IEC	Independent Ethics Committee
i.v.	Intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intra Uterine Device
IUS	Intra Uterine System
IVRS	Interactive Voice Response System
LABA	Long Acting Beta-2 Agonist
LAMA	Long Acting Muscarinic Antagonist
LFT	Liver Function Test
LTRA	Leukotriene Receptor Antagonist
LS Mean	Least squares mean
MDDPI	Multi dose dry powder inhaler
MDI	Metered Dose Inhaler
MF	Mometasone Furoate
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measurements
NYHA	New York Heart Association
OC/RDC	Oracle Clinical/Remote Data Capture
o.d.	Once a day
p.o.	Oral(ly)
PDCO	Pediatric Committee of the European Medicines Agency
PEF	Peak Expiratory Flow
PK	Pharmacokinetic
PRO	Patient Reported Outcome
PSD	Premature patient discontinuation
QTc	Corrected QT interval
REB	Research Ethics Board
SABA	Short Acting Beta-2 Agonist
SAE	Serious Adverse Event
SAMA	Short Acting Anticholinergics
SCS	Systemic Corticosteroids
SDDPI	Single Dose Dry Powder Inhaler
SoC	Standard of Care
SMQ	Standard MEDRA Query
WHO	World Health Organization
SUSAR	Suspected Unexpected Serious Adverse Reactions
TD	Study Treatment Discontinuation
WHO	World Health Organization
WoC	Withdrawal of Consent

[redacted]

2.2 Key Secondary objective

The key secondary objective is to demonstrate the superiority of QMF149 150/80 microgram to MF 200 microgram o.d. in terms of ACQ-7 after 12 weeks of treatment.

2.3 Other secondary objectives

Other secondary objectives will evaluate the efficacy of QMF149 150/80 microgram versus MF 200 microgram o.d. in terms of:

Lung function:

- Trough FEV_1 at Day 2 of treatment period (defined as the mean of 23 hours 15 min and 23 hours 45 min FEV_1 values post dose of Day 1)
- Pre-dose FEV_1 (defined as the mean of -45 min and -15 min FEV_1 values pre-evening dose) at 4 weeks
- Forced Vital Capacity (FVC) and Forced Expiratory Flow between 25% and 75% of FVC (FEF_{25-75}) over 12 weeks
- Morning and Evening Peak Expiratory Flow Rate (PEF) over 4 and 12 weeks of treatment

Symptoms and asthma control:

- Percent of patients achieving the minimal important difference (MID) in ACQ-7 (i.e., at least 0.5 improvement from baseline) at Week 12
- Percentage of asthma symptoms free days, the percentage of nights without nighttime awakenings, and the percentage of mornings without symptoms on awakening as recorded by daily electronic Diary (eDiary) over 12 weeks of treatment
- Asthma control as assessed by the Asthma Control Questionnaire (ACQ-7) at Week 4
- Rescue salbutamol/albuterol usage (mean daily, nighttime and daytime use) from eDiary recordings over 12 weeks of treatment
- Percentage of rescue medication free days over 12 weeks of treatment period

Exacerbations:

The exacerbation data collected during 12 weeks of treatment period will be assessed with respect to the parameters described below. The exacerbation categories are: All exacerbations (mild, moderate, severe) and the combination of moderate or severe:

- Time to first asthma exacerbation by exacerbation category
- Annual rate of asthma exacerbations by exacerbation category
- Quality of life as assessed by Asthma Quality of Life Questionnaire (AQLQ) over 12 weeks of treatment period

The following safety and tolerability endpoints will be evaluated:

- Cumulative incidence of the composite endpoint of serious asthma outcomes (i.e., asthma-related hospitalization, asthma-related intubation, or asthma-related death) over 12 weeks of treatment
- AEs, vital signs, electrocardiogram (ECG), and laboratory analysis (hematology, blood chemistry including glucose and potassium, urinalysis, evening plasma cortisol) over 12 weeks of treatment

[redacted]

[redacted]

3 Investigational plan

3.1 Study design

This study uses a 12-week treatment, randomized, double-blind, double-dummy, parallel-group design. The 12 week treatment epoch will be followed by a 30 day Follow-up epoch. There is a screening visit (Visit 1) where informed consent is obtained and current asthma and other non-asthma medications are reviewed. Where appropriate, concurrent asthma and other medications are adjusted at this visit and prohibited asthma medications are replaced with permitted asthma medications for use throughout the study.

All patients should have been on a stable dose of inhaled low dose corticosteroids (with or without LABA) for at least 1 month prior to Visit 1. Once the concurrent medications comply with the requirements of the study (Section 5.5.7 and Section 5.5.8) patients will enter a Run-in epoch at Visit 101.

