NOVARTIS

Global Clinical Development - General Medicine

QAW039

Clinical Trial Protocol CQAW039A2323 / NCT03629249

A 52-week, multicenter, randomized, double-blind, double-dummy, parallel-group, placebo-controlled study of fevipiprant once daily plus standard-of-care (SoC) for reduction of systemic corticosteroids (oral and parenteral) use in patients with severe asthma

Document type:	Amended Protocol Version
EUDRACT number:	2018-000212-25
Version number:	01 (Clean)
Clinical Trial Phase:	IV
Release date:	05-Dec-2018

[redacted]

Table of contents

Table of contents 2
List of tables 5
List of figures 6
List of abbreviations 7
Glossary of terms 9
Amendment 1 10
Protocol summary 11
1 Introduction 15
1.1 Background 15
1.2 Purpose 17
2 Study objectives and endpoints 18
2.1 Objectives and related endpoints 18
3 Investigational plan 19
3.1 Study design 19
3.2 Rationale for study design 20
3.3 Rationale for dose/regimen, route of administration and duration of treatment 20
3.4 Rationale for choice of comparator 21
3.5 Purpose and timing of interim analyses/design adaptations 22
3.6 Risks and benefits 22
4 Population 23
4.1 Inclusion criteria 23
4.2 Exclusion criteria 24
5 Treatment 27
5.1 Study treatment 27
5.1.1 Investigational and control drugs 27
5.1.2 Additional treatment 28
5.2 Treatment arms 28
5.3 Treatment assignment and randomization 28
5.4 Treatment blinding 29
5.5 Treating the patient 30
5.5.1 Patient numbering 30
5.5.2 Dispensing the study drug 30
5.5.3 Handling of study and additional treatment 30
5.5.4 Instructions for prescribing and taking study treatment 31
5.5.5 Permitted dose adjustments and interruptions of study treatment 32
5.5.6 Rescue medication 33

[redacted]

5.5.7 Concomitant medication 34
5.5.8 Prohibited medication 35
5.5.9 Emergency breaking of assigned treatment code 36
5.6 Study completion and discontinuation 37
5.6.1 Study completion and post-study treatment 37
5.6.2 Discontinuation of study treatment 37
5.6.3 Withdrawal of informed consent 38
5.6.4 Loss to follow-up 39
5.6.5 Early study termination by the sponsor 39
6 Visit schedule and assessments 39
6.1 Information to be collected on screening failures 44
6.2 Patient demographics/other baseline characteristics 44
6.3 Treatment exposure and compliance 45
6.4 Efficacy 45
6.4.1 Systemic corticosteroids use 45
6.4.2 Health status (Patient Reported Outcomes) 45
6.4.3 eDiary 46
6.4.4 Worsening of asthma (and related eDiary alerts) 48
6.4.5 Biologic therapy administered during the treatment period 48
6.4.6 Appropriateness of efficacy assessments 48
6.5 Safety 48
6.5.1 Medical history and physical examination 49
6.5.2 Asthma Exacerbations 49
6.5.3 Vital signs 50
6.5.4 Height and weight 50
6.5.5 Laboratory evaluations 50
6.5.6 Electrocardiogram (ECG) 51
6.5.7 Pregnancy 52
6.5.8 Appropriateness of safety assessments 52
6.6 Other assessments 52
6.6.1 Clinical Outcome Assessments (COAs) 52
[redacted] [redacted] 52
6.6.3 Pharmacokinetics 53
6.6.4 Spirometry 53
6.6.5 Other biomarkers 53
7 Safety monitoring 53
[redacted] 53

7.2 Serious adverse events 55
7.2.1 Definition of SAE 55
7.2.2 SAE reporting 56
7.3 Liver safety monitoring 56
7.4 Renal safety monitoring 57
7.5 Reporting of study treatment errors including misuse/abuse 57
7.6 Pregnancy reporting 58
7.7 Prospective suicidality assessment 58
8 Data review and database management 58
8.1 Site monitoring 58
8.2 Data collection 59
8.3 Database management and quality control 59
8.4 Data Monitoring Committee 60
8.5 Adjudication Committee 60
9 Data analysis 60
9.1 Analysis sets 60
9.2 Patient demographics and other baseline characteristics 61
9.3 Treatments 61
9.4 Analysis of the primary variable(s) 61
9.4.1 Primary Variable(s) 61
9.4.2 Statistical model, hypothesis, and method of analysis 61
9.4.3 Handling of missing values/censoring/discontinuations 64
9.4.4 Sensitivity analyses 64
9.5 Analysis of secondary variables 64
9.5.1 Efficacy variables 64
9.5.2 Safety variables 66
[redacted] 67
9.5.4 Pharmacokinetics 67
9.5.5 DNA 67
9.5.6 Biomarkers 67
9.5.7 PK/PD 67
[redacted]
9.7 Interim analyses 67
9.8 Sample size calculation 68
10 Ethical considerations 70
10.1 Regulatory and ethical compliance 70
[redacted] 70

[redacted]

10.3 Responsibilities of the investigator and IRB/IEC 71
10.4 Publication of study protocol and results 71
10.5 Quality Control and Quality Assurance 71
11 Protocol adherence 71
11.1 Protocol Amendments 72
12 References 73
13 Appendix 1: Clinically notable laboratory values and vital signs 76
14 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements 76
15 Appendix 3: Specific Renal Alert Criteria and Actions 79
16 Appendix 4: List of idiosyncratic drug reactions (IDRs) for investigators 80
17 Appendix 5: Spirometry Guidance 81
17.1 References for appendix 82
18 Appendix 6: Asthma Control Questionnaire (ACQ-5) 84
19 Appendix 7: Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12) 86
20 Appendix 8: Asthma Plan 91
21 Appendix 9: Estimated Equivalence of Inhaled Corticosteroids 92

List of tables

Table 2-1 Objectives and related endpoints 18
Table 5-1 Blinding levels 29
Table 5-2 Medications allowed under certain conditions 34
Table 5-3 Medications to be withheld prior to spirometry 35
Table 5-4 Prohibited medication 35
Table 6-1 Assessment Schedule 41
Table 6-2 Daytime symptom diary scale questions 47
Table 6-3 Nocturnal diary scale question 47
Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse 58
Table 9-1 Frequency distribution of dose to display (non-normal) distribution of US Marketscan database 68
Table 9-2 Other scenario investigated for Fevipiprant single dose EOS greater or equal 250 cells/microliter 69
Table 14-1 Liver Event and Laboratory Trigger Definitions 76
Table 14-2 Follow Up Requirements for Liver Events and Laboratory Triggers 76
Table 15-1 Specific Renal Alert Criteria and Actions 79
Table 16-1 Definition of potential idiosyncratic drug reactions 80

[redacted]

List of figures

Figure 3-1 Study design 19
Figure 9-1 Closed testing procedure for primary objectives 63

[redacted]

List of abbreviations

ACQ-5	Asthma Control Questionnaire
ACR	albumin-creatinine ratio
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AQLQ	Asthma Quality of Life Questionnaire
AST	aspartate aminotransferase
ATS	American Thoracic Society
AV	atrioventricular
b.i.d.	twice a day
BMI	body mass index
BTPS	body temperature and pressure saturated
BTS	British Thoracic Society
BUN	blood urea nitrogen
CFR	Code of Federal Regulation
CK	creatinine kinase
CK-MB	creatine kinase-muscle/brain
CMO&PS	Chief Medical Office and Patient Safety
COA	clinical outcome assessments
CPO	Country Pharma Organization
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRTh2	chemoattractant receptor-homologous molecule expressed on T helper 2 cells
DMC	Data Monitoring Committee
DP2	Prostaglandin D2 receptor
DPI	dry-powder inhaler
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	eosinophil
EOT	End of Treatment
ERS	European Respiratory Society
EU	European Union
FAS	full analysis set
FEV1	Forced Expiratory Volume in 1 second
FVC	full volume capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
HbA1c	Hemoglobin A1c
HCUP	Healthcare Cost and Utilization Project
HD	High Dose
HFA	Hydrofluoroalkanes

[redacted]

HRQOL	health related quality of life
i.v.	intravenous
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled corticosteroids
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IRB	Institutional Review Board
IRT	Interactive Response Technology
IVRS	Interactive voice response system
IWRS	Interactive web response system
LABA	Long-acting beta-agonist
LAMA	Long-acting muscarinic antagonist
LFT	Liver function test
LS	least square
LTRA	Leukotriene Receptor Antagonist
mcg	microgram
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
OCS	Oral corticosteroids
p.o.	oral
PEF	peak expiratory flow
PGD2	Prostaglandin D2
QTc	corrected QT interval
RoW	Rest of World
SABA	Short-acting Beta-agonist
SAE	serious adverse event
sCR	serum creatinine
SCS	Systemic corticosteroids
SmPC	summary of product charateristics
SoC	Standard of Care
SOP	standard operating procedures
SUSAR	Suspected Unexpected Serious Adverse Reactions
TC	Telephone contact
TD	treatment discontinuation
TdP	Torsades de Pointes
Th2	T helper cells 2
UK	United Kingdom
ULN	upper limit of normal
US	United States of America
WHO	World Health Organization
µl	microliter

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”.
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study.
Variable	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 study consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

[redacted]

Amendment 1

Amendment rationale

This protocol is being amended based on health authority feedback. Based on this feedback the following changes have been implemented.

- Modify in-clinic study visit frequencies to 8 weeks intervals after week 12, interspaced with telephone contacts.
- Add additional collection of hematology, clinical chemistry and urinalysis in all in-clinic visits

In addition, clarifications has been included as well

- correct abbreviations on the summary section
- clarifications on treatment of patients after study end
- misspells

Changes to the protocol

Updated visit schedule sequence between telephone contact (TC) and in-clinic visits. In-clinic visits (week 6, 12, 20, 28, 36, 44, 52) TC visits (week 16, 24, 32, 40, 48, 54)

Added additional hematology, clinical chemistry and urinalysis at all in-clinic visits on the visit schedule and assessments section 6

Corrected abbreviations in the summary section on the primary analysis portion.

Clarifications added on sections 5.5.6, 5.6.1 and table 6.1.

Protocol summary

Protocol number	CQAW039A2323
Full Title	A 52-week, multicenter, randomized, double-blind, double-dummy, parallel-group, placebo-controlled study of fevipiprant once daily plus standard-of-care (SoC) for reduction of systemic corticosteroids (oral and parenteral) use in patients with severe asthma
Brief title	SCS avoidance study in severe Asthma Patients
Sponsor and Clinical Phase	Novartis 3b
Investigation type	Drug
Study type	Interventional
Purpose and rationale	There is a correlation between Systemic Corticosteroids (SCS) use and Adverse Events (AEs). Sustained use of SCS is associated with significant side effects, including growth retardation in children, as well as osteoporosis, diabetes, cardiovascular adverse events, muscular weakness, skin atrophy and cataract. This translates in an advantage for AE avoidance for those patients that do not use any SCS. Alternative asthma therapies that reduce the need for SCS are urgently needed, especially if given orally, such as fevipiprant. The overall purpose of this study is to determine the efficacy of fevipiprant (150 mg and 450 mg once daily), compared with placebo, as add-on to GINA 2018 treatment step 4 or 5 standard-of-care (SoC) asthma therapy, in terms of avoidance of SCS use over 52 weeks. This will be measured in patients with inadequately controlled severe asthma (Asthma Control Questionnaire score (ACQ-5) ≥ 1.5) and high eosinophil counts (eosinophil count at Screening Visit ≥ 250 cells/µl), and in the overall patient population regardless of eosinophil counts.
Primary Objective(s)	• In patients with severe asthma and high eosinophil counts receiving flexible SoC asthma therapy, to demonstrate a reduction in the use of SCS with fevipiprant, compared with placebo. • In all patients with severe asthma receiving flexible SoC asthma therapy, to demonstrate a reduction in the use of SCS with fevipiprant , compared with placebo.
Secondary Objectives	• To evaluate the effect of fevipiprant and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy in terms of proportion for patients with no SCS use from the overall population • To evaluate the effect of fevipiprant and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy in terms of general safety / tolerability in the overall population • To evaluate the effect of fevipiprant and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy in terms of proportion of patients receiving continuous SCS during ≥ 30 days, at ≥ 7.5mg/day of prednisone/prednisolone (or equivalent) in the overall population • To evaluate the effect of fevipiprant and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy in terms of Asthma Related Quality of Life Questionnaire (AQLQ+12) in the overall population • To evaluate the efficacy fevipiprant and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy, with respect to change from baseline in Asthma Control Questionnaire (ACQ-5) in the overall population • To evaluate the effect of fevipiprant and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy in terms of time to first prescription of biologic therapy in the overall population • To evaluate the effect of fevipiprant and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy in terms of difference in daytime and nighttime symptom scores

[redacted]

Study design	This study uses a randomized, multicenter, double-blind, double-dummy, placebo-controlled, parallel-group study design. The study will include a Screening period of up to 2 weeks to assess eligibility, a Run-in period of 4 (for high-dose ICS dose patients) or 10 (for mid-dose ICS patients) weeks to evaluate maintenance of asthma control and to collect baseline safety data, a Treatment period of 52 weeks and a Follow-up period of 2 weeks following the last dose of study drug to collect additional data for safety variables.
Population	The study population will consist of approximately 669 male and female patients with uncontrolled asthma aged 18 and above.
Key Inclusion criteria	• Written informed consent must be obtained within 14 days prior to or at Screening Visit before any assessment is performed including any adjustment to asthma medication. • Male and female patients aged ≥ 18 years • Patients with a diagnosis of asthma for a period of at least 3 months prior to Screening Visit with current asthma severity step 4 or 5 (GINA 2018) • Currently on treatment with medium or high dose ICS/LABA +/- other controller (LAMA, LTRA or Theophylline as per GINA) for a minimum of 6 weeks prior to Screening Visit . • Demonstration of inadequate control of asthma based on an ACQ-5 score ≥ 1.5 at Screening Visit and Randomization Visit . • Documented history of at least 1 asthma exacerbation [(that required ≥ 3 consecutive days of oral corticosteroids or ≥ 1 dose of IM or IV corticosteroids or hospitalization (defined as an inpatient stay or > 24-hour stay in an observation area in the emergency room of other equivalent facility,)] within 1 year prior to enrolment • At screening, patients with FEV1 of ≤ 80% of the predicted normal value for the patient, after withholding bronchodilators at Screening Visit and beginning of Run-In Visit . • An increase of ≥ 12% and ≥ 200 ml in FEV1 approximately 10 to 15 minutes after administration of 400 mcg of salbutamol/albuterol prior to randomization (documented historical reversibility is accepted)

Key Exclusion criteria	• Asthma exacerbation, within 6 weeks prior to enrolment (screening) that required SCS, hospitalization, or emergency room visit. Patients who experience an exacerbation between screening to end of run-in, prior randomization, to be considered failures and can be eligible for re-screening only once, 6 weeks after recovering from the exacerbation.
	• Chronic/ maintenance use of OCS for asthma (regular OCS use for over 6 months; continuously or intermittently) within the last year
	• Prior use of biologics (including but not limited to Omalizumab, Mepolizumab, Reslizumab, Dupilumab, Benralizumab etc., for asthma or any other indications) that has potential to interfere/ affect asthma disease progression, in the previous 6 months.
	• Any contra-indications to SCS use e.g. diabetes, narrow angle glaucoma, or any other as defined by the treating physician
	• Pregnant or nursing (lactating) women
	• Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of investigational drug
	• History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
	• Patients requiring SCS use for conditions other than asthma (chronic or intermittent)
	• Patients with a known history of non-compliance to medication or who are unable or unwilling to complete an electronic patient diary or who are unable or unwilling to use Electronic Peak Flow with eDiary device or who are unable to demonstrate good eDiary compliance (defined as > 75% for eDiary compliance) during run-in.
	• Patients who have a clinically significant laboratory abnormality at the Run-in Visit laboratory test including (but not limited to):
	  • Total white blood cell count < 2500 cells/µL
	  • AST or ALT > 2.0 X ULN or total bilirubin > 1.3 X ULN

[redacted]

