- Table 8-3: Included 'sodium' as additional parameter for Chemistry assessment.
- Section 8.5.1: Updated EDTA tubes to Lithium Heparin tubes for Blood collection for IND analysis.
- Table 16-4: Updated the Blood volume.
- Table 16-5: Updated the table to include assessment details of early termination visit.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through for deletions and underlining for insertions.

An opportunity was also taken to make smaller changes such as some minor editorial changes that include correction of typographical errors and some clarifications in wording and acronyms.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Protocol summary

Protocol number	CQMF149G2203

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Full Title	An open-label, two-period, single-sequence, crossover study to compare the systemic exposure of a single inhaled dose of mometasone furoate (MF) when administered alone via the MF Twisthaler® (TH) to a single inhaled dose of QMF149 indacaterol acetate/MF fixed dose combination when administered via the Concept 1 (Breezhaler®) device in ≥ 6 to <12 year old asthma patients
Brief title	This study in pediatric patients with asthma ages ≥ 6 to < 12 years of age compares the pharmacokinetics of mometasone furoate administered alone and in fixed dose combination with indacaterol.
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug; Device: Inhaled dose of mometasone furoate (MF) via MF Twisthaler® (TH), inhaled dose of QMF149 indacaterol acetate/MF fixed dose combination via the Concept 1 Breezhaler® (C1) device
Study type	Interventional
Purpose and rationale	The measurement of systemic exposure to MF delivered by either TH or C1 (in combination with indacaterol) is expected to provide an appropriate assessment of drug delivery to the lungs to support dose selection of MF as part of QMF149. This study will confirm the comparability of mometasone exposure between two formulations and support the QMF149 pediatric development program.
Primary Objective(s)	To compare the systemic exposure of MF resulting from single doses of MF when administered as MF TH 100 µg versus QMF149 75/40 µg C1.
Secondary Objectives	To determine safety and tolerability of QMF149 C1 following its single dose administration in pediatric patients with asthma. To determine the systemic exposure of indacaterol following single dose administration as QMF149 C1.
Study design	This is an open-label, two-period, single-sequence crossover study including 2 single dose treatments of MF TH 100 µg and QMF149 75/40 µg with a washout of at least 4 days between the two treatments. The study will enroll approximately 32 patients with the aim of having 24 completers. The study will include the following: • A screening period of up to 14 days • Two single-dose treatments separated by a 4-7 day washout period (4 days is the minimum washout) • A 30-day investigational drug-free follow-up period
Study population	Approximately 32 male or female children ≥ 6 years and <12 years diagnosed with asthma will be screened, 24 study completers are required for analysis unless interim analysis determines otherwise.
Inclusion criteria	1. Male and female children ≥ 6 years and < 12 years at the time of study entry. 2. Written informed consent by parent(s)/legal guardian(s) for the pediatric patient and assent by the pediatric patient (depending on local

	requirements) must be obtained before any study-specific assessment is performed. 3. Confirmed documented diagnosis of asthma, as defined by national or international asthma guidelines for at least 6 months prior to study enrollment. 4. Patients using low dose ICS as asthma controller therapy for at least 4 weeks prior to first treatment. 5. Patients who are familiar with the use of an inhaler device. 6. Patients must be able to comply with the Study Visit Assessment Schedule which includes approximately 7 hours on two occasions, and agree to blood draws as scheduled. 7. Parents/ legal guardian must be willing and able to attend study visits and assist the child with the procedures outlined in the protocol.
Exclusion criteria	1. Use of other investigational drugs within 5 half-lives of enrollment, or [within 30 days (for small molecules) /until the expected pharmacodynamic effect has returned to baseline (for biologics)], whichever is longer. 2. Patients with weight < 17kg at screening. 3. Patients currently taking MF products for any reason at least 7 days prior to Day 1. Patients can enroll if MF was discontinued at least 7 days prior to Day 1 and MF is substituted with a different steroid during entire study duration to avoid its potential impact on PK assessment. These MF products include inhalation, topical and/or nasal spray formulations. 4. Patients on medium- and high- dose ICS or any dose ICS/LABA combination. 5. Patients taking maintenance controller therapy (eg LABAs and theophylline) within 4 weeks of screening or during the study as outlined in Section 6.2. LTRAs are permitted provided that patients have been on a stable dose for 4 weeks prior to screening. Patients using short-acting bronchodilators on occasional basis as rescue medication can enroll, however, these medications must be withheld at least 8 hours prior to study dosing visits and during PK sampling (please refer to Table 6-2). 6. 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 there of: • Adrenoreceptor agonist agent • Lactose or any of the other excipients of the study drug (including patients with history of galactose intolerance, lactase deficiency or glucose-galactose malabsorption) • Corticosteroids • Indacaterol and/or MF 7. History of chronic lung disease other than asthma within 3 months of first treatment visit (Day 1), cystic fibrosis, mycobacterial or other infection (including active SARS-CoV-2, tuberculosis or atypical mycobacterial disease). 8. History of active bacterial, viral or fungal infection (including SARS-CoV-2) within 6 weeks of first treatment visit (Day 1). 9. Patients who have had an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit within 6 weeks of first treatment visit (Day 1).

	10. Patients who, in the opinion of the investigator, are not able to comply with study treatment or who have any medical or mental disorder, situation, or diagnosis, which could interfere with the proper completion of the study protocol requirements or pose a safety risk while participating in the study. 11. Parent/guardian has a history of psychiatric disease, intellectual deficiency, substance abuse, or other condition (e.g. inability to read, comprehend and write) which will limit the validity of consent for their child to participate in this study. 12. Hemoglobin levels outside normal ranges at screening. 13. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the patient in case of participation in the study. 14. Patients who have a clinically significant ECG abnormality or clinically significant abnormal lab values reported at Screening Visit. 15. Patients with a history of long QT syndrome or whose corrected QT interval (QTc) measured at Screening Visit (Fridericia method) is prolonged (≥ 450 msec for males and females 6 - 12 years old). 16. Use of any prescription drugs, herbal supplements, prescribed medicinal use of cannabis/marijuana, within four weeks prior to initial dosing, and/or over-the-counter (OTC) medication, dietary supplements within two weeks prior to initial dosing. If needed, (i.e. an incidental and limited need) paracetamol/acetaminophen is acceptable, but must be documented in the Concomitant medications / Significant non-drug therapies page of the CRF. 17. History of malignancy of any organ system, treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases. 18. Patient is an immediate family member of the participating investigator, sub-investigator, study coordinator, or employee of the participating investigator. 19. Pregnant or nursing (lactating) females. 20. Inability to properly train in the use of the In-Check DIAL® at screening (at the investigator's discretion). 21. Inability to properly train in the use of the Twisthaler® or Concept 1 Breezhaler® prior to dosing (at the investigator's discretion). 22. History of paradoxical bronchospasm in response to inhaled medicines. 23. Patients receiving any medications in the classes specified in Table 6-2 unless they undergo the required washout period prior to Day 1. 24. Patients who are sexually active.
Study treatment	Treatment A: MF Twisthaler® 100 µg Treatment B: QMF149 Concept 1 Breezhaler® (indacaterol acetate 75 µg/MF 40 µg)
Efficacy assessments	None
Pharmacodynamic assessments	None

[redacted]

Pharmacokinetic assessments	The following parameters will be calculated for MF • AUC0-6h • Cmax • Tmax • AUCinf • Lambda_z • T1/2 • CL/F • Vz/F
Key safety assessments	Adverse event monitoring, physical examinations, monitoring of laboratory markers in blood and urine, ECG.
Data analysis	The primary objective is to compare the systemic exposure to MF resulting from single doses of MF when administered as MF TH 100 µg versus QMF149 75/40 µg C1. Log-transformed PK parameters Cmax and AUC(0-6h) will be analyzed for mometasone furoate by linear fixed effects model with treatment and patient as fixed effect. The estimated mean and 90% confidence interval of treatment difference of test vs. reference (QMF149 vs. MF) will be back transformed to obtain the geometric mean and 90% confidence intervals of the ratio.
Interim analysis	An interim analysis is planned to be performed when 12 patients complete both study treatments and there are at least 3 completers in each of the two age groups ≥ 6 to < 9 year olds and ≥ 9 to < 12 year olds. The interim analysis will be based on preliminary PK and safety data.
Key words	QMF149, pediatric, asthma, PK, Twisthaler®, Concept 1, Breezhaler®

[redacted]

1 Introduction

1.1 Background

Asthma is a chronic inflammatory disorder of the airways associated with hyper-responsiveness of airways that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction within the lung that is often reversible either spontaneously or with treatment. Airflow limitation occurs as a result of obstruction or narrowing of the airways when exposed to precipitating factors. Although exacerbations of asthma are episodic, inflammation is chronic (GINA 2019). Asthma is defined by its clinical, physiological, and pathobiological characteristics.