At Run-in Visit 101 all patients will receive an open-label fluticasone propionate 100 µg b.i.d. delivered via Accuhaler® (if not available in a specific country, open-label fluticasone propionate 125 µg b.i.d. via MDI inhaler or fluticasone propionate in an alternative formulation at an equivalent dose strength) for use throughout the Run-in epoch which will be stopped at Visit 102 (end of Run-in epoch) (Figure 3-1).The screening epoch between Visit 1 and Visit 101 is used to ensure washout of prior asthma medication. Depending on prior asthma medication and washout requirements, the period between Visit 1 and Visit 101 may be shorter than 2 weeks. At Visit 1 (Screening), all patients will be given salbutamol/albuterol to use as rescue medication throughout the study. They will be issued an electronic diary combined with Peak Flow (PEF) meter to record asthma symptoms and rescue medication use. After the end of the Screening epoch (maximum 2 weeks after Visit 1), starting with the Run-in epoch (Visit 101), patients will record Peak Expiratory Flow Rate (PEF) twice daily. The Run-in epoch is three (3) weeks in duration and will be used to assess eligibility of the patients prior to entering the treatment epoch and to collect baseline values for some variables.

Patient can enter the Run-in epoch provided inclusion criteria are met, including those for spirometry (pre-dose percent predicted FEV_1, ATS/ERS criteria, and reversibility) as per spirometry equipment.

Patients who meet the eligibility criteria at Visit 102 will be randomized to one of following two treatment groups with an equal (1:1) randomization ratio:

- QMF149 150/80 microgram o.d. delivered via Concept1
- MF 200 microgram o.d. delivered via Twisthaler®

[redacted]

Randomized patients must have FEV_1 between 60% and < 90% of predicted normal at **both** Visit 101 and Visit 102 and they must qualify for treatment with low dose ICS plus LABA as per GINA 2016 guidelines. At Visit 102, **all** randomized patients must have ACQ-7 ≥ 1.5. Refer to Section 4.1 Inclusion Criteria for ACQ-7 requirements.

Visit 102 (end of Run-in) and Visit 201(Randomization) must take place sequentially on the same day. The assessments at Visit 102 should be performed prior to administration of the first dose of study medication (Visit 201). Reversibility should NOT be done at Visit 102 (Table 6-1). Randomized patients will enter the 12-week Treatment epoch. All patients will receive both Concept1 and Twisthaler® inhalers (double-blind and double-dummy design). During the treatment epoch, patients will be instructed to inhale study medication once daily in the evening (between 5:00 pm and 8:00 pm).

Patients will be followed at regular intervals throughout the 12 week treatment epoch to assess the safety and efficacy of treatment, either by telephone or at clinic visits. Clinic visits are scheduled to take place after 4, and 12 weeks. All clinic visits should occur as scheduled per Table 6-1. Patients will be required to attend the clinic visits to perform trough measurements of lung function (24 hours post dosing) after the first dose of study medication (Visit 201) and after the dose of study medication administered at the clinic after 12 weeks of treatment (Clinic Visit 204). In case of logistical issues, Visit 204 (Week 12) should take place within a 4 day window. If this is not possible, the sponsor should be notified.

Pre-dose FEV_1 measurements will be assessed at Week 4. Telephone reviews of patients' status will be conducted after 8 weeks of treatment. Telephone contact with patients may indicate that a clinic visit is necessary, in which case an unscheduled clinic visit should be arranged as soon as possible and should include safety assessment (AEs, concomitant medications review and unscheduled laboratory exams as appropriate).

A final telephone contact must be conducted at 30-days after last treatment date (telephone Visit 301 or unscheduled visit safety call for patients who discontinue treatment earlier than 12 weeks).

The first dose of study medication will be administered at the clinic in the evening (between 05:00 pm and 08:00 pm) at Visit 201 (Day 1). Subsequent clinic visits will be scheduled so that patients will be reassessed as close as possible to the same time relative to the evening doses. Patients will be instructed not to take their evening dose of study medication on the days of the clinic visits, as these doses will be administered at the clinic under the supervision of study personnel.

[redacted]

[redacted]

asthma exacerbations, quality of life, and safety of the studied QMF149 dose in this specific asthma patient population.

The analyses will be performed in a sample size of approximately 750 patients. The patient population will be described in more detail in the Section 4.