	• Estimated Glomerular Filtration Rate (eGFR) by the Modification of Diet in Renal Disease (MDRD) equation or Bedside Schwartz equation < 55 mL/minute/1.73 m2 • Patients with serious co-morbidities including, but not limited to, neurodegenerative diseases, rheumatoid arthritis and other autoimmune diseases • Patients on > 20 mg of simvastatin, > 40 mg of atorvastatin, > 40 mg of pravastatin, or > 2 mg of pitavastatin. Statin doses less than or equal to these doses as well as other statins will be permitted during the study • Patients on any statin therapy with a CK level > 2 X ULN at Run-in Visit • Patients with a history of conditions other than asthma that could result in elevated eosinophils (e.g., hypereosinophilic syndromes, Churg-Strauss Syndrome, eosinophilic esophagitis). Patients with known parasitic infestation within 6 months prior to Screening Visit are also excluded
Study treatment	• QAW039 150 mg and QAW039 450 mg once daily • placebos to QAW039 150 mg and QAW039 450 mg once daily
Efficacy assessments	• Systemic Corticosteriods use • Health Status (PROs: AQLQ+12, ACQ-5) • Biologic therapy administered during the treatment period
Key safety assessments	• Medical history and physical examination • Adverse events including serious adverse events • Asthma Exacerbations • Vital signs • ECG • Height and weight • Laboratory evaluations (Hematology, Blood chemistry including HbA1c, Urinalysis) • Pregnancy (female patients) • Serious asthma outcomes
Other assessments	None
Data analysis	Approximately 669 patients will be randomized in 1:1:1 ratio in either of the three arms Fevipiprant 450 mg dose, Fevipiprant 150 mg dose or placebo in addition to standard of care. The randomization will be stratified according to patients peripheral blood eosinophil count (< 250 cells/µl or ≥ 250 cells/µl). **Primary analysis:** The primary endpoint of the study is total systemic corticosteroid dose in mg prednisone/prednisolone or equivalent over 52 weeks of treatment. The primary endpoint will be analyzed in subpopulation of patients with eosinophil count ≥ 250 cells/µl and in overall population. Demonstration of total systemic corticosteroid SCS dose used in mg over 52 weeks of treatment for subpopulation of patients with eosinophil count ≥ 250 cells/µl and in overall population will be evaluated using the following primary null hypothesis: • $H_{01\,450}$ eosinophil subgroup: the distribution of the total SCS dose (in mg) in Fevipiprant 450 mg QD plus SoC is equivalent to the distribution of the total SCS dose (in mg) in placebo plus SoC in patients with eosinophil count ≥ 250 cells/µl • H_{02} 150 eosinophil subgroup: the distribution of the total SCS dose (in mg) in Fevipiprant 150 mg QD plus SoC is equivalent to the distribution of the total SCS dose (in mg) in placebo plus SoC in patients with eosinophil count ≥ 250 cells/µl • H_{03} 450 overall population: the distribution of the total SCS dose (in mg)in Fevipiprant 450 mg QD plus SoC is equivalent to the distribution of the total SCS dose (in mg) in placebo plus SoC for the overall population

[redacted]

	• H_{04} 150 overall population: the distribution of the total SCS dose (in mg)in Fevipiprant 150 mg QD plus SoC is equivalent to the distribution of the total SCS dose (in mg) in placebo plus SoC for the overall population The familywise type I error rate will be controlled at the two-sided 5% level across the primary null hypotheses using graphical approach.The total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) over 52 weeks of treatment will be analyzed using the Wilcoxon-Mann-Whitney rank sum test (Van Elteren test). For overall population analysis will be stratified by randomization stratum – blood eosinophils levels (≥ 250 cells/µl and < 250 cells/µl). For subgroup with blood eosinophils ≥ 250 cells/µl, analysis will not include stratification factor. The summary statistics for total SCS dose by treatment group will be provided. The total SCS dose data will be aggregated into monthly data for analysis. For the patients discontinuing treatment early, the total SCS dose for 52 weeks will be obtained as annualized SCS dose. For example if patient took 280 mg for 7 months then for 12 months patient will be taking 280*12/7 = 480mg total SCS dose. Efficacy data collected during the use of biologics will be set to missing, since use of biologics can confound efficacy data. After replacing SCS dose with missing, patient will not have data available for all 12 months, thus total SCS dose will be obtained as annualized dose. **Secondary analysis:** The proportion of patients with free of SCS use over 52 weeks treatment will be summarized by treatment and analyzed using logistic regression in overall population. The model will include treatment and randomization strata as covariates. The proportion of patients requiring ≥ 7.5mg systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) per day continuously for at least 30 days in 52 weeks treatment period will be summarized by treatment and analyzed using logistic regression in overall population. The model will include treatment and randomization strata as covariates. The AQLQ+12 and ACQ-5 score will be analyzed using a MMRM with an unstructured covariance structure with factors for treatment group, time and randomization stratum, as well as the baseline values as continuous linear covariates. The time to first prescription of biologic therapy from first dose of study treatment received over 52 weeks of treatment will be summarized by treatment group. Between-treatment differences will be evaluated using cox regression model. Change from baseline in each endpoint (daytime and nighttime symptom score) will be analyzed using mixed models repeated measures (MMRM) model with factors as treatment group, randomization strata, time interval, time interval by treatment group interaction and the associated baseline as continuous linear covariate. Safety analysis will be based on safety set and analysis will be presented by treatment group. Safety summaries will be provided based on on-treatment data. The on-treatment period lasts from the date of first administration of study treatment to 14 days after the date of the last actual administration of any study treatment.
Key words	Efficacy and safety of QAW039, OCS avoidance, placebo-controlled, add-on to standard of care, flexible background therapy, uncontrolled severe asthma, female and male patient >= 18 years

[redacted]

1 Introduction

1.1 Background

Asthma presents a major global health burden. Despite existing therapies, there is still significant unmet medical need in asthma, with an estimated 300 million people affected worldwide. The World Health Organization (WHO) estimates that 15 million disability–adjusted life years are lost annually due to asthma, representing 1% of the total global burden. It is estimated that asthma accounts for about 1 in every 250 deaths worldwide (Masoli et al 2004). Severe asthma is defined as asthma that requires treatment with high dose of inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids (SCS), including both oral (OCS) and injectable administration, to prevent it from becoming "uncontrolled" or that remains "uncontrolled" despite this therapy. Severe asthma is a heterogeneous condition consisting of multiple phenotypes (American Thoracic Society 2000).

In severe asthma, large cumulative doses of corticosteroids and, in particular, SCS are used to treat patients to maintain control. In a matched cohort study on patients suffering with severe asthma and receiving OCS or not, Zazzali at al. assessed an United States (US) commercial health care claims and found OCS use to be common: 60% of patients with asthma filled at least one OCS prescription over a 2-year period, (Zazzali et al 2015). Patients in the high-OCS group had a mean prednisone-equivalent dose exposure of 4592 mg during the 2 years-study period, compared with 0 mg for the no-OCS group. Moreover, according to data from the Healthcare Cost and Utilization Project (HCUP), corticosteroids were the most common cause of drug-related complications in 2004, accounting for 10% of all drug-related complications and 141,000 hospital stays in the US (Elixhauser A, HCUP Statistical Brief #29. April 2007). Although effective in patients with severe asthma, the use of SCS may be associated with serious systemic side effects such as osteoporosis, cataract, glaucoma, hypothalamic-pituitary-adrenal axis suppression disorders (i.e. iatrogenic form of Cushing's syndrome, adrenal insufficiency, and growth inhibition), myopathies (such as myalgia and muscle atrophy), psychiatric disorders, diabetes, hypertension and an increased risk of infection (Schäcke et al 2002).

Given the prevalent use of SCS in patients with severe asthma, it is important to characterize the adverse effects associated with SCS treatment in asthmatic patients to better understand the comparative risks. Hence, the review of several recent studies helps understand the range of toxicity presented by SCS:

- In a recent analysis of the UK Optimum Patient Care Research Database (OPCRD) and British Thoracic Society (BTS) Difficult Asthma registry, most subjects (92%–93%) with severe asthma examined had at least one condition linked to systemic corticosteroid exposure, with significantly higher prevalence rates than in subjects with mild/moderate asthma and in subjects without asthma (Sweeney et al 2016).
- In a retrospective study using administrative claims data from a subset of asthma patients from a U.S. large commercial database between 2003 and 2014, Dalal et al. found that patients continuously exposed for > 6 months with low (< 5 mg/day), medium (≥ 5-10 mg/day) and high (> 10 mg/day) systemic corticosteroid exposure had a 1.36-fold, 2.28-fold, and 2.42-fold risk, respectively, of developing bone- and muscle-related complications,

such as fractures, relative to patients without exposure to systemic corticosteroid (Dalal et al 2016).

- De Vries et al. reported a significantly increased risk of developing fractures among obstructive airway disease patients exposed to an SCS compared to those never exposed. The total period of follow-up for each patient was taken as the time period from the first SCS prescription until the end of data collection for the UK General Practice Database. This total period of time was then divided into periods of current exposure and past exposure, with patients moving between current and past exposure. Each period of current exposure started with a SCS prescription and ended 3 months after the expected duration of SCS therapy. Depending on the type of fracture, they estimated a relative risk varying from 1.37 to 5.65 for patients with a cumulative dose of SCS between 1 gm and 5 gm, and from 3.00 to 10.61 for patients with a cumulative dose > 5 gm (De Vries et al 2007).
- Lefebvre et al provided preliminary evidence that higher doses and continuous exposure to OCSs were associated with increased risk of AEs (Lefebvre et al 2015).
- The published literature shows that there is a correlation between intermittent or short burst SCS use and AEs, and also a cumulative toxic effect of multiple bursts. In a retrospective cohort study of asthmatic patients 18 years and older in the 2000-2014 US MarketScan data set, subjects taking 4 or more OCS prescriptions within the year had 1.29 times the odds of experiencing a new AE within the year. Each year of this kind of exposure resulted in 1.20 times the odds of having an AE per year. These patients had significantly greater odds of AEs for osteoporosis, hypertension, obesity, type 2 diabetes, gastrointestinal ulcers/bleeds, fractures, and cataracts (odds, 1.21-1.44 depending on the AE). This indicates a cumulative burden on SCS exposure. Exposure to 1 to 3 OCS prescriptions per year was also statistically significantly associated with the development of current and future AEs (Sullivan et al 2018). These studies showcase that intermittent or short bursts of OCS use increases the risk of the well-known side effects and comorbidities of SCS, and an additive effect of repeated doses. Hence, SCS-avoidance strategies, even of short-term bursts, are important to improve patient and populations well-being.

Prostaglandin D2 (PGD2) is one of the major prostanoid inflammatory mediators identified in asthma. The PGD2 type 2 receptor (DP2) usually mediates pre-inflammatory effects. Fevipiprant (QAW039) is a DP2 competitive antagonist in investigation in asthma. It exerts its effect by binding to DP2 receptors on eosinophils, Th2 and ILC2 cells in the blood and tissues; thus, inhibiting migration and activation of these cells into the airway tissues and reducing the release of pro-inflammatory cytokines (Chevalier et al 2005). Since these are the major effector cells and soluble factors driving airway inflammation in asthma, treatment with fevipiprant should result in a decrease in these parameters of airway inflammation as well as a clinical improvement in asthma, thus leading to a decrease of SCS therapy needs and a correlated decrease of the SCS-related AEs. In support of this premise are the results of Phase 2 studies of fevipiprant (Studies A2201, A2206, and A2208) in which fevipiprant demonstrated an improvement in lung function (i.e., forced expiratory volume in 1 second [FEV1]) in the overall population of patients with a range of asthma severities (Study A2206), an improvement in asthma control in patients with more severe asthma as defined by a baseline predicted FEV1 < 70% (Study A2201) or in patients with a baseline Asthma Control Questionnaire-7 total score ≥ 1.5 (Study A2208), and a 71% greater reduction from baseline in sputum eosinophils for

[redacted]

fevipiprant compared to placebo (geometric mean) in patients with severe asthma and sputum eosinophilia over 12 weeks of treatment.

The current SCS avoidance study (Study A2323) presents a novel concept: it will measure future total systemic corticosteroid use when fevipiprant is added to SoC, compared with placebo, in severe asthma patients (Global Initiative for Asthma [GINA] step 4 & 5) who are not on chronic or maintenance use of SCS (i.e. regular SCS use for over 6 months) within the last year prior to study enrollment. This is different to the approach of the OCS sparing studies, which measure reduction of OCS in patients already using chronic OCS at baseline. Considering that only a very small proportion of severe asthmatic patients (3.8%) use chronic OCS, and between 38% (US MarketScan database) and 59% (Bourdin et al 2018) of severe asthmatic patients receive bursts of SCS every year, we consider clinically and scientifically relevant to assess the use of fevipiprant to prevent or reduce the use of SCS in a real world setting where patient-individualized treatment is allowed along GINA guidelines step 4 and 5, allowing flexibility (step-up and step-down) of background control therapy and add-on other maintenance treatment options. The flexibility of the background therapy allows the investigator to increase or decrease doses of medications, or to add or remove medications in the background therapy based on the level of asthma control (see Section 5.5.5). The background therapy will be determined by the investigator however a standardized guidance will be provided as a support documentation.

1.2 Purpose

The overall purpose of this study is to determine the efficacy of fevipiprant (150 mg and 450 mg once daily [OD]), compared with placebo, as add-on to GINA treatment step 4 or 5 standard-of-care (SoC) asthma therapy, in terms of avoidance of SCS use over 52 weeks. This will be measured in patients with inadequately controlled severe asthma and high eosinophil counts (eosinophil count at Visit 1 $\geq$ 250 cells/ µl) and in the overall patient population regardless of eosinophil counts. This stepwise approach is in line with the fevipiprant LUSTER pivotal exacerbation studies (Studies A2307 and A2314). Inadequate control is defined as partly controlled or uncontrolled asthma (GINA 2018) with a value of Asthma Control Questionnaire score (ACQ-5) $\geq$ 1.5.

[redacted]

2 Study objectives and endpoints

2.1 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
In patients with severe asthma and high eosinophil counts (≥ 250 cells/µl) receiving flexible SoC asthma therapy, to demonstrate a reduction in the use of SCS with fevipiprant (150 mg or 450 mg once daily), compared with placebo	Total systemic corticosteroid dose in mg prednisone/prednisolone or equivalent over 52 weeks of treatment
In all patients with severe asthma receiving flexible SoC asthma therapy, to demonstrate a reduction in the use of SCS with fevipiprant (150 mg or 450 mg once daily), compared with placebo	Total systemic corticosteroid dose in mg prednisone/prednisolone or equivalent over 52 weeks of treatment
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
To evaluate the effect of fevipiprant 150 mg and 450 mg and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy in terms of difference in daytime and nighttime symptom scores	Change from baseline in daytime and nighttime symptom scores over 52 weeks of treatment by treatment group
To evaluate the efficacy fevipiprant 150 mg or 450 mg and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy, with respect to change from baseline in Asthma Control Questionnaire (ACQ-5) in the overall population	Change from baseline in Asthma Control Questionnaire (ACQ-5) total score over 52 weeks of treatment
To evaluate the effect of fevipiprant 150 mg and 450 mg and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy in terms of Asthma Related Quality of Life Questionnaire (AQLQ+12) in the overall population	Change from baseline in Asthma Related Quality of Life Questionnaire (AQLQ+12) total score over 52 weeks of treatment
To evaluate the effect of fevipiprant 150 mg and 450 mg and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy in terms of proportion of patients receiving continuous SCS during ≥ 30 days, at ≥ 7.5mg/day of prednisolone or equivalent in the overall population	Proportion of patients requiring ≥ 7.5mg systemic corticosteroid dose in mg prednisone/prednisolone or equivalent per day continuously for at least 30 days
To evaluate the safety and tolerability of fevipiprant 150 mg and 450 mg and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy in the overall population	Adverse events, ECG, vital signs and laboratory analysis over 52 weeks of treatment
To evaluate the effect of fevipiprant 150 mg and 450 mg and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy in terms of proportion for patients with no SCS use from the overall population	Proportion of patients with no SCS use over 52 weeks of treatment
To evaluate the effect of fevipiprant 150 mg and 450 mg and flexible SoC asthma therapy, compared with placebo and flexible SoC asthma therapy in terms of time to first prescription of biologic therapy in the overall population	Time to first prescription of biologic therapy from first dose of study treatment received over 52 weeks of treatment

[redacted]

[redacted]

Objective(s)	Endpoint(s)
[redacted]	

3 Investigational plan

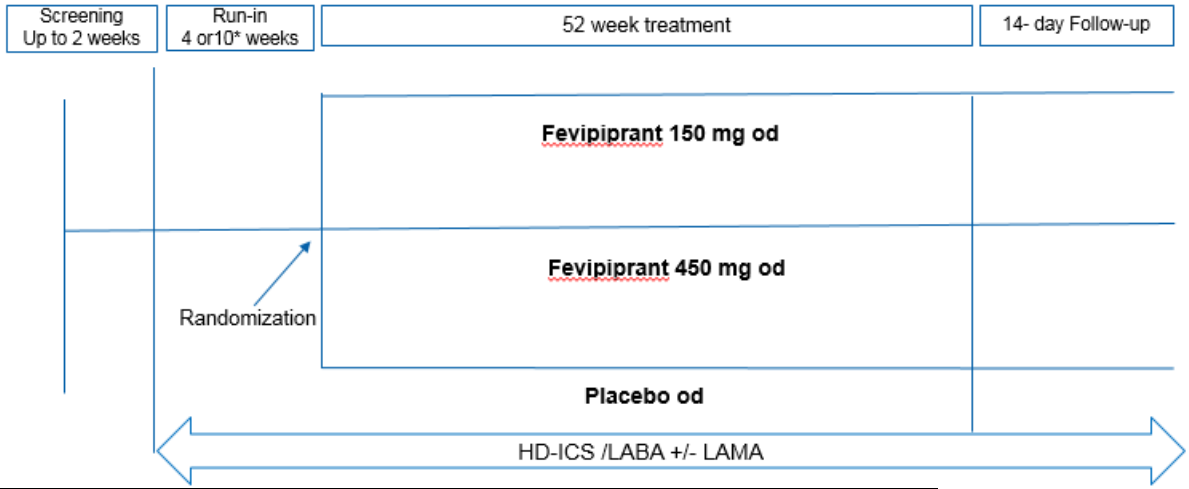
3.1 Study design

This study uses a randomized, multicenter, double-blind, double-dummy, placebo-controlled, parallel-group study design to determine the ability of fevipiprant plus SoC compared with placebo plus SoC to reduce the use of SCS in patients with severe asthma. The study will include:

- a Screening period of up to 2 weeks to assess eligibility;
- a Run-in period of 4 or 10* weeks to evaluate maintenance of asthma control and to collect baseline safety data. Upon completion of the Run-in period, all patients who met eligibility criteria will be randomized to 1 of 3 treatment groups (Fevipiprant 150 mg or 450 mg or placebo once daily) in a ratio 1:1:1. Randomized patients will be stratified according to their peripheral blood eosinophil count (< 250 cells/µl or ≥ 250 cells/µl);
- a Treatment period of 52 weeks and
- a Follow-up period of 2 weeks following the last dose of study drug to collect additional data for safety variables.

