NOVARTIS

Global Clinical Development - General Medicine

QAW039/fevipiprant

Clinical Trial Protocol CQAW039A2317 / NCT03226392

A 12-week, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of QAW039 when added to standard-of-care asthma therapy in patients with uncontrolled asthma

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List of Abbreviations

Abbreviation	Explanation:
ACR	albumin-creatinine ratio
ACQ	asthma control questionnaire
AE(s)	adverse event(s)
Alb	albumin
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AQLQ+12	asthma quality of life questionnaire for 12 years and older
ALP	alkaline phosphatase
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
ATS/ERS	American Thoracic Society/European Respiratory Society
AV	atrioventricular
BMI	body mass index
BTPS	body temperature and pressure saturated
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CK	creatine kinase
CK-MB	creatine kinase isoenzyme MB
CPO	Country Pharma Organization
COA	clinical outcome assessment
CRA	clinical research associate
CRF	case report/record form (paper or electronic)
CRO	contract research organization
CRTh2	chemoattractant receptor-homologous molecule expressed on Th2
CT	computed tomography
DAR	dosage administration record
DDE	direct data entry
DNA	deoxyribonucleic acid
DP2	prostaglandin D2 receptor 2
DPI	dry powder inhaler
DMC	Data Monitoring Committee
DRESS	drug reaction with eosinophilia and systemic symptoms
DS&E	Drug Safety & Epidemiology
ECG	electrocardiogram
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ePEF	electronic peak expiratory flow
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration

Abbreviation	Explanation:
FDC	fixed dose combination
FEV_1	forced expiratory volume in 1 second
[redacted]	[redacted]
γ-GT	gamma-glutamyltransferase
GCP	good clinical practice
GINA	Global Initiative for Asthma
GOLD	Global Initiative For Chronic Obstructive Lung Disease
H_0	null hypothesis
H_a	alternative hypothesis
HbA1c	hemoglobin A1c; glycosylated hemoglobin
hCG	human chorionic gonadotropin
HFA	hydrofluoroalkane
HRQOL	health-related quality of life
hsCRP	high sensitivity C-reactive protein
IB	investigator brochure
ICH	international conference on harmonization of technical requirements for registration of pharmaceuticals for human use
ICS	inhaled corticosteroid
IDR	idiosyncratic drug reactions
IEC	independent ethics committee
IgE	immunoglobulin E
ImmunoCAP®	specific IgE test
IN	investigator notification
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
ITT	intention-to-treat
IUD	intrauterine device
IUS	intrauterine system
LABA	long-acting β-agonist
LAMA	long-acting muscarinic antagonist
LDH	lactate dehydrogenase
LFT	liver function test
LTRA	leukotriene receptor antagonist
MAR	missing at random
MedDRA	medical dictionary for regulatory activities
MDI	metered dose inhaler
MDRD	modification of diet in renal disease study
MID	minimal important difference
MMRM	mixed model repeated measures
MXR	multi-xenobiotic resistance protein
NYHA	New York Heart Association

[redacted]

Abbreviation	Explanation:
OAT3	organic anion transporter 3
OATP1B3	organic anion transporter P1B3
OC/RDC	Oracle Clinical/Remote Data Capture
PCR	protein-creatinine ratio
PEF	peak expiratory flow
PGD2	prostaglandin D2
[redacted]	[redacted]
P-gp	p-glycoprotein
PPS	per-protocol set
PRO	patient reported outcome
PT	prothrombin time
QM	quality management
QOL	quality of life
QTcF	Fridericia QT correction formula
RAST	radioallergosorbent test
SABA	short-acting β-agonist
SAE(s)	serious adverse event(s)
SAF	safety analysis set
sCr	serum creatinine
SCR	screening
SD	standard deviation
SJS	Stevens-Johnson syndrome
SoC	standard of care
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reactions
TBL	total bilirubin
TD	treatment discontinuation
TENS	toxic epidermal necrolysis
Th2	T helper 2
UGT	uridinediphosphate glucuronosyltransferase
ULN	upper limit of normal
WoC	withdrawal of consent
WHO	World Health Organisation
US	United States

[redacted]

Glossary of terms

Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic data capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications reduce the use of paper capture source data during clinical visits. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Epoch/Period	A portion of the study which serves a specific purpose. Typical epoch/periods are: screening/recruitment, wash-out, treatment, and follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient ID	A unique number assigned to each patient upon signing the informed consent
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Source data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy

[redacted]

Study treatment discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

[redacted]

Protocol summary

Protocol number	CQAW039A2317
Full title	A 12-week, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of QAW039 when added to standard-of-care asthma therapy in patients with uncontrolled asthma
Brief title	Study of efficacy and safety of QAW039 when added to standard-of-care asthma therapy in patients with uncontrolled asthma
Sponsor and clinical phase	Novartis, Phase 3
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to determine the efficacy and safety of QAW039 (150 mg once daily), compared with placebo, when added to standard-of-care (SoC) asthma therapy in adult and adolescent (≥ 12 years) patients with uncontrolled asthma with respect to change from baseline in forced expiratory volume in 1 second (FEV1) at the end of 12 weeks of treatment.
Primary objective	To demonstrate the efficacy of QAW039 150 mg once daily as measured by change from baseline in pre-dose FEV1 [in liters], compared with placebo, at the end of the 12-week active-treatment period.
Secondary objectives	1. To demonstrate the efficacy of QAW039 150 mg once daily, compared with placebo, on daytime asthma symptoms over the 12-week active-treatment period. 2. To demonstrate the efficacy of QAW039 150 mg once daily, compared with placebo, on total daily short-acting β-agonist (SABA) use over the 12-week active-treatment period. 3. To demonstrate the efficacy of QAW039 150 mg once daily, compared with placebo, on change from baseline in Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12) scores at the end of the 12-week active-treatment period. 4. To assess the safety of QAW039 150 mg once daily, compared with placebo, with respect to adverse events (AEs), electrocardiograms (ECGs), vital signs and laboratory tests.
Study design	This study uses a randomized, multicenter, double-blind, placebo-controlled, parallel-group study design.
Population	The study population will include: • Males and females aged ≥12 years. • Asthma patients who are already receiving ICS or ICS with one asthma controller medication (see inclusion criterion 4 for allowed ICS doses and combinations) are the target population for this study.

Key inclusion criteria	• Patients must have a diagnosis of asthma (according to GINA 2016) for a period of at least 6 months prior to Visit 1.
	• Patients who have been treated with:
	  • Medium dose ICS, or
	  • High dose ICS, or
	  • Low dose ICS plus long-acting beta agonist (LABA), or
	  • Low dose ICS plus leukotriene receptor antagonist (LTRA), or

[redacted]

	• Medium dose ICS plus LABA. for at least 3 months prior to Visit 1 and the doses have been stable for at least 4 weeks prior to Visit 1. • For patients aged ≥18 years, FEV1 of ≤85% of the predicted normal value for the patient, after withholding bronchodilators at Visit 1 and Visit 101. For patients aged 12 to <18 years, FEV1 of ≤90% of the predicted normal value for the patient, after withholding bronchodilators at Visit 1 and Visit 101. • Patients must have a daytime asthma symptom score (0 to 6 scale) of ≥1 per day during 4 of the last 7 days of the placebo run-in period. • Patients must have a total daily SABA use ≥1 puff per day during 4 of the last 7 days of the placebo run-in period. • Demonstrated reversible airway obstruction as determined by the central reader from the spirometry vendor at Visit 1 or Visit 101. Reversibility is defined as an increase of ≥12% and ≥200 ml in FEV_1 approximately 10 to 15 minutes after administration of 400 mcg of salbutamol/albuterol (or equivalent). Spacer devices are permitted for administration of salbutamol/albuterol (or equivalent) during reversibility testing only. The Investigator or delegate may decide whether or not to use a spacer for the reversibility testing. • If reversibility is not demonstrated at Visit 1, reversibility will be attempted at Visit 101. If not achieved at Visit 101, one additional attempt to demonstrate reversibility is permitted within 4 days following Visit 101 in an ad-hoc visit to meet this eligibility criterion. Review Visit 1 or Visit 101 or the one additional attempt reversibility result from overread by the spirometry vendor central reader prior to randomization. • An asthma control questionnaire (ACQ) score ≥ 1.5 at Visit 199.
Key exclusion criteria	• Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days, whichever is longer. • Patients with a resting QTcF (Fridericia) ≥450 msec (male) or ≥460 msec (female) at Visit 1. • Patients with a 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 • Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test. • 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 study drug. • Patients who have a clinically significant laboratory abnormality at the Visit 1 laboratory test. • 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

[redacted]

	these doses as well as other statins will be permitted during the study. • Patients on rifampin, probenecid, ritonavir and valproic acid (i.e., medications blocking several pathways important for the elimination of QAW039 (broad range uridinediphosphate glucuronosyltransferase (UGT) inhibition and/or inhibition of organic anion transporter 3 (OAT3), organic anion transporter P1B3 (OATP1B3), multi-xenobiotic resistance protein (MXR) and p-glycoprotein (P-gp)). • Patients on any statin therapy with a creatine kinase (CK) level >2 x ULN (upper limit of normal) at Visit 1. • Patients with a history of conditions other than asthma or allergic rhinitis 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 Visit 1 are also excluded.
Study treatment	QAW039 150 mg once daily Placebo once daily
Key efficacy assessments	• Lung function (FEV1) • Asthma symptoms • Short-acting β-agonist (SABA) use • AQLQ+12
Key safety assessments	• Adverse event monitoring • Physical examinations • Vital signs • Laboratory examinations of blood and urine • ECG
[redacted]	
Data analysis	The primary variable for this study is the change from baseline in pre-dose FEV1 at the end of 12 weeks of treatment. Pre-dose FEV1 is the average of the 2 FEV1 assessments taken at 45 minutes and 15 minutes prior to the dosing of study drug at the clinic visit. The baseline FEV1 is defined as mean of the last two FEV1 assessments prior to the first dose of study drug. If any one of these assessments is missing (or is not confirmed to be pre-dose), then the remaining non-missing observation will be considered as baseline. If both assessments are missing (or are not confirmed to be pre-dose) then the last available FEV1 measurement prior to Day 1 on study drug will be used for baseline. If the FEV1 measurements are missing both on Day 1 and at the placebo run-in or screening visits, the respective baseline values will be set to missing. Missing data after discontinuation of double-blind study treatment will be imputed using the jump-to-reference approach. The secondary variables are daytime asthma symptoms, total daily SABA use, and AQLQ+12. Analysis of primary variable: The primary efficacy variable will be analyzed on the full analysis set (FAS) using an analysis of covariance (ANCOVA) model with factors for treatment group, age group (<18 vs. ≥18 years), use or non-use of a second asthma controller medication, and region, as well as the baseline daytime asthma symptom score, baseline total daily SABA use and baseline pre-dose FEV1 as continuous linear covariates.

[redacted]

	The least squares mean ("adjusted mean") change from baseline for each treatment group, the difference in the least squares mean changes between the two treatment groups (QAW039 150mg – placebo), and the two-sided adjusted 95% confidence interval along with the p-value for the difference will be obtained and combined from the primary analysis model through the multiple imputation approach described in Section 9.4.3. The superiority of QAW039 150 mg once daily to placebo as add on to existing asthma therapy is established, if the two-sided p-value is less than 0.05 and the 95% confidence intervals lie entirely to the right of 0 L. Analysis of secondary variables: The secondary variables of this study are change from baseline in daytime asthma symptoms, change from baseline in total daily SABA use, and change from baseline in AQLQ+12 over the 12-week active treatment period. The mean of change from baseline in the daytime asthma symptom scores over the 12 weeks of treatment will be analyzed using an analysis of covariance (ANCOVA) model in a similar fashion as for the primary efficacy variable. The mean of change from baseline in the total daily use of SABA over the 12 weeks of treatment will be analyzed using an ANCOVA model in a similar fashion as for the primary efficacy variable. The change from baseline in AQLQ+12 at week 12 will be analyzed using an ANCOVA model in a similar fashion as for the primary efficacy variable. Six hundred fifty (650) patients (325 per arm) are needed for 90% power to observe a statistically significant difference between QAW039 and placebo at the two-sided 5% significance level in the primary analysis, assuming a treatment difference of 112 mL for the primary endpoint, a standard deviation of 380 mL and a treatment discontinuation rate of 15% with half of the patients discontinuing from study treatment having week 12 assessment of the primary variable.
Key words	QAW039, uncontrolled asthma

[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. Annual worldwide deaths have been estimated at 250 000 (Masoli et al 2004). Uncontrolled asthma has a prevalence of greater than 6 million patients worldwide.