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

This study is a pivotal, multi-center, randomized, double-blind, double-dummy, parallel-group, Phase III study with a 12-week treatment epoch which is required to assess the safety and efficacy of QMF149 in asthma. The primary endpoint will be evaluated over 12 weeks. The dose regimen/route of administration of QMF149 selected (150/80 microgram delivered via Concept1) is based on the findings of previous studies identifying effective and safe doses of the individual components of the FDC, indacaterol and MF) (Section 1.1).

The 12 week duration is considered adequate to demonstrate improvements in the primary endpoint based on the known pharmacodynamic properties of the components of each fixed-dose combination and precedent of other inhaled combination products in asthma.

3.4 Rationale for choice of comparator

MF was selected as the comparator as it is the ICS monocomponent in QMF149 combination formulation and is necessary in order to demonstrate the additional benefit of a LABA (indacaterol acetate 150 microgram) in the QMF149 combination (Appendix 9) as compared to MF monotherapy in patients whose asthma is inadequately controlled with ICS alone. Furthermore, MF in Twisthaler® formulation is approved for treatment in asthma.

The MF inhalation powder formulation is marketed as a MDDPI called Asmanex® Twisthaler® for the treatment of asthma and is currently approved in the Unites States for the treatment of asthma in adults and children ≥ 4 years of age and is approved in over 55 countries world-wide for the treatment of asthma in adults and adolescents ≥ 12 years old. The MF 200 microgram o.d. delivered via Twisthaler® is comparable to MF 80 microgram o.d. delivered via Concept1 (Section 1.1).

3.5 Purpose and timing of interim analyses/design adaptations

No interim analysis for efficacy is planned. It is planned that the independent Data Monitoring Committee (DMC) will review semi-blinded (i.e., treatment groups names as A and B) safety data (Section 8.4). The details of the information flow, confidentiality and specific analysis will be available from the DMC Charter.

3.6 Risks and benefits

ICS/LABA fixed dose combinations are frequently used as controller medications and are foundation therapy in GINA step ≥ 3 (GINA 2016).

QMF149 (indacaterol 150 microgram as an FDC with three doses of MF: 80 microgram, 160 microgram or 320 microgram) is a new once daily ICS/LABA FDC in development for asthma for which a Phase II development was recently successfully completed.

[redacted]

There is evidence of efficacy and safety of the mono components indacaterol and MF in asthma and COPD (indacaterol). In addition, supportive efficacy and safety information was gained from the early QMF149 development in the Twisthaler® device (see Section 1.1) and QMF149 Investigator Brochure. To further investigate the overall risk and benefit evaluation of QMF149 FDC delivered by Concept1, an MF 80 microgram dose in combination with indacaterol acetate (QMF149) is selected for further evaluation in Phase III.

In one large Phase II event driven trial with a duration up to 68 weeks in over 1500 moderate to severe asthma patients including adolescents (12-17 years of age), indacaterol/mometasone 500/400 microgram delivered by Twisthaler® comparable to indacaterol 150/160 microgram delivered by Concept1 showed a favorable efficacy and safety profile over MF alone (Beasley et al 2015).

Further efficacy and safety trials in Phase II included different indacaterol doses on background of MF in Concept1 in moderate to severe asthma (QMF149E2203), a device bridging study with MF in Concept1 (QMF149E2201) and an efficacy and safety study with QMF149 in Concept1 in moderate to very severe COPD patients (QMF149F2202). The studies showed statistically significant improvements in lung function and symptomatic endpoints including exacerbations and confirmed a favorable and robust efficacy and safety profile in Phase II.

In this Phase III study, randomized patients will receive either QMF149 or MF throughout the treatment epoch (12 weeks). Throughout the trial, patients will be given access to rescue medication (i.e., short acting beta-2agonist (SABA)), thus limiting the risk of significant asthmatic AEs. At no time during the study will any patient be without treatment for asthma.

The risk to the patients in participating in this study is that QMF149 is under development and therefore unexpected safety issues may be possible in patients randomized to QMF149 treatment (Section 5.6.2). This risk will be minimized by adherence to the patient eligibility criteria as stated in the study protocol and by close clinical monitoring of all patients. The risks of side effects from the study medication are those known for the individual compounds indacaterol and MF, and no additional risks have been identified that might occur when the two components are administered concurrently or from the same inhaler. Further information can be obtained from the most current QMF149 Investigator's Brochure.

There is evidence that LABA treatment used alone in asthma might cause asthma exacerbations (FDA warning, Advair® Diskus® prescription information). This risk is mitigated by the fact that all patients will have a minimum background therapy of low dose ICS (monotherapy or in combination with LABA, depending on treatment arm).

The potential benefit for the patient includes an improvement in the pulmonary function testing and a potential translation into better asthma control, such as reductions in symptoms and rescue medication use, and improved quality of life. A thorough medical evaluation of the patient's disease and close clinical monitoring for the duration of the study may be considered as additional benefit to the patient.