Approximately 669 patients will be randomized into this study. Please refer to Table 6-1 for clinical visit schedule and list of procedures to be conducted at each visit.

Figure 3-1 Study design



[redacted]

* 4 weeks run-in for patients coming with high-dose ICS/LABA and 10 weeks for patients switching from mid-dose to high-dose ICS/LABA as per protocol during the run-in period.

The study will allow for flexible therapy, meaning that patients can be escalated or de-escalated on their SoC therapy or add any other controller (this is explained in more detail in Section 5.5.5)

3.2 Rationale for study design

The overall purpose of this study is to determine the ability of fevipiprant (150 mg and 450 mg once daily) plus flexible SoC asthma therapy, compared with placebo plus flexible SoC asthma therapy, to reduce the use of SCS in patients with severe asthma and high eosinophil counts (eosinophil count at Visit 1 ≥ 250 cells/µl) as measured by total SCS use over 52 weeks. The study will also determine the ability of fevipiprant (150 mg and 450 mg OD) plus flexible SoC asthma therapy, compared with placebo plus flexible SoC asthma therapy, to reduce use of SCS use in the overall study population. The patient population will be described in more detail in the Section 4 below. The study will allow for flexible background therapy.

As mentioned previously, there is a correlation between SCS use and AEs. Sustained use of SCS is associated with significant side effects, including growth retardation in children, as well as osteoporosis, diabetes, cardiovascular adverse events, muscular weakness, skin atrophy and cataract (Schäcke et al 2002). This translates in an advantage for AE avoidance for those patients that do not use any SCS. Alternative asthma therapies that reduce the need for SCS are urgently needed, especially if given orally, such as fevipiprant. Unlike SCS, fevipiprant can target factors that contribute to asthma severity such as eosinophils.

Hence the primary endpoint of this study is comparing the total SCS use and expecting a lower SCS use especially for those patients who normally would receive high SCS doses. This should translate in lowering the toxicity. Most of the clinical importance would be based on the reduction of the percentage of patients who are the highest users. Given the mentioned correlation, they are the ones with the highest rate of AEs, so they would benefit the most.

The reduction in number of AEs would be especially relevant for those with predisposing conditions. Almost all patients with severe asthma (92%-93%) had at least one condition linked to systemic corticosteroid exposure, (Optimum Patient Care Research Database), so the vast majority of the population would fall into this category.

For yearly SCS usage, 30 days is considered the time threshold for high usage (Dalal et al 2016; Zazzali et al 2015). This encompasses both burst and chronic use.

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

Fevipiprant will be administered at doses of 150 mg and 450 mg once daily as oral film-coated tablets (FCTs) in this study.

A 450 mg once daily dose was selected for inclusion in the study based on the following:

- At a dose of 450 mg once daily, > 98% receptor occupancy is expected for the entire dosing interval in a “typical patient” at steady state allowing inhibition of eosinophil migration over the entire treatment interval.

[redacted]

- A 500 mg once daily dose of fevipiprant was efficacious on the endpoint of pre-dose FEV1 in a sub-set of patients with percent predicted FEV1 < 70% at baseline in Study [CQAW039A2201] (proof-of-concept study). A 450 mg total daily dose was also efficacious on the endpoint of pre-dose FEV1 in study [CQAW039A2206].
- A total daily dose of 450 mg (225 mg twice daily) was evaluated in Study [CQAW039A2208] in patients with severe asthma as add-on to SoC asthma therapy. In this study, fevipiprant caused significant reduction of sputum eosinophilia in patients with severe eosinophilic asthma. The reduction in sputum eosinophils was comparable to that observed with the anti-IL5 antibodies, Mepolizumab (Pavord et al 2012) and Reslizumab (Castro et al 2011; Castro et al 2015). An association between reduction of eosinophilic airway inflammation and frequency of exacerbations has been reported in the literature (Haldar et al 2009; Pavord et al 2012; Wenzel et al 2013; Takaku et al 2013), suggesting fevipiprant may also cause a reduction in the frequency of asthma exacerbations in patients with severe refractory eosinophilic asthma.

The dose of 150 mg once daily was selected for inclusion in the study because it was the lowest dose of fevipiprant with "maximal efficacy" on the endpoint of FEV1 in a prior dose-ranging study (Study [CQAW039A2206]) in patients with moderate-to-severe asthma (GINA 2018 treatment steps 4 and 5) as add-on to low-dose ICS. This dose is ½ log lower than highest dose.

Since the fevipiprant dose of 150 mg was considered the optimal dose (i.e., lowest dose providing maximal efficacy) in a prior dose-ranging study, doses lower than 150 mg will not be included in this study

3.4 Rationale for choice of comparator

During the run-in period the background medication will be standardized and all patients will receive:

Salmeterol/fluticasone 50/500 µg b.i.d. delivered by DPI (dry-powder inhaler) marketed as Seretide® Accuhaler® or Seretide® Diskus®depending on the countries, +/- tiotropium or any Long-acting muscarinic antagonist (LAMA) approved for asthma and/or Leukotriene Receptor Antagonists (LTRAs).

During treatment period patients will be given fevipiprant or placebo as add on therapy in addition to the run-in treatment medications

The use of placebo will permit the assessment of reduction of incidence of total dose of systemic corticosteroids within 52 weeks in patients who are treated with fevipiprant and SoC, in comparison to those continuing solely on existing SoC asthma therapy. Additionally, the use of placebo will permit a controlled evaluation of the safety of fevipiprant in these patients.

This study does not include an active comparator since fevipiprant will be given as add-on therapy to standard of care asthma therapy in patients with severe asthma (GINA 2018 treatment steps 4 and 5).

[redacted]

3.5 Purpose and timing of interim analyses/design adaptations

Flexible scenario

If the results of [CQAW039A2307]/[CQAW039A2314] studies are available before completion of recruitment of the CQAW039A2323 study, and in the case that an optimal dose of fevipiprant has been identified, the study team will decide whether to drop any fevipiprant dose or continue with current doses. There will not be an interim analysis for this study. Any change would be made based on external data and hence there would not be any alpha adjustment. At the decision point, the study team will assess the criterion below:

- [CQAW039A2307]/[CQAW039A2314] results do not recommend one of the fevipiprant dose due to safety concerns / lack of efficacy:
  - In CQAW039A2323 study, recruitment in the corresponding treatment arm will be stopped. To keep the blind the ongoing patients on this arm will be switched to the other fevipiprant dose at the next drug dispensing visit.
  - Final analysis will be based on comparison of selected fevipiprant arm and placebo arm at 5% significance level. The primary hypothesis will be tested first in the subgroup with blood eosinophils $\geq$ 250 cells/µl and then in the overall population for the selected fevipiprant dose.
  - Data collected on the non-optimal arm will be summarized but will not be used for statistical inference.
- Any modifications in CQAW039A2323 study will be contingent upon number of patients recruited at the decision point.
- At this decision point, CQAW039A2323 study data will not be unblinded to make a decision. The decision will be completely based on final results of [CQAW039A2307]/[CQAW039A2314] studies. Thus, there will not be any interim analysis performed for CQAW039A2323. This will control the type I error rate adequately.

Based on [CQAW039A2307]/[CQAW039A2314] results, one dose is selected for launch, and the decision is made that there is no need to compare the control arm with the dose not selected. Then the testing strategy will be to only perform the comparison between the control arm and the dose selected.

This flexible scenario strategy could reduce the total number of patients required to be enrolled in the study.

3.6 Risks and benefits

Fevipiprant is a potent and highly selective oral DP2 antagonist being developed as a potential therapy for patients with severe asthma. DP2 is a receptor for PGD_2 which mediates the activation and migration of T helper 2 (Th2) cells and eosinophils, some of the key inflammatory cell types in asthma. Recruitment of these cells into the lung is partly responsible for the intermittent airway obstruction which leads to wheezing and shortness of breath characteristic of asthma.

The overall clinical experience with fevipiprant includes 24 studies: 15 (nine in healthy volunteers and six in patients) have completed and 9 (five in patients and four in healthy

[redacted]

volunteers) are ongoing. The completed phase 2 studies consist of four in patients with asthma, one in patients with allergic rhinitis and one in patients with atopic dermatitis (Refer to the Investigator's Brochure (IB) for information on the studies of fevipiprant). As of January 2018, over 2830 subjects have been exposed to fevipiprant in the clinical program.

Three Phase 2 studies in patients with asthma evaluated the effect of fevipiprant across the range of asthma severities (mild to severe). In these studies, fevipiprant demonstrated an effect on lung function (FEV1) in patients with moderate-to-severe asthma, and an improvement in quality of life scores and asthma control questionnaire scores in severe patients uncontrolled at baseline. In one study, fevipiprant also demonstrated a reduction in sputum eosinophils in patients with severe asthma.

The potential benefits of fevipiprant therapy need to be balanced against its potential risks. Potential side effects of fevipiprant include: increased heart rate, non-serious arrhythmia such as palpitations, headache, diarrhea, nausea, vomiting, nasopharyngitis, somnolence and dizziness. In humans, one major metabolite of fevipiprant has been identified which is formed by glucuronidation (acyl glucuronide) and partially binds to plasma proteins. In the literature, in vivo binding of acyl glucuronides to proteins has been reported to be associated with rare idiosyncratic drug reactions (IDRs), although a causal connection of protein adduction to IDRs remains uncertain (Regan et al 2010). There have been no IDRs observed with fevipiprant treatment in completed clinical trials as of January 2018. Taking fevipiprant at the doses used in this study with the cholesterol-lowering drug simvastatin has been shown to cause a small increase in the peak blood level of simvastatin.

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

Patients on doses of simvastatin > 20 mg, doses of atorvastatin >40 mg, doses of pravastatin >40 mg, or doses of pitavastatin > 2 mg per day (Elsby et al 2012; Deng et al 2008; Noé et al 2007; Kalliokoski and Niemi 2009), as well as patients on any statins with high creatine kinase (CK) levels (> 2 X ULN (upper limit of normal)) at screening will be excluded from the study. Patients on statin medication who are included in the study will have regular monitoring for relevant symptoms and be subject to discontinuation based on persistent myalgia and/or blood CK levels (Jacobson 2008). Cardiovascular risks will be monitored based on changes in vital signs, ECGs and biochemical parameters. Monitoring of liver function tests (LFT) and renal function will be conducted as described in Section 14 and Section 15, respectively, of this protocol. Surveillance of adverse events for identification of idiosyncratic drugs will be conducted.

Refer to the [QAW039 Investigator's Brochure] for further information about risks and benefits.

4 Population

4.1 Inclusion criteria

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

1. Signed informed consent must be obtained prior to participation in the study and before any assessment is performed including any adjustment to asthma medication.
2. Male and female patients aged ≥18 years

[redacted]

3. Patients with a diagnosis of asthma for a period of at least 3 months prior to Screening Visit with current asthma severity step 4 or 5 (GINA 2018)
4. Currently on treatment with medium or high dose ICS/LABA +/- other controller (i.e. LAMA, LTRA etc. as per GINA) for a minimum of 6 weeks prior to Screening Visit .
5. At screening, patients with FEV1 of ≤80% of the predicted normal value for the patient, after withholding bronchodilators at Screening Visit and beginning of Run-In Visit .
6. An increase of ≥12% and ≥200 ml in FEV1 approximately 10 to 15 minutes after administration of 400 mcg of salbutamol/albuterol prior to randomization (documented historical reversibility is accepted). Spacer devices are not permitted during reversibility testing. All patients must perform a reversibility test at Screening Visit. If reversibility is not demonstrated at that visit, then documented evidence of reversibility that was performed according to ATS/ERS guidelines (ATS/ERS 2005) in the past 5 years is allowed. Where a patient is assessed as eligible based on historical evidence of reversibility, a copy of the original printed spirometry report with relevant spirometry tracings must be available as source documentation. If reversibility is not demonstrated at Screening Visit and documented evidence is not met, then the reversibility test may be repeated at Run-In Visit.
7. Demonstration of inadequate control of asthma based on an ACQ-5 score ≥1.5 at Screening Visit and Treatment Day 1 Visit.
8. Documented history of at least 1 asthma exacerbation [*(that required ≥3 consecutive days of oral corticosteroids or ≥1 dose of IM or IV corticosteroids or hospitalization (defined as an inpatient stay or >24-hour stay in an observation area in the emergency room of other equivalent facility,)*] within 1 year prior to enrolment

4.2 Exclusion criteria

Population fulfilling any of the following criteria are <u>not</u> eligible for inclusion in this study:

1. Asthma exacerbation, within 6 weeks prior to enrolment (screening) that required SCS, hospitalization, or emergency room visit. Patients who experience an exacerbation between screening to end of run-in, prior randomization, to be considered failures and can be eligible for re-screening only once, 6 weeks after recovering from the exacerbation.
2. Chronic/ maintenance use of OCS for asthma (total OCS use days greater than 6 months; continuously or intermittently) within the last year
3. Prior use of biologics (including but not limited to Omalizumab, Mepolizumab, Reslizumab, Dupilumab, Benralizumab etc., for asthma or any other indications) that has potential to interfere/ affect asthma disease progression, in the previous 6 months from run-in period.
4. Any contra-indications of SCS use e.g. diabetes, narrow angle glaucoma, or any other as defined by the treating physician
5. Pregnant or nursing (lactating) women
6. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of investigational drug. Basic contraception methods include:

[redacted]

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For United Kingdom: with spermicidal foam/gel/film/cream/ vaginal suppository
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

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

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

7. Use of other investigational drugs within 5 half-lives of enrollment, or [within 30 days], whichever is longer.
8. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes.
9. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
10. Patients who have smoked or inhaled any substance other than asthma medications within the 6 month period prior to Screening Visit , or who have a smoking history of greater than 10 pack years (Note: 10 pack years = 1 pack /day x 10 yrs., or ½ pack/day x 20 yrs.)
11. Patients requiring SCS use for conditions other than asthma (chronic or intermittent)
12. Patients with a history of chronic lung disease other than asthma, including (but not limited to) chronic obstructive pulmonary disease, clinically significant bronchiectasis (non-clinically significant bronchiectasis may be allowed provided recent [within 3 months prior to Screening Visit] CT scan proof is available), sarcoidosis, interstitial lung disease, cystic fibrosis, and active tuberculosis

[redacted]

13. Patients with history of alcohol or drug abuse within 12 months prior to Screening Visit .
14. Patients with a known history of non-compliance to medication or who are unable or unwilling to complete an electronic patient diary or who are unable or unwilling to use Electronic Peak Flow with eDiary device or who are unable to demonstrate good eDiary compliance (defined as >75% for eDiary compliance) during run-in.
15. Patients who have had a respiratory tract infection or asthma worsening within 4 weeks of Screening Visit. Patients who experience a respiratory tract infection or asthma worsening during screening may be re-screened after 4 weeks after recovery from their respiratory tract infection or asthma worsening
16. Patients with any chronic condition of the respiratory tract which in the opinion of the investigator may interfere with study evaluation or optimal participation in the study
17. Patients who have a clinically significant laboratory abnormality at the Run-in Visit laboratory test including (but not limited to):
    - Total white blood cell count <2500 cells/μL
    - AST or ALT>2.0 X ULN or total bilirubin >1.3 X ULN
    - Estimated Glomerular Filtration Rate (eGFR) by the Modification of Diet in Renal Disease (MDRD) equation or Bedside Schwartz equation <55 mL/minute/1.73 m2
18. Patients with serious co-morbidities including, but not limited to neurodegenerative diseases, rheumatoid arthritis and other autoimmune diseases
19. Patients receiving any medications in the classes listed in Table 5-4 should be excluded unless they meet the criteria as specified in Table 5-4
20. Patients receiving medications in the classes listed in Table 5-2 should be excluded unless the medication has been stabilized for the specified period and the stated conditions have been met
21. Patients who started immunotherapy or desensitization for allergies, within 3 months prior to Screening Visit, or where the maintenance dose is expected to change during the study
22. Inability to comply with all study requirements and demonstrate good medication compliance (>=80% compliance rate) during the run-in period
23. Patients with any medical or psychological condition that, in the investigators opinion, renders the patient unable to understand the nature, scope, and possible consequences of the study
24. Patients with a history of being unable to swallow tablets
25. Patients who have received methotrexate, gold salts, troleandomycin, cyclosporine, azathioprine, other immunomodulator or immumomodulatory drugs or any experimental anti-inflammatory therapies within 6 months of Run-in Visit
26. Patients who have a history of or current treatment for hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis or hepatic failure
27. Patients with a history of immunodeficiency disease or hepatitis B or hepatitis C
28. Patients on >20 mg of simvastatin, > 40 mg of atorvastatin, >40 mg of pravastatin, or >2 mg of pitavastatin 7 days prior to run-in visit. Statin doses less than or equal to these doses as well as other statins will be permitted during the study
29. Patients on any statin therapy with a CK level >2 X ULN at Run-in Visit

[redacted]

30. Patients on rifampin, probenecid, ritonavir and valproic acid (i.e. medications blocking several pathways important for the elimination of QAW039 [broad range UGT inhibition and/or inhibition of OAT3, OATP1B3, MXR and P-gp]) 7 days prior to run-in visit.
31. No person directly associated with the administration of the study is allowed to participate as a study subject
32. No family member of the investigational study staff is allowed to participate in this study
33. History of lactose or milk sensitivity
34. Patients with a history of conditions other than asthma that could result in elevated eosinophils (e.g., hypereosinophilic syndromes, Churg-Strauss Syndrome, eosinophilic esophagitis). Patients with known parasitic infestation within 6 months prior to Screening Visit are also excluded
35. Patients with a history or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study such as:
    - Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree atrioventricular (AV) block without a pacemaker.
    - History of familial long QT syndrome or known family history of Torsades de Pointes.
36. Patients with a resting QTcF (Fridericia) ≥450 msec (male) or ≥460 msec (female) at Screening Visit.
37. Use of agents with known risk of TdP unless it can be permanently discontinued for the duration of the study.