The wide clinical spectrum of asthma is highly variable, and although different cellular patterns have been observed in asthmatic airways, the presence of airway inflammation remains a consistent feature. Despite persistent airway inflammation, asthma symptoms are episodic and the relationship between the intensity of inflammation and the severity of asthma is not clearly established. In most patients, the inflammation affects all airways including the upper respiratory tract and nose, but the physiological effects are most pronounced in medium-sized bronchi. Despite the cellular heterogeneity of inflammatory response, the pattern of inflammation in the airways appears to be similar in all clinical forms of asthma at all ages, whether allergic, non-allergic, or aspirin-induced (GINA 2019). Asthma most often starts early in life and has variable courses and unstable phenotypes which may progress or remit over time. Despite advances in medical management, childhood asthma continues to be a leading cause of emergency department visits, hospitalizations, and school days missed. Children afflicted with uncontrolled asthma have difficulty exercising, sleeping, and participating in the normal activities of childhood (Runge and Hill 2009).

Asthma is the most common childhood chronic disease (Bastain et al 2011) and its prevalence has increased especially among children (GINA 2019). Children under 18 years represent one-third of all asthmatics according to the MMWR Surveillance summary - National surveillance for asthma 1980 to 2004 (United States) (Moorman et al 2007), with data showing that the incidence and prevalence of asthma is increasing more rapidly in children than that in adults, particularly in children under 15 years (Masoli et al 2004). Due to this high impact of asthma on the quality of life of pediatric patients and caregivers, as well as it's costs, several guidelines exist to support clinical care of pediatric asthmatics.

Two types of medications are used to treat asthma: long-term control (“prevention”) medications and quick-relief medications, which reverse acute airflow obstruction. All children who have persistent asthma should be started on a long-term control (“prevention”) medication. Such anti-inflammatory medications are taken daily to reduce airway inflammation. The recommended type and dose of long-term control medication depends on the level of asthma severity and the age of the child. For persistent asthma, these guidelines recommend stepwise intensification of asthma controller medications. Combinations of different controller medications are recommended as preferred treatment options by various guidelines (NIH, GINA, ICON).

[redacted]

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

QMF149 is a fixed-dose combination (FDC) of indacaterol acetate (inhaled LABA with 24 hour duration of action) and mometasone furoate (MF, ICS). QMF149 is approved as maintenance treatment of asthma in adults and adolescents 12 years of age and older not adequately controlled with inhaled corticosteroids and inhaled short acting beta2 agonists. There are three approved dose strengths of QMF in adult and adolescent patients with asthma: 150/80 µg, 150/160 µg, 150/320 µg. A pediatric dose of QMF149 75/40 µg delivered via Concept 1 device is currently being developed as a unit dose dry powder inhaler for children 6 to <12 years of age. The individual components of QMF149 are approved medications: indacaterol as the maleate salt for the treatment of chronic obstructive pulmonary disease (COPD) in adults, and MF for the use in asthma in adult and 4-11 year old pediatric patients (Asmanex Twisthaler®).

Studies CQMF149E2203 and CQAB149B2357 evaluated indacaterol acetate and maleate, respectively delivered via the Concept 1 (Breezhaler®) inhaler in patients with asthma. These two studies support selection of indacaterol dose 150 µg once daily in the adult and adolescent population.

Study CQMF149G2202 in children ≥ 6 years and < 12 years showed that indacaterol acetate (QAB149) 75 µg and 150 µg o.d. doses delivered via Concept 1 inhaler with background ICS therapy demonstrated clinically meaningful improvements in Trough FEV1 after 14 days of treatment. Both doses were well tolerated and no new or unexpected safety signals were observed in the study. Systemic exposure at the 75 µg dose was lower than that observed at the 150 µg dose in adults from other studies, while the 150µg dose in 6-11 year olds was higher than that observed in adults. Overall, the data supported 75 µg as reasonable dose for further evaluation in Phase III.

MF TH 100 µg is a metered dose dry powder inhaler approved as Asmanex Twisthaler®[1] for 4-11 yr old asthma patients.

Fraction of an aerosol containing particles < 5 µm in diameter is termed the fine particle fraction (FPF), and is widely used to describe the potential of an aerosol for delivery to the lower respiratory tract (Dolovich 2000). The fine particle mass (FPM), is the mass portion of the nominal dose (i.e. nominal dose × FPF), which is considered to be delivered to the lungs. MF dose for QMF149 75/40 µg is matched in terms of its FPM (in vitro lung dose) at the corresponding 100 µg MF TH. Systemic availability of MF following oral inhalation is solely due to absorption from lungs since oral bioavailability of MF is low. The FPM of mometasone furoate in QMF149 75/40 µg is matched with MF TH 100 µg. Comparisons of QMF149 75/40 µg delivered via C1 versus MF TH 100 µg in the proposed PK study would compare lung dose

[redacted]

of MF between both formulations and build confidence in dose selection of MF in QMF149 75/40 µg based on data in patient population. Results from the study will provide opportunity to re-evaluate doses/formulation if needed before proceeding to a larger Phase III study in children.

[1] A single dose of the Asmanex Twisthaler® contains 110 µg of mometasone furoate delivering 100 µg of mometasone furoate from the inhaler mouthpiece following actuation.

1.2 Purpose

The purpose of this study is to assess the dose exposure of MF as part of QMF149 Concept 1 that provides systemic exposure comparable to that for the approved dose of MF TH 100 µg in pediatric asthma patients (≥ 6 to < 12 years of age). The safety and tolerability of single orally inhaled doses of QMF149 75/40 µg will also be evaluated when administered via the Concept 1 in this age group. The selected dose will then be studied in a QMF149 Phase III pediatric study.

2 Objectives and endpoints

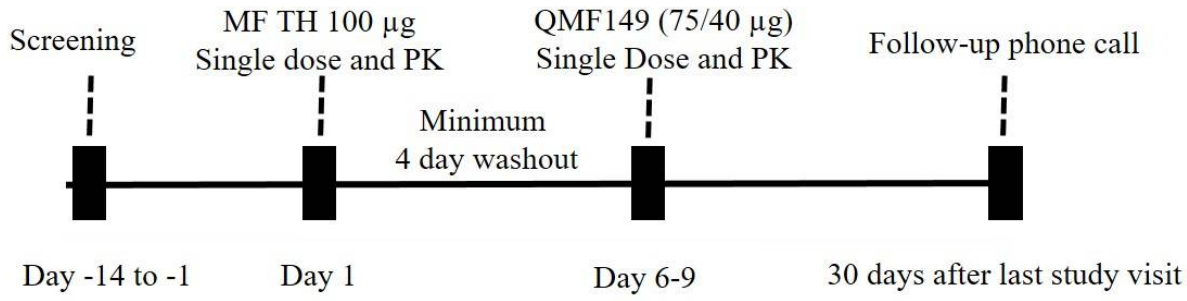
Table 2-1 Objectives and related endpoints

Objective(s)	**Endpoint(s)**
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To compare the systemic exposure of mometasone furoate resulting from single orally inhaled doses of QMF149 75/40 µg administered via the Concept 1 unit dose dry powder inhaler versus the MF Twisthaler® 100 µg metered dose dry powder inhaler in pediatric asthma patients (≥ 6 to < 12 years of age).	• PK parameters (AUC0-6h and Cmax) of MF after single dose administration of QMF149 75/40 µg C1 and MF Twisthaler® (100 µg).
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the systemic exposure of indacaterol resulting from single orally inhaled doses of QMF149 75/40 µg.	• Systemic exposure of indacaterol after single dose administration of QMF149 75/40 µg.
• To evaluate the safety and tolerability of QMF149 75/40 µg after single dose administration in pediatric patients.	• Adverse Events, Serious Adverse Events and defined safety assessments.

3 Study design

[redacted]

Figure 3-1



3.1.1 Study design

This is an open-label, two-period, single-sequence, crossover study to assess the pharmacokinetics, safety and tolerability of single inhaled doses of mometasone furoate (MF) when administered alone via MF Twisthaler® (TH) or as an indacaterol acetate/MF fixed dose combination (QMF149) via the Concept 1 (C1) device in ≥ 6 to <12 year old asthma patients. The study includes two open-label single-dose treatment visits. On the first treatment visit (Day 1) patients receive a single inhaled dose of 100 µg MF administered via the Twisthaler® device. On the second treatment visit (Day 6) patients receive a single inhaled dose of 75/40 µg indacaterol acetate/MF fixed dose combination (QMF149). Both treatments are in addition to their rescue medication and potentially SoC asthma therapy (excluding MF and indacaterol acetate).

Patients currently taking low-dose ICS asthma medications other than MF can enroll in the study. However, since the patients will be provided MF or QMF149 as part of study treatment on Day 1 and Day 6 respectively, patients should be instructed not to take low-dose ICS medication on the 2 treatment days.