Frequent and regular contacts between the patient and site staff will occur in terms of clinic visits and telephone contacts to each patient throughout the 12-week treatment epoch. In addition, safety monitoring (e.g., symptom collection and rescue medication use via electronic diary), assessment of compliance with the study medication regimen, and PEF (twice daily)

[redacted]

Table 6-1 lists all the assessments to be performed for the study and indicates with an "X" the visits at which they will be performed. Patients should be seen for all visits on the designated days or as close as possible to those dates. While Visit 102 (end of Run-in) and Visit 201(Randomization) must take place on the same day, a visit window of 4 days is allowed at Visit 204 as described in Section 3.1 (if this is not possible, the sponsor should be notified). All data obtained for these assessments must be supported in the patients' source documentation.

At Visit 1, all patients will be issued an electronic diary to record asthma symptoms and rescue medication use and at Visit 101, a Peak Flow meter to record Peak Expiratory Flow Rate (PEF) twice daily. The Run-in epoch will be used to assess eligibility of the patients to enter the treatment epoch and to collect baseline values for some variables.

Once patient's eligibility is confirmed (at Visit 102), patient will be randomized to one of the two treatment groups with an equal (1:1) randomization ratio:

- QMF149 150/80 microgram o.d delivered via Concept1
- MF 200 microgram o.d. delivered via Twisthaler®

Visits 102 and 201 should take place sequentially on the same day and Visit 102 assessments should be performed prior to administration of the first dose of study medication (Visit 201).

The scheduled assessments should be performed in the following order: Patient reported outcomes (PROs) (i.e., ACQ, AQLQ), ECG, radial pulse rate, blood pressure and blood /urine samples followed by spirometry (as per Table 6-2).

The details of spirometry assessments are indicated in Table 6-2. An approximate 3 min rest from start of ECG to the start of spirometry manoeuvres should be given. When an ECG is needed to be taken after spirometry, a 10 minute rest from the end of spirometry to start of ECG assessments should be considered.

If other assessments are scheduled at the same time-point, spirometry will take precedence (with the exception of PROs and blood tests) so that it occurs at/or as close as possible to the scheduled time points.

[redacted]

Visit Number	**1**	**101**	**102**	**201**	**202**	**203**[5]	**204**[10]	**Early treatment discontinuation (TD)**	**Premature study discontinuation (PSD)**	**301**[9]
Epoch	**Screen**	**Run-in**		**Treatment**					**PSD**	**Follow-up**
Clinic (C) /Telephone (T)	C	C	C	C	C	T	C	C	T	T
Week – Start of Week	-5 to -3	-3	0	0	4	8	12			16
Day Number	-35 to -21	-21	1	1/2	30	57	84/85[6]			114
Urine analysis (dipstick)		S		S			S	S		
Device training[4]	S	S	S							
Concomitant medication review	X	X	X	X	X	X	X	X	X	X
Physical examination		S					S	S		
Oropharyngeal examination		S	S	S	S		S	S		
Record height (for adult patients only at Visit 101) and weight		X					X[12]	X[12]		
ECG[2]		X		X			X	X		
Vital signs[2]		X	X	X	X		X	X		
Issue rescue medication as necessary	S	S		S	S					
Review rescue medication use		X	X	X	X		X	X		
Spirometry Practice (optional)	S									

[redacted]

6.4.4 Electronic Diary

At Visit 1, all patients will be provided with an electronic diary (referred to as an eDiary) to record rescue medication (salbutamol/albuterol) use and clinical symptoms, the PEF and compliance with the study treatment (starting in Visit 101). The patients will be instructed to routinely complete the eDiary twice daily – at the same time each morning and again approximately 12 hours later in the evening. The eDiary is to be reviewed by study site personnel at each clinic visit until study completion. Sites and patients will receive appropriate training and guidance on the use of the eDiary device. A list of the asthma control eDiary questions is provided in Appendix 7.

6.4.5 Peak Expiratory Flow (PEF)

An electronic Peak Flow Meter part of the eDiary device will be provided to each patient at Visit 101 for the measurement of morning and evening PEF during the Run-in and treatment periods.

PEF will be measured at consistent times for a patient, in the morning and evening each day during the study from Visit 101 to 204 and TD Visit (if applicable). The measurements will be performed using an e-Peak Flow Meter provided to the patients at Visit 101. PEF will be measured twice a day; once in the morning and once approximately 12 hours later in the evening (prior to evening dose) from Run-in throughout the study. Patients should be encouraged to perform morning and evening PEF measurements BEFORE taking rescue medication. At each time point, the patient should be instructed to perform 3 consecutive maneuvers within 10 minutes. These PEF values are captured in the e-PEF/diary. The best of 3 values will be used.