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

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

The following investigational treatment will be supplied by Novartis to the study sites:

- Name: QAW039
- Formulation: tablet
- Unit dose: 2 strengths: 150 mg and 450 mg
- Name: placebos to QAW039 150 mg and QAW039 450 mg
- Formulation: tablet
- Unit dose: matching placebo to QAW039 150 mg, matching placebo to QAW039 450 mg

Please refer to the Investigator Brochure for composition of the QAW039 and placebo tablets.

The investigational treatment (tablets) will be supplied in bottles. The matching placebos for QAW039 will be identical in appearance to their active counterparts and will be identically packaged.

[redacted]

5.1.2 Additional treatment

On the start of the run-in period all patients will be given standard of care treatment (SoC) to be taken daily for the duration of the study:

- Open label salmeterol /fluticasone 50/500 µg b.i.d. (Seretide ® delivered as powder via Diskus®/Accuhaler®)

All patients will be provided with prednisone/prednisolone (or equivalent) tablets as the OCS for use during the study. Prednisone/prednisolone (or equivalent) will either be supplied to the investigator sites locally by Novartis or be provided by the study center and reimbursed by Novartis. The study patients will have a written asthma plan, provided by the Investigator, with instructions and information on how to self-manage their asthma daily, including taking medications appropriately and information on how to recognize and handle worsening asthma, and when, how, and who to contact in an emergency. The investigator should fill in the medication and dosage the patient should be taking during self-management. Adjustments and follow-up of the asthma worsening/exacerbation event can be managed either on the phone or during an unscheduled visit. Unscheduled visits can be necessary to evaluate the best treatment escalation for the patient's current situation. This follows common medical practice, by which patients are prescribed OCS to be self-administered at home based on symptoms (Partridge 2004). The study patients will be instructed to make every effort to call the Investigator before taking the oral steroid and if not possible, as soon as they can, but not later than 48 hours after OCS intake has started.

All patients will be provided with Short-acting Beta-agonist (SABA) (salbutamol/albuterol) which they will be instructed to use throughout the study as rescue medication to treat asthma symptoms on an 'as needed basis'. SABAs will either be supplied to the investigator sites locally by Novartis or be provided by the study center and reimbursed by Novartis.

5.2 Treatment arms

Patients will be assigned at randomization visit to one of the following 3 treatment arms in a ratio of 1:1:1

- QAW039 150 mg once daily (one tablet of blinded QAW039 at 150 mg dosage strength to be given together with one tablet blinded placebo to QAW039 450 mg)
- QAW039 450 mg once daily (one tablet of blinded QAW039 at 450 mg dosage strength to be given together with one tablet blinded placebo to QAW039 150 mg)
- Placebo to QAW039 once daily (one tablet blinded placebo to QAW039 150 mg and one tablet blinded placebo to QAW039 450 mg)

Patients will be instructed to take their investigational treatment (QAW039 or placebo) once daily in the morning without regard to time of food intake. SoC asthma therapy will be taken as directed by the investigator.

5.3 Treatment assignment and randomization

At randomization visit, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a

[redacted]

treatment arm and will specify unique medication numbers for the first packages of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure the treatment assignment is unbiased and concealed from subjects and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supplies using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Randomization will be stratified by peripheral blood eosinophil counts at Run-in Visit (< 250 cells/ml or ≥ 250 cells/ml).

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

5.4 Treatment blinding

This study consists of a double-blind, double-dummy, randomized treatment period.

Subjects, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study. (2) For each dose level of QAW039, the identity of the treatment will be concealed by the use of matching placebo identical in packaging, labeling, schedule of administration, appearance, taste, and odor to QAW039.

A double-dummy design is used because the identity of the study drug cannot be disguised, as the drug products are visibly different in size.

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

Table 5-1 Blinding levels

Role	Time or Event		
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)
Subjects/Patients	B	B	B
Site staff	B	B	B
Unblinded site staff (see text for details)	B	B	B
Drug Supply and Randomization Office	UI	UI	UI
Unblinded sponsor staff (see text for details)	B	B	B
Statistician/statistical programmer/data analysts	B	B	B

[redacted]

Role	Time or Event		
	Randomization list generated	**Treatment allocation & dosing**	**Safety event (single subject unblinded)**
Independent committees used for assessing interim results	NA	NA	NA
All other sponsor staff not identified above	B	B	B
B Remains blinded NA Not applicable UI Allowed to be unblinded on individual patient level			

5.5 Treating the patient

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

5.5.1 Patient numbering

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

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

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

5.5.2 Dispensing the study drug

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

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the 3 treatment arms. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

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

[redacted]

protocol. Technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance.

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

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

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

5.5.3.2 Handling of additional treatment

The following non-study treatment and rescue medication has to be monitored:

- salmeterol /fluticasone 50/500 µg b.i.d. or 50/250 µg b.i.d via Diskus®/Accuhaler® used as SoC
- prednisone/prednisolone (or equivalent) tablets (oral corticosteroids) used as rescue or preventive medication
- SABA (such as salbutamol 100 mcg or albuterol 90 mcg)
- tiotropium or "any LAMA approved for asthma"
- LTRA (if started prior of study entry)

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

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

5.5.4 Instructions for prescribing and taking study treatment

Study treatment will be double-blind, double-dummy, and placebo-controlled during the treatment period. QAW039 will be supplied as tablets. Since the tablets for QAW039 150 mg and QAW039 450 mg are not identical, treatment will be double-dummy and patients will take 2 tablets of study medication (one tablet of blinded QAW039 at 150 mg dosage strength to be given together with one tablet blinded placebo to QAW039 450 mg or one tablet of blinded QAW039 at 450 mg dosage strength to be given together with one tablet blinded placebo to

[redacted]

QAW039 150 mg or one tablet blinded placebo to QAW039 150 mg and one tablet blinded placebo to QAW039 450 mg) once daily as described below.

During the run-in period all eligible patients will start:

Salmeterol/fluticasone 50/500 µg b.i.d. delivered by DPI (dry-powder inhaler) is marketed as Seretide® Accuhaler® or Seretide® Diskus® depending on the countries +/- tiotropium (or any LAMA approved for asthma) and/or LTRAs.

If a patient experiences an asthma exacerbation during the run-in period, the patient is considered run-in failure and can be re-screened only once 6 weeks after full recovery from the exacerbation.

At Randomization Visit, patients will be stratified according to their peripheral blood eosinophil counts at Run-In Visit (< 250 cells/ml or ≥ 250 cells/ml). Each randomized patient will then enter a 52-week treatment period where they will receive one of the following 3 treatments: (i) QAW039 150 mg once daily or (ii) QAW039 450 mg once daily or (iii) placebo once daily given on top of their individual background asthma treatment. All patients in this study will continue to receive their asthma medications as background treatment. The investigational treatment will be dispensed in medication packs (bottles) at dispensation visit during the treatment period to cover the treatment period between patient visits and to allow for late visits and other unforeseen events. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the appropriate CRF.

At clinic visits, patients will receive a witnessed dose of study medication. These in-clinic witnessed doses will be given after the completion of all pre-dose assessments (see Section 6) and should be given at approximately the same time at each clinic visit. Between clinic visits, patients will take study medication once daily in the morning. Patients will be instructed to take their study medication at approximately the same time each morning.

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

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

5.5.5 Permitted dose adjustments and interruptions of study treatment

For patients who are unable to tolerate the protocol-specified dosing scheme, dose interruptions of investigational drug are permitted in order to keep the patient on study drug. The following guidelines must be followed:

Any interruption of study medication should be for the shortest time period possible. Any interruption of any duration must be recorded.

To reflect as near as possible the clinical practice setting in this trial, there is freedom to use flexible asthma background therapy, allowing to escalate ("step-up") and de-escalate ("step-down") the asthma background medication.

[redacted]

Stepping-up asthma treatment

As recommended by GINA guidelines (GINA 2018), the treating physician may "step-up" patient's background medication and/or add-on maintenance treatment options if they remain uncontrolled or experience asthma exacerbations. Examples of background medication and add-on other maintenance treatment options: tiotropium (or any LAMA approved for asthma), oral or injectable corticosteroids, biologic therapy (only those approved for asthma, not in investigation and according to SmPC and local regulations), among others. These medications should be used according to approved local labels.

Patients with "step-up" or add-on maintenance treatment(s) should continue on study treatment.

NOTE: LTRAs are not allowed as part of the stepping-up asthma treatment.

Stepping-down treatment when asthma is well controlled

As per GINA guidelines and as part of periodic reassessment of disease control the investigator should consider stepping down treatment once good asthma control has been achieved and maintained to find the minimum effective treatment that controls symptoms and exacerbations while minimizing side-effects (GINA 2018). The treating physician may "step-down" patient's background medication according to GINA. The reduction of the dose of the ICS will be allowed after the investigator has withdrawn any other add-on medication such as OCS or tiotropium (or any LAMA approved for asthma).

GINA guidelines recommend choosing an appropriate time for step-down (no respiratory infection, patient not travelling) and document baseline status (symptom control and lung function), provide a written asthma action plan, monitor symptoms, and book a follow-up visit.

These changes must be recorded on the Prior and Concomitant Medications CRF.

5.5.6 Rescue medication

At Run-In Visit all patients will be provided with a SABA, (primary rescue medication such as salbutamol 100 mcg or albuterol 90 mcg) which they will be instructed to use throughout the study as rescue medication on an 'as needed basis'. Patients will be advised that between visits they can take their rescue medication for symptoms of asthma. Rescue medication (i.e., SABAs) will either be supplied to the investigator sites locally by the Novartis CPO or provided by the study center and reimbursed by Novartis. Nebulized salbutamol/albuterol is not allowed as rescue medication and will not be supplied.

As part of their written asthma plan, patients will receive OCS (add on rescue medication such as prednisone/prednisolone (or equivalent) tablets) to use as instructed by the treating physician. There will be an asthma plan (given as a reference), which is described in Section 20 and that will be used to standardize the initial rescue treatment of the acute asthma exacerbation and/or symptoms. To standardize measurements, patients will be instructed not to use their rescue medication upon rising in the morning on days requiring spirometric assessments indicated in Table 6-1, unless absolutely necessary. If SABA medication is taken within 6 hours prior to spirometry at any of the scheduled visits, the visit should be rescheduled to the next possible day. However, if spirometry is performed within 6 hours of the use of rescue medication then this information will be recorded by the study site staff. Daily use of SABA medication (the number of puffs taken in the previous 12 hours) will be recorded (once in the morning and once

[redacted]

in the evening) by the patient on the eDiary as well as OCS intake. Unless clinically indicated, the type of rescue medication (i.e., SABA) a patient uses, the device used to deliver the medication (e.g. dry powder or HFA) and the way it is administered (e.g. with a spacer device) should not be adjusted.

5.5.7 Concomitant medication

The medications in Table 5-2 are only permitted under the circumstances given. This table is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria.

Table 5-3 indicates the wash-out periods for allowed asthma medications prior to spirometry assessments

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

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

Table 5-2 Medications allowed under certain conditions

Class of medication	Conditions
Inhaled corticosteroids (ICS)	Medium or High dose* daily or equivalent. Used for at least 6 weeks prior to Screening Visit. Must be taken with LABA with or without a third therapy (LTRA or theophylline or LAMA) or with LABA/LAMA or with LABA/LTRA
Long-acting inhaled β_2-agonist (LABAs)	Permitted if used for at least 6 weeks prior to Screening Visit. Must be taken with medium - high dose* ICS
Fixed dose combinations of ICS and LABA (FDC)	Permitted at medium high dose if used at least 6 weeks prior to Screening
Leukotriene receptor antagonist (LTRAs)	Permitted if used for at least 6 weeks prior to Screening Visit. Must be taken with medium - high dose* ICS - New onset of LTRA during study is not allowed
Theophylline	Permitted if used at least 6 weeks prior to Screening Visit . Must be taken with medium - high dose* ICS
Long-acting muscarinic antagonists (LAMAs)	Permitted if used for at least 6 weeks prior to Screening Visit. Must be taken with medium - high dose* ICS
Maintenance oral corticosteroids for treatment of asthma	Less than 6 months during the previous year
Short-acting β_2-agonist (SABAs)	Rescue medication to be taken as needed. Nebulized salbutamol/albuterol in not allowed as rescue medication, however can be taken if prescribed during exacerbation
Maintenance immunotherapy for allergies	Stable-dose for at least 3 months prior to screening and the dose remains stable throughout the study
Inactivated influenza vaccine pneumococcal vaccination or any other inactivated vaccine	Not administered within 48 hours prior to a study visit

[redacted]

Class of medication	Conditions
Topical corticosteroids for treatment of eczema	Recommended doses and dosage regimens
Antihistamines (e.g., loratadine, cetirizine)	Stable dose for at least 1 month prior to Screening Visit and the dose remains stable throughout the study
Nasal anticholinergic	Treatment regimen has been stable for at least 1 month prior to Screening Visit. In the case of as needed use, providing an established pattern of use, has been documented
Nasal corticosteroids	
Nasal or ophthalmological preparations of nedocromil	
Nasal or ophthalmological preparations of antihistamines	

*See GINA 2018 or Section 21 for definition of medium and high dose ICS

Table 5-3 Medications to be withheld prior to spirometry

Class of medication	Last dose prior to spirometry
Short-acting β_2-agonists	≥ 6 hours
Long-acting β_2-agonists (LABAs) given twice daily	≥ 12 hours
LABAs given once daily	≥ 24 hours
Fixed dose combinations of LABA and inhaled corticosteroid (ICS) given twice daily	≥ 12 hours
Long-acting muscarinic antagonists (LAMAs)	≥ 24 hours

5.5.8 Prohibited medication

Use of the treatments displayed in the below table is NOT allowed* according to the table below. Each concomitant drug must be individually assessed against all exclusion criteria and the tables below to see if it is allowed. If in doubt, the investigator should contact the Novartis medical monitor or designee before randomizing a patient or allowing a new medication to be started. This table is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria. These medications are also prohibited if administered for other indications.

Table 5-4 Prohibited medication

Medication	Prohibition period (Minimum cessation prior to start of run-in Visits)
Other investigational drugs	30 days or 5 half-lives, whichever is longer
Live attenuated vaccine	30 days
Other CR Th2 antagonists (e.g., ramatroban)	7 days or 5 half-lives whichever is longer
Short-acting anticholinergics	8 hours
Fixed combinations of short-acting β_2-agonists and short-acting anticholinergics	8 hours
Systemic mast cell stabilizers (e.g.,cromoglycate, nedocromil, ketotifen)	7 days
Monoclonal antibodies, investigational or approved, for the treatment of asthma (e.g., omalizumab)*	6 months

[redacted]

Medication	**Prohibition period (Minimum cessation prior to start of run-in Visits**)
Simvastatin > 20 mg, atorvastatin > 40 mg,pravastatin > 40 mg, or pitavastatin > 2 mg totaldaily dose	7 days
Rifampin, probenecid, ritonavir and valproic acid (i.e. medications blocking several pathways important for the elimination of QAW039 (broadrange UGT inhibition and/or inhibition of OAT3, OATP1B3, MXR and P-gp)).	7 days
Methotrexate, gold salts, cyclosporine,troleandomycin, azathioprine, otherimmunomodulator drugs	6 months
Systemic (oral, intravenous, intramuscular) corticosteroids for non-asthma conditions	3 months
LTRAs	New onsets (during study duration)
*Biologics are allowed directly after randomization as part of the flexible therapy.	