The study will include the following:

- A screening period of up to 14 days
- Two single-dose treatment periods separated by a 4-7 day washout period (4 days is minimum washout)
- A 30-day investigational drug-free follow-up period

4 Rationale

4.1 Rationale for study design

This is an open-label, two-period, single-sequence, crossover study in 24 asthma patients aged ≥ 6 to <12 years. The trial is designed to compare the systemic exposure of single inhaled doses of mometasone furoate (MF) when administered alone as MF TH 100 µg or as an indacaterol acetate/MF fixed dose combination (QMF149 75/40 µg) via the Concept 1 (C1) device.

Blood samples for assessment of MF concentrations will be collected from pre-dose to 6 hours after each dose of MF TH or QMF149 C1. Based on data in CQMF149E2101, blood collection up to 6 hours is considered adequate since the MF PK parameter AUC0-6h is projected to be

approximately 40-50% of AUC0-24h after single inhalation dose of MF TH or QMF149 Concept 1. This provides reasonable data for comparison of the two formulations. Since the Tmax of MF is approximately 1h post inhalation dose of MF TH or QMF149 C1, the planned PK sampling schedule allows reliable assessment of Cmax for comparative assessment of both formulations.

Single-dose assessment is preferred as it is a more sensitive marker to measure bioavailability. The crossover study design is favored to assess relative bioavailability between two formulations as each patient serves as his/her own matched control, thereby requiring fewer patients to attain the same level of statistical power or precision as a parallel design. Single-sequence crossover design including administration of MF TH in the first treatment period followed by QMF149 administration in the second treatment period enables a shorter washout duration of 4 days based on MF T1/2 (mean: 12-13 hr) following MF administration via TH or C1 in adult healthy volunteers.

This study planned in ≥ 6 to < 12 years old pediatric asthma patients will confirm the comaparability of mometasome exposure between two formulations and support the QMF149 pediatric development program. Due to ethical considerations, healthy volunteers in this pediatric age group are not being considered. A study in adult healthy volunteers was not considered due to the difficulty in extrapolation of PK data of inhaled therapies from adults to pediatric patients resulting from differences in inhalation pattern, lung and airway geometry, and surface area between both age groups.

4.1.1 Rationale for choice of background therapy

Patients may continue to receive their background asthma therapy (e.g. low dose ICS) throughout the study . Since the purpose of the study is to assess PK, safety and tolerability of QMF149 there is no need to alter the background medication (with the exception of mometasone furoate and those listed on Table 6-2). Background treatments of low dose ICS are not anticipated to have potential for drug-drug interaction with either QMF149 or MF TH. Strong CYP3A inhibitor or inducer medications should be discontinued at least 7 days prior to both study treatments. Further information on prohibited medications are outlined in Table 6-2.

4.2 Rationale for dose/regimen and duration of treatment

QMF149 75/40 µg is a fixed dose combination of indacaterol 75 µg and mometasone furoate 40 µg intended for children (≥ 6 - < 12 years old) and planned for testing in Phase 3 study. While the 75 µg dose level of indacaterol was determined from a DRF study (QMF149G2202), the 40 µg dose level for MF is planned based on equivalent lung dose of QMF149 C1 to MF TH 100 µg. MF TH 100 µg is used as a comparator to QMF149 C1 for evaluation of systemic exposure of mometasone.

A single-dose assessment is preferred as it is a more sensitive marker to measure bioavailability. Mouth rinsing is recommended to reduce the potential incidence of oral candidiasis in the presence of MF. A washout duration of at least 4 days allows complete washout of MF concentrations prior to subsequent QMF149 treatment based on a mean T1/2 of 12-13 hr. following MF administration via TH or C1 in adult healthy volunteers (Study QMF149E2101).

[redacted]

As noted the single-sequence crossover design including administration of MF TH in the first treatment period followed by QMF149 administration in the second treatment period enables a shorter washout duration of 4 days between treatments.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Placebo control is not required as it does not support the primary pharmacokinetic endpoint.

4.4 Purpose and timing of interim analyses/design adaptations

A planned interim analysis (IA) will be conducted to support decision making when 12 patients have completed both treatment visits (MF TH 100 µg and QMF149 75/40 µg) with all planned PK and safety data collected. There must be at least 3 patients within each age strata ≥ 6 to < 9 years and ≥ 9 to < 12 years for the IA to occur. At interim analysis, PK data and safety data will be assessed and a decision will be made to either stop the study or proceed forward to full recruitment. This decision will depend on the ability to confirm the MF dose, or if more data is needed (possibly due to study performance, e.g., the need for better patient training).

For detailed information, refer to Section 12.7

4.5 Risks and benefits

This is a single-dose study evaluating the phamacokinetics and safety of MF from MF TH and QMF149; there are no efficacy evaluations being assessed in this study. Assessing the pharmacokinetic profile is an important step in establishing overall benefit/risk for the pediatric population.

The risk to patients in this trial will be minimized by compliance with the eligibility criteria and by close clinical monitoring.

Data from this study will confirm if the MF dose in the QMF149 pediatric formulation is similar to the approved MF TH pediatric dose (100 µg daily). The confirmed dose will be used to support the QMF149 pediatric development program allowing for the evaluation of efficacy in a larger pediatric population.

QMF149 150/80 µg, QMF149 150/160 µg, and QMF149 150/320 µg strengths have been approved for use in adult and adolescent asthma patients (QVM149B2301 and QVM149B2303) and the risk to pediatric patients exposed to QMF149 75/40 µg in this study is considered low. Inhaled doses of 75µg and 150 µg/day of indacaterol administered via the Concept 1 device for 14 days were well tolerated (CQMF149G2202) in ≥ 6 to <12 year old asthma patients and MF TH 100 µg is already approved as a maintenance treatment of asthma in this pediatric patient population. In the studies mentioned above, risks associated with indacaterol were consistent with what is known in the LABA class.

LABA treatments used alone without ICS in asthma may cause severe asthma exacerbations. This safety concern is mitigated in the study as LABA alone will not be allowed to the patients and instead it is administered together with ICS MF as a FDC product QMF149.

[redacted]

Potential safety risk to pediatric patients in the study is minimized by using a single dose inhalation of QMF149 75/40 µg for assessment of MF pharmacokinetic profile and by adherence to the inclusion/exclusion criteria and close clinical monitoring of vital signs on day of dosing and safety follow up. Patients may continue to receive their background asthma therapy (with the exception of those listed in Table 6-2)

For female patients of childbearing potential refer to Section 8.4.3.

The risks of side effects are well characterized in adult and adolescent population with asthma from the QMF149 studies mentioned above. Investigators should withdraw a patient if they feel, based on their medical judgment, that this would be best for the patient, or after occurrence of any of the discontinuation criteria listed in Section 9.1.1.

There is no placebo arm, which mitigates risk of under-treatment.

Pediatric patients participating in the trial may have a small risk of oral and esophageal candidiasis (thrush), a known adverse effect of MF. The risk of this will be minimized by rinsing of the oral cavity after each dosing. Systemic effects may occur with inhaled corticosteroids, particularly at high doses prescribed for prolonged periods while the present study is prescribing a single dose of QMF149 and MF. These effects are much less likely to occur than with oral corticosteroids and may vary in individual patients and between different corticosteroid preparations.

Asthma patients may be at higher risk of complications from the SARS-CoV-2 infection. Since this study requires clinic visits there maybe an increased risk for transmission of SARS-CoV-2. Clinical sites must take all necessary hygienic measures to avoid infection.

5 Study Population

The study population will consist of 24 male or female children ≥ 6 years and < 12 years of age with a documented diagnosis of asthma for at least 6 months prior to study enrollment. Patients may use rescue medication (e.g., SABA) with or without asthma controller therapy. It is intended that approximately 32 patients will need to be enrolled to yield 24 patients who each complete the 2 dosing PK collection study visits. Dropouts and non-completers will be replaced if needed. Patients will be stratified into two age groups; ≥ 6 to < 9 years and ≥ 9 to < 12 years (at least 6 patients in each of the two age groups) to ensure approximate equal enrollment and PK assessment across the entire desired age range.

5.1 Inclusion criteria

Patients eligible for inclusion in this study must meet **all** of the following criteria:

1. Male and female children ≥ 6 years and < 12 years at the time of study entry.
2. Written informed consent by parent(s)/legal guardian(s) for the pediatric patient and assent by the pediatric patient (depending on local requirements) must be obtained before any study-specific assessment is performed.
3. Confirmed documented diagnosis of asthma, as defined by national or international asthma guidelines for at least 6 months prior to study enrollment.

[redacted]

4. Patients using low-dose ICS as asthma controller therapy for at least 4 weeks prior to first treatment.
5. Patients who are familiar with the use of inhaler device.
6. Patients must be able to comply with the Study Visit Assessment Schedule which includes approximately 7 hours on two occasions, and agree to blood draws as scheduled.
7. Parents/ legal guardian must be willing and able to attend study visits and assist the child with the procedures outlined in the protocol.

5.2 Exclusion criteria

Patients meeting any of the following criteria are not eligible for inclusion in this study.