6.4.6 Rescue Medication Usage

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

6.4.7 Investigational Medication Usage

In order to ensure compliance and safety follow-up, the patients will be requested to record once per week in the eDiary whether he/she missed any dose and from which inhalation device.

6.4.8 Worsening of asthma

Investigators and patients will be instructed how to deal with worsening of asthma symptoms. The data captured in the eDiary will also be used to alert the patient and/or investigator to possible signs of worsening asthma and to possible asthma exacerbation. The investigator must provide the patient with written instructions to contact the investigator if at any time during the trial from the Run-in onwards if one or more of the following criteria of worsening asthma develop:

[redacted]

eCRF. Significant findings made after informed consent (Visit 1) is given which meet the definition of an AE must be recorded on the AE screen of the patient's eCRF.

6.5.2 Vital signs

Systolic and diastolic blood pressure and radial pulse rate (over a 30 second interval), performed in the sitting position, will be recorded at each scheduled clinic visits as detailed in Table 6-2. (at Visits 101, 102, 201, 202, 204 or TD Visit, if applicable). Vital sign should be measured directly after the ECG assessments.

6.5.3 Height and weight

Height in centimeters (cm) will be measured at Visit 101 for all patients. In adolescents the height will additionally be measured at Visit 204 (or TD Visit if applicable). Body weight (to the nearest 0.1 kilogram in indoor clothing, but without shoes) will be measured at Visit 101, 204 (or TD Visit if applicable). BMI will be calculated based on height and weight.

6.5.4 Laboratory evaluations

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

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

Safety laboratory assessments (hematology, clinical chemistry, urinalysis [redacted]) will be performed at Visit 101, 201, 204 and TD Visit if applicable.

6.5.4.1 Hematology

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

6.5.4.2 Clinical chemistry

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

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

6.5.4.3 Urinalysis

Dipstick measurements for specific gravity, pH, protein, glucose and blood will be performed at Visits 101, 201, and 204, or TD (if applicable).

[redacted]

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

6.5.4.4 Hepatotoxicity

Any liver event which meets the criteria for "**medically significant**" event as outlined in Table 8-1 in Appendix 8 should follow the **standard procedures for SAE reporting** as described in Section 7.2.

6.5.4.5 Plasma Cortisol

Evening plasma cortisol will be measured at Visits 201, 204 and TD Visit if applicable. The sampling point is as shown in Table 6-1 and Table 6-2.

6.5.5 Electrocardiogram (ECG)

ECGs should be recorded after 10 minutes rest in the supine position to ensure a stable Baseline.

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

Centralized ECG equipment

At Visit 101, a Screening ECG will be measured to test for eligibility for trial inclusion. (Patients whose ECG is abnormal at Screening due to technical/mechanical faults may be re-screened.) At Visits 201, and 204, ECGs will be measured at -35min pre-dose (evening dose) and post dose 1 hour, as indicated in Table 6-2. All ECGs should include 12 standard leads. An ECG tracing will be taken for those patients who prematurely discontinue from the study treatment.

For each ECG performed original trace should be printed. Each 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 and will be dated and signed. The patient's number, the date, actual time of the tracing, and Study Code must appear on each page of the tracing.

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

Clinically significant ECG findings at Baseline must be discussed with the sponsor before administration with study drug.

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.

[redacted]

[redacted]

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign including abnormal laboratory findings, symptom or disease) in a patient or clinical investigation patient after providing written informed consent for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

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

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

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

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

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

- The severity grade:
  Mild: usually transient in nature and generally not interfering with normal activities
  Moderate: sufficiently discomforting to interfere with normal activities
  Severe: prevents normal activities
- Its relationship to the study treatment (Yes or No):
  "No Relationship to study treatment or other investigational treatment" or
  "Relationship to study treatment" or
  "Relationship to other investigational treatment" or
  "Relationship to both study treatment and other investigational treatment or indistinguishable".
- Its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.

[redacted]

- Whether it constitutes a SAE, as defined in Section 7.2 and which seriousness criteria have been met.
- Action taken regarding the study treatment. All AEs should be treated appropriately. Treatment may include one or more of the following:
    - no action taken (e.g., further observation only)
    - [investigational] treatment dosage increased/reduced
    - [investigational] treatment interrupted/withdrawn
    - concomitant medication or non-drug therapy given
    - patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
    - its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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

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

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

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any 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

[redacted]

- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention.