5.5.9 Emergency breaking of assigned treatment code

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

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

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

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

Study drug must be discontinued after emergency unblinding. Study drug must also be discontinued for any patient whose treatment code has been inadvertently broken or for any other non-emergency reason.

Of note, the patient may continue in the study after discontinuing study drug.

[redacted]

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol.

Study completion for a patient will occur after he/she has completed 52 weeks of treatment (through the follow-up visit) or they have prematurely withdrawn. Completion of the study will be when all randomized patients have completed 52 weeks of treatment and the post-treatment follow-up visit.

Patients who have been screened when enrolment target has been met will be allowed to proceed onto study participation.

At the time of study completion or early termination, all patients will be placed on the appropriate asthma treatments as per the investigator judgement.

For all patients a safety follow-up visit should be conducted (e.g. by telephone) 14 days after last dose of study drug. The information to be collected at this follow up visit includes adverse events, and SAEs.

When the patient has completed all scheduled study assessments or prematurely withdrawn from the study, the investigator must contact the IRT to record the patient completion /discontinuation and complete applicable eCRF.

5.6.2 Discontinuation of study treatment

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

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Study treatment must be discontinued under the following circumstances:

- Withdrawal of informed consent (and the investigator must prematurely withdraw the patient from the study);
- Pregnancy;
- Female subjects non-compliant with the chosen effective method of contraception during the study: The investigator must provide appropriate advice on the continued use of effective contraception for at least one week (at least 5 half-lives of QAW039) after study drug discontinuation and follow up with the subject as appropriate at least to the end of this period;
- Any protocol deviation that results in a significant risk to the patient’s safety;
- Liver laboratory test abnormality / event (see Section 14):
  - Abnormal liver laboratory results requiring discontinuation – refer to Table 14-2 - Appendix 2;
- If the investigator considers it appropriate after the confirmation of a liver safety monitoring signal:

[redacted]

  - ALT or AST ≥ 2.5 x ULN **and** total bilirubin ≥ 1.5 x ULN (Section 14);
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study;
- Premature unblinding of study treatment for a patient for any reason; please refer to Section 5.5.9;
- Total white blood cell count < 1000 cells/µL;
- If patients on statin therapy complain of persistent muscle pain without any obvious cause for greater than 3 days accompanied by increase in CK levels > 10 x ULN or persistent intolerable muscle pain regardless of the accompanying CK level;
- If a patient develops a medical condition that requires consistent use of prohibited treatment as per Section 5.5.8 or if patient exhibits a behavior of non-compliance regarding prohibited medication.

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent section,). **Where possible, they should return for the assessments indicated** in the Assessment schedule (Table 6-1).

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

- new / concomitant treatments including OCS use
- adverse events / Serious Adverse Events

If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule. The information already collected during the study including patient's samples will still be used according to applicable laws.

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

5.6.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

[redacted]

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

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

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

5.6.4 Loss to follow-up

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

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come for a final visit) and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

6 Visit schedule and assessments

Visits must be scheduled to allow randomized study drug to be taken in the morning.

[redacted]

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed.

Patients must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Patients, who discontinue study treatment before completing the study and will accept to remain in the study, will return for study visits as described in Section 5.6. If they fail to return for these assessments for unknown reasons, every effort should be made to contact them as specified in Section 5.6. At the very least, patients should be asked if they can be contacted by phone by study personnel at the date they would have been scheduled to end the follow up period (2 weeks after premature drug discontinuation) to ask about surgery and procedures, SAEs, AEs and asthma exacerbations. The following assessments are scheduled to be performed in order as follows: Patient reported outcome (PRO) questionnaires (i.e. AQLQ and ACQ), ECG, Vital signs (pulse rate, body temperature and blood pressure), blood sample/urine samples, followed by spirometry.

[redacted]

Table 6-1 Assessment Schedule

Period	Screening		Treatment													Post-Treatment Follow Up
Visit Name	Screening	Run-In[1,2]	Treatment[3]												EOT or TD	
Days	-42 to -28	-28 to -1	1	1	42	84	112	140	168	196	224	252	280	308	336	364	378
Weeks	-6 to -4	-4 to -1	1	1	6	12	16	20	24	28	32	36	40	44	48	52	54
Telephone Contact							TC		TC		TC		TC		TC		TC
Informed consent	X																
Inclusion / Exclusion criteria	X	X	X														
Demography	X																
Physical Examination	S															S	
Medical history/current medical conditions[4]	X	X	X														
Asthma exacerbation history	X																
Surgeries and procedures		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Smoking history	X																
Prior medications	X																
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety Follow up Call																	S
Vital Signs	X	X	X		X	X		X		X		X		X		X	
Body Height	X																
Body Weight	X		X													X	
Electrocardiogram (ECG)	X															X	
Hematology		X		X	X	X		X		X		X		X		X	
Blood sample for serum IgE level		X															
HbA1C		X														X	
Clinical Chemistry		X		X	X	X		X		X		X		X		X	
Pregnancy Test (serum)		X															
Urinalysis	X			X	X	X		X		X		X		X		X	
Pregnancy Test (Urine)			S		S	S		S		S		S		S		S	

[redacted]

Period	Screening			Treatment													Post-Treatment Follow Up
Visit Name	Screening	Run-In[1,2]		Treatment[3]												EOT or TD	
Days	-42 to -28	-28 to -1	1	1	42	84	112	140	168	196	224	252	280	308	336	364	378
Weeks	-6 to -4	-4 to -1	1	1	6	12	16	20	24	28	32	36	40	44	48	52	54
Contact IRT (IVRS/IWRS)	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Randomization				S													
Drug dispensation				S		S		S		S		S		S			
Check IMP compliance					S	S	S	S	S	S	S	S	S	S	S	S	
Study drug administration				Daily													
Rescue medication dispense[5]		S		As Needed													
Rescue medication review		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	
Spirometry with Reversibility Test[6]	X	X															
Spirometry				X						X						X	
Asthma exacerbation[7]		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Asthma Quality of Life Questionnaire		X	X		X	X		X		X		X		X		X	
Asthma control questionnaire (ACQ-5)	X		X		X	X		X		X		X		X		X	
[redacted]																	
eDiary Handout	S																
eDiary training	S	S	S														
eDiary/ePEF[8]		X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Check eDiary Compliance		S	S		S	S	S	S	S	S	S	S	S	S	S	S	
Study completion information																X	

[redacted]

Period	Screening			Treatment													Post-Treatment Follow Up
Visit Name	Screening	Run-In[1,2]		Treatment[3]												EOT or TD	
Days	-42 to -28	-28 to -1	1	1	42	84	112	140	168	196	224	252	280	308	336	364	378
Weeks	-6 to -4	-4 to -1	1	1	6	12	16	20	24	28	32	36	40	44	48	52	54

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
[1] Patients experiencing an asthma exacerbation between screening to end of run-in, prior randomization, to be considered failures and can be eligible for re-screening only once, 6 weeks after recovering from the exacerbation
[2] Patients switching from a mid-dose ICS to high dose (as per protocol) will require 6 additional weeks of run-in (total of 10 weeks of Run-In)
[3] Randomization Visit is at Day 1
[4] Including Protocol solicited events for Asthma
[5] OCS and SABA
[6] If reversibility is not met at Screening, historical reversibility will be assessed for inclusion, if not available a Run-in reversibility will be required.
[7] In case of an asthma exacerbation, the patient should be encouraged by the site to contact it for advice. If necessary, an unscheduled visit to the site may be arranged.
[8] eDiary will include Asthma Daily Symptoms questionnaire

[redacted]

6.1 Information to be collected on screening failures

All subjects who have signed informed consent but not randomized will have the disposition, demographics, inclusion/exclusion, informed consent, rescreening, withdrawal of consent (if subject withdrew consent) and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator or primary care physician and collected only in the source data.

All patients who have signed informed consent and have received high dose ICS/LABA medication, but discontinue prior to randomization (run-in failures) should have all data for the visits they attended and the summary pages (Adverse Event, Concomitant Medication, Dosage Administrative Record) completed. All adverse events occurring after informed consent is signed should be recorded on the Adverse Event CRF.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

6.2 Patient demographics/other baseline characteristics

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

- Age (calculated)
- Sex
- Race and ethnicity
- Patients initials (where allowed by local legislation)
- Height and Weight
- BMI (calculated)
- Baseline physical examination (not databases other than in the context of relevant medical history)
- Vital signs
- ECG
- Date of diagnosis of asthma
- Relevant medical history/ current medical condition present before signing the informed consent
- Smoking history and status
- Asthma Quality of Life (AQLQ+12)
- Asthma Control (ACQ-5)
- Blood eosinophil counts at Run-in Visit
- Prior concomitant medication (Both asthma related and non-asthma related)
- Pre and post-bronchodilator spirometry (run-in spirometry and reversibility testing)

[redacted]

6.3 Treatment exposure and compliance

Study drug compliance will be assessed by the investigator and/or study personnel at designated visits by recording tablet counts from the previously dispensed bottles. This information must be captured in the source document at each visit. All study drug dispensed and returned must be recorded in the Drug Accountability Log. Where necessary, the Investigator will discuss compliance issues with the patient.

Start and end dates of only missed doses of study drug administered since the last dispensing visit will be recorded in the eCRFs (study drug dosage administration record summary page) at visits specified in the table of assessments (Table 6-1).

All doses of study drug taken at the clinic visits must be from the newly assigned medication bottles, **except at** EOT **Visit when the medication returned by the patient should be used.**

6.4 Efficacy

The following assessments of efficacy will be performed:

- Systemic Corticosteroids use
- Health Status (PROs: AQLQ+12, ACQ-5)
- Biologic therapy administered during the treatment period

6.4.1 Systemic corticosteroids use

All patients will be provided with Oral Corticosteroids that can be used according to the asthma plan.

The total amount of daily OCS (number of tablets taken in the previous 12 hours) will be recorded morning and evening by the patient, in the eDiary/PEF

Investigators should instruct patients to record any OCS intake during the treatment period, on the eDiary/PEF device. At each study visit investigators and/or study personnel will count the number of OCS capsules taken (as part of the drug accountability), review OCS intake recorded on the eDiary by the patient, interview the patient on doses taken and enter it on the eCRF along with the start date, end date and the reason for the OCS intake.

Patients will be asked to return all unused non-study treatments and packaging at the end of the study or at the time of discontinuation from the study.

During certain circumstances (e.g. Hospitalization) patients might be taken injectable corticosteroids. This data will also be collected on the eCRF.

6.4.2 Health status (Patient Reported Outcomes)

A patient-reported outcome (PRO) is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else. Patient-reported outcomes may provide quantitative information for patients regarding the 'impact on daily life', which is of key importance, for patients and their physicians and also for health technology assessments.In this study, two PROs are used to assess the impact of uncontrolled asthma and the disease's management: Asthma Quality of Life Questionnaire (AQLQ+12) and the shortened version of Asthma Control Questionnaire (ACQ-5).All PROs

[redacted]

should always be completed before any other assessments are performed to avoid influencing the responses. When occurring at the same visit they are to be completed in the following order: AQLQ+12 and ACQ-5.

6.4.2.1 Asthma Quality of Life Questionnaire (AQLQ+12)

The AQLQ+12 is a 32-item disease specific questionnaire designed to measure functional impairments that are most important to patients with asthma (the questionnaire is included in Section 19). It consists of 4 domains symptoms, emotions, exposure to environmental stimuli and activity limitation. Patients are asked to recall their experiences during the previous 2 weeks and to score each item on a 7-point scale (Juniper et al 1992, Juniper et al 1993, Juniper et al 2005b). The overall AQLQ score is the mean response to all 32 questions. Clinically important differences in scores between any two assessments have been determined by the authors of the AQLQ. Changes in scores of 0.5 to 1.0 are considered clinically meaningful; 1.0 to 1.5 as moderate and > 1.5 as marked clinically important differences for any individual domain or for the overall summary score (Juniper et al 1994).

The AQLQ should be completed by the patient at the investigator's site as per the Assessment Schedule table (see Section 6).

6.4.2.2 Asthma Control Questionnaire (ACQ-5)

In this study, the ACQ-5 will be used to assess improvements in asthma symptom control. The original ACQ consists of 7 items: 5 items on symptom assessment, 1 item on rescue bronchodilator use, and 1 item on airway calibre (% FEV1 predicted). As the Spirometry assessments are performed centrally, the rescue bronchodilator use and % FEV1 predicted are not included in the version of ACQ chosen for this study.

The ACQ-5 will be self-administered at the clinic and it only takes a few minutes to complete. Patients will be asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0=no impairment, 6=maximum impairment). The questions are equally weighted and the ACQ-5 score is the mean of the 5 questions and therefore between 0 (totally controlled) and 6 (severely uncontrolled) (Juniper et al 1999; Juniper et al 2005a).

The ACQ-5 should be completed by the patient at the investigator's site as per the Assessment Schedule table (see Section 6).

6.4.3 eDiary

All patients will be provided with a patient electronic diary (referred to as eDiary/ePEF) to record daily asthma symptoms, peak flow, rescue medication (salbutamol/albuterol) and OCS use. Patients will be instructed to routinely complete the patient diary twice daily – at the same time each morning and each evening, approximately 12 hours apart. The eDiary/ePEF recordings are to be reviewed at the clinic visits as detailed in Table 6-1 until study completion. Sites and patients will receive appropriate training and guidance on the use of the eDiary device.

The study will use the asthma diary (Santanello et al 1997). The information detailed below will be collected in the eDiary/ePEF. Daytime asthma symptoms will be rated on a 0 to 6 scale and nocturnal asthma symptoms will be rated on a 0 to 3 scale

[redacted]

6.4.3.1 Daily Symptom Scores

The asthma diary contains daytime and nocturnal asthma symptom questions as delineated below. The format of the electronically administered asthma diary may vary.

Symptom diary scale questions

Table 6-2 Daytime symptom diary scale questions

1) How often did you experience asthma symptoms today?						
0	1	2	3	4	5	6
None of the time						All of the time
2) How much did your asthma symptoms bother you today?						
0	1	2	3	4	5	6
Not at all bothered						Severely bot hered
3) How much activity could you do today?						
0	1	2	3	4	5	6
More than usual activity						Less than usual activity
4) How often did your asthma affect your activities today?						
0	1	2	3	4	5	6
None of the time						All of the time

Table 6-3 Nocturnal diary scale question

1) Did you wake up with asthma symptoms?			
This can be awakening in the middle of the night or on awakening in the morning			
No	Once	More than once	Awake "all night"

6.4.3.2 Number of inhalations of Rescue Medication

The total number of inhalations used of rescue medication (number of puffs taken in the previous 12 hours) will be recorded morning and evening by the patient, in the eDiary/ePEF.

6.4.3.3 Peak expiratory flow (PEF)

PEF will be measured at consistent times for a patient, in the morning and evening each day during the study from Run-In to study completion. The measurements will be performed, using an eDiary/ePEF provided to the patients.

Patients should be encouraged to perform morning and evening PEF measurements BEFORE the use of any rescue medication, and patients will be asked to record if they have taken their SABA medication 6 hours prior to the peak flow assessment.

At each time point, the patient will be instructed to perform 3 consecutive maneuvers within approximately 10 minutes. These PEF values are captured in the eDiary /ePEF

[redacted]

6.4.4 Worsening of asthma (and related eDiary alerts)

Asthma worsening criteria will be programmed into the eDiary/ePEF apart from criterion 4 below.

The data captured in the eDiary/ePEF will be used to alert the patient and/or investigator to possible signs of worsening asthma.

The investigator should instruct the patient to contact the investigator if the patient develops one or more of the following asthma worsening criteria at any time during the trial from the run-in onwards. Patients may also receive an alert via their eDiary requesting them to contact their investigator:

1. An increase in SABA use on at least 2 of any 3 consecutive days exceeding the equivalent of 8 puffs/day (diary alert) *;
2. Nighttime awakenings requiring SABA use on at least 2 out of any 3 consecutive nights (diary alert)*;
3. <60% of PEF compared to baseline (diary alert)*; or
4. Urgent unscheduled clinic visit due to asthma-related deterioration.

*Note: The baseline for the run-in period is set the start of Run-in. The baseline during the treatment is set at the beginning of treatment (Day 1).

If patients develop any of the above criteria, the patient should notify the investigator and be evaluated by the investigator and treated as clinically appropriate. If any of these criteria are met while a patient is in the treatment or run-in periods of the study, they may be withdrawn if, in the opinion of the investigator, 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 the patient's progress until the asthma worsening has resolved.

6.4.5 Biologic therapy administered during the treatment period

As part of the flexible therapy, investigators are allowed to prescribe biologics from randomization visit onwards.

Given the delay to get access to the treatment in some countries, the date of prescription by the investigator should be recorded in addition to the start date and end date of the treatment. The dose, unit and reason for the treatment will also be collected.

6.4.6 Appropriateness of efficacy assessments

The measures described above are standard outcome measures in asthma studies.

6.5 Safety

The following safety assessments will be performed:

- Medical history and physical examination
- Adverse events including serious adverse events
- Asthma Exacerbations

[redacted]

- Height and weight
- ECG
- Laboratory evaluations (Hematology, Blood chemistry including HbA1c, Urinalysis)
- Pregnancy (female patients); additional pregnancy testing might be performed if requested by local requirements
- Serious asthma outcomes (asthma-related hospitalizations, intubations or deaths)

Spirometry will also be used to monitor the safety of patients during the study. Patients will be provided with an eDiary/ePEF. The data captured in the eDiary/ePEF will be used to alert the patient and/or investigator to possible signs of worsening of asthma.