1. Use of other investigational drugs within 5 half-lives of enrollment, or [within 30 days (for small molecules) /until the expected pharmacodynamic effect has returned to baseline (for biologics)], whichever is longer.
2. Patients with weight < 17kg at screening.
3. Patients currently taking MF products for any reason at least 7 days prior to Day 1. Patients can enroll if MF was discontinued at least 7 days prior to Day 1 and MF is substituted with a different steroid during entire study duration to avoid its potential impact on PK assessment. These MF products include inhalation, topical and/or nasal spray formulations.
4. Patients on medium- and high- dose ICS or any dose ICS/LABA combination.
5. Patients taking maintenance controller therapy (eg LABAs and theophylline) within 4 weeks of screening or during the study as outlined in Section 6.2. LTRAs are permitted provided that patients have been on a stable dose for 4 weeks prior to screening. Patients using short-acting bronchodilators on occasional basis as rescue medication can enroll, however, these medications must be withheld at least 8 hours prior to study dosing visits and during PK sampling (please refer to Table 6-2).
6. 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 there of:
   - Adrenoreceptor agonist agent
   - Lactose or any of the other excipients of the study drug (including patients with history of galactose intolerance, lactase deficiency or glucose-galactose malabsorption)
   - Corticosteroids
   - Indacaterol and/or MF
7. History of chronic lung disease other than asthma within 3 months of first treatment visit (Day 1), cystic fibrosis, mycobacterial or other infection (including active SARS-CoV-2, tuberculosis or atypical mycobacterial disease).
8. History of active bacterial, viral or fungal infection (including SARS-CoV-2) within 6 weeks of first treatment visit (Day 1).
9. Patients who have had an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit within 6 weeks of first treatment visit (Day 1).

[redacted]

10. Patients who, in the opinion of the investigator, are not able to comply with study treatment or who have any medical or mental disorder, situation, or diagnosis, which could interfere with the proper completion of the study protocol requirements or pose a safety risk while participating in the study.
11. Parent/guardian has a history of psychiatric disease, intellectual deficiency, substance abuse, or other condition (e.g. inability to read, comprehend and write) which will limit the validity of consent for their child to participate in this study
12. Hemoglobin levels outside normal ranges at screening.
13. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the patient in case of participation in the study.
14. Patients who have a clinically significant ECG abnormality or clinically significant abnormal lab values reported at Screening Visit.
15. Patients with a history of long QT syndrome or whose corrected QT interval (QTc) measured at Screening Visit (Fridericia method) is prolonged (≥ 450 msec for males and females 6 - 12 years old).
16. Use of any prescription drugs, herbal supplements, prescribed medicinal use of cannabis/marijuana, within four weeks prior to initial dosing, and/or over-the-counter (OTC) medication, dietary supplements within two weeks prior to initial dosing. If needed, (i.e. an incidental and limited need) paracetamol/acetaminophen is acceptable, but must be documented in the Concomitant medications / Significant non-drug therapies page of the CRF.
17. History of malignancy of any organ system, treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
18. Patient is an immediate family member of the participating investigator, sub-investigator, study coordinator, or employee of the participating investigator.
19. Pregnant or nursing (lactating) females.
20. Inability to properly train in the use of the In-Check DIAL® at screening (at the investigator's discretion)
21. Inability to properly train in the use of the Twisthaler® or Concept1 Breezhaler® prior to dosing (at the investigator's discretion).
22. History of paradoxical bronchospasm in response to inhaled medicines.
23. Patients receiving any medications in the classes specified in Table 6-2 unless they undergo the required washout period prior to Day 1.
24. Patients who are sexually active.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

[redacted]

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	**Pharmaceutical Dosage Form**	**Route of Administration**	**Presentation**	**Sponsor (global or local)**
QMF149 75/40 µg	Capsule for Inhalation	Oral inhalation	Open-label blister delivered via C1 device (Breezhaler®)	Sponsor (global)
Mometasone fuorate 110[1] µg	Dry Powder Inhalation	Oral inhalation	Open-label Twisthaler® (metered dose inhaler)	Sponsor (global)

[1] A single dose of the Asmanex Twisthaler® contains 110 µg of mometasone furoate delivering 100 µg of mometasone furoate from the inhaler mouthpiece following single actuation.

The Twisthaler® inhaler is a multi-dose dry powder inhaler (MDDPI), with all doses pre-loaded in the device. The Concept 1 Breezhaler® device is a unit dose dry powder inhaler (UDDPI), which requires loading of the dose prior to each use. The following medication/devices will be prepared by Novartis and supplied to the Investigator as open labeled medication:

- Treatment A: Mometasone furoate delivered via Twisthaler®inhaler, (MF 100µg TH)
- Treatment B: Fixed dose combination of 75 µg indacaterol acetate and 40 µg mometasone furoate delivered as powder in hard capsules via Concept1 Breezhaler® inhaler (QMF149 75/40 µg C1)

Under no circumstances is an alternative inhalation device to be used for the administration of either study medication during the treatment period. Additionally, the use of spacers is not permitted in this study.

Study medication should be administered to patients in the morning between the hours of 07:00 am and 12:00 noon, on Days 1 and 6. After inhalation of study medication, patients should rinse their mouth with water. Water used for mouth rinsing should be spat out and NOT swallowed. Patients are encouraged to consume a small snack approximately 1 hour post-dose and a meal approximately 4 hours post-dose. Snack and meal times should be recorded on the CRF and food content should be recorded in source documents.

On the day of screening (Screening Visit), patients will be instructed to inhale through the In-Check DIAL® inhalation training device which will simulate inhalation resistance from the Asmanex Twisthaler® and C1 Breezhaler® devices. On treatment Day 1, patients will be trained in the use of MF Twisthaler® (Asmanex) device with a training Twisthaler® device which does not contain inhalation powder. On Treatment Day 6, patients will be trained on the use of C1 (Breezhaler®) device loaded with an empty capsule which does not contain inhalation powder.

[redacted]

All inhalation device training should be documented in source. Training with inhalation devices at Days 1 and 6 will be followed by actual study drug administration.

The devices containing study medication that will be used for dosing will be IRT assigned. At the investigator's discretion, patients who cannot demonstrate an appropriate inhalation maneuver at the screening visit should not be enrolled in the study. Patients will be instructed by study personnel on the correct inhalation technique and dosing instructions for the device. Dosing will be supervised by the site personnel. Study drug supply and dispensation instructions are provided in Section 6.1.3. Instructions for inhalation training and use of both the Twisthaler® and the Concept 1 devices are provided in the QMF149G2203 Patient Inhalation Training, Device Training and Study Drug Administration Manual.

6.1.2 Additional study treatments

No other study treatment beyond MF 100 µg Twisthaler® and QMF149 75/40 µg C1 Breezhaler® are included in this trial.

6.1.3 Supply of study treatment

MF TH 100 will be supplied by Novartis and labeled in accordance to local country requirements. QMF149 75/40 µg will be supplied by Novartis and labeled in accordance to local country requirements.

Day 6 study medication QMF149 75/40 µg (administered using the C1 device) must be stored under refrigeration. This dose must be brought to room temperature at least one hour prior to patient dosing.

6.1.4 Treatment arms/group

All patients will receive an inhaled single dose of MF TH 100 µg on Day 1 and an inhaled single dose of QMF149 75/40 µg on Day 6 .

6.1.5 Treatment duration

The planned treatment is 1 treatment, single dose each for MF 100 µg TH and QMF149 75/40 µg. For patients that discontinue from treatment, refer to Section 9.1.1.

6.2 Other treatment(s)

No additional treatment beyond investigational drug is included in this trial. Patients may continue to use asthma rescue medication and SoC asthma therapy as outlined in the inclusion criteria.

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered within 30-days prior to enrolment and after the patient was enrolled into the study must be recorded on the appropriate Case Report Forms.

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

[redacted]

assigning the study treatment to patient or allowing a new medication to be started. If the patient is already enrolled, contact Novartis to determine if the patient should continue participation in the study.

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

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Prohibited asthma-related medications, as listed in Table 6-2, must not be taken during the study. The specified minimum washout periods are described in Table 6-2. Each concomitant drug must be individually assessed against all exclusion criteria and the tables below to see if it is allowed. If in doubt, the investigator should contact the medical monitor before including a patient or allowing a new medication to be started.

6.2.2 Prohibited medication

Use of the treatments displayed in the below table are either prohibited or allowed only under certain conditions.