According to asthma guidelines, the goal of treatment is to "achieve and maintain control of the clinical manifestations of the disease for prolonged periods" (GINA pocket guide 2016). Current asthma guidelines recognize that the assessment of asthma severity reflects the underlying disease state as well as the perceived response to treatment and, based on assessment, asthma severity may change over time. Therefore, current asthma treatment guidelines classify patients based on 2 factors: control of asthma and future risk (e.g., risk of exacerbations). For patients older than 5 years with asthma, guidelines recommend assignment of patients to 1 of the 5 "treatment steps" based on current asthma controller treatment or, if a de novo presentation, assignment based on severity to either Step 2 or Step 3. Asthma control is then periodically assessed (~every 3 months) based on a patient's asthma symptoms, severity, response to current medications, and future risk. Patients are assessed as "controlled," "partly controlled," or "uncontrolled" according to an algorithm and treatment is adjusted to achieve or maintain control at the lowest treatment step (GINA pocket guide 2016).

The treatment guidelines recommend initiation of short-acting ß-agonists (SABAs) for patients older than 5 years with occasional symptoms, followed by addition of controller medications (e.g., inhaled corticosteroids (ICS), inhaled corticosteroid/long-acting ß-agonists (LABA) combinations, leukotriene modifiers etc.) according to the stepwise treatment paradigm to achieve and maintain control as described above (GINA pocket guide 2016). Following current guidelines, most patients are able to achieve asthma control with currently available therapies. Approximately 5% of patients have a refractory form of asthma which is associated with increased risk of hospitalization and death, and about 50% of medical costs associated with asthma care (ATS 2005).

While only an estimated 5% of patients with asthma fulfill criteria for a diagnosis of refractory asthma, as many as 40% of patients do not achieve control with currently available asthma treatment (Fuhlbrigge et al 2009). Failure to respond to therapy may be due to multiple factors, including poor adherence, inadequate inhaler technique (inhaled therapies) or corticosteroid resistance. Thus, there is a need for new, effective anti-inflammatory therapies for asthma.

Prostaglandin D2 receptor 2 (DP2) also known as the chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTh2) receptor is a receptor for prostaglandin D2 (PGD2) which is one of the major prostanoid inflammatory mediators identified in asthma. Fevipiprant (QAW039) is a DP2 antagonist expected to provide benefit in asthma by binding to prostaglandin D2 receptor 2 (DP2)on eosinophils, basophils, and T lymphocytes in the

[redacted]

blood and tissues; thus, inhibiting migration and activation of these cells into the airway tissues and blocking the PGD2-driven release of T helper 2 (Th2) cytokines (Chevalier et al 2005). Since these are the major effector cells and soluble factors driving airway inflammation in asthma, treatment with QAW039 (fevipiprant) should result in a decrease in these parameters of airway inflammation as well as a clinical improvement in asthma. In support of this premise are the results of Phase 2 studies of QAW039 (CQAW039A2201, CQAW039A2206, and CQAW039A2208) in which QAW039 demonstrated an improvement in lung function (i.e., forced expiratory volume in 1 second [FEV1]) in patients across a range of asthma severities, an improvement in asthma control in patients with more severe asthma, and a fall in sputum eosinophils of 71% (geometric mean) in patients with severe asthma and sputum eosinophilia over 12 weeks of treatment.

1.2 Purpose

The purpose of this study is to determine the efficacy and safety of QAW039 (150 mg once daily), compared with placebo, when added to standard-of-care (SoC) asthma therapy in adult and adolescent (≥12 years) patients with uncontrolled asthma with respect to change from baseline in FEV1 at the end of 12 weeks of treatment.

2 Study objectives and endpoints

2.1 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective To demonstrate the efficacy of QAW039 150 mg once daily as measured by change from baseline in pre-dose FEV1 [in liters], compared with placebo, at the end of the 12-week active-treatment period.	**Endpoint for primary objective** Change from baseline in pre-dose FEV1 (L) at Week 12.
Secondary Objectives 1. To demonstrate the efficacy of QAW039 150 mg once daily, compared with placebo, on daytime asthma symptoms over the 12-week active-treatment period. 2. To demonstrate the efficacy of QAW039 150 mg once daily, compared with placebo, on total daily short-acting β-agonist (SABA) use over the 12-week active-treatment period. 3. To demonstrate the efficacy of QAW039 150 mg once daily, compared with placebo, on change from baseline in Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12) score at the end of the 12-week active-treatment period. 4. To assess the safety of QAW039 150 mg	**Endpoints for secondary objectives** 1. Change from baseline in daytime asthma symptom score over 12 weeks of treatment. 2. Change from baseline in number of puffs of SABA taken per day over 12 weeks of treatment. 3. Change from baseline in AQLQ+12 score at Week 12. 4. Summaries of treatment-emergent adverse events, systolic and diastolic blood pressure,

Objective(s)	Endpoint(s)
once daily, compared with placebo, with respect to adverse events (AE), electrocardiograms (ECGs), vital signs, and laboratory tests.	pulse rate, body weight, ventricular rate, RR interval, PR interval, QRS duration, heart rate, and Fridericia's QTc, laboratory values and change from baseline for continuous laboratory values.

[redacted]

[redacted]

3 Investigational plan

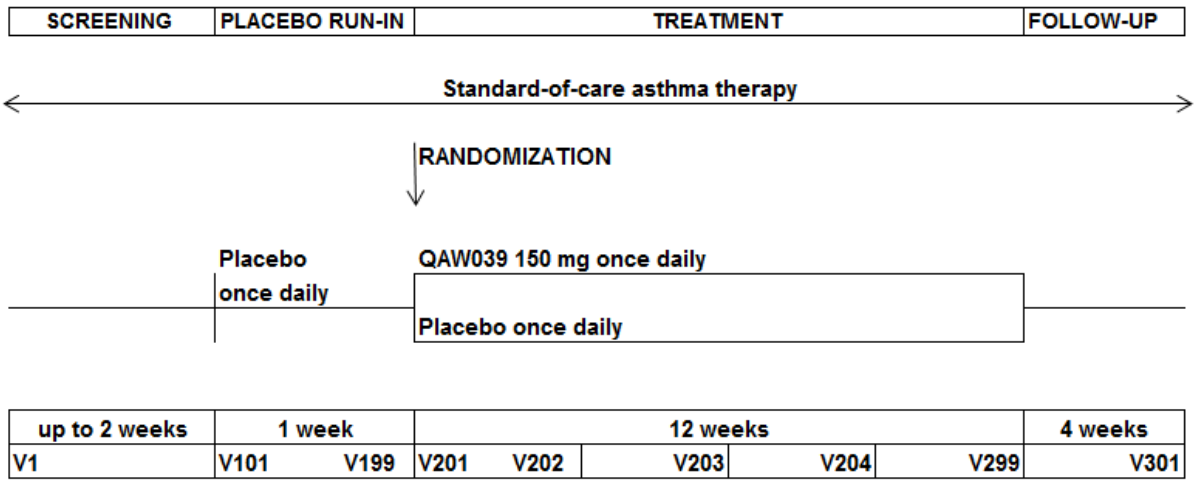
3.1 Study design

This study uses a randomized, multicenter, double-blind, placebo-controlled parallel-group study design in which QAW039 or placebo is added to incoming SoC asthma therapy (Figure 3-1). Asthma patients who are already receiving ICS or ICS with one asthma controller medication (see inclusion criterion 4 for allowed ICS doses and combinations) are the target population for this study. Patients will continue to receive the SoC asthma medication they were receiving at Visit 1 throughout the remainder of the study. **No change in SoC asthma medication and no dosage adjustments will be permitted throughout the study.**

Within 14 days prior to or at Visit 1, an informed consent will be obtained from patients before any study related assessments or procedures are performed. All patients signing informed consent must be registered in the Interactive Response Technology (IRT). Asthma and other medications and eligibility criteria will be reviewed. Patients will be instructed regarding medications to be withheld prior to spirometry for Visit 1 (See Section 5.5.7). The study will include:

- a **Screening period** of up to 2 weeks to assess eligibility. Patients will also practice completing the electronic peak expiratory flow (ePEF)/eDiary device during this period.
- **a Placebo Run-in period** of 1 week to collect baseline data for efficacy variables and compliance with the ePEF /eDiary device. Eligibility for randomization will be determined during the placebo run-in period.
- **a Treatment period** of 12 weeks; and
- **a Follow-up period** of 4 weeks, study drug-free, following the last dose of study drug. **Note:** the follow-up period applies to all patients **except** those patients who enter the safety study (CQAW039A2315) directly after Visit 299.

Figure 3-1 Study design



[redacted] during the screening or placebo run-in periods must be designated as screening failure or run-in failure. Patients who experience an asthma exacerbation during screening may be re-screened 4 weeks after complete recovery from the exacerbation. All patients must demonstrate FEV1 reversibility as determined by the central reader from the spirometry vendor for study eligibility. If reversibility is not demonstrated at Visit 1, reversibility will be attempted at Visit 101. If not achieved at Visit 101, then one additional attempt to demonstrate reversibility is permitted within 4 days following Visit 101 in an ad-hoc visit to meet this eligibility criterion.

Clinic visits will be scheduled approximately 2, 4, 8, and 12 weeks after randomization during the active-treatment period. Since the primary endpoint is pre-dose FEV1, patients will receive witnessed doses of study drug at clinic visits after spirometry is performed for the FEV1 assessment. This will allow for appropriate assessment of pre-dose FEV1.

A follow-up visit will occur approximately 4 weeks (i.e., approximately 30 days) following the last dose of study drug to complete safety assessments and pregnancy testing (if applicable). Please refer to the assessment schedule (Section 6) for a list of procedures to be conducted at each visit.

A Safety Study of QAW039 is planned. At sites participating in the Safety Study CQAW039A2315, patients who successfully complete 12 weeks of treatment in this study (CQAWA0392317 [hereafter referred to as Study A2317]) may be offered participation in the Safety Study; patient participation in the Safety Study will be optional. The study design and procedures for the Safety Study will be described in a separate protocol.

Periodic unblinded safety reviews will be conducted by an independent Data Monitoring Committee (DMC) for the duration of the trial.

3.2 Rationale for study design

The patient population will be described in more detail in Section 4 below.

This randomized, double-blind, parallel-group, placebo-controlled, design supports the assessment of efficacy as well as safety of QAW039 as add-on treatment for patients with asthma inadequately controlled on ICS or ICS with a second controller medication. According to Global Initiative for Asthma (GINA) guidelines, the goals of asthma therapy are to attain asthma control and reduce future risk of asthma worsening while maintaining minimal side effects of therapy. By maintaining good asthma control in patients with appropriate use of therapies, potential future risk to patients may be reduced. The endpoints included in this study measure objective and symptomatic parameters of asthma control (objective: lung function [FEV1, [redacted]]; symptomatic parameters: daytime [redacted] asthma symptoms, SABA use, quality of life (QOL), [redacted]) in patients over 12 weeks of therapy.

Patient population

The overall purpose for the study is to determine whether QAW039 150 mg improves lung function as measured by change from baseline in pre-dose FEV1 in patients aged ≥12 years. These patients represent a **subset** of moderate asthma patients treated according to GINA

[redacted]

2016 (treatment steps 3 and 4). This study will confirm results from a prior study of QAW039 (Study CQAW039A2206).

A prior Phase 2 study of QAW039 (Study CQAW039A2206) in patients with moderate-to-severe asthma showed a statistically significant improvement in pre-dose FEV1 (L), after 12 weeks of treatment with QAW039 on top of low-dose ICS, compared with placebo on top of low-dose ICS (p=0.0035), with a clinically relevant maximum model-averaged difference to placebo of 112 ml. In this study, a total daily dose of 150 mg provided maximum efficacy as determined by pre-dose FEV1.

Screening period

The screening period allows for assessment of patient entry criteria and for patients to become familiar with spirometry measurement and daily eDiary entry prior to the collection of baseline values.

Patients experiencing an asthma exacerbation during the screening period must be designated as a screening failure. Patients who experience an asthma exacerbation during screening may be re-screened 4 weeks after complete recovery from the exacerbation.

Re-screening of patients is permitted once during the screening period.

Placebo run-in

The placebo run-in period allows for the determination of level of asthma control based on [redacted], FEV1 reversibility as determined by the central reader at the spirometry vendor, SABA use, and daytime asthma symptom scores for eligibility for randomization into the 12-week active treatment period. This period also allows for the collection of baseline data for all efficacy variables. During this period, patients will become familiar with administration of investigational treatment and patient's compliance with an Electronic Peak Flow/ eDiary device will be assessed.

Patients experiencing an asthma exacerbation during the placebo run-in period must be designated as a run-in failure.

Treatment period

During this period, oral QAW039 150 mg or matching placebo (1:1) will be administered once daily for 12 weeks added to SoC asthma therapy (as defined in inclusion criterion 4), with the last dose given at Week 12 and final assessment for the treatment period at Week 12. The 12-week treatment duration is considered sufficient to demonstrate an effect of QAW039 on the primary endpoint, pre-dose FEV1, in this Phase 3 study since QAW039 has previously demonstrated significant effects on pre-dose FEV1 in 12-week Phase 2 studies.

