NOVARTIS

Global Clinical Development - General Medicine

QAW039/Fevipiprant

Clinical Trial Protocol CQAW039A2315 / NCT03052517

A 2-treatment period, randomized, placebo-controlled, multicenter parallel-group study to assess the safety of QAW039 when added to existing asthma therapy in GINA steps 3, 4 and 5 patients with uncontrolled asthma

Document type:	Clinical Trial Protocol
EUDRACT number:	2016-001560-11
Version number:	v01 Clean
Clinical trial phase:	III
Release date:	17-Jan-2018

Clinical Trial Protocol Template Version 3.3 (February 2017)

[redacted]

Table of contents

[redacted]

[redacted]

[redacted]

List of tables

[redacted]

List of figures

[redacted]

List of abbreviations

ACQ-5	Asthma Control Questionnaire 5
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse Event
AHR	Airway hyper-responsiveness
ALT	Alanine Aminotransferase
AQLQ	Asthma Quality of Life Questionnaire
AST	Aspartate Aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
AV block	Atrioventricular block
ATS/ERS	American Thoracic Society/European Respiratory Society
BMI	Body Mass Index
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CK	Creatine Kinase
CK-MB	Test measuring the amount of an isoenzyme of creatine kinase (CK) in your blood
Cmax	Maximum concentration
COA	Clinical Outcome Assessments
CPO	Country Pharma Organization
CQA	Compliance Quality Assurance
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRTh2	Chemoattractant receptor-homologous molecule expressed on Th2
CRO	Contract Research Organization
CT scan	Computed tomography scan
DAR	Dose administration record
DK-PGD2	13, 14-Dihydro-15-keto-prostaglandin D2
DMC	Data Monitoring Committee
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
FAS	Full analysis set
FCT	Film-coated Tablets
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 second

[redacted]

GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HbA1C	Glycated hemoglobin
hCG	Human chorionic gonadotropin
HFA	Hydrofluoralkane
hsCRP	High reactive C-reactive protein
IB	Investigator Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled corticosteroids
IDR	Idiosyncratic drug reactions
IEC	Independent Ethics Committee
IgE	Immunoglobulin
IL-5	Interleukin 5
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine system
LABA	Long-acting beta-agonists
LAMA	Long-acting Muscarinic Antagonist
LDH	Lactate dehydrogenase
LFT	Liver function test
LTRA	Leukotriene Receptor Antagonist
MAA	Marketing Authorization Application
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities
MID	Minimal important difference
MMRM	Mixed Model for Repeated Measures
MXR	Multixenobiotic resistance
NDA	New Drug Application
NP	New Patients not previously participating in a phase 3 study of QAW039
NYHA	New York Heart Association
OAT3	Organic Anion Transporters
OC/RDC	Oracle Clinical/Remote Data Capture
OCS	Oral corticosteroids
PGD2	Prostaglandin D2
P-gp	P-glycoprotein
POC	Proof of Concept
PP	Patients previously participating in a phase 3 study of QAW039
PRO	Patient Reported Outcome
QM	Quality management

[redacted]

QoL	Quality of Life
QTc	Corrected QT Interval
QTcF	QT interval corrected using Fridericia's formula
RAST	Radioallergosorbant Test
SABA	Short-acting beta-agonists
SAE	Serious Adverse Event
SAF	Safety Set
SCR	Screened set
SMQ	Standardized medical query
SoC	Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reactions
TD	Study Treatment Discontinuation
Th2	T helper type 2
UGT	UDP-glucuronosyltransferase
UK	United Kingdom
ULN	Upper limit normal
UNS	Unscheduled
WHO	World Health Organization
WoC	Withdrawal of Consent
y-GT	Gamma-glutamyl transpeptidase

[redacted]

Glossary of terms

Cohort	A specific group of patients/subjects fulfilling certain criteria
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electrocardiography	Electrocardiography is the process of recording the electrical activity of the heart over a period of time using electrodes placed on the skin.
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)
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.
Epoch (Period)	A portion of the study which serves a specific purpose. Typical epochs and/or 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.”
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients/subjects with established disease and in those with newly-diagnosed disease.
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
QAW039A	Fevipiprant
Fridericia’s Correction Formula	A formula which takes into account the physiologic shortening of the QT interval which occurs as the heart rate increases, permitting comparison of the QT interval across a range of rates.
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
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date

[redacted]

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]

Amendment 1

Amendment rationale

This protocol is being amended to remove references and discussions related to the Oral Corticosteroid Tapering Study (QAW039A2319), a Phase 3 study, which was cancelled due to business reasons before being initiated. The removal of references and analyses pertaining to QAW039A2319 required the following changes:

- [redacted]
- Updated Section 3.1 Study Design to remove the Oral Corticosteroid Tapering Study from the discussion involving the dose-response relationship;
- Updated Section 3.3 Rationale for dose/regimen, route of administration and duration of treatment to remove the Oral Corticosteroid Tapering Study from the discussion involving the dose-response relationship;
- Updated Section 5.3 Treatment assignment and randomization to remove the Oral Corticosteroid Tapering Study from the randomization scheme ;
- Updated Table 5-1 titled Randomization Allocation of Patients into Treatment Groups to remove the Oral Corticosteroid Tapering Study from the randomization ratio
- Updated Table 5-2 titled Medications allowed under certain conditions to remove references medication requirements for patients entering the trial from the Oral Corticosteroid Tapering Study;
- Updated Section 9.4.2 Statistical model, hypothesis, and method of analysis to remove the Oral Corticosteroid Tapering Study from the randomization stratum for the primary variables;
- Updated Section 9.5.2 Safety variables to remove the Oral Corticosteroid Tapering Study from the randomization stratum for the secondary safety endpoints;
- [redacted]
- Updated sample size in the Protocol Summary and Section 9.8 Sample size calculations as the removal of the Oral Corticosteroid Tapering Study requires the addition of more patients
- Updated Table 9-1 titled Assumed placebo event rates for power calculations and Table 9-2 titled Power (%) for non-multiplicity adjusted confidence interval to exclude no-difference versus placebo for the primary safety variables as the removal the Oral Corticosteroid Tapering Study changed power calculations.
- Added Table 9-3 titled Power (%) for a non-multiplicity adjusted confidence interval to exclude no-difference versus placebo for the primary safety variables based on different sample size scenarios.

[redacted]

Changes to the protocol

The described changes in the aforementioned amendment rationale are implemented throughout the protocol in the sections noted.

The opportunity was also taken to:

- Within the Protocol Summary and Section 2.1, one of the primary objectives was modified to state "study treatment discontinuations due to treatment emergent AEs". A patient may continue in the study after discontinuing study treatment. Therefore, the evaluation of treatment emergent AEs leading to study treatment discontinuations are more clinically relevant to the evaluation of drug safety.
- In inclusion criterion 6b, FEV1 has been aligned with the core Phase 3 studies in which the lower limit of the percent predicted FEV1 was removed from the protocols (Protocol summary, Section 4.1 [inclusion criteria]).
- Within the Protocol Summary, added a clarification HbA1c is a key safety assessment for new patients since prior patients would have already met this inclusion criterion in the previous study.
- Removal of the exclusion criteria within the Protocol Summary and Section 4.2 which stated "Patients who developed a condition during the prior phase 3 study of QAW039 that would exclude them from participating in the study" as this was already addressed by inclusion criteria 3a which states "Patient is able to safely continue into the study as judged by the investigator".
- Clarified exclusion 4b which is listed within the Protocol Summary and Section 4.2 as the intent was to exclude randomized patients in order to prevent duplicate patients. The new text states "Patients who have participated in another study of QAW039 (i.e. - the patient was randomized into another study of QAW039").
- Updated Section 3.6 Risks and Benefits in order to update the clinical experience and exposure provided in the latest Investigator's Brochure.
- Updated exclusion 17b in Section 4.2 to include allergic rhinitis as this could result in elevated eosinophils and is considered to be a common co-morbidity in patients with asthma.
- In Section 5.5.7 and Table 5-2, removal of text pertaining to the duration of a burst of rescue systemic corticosteroids as based on the investigator's clinical judgement.
- Added atopic dermatitis to Table 5-2 as this is another name for eczema.
- Within Table 5-4, corrected the minimum cessation of prohibited medications to start prior to Visit 1 which is consistent with the exclusion criteria in Section 4.2.
- Allow for as needed use of antihistamines within Table 5-2 Medications allowed under certain conditions as this class of medications is commonly used to treat allergic rhinitis, a common co-morbidity in patients with asthma.
- Shorten minimum cessation prior to Visit 1 for monoclonal antibodies, investigational or approved, for the treatment of asthma (e.g., omalizumab) from 6 months to 5 months within Table 5-2 Medications allowed under certain conditions. Cessation time for monoclonal antibodies used for the treatment of asthma was revised based on a review of the half-lives of all the monoclonal antibodies for the treatment of asthma

[redacted]

that became recently available. Approximately 5 half-lives (i.e., 5 months) is the required cessation time for monoclonal antibodies to treat asthma.