A central laboratory will be used to analyze and report blood chemistry/hematology/urinalysis and urine chemistries.

A central ECG vendor will be used to collect, assess and report ECGs.

6.5.1 Medical history and physical examination

A complete physical examination will be performed at Screening Visits and EOT visit, or TD (if a patient discontinues investigational treatment but continues with study participation). It will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

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

6.5.2 Asthma Exacerbations

The following definitions of exacerbations are used in this study.

A **mild asthma exacerbation** is defined as one or more of the following:

- Increase of asthma symptoms
- An increase in SABA use on at least 2 of any 3 consecutive days exceeding the equivalent of 8 puffs/day (diary alert)
- Nighttime awakenings requiring SABA use on at least 2 out of any 3 consecutive nights (diary alert)
- <60% of PEF compared to baseline (diary alert)

A **moderate asthma exacerbation** is defined as treatment with 'rescue' systemic corticosteroids for greater than or equal to 3 days either as an outpatient or in emergency department visits (Emergency department visit less than or equal to 24 hours).

[redacted]

A **severe asthma exacerbation** is defined as:

- Treatment with 'rescue' systemic corticosteroids for greater than or equal to 3 days and hospitalization; or
- Treatment with 'rescue' systemic corticosteroids for greater than or equal to 3 days and emergency department visit (greater than 24 hours*); or
- Death due to asthma

*An emergency room visit greater than 24 hours is considered to be a hospitalization.

'Rescue' systemic corticosteroids are tablets, suspension, or injection, or an increase of a patient's maintenance systemic corticosteroids of ≥2 fold (i.e., at least doubling of the maintenance dose of systemic corticosteroids). A single depo-injectable dose of corticosteroid will be considered the equivalent to a 3-day course of systemic steroids (Reddel et al 2009). Endotracheal intubations will be captured on the CRF.

Scheduled spirometry should not be performed during an exacerbation until it has completely resolved.

If patients experience an asthma attack/exacerbation requiring systemic corticosteroids, hospitalization, or emergency room visit during the screening period, they may be re-screened once with the re-screening of the patient occurring 6 weeks or more after recovery from the asthma exacerbation.

In case of an asthma exacerbation, the patient should be encouraged by the site to contact it for advice. If necessary, an unscheduled visit to the site may be arranged.

6.5.3 Vital signs

Vital signs will be performed at site visits specified in the table of assessments (Table 6-1). Measurements will include systolic and diastolic blood pressure, pulse rate, and body temperature.

6.5.4 Height and weight

Height in centimeters (cm) will be measured at the visits specified in the table of assessments (See Table 6-1).

Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at the visits specified in the table of assessments (See Table 6-1).

Body Mass Index (BMI) will be calculated as the weight in kg divided by the height in meters squared.

6.5.5 Laboratory evaluations

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

Details on clinically notable laboratory findings are defined in Section 13.

[redacted]

6.5.5.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured according to the assessment schedule in Table 6-1. Other reflex testing will be performed as outlined in the laboratory manual.

6.5.5.2 Clinical chemistry

BUN/urea, creatinine, creatine kinase, total bilirubin, AST, ALT, alkaline phosphatase, gamma-glutamyl transpeptidase, lactate dehydrogenase, sodium, potassium, chloride, calcium, magnesium, iron, bicarbonate, cholesterol, triglycerides, high-sensitivity C-reactive protein, phosphorus, total protein, albumin, glucose, uric acid, amylase, lipase, CK-MB and Troponin-I (in response to CK results outside of the normal range), HbA1c (collected at start of Run-in Visit and EOT only) and immunoglobulins (total and specific IgE, as specified in the laboratory manual), will be measured according to the assessment schedule in Table 6-1. Other reflex testing will be performed as outlined in the laboratory manual.

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

All patients with laboratory tests containing clinically significant abnormalities should be followed until the values return to within the normal ranges or until a clinical explanation is identified, even after study medication has discontinued.

6.5.5.3 Urinalysis

Urine for urinalysis and urine chemistry will be collected according to the collection schedule in Table 6-1. All samples for urinalysis and urine chemistry will be sent to the central laboratory for analysis. The urinalysis evaluation by the central laboratory will include a urine dipstick for specific gravity, protein, glucose, leukocytes and blood and, if required, a microscopic examination. Urine chemistry and microscopic examination of the urine will be performed by the central laboratory as delineated in Section 15 “Specific Renal Alert Criteria and Actions” and in Section 7.4 “Renal Safety Monitoring” of this protocol. Other reflex testing will be performed as outlined in the laboratory manual.

6.5.6 Electrocardiogram (ECG)

ECGs will be measured according to the assessment schedule in Table 6-1. At Screening Visit, an ECG will be measured to test for eligibility for trial inclusion.

ECGs must be recorded according to the ECG investigator manual in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is PRO collection first, followed by ECG, and then other study procedures. The Fridericia QT correction formula (QTcF) must be used for clinical decisions.

Single 12 lead ECGs are to be collected with ECG machines supplied by the core laboratory. Full details of all procedures relating to the ECG collection and reporting will be contained in an investigator manual to be provided to each investigator site.

The original trace will be sent electronically for central review directly from the ECG machine. Two ‘identical’ duplicate print-outs will be generated and kept at the investigator site as source

[redacted]

documentation and as back-up for submission to the central laboratory in case of problems with the electronic transmission. Each page of the ECG tracing must be labeled with study number (CQAW039A2323), subject initials (where this is allowed according to local regulations), subject number, date and time, and filed in the study site source documents.

For any ECGs with subject safety concerns, two additional ECGs must be performed to confirm the safety finding and copies forwarded to the central ECG laboratory for assessment. Clinically significant ECG findings prior to dosing with study drug must be discussed with the Novartis responsible person or designee.

Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE CRF / e(CRF) page as appropriate.

In the event that the central cardiologist reports that an ECG is abnormal, then the investigator must comment as to whether the ECG abnormality is either clinically significant or clinically insignificant. If necessary a cardiologist may be consulted.

6.5.7 Pregnancy

All women of child bearing potential will have a serum pregnancy test at start of Run-In Visit and a urine pregnancy test at all site visits. No pregnancy testing will be performed when the visit is performed as a telephone call.

Pregnancy testing will begin at the visit a patient is first identified as being of child bearing potential.

In countries where monthly pregnancy testing is required for women of child-bearing potential by local laws or regulations, these patients will perform home urine pregnancy testing on the day of all telephone visits. These female patients will report the results of their home urine pregnancy test as “positive” or “negative” to study site staff as part of the telephone visit and the results will be recorded in source documents.

A positive urine pregnancy test requires immediate interruption of study medication until serum β-hCG is performed and found to be negative. If positive, the patient must be discontinued from the study treatment.

6.5.8 Appropriateness of safety assessments

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

6.6 Other assessments

Not applicable

6.6.1 Clinical Outcome Assessments (COAs)

Please refer to Section 6.4.2

[redacted]

[redacted]

6.6.3 Pharmacokinetics

Not applicable.

6.6.4 Spirometry

All clinic visits must occur in the morning. Please refer to Section 6 and Table 6-1 for full details of the scheduling of spirometry measurements. During the treatment period, the spirometry assessment should be done pre-dose.

Equipment for spirometry assessments will be provided to all study sites by a Central Spirometry vendor, and pre randomization measurements will be reviewed by trained spirometry overreaders at the central vendor. The final spirometry assessments for study qualification will be those provided by the spirometry overreaders of the central spirometry vendor.

Please refer to the Spirometry Guidance, in Section 17 , for full details on performing spirometry. Reversibility testing must be conducted in the morning

6.6.5 Other biomarkers

Not applicable.

7 Safety monitoring

7.1 Adverse events

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

The investigator has the responsibility for managing the safety of individual subject 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 subject at each visit during the study. Adverse events also may be detected when they are volunteered by

[redacted]

the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded 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 7.2.1)

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 subject
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 7.2.1 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment
6. All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose Reduced/increased
   - Drug interrupted/withdrawn
7. its outcome i.e., its recovery status or whether it was fatal

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

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

Adverse event monitoring should be continued for at least 14 days (or 5 half-lives or end of study visit, whichever is longer) following the last dose of study treatment

Information about adverse drug reactions for the investigational drug can be found in the Investigator Brochure (IB).

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

[redacted]

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 subjects with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 13.

7.2 Serious adverse events

7.2.1 Definition of SAE

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

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition under study .
- 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
- social reasons and respite care in the absence of any deterioration in the subject's general condition
- 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
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

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

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

[redacted]

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.

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 following the last administration of study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

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 Chief Medical Office and Patient Safety 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.

Any SAEs experienced after the 30 day period following the last administration of study treatment should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

7.3 Liver safety monitoring

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

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

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate CRFs

Please refer to Table 14-1 - Appendix 2 in Section 14 for complete definitions of liver laboratory triggers and liver events.

[redacted]

Every liver event defined in Table 14-1 - Appendix 2 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 14-2 - Appendix 2. Repeat liver function test (LFT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
- These investigations can include based on investigator's discretion: 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 the procedures performed must be recorded as appropriate in the CRF

7.4 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

Serum event:

- Confirmed (after ≥24 hours) increase in serum creatinine (sCr) of ≥25% compared to baseline during normal hydration status

Urine event:

- Albumin-creatinine ratio (ACR) ≥1g/g or ≥100 mg/mmol.
- Protein-creatinine ratio (PCR) ≥1g/g or ≥100 mg/mmol.

Every renal laboratory trigger or renal event as defined in Table 15-1 - Appendix 3 should be followed up by the investigator or designated personnel at the trial site as summarized in Section 15.

7.5 Reporting of study treatment errors including misuse/abuse

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

[redacted]

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be 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 7-1 Guidance for capturing the study treatment errors including misuse/abuse

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

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

7.6 Pregnancy reporting

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

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

7.7 Prospective suicidality assessment

Not applicable

8 Data review and database management

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

8.1 Site monitoring

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

[redacted]

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

The investigator must give to the filed 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 subjects will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to US CFR 21 Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis personnel will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

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

[redacted]

Spirometry readings 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.Diary data will be entered into an electronic diary by the patient and patients will fill in their PRO data in a site-based tablet. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis personnel.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Randomization codes and data about all study treatment (s) dispensed to the subject 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 data will be sent electronically to Novartis at specific timelines.

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

Once all the necessary 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/moved to restricted area to be accessed by independent programmer and statistician**. Any changes to the database after that time can only be made after written agreement by Novartis development management.

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

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

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

9.1 Analysis sets

The screened set (SCR) will include all patients who provided informed consent.

[redacted]

The randomized set (RAN) will include all patients that were randomized. Data from these patients will be analyzed according to the treatment to which the patient was assigned at randomization.

The full analysis set (FAS) will include all randomized patients who received at least one dose of study drug. It was considered reasonable to limit the FAS to patients who took trial medication, because the decision on whether or not treatment is started will not be influenced by the treatment group assignment due to the effective treatment blinding procedures described in Section 5.4. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.

The safety set (SAF) will include all patients who received at least one dose of study drug. Patients will be analyzed according to the treatment they received.

The analysis of the primary objective will be performed on the FAS. The FAS will be used for the analysis of all other efficacy variables. The SAF will be used in the analysis of all safety variables.

9.2 Patient demographics and other baseline characteristics

Patient demographics and baseline characteristics measured before randomization will be summarized by treatment group for the FAS.

9.3 Treatments

The safety set will be used for the analysis below.

A data listing and a summary of the study drug administered will be provided.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

A listing and summary of rescue medications will be provided.

9.4 Analysis of the primary variable(s)

The primary analysis for this study will be conducted according to the intention to treat principle.

9.4.1 Primary Variable(s)

The primary endpoint for this study is total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) over 52 weeks of treatment.

9.4.2 Statistical model, hypothesis, and method of analysis

The primary endpoint will be analyzed in subpopulation of patients with eosinophil count ≥ 250 cells/µl and in overall population. The primary null hypotheses are:

- $H_{01\ 450\ \text{eosinophil subgroup}}$: the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in Fevipiprant 450 mg QD plus SoC is equivalent to the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in placebo plus SoC in patients with eosinophil count ≥ 250 cells/µl

[redacted]

- $H_{02\ 150\ \text{eosinophil subgroup}}$: the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in Fevipiprant 150 mg QD plus SoC is equivalent to the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in placebo plus SoC in patients with eosinophil count ≥ 250 cells/µl
- $H_{03\ 450\ \text{overall population}}$: the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in Fevipiprant 450 mg QD plus SoC is equivalent to the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in placebo plus SoC for the overall population
- $H_{04\ 150\ \text{overall population}}$: the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in Fevipiprant 150 mg QD plus SoC is equivalent to the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in placebo plus SoC for the overall population

The primary alternate hypotheses are:

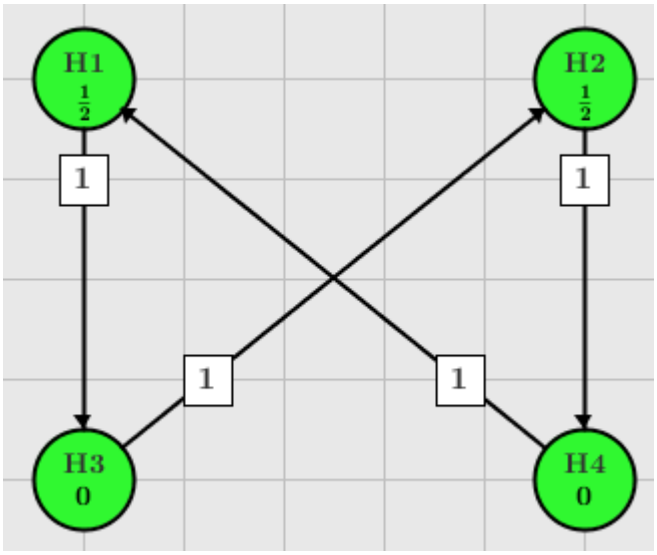
- $H_{A1\ 450\ \text{eosinophil subgroup}}$: the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in Fevipiprant 450 mg QD plus SoC is different to the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in placebo plus SoC in patients with eosinophil count ≥ 250 cells/µl
- $H_{A2\ 150\ \text{eosinophil subgroup}}$: the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in Fevipiprant 150 mg QD plus SoC is different to the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in placebo plus SoC in patients with eosinophil count ≥ 250 cells/µl
- $H_{A3\ 450\ \text{overall population}}$: the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in Fevipiprant 450 mg QD plus SoC is different to the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in placebo plus SoC for the overall population
- $H_{A4\ 150\ \text{overall population}}$: the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in Fevipiprant 150 mg QD plus SoC is different to the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) in placebo plus SoC for the overall population

Familywise type I error rate control

The familywise type I error rate will be controlled at the two-sided 5% level across the primary null hypotheses using graphical approach specified by Figure 9-1 (Bretz et al 2009).

[redacted]

Figure 9-1 Closed testing procedure for primary objectives



Vertices with associated weights denote the individual null hypotheses and their local significance levels (initially the alpha is split 50%:50% across the primary null hypotheses regarding the subgroup with blood eosinophils ≥ 250 cells/µl for the 2 fevipiprant doses). Directed edges between the vertices specify how the local significance levels are propagated in case of significant results.

Initially, 50% of the alpha is assigned to each of the primary null hypotheses regarding the subgroup with blood eosinophils ≥ 250 cells/µl for the Fevipiprant 450 mg QD and Fevipiprant 150 mg QD doses, respectively. Once this first primary null hypothesis for a dose has been rejected, the alpha will be distributed to the other null hypothesis regarding the overall population for the same dose. If the null hypothesis regarding the primary endpoint for the overall population is rejected for a dose, then alpha is reassigned to the primary null hypotheses regarding the subgroup with blood eosinophils ≥ 250 cells/µl for the other dose. Alpha will only be reassigned from the null hypotheses for a dose to the null hypotheses for the other dose once all null hypotheses for the dose to which the alpha was originally assigned have been rejected.

Statistical model for primary variable

The total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) over 52 weeks of treatment will be analyzed using the Wilcoxon-Mann-Whitney rank sum test (Van Elteren test). For overall population analysis will be stratified by randomization stratum – blood eosinophils levels (≥ 250 cells/µl and < 250 cells/µl). For subgroup with blood eosinophils ≥ 250 cells/µl, analysis will not include stratification factor. The summary statistics for total SCS dose by treatment group will be provided.

The details and justification of primary as well as supplementary estimands are detailed in Estimand charter or statistical analysis plan (SAP).

The primary estimand will quantify the treatment effect based on on-treatment data. The total SCS dose data will be aggregated into monthly data for analysis. The primary estimand will account for different post-randomization events as follows:

- Use of rescue medications: Efficacy data collected during use of rescue medication will be used for analysis.