Follow-up period

The 4-week wash out period will monitor the safety and tolerability profile after the last dose of study drug.

[redacted]

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 the last dose of study drug and follow up with the subject as appropriate.

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

The dose of 150 mg once daily was selected for inclusion in the study because it was the lowest dose of QAW039 with "maximal efficacy" on the endpoint of pre-dose FEV1 in a prior dose-ranging study (Study CQAW039A2206) in patients with moderate-to-severe asthma (GINA treatment steps 3 and 4) as add-on to low-dose ICS.

3.4 Rationale for choice of comparator

All patients in this study will receive SoC asthma therapy (as defined in inclusion criterion 4) during the screening period, the placebo run-in period, and the treatment period. QAW039 or placebo will be administered as add-on therapy.

Placebo was chosen as the comparator as it will permit the assessment of improvement in terms of pre-dose FEV1 for patients with uncontrolled disease who are treated with QAW039 plus SoC asthma therapy, in comparison to those solely on SoC asthma therapy. Additionally, the use of placebo will permit a controlled evaluation of the safety of QAW039 plus SoC asthma therapy, compared with SoC asthma therapy in these patients. Further, patients will be allowed the use of SABAs as rescue medication when required.

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.6 Risks and benefits

QAW039 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 (Th-2) 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 QAW039 includes 15 studies: 11 (six in healthy volunteers and five in patients) have completed and four (three in patients and one in healthy volunteers) are ongoing. The completed phase 2 studies consist of three 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 QAW039). As of 31-Jan-2016, >1400 patients have been exposed to QAW039.

Three Phase 2 studies in patients with asthma evaluated the effect of QAW039 across the range of asthma severities (mild to severe). In these studies, QAW039 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, QAW039 also demonstrated a reduction in sputum eosinophils in patients with severe asthma.

The potential benefits of QAW039 therapy need to be balanced against its potential risks. Potential side effects of QAW039 include: increased heart rate, non-serious arrhythmia such as palpitations, headache, diarrhea, nausea, vomiting, nasopharyngitis, somnolescence and dizziness. In humans, one major metabolite of QAW039 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 QAW039 treatment in completed clinical trials as of 31-Jan-2016. Taking QAW039 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, Noe et al 2007, and 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 Appendix 2 and Appendix 3, 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

The study population will include:

- Males and females aged ≥12 years.
- Asthma patients who are already receiving ICS or ICS with one asthma controller medication (see inclusion criterion 4 for allowed ICS doses and combinations) are the target population for this study.
- Approximately 1857 patients will be screened to randomize approximately 650 patients in a 1:1 ratio into the study worldwide.
- An estimated 15% of patients will discontinue their study drug during the treatment period; these patients will not be replaced.

4.1 Inclusion criteria

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

[redacted]

1. Written informed consent and assent (if applicable) must be obtained within 14 days prior to or at Visit 1 before any assessment is performed including any adjustment to asthma medication.
2. Male and female patients at a minimum age of 12 years (or higher minimum age limit as allowed by health authority and/or independent ethics committee/institutional review board (IEC/IRB) approvals).
3. Patients must have a diagnosis of asthma (according to GINA 2016) for a period of at least 6 months prior to Visit 1.
4. Patients who have been treated with:
   - Medium dose ICS, or
   - High dose ICS, or
   - Low dose ICS plus long-acting beta agonist (LABA), or
   - Low dose ICS plus leukotriene receptor antagonist (LTRA), or
   - Medium dose ICS plus LABA.

   for at least 3 months prior to Visit 1 and the doses have been stable for at least 4 weeks prior to Visit 1.
5. For patients aged ≥18 years, FEV1 of ≤85% of the predicted normal value for the patient, after withholding bronchodilators at Visit 1 and Visit 101. For patients aged 12 to <18 years, FEV1 of ≤90% of the predicted normal value for the patient, after withholding bronchodilators at Visit 1 and Visit 101.

   NOTE: Withholding of bronchodilators prior to spirometry:
   - Short-acting β2-agonists (SABAs) ≥ 6 hours;
   - Long-acting β2-agonists (LABAs) given twice daily ≥ 12 hours;
   - LABAs given once daily ≥ 24 hours;
   - Fixed dose combinations (FDC) of LABA and ICS given twice daily ≥ 12 hours; and
   - Fixed dose combinations of LABA and ICS given once daily ≥ 24 hours.
6. Patients must have a daytime asthma symptom score (0 to 6 scale) of ≥1 per day during 4 of the last 7 days of the placebo run-in period.
7. Patients must have a total daily SABA use ≥1 puff per day during 4 of the last 7 days of the placebo run-in period.
8. Demonstrated reversible airway obstruction as determined by the central reader from the spirometry vendor at Visit 1 or Visit 101. Reversibility is defined as an increase of ≥12% and ≥200 ml in FEV_1 approximately 10 to 15 minutes after administration of 400 mcg of salbutamol/albuterol (or equivalent). Spacer devices are permitted for administration of salbutamol/albuterol (or equivalent) during reversibility testing only. The Investigator or delegate may decide whether or not to use a spacer for the reversibility testing.
   - If reversibility is not demonstrated at Visit 1, reversibility will be attempted at Visit 101. If not achieved at Visit 101, then one additional attempt to demonstrate reversibility is permitted within 4 days following Visit 101 in an ad-hoc visit to meet this eligibility criterion.

[redacted]

Review Visit 1 or Visit 101 or the one additional attempt reversibility result from overread by the spirometry vendor central reader prior to randomization.

9. An ACQ score ≥ 1.5 at Visit 199.

4.2 Exclusion criteria

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

1. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days, whichever is longer.
2. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes to QAW039.
3. History of lactose or milk sensitivity.
4. 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.
5. Patients with a resting QTcF (Fridericia) ≥450 msec (male) or ≥460 msec (female) at Visit 1.
6. Use of agents known to prolong the QT interval unless it can be permanently discontinued for the duration of the study.
7. Patients with a 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.
8. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
9. 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 study drug. Basic contraception methods include:
   - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject) if allowed as an effective method of contraception by local regulations. 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) or tubal ligation at least six weeks before taking study treatment. 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 patients on the study, the vasectomized male partner must be the sole partner for that subject

[redacted]

- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) if allowed as an effective method of contraception by local regulations. For United Kingdom: with spermicidal foam/gel/film/cream/ vaginal suppository
- Use of oral, 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
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)

*Not approved in Japan

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

In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the informed consent form (ICF).

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

10. Patients who have smoked or inhaled any substance other than asthma medications within the 6 month period prior to Visit 1, or who have a cigarette 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 who have had an asthma exacerbation requiring systemic corticosteroids, hospitalization, or emergency room visit within 6 weeks prior to Visit 1.
12. Patients who have an asthma exacerbation requiring systemic corticosteroids, hospitalization or emergency room visit during the screening or placebo run-in periods. Patients who experience an asthma exacerbation during screening may be re-screened 4 weeks after complete recovery from the exacerbation.
13. Patients who have had a respiratory tract infection or asthma worsening within 4 weeks of Visit 1. Patients who experience a respiratory tract infection or asthma worsening during screening may be re-screened after 4 weeks after recovery.
14. 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.
15. Patients with a history of chronic lung disease other than asthma, including (but not limited to) chronic obstructive pulmonary disease (as defined by Global Initiative For Chronic Obstructive Lung Disease (GOLD) standards), bronchiectasis, (non-clinically significant bronchiectasis may be allowed provided recent (within 3 months prior to Visit 101) computed tomography (CT) scan proof is available), sarcoidosis interstitial lung disease, cystic fibrosis, and tuberculosis.
16. Patients with a history of conditions other than asthma or allergic rhinitis that could result in elevated eosinophils (e.g., hypereosinophilic syndromes, Churg-Strauss Syndrome,

[redacted]

eosinophilic esophagitis). Patients with known parasitic infestation within 6 months prior to Visit 1 are also excluded.

17. Patients with uncontrolled diabetes having an hemoglobin A1c (HbA1c) test result ≥8% at the Visit 1 laboratory test.
18. Patients who have a clinically significant laboratory abnormality at the Visit 1 laboratory test including (but not limited to):
    - Total white blood cell count <2500 cells/μL;
    - Aspartate aminotransferase (AST) or alanine aminotransferase (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 study (MDRD) equation or Bedside Schwartz equation <55 mL/minute/1.73 m2.
19. Patients who in the judgment of the investigator have a clinically significant condition such as (but not limited to) unstable ischemic heart disease, New York Heart Association (NYHA) Class III/IV left ventricular failure, arrhythmia, uncontrolled hypertension, cerebrovascular disease, neurodegenerative diseases, or other neurological disease, uncontrolled hypo- and hyperthyroidism and other autoimmune diseases, hypokalemia, hyperadrenergic state, or ophthalmologic disorder or patients with a medical condition that might compromise patient safety or compliance, interfere with evaluation, or preclude completion of the study.
20. Patients with a history of myocardial infarction within 12 months of Visit 1.
21. Patients with serious co-morbidities including, but not limited to, neurodegenerative diseases, rheumatoid arthritis and other autoimmune diseases.
22. Patients with a history of alcohol or drug abuse within 12 months prior to Visit 1.
23. Patients with a weight <30 kg at Visit 1.
24. Patients aged 12 to <18 years below the third percentile for weight by age at Visit 1 (based on local growth charts or the United States Center for Disease Control growth charts (Center for Disease Control and Prevention, 2000) if local growth charts are not available).
25. Patients receiving any other asthma treatment that is not stipulated in Inclusion Criterion #4.
26. Patients receiving any medications in the classes listed in Table 5-3 must be excluded unless they meet the criteria as specified in Table 5-3.
27. Patients receiving medications in the classes listed in Table 5-1 must be excluded unless the medication has been stabilized for the specified period and the stated conditions have been met.
28. Patients who started immunotherapy or desensitization for allergies, within 3 months prior to Visit 1, or where the maintenance dose is expected to change during the study.
29. 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 the Electronic Peak Expiratory Flow (PEF) with eDiary device or who are unable to demonstrate good eDiary compliance (defined as >70% compliance) during the placebo run-in period.

[redacted]

30. Inability to comply with all study requirements and demonstrate good study drug compliance (≥ 80% compliance) during the placebo run-in period.
31. Patients with any medical or psychological condition that, in the investigator's opinion, renders the patient unable to understand the nature, scope, and possible consequences of the study.
32. Patients with a history of being unable to swallow tablets.
33. Patients who have received methotrexate, oral gold, troleandomycin, cyclosporine azathioprine or any experimental anti-inflammatory therapies within 6 months of Visit 101.
34. Patients with regular use of oral or systemic corticosteroids within 12 months or any intra-articular or short-acting, intramuscular corticosteroid within 1 month or intramuscular, long acting depot corticosteroids within 3 months of Visit 101.
35. 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.
36. Patients with a history of immunodeficiency disease or hepatitis B or hepatitis C.
37. 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.
38. Patients on any statin therapy with a CK level >2 x ULN at Visit 1.
39. Patients on rifampin, probenecid, ritonavir and valproic acid (i.e. medications blocking several pathways important for the elimination of QAW039 (broad range uridine-diphosphate glucuronosyltransferase (UGT) inhibition and/or inhibition of organic anion transporter 3 (OAT3), organic anion transporter P1B3 (OATP1B3), multi-xenobiotic resistance protein (MXR) and p-glycoprotein (P-gp)).
40. No person directly associated with the administration of the study is allowed to participate as a study subject.
41. No family member of the investigational study staff is allowed to participate in this study.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

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

- Name: QAW039
- Formulation: tablet
- Unit dose: 1 strength: 150 mg

Please refer to the Investigator's Brochure for composition of the QAW039 tablets.

- Name: QAW039 placebo
- Formulation: tablet
- Unit dose: matching placebo to QAW039 150 mg

[redacted]

Please refer to the Investigator's Brochure for composition of the 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.

5.1.2 Additional treatment

All patients will continue to receive SoC asthma therapy during the screening period, the placebo run-in period and the treatment period throughout the trial. No dosage adjustments of the patient's SoC asthma therapy will be permitted during the study.

Short bursts of rescue systemic corticosteroids are allowed for treatment of asthma exacerbations, as clinically indicated (see Section 6.4.3).

5.2 Treatment arms

During the placebo run-in period, all patients will receive placebo to QAW039 once daily (one tablet blinded placebo to QAW039 150 mg).

Patients will be assigned to one of two treatment arms as follows in a 1:1 ratio in the treatment period:

- QAW039 150 mg once daily
- Matching placebo to QAW039 150 mg, once daily

Patients will be instructed to take their study drug (QAW039 or placebo) once daily in the morning without regard to time of food intake. Further instructions on when patients have to take the study drug are found in Section 5.5.4.