- Added Visit 401 clarification in Section 5.6.1 Study completion and post study treatment. Visit 401 can be conducted as a telephone visit only for males and females of non-child bearing potential. Females of child-bearing potential must come to the clinic for a pregnancy test.
- Reconciled discontinuation criterion in Section 5.6.2 with exclusion 7b by adding to the discontinuation criteria the following: "Patients with QTcF (Fridericia) ≥450 msec (male) or ≥460 msec (female) at Visit 201 on the ECG Analysis Report provided by the ECG core laboratory".
- Adjust the timing of the spirometry assessments so that assessments may be performed between 6:00 A.M. and 10:00 A.M. (± 1 hour) in Section 6 Visit schedule and assessments and Section 6.4.1. Based on investigator input, for practical reasons with visit scheduling and workflow, the time window to complete spirometry assessments was increased +/- 1 hour.
- Allowing a single rescreening of new patients in Section 6 Visit schedule and assessments and Section 6.4.2.
- Clarified in Section 6 Visit schedule and assessments that the RAST/ImmunoCap Test is only required for patients who have not previously participated in a study of QAW039
- Clarify in Section 6.4.1 [spirometry (FEV1 and FVC)] that the final spirometry assessments will be those provided by the spirometry overreaders of the central spirometry vendor.
- Clarify in Section 6.5.5 [electrocardiogram (ECG)] that the final ECG assessments will be those provided by the central cardiologist ECG overreaders of the central vendor.
- In Section 10.2 Informed consent procedures, added new Novartis template language
- In Section 10.5 Quality Control and Quality Assurance, added new Novartis template language

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

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in the protocol amendment.

[redacted]

Protocol summary

Protocol number	CQAW039A2315
Title	A 2-treatment period, randomized, placebo-controlled, multicenter parallel-group study to assess the safety of QAW039 when added to existing asthma therapy in GINA steps 3, 4 and 5 patients with uncontrolled asthma.
Brief title	Study of safety of QAW039 in male and female patients (≥ 12 years) with asthma inadequately controlled with standard-of-care asthma therapy.
Sponsor and Clinical Phase	Novartis, Phase 3
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The overall purpose of this study is to provide long-term safety data for fevipiprant (QAW039) (150 mg once daily and 450 mg once daily), compared with placebo, when added to the Global Initiative for Asthma (GINA) steps 3, 4, and 5 standard-of-care (SoC) asthma therapy (GINA 2016), in adult and adolescent (≥12 years) patients with moderate-to-severe asthma. This study is a 2-treatment period, randomized, multicenter parallel-group study. Treatment Period 1 is a 52-week, double-blind treatment period in which QAW039 or placebo is added to GINA steps 3, 4 and 5 (SoC) asthma therapy. Treatment Period 2 is an optional 104-week, single-blind treatment period in which patients will receive QAW039 or placebo added to GINA steps 3, 4 and 5 SoC asthma therapy. The study will include patients who completed a prior Phase 3 study of QAW039, as well as patients who have not previously participated in a study of QAW039. The inclusion of patients who received QAW039 in a prior Phase 3 study into Study A2315 will lengthen the duration of exposure to QAW039. The inclusion of patients who have not previously participated in a study of QAW039, along with patients who received placebo in a prior Phase 3 study, will allow for an increase in the number of patients with long-term exposure to QAW039. Therefore, by including these 2 categories of patients, the total number of patients treated with QAW039, as well as the duration of exposure to QAW039 treatment, will be substantially increased, supporting evaluation of the safety profile of QAW039.
Primary Objective(s)	<u>Treatment Period 1 (double-blind, 52-week treatment period):</u> In patients with moderate-to-severe asthma receiving SoC asthma therapy, to evaluate the long-term safety of QAW039 (150 mg once daily and 450 mg once daily), compared with placebo, as assessed by: • treatment emergent adverse events (AEs); • treatment emergent serious adverse events (SAEs); and • study treatment discontinuations due to treatment emergent AEs. <u>Treatment Period 1 and Treatment Period 2 combined:</u> In patients with moderate-to-severe-asthma receiving SoC asthma therapy, to evaluate the long-term safety of QAW039 (150 mg once daily and 450 mg once daily), compared with placebo, as assessed by: • treatment emergent AEs

	• treatment emergent SAEs; and • study treatment discontinuations due to treatment emergent AEs.
Secondary Objectives	Treatment Period 1 (double-blind, 52-week treatment period): In patients with moderate-to-severe asthma receiving SoC asthma therapy, to evaluate the long-term safety of QAW039 (150 mg once daily and 450 mg once daily), compared with placebo, as assessed by: • the rate of patients with at least 1 treatment emergent AE by primary system organ class; and. • the rate of treatment emergent patient deaths and patient hospitalizations (any visit to the hospital requiring an overnight stay or an emergency room visit greater than 24 hours) due to an asthma exacerbation. Treatment Period 1 and Treatment Period 2 combined: In patients with moderate-to-severe-asthma receiving SoC asthma therapy, to evaluate the long-term safety of QAW039 (150 mg once daily and 450 mg once daily), compared with placebo, as assessed by: • the rate of patients with at least 1 treatment emergent AE by primary system organ class; and • the rate of treatment emergent patient deaths and patient hospitalizations (any visit to the hospital requiring an overnight stay or an emergency room visit greater than 24 hours) due to an asthma exacerbation.
Study design	This study is a 2-treatment period, randomized, multicenter parallel-group safety study (Figure 3-1). Treatment Period 1 is a 52-week, double-blind treatment period in which QAW039 or placebo is added to GINA steps 3, 4 and 5 SoC asthma therapy. Treatment Period 2 is an optional 104-week, single-blind treatment period in which patients will receive QAW039 or placebo added to GINA steps 3, 4 and 5 SoC asthma therapy. The study will include the following: • Screening Period of up to 2 weeks to assess eligibility of new patients; • Treatment Period 1—double-blind period of 52 weeks • Treatment Period 2—single-blind period of 104 weeks; • Follow-up Period of 4 weeks, investigational and drug-free, following the last dose of study drug.
Population	The study population will include males and females aged ≥12 years with inadequately controlled asthma on treatment at GINA steps 3, 4 and 5). Two categories of patients will be enrolled: • Patients who completed a prior Phase 3 study of QAW039 on active study treatment, and • Patients with inadequately controlled asthma who have not previously participated in a study of QAW039.
Key Inclusion criteria	Patients completing a prior Phase 3 study of QAW039: • Informed consent and assent (if applicable). • Completion of the Treatment Period (on blinded study drug) of a prior Phase 3 study of QAW039. • Patient is able to safely continue into the study as judged by the investigator. Patients who have not previously participated in a study of QAW039: • Informed consent and assent (if applicable).

[redacted]

	• Male and female patients at a minimum age of 12 years (or higher minimum age limit as allowed by health authority and/or ethics committee/institutional review board (IRB) approvals)
	• A diagnosis of asthma (according to GINA 2016) for a period of at least 24 months prior to Screening visit (Visit 1).
	• Patients have been treated with GINA steps 4 or 5 standard-of-care (SoC) asthma therapy for at least 3 months prior to Visit 1. The doses must have been stable for at least 4 weeks prior to Visit 1.
	• Demonstration of inadequate control of asthma based on an Asthma Control Questionnaire (ACQ) score ≥1.5 at Visit 1.
	• For patients aged ≥18 years, forced expiratory volume in the first second (FEV1) of ≤85% of the predicted normal value for the patient, after withholding bronchodilators at Visit 1.
	• For patients aged 12 to <18 years, FEV1 of ≤90% of the predicted normal value for the patient, after withholding bronchodilators at Visit 1.
	• A clinical diagnosis of asthma supported by at least one of the following:
	  • An increase of ≥12% and ≥200 ml in FEV1 approximately 10 to 15 minutes after administration of 400 mcg of salbutamol/albuterol (or equivalent dose) prior to randomization. Spacer devices are not permitted during reversibility testing. All patients must perform a reversibility test at Visit 1.
	If reversibility is not demonstrated at Visit 1, the following historical information may be used:
	  • Documented evidence of reversibility performed according to American Thoracic Society/European Respiratory Society (ATS/ERS) (ATS/ERS 2005) or country-specific guidelines within the 2 years prior to Visit 1.
	  • Documented evidence of a positive airways hyper-responsiveness (AHR) test result within the 2 years prior to Visit 1, defined as a provoked fall in FEV1 of 20% by methacholine at ≤8 mg/ml (or histamine ≤10 mg/ml or acetylcholine <20 mg/mL) when not on ICS or ≤16 mg/ml (or histamine ≤20 mg/ml or acetylcholine <40 mg/mL) on ICS therapy performed according to ATS/ERS guidelines.