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

Table 6-2 Prohibited medications

Prohibited Medication	Instruction
Fixed combinations of short-acting β2-agonist and short-acting anticholinergics	Must be discontinued at least 8 hours prior to dosing on treatment day 1.
Medium and high-dose ICS and ICS/LABA combinations	Patients taking these treatments are excluded per Exclusion 4 (Section 5.2)
Asthma maintenance controller therapies (e.g. LABAs and theophylline)	Patients taking these medications within 4 weeks of screening or during the study are excluded per Exclusion 5 (Section 5.2)
Salbutamol/albuterol (SABA) and Short-acting anti-muscarinic (SAMA)	It should be noted that SABA and SAMA are permitted at screening and between dosing visits, as required for rescue medication. **SABA/SAMA must be withheld at least 8 hours prior to study dosing visits and during PK sampling. If SABA/SAMA is taken within 8 hours of a clinic visit, the clinic should be notified and the visit rescheduled.**
Inhaled, topical, or nasal steroid therapies containing MF (investigator to provide alternative medications)	Must be discontinued at least 7 days prior to dosing on treatment day 1
Any drug with the potential to prolong QT Interval	14 days or 5 half-lives, whichever is longer prior to dosing visits

[redacted]

Prohibited Medication	Instruction
Strong inhibitors and inducers of cytochrome CYP3A	7 days prior to dosing visits
Noradrenaline reuptake inhibitors	7 days prior to dosing visits
Other investigational drugs	30 days or 5 half-lives, whichever is longer prior to dosing visits

6.2.3 Rescue medication

It should be noted that SABA and SAMA are permitted at screening and between dosing visits, as required for rescue medication.

SABA/SAMA must be withheld at least 8 hours prior to study dosing visits and during PK sampling. If SABA/SAMA is taken within 8 hours of a clinic visit, the clinic should be notified and the visit rescheduled.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is enrolled for screening and is retained for the patient throughout his/her participation in the trial. A new Patient No. will be assigned at every subsequent enrollment if the patient is re-screened. The Patient No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential Patient Number suffixed to it, so that each patient's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Patient No. available.

A new ICF/patient assent will need to be signed if the investigator chooses to re-screen the patient after a patient has screen failed, and the patient will be assigned a new Patient No.

6.3.2 Treatment assignment, randomization

Patient randomization will not be performed in this open-label study. The assignment of a patient to a particular age strata will be coordinated by the sponsor via IRT.

6.4 Treatment blinding

Treatment will be open to patients, investigator staff, persons performing the assessments, and the CTT.

6.5 Dose escalation and dose modification

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

6.5.1 Dose modifications

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

[redacted]

6.5.2 Follow-up for toxicities

6.5.2.1 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with total bilirubin increase may be indicative of potentially severe DILI, and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and total bilirubin value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and total bilirubin value at baseline: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN
- For patients with elevated AST or ALT or total bilirubin value at baseline: [AST or ALT > 2 x baseline] OR [AST or ALT >300 U/L] whichever occurs first combined with [total bilirubin > 2 x baseline AND > 2.0 x ULN]

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before DILI is assumed as the cause of liver injury.

A detailed history, including relevant information such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR, alkaline phosphatase, albumin, and creatine kinase. If available, testing of Glutamate Dehydrogenase (GLDH) is additionally recommended.

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury. For children, there are caveats to calculating the R-ratio as normal levels of ALP are higher than in adults with standard ranges varying by developmental age. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury.

Table 6-3 provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT abnormalities.

Table 6-3 Hepatic Disease Assessment

Disease	Assesment
Hepatitis A, B, C, E	• IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV

[redacted]

Disease	Assesment
Autoimmune hepatitis	• Antinuclear Antibodies (ANA) & Anti-Smooth Muscle Antibody (ASMA) titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic Congestive heart failure, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	• Ceruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

Other causes should also be considered based upon participants' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; Cardiovascular Disease / ischemic hepatitis – ECG, prior hypotensive episodes; Type 1 diabetes / glycogenic hepatitis).

Following appropriate causality assessments, as outlined above, the causality of the treatment is estimated as "probable" i.e. >50% likely, if it appears greater than all other possible causes of liver injury combined. The term "treatment-induced" indicates *probably caused* by the treatment, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant," and thus, meet the definition of SAE and should be reported as SAE using the term "potential treatment-induced liver injury." All events should be followed up with the outcome clearly documented.

Refer to Section 10.2.1 for further liver safety monitoring.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Treatment in this study will only be given on-site under the supervision of study site staff. Pharmacokinetic parameters (measures of treatment exposure) will be determined in all patients treated with both MF 100 µg Twisthaler® and QMF149 75/40 µg C1 Breezhaler®, as detailed in Pharmacokinetics Section 8.5.1.

6.6.2 Recommended treatment of adverse events

Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

6.7 Preparation and dispensation

Each study site will be supplied with packed study drug as described under investigational and control drugs section (Section 6.1.1).

[redacted]

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the patient by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document. QMF149 75/40 µg is stored refrigerated at 5°C+/- 3°C. This medication kit has to be taken out of the refrigerator a minimum 1 hour in advance of inhalation to allow medication and Concept 1 device to equilibrate to room temperature. Asmanex Twisthaler® 100 mcg is stored in accordance to the labeled storage condition, "Do not store above 25°C. Do not refrigerate. Do not freeze. Protect from moisture".

Study site staff should refer to QMF149G2203 Patient Inhalation Training and Study Drug Administration Manual in preparation for inhalation training and study medication administration.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 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 designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels or in the Investigator's Brochure. QMF149 75/40 µg will be delivered refrigerated at 5°C+/- 3°C. The medication kit must be removed from refrigeration at least 1 hour in advance of administration allowing the medication and Concept 1 device to equilibirate to room temperature. Asmanex Twisthaler® 100 mcg must be stored according to the labeled storage condition, "Do not store above 25°C. Do not refrigerate. Do not freeze. Protect from moisture." Asmanex Twisthaler® 100 mcg is delivered in a carton box containing the inhaler in an aluminum foil pouch. This protective pouch should be opened only on the day of dosing.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO 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.

After use both inhalation devices should be stored at the site until the conclusion of the study. At the conclusion 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.

[redacted]

6.7.2 Instruction for prescribing and taking study treatment

Patients will be instructed to come to the study center accounting for an appropriate amount of time to complete inhalation training and predosing assessments prior to study drug administration. On Day 6 the clinical site needs to ensure QMF149 75/40 µg will be removed from refrigeration and brought to room temperature at least one hour prior to patient dosing.

It should be noted that SABA and SAMA are permitted at screening and between dosing visits, as required for rescue medication.

SABA/SAMA must be withheld at least 8 hours prior to study dosing visits and during PK sampling. If SABA/SAMA is taken within 8 hours of a clinic visit, the clinic should be notified and the visit rescheduled.

Patients currently taking low-dose ICS asthma medications other than MF are permitted to enroll in the study however these patients should be instructed not to take low-dose ICS medication on the two treatment days since MF or QMF149 will be provided as part of study treatment on Day 1 and Day 6 respectively. Patients taking medium and/or high dose ICS are excluded from the study.

After inhalation of study drug patients should rinse their mouth with water. Water used for mouth rinsing should be spat out and NOT swallowed. If after inhalation of study drug the patient sneezes, coughs, vomits or exhibits rejection of inhaled study drug, the event and timing relative to dosing must be documented in source. Patients who have not received or retained a full dose of study drug cannot be re-dosed during a study visit and should be discontinued.

All patients will be trained in the use of Concept 1 and Twisthaler® devices per QMF149G2203 Patient Inhalation Training and Study Drug Administration Manual. Patients must demonstrate correct use of both inhalation devices prior to study medication dosing. Inhalation training devices will be supplied by Novartis. On both treatment days, the study drug will be administered at the study center, after completion of all pre-dose procedures. The date and time of dose administration of study drug at each site visit will be recorded on the Dosage Administration Record CRF.

7 Informed consent procedures

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

In cases where the patient's representative(s) 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

[redacted]

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.

Female patients 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.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) (and/or CDS for marketed drugs). 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 investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the patient/parent(s)/guardian(s).

The following informed consents are included in this study:

- Main study consent (parental/guardian consent)
- Patient assent, which also includes as applicable:
  - Pregnancy Outcomes Reporting Consent for female patient

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

Patients should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed in the Early Termination visit column of the assessment schedule table will be performed. At this final visit all adverse event and concomitant medications should be recorded on the CRF.

For patients already started Day 1, the COVID 19 pandemic (or any other reason) may limit or prevent an on-site study visit(s). These patients should be discontinued and a phone or virtual visit will occur for safety monitoring and discussion of the patient´s health status including 30 days safety follow up. If the patient can attend the Early Termination visit after Day 1, safety monitoring, discussion of the patient´s health status, and urine pregnancy test (dipstick) should be performed as the early termination visit, then 30 days safety follow up will be performed.

Refer to Section 9.1.1 for study discontinuation.