5.3 Treatment assignment and randomization

At Visit 201, all eligible patients will be randomized via Interactive Response Technology (IRT) to 1 of the 2 treatment arms (QAW039 150 mg once daily or matching placebo once daily) in a 1:1 fashion. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

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

Randomization will be stratified by patient age at Visit 1 (<18 years or ≥18 years) and use or non-use of a second asthma controller medication at Visit 1. Treatment randomization will be stratified at the regional level.

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

5.4 Treatment blinding

This study consists of a single-blind run-in period (i.e., only patients will be blinded to the identity of the treatment) followed by a double-blind randomized treatment period.

Patients, 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 involved in the study with the following exceptions: the external DMC, independent of the QAW039 study team, will have access to unblinded data. Please refer to Section 8.4 for details. (2) For QAW039, the identity of the treatment will be concealed by the use of placebo identical in packaging, labeling, schedule of administration, appearance, taste, and odor to QAW039.

Unblinding should only occur in the case of patient emergencies (see Section 5.6) and at the conclusion of the study. In addition, the independent DMC will be unblinded for the purpose of safety reviews.

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.

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number 2, the third

[redacted]

patient is assigned patient number 3). 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. Only the assigned patient number must be entered in the field labeled "Patient ID" on the EDC data entry screen (e.g. enter '1', '2', etc.). Once assigned to a patient, the patient number will not be reused. If the patient fails to be randomized for any reason, the IRT must be notified within 2 days that the patient was not randomized. The reason for not being randomized will be entered on the Screening Log, and the Demography electronic case report form (eCRF) should also be completed.

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

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

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

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

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients 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 (rescue medication) has to be monitored:

[redacted]

- SABA (such as salbutamol 100 mcg or albuterol 90 mcg)

The non-study treatment must be handled and stored according to label, kept in a secured location and dispensed only in accordance with the protocol.

The investigator must maintain an accurate record of dispensing of the above-mentioned treatment in a drug accountability log / inventory log / source documents. Monitoring of drug accountability will be performed by monitors during site visits and at the completion of the study. Patients will be asked to return all unused SABA 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 drug will be single-blind during the placebo run-in and double-blind, placebo-controlled after randomization. At clinic visits, patients will receive a witnessed dose of study drug and, therefore, will be instructed to withhold study drug and SoC asthma therapy prior to each clinic visit. These in-clinic witnessed doses should be given after completion of all pre-dose assessments and at approximately the same time at each clinic visit. Between clinic visits, patients will take study drug once daily in the morning. Patients will be instructed to take their study drug at approximately the same time each morning, with or without food.

At Visit 101, all eligible patients will be given oral placebo to QAW039 during the placebo run-in period for approximately 1 week and will be instructed on the intake of study drug. **In order to maintain the blind from the patient's point of view, investigators must not divulge information regarding the fact that all individuals will be assigned to placebo during the placebo run-in period**. At Visit 201, patients will be randomized and stratified according to patient age (<18 or ≥18 years) and use or non-use of a second asthma controller medication at Visit 1. Treatment randomization will be stratified at the regional level. Each randomized patient will then enter a 12-week treatment period where they will receive one of the following 2 treatments: (1) QAW039 150 mg once daily given orally or (2) matching placebo to QAW039 150 mg once daily given orally. The study drug will be dispensed in kits at each site 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 during the study must be recorded on the dosage administration record (DAR) CRF. All kits of study drug assigned by IRT will be recorded/databased in the IRT system.

The investigator must promote compliance by instructing the patient to take the study drug 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 drug as prescribed.

5.5.5 Permitted dose adjustments and interruptions of study treatment

QAW039 and background asthma therapy dose adjustments are not permitted.

QAW039 treatment interruption is only permitted in the following situations:

- A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative.

[redacted]

- An investigator considers an interruption is necessary for the treatment of an adverse event.

Interruption to study drug must be recorded on the dosage administration record eCRF.

5.5.6 Rescue medication

At Visit 1 all patients will be provided with a SABA (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 study sites locally by Novartis or provided by the study site to the patient and reimbursed by Novartis.

Nebulized salbutamol/albuterol is not allowed as rescue medication and will not be supplied.

No other rescue treatment is permitted and use of a spacer for rescue medication is not allowed at any time throughout the study.

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 rescue medication is taken within 6 hours prior to spirometry, this information will be recorded by the study site staff using the equipment provided by the central spirometry vendor. Additionally, if rescue medication is taken within 6 hours prior to spirometry at any of the scheduled visits, the visit must be rescheduled to the next possible day.

Daily use of rescue medication (the number of puffs taken in the previous 12 hours) will be recorded (once in the morning and once in the evening) by the patient using ePEF/ eDiary.

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 hydrofluoroalkane (HFA)) and the way it is administered (e.g., with a spacer device) must not be adjusted. Any changes relating to the above must be recorded on the Concomitant medications eCRF after the start of study drug.

5.5.7 Concomitant medication

The medications in Table 5-1 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 5-1 Medications allowed under certain conditions

Class of medication	Condition
Inhaled corticosteroids (ICS)	• Medium dose ICS, or • High dose ICS, or • Low dose ICS plus LABA, or • Low dose ICS plus LTRA, or • Medium dose ICS plus LABA Used for at least 3 months prior to Visit 1 and dose(s) stable for at least 4 weeks prior to Visit 1.

[redacted]

	Dose adjustments are not permitted throughout the study.
Long-acting inhaled β-2 agonists (LABAs)	Allowed as the second asthma controller medication when taken with low or medium dose ICS. Used for at least 3 months prior to Visit 1 and dose stable for at least 4 weeks prior to Visit 1. Dose adjustments are not permitted during the study.
Fixed dose combinations of ICS and LABA (FDC)	Allowed as ICS (low or medium dose) with a LABA. Used for at least 3 months prior to Visit 1 and doses stable for at least 4 weeks prior to Visit 1. Dose adjustments are not permitted during the study.
Leukotriene receptor antagonists (LTRAs)	Allowed as the second asthma controller medication when taken with low dose ICS. Used for at least 3 months prior to Visit 1 and dose stable for at least 4 weeks prior to Visit 1. Dose adjustments are not permitted during the study.
Oral corticosteroids for treatment of asthma	Short bursts of rescue systemic corticosteroids are allowed for treatment of asthma exacerbations, as clinically indicated.
Short-acting β_2-agonist (SABAs)	Rescue medication to be taken as needed.
Maintenance immunotherapy for allergies	Stable dose for at least 3 months prior to Visit 1 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.
Topical corticosteroids for treatment of eczema	Recommended doses and dosage regimens.
Antihistamines (e.g., loratadine, cetirizine)	Recommended doses and dosage regimens
Nasal anticholinergics Nasal corticosteroids Nasal or ophthalmological preparations of nedocromil Nasal or ophthalmological preparations of antihistamines	Treatment regimen has been stable for at least 1 month prior to Visit 1. In the case of as needed use, providing an established pattern of use has been documented.

*See Appendix 6 for the GINA 2016 definition of medium and high dose ICS.

Table 5-2 indicates the wash-out periods for allowed asthma medications prior to spirometry assessments.

[redacted]

Table 5-2 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
Fixed-dose combinations of LABA and ICS given once daily	≥ 24 hours

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

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

5.5.8 Prohibited medication

Use of the treatments displayed in Table 5-3 is NOT allowed after Visit 101. 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 must 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 must be assessed for adherence to the indication and other inclusion/exclusion crtieria.

These medications are also prohibited if administered for other indications.

Table 5-3 Prohibited medication

Class of medication	Minimum cessation prior to Visit 101
Other investigational drugs	30 days or 5 half-lives, whichever is longer
Live attenuated vaccine	30 days
Other DP2 antagonists (e.g., ramatroban)	7 days or 5 half-lives, whichever is longer
Short-acting anticholinergics	8 hours
Long-acting anticholinergics	7 days
Fixed combinations of short-acting β_2 agonists and short-acting anticholinergics	8 hours
Mast cell stabilizers (e.g., cromoglycate, nedocromil, ketotifen)	7 days
Monoclonal antibodies, investigational or approved, for the treatment of asthma (e.g., omalizumab)	5 months
Simvastatin >20 mg, atorvastatin >40 mg, pravastatin >40 mg, or pitavastatin >2 mg total	7 days

[redacted]

Class of medication	Minimum cessation prior to Visit 101
daily dose	
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
Methotrexate, gold salts, cyclosporine, troleandomycin, azathioprine, other immunomodulator drugs or immunomodulatory monoclonal antibodies	6 months

Abbreviation: DP2 (prostaglandin D2 receptor 2)

5.5.9 Emergency breaking of assigned treatment code

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

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

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

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

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.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

Study completion for a patient will occur after he/she has completed 12 weeks of treatment (through to Visit 299) or has prematurely withdrawn. Completion of the study will be when

all randomized patients have completed 12 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.

A Safety Study of QAW039 is planned. At sites participating in the Safety Study, patients who successfully complete 12 weeks of treatment in this study (Study A2317) may be offered participation in the Safety Study; patient participation in the Safety Study will be optional. Patients not entering the Safety study will complete the follow-up period and will not be given further access to study drug because the risk/benefit ratio will not yet have been substantiated and there are already other marketed therapeutic alternatives available to treat these patients. At the time of study completion or early termination, all patients will be placed on the appropriate asthma treatment as prescribed by the investigator.

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 the study completion visit (Visit 299) or premature study drug discontinuation and must follow up with the subject as appropriate at least to the end of this period.

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

5.6.2 Discontinuation of study treatment

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

Patients may voluntarily discontinue study drug (discontinue double-blind study drug but continue with study participation) at any time. **Patients who wish to discontinue double-blind study drug will be asked to remain in the study and complete all study visits. Patients withdrawn from study drug will receive SoC asthma therapy according to investigator judgment.**

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

Study drug **must** be discontinued under the following circumstances:

- Patient wish;
- Pregnancy (see Section 6.5.6 and Section 7.6);
- Any situation in which study participation might result in a safety risk to the patient;
- Female patients 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;
- Liver laboratory test abnormality / event (see Appendix 2):
- Abnormal liver laboratory results requiring discontinuation – refer to Table 14-2;

[redacted]

- If the investigator considers it appropriate after the confirmation of a liver safety monitoring signal:
  - ALT or AST ≥5xULN, **or**
  - ALT or AST ≥ 2.5xULN **and** total bilirubin ≥ 1.5xULN (Appendix 2);
- 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 drug for a patient for any reason;
- 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 patient should NOT be considered withdrawn from the study. The patient should return to the clinic as soon as possible, after discontinuation of study drug, for a study treatment discontinuation visit. Treatment discontinuation visit assessments detailed in the "treatment discontinuation visit" (TD) in Table 6-1 should be completed and recorded in the eCRF. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the dosage administration record eCRF.

The investigator and study staff must discuss with the patient his/her continued participation in the study and request he/she continues attending study visits according to the study visit schedule with all assessments completed up to Visit 299. If the patient cannot or is unwilling to attend any further visit(s), the site staff should maintain regular phone contact with the patient, or with a person pre-designated by the patient. This phone contact should preferably be done according to the study visit schedule.

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

- new / concomitant treatments
- adverse events/Serious Adverse Events (SAE)

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

If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.9.

5.6.2.1 Asthma worsening alerts

The data captured in the patient eDiary will be used in conjunction with the patient's asthma characteristics to monitor the patient's asthma. Patients will be instructed to call the study site if they experience symptoms of worsening asthma. Additionally, the eDiary will be

[redacted]

programed to generate some alerts of signs of possible worsening asthma based on data collected. These alerts will be sent to the patient and/or to the investigator.

The patient's personal best PEF in the clinic at Visit 101 will be set as the patient's baseline for the placebo run-in period, and the personal best PEF in the clinic at Visit 199 will be set as the patient's baseline for the treatment period.

5.6.3 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- Does not allow analysis of already obtained biologic material

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information.

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

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

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

5.6.4 Loss to follow-up

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

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely discontinued patient. The investigator may be informed of additional procedures to be followed in order to ensure

[redacted]

that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

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

Table 6-1 lists all of the assessments and indicates with an "X" or "S" when the visits are performed. Assessments marked with "S" are documented in source documentation only and will not be entered into the eCRF.

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 drug before completing the study and accept to remain in the study will return for study visits as described in Section 5.6.2. If they fail to return for these assessments for unknown reasons, every effort should be made to contact them as specified in Section 5.6.2. 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 (4 weeks after premature study drug discontinuation) to ask about concomitant medication use, surgery and procedures, SAEs, AEs and asthma exacerbations.

Patients will be required to attend the clinic in the morning at approximately the same time, so that pre-dose FEV1 assessments can be performed between 6 AM and 10 AM ±1 hour. Efficacy and safety assessments will be completed prior to QAW039 or placebo administration in the clinic.