Key Exclusion criteria	<u>Patients completing a prior phase 3 study of QAW039:</u> • Pregnant or nursing (lactating) women. • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of study drug. • Patients who did not complete the Treatment Period on blinded study drug of the prior phase 3 study of QAW039 they participated in. • Inability to comply with all study requirements. • Patients who experienced a serious and drug-related AE in the prior phase 3 study of QAW039 they participated in. <u>Patients who have not previously participated in a study of QAW039:</u> • Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days, whichever is longer. • Patients who have participated in another trial of QAW039 (i.e., the patient was randomized into another study of QAW039).

[redacted]

	• Patients with a resting QTcF (Fridericia) ≥450 msec (male) or ≥460 msec (female) at Visit 1 or Visit 201 on the ECG Analysis Report provided by the ECG core laboratory. • Use of agents known to prolong the QT interval unless it can be permanently discontinued for the duration of the study. • 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. • 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 on >20 mg of simvastatin, > 40 mg of atorvastatin, >40 mg of pravastatin, or >2 mg of pitavastatin. Statin doses less than or equal to these doses as well as other statins will be permitted during the study. • Patients on rifampin, probenecid, ritonavir and valproic acid (i.e., medications blocking several pathways important for the elimination of QAW039 [broad range UDP-glucuronosyltransferase (UGT) inhibition and/or inhibition of organic anion transporters (OAT3), OATP1B3, multixenobiotic resistance (MXR) and p glycoprotein (P-gp)].
Study treatment	• QAW039 150 mg once daily • QAW039 450 mg once daily • Placebo to QAW039 150 mg once daily • Placebo to QAW039 450 mg once daily
Efficacy assessments	None for primary or secondary objectives
Key safety assessments	• AEs including SAEs • History and physical examinations • Vital signs • Hematology • Blood chemistry including but not limited to liver function tests (LFTs), metabolic panels, amylase, lipase and hsCRP. • CK-MB and Troponin I (in response to CK results outside of the normal range) • HbA1c (collected at screening only for new patients) • Urinalysis and urine chemistry • Pregnancy tests (females of childbearing potential) • Electrocardiogram (ECGs)
Other assessments	[redacted], ACQ [redacted]
Data analysis	The primary variables for the study are the time-to-first treatment emergent AE, time-to-first treatment emergent SAE and the time-to-first treatment emergent AE leading to discontinuation from study treatment. The primary variables will be analyzed on the safety set (SAF) by a stratified Cox regression model stratified by randomization stratum. • patients on QAW039 150 mg once daily treatment in Studies QAW039A2307 and QAW039A2314,

[redacted]

	• patients on QAW039 450 mg once daily treatment in Studies QAW039A2307 and QAW039A2314, • patients on placebo in Studies QAW039A2307and QAW039A2314, • patients on QAW039 150 mg once daily treatment in Studies QAW039A2316 and QAW039A2317, • patients on placebo in Studies QAW039A2316 and QAW039A2317, • patients who have not previously participated in a study of QAW039, and treatment group, severity of asthma (GINA treatment steps 3, 4 and 5), and region as fixed class effects. Hazard ratios comparing QAW039 450 mg once daily, QAW039 150 mg once daily, placebo treatments with regard to time to first treatment emergent AEs and their corresponding 95% profile likelihood confidence intervals will be presented. Safety summaries will be primarily based on on-treatment data for the safety set with selected tables also presented for all the data after the first intake of study drug, while all databased safety data will be listed. Approximately 1000 patients are expected to complete prior QAW039 Phase 3 studies and join the current Study A2315, based on the following assumptions. • In the prior QAW039 Phase 3 studies, 85% of randomized patients are expected to complete the prior study and eligible for participation in the current study. • It is estimated that 50% of those eligible patients from Studies A2307 and A2314 will enter in the current study • It is estimated that 25% of those eligible patients from Studies A2316 and A2317 will enter in the current study In addition, new patients (i.e., patients who have not previously participated in a study of QAW039) will also be recruited according to local regulatory requirements in certain countries. It is currently anticipated that approximately 570 newly recruited patients will be enrolled in the current study. Thus, the anticipated total sample size of this study is approximately 1,570 patients. This number of patients participating in the safety study will ensure 6-month exposure for each QAW039 dose clearly across the whole Phase 3 program in excess of the 300 to 600 patients (as well as in excess of 100 patients exposed for at least 1 year) suggested by ICH E1 at the time of the first regulatory submission for QAW039. The number of new patients and total patients may be subject to change depending on the actual participation of patients from prior QAW039 Phase 3 studies, the actual dropout rate in the current study and the local regulatory requirements.
Key words	Safety of QAW039, placebo-controlled, add-on to standard of care, uncontrolled severe asthma, female and male patients ≥12 years.

[redacted]

1 Introduction

1.1 Background

Asthma presents a major global health burden. Despite existing therapies, there is still significant unmet medical need in asthma, with an estimated 300 million people affected worldwide. The World Health Organization (WHO) estimates that 15 million disability–adjusted life years are lost annually due to asthma, representing 1% of the total global burden. Annual worldwide deaths have been estimated at 250,000 (Masoli, et al 2004).

Severe asthma is defined as asthma that requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids to prevent it from becoming "uncontrolled" or that remains "uncontrolled" despite this therapy. Severe asthma is a heterogeneous condition consisting of phenotypes such as eosinophilic asthma (Chung, et al 2014). This subgroup has also been defined as "refractory" asthma (Proceedings of the ATS workshop on refractory asthma 2000).

Recurrent exacerbations are a major problem in some patients with severe asthma and may be more common in the subgroup with eosinophilic airway inflammation (Haldar, et al 2009). A number of therapeutic interventions impact on eosinophilic airway inflammation as measured by sputum eosinophilia. These include inhaled and oral corticosteroids (OCS) and a number of biologic therapies (including anti-interlukin-5 (IL-5), anti-IL-5R, anti-immunoglobulin (IgE), and anti-IL-4Rα therapies). Generally, when a therapeutic agent has successfully suppressed sputum eosinophil levels, evidence of efficacy, as measured by a reduction in asthma exacerbations, has also been demonstrated (Pavord, et al 2012; Nowak, et al 2015; Wenzel, et al 2013; Takaku, et al 2013).

In more severe asthma, inhaled and oral corticosteroids may not be as effective in reducing sputum eosinophilia as they are in milder disease (Wenzel 2005; Nair, et al 2009). Consequently, there remains a need for well tolerated, easily-administered, anti-inflammatory therapies with the capability of supressing sputum eosinophilia and reducing asthma exacerbations, particularly, for those patients appearing to be steroid resistant.

Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTh2) is a receptor for prostaglandin D2 (PGD_2) which is one of the major prostanoid inflammatory mediators identified in asthma. Fevipiprant (QAW039) is a CRTh2 antagonist expected to provide benefit in asthma by binding to CRTh2 receptors on eosinophils, basophils, and T lymphocytes in the blood and tissues; thus, inhibiting migration and activation of these cells into the airway tissues and blocking the PGD_2-driven release of T helper type 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 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 (CQAWA2201, CQAWA2206, and CQAWA2208) 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

Study CQAWA2315 (also referred to as Study A2315 in this document) is a 2-treatment period, randomized, multicenter, parallel-group study. **Treatment Period 1** is a 52-week, double-blind treatment period in which QAW039 or placebo is added to GINA steps 3, 4 and 5 standard-of-care (SoC) asthma therapy. **Treatment Period 2** is an optional 104-week, single-blind treatment period in which patients may elect to continue to receive QAW039 or placebo added to GINA steps 3, 4 and 5 SoC asthma therapy.

The purpose of this study is to provide long-term safety data for QAW039 (150 mg once daily and 450 mg once daily), compared with placebo, when added to GINA steps 3, 4, and 5 SoC asthma therapy (GINA 2016), in adult and adolescent (≥12 years) patients with moderate-to-severe asthma. The study will include patients completing a prior Phase 3 study of QAW039, as well as patients who have not previously participated in a study of QAW039. The inclusion of patients who received QAW039 in a prior Phase 3 study into Study A2315 will lengthen the duration of exposure to QAW039. The inclusion of patients who have not previously participated in a study of QAW039, along with patients who received placebo in a prior Phase 3 study, will allow for an increase in the number of patients with long-term exposure to QAW039. Therefore, by including these 2 categories of patients, the total number of patients treated with QAW039, as well as the duration of exposure to QAW039 treatment, will be substantially increased, supporting evaluation of the safety profile of QAW039.