[redacted]

Table 8-1 Assessment Schedule

Period	**Screening**	**Treatment**		**Early Termination**	**Follow Up**
Visit Name	**Screening**	**Day 1**	**Day 6**		**Day 36**[1]
Days	**-14 to -1**	**1**	**6 -0 +3**	**-**	**36**
Obtain parental Informed Consent / patient assent (if applicable)	X				
Register Patient and Visit in IRT	X	X	X		
Demography	X				
Inclusion / Exclusion criteria[2]	X	X			
Medical history/current medical conditions	X				
Prior/ concomitant medication review	X	X	X	X	
AE/SAE	X	X	X	X	X
Device training	X	X	X		
Physical Examination	X	X	X	X	
Hematology	X		X	X	
Clinical Chemistry	X		X	X	
Urinalysis	X		X	X	
Pregnancy and assessments of fertility[3]	X	X	X	X	
Electrocardiogram (ECG)	X		X	X	
Vital Signs	X	X	X	X	
Height and Weight	X				
Telephone patient/parent/legal guardian in advance of study visit[4]		X	X		
Dose administration		X	X		
PK blood collection		X	X		
Snack/Meal[5]		X	X		
Safety Follow up Call					X

[redacted]

Period	**Screening**	**Treatment**		**Early Termination**	**Follow Up**
Visit Name	**Screening**	**Day 1**	**Day 6**		**Day 36**[1]
Days	**-14 to -1**	**1**	**6 -0 +3**	**-**	**36**
	[X] Assessment to be recorded in the clinical database or received electronically from a vendor [1] This would occur 30 days after last study treatment. [2] Inclusion/Exclusion evaluation at screening is recorded in CRF. Inclusion/Exclusion prior to dosing on Day 1 should be documented in source. [3] Serum pregnancy test at screening (approximately 0.5 mL blood volume) and urine pregnancy test during treatment visits [4] Patient/Parent/Legal Guardian should be reminded to withhold controller ICS on Days 1 and 6 study visits AND to withhold rescue medication within 8 hours of Days 1 and 6 study visits. [5] Patients should consume a small snack approximately 1 hour post-dose and a meal approximately 4 hours post-dose. Snack and meal times should be recorded on the CRF and food content should be recorded in source documentation.				

[redacted]

8.1 Screening

Screening

It is permissible to re-screen a patient once after 2 weeks (14 days) if s/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

8.1.1 Information to be collected on screening failures

Patients who sign an informed consent form and are subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a serious adverse event during the screening period (see SAE section for reporting details).

Patients who sign an informed consent and are considered eligible but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition Case Report Form.

8.2 Participant demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected for all patients include age (DOB as permitted), sex, race, and ethnicity date of diagnosis of asthma and prior/concomitant asthma medication. Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF. Relevant medical history/current medical conditions present before signing informed consent (diagnosis, not symptoms) should also be collected.

8.3 Efficacy

Not applicable.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE Section 10.

[redacted]

Table 8-2 Safety assessments

Assessment	Specification
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 or any other evaluations the investigator considers appropriate based on the patients clinical status at the clinic at the time of the visit. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after the written informed consent/assent is provided which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the CRF.
Vital signs	Body temperature, systolic and diastolic blood pressure and radial pulse rate (over a 30 sec interval), performed in the sitting position, will be recorded at each scheduled clinic visits. Please refer to Section 16.4 for time points of vital signs measurements post study treatment on Day1 and 6. Clinically notable vital signs are defined in Section 16.1.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. All patients with laboratory tests containing clinically significant abnormalities should be followed regularly until the values return to within the normal ranges or until a valid reason other than drug-related adverse experiences is identified, even after the medication has discontinued.

Safety Laboratory assessments (hematology and clinical chemistry) will be performed at Screening and at 6 hour post QMF149 dose on Day 6.

Clinically notable laboratory findings are defined in Section 16.1.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

Table 8-3 Laboratory evaluations

Test Category	Test Name
Hematology	Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured. Peripheral blood eosinophil counts will be captured with a unit of cells/ mcL.

[redacted]

Test Category	Test Name
Chemistry	Albumin, alkaline phosphatase, aspartate aminotransferase (AST) or Serum Glutamic *Oxaloacetic Transaminase (SGOT), alanine aminotransferase (ALT) or Serum Glutamic Pyruvic Transaminase (SGPT), bilirubin, creatinine, γ-GT, glucose, sodium, 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.
Urinalysis	Dipstick measurements for specific gravity, pH, protein, glucose and blood will be performed at Screening and Day 6. If the urine dipstick is abnormal, the sample will be sent to central laboratory for additional testing, including assessment of WBC and RBC sediments. Macroscopic Panel (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)
Pregnancy Test	Serum / Urine pregnancy test (refer to Section 8.4.3)

8.4.2 Electrocardiogram (ECG)

ECGs must be recorded after the patient rests (10 minutes if possible) in the supine position to ensure a stable baseline. When the ECG recording time coincides with vital signs, and blood draws, the ECG should be performed first, followed by vital signs and the blood draws.

Centralized ECG

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

ECG will be measured at Screening and on Day 6 at pre-dose and 20-min- post-dose of study medication as indicated in Section 16.4. ECGs should include 12 standard leads. ECG will be sent electronically for central review directly from the ECG machine. One print-out will be generated and kept at the investigator site as source documentation 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 ECG group to each investigator site.

In the event that the central cardiologist reports that an ECG is abnormal, the investigator must assess whether the ECG abnormality is clinically significant or not. A clinically significant abnormality should be reported as an AE. If necessary a pediatric cardiologist may be consulted. Clinically significant ECG findings at baseline must be discussed with the sponsor before administration with investigational treatment. If a patient experiences a clinically significant change in cardiac rhythm or other clinically significant cardiovascular abnormality, the investigator should consider withdrawing the patient from the study. Clinically significant abnormalities should be recorded on the relevant section of the medical history/Current medical conditions/AE CRF page as appropriate.

[redacted]

8.4.3 Pregnancy and assessments of fertility

Females of child-bearing potential are defined as all females physiologically capable of becoming pregnant. This includes female pediatric patients who are menarchal or who become menarchal during the study and may participate in this study.

Serum pregnancy test will be performed for all females of child-bearing potential according to the protocol assessment schedule (Table 8-1).

All menarchal girls and their parents/caregivers should be informed about the potential risks of pregnancy and the need to prevent pregnancy during the study. It is important to be sensitive in introducing this issue, as understanding and comprehension of puberty, sexual activity, pregnancy and contraception is influenced by age, as well as factors such as precocity, socio(educational) economic and familial background. These discussions with the patient and her parents/caregivers are therefore best performed by investigators familiar with the pediatric patient and her family and should be guided by requirements of the local regulatory authorities. These discussions should take into account the socio-economic, cultural factors and religious beliefs of the patient and her family.

The investigator should also discuss the management of the pregnancy test results with the patient and her parents/guardians. The privacy of the patient should be considered in accordance with the local law and ethics. Additional pregnancy tests may be performed at the investigator's discretion during the study. Patients becoming pregnant must be discontinued from study drug.

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

Abstinence from sexual activity while participating in a clinical trial should be encouraged in this category of patients. Sexually active patients are excluded from participation in the study.

Assessments of fertility

Female patients who have reached menarche (and therefore are of child-bearing potential) will have a serum pregnancy test at screening and a urine pregnancy test during both dosing visits (performed prior to dosing) as noted in the visit schedule of assessments (Table 8-1). If the serum pregnancy test performed at the Screening Visit is positive, the patient cannot participate in the study (Exclusion 19). If the urine pregnancy test performed prior to dosing (at Days 1 and 6) is found to be positive,

study drug must not be administered until serum β-hCG is performed and found to be negative. If serum β-hCG test is positive, the patient must be discontinued from the study.

8.4.4 Appropriateness of safety measurements

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

8.5 Additional assessments

No additional tests will be performed on patients entered into this study.

[redacted]

8.5.1 Pharmacokinetics

PK samples will be collected at the visits defined in the assessment schedule. Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing and shipment. Residual samples will be retained for additional PK analysis if necessary.

The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol. Pharmacokinetic (PK) samples will be obtained and evaluated in all patients at all dose levels.

Mometasone furoate and indacaterol will be determined by a validated LC-MS/MS method; the anticipated Lower Limit of Quantification (LLOQ) is 0.25 pg/mL for mometasone and 5.0 pg/mL for indacaterol. Concentrations will be expressed in mass per volume units and will refer to the free base. Concentrations below the LLOQ will be reported as "zero" and missing data will be labeled as such in the Bioanalytical Data Report.

Blood collection (Table 16-4):

- 2 mL blood per sample, EDTA tubes (plasma): Day 1 and Day 6: pre-dose, 0.5, 1, 2, 3, and 6h post-dose for MF analysis
- 1 mL blood per sample, Lithium Heparin tubes (plasma): Day 6 pre-dose, 0.25 and 1 h post-dose for IND analysis

Analytes, media and methods: Determination of mometasone furoate in plasma will be performed by a validated LC-MS/MS method with an LLOQ at 0.25 pg/mL for mometasone furoate and 5 pg/mL for indacaterol.

The following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher): Cmax, Tmax, AUC0-6h from the MF plasma concentration-time data.

To maintain the consistency for any potential effect of food on the PK profile of mometasone, all patients are encouraged to consume a snack approximately 1 hour post-dosing and a meal approximately 4 hours post-dosing.