When the following assessments are scheduled to be performed at the same time-point, the order of priority will be as follows:

1. **Question on medication withholding for spirometry**
   If the patient has not withheld medications as specified in the protocol before a particular visit, the visit must be rescheduled;
2. **Patient Reported Outcome (PRO) instruments** to be completed in the following order: [redacted], AQLQ+12, [redacted] at certain clinic visits;
3. **Vital signs;**
4. **ECGs;**
5. **Samples for urinalysis/hematology/blood chemistry** (At Visit 1, there is no specified order for collection of samples. At all other applicable visits, collect samples prior to the 1st pre-dose spirometry [which is the -45 minute pre-dose spirometry] or between the 1st and 2nd pre-dose spirometry measurements);
6. **Samples for radioallergosorbent test (RAST)/ImmunoCAP test, [redacted] at certain clinic visit(s)** (At Visit 1, there is no specified order for collection of samples. At all other applicable visits, collect samples prior to the 1st pre-dose spirometry [which is the -45 minute pre-dose spirometry] or between the 1st and 2nd pre-dose spirometry measurements);
7. **Spirometry.** Spirometry assessments must be timed so that the Visit 1 spirometry assessment and all pre-dose spirometry assessments can be performed between 6 AM and

[redacted]

10 AM ±1 hour and other tests must be performed as close as possible to those spirometry times. During the treatment period, two pre-dose spirometry assessments must be performed as follows:

- First pre-dose spirometry assessment: **approximately** 45 minutes prior to the dosing of study drug at the clinic visit.
- Second pre-dose spirometry assessment: **approximately** 15 minutes prior to the dosing of study drug at the clinic visit.

8. **Reversibility at certain visits (spirometry after administration of SABA) may be performed after 10 AM ±1 hour.**
9. **In-clinic witnessed dosing of study drug.**

[redacted]

Table 6-1 Assessment schedule

Period	Screen	Placebo Run-in		Treatment						Follow-up	Notes
Visit Number (Site visits)	1	101	199	201	202	203	204	TD	299	301	Follow-up Visit 301 is only applicable for patients not participating in the safety study.
Treatment Week	-3	-1	0	0	2	4	8	TD	12	16	Visit 199 and Visit 201 occur on the same day.
Treatment Day	-21	-7	1	1	14	28	56		84	112	
Informed consent and assent (if applicable)	X										ICF must be obtained within 14 days of Visit 1 or at Visit 1.
Ask question on withholding of medication before clinic visits	S		S		S	S	S	S	S		If the patient has not withheld medications as specified in the protocol before a particular visit, the visit must be rescheduled.
Demographics	X										
Medical history	X										
Medical History – Protocol solicited events for asthma	X										
Asthma exacerbation history	X										
Smoking history	X										
Prior/concomitant medication (asthma and non-asthma medications) review	X		X		X	X	X	X	X		
Inclusion/exclusion criteria	X		X								
Review and record surgeries and procedures	X		X		X	X	X	X	X		
Physical examination	S							S	S		
Abbreviated physical examination			S		S	S	S				Heart and lungs only.
ACQ-5 in clinic			X		[redacted]						
AQLQ+12 in clinic			X			X		X	X		

[redacted]

Period	Screen	Placebo Run-in		Treatment						Follow-up	Notes
Visit Number (Site visits)	1	101	199	201	202	203	204	TD	299	301	Follow-up Visit 301 is only applicable for patients not participating in the safety study.
Treatment Week	-3	-1	0	0	2	4	8	TD	12	16	Visit 199 and Visit 201 occur on the same day.
Treatment Day	-21	-7	1	1	14	28	56		84	112	
[redacted]											
Train patient and assess patient's ability to use eDiary/ePEF and dispense eDiary/ePEF	S										
Review eDiary /ePEF compliance		S	S†								† eDiary/ePEF compliance must be assessed prior to randomizing the patient.
Review eDiary/ePEF entries		S	S		S	S	S	S	S		
Height	X							X	X		
Weight	X		X					X	X		
Vital signs	X	X	X		X	X	X	X	X		Systolic/diastolic blood pressure, radial pulse (sitting), and body temperature.
Electrocardiogram	X							X			
Electrocardiogram (Pre-dose)				X					X		
Pregnancy test—serum (women of child bearing potential)	X										Pregnancy testing will begin at the visit a patient is first identified as being of child bearing potential. If positive, the patient must not be randomized.
Pregnancy test—urine dipstick test in clinic (women of child bearing potential)			X			X	X	X	X	X	Pregnancy testing will begin at the visit a patient is first identified as being of child bearing potential. A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be

Period	Screen	Placebo Run-in		Treatment						Follow-up	Notes
Visit Number (Site visits)	1	101	199	201	202	203	204	TD	299	301	Follow-up Visit 301 is only applicable for patients not participating in the safety study.
Treatment Week	-3	-1	0	0	2	4	8	TD	12	16	Visit 199 and Visit 201 occur on the same day.
Treatment Day	-21	-7	1	1	14	28	56		84	112	
											negative. If positive, the patient must be discontinued from study drug.
Urinalysis and urine chemistry (central laboratory)	X			X				X	X		
Blood sample for hematology and chemistry (central laboratory)	X			X				X	X		No fasting requirement prior to blood sampling.
Blood sample for RAST/ImmunoCAP test (central laboratory)	X										
Review Visit 1 laboratory results		S									If results for chemistry, hematology, HbA1c, RAST/ImmunoCAP, urine chemistry and urinalysis are missing, obtain a repeat for the missing result.
[redacted]											
Parasitic screening	S										Only if required by health authority and/or ethics committee/ institutional review board. Sites should use local laboratories.
Spirometry (centralized)	X							X			
1st Pre-dose Spirometry (centralized) approximately - 45 min. pre-dose		X		X	X	X	X		X		To be performed approximately 45 min. prior to in-clinic witnessed study drug administration.
2nd pre-dose Spirometry (centralized) approximately -15 min. pre-dose		X£		X	X	X	X		X		To be performed approximately 15 min. prior to in-clinic witnessed study drug administration.

[redacted]

Period	Screen	Placebo Run-in		Treatment						Follow-up	Notes
Visit Number (Site visits)	1	101	199	201	202	203	204	TD	299	301	Follow-up Visit 301 is only applicable for patients not participating in the safety study.
Treatment Week	-3	-1	0	0	2	4	8	TD	12	16	Visit 199 and Visit 201 occur on the same day.
Treatment Day	-21	-7	1	1	14	28	56		84	112	
											[£]To be performed prior to reversibility test.
Reversibility test (spirometry after administration of short-acting β-agonist [SABA])	X[**]	X[α,ß **]									[α]To be performed prior to in-clinic witnessed study drug administration. [ß]To be performed after the second (-15 min.) pre-dose spirometry (may be performed after 10 AM ± 1 h). ****If reversibility is NOT demonstrated at Visit 1, reversibility will be attempted at Visit 101. If not achieved, then one additional attempt allowed within 4 days following Visit 101.**
Review Visit 1 or Visit 101 or the one additional attempt reversibility result from overread			S								
Asthma exacerbation monitoring	X	X	X	X	X	X	X	X	X	X	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.
Serious adverse event monitoring	X	X	X	X	X	X	X	X	X	X	
Adverse event monitoring	X	X	X	X	X	X	X	X	X		
Liver event monitoring	X	X	X	X	X	X	X	X	X	X	If applicable, review lab results and clinical events as per Section 7.3.
Renal event monitoring	X			X				X	X		If applicable, review lab results as per Section 7.4.

[redacted]

Period	Screen	Placebo Run-in		Treatment						Follow-up	Notes
Visit Number (Site visits)	1	101	199	201	202	203	204	TD	299	301	Follow-up Visit 301 is only applicable for patients not participating in the safety study.
Treatment Week	-3	-1	0	0	2	4	8	TD	12	16	Visit 199 and Visit 201 occur on the same day.
Treatment Day	-21	-7	1	1	14	28	56		84	112	
Record deaths	X	X	X	X	X	X	X	X	X	X	
Contact IRT	S	S	S	S	S	S	S	S	S	S	
Randomize patient through IRT				S							
Assess and dispense rescue SABA to be used on an as-needed basis	S*	S	S	S	S	S	S	S	S**		*dispense SABA only **assess SABA only
Dispense study drug		S		S	S	S	S				Patients will be instructed to take study drug in the morning.
Assess compliance with study drug (count tablets in returned bottles)			S		S	S	S	S	S		
In-clinic witnessed study drug intake		X		X	X	X	X		X		Complete Dosage Administration Record (DAR)-Visit – at site visit.
Complete Study Drug Dosage Administration Record-Summary page			X		X	X	X	X	X		Complete DAR- Summary at each indicated visit to record compliance
Complete Study Disposition page (screening)	X										
Complete Study Disposition page (run-in)			X								
Complete Study Disposition page (end of treatment)									X		
Complete Study Disposition page (follow-up)										X	For patients not participating in the safety study.
Complete Withdrawal of	X	X	X	X	X	X	X	X	X	X	

[redacted]

Period	Screen	Placebo Run-in		Treatment						Follow-up	Notes
Visit Number (Site visits)	1	101	199	201	202	203	204	TD	299	301	Follow-up Visit 301 is only applicable for patients not participating in the safety study.
Treatment Week	-3	-1	0	0	2	4	8	TD	12	16	Visit 199 and Visit 201 occur on the same day.
Treatment Day	-21	-7	1	1	14	28	56		84	112	
informed consent form (if patient withdraws consent)											
Re-screening of patient	X										Re-screening of patients is permitted once. **Once a patient enters the placebo run-in period, the patient may not be re-screened.** If a patient is re-screened, a new informed consent (and assent if applicable) must be obtained.
Appointment for next clinic visit	S	S		S	S	S	S	S	S		
Dispense patient card	S										
Discuss optional participation in safety study									S		
Collect patient card									S*	S	* If participating in the safety study.

Abbreviations: TD (treatment discontinuation), ICF (informed consent form), ACQ-5 (asthma control questionnaire-5), AQLQ+12 (asthma quality of life questionnaire for 12 years and older, [redacted] eDiary/ePEF (electronic peak expiratory flow), ECG (electrocardiogram), RAST (radioallergosorbent test), HbA1c (hemoglobulin A1c), [redacted] IRT (interactive response technology).

[redacted]

6.1 Information to be collected on screening failures

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

All patients who have signed informed consent and have received placebo study medication, but discontinue prior to randomization (run-in failures) must have all data for the visits they attended, the summary pages (adverse event, concomitant medication, dosage administrative record), and screening and placebo run-in disposition pages completed. All adverse events **occurring after informed consent is signed** must be recorded on the Adverse Event eCRF.

6.2 Patient demographics/other baseline characteristics

The following demographics and baseline characteristics will be collected on all patients:

- Age
- Gender
- Race and ethnicity
- Height
- Weight
- Body mass index (BMI)
- Duration of asthma
- Number of exacerbations in prior year
- Atopic Yes/No (RAST/ImmunoCap)
- Smoking history
- Reversibility (demonstrated)
- FEV1
- [redacted]
- Baseline ACQ-5
- Baseline AQLQ+12
- [redacted]
- ICS use alone/ICS plus a second controller
- Relevant medical history/current medical condition present before signing informed consent. Where possible, diagnoses and not symptoms will be recorded.

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.

6.3 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

[redacted]

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.

Start and end dates of doses of study drug administered since the last dispensing visit will be recorded in the eCRFs (study drug dosage administration record (DAR)-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 Visit 299 when the medication returned by the patient should be used.**

6.4 Efficacy

6.4.1 Spirometry (Pre-dose FEV1 [redacted])

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.

Equipment for spirometry assessments will be provided to all study sites by a Central Spirometry vendor, and overread of spirometry assessments will be performed by trained spirometry technicians at the central vendor.

Please refer to the Spirometry Guidance, in Appendix 5 (Spirometry Guidance), for full details on scheduling and performing spirometry. Reversibility testing must be conducted in the morning.

6.4.2 eDiary for daily asthma symptoms, [redacted] and rescue medication use

The study will use the asthma diary reported by Santanello et al (1997). This asthma diary was validated in studies of patients aged 18 to 65 years (Santanello et al. 1997). The diary was subsequently included as a measure in placebo-controlled studies of montelukast in patients aged 15 years and older (Reiss et al. 1998, Malmstrom et al. 1999) and shown to be responsive to both montelukast and inhaled beclomethasone therapy in this age range. **All patients will complete the asthma diary regardless of age.**

All patients will be provided with a patient electronic diary (referred to as eDiary or eDiary/ePEF) to record daily asthma symptoms, [redacted], and SABA (salbutamol/albuterol) 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 each clinic visit as detailed in Table 6-1 until study completion. Sites and patients will receive appropriate training and guidance on the use of the eDiary/ePEF device.

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.

6.4.2.1 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.