2 Study objectives and endpoints

2.1 Primary objective(s)

Treatment Period 1 (double-blind, 52-week treatment period):

In patients with moderate-to-severe asthma receiving SoC asthma therapy, to evaluate the long-term safety of QAW039 (150 mg once daily and 450 mg once daily), compared with placebo, as assessed by:

- treatment emergent adverse events (AEs);
- treatment emergent serious adverse events (SAEs); and
- study treatment discontinuations due to treatment emergent AEs.

Treatment Period 1 and Treatment Period 2 combined:

In patients with moderate-to-severe-asthma receiving SoC asthma therapy, to evaluate the long-term safety of QAW039 (150 mg once daily and 450 mg once daily), compared with placebo, as assessed by:

- treatment emergent AEs
- treatment emergent SAEs; and
- study treatment discontinuations due to treatment emergent AEs.

[redacted]

2.2 Secondary objective(s)

Treatment Period 1 (double-blind, 52-week treatment period):

In patients with moderate-to-severe asthma receiving SoC asthma therapy, to evaluate the long-term safety of QAW039 (150 mg once daily and 450 mg once daily), compared with placebo, as assessed by:

- the rate of patients with at least 1 treatment emergent AE by primary system organ class; and
- the rate of treatment emergent patient deaths and patient hospitalizations (any visit to the hospital requiring an overnight stay or an emergency room visit greater than 24 hours) due to an asthma exacerbation.

Treatment Period 1 and Treatment Period 2 combined:

In patients with moderate-to-severe-asthma receiving SoC asthma therapy, to evaluate the long-term safety of QAW039 (150 mg once daily and 450 mg once daily), compared with placebo, as assessed by:

- the rate of patients with at least 1 treatment emergent AE by primary system organ class; and
- the rate of treatment emergent patient deaths and patient hospitalizations (any visit to the hospital requiring an overnight stay or an emergency room visit greater than 24 hours) due to an asthma exacerbation.

[redacted]

[redacted]

3 Investigational plan

3.1 Study design

This study is a 2-treatment period, randomized, multicenter parallel-group safety study (Figure 3-1). Treatment Period 1 is a 52-week, double-blind treatment period in which QAW039 or placebo is added to GINA steps 3, 4 and 5 SoC asthma therapy. Treatment Period 2 is an optional 104-week, single-blind treatment period in which patients will receive QAW039 or placebo added to GINA steps 3, 4 and 5 SoC asthma therapy. **Note:** For the purpose of this study, single-blind will mean investigators and patients will remain blinded while all Novartis personnel will be unblinded.

Eligible patients will include patients completing a prior Phase 3 study of QAW039, as well as patients who have not previously participated in a study of QAW039.

Patients who successfully complete the treatment period of a prior Phase 3 study of QAW039 will be permitted to enter Study A2315 directly upon the completion of the treatment period of the prior study without completing an off drug follow-up period in the prior study. For these patients completing a prior Phase 3 study of QAW039, the last visit of the treatment period in the prior study and Visit 1 of Study 2315 will occur on the same day (i.e., on the last day of study drug treatment in the prior study). Additionally, for patients completing a prior Phase 3 study of QAW039, Visit 201 of Study 2315 will occur the following day (1 day after completion of the last visit of the treatment period of the prior study and Visit 1 of this study [Study A2315]) so there is not any interruption in study drug treatment.

For patients who have not previously participated in a study of QAW039, Visit 1 and Visit 201 of Study 2315 will occur approximately two weeks apart (i.e., Visit 201 should occur approximately two weeks after Visit 1 in Study 2315). This will allow for review of inclusion/exclusion criteria and laboratory values.

For Treatment Period 1 in Study A2315, an informed consent (and assent, if applicable) may be obtained within 14 days prior to or at Visit 1 and before any study-related assessments or procedures are performed. For patients who participated in a prior Phase 3 study, the consent (and assent, if appropriate) for Treatment Period 1 of Study A2315 may be obtained on the last day of the treatment period of the prior Phase 3 study.

For Treatment Period 2, an informed consent (and assent if applicable) will be obtained at Visit 301 for those patients agreeing to participate in this treatment period.

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 visits with spirometry (which includes Visit 1) (See Section 5.5.8).

The study will include the following:

Screening Period of up to 2 weeks to assess eligibility of new patients;

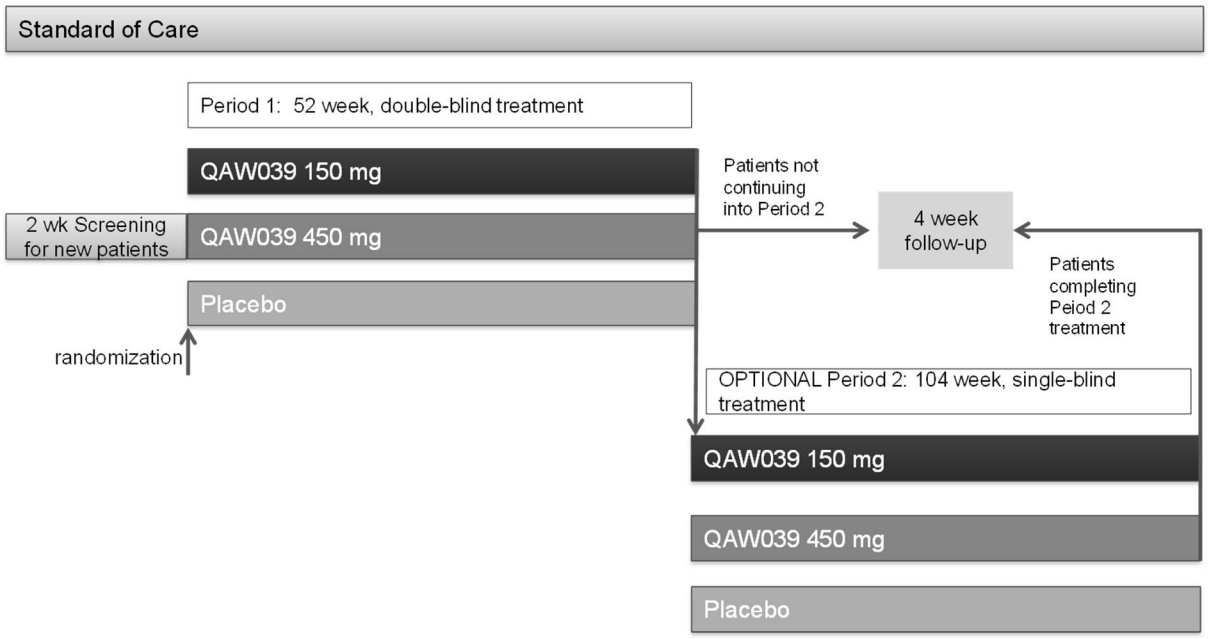
Treatment Period 1—double-blind period of 52 weeks;

Treatment Period 2—single-blind period of 104 weeks;

Follow-up Period of 4 weeks, investigational and drug-free, following last dose of study drug.

[redacted]

Figure 3-1 Study design



Note: As information becomes available from ongoing studies, a decision to proceed with one or both doses of QAW039 in either a controlled or an open label fashion may take place during the conduct of this study.

In Treatment Period 1, patients meeting eligibility criteria will be randomized to 1 of 3 treatments (QAW039 150 mg once daily, QAW039 450 mg once daily, or placebo once daily) in an approximate ratio of 3:3:1. During Treatment Period 2, patients will continue receiving the same treatment they received in Treatment Period 1.

During Treatment Period 1, investigators, patients, and Novartis personnel monitoring the study will be blinded to study treatment. During Treatment Period 2, investigators and patients will continue to remain blinded to study treatment while Novartis personnel monitoring the study will not be blinded to treatment.

To support worldwide registration of QAW039 and to address health authority requests, there may be interim analyses of the study. Should an interim analysis occur during Treatment Period 1, Novartis personnel monitoring the study will be unblinded to study treatment; however, investigators and patients will continue to remain blinded to study treatment.

During Treatment Period 1 and Treatment Period 2, all patients will continue to receive SoC asthma therapy according to the investigator's judgment. During Treatment Period 1 and Treatment Period 2 of this study, investigators may adjust a patient's SoC asthma therapy according to their clinical judgment.