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

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (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 (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 AEs (serious and non-serious) are captured on the eCRF. SAEs are also required for individual reporting to Drug Safety & Epidemiology DS&E) as per Section 7.2.2.

7.2.2 SAE reporting

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

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

[redacted]

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

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

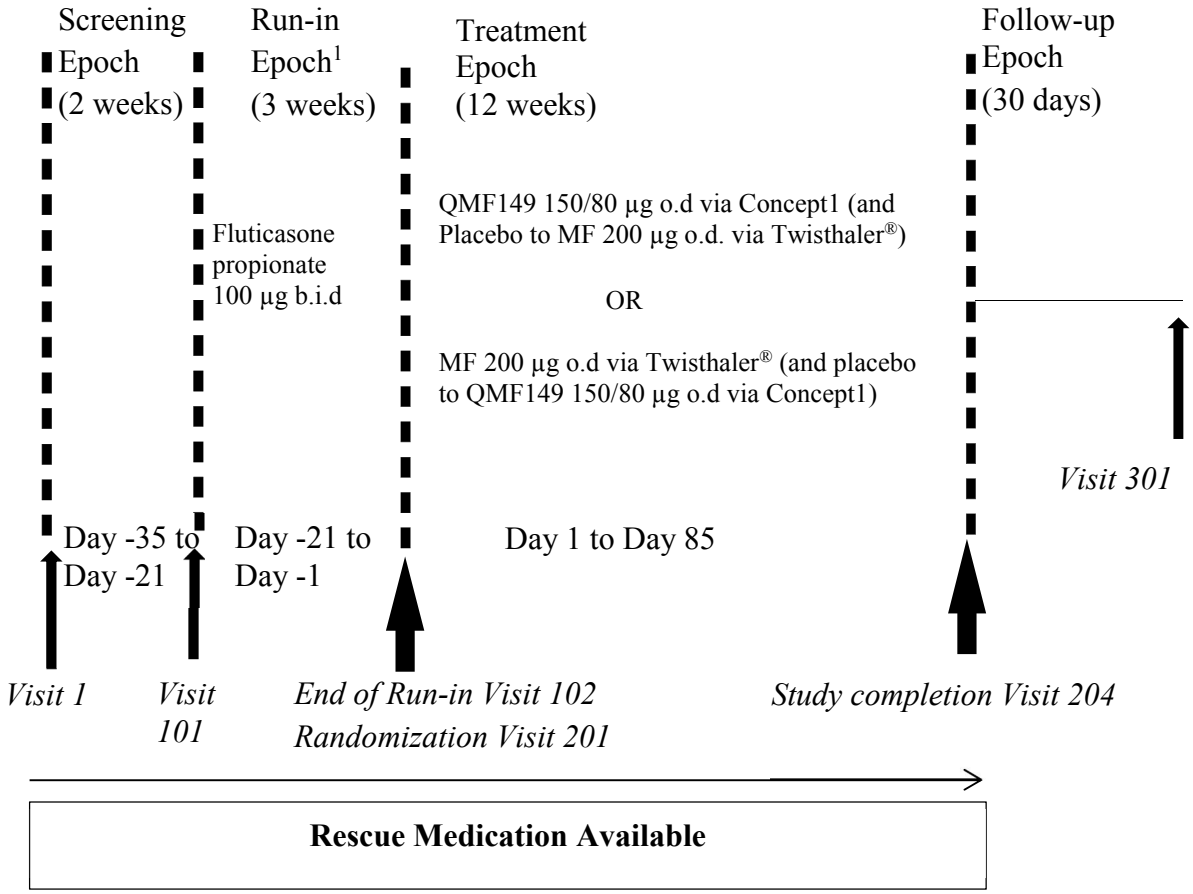
[redacted]

Glossary of terms

Dosage	Dose of the study treatment given to the patient in a time unit (e.g., 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g., prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
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
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Medication pack number	A unique identifier on the label of each investigational drug package
Patient ID	A unique number assigned to each patient upon signing the informed consent
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug Run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Patient Number	A number assigned to each patient who enrolls into the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

[redacted]

Figure 3-1 Study Design



[1] Please refer to Table 5-1 for details of adjustments to concomitant asthma medications and specified minimum washout periods prior to Run-in (Visit 101) and/or Randomization (Visit 201). For Run-in medication, fluticasone propionate 100 µg b.i.d should be delivered via Accuhaler® or fluticasone propionate 125 µg b.i.d. via Metered Dose Inhaler (MDI) will be accepted. In case it is not available in a particular country, fluticasone propionate in an alternative formulation at an equivalent dose strength may be used.