[redacted]

Daytime symptom diary scale questions

How often did you experience asthma symptoms today?

0 1 2 3 4 5 6

None of the time — All of the time

How much did your asthma symptoms bother you today?

0 1 2 3 4 5 6

Not at all bothered — Severely bothered

How much activity could you do today?

0 1 2 3 4 5 6

More than usual activity — Less than usual activity

How often did your asthma affect your activities today?

0 1 2 3 4 5 6

None of the time — All of the time

[redacted]

6.4.2.2 Number of inhalations of rescue medication

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

[redacted]

[redacted]

6.4.2.4 Worsening of asthma (and related eDiary alerts)

Asthma worsening criteria will be programmed into the eDiary/ePEF.

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

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

The patient's personal best PEF in the clinic at Visit 101 will be set as the patient's baseline for the placebo run-in period, and the personal best PEF in the clinic at Visit 199 before dosing will be set as the patient's baseline for the treatment period.

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 screening, placebo run-in, or treatment 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.

6.4.3 Asthma exacerbations

The following definitions of exacerbations are used in this study:

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.

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).

*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 greater than 2 fold (i.e., greater than doubling 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.

[redacted]

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

Patients experiencing an asthma exacerbation during the screening or placebo run-in periods must be designated as screening or run-in failures. Patients who experience an asthma exacerbation during screening may be re-screened 4 weeks after complete recovery from the exacerbation.

6.4.4 Appropriateness of efficacy assessments

The measurements described above are standard outcome measures in asthma trials.

6.5 Safety

The following safety assessments as delineated in Table 6-1 will be performed:

- History and physical examination
- Vital signs
- Hematology
- Blood chemistry including but not limited to
  - Liver function tests: ALT, AST, total bilirubin
  - Metabolic panel: sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN)/urea, creatinine, glucose, calcium, phosphorus, magnesium, total protein, albumin (Alb), gamma-glucoronyl transferase (γ-GT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), creatine kinase (CK), iron, uric acid, cholesterol, triglycerides
  - amylase, lipase
  - High sensitivity C-reactive protein (hsCRP)
  - Creatine kinase isoenzyme–MB (CK-MB) and Troponin-I (in response to CK results outside of the normal range)
  - Glycosylated hemoglobin (HbA1c) (collected at Visit 1 only)
- Urinalysis and urine chemistry
- Pregnancy test (Pregnancy testing will begin at the visit when a patient is first identified as being of child bearing potential)
- ECG
- Adverse events including serious adverse events

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 asthma.

A central laboratory will be used to analyze and report blood chemistry/hematology and urinalysis/ urine chemistry. A central ECG vendor will be used to collect, assess and report ECGs.

A Data Monitoring Committee will be set up to overview safety. See Section 8.4 for details.

[redacted]

6.5.1 Physical examination

A complete physical examination will be performed at visits specified in the table of assessments (Table 6-1). 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.

Abbreviated physical examinations will be performed at visits as indicated in Table 6-1. These will include the examination of the lungs and heart.

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 Vital signs

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

6.5.3 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.

6.5.4 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.

Clinically notable laboratory findings are defined in Appendix 1.

6.5.4.1 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.

[redacted]

6.5.4.2 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 Visit 1 only) [redacted] ([redacted] RAST/ImmunoCAP test), will be measured according to the assessment schedule (Table 6-1). Other reflex testing will be performed as outlined in the laboratory manual.

If the total bilirubin concentration is increased above 1.5 times 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 must be followed until the values return to within the normal ranges or until a clinical explanation is identified, even after study drug has discontinued.

6.5.4.3 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 Table 15-1 "Specific Renal Alert Criteria and Actions" in Section 7.4 "Renal Safety Monitoring" of this protocol". Other reflex testing will be performed as outlined in the laboratory manual.

6.5.5 Electrocardiogram (ECG)

ECGs will be measured according to the assessment schedule in Table 6-1. At Visit 1, 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 (see Section 6). 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 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 (CQAW039A2317), subject initials (where this is allowed according to local regulations), subject number, date and time, and filed in the study site source documents.

[redacted]

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.

6.5.6 Pregnancy and assessments of fertility

All women and adolescent girls of child bearing potential will have serum pregnancy test according to the assessment schedule in Table 6-1. Pregnancy testing will begin at the visit a patient is first identified as being of child bearing potential.

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

6.5.7 Appropriateness of safety measurements

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

6.6 Other assessments

In addition to patient reported outcomes at the visits indicated in Table 6-1, [redacted]

6.6.1 Clinical Outcome Assessments (COAs)

6.6.1.1 Patient Reported Outcomes (PRO)

The impact of QAW039 on various aspects of patient's health status will be assessed by the following measures:

- Asthma Control Questionnaire-5 (ACQ-5) to assess improvement in asthma symptom control;
- Asthma Quality of Life Questionnaire+12 (AQLQ+12) to measure health-related quality of life (HRQOL); and
- [redacted]

All questionnaires will be completed in the language most familiar to the respondent, at the scheduled study visit prior to the patient seeing the investigator for any clinical assessment or evaluation. The patient must be given sufficient instruction, space, time and privacy to complete the questionnaire. The study coordinator must check the responses to the questionnaire for completeness and encourage the patient to complete any missing responses.

Available training materials related to the administrative procedures of the questionnaires will be provided to the sites.

[redacted]

All patients will complete the PRO questions via a handheld electronic device or an electronic tablet. Patients must be given sufficient space and time to complete all study PROs. If patients experience any difficulties with submission after they complete the PROs, the study staff must assist them with submitting their PRO responses. Attempts must be made to collect responses to all PROs for all patients, including from those who prematurely discontinue prior to the study evaluation completion visit, however, if patients refuse to complete PROs, this must be documented in study source records. Patient's refusal to complete study PROs are not protocol deviations.

Completed questionnaires will be reviewed and examined by the investigator, before the clinical examination, for responses that may indicate potential adverse events (AEs) or serious adverse events (SAEs). The investigator must review not only the responses to the questions in the questionnaires but also for any unsolicited comments written by the patient. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Section 7.1 and Section 7.2 of the protocol.

The PROs ACQ-5, AQLQ+12, [redacted] questionnaires should always be completed before any other assessments and in the following order when done at the same visits (see Section 6):

- ACQ-5
- AQLQ+12
- [redacted]

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 caliber (% FEV_1 predicted). The rescue bronchodilator use and % FEV_1 predicted items are not included in the ACQ-5. The ACQ was originally validated in patients with asthma over aged 17 years (Juniper et al 1999, Juniper et al 2006), and is one of several asthma control measures recommended by the GINA Guidelines. The ACQ has been fully validated, including patients aged from 6 to 16 years (Juniper et al 2010) and including a minimal important difference (MID) or smallest change that can be considered clinically important (0.5).

The ACQ-5 will be self-administered at the clinic and 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: therefore, between 0 (totally controlled) and 6 (severely uncontrolled) (Juniper et al 1999; Juniper et al 2005; Juniper et al 2006).

The ACQ will be collected in an electronic format. The ACQ will be completed by patients at the visits specified in the table of assessments (See Table 6-1). The questionnaire must be completed before the AQLQ+12 and before any other assessments (see Section 6). The appropriate language version(s) of the questionnaire will be used in each participating country. The same language version of the questionnaire must be used by a particular patient throughout the study.

[redacted]

The study coordinator must be familiar with the instrument and the associated user guides and training materials provided. Patients must complete the questionnaire in a quiet area and are allowed to ask questions; however the site staff must take care not to influence the patient's response. In response to a question, patients must be instructed to provide the truest or best response for them.

Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12)

In this study, the disease-specific AQLQ+12 will be used to measure health-related quality of life in patients. The measure was originally validated for use in patients with asthma aged "12 to 80 years (Juniper et al 2005)".

The AQLQ+12 comprises a total of 32 individual questions that span a total of four domains: symptoms, activity limitation, emotional function, and environmental stimuli. Test-retest reliability, construct validity (cross-sectional and longitudinal), and responsiveness have been demonstrated (see Appendix 8).

The AQLQ+12 will be self-administered at the clinic. It takes about 4 to 5 minutes to complete. Patients are asked to recall their experiences during the previous 2 weeks and to score each item on a 7-point scale (7 = not at all impaired to 1 = severely impaired). The AQLQ+12 yields individual domain scores, which is the mean of all items in each domain, and an overall score, which is the mean of all 32 individual responses. Higher scores indicate less impairment in HRQOL.

The AQLQ+12 will be collected in an electronic format. The questionnaire will be completed by patients at the visits specified in the table of assessments (See Table 6-1).

The appropriate language version(s) of the questionnaire will be used in each participating country. The same language version of the questionnaire must be used by a particular patient throughout the study.

The study coordinator must be familiar with the instrument and the associated user guides and training materials provided. The patient must complete the questionnaire in a quiet area and be allowed to ask questions; however site staff must take care not to influence the patient's responses. The patient will be instructed to provide the truest and for them best response.

7 Safety monitoring

7.1 Adverse events

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

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

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

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

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

- The severity grade:
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment
  - Yes
  - No
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding investigational treatment

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

- no action taken (e.g. further observation only)
- investigational treatment dosage increased/reduced
- investigational treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of an SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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

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

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the

[redacted]

investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

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

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

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

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

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

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

[redacted]

7.2.2 SAE reporting

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

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

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

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology (DS&E) 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 European Union (EU) Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

7.3 Liver safety monitoring

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

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

[redacted]

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

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

Every liver laboratory trigger or liver event as defined in Table 14-1 of Appendix 2 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 14-2 in Appendix 2.

For the liver laboratory trigger:

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

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

Repeat laboratory tests must be entered on the appropriate unscheduled local laboratory CRF page.

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

For the liver events:

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

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

7.4 Renal safety monitoring

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.

[redacted]

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

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

7.5 Reporting of study treatment errors including misuse/abuse

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

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

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

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

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

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

Abbreviation: eCRF (electronic case report form), AE (adverse event), SAE (serious adverse event).

7.6 Pregnancy reporting

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

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

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

[redacted]

7.7 Idiosyncratic drug reactions monitoring

IDRs are adverse drug reactions that do not occur in most patients (i.e., they are rare, occurring 1 in 10,000 to 1 in 100,000 patients) and do not result from known pharmacological effects of a drug. Their onset is unpredictable and they may involve one or more organ systems, most notably the immune system, liver and blood cells.

The investigator should pay special attention to any adverse events which may be a potential IDR reported by a patient. If such an event occurs, the investigator should report the event as per standard adverse event reporting procedures (i.e., serious adverse events for those meeting serious criteria and non-serious adverse events for those meeting non-serious adverse event criteria as defined in the protocol).

The investigator may be also be contacted by Novartis regarding AEs that may resemble an IDR. A list of terms considered IDRs are provided in Appendix 4.

Events with potential to be IDRs will be identified thorough a pre-specified search algorithm based on the standardized medical dictionary for regulatory activities (MedDRA) Queries as described in the study analysis plan. These events will be reviewed by the DMC on a regular basis.

8 Data review and database management

8.1 Site monitoring

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

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the

[redacted]

inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Oracle Clinical/Remote Data Capture (OC/RDC) system. Designated investigator site staff will not be given access to the system until they have been trained.

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

8.3 Database management and quality control

Novartis staff (or contract research organization (CRO) working on behalf of Novartis) review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data.

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

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Spirometry and ECG readings will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

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 (or designated CRO).

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

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.

[redacted]

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

An independent, external data monitoring committee (DMC) will be set up to review safety data (including specific safety summaries for adolescent participants) from this trial and other Phase 3 trials in the QAW039 asthma development program. The DMC will consist of a group of experts independent of the sponsor; analyses for the DMC will be prepared by individuals independent of the sponsor and sponsor personnel will remain fully blinded to results until the final clinical database lock as described in Section 5.4. Based on the safety implications of the data, the DMC may recommend modification or termination of the study. No statistical adjustment will be made to the final analysis. Full details on procedures, the DMC and futility criteria will be specified in a DMC charter.

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.

The primary efficacy analysis of this pivotal trial will be based on the data of this trial alone. In addition, efficacy data will also be pooled with the other identical Phase 3 trial and the pooled data will be used to fully characterize efficacy in the asthma patient population studied in these trials.

9.1 Analysis sets

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

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 study drug 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 per-protocol set (PPS) will include all patients in the FAS without any major protocol deviations such as violation of major entry criteria or low compliance. Patients may also be considered censored for the PPS analysis at the time of major post-baseline protocol deviations. Major protocol deviations will be defined in the study specification document

prior to database lock and the un-blinding of the study. Patients will be analyzed according to the treatment they received.