Clinic visits will be scheduled approximately 4 weeks after randomization, approximately 13 weeks after randomization, and then at approximately 13-week intervals during the active-treatment periods. A follow-up visit will occur approximately 4 weeks (i.e., approximately 30

days) following the last dose of study therapy to complete safety assessments and pregnancy testing (if applicable). **Please refer to the assessment schedule (Table 6-1) for a list of procedures to be conducted at each visit.**

Two doses of QAW039 (150 mg once daily and 450 mg once daily) have been included in this study (see Section 3.3 for a rationale supporting inclusion of these doses). The 2 doses of QAW039 included in this study are also being evaluated in other Phase 3 studies of QAW039 in patients of various asthma severities. Two studies (CQAW039A2307 and QAW039A2314) will evaluate the dose-response relationship of QAW039 (dosed at 150 mg once daily and 450 mg once daily) in patients with severe asthma.

Periodic unblinded safety reviews by an independent Data Monitoring Committee (DMC) will be conducted during the course of the study.

3.2 Rationale for study design

Asthma is a chronic condition with medications used in patients over long periods of time; therefore, it is important to assess the safety profile of new therapies (such as QAW039) in this setting (i.e., during long-term treatment) to determine whether the safety profile of the respective therapy is maintained with long-term treatment. The purpose of this study is to provide long-term safety data for QAW039 (150 mg once daily and 450 mg once daily), compared with placebo, when added to GINA steps 3, 4, and 5 SoC asthma therapy (GINA 2016), in adult and adolescent (≥12 years) patients with moderate-to-severe asthma.

The 2-treatment period, randomized, multicenter parallel-group, study design supports the assessment of the long-term safety profile of QAW039 as add-on treatment for patients with asthma otherwise treated according to GINA 2016 (steps 3, 4, and 5) guidelines. The study is randomized with a control arm (placebo plus standard of care), because a controlled study provides a better assessment of AE data than an open, uncontrolled study in which there is no ability to compare the AEs on treatment with a known control. Additionally, a control arm helps to reduce any potential bias in reporting of adverse events that would result from an open-label study design. The study duration of 3 years (156 weeks) will provide sufficient time for the assessment of the long-term safety profile of QAW039.

Treatment Period 1 is a 52-week, double-blind treatment period. This treatment period will permit a blinded, controlled evaluation of 52-week safety data. Treatment Period 2 is an optional 104-week, single-blind treatment period which will provide longer-term safety data in a controlled, single-blind fashion. Given the long duration of the study and the inclusion of placebo (in addition to SoC asthma therapy) in Treatment Period 1 and Treatment Period 2, investigators will be permitted to adjust a patient's SoC therapy according to their medical judgment during the study.

The study will include patients who completed a prior Phase 3 study of QAW039, as well as patients who have not previously participated in a study of QAW039. The inclusion of patients who received QAW039 in a prior Phase 3 study into Study A2315 will lengthen the duration of exposure to QAW039. The inclusion of patients who have not previously participated in a study of QAW039, along with patients who received placebo in a prior Phase 3 study, will allow for an increase in the number of patients with long-term exposure to QAW039. Therefore, by including these 2 categories of patients, the total number of patients treated with QAW039, as well as the duration of exposure to QAW039 treatment, will be substantially increased, supporting evaluation of the safety profile of QAW039.

The endpoints included in this study will assess parameters of the safety profile (treatment emergent AEs, discontinuations due to AEs, laboratory values, and ECGs) of QAW039 over 3 years (156 weeks) of treatment.

Screening Period

The screening period allows for assessment of patient entry criteria, for patients to become familiar with study measurements, and to collect baseline values.

Treatment Period

During Treatment Period 1, patients will receive QAW039 150 mg once daily plus SoC asthma therapy, QAW039 450 mg once daily plus SoC asthma therapy, or placebo plus SoC asthma therapy, respectively, over a 52-week treatment duration in a double-blind fashion. QAW039 at both doses and placebo will be given as oral tablets.

Overall, the ratio of patients in this study receiving QAW039 150 mg once daily, QAW039 450 mg daily, and placebo will be approximately 3:3:1. The overall 3:3:1 randomization ratio allows for a larger number of patients to receive QAW039 (at either the 150 mg or 450 mg dose) plus SoC asthma therapy compared with those who will receive placebo plus SoC asthma therapy.

During Treatment Period 2, patients will receive the same medication they received during Treatment Period 1 (QAW039 150 mg once daily plus SoC asthma therapy, QAW039 450 mg once daily plus SoC asthma therapy, or placebo plus SoC asthma therapy) over a 104-week treatment duration in a single-blind fashion.

The last dose of study drug will be given at Week 156 and the final assessment for the treatment period will be at Week 160.

Follow-up period

This period will monitor the safety and tolerability profile for 4 weeks after the last dose of study drug.

The investigator must provide appropriate advice on the continued use of basic 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.

[redacted]

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

QAW039 will be administered at doses of 150 mg once daily and 450 mg once daily as oral film-coated tablets (FCTs) in this study. The rationale supporting the inclusion of these 2 doses is below.

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

- At a dose of 450 mg once daily, >98% receptor occupancy is expected for the entire dosing interval in a "typical patient" at steady state allowing inhibition of eosinophil migration over the entire treatment interval.
- A 500 mg once daily dose of QAW039 was efficacious on the endpoint of predose FEV1 in a sub-set of patients with % predicted FEV1 <70% at Baseline in Study CQAW039A2201 proof-of-concept study (PoC).
- In study CQAW039A2206, a 450 mg total daily dose of QAW039 was also efficacious on the endpoint of predose FEV1.
- A total daily dose of 450 mg (225 mg twice daily) was evaluated in Study CQAW039A2208 in patients with severe asthma as add-on to SoC asthma therapy. In this study, QAW039 caused significant reduction of sputum eosinophilia in patients with severe eosinophilic asthma. The reduction in sputum eosinophils was comparable to that observed with the anti-IL5 antibodies, Mepolizumab (Pavord, et al 2012) and Reslizumab (Castro, et al 2011 and Castro, et al 2015). An association between reduction of eosinophilic airway inflammation and frequency of exacerbations has been reported in the literature (Haldar, et al 2009; Pavord, et al 2012;Nowak et al 2015; Wenzel, et al 2013; Takaku, et al 2013), suggesting QAW039 may also cause a reduction in the frequency of asthma exacerbations in patients with severe eosinophilic asthma.

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 predose FEV1 in a prior dose-ranging study (Study CQAW039A2206) in patients with moderate-to-severe asthma (GINA treatment steps 4 and 5) as add-on to low-dose ICS. This dose is 0.5 log lower than highest dose.

Since the QAW039 dose of 150 mg was considered the optimal dose (i.e., lowest dose providing maximal efficacy) in a prior dose-ranging study, doses lower than 150 mg will not be included in this study.

The 2 doses of QAW039 included in this study are also being evaluated in other Phase 3 studies of QAW039 in patients of various asthma severities:

- patients with severe asthma at GINA steps 4 and/or 5: QAW039 at 150 mg once daily and 450 mg once daily are being evaluated in CQAW039A2307 and CQAW039A2314; and
- patients with moderate-to-severe asthma at GINA steps 3 and 4: QAW039 at 150 mg once daily is being evaluated in CQAW039A2316 and CQAW039A2317.

Note: Two studies (CQAW039A2307 and QAW039A2314) will evaluate the dose-response relationship of QAW039 (dosed at 150 mg once daily and 450 mg once daily) in patients with

[redacted]

severe asthma. [redacted]

3.4 Rationale for choice of comparator

In both Treatment Period 1 and Treatment Period 2, patients will receive QAW039 or placebo administered as add-on therapy to SoC asthma therapy.

The inclusion of placebo will permit a controlled assessment of safety parameters in patients who are treated with QAW039, in comparison to those continuing solely on existing SoC asthma therapy, and reduce any potential bias in reporting of adverse events that would be introduced if the study was conducted in an open-label fashion.

This study does not include an active comparator since QAW039 will be given as add-on therapy to SoC asthma therapy in patients with moderate-to-severe asthma (GINA steps 3, 4 and 5).

3.5 Purpose and timing of interim analyses/design adaptations

An independent Data Monitoring Committee (see Section 8.4) will conduct periodic unblinded safety reviews of the accumulating data from this study and other Phase 3 studies of the QAW039 asthma development program to ensure safety of study participants. To support worldwide registration of QAW039 and to address health authority requests, interim analyses of Study A2315 may be conducted with results being submitted to health authorities. Once all patients have completed or discontinued Treatment Period 1, a report based on Treatment Period 1 data will be produced and results may be published.

3.6 Risks and benefits

QAW039 is a potent and highly selective oral CRTh2 receptor antagonist being developed as a potential therapy for patients with severe asthma. CRTh2 is a receptor for PGD_2 which mediates the activation and migration of 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 fevipiprant includes 16 studies: 13 (seven in healthy volunteers and six in patients) have completed and three (two in patients and one in healthy volunteers) are ongoing. The completed Phase II studies consist of four in patients with asthma, one in patients with allergic rhinitis and one in patients with atopic dermatitis (AD). Two Phase III studies (CQAW039A2307 and CQAW039A2314) in asthma and one Phase I study in healthy volunteers (CQAW039A2116) are ongoing. As of January 2017 over 1730 subjects have been exposed to QAW039.