Due to a drug substance coating effect on inner plastic surfaces of the inhaler, the first delivered dose and Fine Particle Mass (FPM) from fresh C1 Breezhaler® device delivered dose and fine particle mass is known to be generally slightly lower compared to the average delivered doses.

For comparison purpose of MF delivered in QMF149 through C1 Breezhaler® and MF delivered by Twisthaler® the blood exposure values (e.g., Cmax, AUC0-6h) obtained with C1 Breezhaler® will be multiplied with the factor FPM_{primed} (MF) / $FPM_{unprimed}$ (MF) to assess equivalent MF component doses.

9 Study discontinuation and completion

9.1 Discontinuation and completion

Completion of the study will be when the last patient has completed Day 6 treatment and PK sample collection and safety assessments. 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.

9.1.1 Study treatment discontinuation and study discontinuation

If the patient cannot properly and sufficiently inhale the dose of study medication at each treatment visit and if the patient does not provide a PK sample at each designated timepoint on both treatment days, the patient must be discontinued from the study.

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

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

Study treatment must be discontinued under the following circumstances:

- Patients who have not received or retained a full dose of study drug cannot be re-dosed during a study visit and should be discontinued
- Patient`s or parent/legal guardian's wish including withdrawal of informed consent
- Administration of a prohibited medication
- ECGs:
  - At predose time on Day 6, if the absolute QTcF ≥ 450 msec or an increase from baseline of > 60 msec on 2 adequate ECGs at least a minute apart and the physician interprets the data from ECG machine to not initiate study treatment.
  - 2nd or 3rd degree AV block
  - Atrial or ventricular arrhythmias (as judged clinically significant by the investigator)
- Any severe AE or SAE considered possibly related to the study medication
- Adverse events for which continuation of the study drug would be detrimental
- If a patient develops a medical condition that requires use of prohibited treatment as per Section 6.2.2, or if patient exhibits a behavior of non-compliance regarding prohibited medications.
- Pregnancy (see Section 10.1.4)
- Any situation in which study participation might result in a safety risk to the patient
- Clinically significant abnormal laboratory value(s) for children 6 to < 12 years, as per the discretion of the physician
- Any other protocol deviation that results in a significant risk to the patient's safety
- If the COVID 19 pandemic (or any other reason including any public health emergency) limits or prevents an on-site study visit(s), then such patients should be discontinued

If discontinuation of study treatment occurs, the patient should NOT be considered withdrawn from the study. The patient should return to the clinic as soon as possible, after discontinuation of study drug, for a study treatment discontinuation visit (End of Treatment will act as an early discontinuation visit in this case) and directly move into the 30 day follow-up period. Early Termination visit assessments detailed in the Table 8-1 should be completed and recorded in

[redacted]

the eCRF. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this in the Study Disposition eCRF.

The data which must continue to be collected for all discontinued patients are adverse event and serious adverse events for up to 30 days after drug discontinuation until the end of the study follow-up visit. Documentation of attempts to contact the patient must be recorded in the source documentation.

If the patient fails to return for an end of study visit for unknown reasons, every effort should be made to contact them. For patients already started Day 1, the COVID 19 pandemic (or any other reason) may limit or prevent an on-site study visit(s). These patients should be discontinued and a phone or virtual visit will occur for safety monitoring and discussion of the participant´s health status including 30 days safety follow-up. If patients cannot visit the site to have a urine pregnancy test done, the urine pregnancy test can be performed at home and the result reported to the site. If the patient can attend the early termination visit after Day 1, safety monitoring, discussion of the participant´s health status, and urine pregnancy test (dipstick) should be performed as the early termination visit, then 30 days safety follow up will be performed.

9.1.1.1 Replacement policy

Twenty-four (24) patients must complete the two (2) dosing PK collection study visits which includes all PK sampling timepoints. Dropouts and non-completers will be replaced as needed. Patients who have received a dose of study treatment and who drop-out or discontinue for any reason, may be re-screened after a minimum of 14 days.

9.1.2 Withdrawal of informed consent

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

- Participate in the study anymore and
- Does not want any further visits or assessments and
- Does not want any further study related contacts and
- Does not allow analysis of already obtained biologic material.In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient`s or parent's/ legal guardian's decision to withdraw their consent and record this information. Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

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

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment table. Where consent to the use of personal and coded data is not required, patient

[redacted]

therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

9.1.3 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to patients enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider patient welfare and safety. Should early termination be necessary, patients must be seen as soon as possible. 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 or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

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

Patients that completed the study or prematurely discontinued will not be given further access to the investigational treatment.

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

All treated patients should have a safety follow-up call conducted 30 days after last administration of study treatment. All SAEs reported during this time period must be reported as described in Section 10.1.3 . Documentation of attempts to contact the patient should be recorded in the source documentation.

[redacted]

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 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 patient or clinical investigation patient after providing written informed consent for participation in the study. 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 investigator has the responsibility for managing the safety of individual patient and identifying adverse events.

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

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.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. 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
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be ‘Not suspected’. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single patient.
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.
6. Its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving; recovered/resolved with sequelae; fatal; or unknown)

[redacted]

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

- Drug interrupted/withdrawn
- Concomitant medication or non-drug therapy given
- Patient hospitalized/hospitalisation prolonged
- No action taken (i.e. further observation only)

Conditions that were already present at the time of informed consent should be recorded in medical history of the patient.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

To ensure patient safety, every adverse event, occurring after the patient has provided informed consent and until end of the trial for each patient must be reported.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

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 patients with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 16.1.

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).

10.1.2 Serious adverse events

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:

[redacted]

  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (asthma)
  - 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 to prevent one of the outcomes listed above.

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

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (see Annex IV, ICH-E2D Guideline (2003)).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline (2003)).

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

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

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

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

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

[redacted]

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.

10.1.4 Pregnancy reporting

Pregnancies

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

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

Pregnancy tests are required of female patients partcipating in the study who have reached menarche. For details regarding pregnancy testing please refer to Table 8-1 and Section 8.4.3.

Tracking of pregnancy cases occurs until after Expected Delivery Date (EDD) for all prospective pregnancy cases received from clinical studies

- EDD +1 month (mandatory for all cases). Requesting the pregnancy outcome and othe rclinically relevant pregnancy data or changes in data
- EDD+2 month (mandatory if no answer is obtained after request at EDD+1 month). A reminder letter for the outcome
- The follow up at EDD+3 and EDD+12 months is mandatory for all cases of live birth and unknown outcome. Information on the status of the baby 3 months after delivery and information on any development issue or abnormality that would not be seen at birth must be collected

10.1.5 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.

[redacted]

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (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

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.1.6 Concept 1 related adverse event reporting

Any Concept 1 device related adverse events must be reported to Novartis within 24 hours of learning of its occurrence. Concept 1 device related adverse events must be recorded on the relevant device-related pages of the CRF. Country regulations have to be followed for the Concept 1 device related adverse events reporting to Health Authorities and/or Ethics Committees.

The investigator has the responsibility for managing the safety of individual patients.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed. The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as (S)AE):

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

Please refer to Table 16-1 in Section 16.2 for complete definitions of liver laboratory triggers and liver events.

Once a participant is exposed to study treatment, every liver laboratory trigger or liver event as defined in Table 16-1 of Section 16.2 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 16-2 in Section 16.2.

[redacted]

For the liver laboratory trigger:

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

These LFT repeats will be performed using the central laboratory . If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. 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 initial elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment, Section 9.1.1) 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, obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

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

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the RAVEX 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.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate. After final database lock, the investigator will receive copies of the patient data for archiving at the investigational site. All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

[redacted]

11.2 Database management and quality control

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

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system.

Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

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

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

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.

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.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) 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 data capture / data entry, 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).

[redacted]

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. 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 will be disclosed.

12 Data analysis and statistical methods

12.1 Analysis sets

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

The Safety Set includes all patients who received at least one dose of study treatment. Patients will be analyzed according to the study treatment received, where treatment received is defined as the assigned treatment if the patient took at least one dose of that treatment or the first treatment received if the assigned treatment was never received.

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

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data be listed by patient. Descriptive statistics will be presented for all patients for the Safety set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical history, current medical conditions, results of laboratory screens and any other relevant information will be listed by patient.

12.3 Treatments

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by patient.

12.4 Analysis of the primary endpoint(s)/estimand(s)

The primary objective of this study to compare the systemic exposure of mometasone furoate resulting from single orally inhaled doses of QMF149 75/40 administered via the Concept 1 versus the MF Twisthaler® (100 µg) in pediatric asthma patients (≥ 6 to < 12 years of age). All patients evaluated for pharmacokinetic (PK) parameter data will be included in the pharmacokinetic data analysis.

[redacted]

12.4.1 Definition of primary endpoint(s)

The primary PK parameters of interest are Cmax, and AUC0-6h of MF after single dose administration of QMF149 75/40 μg C 1 and MF TH 100 μg.