[redacted]

- Early discontinuation of study treatment (prior to completing 52 weeks of treatment period): For the patients discontinuing treatment early, the total SCS dose for 52 weeks will be obtained as annualized SCS dose. For example if patient took 280 mg for 7 months then for 12 months patient will be taking 280*12/7=480mg total SCS dose.
- Use of biologics prior to discontinuation of treatment: Efficacy data collected during the use of biologics will be set to missing, since use of biologics can confound efficacy data. After replacing SCS dose with missing patient will not have data available for 12 months, thus total SCS dose will be obtained as annualized dose.

9.4.3 Handling of missing values/censoring/discontinuations

Some patients may discontinue early and may not complete the entire study duration. For the patients discontinuing treatment early, the total SCS dose for 52 weeks will be obtained as annualized SCS dose. For example if patient took 280 mg for 7 months then for 12 months patient will be taking 280*12/7=480mg total SCS dose. Efficacy data collected during the use of biologics will be set to missing, since use of biologics can confound efficacy data. After replacing SCS dose with missing, patient will not have data available for all 12 months, thus total SCS dose will be obtained as annualized dose.

9.4.4 Sensitivity analyses

The details on sensitivity analysis will be provided in SAP.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

Proportion of patients with no SCS use over 52 weeks of treatment

The proportion of patients with no SCS use over 52 weeks treatment will be summarized by treatment and analyzed using logistic regression in overall population. The model will include treatment and randomization strata as covariates. Estimates of the odds ratio between treatment groups will be displayed along with associated 95% confidence intervals and two-sided p-values.

Proportion of patients requiring ≥ 7.5mg systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) per day continuously for at least 30 days

The proportion of patients requiring ≥ 7.5mg systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) per day continuously for at least 30 days in 52 weeks treatment period will be summarized by treatment and analyzed using logistic regression in overall population. The model will include treatment and randomization strata as covariates. Estimates of the odds ratio between treatment groups will be displayed along with associated 95% confidence intervals and two-sided p-values.

Asthma Quality of Life Questionnaire (AQLQ+12)

The 32 items in the AQLQ are divided into 4 domain- specific scores and a total score as follows:

- Symptoms = Mean of Items 6,8,10,12,14,16,18,20,22,24,29,30 (12 items)

[redacted]

- Activity limitation = Mean of Items 1,2,3,4,5,11,19,25,28,31,32 (11 items)
- Emotional function = Mean of Items 7,13,15,21,27 (5 items)
- Environmental stimuli = Mean of Items 9,17,23,26 (4 items)
- Overall score = Mean of Items 1 to 32 (32 items)

Each item of the AQLQ is equally weighted and scored along a 7-point scale, where 1 indicates maximal impairment and 7 indicates no impairment. Thus, higher scores indicate better asthma-related HRQOL. There is a mean score calculated for each of the four domains, as well as an overall quality of life score, which is the mean score of all 32 items. The resultant overall scores will be between 1 and 7.

The developer suggests no more than 10% of missing data. This means no more than 3 missing responses for the overall score and no more than 1 missing response per domain. For the symptoms and activity domain scores, one missing value per domain is allowed. For the emotional function and environmental stimuli domain scores, no missing values are allowed. If these limits for missing questions are exceeded, the variable will be considered missing and imputation method will be detailed in statistical analysis plan.

The minimal important difference (MID), defined as "the smallest difference in score which patients perceive as beneficial and would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management," of 0.5 has been established for this questionnaire as clinically significant (Juniper et al 1994).

The AQLQ score will be analyzed using a mixed model for repeated measures (MMRM) with an unstructured covariance structure with factors for treatment group, time and randomization stratum, as well as the baseline AQLQ as continuous linear covariates.

The null hypothesis will be tested for overall population for each dose group using this model versus two-sided alternative hypotheses. For each dose group the null hypothesis is that the treatment difference compared to placebo at the week 52 visit is equal to zero, while the alternative hypothesis is that the treatment difference to placebo at week 52 visit is not equal to zero.

Asthma Control Questionnaire (ACQ-5)

The ACQ measures asthma symptom control and consists of 7 items. It includes the 5 most important symptoms, 1 about rescue bronchodilator use and 1 about airway calibre (FEV1 % predicted pre-bronchodilator). Patients will be asked to recall their experiences during the past one week and to response items 1-6 (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheeze, and rescue short-acting β2-agonist use) on a 7-point scale (0 – totally controlled, 6 – extremely poorly controlled). The ACQ-5 score calculated based on the 5 questions of the 5 most important symptoms. The 5 questions of the ACQ-5 are equally weighted. The ACQ-5 score is the mean of the responses to the 5 questions. The resultant score will be between 0 and 6.

A score of 1.5 at baseline indicates patients who entered the study had inadequately controlled asthma (Juniper et al 2006). In addition, the minimal important difference (MID) or smallest change that can be considered clinically important is 0.5.

[redacted]

The ACQ-5 score will be analyzed using a MMRM with an unstructured covariance structure with factors for treatment group, time and randomization stratum, as well as the baseline ACQ-5 as continuous linear covariates.

The null hypothesis will be tested for overall population for each dose group using this model versus two-sided alternative hypotheses. For each dose group the null hypothesis is that the treatment difference compared to placebo at the week 52 visit is equal to zero, while the alternative hypothesis is that the treatment difference to placebo at week 52 visit is not equal to zero.

Time to first prescription of biologic therapy from first dose of study treatment received over 52 weeks of treatment

The time to first prescription of biologic therapy from first dose of study treatment received over 52 weeks of treatment will be summarized by treatment group. Between-treatment differences will be evaluated using cox regression model.

Change from baseline in daytime and nighttime symptom scores in 52 weeks of treatment

Change from baseline in each endpoint (daytime and nighttime symptom score) will be analyzed using mixed models repeated measures (MMRM) model with factors as treatment group, randomization strata, time interval, time interval by treatment group interaction and the associated baseline as continuous linear covariate. Estimates of the LS means between treatment groups will be displayed along with associated 95% confidence intervals and two-sided p-values.

9.5.2 Safety variables

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period lasts from the date of first administration of study treatment to 14 days after the date of the last actual administration of any study treatment.

Adverse events

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

The number (and percentage) of subjects with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term

[redacted]

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment.

The adverse events of special interest will be listed and summarized by treatment group.

A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by treatment group, subject, and visit and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment group.

12-lead ECG

All ECG data will be listed by treatment group, subject and visit, abnormalities will be flagged. Summary statistics will be provided by treatment.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and visit and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment group. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

[redacted]

9.5.4 Pharmacokinetics

Not applicable.

9.5.5 DNA

Not applicable.

9.5.6 Biomarkers

Not applicable

9.5.7 PK/PD

Not applicable

[redacted]

9.7 Interim analyses

Not Applicable

[redacted]

9.8 Sample size calculation

The historical data (US Marketscan database) shown in Table 9-1 indicates that the distribution of the total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) across patients is not normal; rather the distribution is skewed; hence using a normal distribution assumption is not appropriate. In addition, the proportion of patients with 0 total systemic corticosteroid dose in mg prednisone/prednisolone (or equivalent) is quite high (>30%) therefore a transformation that could normalize the distribution is not feasible. As a consequence, a non-parametric method based on rank analysis will be used to analyze the primary end-point. The formula developed for the Wilcoxon-Mann-Whitney test adjusting for ties (Zhao et al 2008) has been used to estimate the sample size. A 1:1:1 randomization was used. There are four hypotheses to be tested for primary endpoint as stated in Section 9.4.2.

Table 9-1 Frequency distribution of dose to display (non-normal) distribution of US Marketscan database

	HD ICS/LABA+LAMA 6 weeks		**HD ICS/LABA+LTRA 6 weeks**		**HD ICS/LABA 6 weeks**	
Outcomes	n=1562		n=7409		n=18471	
Dose Category (Count/%)						
0 (0mg)	533	34.1%	2901	39.2%	8211	44.5%
1 (>0 - 50 mg)	5	0.3%	20	0.3%	46	0.2%
2 (>50 - 100 mg)	25	1.6%	90	1.2%	214	1.2%
3 (>100 - 150 mg)	107	6.9%	595	8.0%	1376	7.4%
4 (>150 - 200 mg)	62	4.0%	358	4.8%	904	4.9%
5 (>200 - 250 mg)	90	5.8%	335	4.5%	808	4.4%
6 (>250 - 300 mg)	50	3.2%	313	4.2%	789	4.3%
7 (>300 - 350 mg)	40	2.6%	184	2.5%	426	2.3%
8 (>350 - 400 mg)	47	3.0%	216	2.9%	608	3.3%
9 (>400 - 450 mg)	44	2.8%	219	3.0%	519	2.8%
10 (>450 - 500 mg)	34	2.2%	181	2.4%	396	2.1%
11 (>500 - 550 mg)	24	1.5%	141	1.9%	308	1.7%
12 (>550 - 600 mg)	39	2.5%	221	3.0%	479	2.6%
13 (>600 - 650 mg)	19	1.2%	99	1.3%	237	1.3%
14 (>650 - 700 mg)	16	1.0%	80	1.1%	214	1.2%
15 (>700 - 750 mg)	28	1.8%	103	1.4%	252	1.4%
16 (>750 mg)	399	25.5%	1353	18.3%	2684	14.5%

Table 9-2 represents the selected scenario for the null and alternative hypothesis and the sample size under a 90% power and an overall alpha two sided of 5%. As we have two doses to test, the alpha considered for the sample size is 2.5% two sided.

Under the assumptions specified above and scenarios described in Table 9-2, 134 patients per arm in the subpopulation with eosinophils count ≥ 250 cells/µl and 201 patients per arm in the overall population corresponding to a total sample size of 603 patients provide greater than 90% power for primary null hypotheses. Assuming 10% treatment discontinuation rate, a total of 669 patients are needed.

[redacted]

alpha 2.5% power 90%	0-50mg/ year	>50-150 mg/ year	>150-300 mg/ year	>300-450 mg/ year	>450-600 mg/ year	>600 mg/ year	High EoS	Full population	+10%
Placebo	42.7%	8.8%	13.5%	8.4%	6.6%	20.0%	-	-	-
Fevi	60.0%	15.0%	9.0%	3.0%	3.0%	10.0%	402	603	669

We have looked also at other possible distributions for both fevipiprant and placebo under a power of 80% or 90% and alpha 0.025 two sided. Table 9-2 provides other scenarios for the placebo and the Fevi group. Even if we deviate from the original scenario, other possible distributions provide still good power.

Table 9-2 Other scenario investigated for Fevipiprant single dose EOS greater or equal 250 cells/microliter

alpha 2.5%	0-50mg /year	>50-150 mg/year	>150-300 mg/year	>300-450 mg/year	>450-600 mg/year	>600 mg/year	Power under the assumption of 134 pts per arm
Placebo	0.0%	10.0%	25.0%	25.0%	15.0%	25.0%	-
Scenario 1 Fevi	5.0%	25.0%	25.0%	20.0%	10.0%	15.0%	96%
alpha 2.5%	**0-50mg/year**	**>50-150 mg/year**	**>150-300 mg/year**	**>300-450 mg/year**	**>450-600 mg/year**	**>600 mg/year**	
Placebo	20.0%	5.0%	20.0%	10.0%	15.0%	30.0%	-
Scenario 2 Fevi	35.0%	20.0%	30.0%	5.0%	5.0%	5.0%	100%
alpha 2.5%	**0-50mg/year**	**>50-150 mg/year**	**>150-300 mg/year**	**>300-450 mg/year**	**>450-600 mg/year**	**>600 mg/year**	
Placebo	42.7%	8.8%	13.5%	8.4%	6.6%	20.0%	-
Scenario 3 Fevi	57.0%	18.0%	9.0%	3.0%	3.0%	10.0%	85%
Scenario 4 Fevi	55.0%	14.0%	14.0%	5.0%	3.0%	9.0%	75%
alpha 2.5%	**0-50mg/year**	**>50-150 mg/year**	**>150-300 mg/year**	**>300-450 mg/year**	**>450-600 mg/year**	**>600 mg/year**	
Placebo	0.0%	10.0%	25.0%	25.0%	15.0%	25.0%	-
Scenario 5 Fevi	5.0%	25.0%	20.0%	20.0%	12.0%	18.0%	82%

Based on clinical judgment different scenarios are considered in the above table

The following formula to calculate the sample size has been used (Zhao et al 2008):

$$N = \frac{(Z_{\alpha/2} + Z_{\beta})^2 (1 - \sum_{c=1}^{D} ((1-t)p_c + tq_c)^3)}{12t(1-t)(\sum_{c=2}^{D} p_c \sum_{d=1}^{c-1} q_d + 0.5 \sum_{c=1}^{D} p_c q_c - 0.5)^2}$$

Where,

N is the total sample size for a 2 arm trial.

[redacted]

t is the randomization ratio

p_c are the % of patients in category c for the experiment arm

q_c are the % of patients in category c for the control arm

D is number of categories

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

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

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

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 subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

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

[redacted]

10.3 Responsibilities of the investigator and IRB/IEC

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

10.4 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (**defined as last patient last visit**) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.)

10.5 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.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects 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 participants.

[redacted]

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

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject 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 subject 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.

12 References

References are available upon request

ATS (2000). Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. American Thoracic Society. Am. J. Respir. Crit. Care Med. p. 2341-51.

ATS/ERS (2005) Recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am. J. Respir. Crit. Care Med; p. 912-30.

Bourdin A et al. (2018), abstr. CO01-4, actualisé Impact de l'asthme sévère en France: une étude à partir de l'échantillon généraliste de bénéficiaires".

Bretz F, Maurer W, Brannath W, et al (2009) A graphical approach to sequentially rejective multiple test procedures. Stat Med; p. 586-604.

Castro M, Mathur S, Hargreave F, et al (2011) Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am. J. Respir. Crit. Care Med. p. 1125-32.

Castro M, Zangrilli J, Wechsler ME, et al (2015) Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med p. 355-66.

Chevalier E, Stock J, Fisher T, et al (2005) Cutting edge: chemoattractant receptor-homologous molecule expressed on Th2 cells plays a restricting role on IL-5 production and eosinophil recruitment. J. Immunol. p. 2056-60.

Dalal AA, Duh MS, Gozalo L, et al (2016) Dose-Response Relationship Between Long-Term Systemic Corticosteroid Use and Related Complications in Patients with Severe Asthma. J Manag Care Spec Pharm p. 833-47.

De Vries F, Bracke M, Leufkens HG, et al (2007) Fracture risk with intermittent high-dose oral glucocorticoid therapy. Arthritis Rheum. p. 208-14.

Deng JW, Song IS, Shin HJ, et al (2008) The effect of SLCO1B1*15 on the disposition of pravastatin and pitavastatin is substrate dependent: the contribution of transporting activity changes by SLCO1B1*15. Pharmacogenet. Genomics p. 424-33.

Elsby R, Hilgendorf C, Fenner K (2012) Understanding the critical disposition pathways of statins to assess drug-drug interaction risk during drug development: it's not just about OATP1B1. Clin. Pharmacol. Ther. p. 584-98.

Global Initiative for Asthma (GINA) (2018) Global Strategy for Asthma Management and Prevention. Available from: http://www.ginasthma.org/.

Haldar P, Brightling CE, Hargadon B, et al (2009) Mepolizumab and exacerbations of refractory eosinophilic asthma. N. Engl. J. Med. p. 973-84.

Jacobson TA (2008) Toward "pain-free" statin prescribing: clinical algorithm for diagnosis and management of myalgia. Mayo Clin. Proc. p. 687-700.

[redacted]

Juniper EF, Bousquet J, Abetz L, et al (2006) Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med p. 616-21.

Juniper EF, Guyatt GH, Epstein RS, et al (1992) Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax p. 76-83.

Juniper EF, Guyatt GH, Ferrie PJ, et al (1993) Measuring quality of life in asthma. Am. Rev. Respir. Dis. p. 832-8.

Juniper EF, Guyatt GH, Willan A, et al (1994) Determining a minimal important change in a disease-specific Quality of Life Questionnaire. J Clin Epidemiol p. 81-7.

Juniper EF, O'Byrne PM, Guyatt GH, et al (1999) Development and validation of a questionnaire to measure asthma control. Eur. Respir. J. p. 902-7.

Juniper EF, Svensson K, Mörk AC, et al (2005)a Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med p. 553-8.

Juniper EF, Svensson K, Mörk AC, et al (2005)b Modification of the asthma quality of life questionnaire (standardised) for patients 12 years and older. Health Qual Life Outcomes p. 58.

Kalliokoski A, Niemi M (2009) Impact of OATP transporters on pharmacokinetics. Br. J. Pharmacol. p. 693-705.

Lefebvre P, Duh MS, Lafeuille MH, et al (2015) Acute and chronic systemic corticosteroid-related complications in patients with severe asthma. J. Allergy Clin. Immunol. p. 1488-1495.

Masoli M, Fabian D, Holt S, et al (2004) The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy p. 469-78.

Noé J, Portmann R, Brun ME, et al (2007) Substrate-dependent drug-drug interactions between gemfibrozil, fluvastatin and other organic anion-transporting peptide (OATP) substrates on OATP1B1, OATP2B1, and OATP1B3. Drug Metab. Dispos. p. 1308-14.

Partridge MR (2004) Written asthma action plans. Thorax p. 87-8.

Pavord ID, Korn S, Howarth P, et al (2012) Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet p. 651-9.

Reddel HK, Taylor DR, Bateman ED, et al (2009) An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am. J. Respir. Crit. Care Med. p. 59-99.