Four Phase 2 studies examined the effect of fevipiprant in patients with asthma across the range of asthma severities (mild to severe). In these studies, QAW039 demonstrated an effect

[redacted]

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-2017. 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 subjects 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 et al 2009), as well as patients on any statins with high CK levels (>2 X ULN) 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 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 benefits and risks.

4 Population

The study population will include males and females aged ≥12 years with moderate-to-severe asthma on SoC asthma therapy at GINA steps 3, 4, and 5. Two categories of patients will be enrolled:

- Patients completing a prior phase 3 study of QAW039: Patients who completed a prior Phase 3 study of QAW039 on active study treatment (i.e., did not discontinue blinded study treatment prematurely); and
- Patients with inadequately controlled asthma who have not previously participated in a study of QAW039.

[redacted]

4.1 Inclusion criteria

Patients completing A PRIOR PHASE 3 STUDY OF QAW039:

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

1a. Informed consent and assent (if applicable) may be obtained at Visit 1 or within 14 days of Visit 1. Informed consent and assent (if applicable) must be obtained before any study assessment is performed.

2a. Completion of the treatment period (on blinded study drug) of a prior Phase 3 study of QAW039 (i.e., did not discontinue blinded study treatment prematurely).

3a. Patient is able to safely continue into the study as judged by the investigator.

Patients who HAVE NOT PREVIOUSLY PARTICIPATED IN A STUDY OF QAW039:

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

1b. Informed consent and assent (if applicable) may be obtained at Visit 1 or within 14 days of Visit 1. Informed consent and assent (if applicable) must be obtained before any study assessment is performed.

2b. Male and female patients at a minimum age of 12 years (or higher minimum age limit as allowed by health authority and/or ethics committee/institutional review board (IRB) approvals).

3b. Patients must have a diagnosis of asthma (according to GINA 2016) for a period of at least 24 months prior to screening visit (Visit 1).

4b. Patients have been treated with GINA steps 4 or 5 standard-of-care (SoC) asthma therapy for at least 3 months prior to Visit 1. The doses must have been stable for at least 4 weeks prior to Visit 1.

5b. Demonstration of inadequate control of asthma based on an ACQ score ≥1.5 at Visit 1.

6b. For patients aged ≥18 years, FEV1 of ≤85% of the predicted normal value for the patient, after withholding bronchodilators at Visit 1. For patients aged 12 to <18 years, FEV1 of ≤90% of the predicted normal value for the patient, after withholding bronchodilators at Visit 1.

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 of LABA and ICS given twice daily ≥ 12 hours;
- Fixed dose combinations of LABA and ICS given once daily ≥ 24 hours; and
- Long-acting muscarinic antagonists (LAMAs) ≥ 24 hours.

7b. A clinical diagnosis of asthma supported by at least one of the following:

- 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 dose) prior to randomization. Spacer devices are not permitted during reversibility testing. All patients must perform a reversibility test at the Visit 1.

[redacted]

If reversibility is not demonstrated at Visit 1, the following historical information may be used:

- Documented evidence of reversibility performed according to American Thoracic Society/European Respiratory Society (ATS/ERS) (ATS/ERS 2005) or country-specific guidelines within the 2 years prior to Visit 1. Where a patient is assessed as eligible based on historical evidence of reversibility, a copy of the original printed spirometry report with relevant spirometry tracings must be available as source documentation.
- Documented evidence of a positive airways hyper-responsiveness (AHR) test result within the 2 years prior to Visit 1, defined as a provoked fall in FEV_1 of 20% by methacholine at ≤8 mg/ml (or histamine ≤10 mg/ml or acetylcholine <20 mg/mL) when not on ICS or ≤16 mg/ml (or histamine ≤20 mg/ml or acetylcholine <40 mg/mL) on ICS therapy performed according to ATS/ERS guidelines.

4.2 Exclusion criteria

Patients completing A PRIOR PHASE 3 STUDY OF QAW039:

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

1a. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.

2a. 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 basic 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 subjects on the study, the vasectomized male partner must be the sole partner for that subject.
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) if allowed as basic method of contraception by local regulations. For United Kingdom (UK): 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).

[redacted]

*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.

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.

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

3a. Patients who did not complete the treatment period on blinded study drug of the prior Phase 3 study of QAW039 they participated in.

4a. Inability to comply with all study requirements.

5a. Patients who experienced a serious and drug-related AE in the prior Phase 3 study of QAW039 they participated in.

Patients who HAVE NOT PREVIOUSLY PARTICIPATED IN A STUDY OF QAW039:

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

1b. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days, whichever is longer.

2b. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes to QAW039.

3b. History of lactose or milk sensitivity.

4b. Patients who have participated in another study of QAW039 (i.e., the patient was randomized into another study of QAW039).

5b. Patients with a history or current diagnosis of ECG abnormalities indicating significant risk of safety for patients/subjects participating in the study such as: clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree atrioventricular (AV) block without a pacemaker.

6b. History of familial long QT syndrome or known family history of Torsades de Pointes.

7b. Patients with a resting QTcF (Fridericia) ≥450 msec (male) or ≥460 msec (female) at Visit 1 or Visit 201.

8b. Use of agents known to prolong the QT interval unless it can be permanently discontinued for the duration of the study.

[redacted]

9b. 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.

10b. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.

11b. 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 basic 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 subjects on the study, the vasectomized male partner must be the sole partner for that subject.
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) if allowed as basic method of contraception by local regulations. For UK: 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*. *Not approved in Japan
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).

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.

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.

12b. 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 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.).

[redacted]

13b. Patients who have had an asthma exacerbation requiring systemic corticosteroids, hospitalization, or emergency room visit within 6 weeks prior to Visit 1. If patients experience an asthma exacerbation requiring systemic corticosteroids, hospitalization or emergency room visit during screening, they may be rescreened once, ≥6 weeks after recovery from the exacerbation.

14b. 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 from their respiratory tract infection or asthma worsening.

15b. 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.

16b. 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 1] CT scan proof is available), sarcoidosis interstitial lung disease, cystic fibrosis, and tuberculosis.

17b. Patients with a history of conditions other than asthma, allergic rhinitis or sinusitis 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.

18b. Patients with uncontrolled diabetes having an HbA1c test result ≥8% at the Visit 1 laboratory test.

19b. 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
- AST or ALT>2.0 X ULN or total bilirubin >1.3 X ULN
- Estimated Glomerular Filtration Rate (eGFR) by the Modification of Diet in Renal Disease (MDRD) equation or Bedside Schwartz equation <55 mL/minute/1.73 m2

20b. 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.

21b. Patients with a history of myocardial infarction 12 months of Visit 1.

[redacted]

22b. Patients with serious co-morbidities including, but not limited to, neurodegenerative diseases, rheumatoid arthritis and other autoimmune diseases.

23b. Patients with a history of alcohol or drug abuse within 12 months prior to Visit 1.

24b. Patients with a weight <30 kg.

25b. Patients aged 12 to <18 years below the 3rd percentile for weight by age (based on local growth charts or the United States Center for Disease Control growth charts, if local growth charts are not available) (Center for Disease Control and Prevention 2000).

26b. Patients receiving any medications in the classes listed in Table 5-4 must be excluded unless they meet the criteria as specified in Table 5-4.

27b. Patients receiving medications in the classes listed in Table 5-2 must be excluded unless the medication has been stabilized for the specified period and the stated conditions have been met.

28b. 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.

29b. Inability to comply with all study requirements.

30b. Patients with any medical or psychological condition that, in the investigators opinion, renders the patient unable to understand the nature, scope, and possible consequences of the study.

31b. Patients with a history of being unable to swallow tablets.

32b. Patients who have received methotrexate, oral gold, troleandomycin, cyclosporine azathioprine or any experimental anti-inflammatory therapies within 6 months of Visit 1.

33b. Patients with regular use of oral or systemic corticosteroids for diseases other than asthma within the 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 1.

34b. 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.

35b. Patients with a history of immunodeficiency disease or hepatitis B or hepatitis C.

36b. Patients on any statin therapy with a CK level >2 X ULN at Visit 1.

37b. 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.

38b. Patients on rifampin, probenecid, ritonavir and valproic acid (i.e., medications blocking several pathways important for the elimination of QAW039 [broad range UGT inhibition and/or inhibition of OAT3, OATP1B3, MXR and P-gp]).