The safety set (SAF) will include all patients who received at least one dose of double-blind 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 PPS will be used for the supportive analysis of the primary and the secondary variables. 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 including age (calculated from date of birth to date of Visit 1), sex, race, ethnicity, height, weight, body mass index (BMI), relevant medical history, including smoking history, asthma duration, use of long-acting beta-agonists, ICS dose ranges (medium, high) pre- and post- bronchodilator FEV1, percent predicted FEV1, [redacted], AQLQ+12 score, [redacted], number of exacerbations in the previous year, and daytime asthma symptom scores will be summarized by treatment group for the FAS. Categorizations of age will include at least the categories of <18, 18 to <65, 65-74, 75-84 and ≥85 years of age.

9.3 Treatments

The duration of exposure, the number of patients randomized who completed the foreseen course of study drug and the number of patients who discontinued from the study drug will be summarized.

Medications started and stopped prior to study drug, taken concomitantly, and started following last study drug dose (if applicable) will be summarized by treatment group in separate tables in the SAF. Concomitant therapies will be recorded, listed and summarized separately for asthma related medications / non-drug therapies and other medications. Concomitant asthma related medications will be summarized by pre-defined category. Concomitant medications not related to asthma will be summarized by anatomical therapeutic chemical (ATC) class and preferred term. More than one ATC class per medication is possible and the medication will be reported under all applicable classes.

SABA usage (number of puffs) during the placebo run-in period will be summarized.

Usage of asthma medication (e.g., LABA, ICS) at baseline will be summarized (if applicable). Patients taking prohibited concomitant medications will be noted in the summary of protocol deviations.

Compliance with study drug over the entire study will be summarized as the percentage of days with study drug intake during the period from first intake to last intake.

9.4 Analysis of the primary variable(s)

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

[redacted]

9.4.1 Primary Variable(s)

The primary variable for this study is the change from baseline in pre-dose FEV1 at the end of 12 weeks of treatment. Pre-dose FEV1 is the average of the two FEV1 assessments taken at 45 minutes and 15 minutes prior to the dosing of study drug at the clinic visit. The baseline FEV1 is defined as mean of the two FEV1 assessments prior to the first dose of study drug at the randomization visit. If any one of these assessments is missing (or is not confirmed to be pre-dose), then the remaining non-missing observation will be considered as baseline. If both assessments are missing (or are not confirmed to be pre-dose) then the last available FEV1 measurement prior to Day 1 on study drug will be used for baseline. If the FEV1 measurements are missing both on Day 1 and at the placebo run-in or screening visits, the respective baseline values will be set to missing.

The secondary variables are daytime asthma symptoms, total daily SABA use and AQLQ+12. Their definition and analysis is described in Section 9.5.

Efficacy measurements (i.e., daily asthma symptom scores, FEV1) taken within 7 days of systemic corticosteroid use and/or within 6 hours of rescue medication (SABA) use will be censored (set to missing). Additionally, if the pre-dose FEV1 is taken within 12 hours of LABA (including fixed dose combinations of LABA and ICS) use or 24 hours of tiotropium, then the individual FEV1 value will be set to missing.

9.4.2 Statistical model, hypothesis, and method of analysis

The primary objective of the study is to evaluate superiority of QAW039 150 mg once daily over placebo (with SoC asthma therapy as the background therapy) by testing the following null hypothesis (H_0) versus the alternative hypothesis (H_a):

H_0: There is no difference in the change from baseline in pre-dose FEV1 at week 12 post-baseline for the patients treated with QAW039 150 mg once daily compared with placebo.

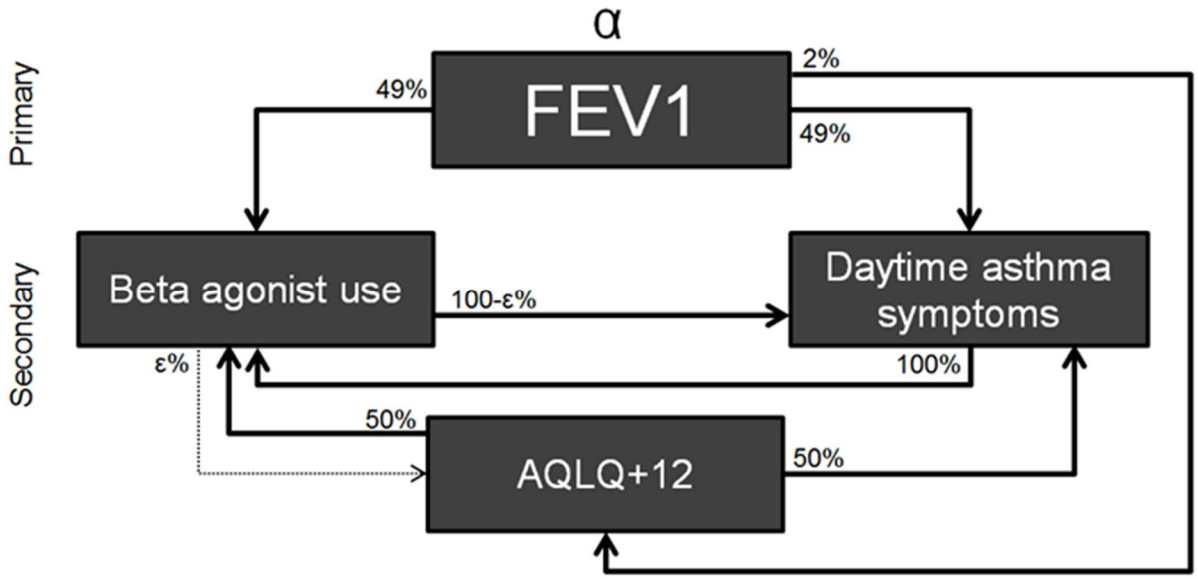
H_a: There is a difference in the change from baseline in pre-dose FEV1 at week 12 post-baseline for the patients treated with QAW039 150 mg once daily compared with placebo.

Familywise type I error rate control

The familywise type I error rate will be controlled at the two-sided 5% level across the primary and secondary null hypotheses using the closed testing procedure shown in Figure 9-1 using the graphical method of Bretz et al 2009. In this closed testing procedure, the primary null hypothesis about pre-dose FEV1 acts as a gatekeeper for the secondary null hypotheses.

[redacted]

Figure 9-1 Closed testing procedure for primary and secondary objectives



Vertices with associated weights denote the individual null hypotheses and their local significance levels. Directed edges between the vertices specify how the local significance levels are propagated in case of significant results. ε is set to a very small number in practice. Abbreviations: FEV1 (forced expiratory volume in 1 second); AQLQ+12 (asthma quality of life questionnaire for 12 years and older).

Initially, the alpha is assigned to the primary null hypothesis. Once the primary null hypothesis has been rejected, then 98% of the alpha will be distributed equally amongst the secondary null hypotheses of daytime asthma symptoms and total daily SABA use, respectively, and 2% of the alpha will be assigned to the null hypothesis for AQLQ+12. If one of the secondary null hypotheses is rejected, its local significance level will be propagated to the other secondary null hypotheses as illustrated in Figure 9-1.

Statistical model for primary variable

The primary efficacy variable will be analyzed on FAS using an analysis of covariance (ANCOVA) model with factors for treatment group, age group (<18 vs. ≥18 years), use or non-use of a second asthma controller medication at study entry, and region, as well as the baseline daytime asthma symptom score, baseline total daily SABA use and baseline pre-dose FEV1 as continuous linear covariates.

The least squares mean ("adjusted mean") change from baseline for each treatment group, the difference in the least squares mean changes between the two treatment groups (QAW039 150mg – placebo), and the two-sided adjusted 95% confidence interval along with the p-value for the difference will be obtained and combined from the primary analysis model through the multiple imputation approach described in Section 9.4.3. The superiority of QAW039 150 mg once daily to placebo as add on to SoC asthma therapy is established if the two-sided p-value is less than 0.05 and the 95% confidence intervals lie entirely to the right of 0 L.

Summary statistics for the primary variable

Summaries of absolute values and change from baseline in pre-dose FEV1 by treatment group and visit will be presented. Figures will be produced to visually show the mean pre-dose

[redacted]

FEV1 and the mean change from baseline in pre-dose FEV1 by visit over study period for each treatment group.

9.4.3 Handling of missing values/censoring/discontinuations

Despite all attempts to ensure complete follow-up for all patients, some patients may not be followed for pre-dose FEV1 for the whole planned study duration. Missing data after discontinuation of double-blind study treatment will be imputed using the jump to reference approach (Carpenter et al 2013). Intermittent missing data prior to discontinuation of double-blind study treatment will be imputed under a missing at random assumption.

A large number of imputed datasets will be created, with their number chosen based on computational feasibility, but at least 1,000. Each dataset will be analyzed using the model described in Section 9.4.2 and the results will be combined using Rubin's rule (Barnard and Rubin 1999) for final inference.

The average of the two FEV1 assessments will only be formed after multiple imputations so that if one of the two FEV1 assessments at a visit is missing, the average will be between the one available assessment and a second imputed assessment. In the situation when both FEV1 values at the randomization visit are missing, the values from preceding visits will be used as described in Section 9.4.1. Retrieved data after the discontinuation of study drug (retrieved drop-out) will remain in the analysis without further imputation for all treatment groups.

9.4.4 Supportive analyses

The primary and the secondary analyses will be repeated for the PPS.

The analysis results and the imputed data for different methods for imputing missing data will be compared.

In a sensitivity analysis, data will be analyzed in the same manner as for the primary analysis, but with missing data imputed using pattern mixture approach combining the jump to reference and the randomized-arm missing at random approaches (Carpenter, et al 2013) by distinguishing the following two cases:

1. A continued treatment effect for QAW039 150 mg patients being lost to follow-up for reasons likely to be unrelated to study drug (e.g. lost to follow-up, withdrew consent) will be assumed (randomized-arm missing at random).
2. Same treatment effect as placebo will be imputed for QAW039 150 mg patients that discontinue study drug and are lost to follow-up due to (or following a study drug discontinuation due to) lack of efficacy, adverse events or death (jump to reference).

If feasible, retrieved drop-out will be used to impute missing post-study drug discontinuation data as a sensitivity analysis. While retrieved drop-outs may be a particularly suitable basis for imputing data for non-retrieved drop-outs as it is most close to the ITT principal, this analysis may not be feasible or may require simplification of the imputation model, because observed post-study drug discontinuation data may be sparse.

The primary efficacy variable will also be analyzed using a repeated measurement analysis model in which treatment, age group (<18 vs. ≥18 years), use or non-use of a second asthma controller medication at study entry, region, visit (where FEV1 measurement is taken per

[redacted]

assessment schedule Table 6-1) and treatment-by-visit interaction will be included as fixed-effect factors, and baseline pre-dose FEV1 value as well as the baseline daytime asthma symptom score, baseline total daily SABA use and visit-by-baseline FEV1 as covariates. A common unstructured covariance matrix among visits for each treatment group will be used. The analysis will be performed based on all available on-treatment data up to week 12 and based on a likelihood method with an assumption of missing at random (MAR) for missing data assuming a hypothetical situation of continued treatment. On-treatment data is defined as all available data collected while patients took the study drug up to the Week 12 visit. The estimated treatment differences for all treatment comparisons will be tabulated along with the associated 95% confidence intervals and two-sided p-values.

In a tipping point analysis it will be explored by how much the imputed continuous missing data for the investigational and the placebo arm would have had to change compared to the imputations in the primary analysis in order to alter the trial conclusions. This will include an exploration of the possibility that patients with missing data from the investigational arm has worse outcomes than patients with missing data from the placebo arm.

In a further rank-based sensitivity analysis for the primary endpoint, patients will be ranked from smallest to largest in the following sequence with high ranks denoting greater efficacy.

1. patients that died
2. patients that withdrew from the trial
3. patients that completed the trial

Within category 3, patients with higher FEV1 change from baseline will be ranked greater than patients with lower change from baseline. Within categories 1 and 2, patients that withdraw from the trial later will get higher ranks than patients that withdraw early. In case patients withdraw at same study day, patients with higher FEV1 change from baseline at the last assessment are assigned a higher rank. In case of ties in the FEV1 values or no available post-baseline assessments of the primary variable, we use midranks. A Wilcoxon rank-sum test stratified by age group (<18 vs. ≥18 years), use or non-use of a second asthma controller medication, and region will be used to analyze the ranked data.

Subgroups

The primary and secondary analyses will also be conducted by subgroup including for key demographic (e.g., age, sex, race, BMI, geographic region) and disease related subgroups (e.g. number of exacerbations in the previous year, use or non-use of a second asthma controller medication, baseline FEV1 tertiles, ACQ tertiles, [redacted]).

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The secondary variables of this study are change from baseline in daytime asthma symptoms, change from baseline in total daily SABA use, and change from baseline in AQLQ+12 over the 12 weeks of treatment. The local significance level for each secondary null hypothesis will be determined based on the closed testing procedure specified by Figure 9-1. A range of

[redacted]

sensitivity analyses will be conducted on secondary endpoints under different missing data handling approaches in a similar fashion as those described in Section 9.4.4.