Regan SL, Maggs JL, Hammond TG, et al (2010) Acyl glucuronides: the good, the bad and the ugly. Biopharm Drug Dispos p. 367-95.

Santanello NC, Barber BL, Reiss TF, et al (1997) Measurement characteristics of two asthma symptom diary scales for use in clinical trials. Eur. Respir. J. p. 646-51.

Schäcke H, Döcke WD, Asadullah K (2002) Mechanisms involved in the side effects of glucocorticoids. Pharmacol. Ther. p. 23-43.

[redacted]

Sullivan PW, Ghushchyan VH, Globe G, et al (2018) Oral corticosteroid exposure and adverse effects in asthmatic patients. J. Allergy Clin. Immunol. p. 110-116.e7.

Sweeney J, Patterson CC, Menzies-Gow A, et al (2016) Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. Thorax p. 339-46.

Takaku Y, Soma T, Nishihara F, et al (2013) Omalizumab attenuates airway inflammation and interleukin-5 production by mononuclear cells in patients with severe allergic asthma. Int. Arch. Allergy Immunol. p. 107-17.

Wenzel S, Ford L, Pearlman D, et al (2013) Dupilumab in persistent asthma with elevated eosinophil levels. N. Engl. J. Med. p. 2455-66.

Zazzali JL, Broder MS, Omachi TA, et al (2015) Risk of corticosteroid-related adverse events in asthma patients with high oral corticosteroid use. Allergy Asthma Proc p. 268-74.

Zhao YD, Rahardja D, Qu Y (2008) Sample size calculation for the Wilcoxon-Mann-Whitney test adjusting for ties. Stat Med p. 462-8.

13 Appendix 1: Clinically notable laboratory values and vital signs

The central laboratory will flag laboratory values falling outside of the normal ranges on the central laboratory reports. Investigators are responsible for reviewing these abnormal values for clinical significance, signing the laboratory reports to indicate their review, and reporting values considered clinically significant in the appropriate electronic case report form (eCRF).

Any clinically significant abnormal laboratory value should be evaluated and followed-up by the investigator until normal or a cause for the abnormality is determined.

See Section 14 for specific liver event and laboratory test trigger definitions and follow-up requirements. See Section 15 for specific renal alert criteria and actions.

For electrocardiograms (ECGs), a notable QTc value is defined as a QTcF (Fridericia) interval of ≥450 msec for males or ≥460 msec for females – all such ECGs will be flagged by the Central contract research organization (CRO) and require assessment for clinical relevance and continuance of the patient by the Investigator.

14 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 14-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN
	• ALP > 2 × ULN (in the absence of known bone pathology)
	• TBL > 2 × ULN (in the absence of known Gilbert syndrome)
	• ALT or AST > 3 × ULN and INR > 1.5
	• Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)
	• Any clinical event of jaundice (or equivalent term)
	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	• Any adverse event potentially indicative of a liver toxicity*
*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL (total bilirubin), ULN (upper limit of normal).	

Table 14-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	**Actions required**	**Follow-up monitoring**
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

[redacted]

Criteria	Actions required	Follow-up monitoring
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT 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	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT 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	Investigator discretion

[redacted]

Criteria	Actions required	Follow-up monitoring
	• If elevation is confirmed, initiate close observation of the patient	Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT 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 • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

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

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

ULN (upper limit of normal), ALT (alanine aminotransferase), AST (aspartate aminotransferase), TBL (total bilirubin), ALP (alkaline phosphatase), INR (international normalized ratio), PT (prothrombin time), Alb (albumin), LFT (lung function test), CRF (case report form).

[redacted]

15 Appendix 3: Specific Renal Alert Criteria and Actions

Table 15-1 Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase 25% – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥50% compared to baseline	Follow up within 24-48h if possible Consider study treatment interruption Consider patient hospitalization /specialized treatment
Urine Event	
Albumin-creatinine ratio (ACR) ≥1g/g or ≥100 mg/mmol; Protein-creatinine ratio (PCR)≥1 g/g or ≥100 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider study treatment interruption / or discontinuation
For all renal events	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor patient regularly (frequency at investigator's discretion) until either: Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.	

16 Appendix 4: List of idiosyncratic drug reactions (IDRs) for investigators

Table 16-1 Definition of potential idiosyncratic drug reactions

Type of reaction	Possible events diagnoses and signs/symptoms
Anaphylaxis	Anaphylactic/anaphylactoid reactions
Angioedema: diagnosis and/or signs and symptoms	Angioedema, site specific angioedema urticaria, anisarca/generalized edema urticaria
Severe skin reactions	Acute generalised exanthematous pustulosis, Cutaneous vasculitis, Drug reaction with eosinophilia and systemic symptoms (DRESS), Epidermal necrosis, Toxic skin eruption , Oculomucocutaneous syndrome, Skin necrosis, Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TENS)
Agranulocytosis and other cytopenic events	Agranulocytosis, aplastic anemia, pancytopenia
Other hypersensitivity reactions	Other suspected hypersensitivity to suspected drug
Liver reactions	Any event that qualifies as a liver laboratory trigger or event as defined in Appendix 2

While this list is intended as a guide to the investigator, other potential IDRs may arise.

[redacted]

17 Appendix 5: Spirometry Guidance

Equipment

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

Calibration

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

Preparing the test subject

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

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

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

Performing Spirometry

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

Number of trials

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

Acceptability

An acceptable maneuver has the following characteristics:

- No hesitation or false start;

[redacted]

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

Overall acceptability will be determined by expert over-read by spirometry vendor.

Repeatability

The 2 largest forced expiratory volume in 1 second (FEV1) values from 3 acceptable maneuvers should not vary by more than 0.150 L.

If patient does not meet the repeatability or acceptability criteria during the screening period, patient may be rescreened once or allow one spirometry retest.

Recording of data

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

Predicted normal

For all patients, this study will utilize the global lung function 2012 equations (GLI2012) published by Quanjer et al 2012[2] or Japanese Respiratory Society[3].

Reversibility

All reversibility evaluations should follow the recommendations of the ATS/ERS Task force: Standardization of Lung Function Testing[1]. A pre-bronchodilator spirometry assessment should be performed after withholding of specified medications as specified in Table 5-3 "Medications to be withheld prior to spirometry".

Administer 400µg of salbutamol/albuterol (or equivalent) following the completion of the pre-bronchodilator assessment. Spacers will be allowed for the administration of salbutamol/albuterol (or equivalent) for reversibility testing. Post-bronchodilator spirometry assessment is then performed approximately 10 to 15 minutes after administration of the salbutamol/albuterol.

Reversibility is calculated as:

100 x FEV1 (post-bronchodilator) – FEV1 (pre-bronchodilator)

/ FEV1 (pre-bronchodilator)

Patients will be considered reversible if an increase of at least 12% (and 200 mL) is demonstrated after administration of the salbutamol/albuterol.

17.1 References for appendix

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

[2]Quanjer PH, Stanojevic S, Cole TJ, Baur X, L Hall GL, et al (2012) Multi-ethnic reference values for spirometry for the 3-95 yr age range: the global lung function 2012 equations. Report

[redacted]

of the Global Lung Function Initiative (GLI), ERS Task Force to establish improved Lung Function Reference Values. Eur Resp J; 40:1324-1343.

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

[redacted]

18 Appendix 6: Asthma Control Questionnaire (ACQ-5)

ASTHMA CONTROL QUESTIONNAIRE
(SYMPTOMS ONLY)

For further information:

Elizabeth Juniper, MCSP, MSc
Professor
20 Marcuse Fields,
Bosham,
West Sussex,
PO18 8NA. UK
Telephone: + 44 (0) 1243 572124
Fax: + 44 (0) 1243 573680
E-mail: juniper@qoltech.co.uk
Web: www.qoltech.co.uk

December 2002

SYMPTOMS ONLY MODIFIED 30 JAN 04 NORTH AMERICAN ENGLISH

[redacted]

ASTHMA CONTROL QUESTIONNAIRE© Page 1 of 1

Please answer questions 1 - 5

Circle the number of the response that best describes how you have been during the past week.

1. On average, during the past week, how often were you **woken by your asthma** during the night?
   - 0 Never
   - 1 Hardly ever
   - 2 A few times
   - 3 Several times
   - 4 Many times
   - 5 A great many times
   - 6 Unable to sleep because of asthma

2. On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?
   - 0 No symptoms
   - 1 Very mild symptoms
   - 2 Mild symptoms
   - 3 Moderate symptoms
   - 4 Quite severe symptoms
   - 5 Severe symptoms
   - 6 Very severe symptoms

3. In general, during the past week, how **limited were you in your activities** because of your asthma?
   - 0 Not limited at all
   - 1 Very slightly limited
   - 2 Slightly limited
   - 3 Moderately limited
   - 4 Very limited
   - 5 Extremely limited
   - 6 Totally limited

4. In general, during the past week, how much **shortness of breath** did you experience because of your asthma?
   - 0 None
   - 1 A very little
   - 2 A little
   - 3 A moderate amount
   - 4 Quite a lot
   - 5 A great deal
   - 6 A very great deal

5. In general, during the past week, how much of the time did you **wheeze**?
   - 0 Not at all
   - 1 Hardly any of the time
   - 2 A little of the time
   - 3 A moderate amount of the time
   - 4 A lot of the time
   - 5 Most of the time
   - 6 All the time

SYMPTOMS ONLY MODIFIED 30 JAN 04 NORTH AMERICAN ENGLISH

[redacted]

19 Appendix 7: Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12)

ASTHMA QUALITY OF LIFE QUESTIONNAIRE WITH STANDARDISED ACTIVITIES (AQLQ(S))

SELF-ADMINISTERED

(≥12 years)

For further information:

Elizabeth Juniper, MCSP, MSc
Professor
20 Marcuse Fields
Bosham, West Sussex
PO18 8NA, England
Telephone: +44 1243 572124
Fax: +44 1243 573680
E-mail: juniper@qoltech.co.uk
Web: http://www.qoltech.co.uk

APRIL 2008

[redacted]

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

Please complete **all** questions by circling the number that best describes how you have been during the **last 2 weeks as a result of your asthma.**

HOW **LIMITED** HAVE YOU BEEN **DURING THE LAST 2 WEEKS** IN THESE ACTIVITIES **AS A RESULT OF YOUR ASTHMA?**

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
1. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
2. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
3. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
4. WORK/SCHOOL-RELATED ACTIVITIES* (tasks you have to do at work/in school)	1	2	3	4	5	6	7
5. SLEEPING	1	2	3	4	5	6	7

*If you are not employed or self-employed, these should be tasks you have to do most days.

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS?**

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
6. How much discomfort or distress have you felt over the last 2 weeks as a result of CHEST TIGHTNESS?	1	2	3	4	5	6	7

[redacted]

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
7. Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7
8. Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
9. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO CIGARETTE SMOKE?	1	2	3	4	5	6	7
10. Experience a WHEEZE in your chest?	1	2	3	4	5	6	7
11. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF CIGARETTE SMOKE?	1	2	3	4	5	6	7

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS**?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
12. How much discomfort or distress have you felt over the last 2 weeks as a result of COUGHING?	1	2	3	4	5	6	7

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
13. Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
14. Experience a feeling of CHEST HEAVINESS?	1	2	3	4	5	6	7

[redacted]

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
15. Feel CONCERNED ABOUT THE NEED TO USE MEDICATION for your asthma?	1	2	3	4	5	6	7
16. Feel the need to CLEAR YOUR THROAT?	1	2	3	4	5	6	7
17. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO DUST?	1	2	3	4	5	6	7
18. Experience DIFFICULTY BREATHING OUT as a result of your asthma?	1	2	3	4	5	6	7
19. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF DUST?	1	2	3	4	5	6	7
20. WAKE UP IN THE MORNING WITH ASTHMA SYMPTOMS?	1	2	3	4	5	6	7
21. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
22. Feel bothered by HEAVY BREATHING?	1	2	3	4	5	6	7
23. Experience asthma symptoms as a RESULT OF THE WEATHER OR AIR POLLUTION OUTSIDE?	1	2	3	4	5	6	7
24. Were you WOKEN AT NIGHT by your asthma?	1	2	3	4	5	6	7
25. AVOID OR LIMIT GOING OUTSIDE BECAUSE OF THE WEATHER OR AIR POLLUTION?	1	2	3	4	5	6	7

[redacted]

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
26. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
27. Feel AFRAID OF GETTING OUT OF BREATH?	1	2	3	4	5	6	7
28. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
29. Has your asthma INTERFERED WITH GETTING A GOOD NIGHT'S SLEEP?	1	2	3	4	5	6	7
30. Have a feeling of FIGHTING FOR AIR?	1	2	3	4	5	6	7

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS**?

	Severely Limited Most Not Done	Very Limited	Moderately Limited Several Not Done	Slightly Limited	Very Slightly Limited Very Few Not Done	Hardly Limited At All	Not Limited Have Done All Activities
31. Think of the OVERALL RANGE OF ACTIVITIES that you would have liked to have done during the last 2 weeks. How much has your range of activities been limited by your asthma?	1	2	3	4	5	6	7

[redacted]

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

Page 5 of 5

HOW LIMITED HAVE YOU BEEN DURING THE LAST 2 WEEKS?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
32. Overall, among ALL THE ACTIVITIES that you have done during the last 2 weeks, how limited have you been by your asthma?	1	2	3	4	5	6	7

DOMAIN CODE:

Symptoms: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30
Activity Limitation: 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32
Emotional Function: 7, 13, 15, 21, 27
Environmental Stimuli: 9, 17, 23, 26

20 Appendix 8: Asthma Plan

An asthma plan should be completed for each patient and given to the patient to manage their asthma symptoms. The medicines taken should be written including dose strength.

Asthma Plan

Doctor:_____ Doctor's Phone Number:_____ Emergency Phone Number:_____

Doing Well

- No cough, wheeze, chest tightness, or shortness of breath during day or night
- Can do usual activities

Take these long-term control medications each day

Medicine	How much to take (dose)	When to take it

Asthma Is Getting Worse

- Cough, wheeze, chest tightness, or shortness of breath, or
- Waking at night due to asthma, or
- Can do some, but not all, usual activities

First

Add: quick-relief medicine SABA (such as salbutamol 100 mcg or albuterol 90 mcg) and keep taking your medicine listed above

- SABA: _____ 2 puffs, every 20 minutes for up to 1 hour

If your symptoms return to Green after 1 hour of above treatment

- Continue monitoring to be sure you stay in the green

Or

If your symptoms do not return to Green after 1 hour of above treatment

Second

- Take: SABA: _____ 2 puffs , every 20 minutes for up to 1 hour
- Add: Oral Steroid: _____ per day
- **Please make every effort to call your doctor before you take the oral steroid. If not possible within 48 hrs**

Medical Alert

- Very short of breath, or
- Quick-relief medications have not helped, or
- Can not do usual activities, or
- Symptoms are same or get worse after 24 hours in Yellow

Take these medicines:

- SABA: _____ 2 puffs , every 20 minutes for up to 1 hour
- Oral Steroid: _____ per day

- **Then call your doctor NOW** Go to the hospital or call an ambulance if:
- You are still on the red after 15 minutes and
- You have not reached your doctor

Danger Signs

- Trouble walking and talking due to shortness of breath
- Lips or fingernails are blue

- Take 4 or 6 puffs of SABA: _____ and
- Go to the hospital or call for an ambulance _____ **NOW**

phone

[redacted]

21 Appendix 9: Estimated Equivalence of Inhaled Corticosteroids

Box 8. Low, medium and high daily doses of inhaled corticosteroids (mcg)

Inhaled corticosteroid	Adults and adolescents			Children 6–11 years		
	Low	Medium	High	Low	Medium	High
Beclometasone dipropionate (CFC)*	200–500	>500–1000	>1000	100–200	>200–400	>400
Beclometasone dipropionate (HFA)	100–200	>200–400	>400	50-100	>100-200	>200
Budesonide (DPI)	200–400	>400–800	>800	100–200	>200–400	>400
Budesonide (nebules)				250–500	>500–1000	>1000
Ciclesonide (HFA)	80–160	>160–320	>320	80	>80-160	>160
Fluticasone furoate (DPI)	100	n.a.	200	n.a.	n.a.	n.a.
Fluticasone propionate(DPI)	100–250	>250–500	>500	100–200	>200–400	>400
Fluticasone propionate (HFA)	100–250	>250–500	>500	100–200	>200–500	>500
Mometasone furoate	110–220	>220–440	>440	110	≥220–<440	≥440
Triamcinolone acetonide	400–1000	>1000–2000	>2000	400–800	>800–1200	>1200

CFC: chlorofluorocarbon propellant; DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant. *Included for comparison with older literature.

From the Global Strategy for Asthma Management and Prevention 2018, © Global Initiative for Asthma (GINA) all rights reserved. Available from http://www.ginasthma.org.

For the purposes of calculating total daily dose for the study, if the table has the medication dose listed by DPI, but not MDI, then use the DPI classification as a reference and vice versa (i.e., if the table has the medication dose listed by MDI, but not DPI, then use the MDI classification). For ICS/LABA combination ICS/LABA products, the highest approved maintenance dose in the local country will meet this ICS criterion

[redacted]