[redacted]

39b. Patients who have received biologic therapy for the treatment of asthma within 5 months of Visit 1.

40b. No person directly associated with the administration of the study is allowed to participate as a study subject.

41b. 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 investigational treatment will be supplied by Novartis to the study sites:

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

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

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

5.1.2 Additional treatment

No additional maintenance asthma treatment beyond investigational treatment will be provided for this trial.

All patients will be provided with SABAs (salbutamol/albuterol/other SABA) which they will be instructed to use throughout the study as rescue medication on an ‘as needed basis’.

SABAs will either be supplied to the investigator sites locally by Novartis or be provided by the study center and reimbursed by Novartis.

5.2 Treatment arms

Treatment Period 1

Overall, the ratio of patients in this study receiving QAW039 150 mg once daily, QAW039 450 mg daily, and placebo will be approximately 3:3:1. At Visit 201, patients will be assigned to receive:

[redacted]

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

Patients will be instructed to take their study medication (QAW039 or placebo) once daily at approximately the same time each morning without regard to time of food intake.

SoC asthma therapy will be taken as directed by the investigator.

Treatment Period 2

Patients will be assigned at Visit 301 to the same treatment they received in Treatment Period 1. Patients will receive either:

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

Patients will be instructed to take their study medication (QAW039 or placebo) once daily at approximately the same time each morning without regard to time of food intake.

SoC asthma therapy will be taken as directed by the investigator.

5.3 Treatment assignment and randomization

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

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

[redacted]

Note: Enrollment to patient strata may be restricted by the Sponsor prior to the end of overall recruitment in order to achieve the desired distribution in the trial population.

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

Details of randomization scheme

Overall, there is an **approximately 85% chance patients will receive QAW039 in Study A2315.** For **patients who participated in a prior Phase 3 study**, there is **at least 57% chance a patient will remain on the same QAW039 dose** they received in the prior study in Study A2315.

Patients completing A PRIOR PHASE 3 STUDY OF QAW039 with 3 treatment arms (QAW039A2307 and QAW039A2314) will be randomized to treatment in Study A2315 as delineated below.

- Patients who received QAW039 450 mg once daily in a prior study will be assigned to QAW039 450 mg once daily, QAW039 150 mg once daily, or placebo in a 5:1:1 ratio.
- Patients who received QAW039 150 mg once daily in a prior study will be assigned to QAW039 450 mg once daily, QAW039 150 mg once daily, or placebo in 1:5:1 ratio.
- Patients on placebo in a prior study will be assigned to QAW039 450 mg once daily, QAW039 150 mg once daily, or placebo in 3:3:1 ratio.

Patients completing A PRIOR PHASE 3 STUDY OF QAW039 with 2 treatment arms (QAW039A2316, QAW039A2317) will be randomized to treatment in Study A2315 as delineated below.

- Patients who received QAW039 150 mg once daily in a prior study will be assigned to QAW039 450 mg once daily, QAW039 150 mg once daily, or placebo in 2:4:1 ratio.
- Patients who received placebo in prior study will be assigned to QAW039 450 mg once daily, QAW039 150 mg once daily, or placebo in 4:2:1 ratio.

Patients who HAVE NOT PREVIOUSLY PARTICIPATED IN A STUDY OF QAW039 will be randomized to treatment in Study A2315 as follows: QAW039 450 mg once daily, QAW039 150 mg once daily, or placebo in a 3:3:1 ratio.

Treatment randomization will be stratified at the regional level.

Table 5-1 shows the randomized allocation of patients into treatment groups in Study A2315.

[redacted]

Table 5-1 Randomized Allocation of Patients into Treatment groups

Patients completing A PRIOR PHASE 3 STUDY OF QAW039: treatment allocation in Study A2315			
Prior study	Treatment group in prior study	Randomization ratio in Study A2315	Treatment group in Study A2315
CQAW039A2307 CQAW039A2314	450 mg once daily	5 1 1	QAW039 450 mg once daily QAW039 150 mg once daily Placebo
	150 mg once daily	1 5 1	QAW039 450 mg once daily QAW039 150 mg once daily Placebo
	Placebo	3 3 1	QAW039 450 mg once daily QAW039 150 mg once daily Placebo
CQAW039A2316 CQAW039A2317	150 mg once daily	2 4 1	QAW039 450 mg once daily QAW039 150 mg once daily Placebo
	Placebo	4 2 1	QAW039 450 mg once daily QAW039 150 mg once daily Placebo
Patients who HAVE NOT PREVIOUSLY PARTICIPATED IN A STUDY OF QAW039: treatment allocation in Study A2315			
Prior study	Treatment group in prior study	Randomization ratio in Study A2315	Treatment group in Study A2315
Not applicable	Not applicable	3 3 1	QAW039 450 mg once daily QAW039 150 mg once daily Placebo

5.4 Treatment blinding

Patients, investigator staff, persons performing the assessments, and data analysts will remain blinded to the identity of the treatment from the time of randomization until interim analyses are conducted to support regulatory submissions, 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 for the purpose of safety reviews and at the time of the interim analyses. (2) For each dose level, the identity of the treatments will be concealed by the use of placebos identical in packaging, labeling, schedule of administration, appearance, taste, and odor to QAW039. Across dose levels, a double-dummy design is used because the identity of the study drug cannot be disguised, as the drug products are visibly different.

[redacted]

All data up to the first interim analysis of Study A2315 will be collected with the Novartis study team being blinded to study treatment. At the time of the first interim analysis, Novartis personnel will be unblinded to treatment in order to facilitate worldwide Marketing Authorization Application/New Drug Application (MAA/NDA) filings while investigators and patients will remain blinded to treatment through the remainder of the study. Additional, interim analyses, as regarded appropriate, may be conducted (e.g., to provide additional data for regulatory submissions). Study modifications are not planned based on any interim analysis.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.10), at the time of interim analyses (see Section 9.7), 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,

Upon signing the informed consent form, the patient is assigned the next sequential number by the investigator. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site must select the CRF book with a matching Subject Number from the 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 case report form (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/subjects are assigned consecutive numbers (e.g. the second patient is assigned patient number 2, the third 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. For studies using eCRFs, 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 CRF/eCRF*)* should also be completed. **In addition, it is crucial that the investigator indicates the trial, center and patient identifiers that uniquely identify the patient in any preceding Phase 3 studies.**

5.5.2 Dispensing the study drug

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

[redacted]

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 "three" treatment arms and a specific visit. 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 Pharmaceutical Office (CPO) Quality Assurance.

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

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

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

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Treatment Period 1

Study treatment will be double-blind, double-dummy, and placebo-controlled during Treatment Period 1. QAW039 and placebo will be supplied as tablets. Since the tablets for QAW039 450 mg and QAW039 150 mg are not identical, treatment will be double-dummy and patients will take 2 tablets of study medication (1 tablet of QAW039 450 mg or matching placebo and 1 tablet of QAW150 mg or matching placebo) once daily as described below.

At Visit 201, eligible patients will be randomized into Treatment Period 1 (52-week double-blind treatment period) where they will receive 1 of the following 3 oral treatments:(i)

[redacted]

QAW039 150 mg once daily or (ii) QAW039 450 mg once daily or (iii) placebo once daily given on top of their individual background SoC asthma therapy. The investigational treatment (tablets) will be dispensed in medication 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 and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

At designated clinic visits (see Table 6-1 Assessment Schedule), patients will receive a witnessed dose of study medication (QAW039 or placebo). These in-clinic witnessed doses should be given at approximately the same time at each clinic visit. Between clinic visits, patients will be instructed to take study medication (QAW039 or placebo) once daily at approximately the same time each morning without regard to time of food intake.

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

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

SoC asthma therapy will be taken as directed by the investigator.

Treatment Period 2

Study treatment will be single-blind, double-dummy, and placebo-controlled during Treatment Period 2. QAW039 will be supplied as tablets. Since the tablets for QAW039 450 mg and QAW039 150 mg are not identical, treatment will be double-dummy and patients will take 2 tablets of study medication (1 tablet of QAW039 450 mg or matching placebo and 1 tablet of QAW150 mg or matching placebo) once daily as described below.

Patients entering Treatment Period 2 (104-week single-blind treatment period) will continue to receive the same study treatment they received during Treatment Period 1. Patients will receive (i) QAW039 150 mg once daily or (ii) QAW039 450 mg once daily or (iii) placebo once daily given on top of their individual background SoC asthma therapy. The investigational treatment (tablets) will be dispensed in medication packs 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 and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

At designated clinic visits (see Table 6-1 Assessment Schedule), patients will receive a witnessed dose of study medication (QAW039 or placebo). These in-clinic witnessed doses should be given at approximately the same time at each clinic visit. Between clinic visits, patients will be instructed to take study medication (QAW039 or placebo) once daily at approximately the same time each morning without regard to time of food intake.