9.5.1.1 Daytime asthma symptoms in patients

Daytime asthma symptoms are evaluated through four questions and each of them will be rated on a scale of 0 to 6. Higher scores indicate more severe asthma-related symptoms. A mean score will be calculated for the responses to 4 questions. The main analysis of the secondary endpoint of daytime symptoms will be performed for all patients over the entire age range (12 years and older). The baseline of daytime asthma symptoms will be defined as the average of the mean daytime asthma symptom score during the placebo run-in period. The mean of change from baseline in the daytime symptom scores over the 12 weeks of treatment will be analyzed using an analysis of covariance (ANCOVA) model in a similar fashion as the primary efficacy variable. The null hypothesis is that the treatment difference compared to placebo over the 12 weeks of treatment = 0, while the alternative hypothesis is that the treatment difference to placebo over the 12 weeks of treatment ≠ 0. This model will be fitted to each of multiple imputations generated using a jump-to-reference approach as for the primary analysis.

The asthma diary included in this study to measure daytime asthma symptoms was validated in studies of patients aged 18 to 65 years (Santanello et al 1997). It was subsequently included as a measure in placebo-controlled studies of montelukast in patients aged 15 years and older (Reiss et al. 1998 and Malmstrom et al. 1999) and shown to be responsive to both montelukast and inhaled beclomethasone therapy in this age range. Given the performance characteristics, particularly the responsiveness to asthma therapies, of the asthma diary are known for patients aged 15 years and older, a supportive analysis of the secondary endpoint of daytime symptoms will be included and be limited to patients aged 15 years and older.

9.5.1.2 Total daily use of SABA

Total daily use of SABA (the number of puffs taken in the previous 24 hours) by the patient will be analyzed using ePEF/ eDiary data. The baseline of SABA use will be defined as the average of total daily SABA use during the placebo run-in period. The mean of change from baseline in the total daily use of SABA over the 12 weeks of treatment will be analyzed using an ANCOVA model in a similar fashion as the primary efficacy variable. The null hypothesis is that the treatment difference compared to placebo over the 12 weeks of treatment = 0, while the alternative hypothesis is that the treatment difference to placebo over the 12 weeks of treatment ≠ 0. This model will be fitted to each of multiple imputations generated using a jump-to-reference approach as for the primary analysis.

9.5.1.3 AQLQ+12

The change from baseline in AQLQ+12 at week 12 will be analyzed using an ANCOVA model in a similar fashion as the primary efficacy variable. The baseline of AQLQ+12 is defined as the last assessment prior to the first dose of study drug. Missing data of AQLQ+12 overall score will be imputed a jump-to-reference approach as for the primary analysis.

[redacted]

9.5.1.4 Summary statistics for the secondary variables

Summaries of absolute values and change from baseline in the three secondary variables will be presented by visit and by treatment group. Figures will be produced to visually show the mean and the mean change from baseline by visit over study period for each treatment group.

9.5.2 Safety variables

All safety data will be summarized for the safety set.

9.5.2.1 Adverse events

Adverse events after informed consent including asthma exacerbations will be summarized and listed.

Adverse events starting on or after the time of the first intake of study drug will be classified as treatment-emergent adverse events. Any adverse events that started during the study after informed consent before the time of the first intake of study drug will be classified as a prior adverse events and not included in tabulations of treatment emergent adverse events.

The following treatment emergent adverse event summaries will be produced, overall by system organ class and preferred term, overall by system organ class, preferred term and maximum severity, suspected drug-related adverse events by system organ class and preferred term, serious adverse events by system organ class and preferred term, and adverse events leading to permanent discontinuation of study-drug by system organ class and preferred term.

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

Selected adverse events of special interest may be summarized and analyzed as well.

9.5.2.2 Vital signs

Data of the vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) will be summarized by treatment and scheduled visit. The maximum and minimum systolic blood pressure, diastolic blood pressure, and pulse rate post-baseline (including values from post-baseline unscheduled and premature discontinuation visits) can also be summarized by treatment. Absolute body weight will be summarized by scheduled visit. The change from baseline to each scheduled post-baseline visit will be summarized by vital sign parameter, scheduled visit and treatment with standard descriptive statistics.

Notable values and notable changes from baseline in vital signs will be summarized.

9.5.2.3 Electrocardiogram (ECG)

The changes from baseline will be summarized by ECG parameter, schedule visit where baseline and post baseline values are both available.

The following quantitative variables will be summarized by treatment at each scheduled post-baseline visit: ventricular rate, QT interval, RR interval, PR interval, QRS duration, heart rate, and Fridericia's QTc. The maximum QTc (including values from post-baseline unscheduled and premature discontinuation visits) will also be summarized.

[redacted]

Notable values and notable changes from baseline in quantitative ECG variables will be summarized.

9.5.2.4 Laboratory data

All laboratory data will be listed with abnormal values flagged. The laboratory values and the change from baseline for continuous laboratory parameters will be summarized at each visit. A frequency table of results for categorical laboratory parameters will be produced for the whole study duration.

Shift tables relative to the normal reference ranges will be used to summarize the change from baseline to post-baseline for each laboratory parameter. For each laboratory parameter, the patients will be classified into one of the four mutually exclusive groups (low, normal, high, and low + high).

For selected laboratory parameters, the number and percentage of patients with newly occurring or worsening laboratory abnormalities meeting the clinically notable criteria will be summarized by laboratory parameter at any time-point over the treatment period, considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits. Patients with any newly occurring or worsening value meeting the clinically notable criteria will be counted under the applicable criteria.

[redacted]

9.7 Interim analyses

Not applicable.

9.8 Sample size calculation

The primary objective is to demonstrate that QAW039 150 mg is superior to placebo in pre-dose FEV1 following 12 weeks of post-baseline treatment. A difference of 112 mL in pre-dose FEV1 during treatment was assumed, which is similar to the model-averaged effect seen in study QAW039A2206. The standard deviation (SD) of 380 mL and between-visit correlation for pre-dose FEV1 was based on study QAW039A2206 in a similar population. A treatment discontinuation rate of 15% was assumed based on QAW039A2206 and it was assumed that half of the patients discontinuing study treatment would have week 12 FEV1

[redacted]

values. Simulations were used to determine the sample size due to the complex jump-to-reference missing data imputation approach for the primary analysis.

Under the outlined assumptions, a sample size of 650 patients (325 per arm) will be needed to have 90% power to observe a statistically significant difference between QAW039 and placebo at the two-sided 5% significance level in the primary analysis as shown in Table 9-1. The table also shows the sensitivity of the power to deviations from the assumptions.

Table 9-1 Result of power simulations for the primary variable

Treatment effect (mL)	Discontinuation rate	Sample size	Power
112	15%	650	90.3
112	20%	650	85.9
100	15%	650	80.9

Based on 10,000 simulated trials per scenario and 250 multiple imputations for each trial. Simulations were conducted using SAS/STAT® 13.1 software, Version 9.4 of the SAS System for Linux.

9.8.1 Power for the secondary objectives

If statistical significance is achieved in the primary test, the tests for the secondary variables will be performed. The local significance level for each secondary null hypothesis will be determined based on the closed testing procedure shown in Figure 9-1.

As differences in FEV1 to placebo for QAW039 150 mg once daily and montelukast 10 mg once daily appeared to be of similar magnitudes in study QAW039A2206, the power calculations for the two secondary objectives (change from baseline in daytime asthma symptoms and change from baseline in total daily SABA use) are based on the assumptions from the results of two studies comparing montelukast 10 mg once daily with placebo (Reiss et al 1998, Malmstrom et al 1999). These studies suggest an averaged difference of 0.26 for change from baseline in daytime asthma symptoms between montelukast and placebo after 12 weeks of treatment and a SD of 0.94. The two studies also suggest an averaged difference of -1.34 point difference in the change from baseline in the number of daily SABA puffs between montelukast and placebo with a standard deviation of 3.82. We assume a clinically important true improvement of at least 0.5 in AQLQ+12 after 12 weeks treatment for patients that remain on treatment and a standard deviation (SD) of 1. As shown in Table 9-2 all secondary endpoints have an adequate conditional power once the primary null hypothesis has been rejected, but will each have an even higher conditional power once the null hypotheses relating to the other secondary variables have been rejected.

[redacted]

Table 9-2 Power simulations for secondary variables

	Daytime asthma symptoms	Total daily rescue medication use	AQLQ+12
Difference of effect (δ)	-0.26	--1.34 number of puffs	0.5
SD (σ)	0.94	3.82 number of puffs	1
Local two-sided significance level once primary null hypothesis is rejected	0.0245	0.0245	0.001
Power	74%	97%	98%
Local two-sided significance level once primary and the other two secondary hypotheses are rejected	0.05	0.05	0.05
Power	83%	98%	> 99%

Power statements are based on 10,000 simulated trials per scenario and 250 multiple imputations using a jump-to-reference approach for each simulated trial. Simulations were conducted using SAS/STAT® 13.1 software, Version 9.4 of the SAS System for Linux. We assumed a treatment discontinuation rate of 15% with half of the patients discontinuing from study treatment completing the trial. The correlation structure was assumed to be the same as for the primary endpoint.
Abbreviation: AQLQ+12 (asthma quality of life questionnaire for 12 years and older).

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, United States Code of Federal Regulations (US CFR) 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if applicable after such consent has been provided by a legally acceptable representative(s) of the patient. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

For trials using an Electronic Informed Consent system where a date/timestamp is automatically generated, the system-generated date/timestamp is sufficient; additional input of the date at the time of consent is not required by the patient.

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

[redacted]

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

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

10.4 Publication of study protocol and results

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

10.5 Quality Control and Quality Assurance

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

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

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

11 Protocol adherence

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

[redacted]

additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction, 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.

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

11.1 Protocol amendments

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

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Santanello NC, Barber BL, Reiss TF et al (1997) Measurement characteristics of two asthma symptom diary scales for use in clinical trials. Eur Resp J; 10: 646-651.

[redacted]

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 Appendix 2 for specific liver event and laboratory test trigger definitions and follow-up requirements. See Appendix 3 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.

[redacted]

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.

Abbreviations: ULN (upper limit of normal), ALT (alanine aminotransferase), AST (aspartate aminotransferase), TBL (total bilirubin), ALP (alkaline phosphatase), INR (international normalized ratio).

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 Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	Discontinue the study treatment immediately Hospitalize if clinically appropriate Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	Discontinue the study treatment immediately Hospitalize, if clinically appropriate Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 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 Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	Discontinue the study treatment immediately Hospitalize if clinically appropriate	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

[redacted]

Criteria	Actions required	Follow-up monitoring
	Establish causality Complete liver CRF	
> 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 γGT 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 Complete liver 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 Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	Discontinue the study treatment immediately Hospitalize the patient Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	Consider study treatment interruption or discontinuation Hospitalization if clinically appropriate Establish causality Complete liver 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.

Abbreviations: ULN (upper limit of normal), ALT (alanine aminotransferase), AST (aspartate aminotransferase), TBL (total bilirubin), ALP (alkaline phosphatase), INR (international normalized ratio), PT, 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)≥ 1g/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;
- 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 (FEV_1) 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 [redacted] from any of the acceptable curves are recorded. (The greatest FEV1 [redacted] 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 5-2 "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 salbumatol/albuterol.

Reversibility is calculated as:

[redacted]

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

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

*NOTE: At visits with two pre-dose spirometry assessments (please see Table 6-1 for schedule of assessments) the FEV_1 from the 2nd pre-dose spirometry assessment (performed approximately 15 min prior to in-clinic witnessed study drug administration) should be used for FEV1 (pre-bronchodilator).

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, Culver B, Enright PL, Hankinson JL, Zheng J, Stocks J and the ERS Global Lung Function Initiative (2012) Multi ethnic reference values for spirometry for the 3-95 year age range: the global lung function 2012 equations. Report of the Global Lung Function Initiative (GLI), ERS Task Force to establish improved Lung Function Reference Values. Eur Resp J; 40:1324-1343.

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

[redacted]

18 Appendix 6: 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.

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For the purposes of calculating total daily dose for the study, if the table has the medication dose listed by dry powder inhaler (DPI), but not metered dose inhaler (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).

[redacted]

19 Appendix 7: Asthma Control Questionnaire (ACQ-5)

A SAMPLE of the Asthma Control Questionnaire – 5 is included below. The format of the administered test may vary.

ASTHMA CONTROL QUESTIONNAIRE
(SYMPTOMS ONLY)

For further information:

Elizabeth Juniper, MCSP, MSc
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20 Marcuse Fields,
Bosham,
West Sussex,
PO18 8NA. UK
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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]

20 Appendix 8 : Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12)

A SAMPLE of the Asthma Quality of Life Questionnaire for 12 years and older is included below. The format of the administered test may vary.

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

SELF-ADMINISTERED
(≥12 years)

For further information:

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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: _____

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

[redacted]