12.4.2 Statistical model, hypothesis, and method of analysis

Log-transformed PK paramters Cmax and AUC(0-6h) will be analyzed for mometasone furoate by linear fixed effects model with treatment and patient as fixed effect. The estimated mean and 90% confidence interval of treatment difference of test vs reference (QMF149 vs MF) will be back transformed to obtain the geometric mean and 90% confidence intervals of the ratio.

12.4.3 Handling of missing values not related to intercurrent event

All drug concentrations below the lower limit of quantification (LLOQ) will be reported as "zero" and will be treated as zero for the calculation of PK parameters.

Patients with missing PK parameters (e.g. Cmax, AUClast, AUCinf) in one period will be excluded from the primary analysis.

In case a certain PK time point is not collected and missing in data, PK parameters may not be calculated from this treatment.

12.5 Analysis of secondary endpoints/estimands

For all safety analyses, the safety set will be used.

12.5.1 Safety endpoints

Adverse events

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

All treatment emergent AEs will be summarized and listed.

AEs starting on or after the time of the first inhalation of study drug and until 30 days after the last inhalation will be classified as a treatment emergent AE. Any AEs that started during the study after signing informed consent and before the time of the first inhalation of study drug will be classified as a prior AE and will not be included in tabulations of the treatment emergent AEs.

The following treatment emergent AE summaries will be produced:

- by treatment, system organ class and preferred term,
- by treatment, system organ class, preferred term and maximum severity

suspected drug-related AEs by system organ class and preferred term, SAEs by system organ class and preferred term, and AEs leading to 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.

[redacted]

Vital signs

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

12-lead ECG

PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each participant during the study. ECG data will be read and interpreted centrally. All ECG data will be listed by treatment sequence, patientand visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

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

12.5.2 Pharmacokinetics

Indacaterol and mometasone furoate plasma concentration data will be listed by treatment, patient, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum.

Indacaterol and mometasone furoate pharmacokinetic parameters will be listed by treatment and patient. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented. PK parameters AUC0-6h and Cmax will be used for comparsion of MF exposure after the two treatments. Additional parameters such as Tmax and half-life may be calculated for additional qualitative assessments.

Table 12-1 Non-compartmental pharmacokinetic parameters

AUC0-6h	The AUC from time zero to the last sampling time point 6h (mass x time x volume-1)
AUCinf	The AUC from time zero to infinity (mass x time x volume-1)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
Lambda_z	Smallest (slowest) disposition (hybrid) rate constant (time-1) may also be used for terminal elimination rate constant (time-1)
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CL/F	The total body clearance of drug from the plasma (volume x time-1)

[redacted]

Vz/F	The apparent volume of distribution during terminal phase (associated with λz) (volume)

12.6 Analysis of exploratory endpoints

Not applicable.

12.7 Interim analyses

An interim analysis is planned to be performed when 12 patients complete both study treatment and there are at least 3 completers in each of the two age groups ≥ 6 to < 9 year olds and ≥ 9 to <12 year olds. The interim analysis will be based on preliminary PK and safety data. An estimate of the systemic exposure as measured by the PK parameter ratios (QMF149 Concept 1 Breezhaler® vs MF Twisthaler®) together with corresponding 90% confidence intervals will be calculated in order to enable early decision making (e.g., study termination due to having achieved the primary objectives). Rationale for study continuation may include measures such as a review of training procedure for inhaler use by patients or sample size re-estimation.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Approximately 32 patients will be recruited in order to obtain 24 completers in this study considering 25% of drop out rate. The sample size of 24 complete patients is considered to yield satisfactory precision in the estimation of the systematic exposure, as measured by the ratio of the PK parameter Cmax, AUC(0-6h) of QMF149 Concept 1 Breezhaler® vs MF Twisthaler®.

With 24 complete patients, the 90% confidence intervals of the PK parameter (AUC (0-6h) and Cmax) ratios (QMF149 Concept 1 Breezhaler® vs MF Twisthaler®) are expected to be within 72% to 138% with 90% coverage probability. The calculation was based on an assumed 2-fold increase in variability in pediatric population compared to adults who showed intra-patient CV of 30% in the CQMF149E2101 study.

13 Ethical considerations and administrative procedures

13.1 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 with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. 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.

13.3 Publication of study protocol and results

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

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, 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.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study patients. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study patients.

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.

[redacted]

14.1 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 required for patient safety 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, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

[redacted]

15 References

References are available upon request

Annex IV, ICH-E2D Guideline (2003) Available from www.ich.org.

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Moorman JE, Rudd RA, Johnson CA, et al (2007) National surveillance for asthma—United States, 1980-2004. MMWR Surveill Summ; 56(8):1-54.

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Woolcock A, Lundback B, Ringdal N, et al (1996) Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. Am J Respir Crit Care Med 153:1481–1488.

[redacted]

16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

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

[redacted]

16.2 Appendix 2: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*
If ALT or AST abnormal at baseline:	• ALT or AST > 2x baseline or > 300 U/L (whichever occurs first)

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

Table 16-2 Follow up requirements for liver laboratory triggers with liver symptoms

ALT	**TBL**	**Liver Symptoms**	**Action**
ALT increase without bilirubin increase:			
If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal For patients with Gilbert's syndrome: No change in baseline TBL	None	• **No change to study treatment** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms.
If normal at baseline: ALT > 5 x ULN for more than two weeks **If elevated at baseline:** ALT > 3 x baseline	Normal For patients with Gilbert's syndrome: No change in baseline TBL	None	• **Interrupt study drug** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and

[redacted]

ALT	TBL	Liver Symptoms	Action
or > 300 U/L (whichever occurs first) for more than two weeks			GLDH in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:			
If normal at baseline: ALT > 3 x ULN	TBL > 2 x ULN (or INR > 1.5) For patients with Gilbert's syndrome: Doubling of direct bilirubin	None	
If elevated at baseline: ALT > 2 x baseline or > 300 U/L (whichever occurs first)			
If normal at baseline: ALT > 3 x ULN	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	
If elevated at baseline: ALT > 2 x baseline or > 300 U/L (whichever occurs first)			

Table 16-3 Follow up requirements for liver laboratory triggers

Criteria	Actions required	Follow-up monitoring
Total Biliruin (isolated)		
>1.5 – 3.0 ULN	• Maintain treatment • Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution[a] to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	• Interrupt treatment • Repeat LFT within 48-72 hours • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Monitor LFTs weekly until resolution[a] to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution[a] (frequency at investigator discretion)

[redacted]

Criteria	Actions required	Follow-up monitoring
	• Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate CRF	
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate CRF	Investigator discretion
[a]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death. *These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms ULN: upper limit of normal		

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

[redacted]

16.3 Appendix 3: Blood volumes

Table 16-4 Blood volume

Study Period	**Time (h)[1]**	**Safety**	**PK**			
		mL	**Dose Reference ID**	**Sample no. (MF analysis)**	**Sample no. (IND analysis)**	**mL**
Screening (days -14 to -1)		5.5				
Day 1 Treatment	0 (pre-dose)		MF TH 100 µg	101		2
	0.5		MF TH 100 µg	102		2
	1		MF TH 100 µg	103		2
	2		MF TH 100 µg	104		2
	3		MF TH 100 µg	105		2
	6		MF TH 100 µg	106		2
Day 6 Treatment	0 (pre-dose)		QMF149 75/40 µg	201	301	3
	0.25			-	302	1
	0.5		QMF149 75/40 µg	202		2
	1		QMF149 75/40 µg	203	303	3
	2		QMF149 75/40 µg	204		2
	3		QMF149 75/40 µg	205		2
	6	5.5	QMF149 75/40 µg	206		2
Sub-total blood volume		11				27
TOTAL Blood volume (mL)						38

[1] Time window of ± 5 min for samples up to 3 h and ± 30 min for sample at 6 h. Predose samples should be collected within 2 hour window prior to dosing.

[redacted]

16.4 Appendix 4: Pharmacokinetic/Vital signs/ECG/Lab assessment timed schedule on Days 1 and 6

Table 16-5 PK/VS/ECG/Lab Assessments

PK/VS/ECG/Lab assessment timed schedule Time point vs. 0 (dose time, hours)*	**Vital Signs****			**ECG**			**PK**			**Hematology/ chemistry**		
	Day 1	Day 6	Early Term	Day 1	Day 6	Early Term	Day 1	Day 6	Early Term	Day 1	Day 6	Early Term
Pre-dose	X	X	X		X	X	X*	X*				X
15 minutes		X						X				
20 minutes					X							
30 minutes							X	X				
1 hour		X					X	X				
2 hours							X	X				
3 hours							X	X				
6 hours							X	X			X	

Note: For Time points where multiple procedures occur, the following order is recommended: e.g. vital signs, PK, and lab. The PK blood draw should be ± 5 min for samples up to 3 h and ± 30 min for sample at 6 h. Predose samples should be collected within 2 hour window prior to dosing.

*If a local anesthetic is used for placing the indwelling catheter, the time for it to take effect has to be accounted for prior to any assessment.

** Please refer to Table 8-2 for details.

[redacted]