3.2 Rationale for study design

In order to optimize the rigor of the study and minimize bias, a randomized, double-blind parallel group design is used. This design is appropriate to determine the benefit of the addition of a LABA in a fixed dose combination with low dose ICS as compared to low dose ICS monotherapy. The study design does not include a placebo control, as this would not be considered ethical in this population of asthmatic patients who are symptomatic.

The primary objective of the trial is to evaluate the efficacy and safety of QMF149 150/80 microgram o.d. via Concept1 compared to MF 200 microgram via Twisthaler® in poorly (i.e., inadequately) controlled symptomatic patients as measured by trough FEV_1. In addition, secondary endpoints will provide data related to asthma control (ACQ), rescue medication use,

measurements at regular intervals throughout the study will help assess status of the patient's asthma symptom control. eDiary data will be transmitted electronically from the device to the investigator daily. Therefore, investigators will be able to monitor the patients closely throughout the study in case of an early indication of worsening symptoms.

In the event of worsening asthma symptoms, guidance to manage potential worsening of asthma symptoms is available to the investigators in accordance with 6 guideline recommendations. Patients will be provided with clear written instructions on contacting the investigator in case of worsening of their symptoms.

The investigator must discontinue study treatment or withdraw the patient from the study if, he/she believes that continuation would be detrimental to the patient's well-being. Patients are also instructed that they can withdraw from the study at any time, and for any reason. Patients will be followed up for safety for 30 days after they have stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later)

In summary, based on the available data of QMF149 and the efficacy and safety data of the marketed monotherapy components, it is anticipated that QMF149 150/80 microgram will have a favorable benefit to risk profile in this patient population with asthma.

4 Population

The study population will consist of approximately 750 males and females with a diagnosis of asthma ≥ 12 and ≤ 75 years of age. Approximately 50 patients enrolled in the study will be adolescents (≥ 12 and < 18).

Adolescent patients with a diagnosis of asthma should be symptomatic on low dose ICS (ACQ-7 ≥ 1.5). Patients more adequately controlled taking low dose ICS/LABA (ACQ-7 score ≥ 1 and < 1.5) may also be included, however they can only be enrolled to double-blind treatment if ACQ-7 score is ≥ 1.5 at the time of randomization. The ACQ-7 thresholds for level of control are consistent with published literature (Juniper 2006). Although Juniper does not specifically define 'adequate control', it can be reasonably estimated to be around 1, which is considered the crossover point between 'well controlled' and 'not well controlled' asthma (Juniper 2006); therefore a range of ≥ 1 to < 1.5 is considered acceptable as an appropriate range for 'adequately' controlled asthma.

Adult patients with a diagnosis of asthma should be symptomatic on low dose ICS or low dose ICS/LABA with ACQ-7 score ≥ 1.5.

It is anticipated 1370 patients will need to be screened in order to randomize approximately 750 patients into the two treatment groups with a randomization ratio of 1:1 (i.e., approximately 375 patients per treatment group). At least 676 randomized patients (338 per treatment group) are needed to complete the study.

Drop-outs after randomization will not be replaced. This study will enroll multi-nationally and patients will be stratified according to prognostic factors of age (≥ 12 to < 18 years or ≥ 18) and non-prognostic factor region to achieve improved homogeneity within each stratum.

[redacted]

Table 6-1 Assessment schedule

Visit Number	**1**	**101**	**102**	**201**	**202**	**203[5]**	**204[10]**	**Early treatment discontinuation (TD)**	**Premature study discontinuation (PSD)**	**301[9]**
Epoch	**Screen**	**Run-in**		**Treatment**					**PSD**	**Follow-up**
Clinic (C) /Telephone (T)	C	C	C	C	C	T	C	C	T	T
Week – Start of Week	-5 to -3	-3	0	0	4	8	12			16
Day Number	-35 to -21	-21	1	1/2	30	57	84/85[6]			114
Obtain Informed Consent and/or assent (including for sub-group)	X[11]									
Current medication review/ adjustment	X									
Inclusion/exclusion criteria	X	X	X							
Randomization via IRT				S						
Medical History, Demography	X									
History of Asthma exacerbation	X									
Smoking history and status	X									
Run-in medication		X								
Pregnancy test (serum)[1]		X			X		X	X		
Pregnancy test (urine) [1]	X		X							

[redacted]

Visit Number	**1**	**101**	**102**	**201**	**202**	**203[5]**	**204[10]**	**Early treatment discontinuation (TD)**	**Premature study discontinuation (PSD)**	**301[9]**
Epoch	**Screen**	**Run-in**		**Treatment**					**PSD**	**Follow-up**
Clinic (C) /Telephone (T)	C	C	C	C	C	T	C	C	T	T
Week – Start of Week	-5 to -3	-3	0	0	4	8	12			16
Day Number	-35 to -21	-21	1	1/2	30	57	84/85[6]			114
Screening spirometry and FEV_1 reversibility test (SABA)		X								
Spirometry[2]			X	X	X		X	X		
Issue eDiary[5]	X									
Issue Peak Flow meter		S								
Review and upload eDiary recordings[5]			S		S		S	S		
Administer study drug at visit				X	X		X			
Dispense study medication via IRT				X	X					
Call IRT for visit confirmation	S	S		S	S		S	S	S	S
Collect unused study medication					S		S	S		
Record interruption/changes in Drug Administration to assess compliance					X	X	X	X		
AE recordings	X[14]	X	X	X	X	X	X	X	X	X

[redacted]

Asthma Worsening Criteria alerts

- > 20% decrease in FEV_1 from Baseline value (this criterion applies to Investigator review at the time of a study visit or possibly an alert setting if device structured to capture)
- > 50% increase in SABA use and > 8 puffs per day on 2 out of any 3 consecutive days compared to Baseline
- ≥ 20% decrease in am or pm PEF from Baseline on 2 out of any 3 consecutive days compared to Baseline
- < 60% of PEF compared to Baseline
- Nighttime awakenings requiring SABA use on at least 2 out of any 3 consecutive nights
- Urgent unscheduled clinic visit due to asthma related deterioration

Note: The reference for the worsening of asthma during the Run-in epoch would be the FEV_1 and PEF taken at Visit 101. The Baseline FEV_1 for the treatment epoch is taken at treatment Day 1 (Visit 201). The Baseline PEF (morning and evening) for the treatment epoch is calculated at Visit 102 and is the mean of the best of the three daily PEF measurements over the Run-in period.

If any of the above criteria, including the alert from eDiary are met while a patient is in the Run-in or treatment epoch, the investigator should assess the patient's condition. If this occurs during the Run-in epoch, and it is considered a clinically significant asthma worsening in the investigator's opinion, the patient should be treated for asthma worsening as appropriate and discontinued prior to randomization. Once the condition is resolved, if eligibility criteria are met, the patient may be considered for re-screening.

The alerts which are trigged by above criteria are in place to detect early onset of asthma worsening at any time during the study to help direct early intervention. Therefore the investigator should do the following when alerts are received:

- Review alert trends over time, in particular PEF decreases.
- Call the patient promptly to assess the clinical status when any specific alert type (e.g., PEF < 60%) is received on consecutive days. This may include urgent clinic visits as appropriate and/or immediate treatment.
- Implement prompt clinical treatment as deemed necessary by the investigator.

If patient believes that his/her symptoms are worsening and/or has received alerts as outlined above the patient should notify the investigator in order to be evaluated and treated as clinically appropriate. Patient should be instructed to visit emergency room / hospital if deemed necessary.

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

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

6.4.9 Asthma Exacerbation

A **severe asthma** exacerbation (Draft note for guidance on clinical investigation of medicinal products for treatment of asthma: CHMP/EWP/2922/01 Rev.1) is defined as an aggravation of

[redacted]

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

6.5.6 Serious asthma outcomes

Asthma-related hospitalizations, asthma-related intubations or asthma-related deaths over the 12-week treatment epoch will be recorded and will all be reviewed by the Adjudication Committee. Hospitalization is defined as an inpatient stay or a ≥ 24 hour stay in an observation area in an emergency department or other equivalent facility.

6.5.7 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. A plasma and urine pregnancy test will be performed (tests provided by the Central Laboratory) per Assessment Table 6-1. A positive urine pregnancy test at Visit 1, Visit 102 and positive serum pregnancy test at Visit 101 or Visit 202 or Visit 204 or TD Visit if applicable or at any time during the study requires the patient to be discontinued from the study treatment. Refer to Section 5.6.2 and Section 7.4 for more details.

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

6.5.8 Appropriateness of safety measurements

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

[redacted]

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

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study drug a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study drug 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 European Union (EU) Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.2.3 Pneumonia reporting

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

7.3 Liver safety monitoring

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

The following two categories of abnormalities/AEs 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 eCRF pages

[redacted]

Appendix 9: ICS Dose Level

Table 9-1 Low, Medium and High Daily Doses of Inhaled Glucocorticosteroids for Adults and Adolescents (12 years and older) (GINA 2016)

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

CFC: chlorofluorocarbon propellant; DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant
*Beclomethasone dipropionate CFC is included only for comparison with older literature
**As per Relvar SmPC

[redacted]