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

The investigator must promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's

[redacted]

safety and the validity of the study. The patient must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

SoC asthma therapy will be taken as directed by the investigator.

5.5.5 Permitted dose adjustments and interruptions of study treatment

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

QAW039 treatment 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 medication until serum β-hCG is performed and found to be negative.
- An investigator considers an interruption is necessary for the treatment of an AE.

Interruption to treatment must be recorded on the Dosage Administration Record CRF.

5.5.6 Rescue medication

At the start of screening (Visit 1), all patients will be provided with a SABA (such as salbutamol/albuterol/other SABA) which they will be instructed to use throughout the study as rescue medication on an 'as needed' basis. Nebulized salbutamol or albuterol or other SABA is not allowed as rescue medication and will not be supplied. During the active treatment periods, salbutamol or albuterol or other SABA should be taken for rescue purposes only when absolutely required for symptoms of asthma.

Unless clinically indicated, the type of SABA a patient uses, the device used to deliver the medication (e.g., dry powder or hydrofluoralkane (HFA)) and the way it is administered (e.g., with a spacer device), should not be adjusted. Any changes relating to the above must be recorded on the Concomitant medications (e)CRF/ significant non-drug therapies eCRF. In order to standardize measurements, patients should be instructed to abstain from taking SABA rescue medication (e.g., salbutamol/albuterol) within 6 hours of the start of each visit where spirometry is being performed unless absolutely necessary. **If rescue medication is taken within 6 hours prior to a spirometry visit, the visit should be rescheduled, preferably to the next day.** The investigator must use their judgment when deciding how many times a visit for an individual patient should be rescheduled. In the event that a patient uses a dose of rescue medication (i.e., SABA) after taking study medication at any visit, the visit should continue as planned. In this case, the rescue medication intake will be captured through the central spirometer.

Rescue medication (i.e., SABA) will either be supplied to the investigator sites locally by Novartis or provided by the study center and reimbursed by Novartis.

Patients should be instructed to return any expired and used or unused rescue medication to the site where it should be disposed of appropriately.

[redacted]

5.5.7 Background therapy

All patients will continue to receive SoC asthma medication throughout the study. During the active treatment periods (Treatment Period 1 and Treatment Period 2) of this study, investigators may adjust a patient's SoC asthma therapy according to their clinical judgment. Any changes relating to SoC asthma therapy must be recorded on the Concomitant medications (e)CRF / significant non-drug therapies eCRF.

Short bursts of rescue systemic corticosteroids are allowed for treatment of asthma exacerbations, as clinically indicated (see Section 6.4.2).

5.5.8 Concomitant medication

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

The medications in Table 5-2 are permitted under the circumstances given. **Patients completing a prior phase 3 study of QAW039 will enter this study on the same SoC asthma therapy they were taking in the prior study (which may include low, medium, or high dose ICS) and at the doses they were taking at the last treatment visit of their respective Phase 3 studies.**

Table 5-2 Medications allowed under certain conditions

Class of medication	Condition
Inhaled corticosteroids (ICS)	Medium-dose or High-dose ICS*. Used for at least 3 months prior to Visit 1 and stable for at least 4 weeks prior to Visit 1.
Long-acting inhaled β-2 agonists (LABAs)	Recommended doses and dosage regimens. Used for at least 3 months prior to Visit 1 and stable for at least 4 weeks prior to Visit 1. Must be taken with an ICS.
Fixed dose combinations of ICS and LABA (FDC)	Recommended doses and dosage regimens. Used for at least 3 months prior to Visit 1 and stable for at least 4 weeks prior to Visit 1.
Leukotriene receptor antagonists (LTRAs)	Recommended doses and dosage regimens. Used for at least 3 months prior to Visit 1 and stable for at least 4 weeks prior to Visit 1.
Theophylline	Recommended doses and dosage regimens Used for at least 3 months prior to Visit 1 and stable for at least 4 weeks prior to Visit 1.
Long-acting muscarinic antagonists	Recommended doses and dosage regimens

(LAMAs)	Used for at least 3 months prior to Visit 1 and stable for at least 4 weeks prior to Visit 1.
Mast cell stabilizers (e.g., cromoglycate, nedocromil, ketotifen)	Recommended doses and dosage regimens Used for at least 3 months prior to Visit 1 and stable for at least 4 weeks prior to Visit 1.
Maintenance oral corticosteroids for treatment of asthma	Used for at least 3 months prior to Visit 1 and stable for at least 4 weeks prior to Visit 1. Note: Short bursts of rescue systemic corticosteroids are allowed for treatment of asthma exacerbations, as clinically indicated.
Monoclonal antibodies for the treatment of asthma	Recommended doses and dosage regimens May be added as SoC asthma therapy during study. Must not have been administered less than 5 months prior to Visit 1.
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/ atopic dermatitis	Recommended doses and dosage regimens.
Antihistamines (e.g., loratadine, cetirzine)	Recommended doses and dosage regimens
Nasal anticholinergics	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.
Nasal corticosteroids	
Nasal or ophthalmological preparations of nedocromil Nasal,ophthalmological, or oral preparations of antihistamines	
* Not applicable for patients entering this study from a prior Phase 3 study in which they were receiving low-dose ICS.	

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

Table 5-3 Medications to be withheld prior to spirometry

Class of medication	Last dose prior to spirometry
SABAs	≥ 6 hours
LABAs given twice daily	≥ 12 hours
LABAs given once daily	≥ 24 hours
Fixed dose combinations of LABA and ICS given twice daily	≥ 12 hours
Fixed dose combinations of LABA and ICS given	≥ 24 hours

[redacted]

Class of medication	Last dose prior to spirometry
once daily	
LAMAs	≥ 24 hours

5.5.9 Prohibited medication

Use of the treatments displayed in Table 5-4 is NOT allowed after the start of investigational drug at Visit 1. Table 5-4 is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion crtieria.

These medications are also prohibited if administered for other indications.

Table 5-4 Prohibited medications

Class of medication	Minimum cessation prior to Visit 1
Other investigational drugs	30 days or 5 half-lives, whichever is longer
Live attenuated vaccine	30 days
Other CRTH2 antagonists (e.g., ramatroban)	7 days or 5 half-lives whichever is longer
Short-acting anticholinergics	8 hours
Fixed combinations of SABAs and short-acting anticholinergics	8 hours
Simvastatin >20 mg, atorvastatin >40 mg, pravastatin >40 mg, or pitavastatin >2 mg total daily dose	7 days
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 for the treatment of conditions other than asthma	6 months

5.5.10 Emergency breaking of assigned treatment code

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

[redacted]

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.

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

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

Study completion for a patient can occur after he/she has completed 52 weeks of treatment in Treatment Period 1, or after the additional 104 weeks of treatment in optional Treatment Period 2 (total of 156 weeks of treatment) or if they have prematurely withdrawn. Completion of the study will be when all randomized patients have met the definition of study completion described above and have completed the post-treatment follow-up visit.

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

Patients completing the study after Treatment Period 1 or Treatment Period 2 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.

For all patients/subjects a safety follow-up visit (visit 401) should be conducted (e.g. by telephone for males and females of non-child bearing potential; women of childbearing potential must come in to the clinic for pregnancy testing at Visit 401) 30 days after last visit (299, Week 52 for patients not continuing into Treatment Period 2 and visit 399, week 156 for patients completing Treatment Period 2). The information to be collected at this follow up visit includes concomitant medications, adverse events, pregnancy testing and survival status.

The investigator must provide appropriate advice on the continued use of basic contraception for at least one week (at least 5 half-lives of QAW039) after study completion (Visit 299 or Visit 399, as appropriate) or premature study drug discontinuation and 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.

[redacted]

5.6.2 Discontinuation of Study Treatment

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

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

Study treatment must be discontinued under the following circumstances:

- Patient wish;
- Pregnancy (see Section 6.5.6 and Section 7.7);
- If a patient develops a medical condition that requires consistent use of prohibited treatment as per Section 5.5.9 or if patient exhibits a behavior of non-compliance regarding prohibited medications.
- Any situation in which study participation might result in a safety risk to the patient;
- Female subjects non-compliant with the chosen basic method of contraception during the study.
  The investigator must provide appropriate advice on the continued use of basic 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;
- 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;
- Premature unblinding of study treatment for a patient for any reason;
- Total white blood cell count <1000 cells/µL;
- Patients with QTcF (Fridericia) ≥450 msec (male) or ≥460 msec (female) at Visit 201 on the ECG Analysis Report provided by the ECG core laboratory.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 >10xULN or persistent intolerable muscle pain regardless of the accompanying CK level.

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 "unscheduled 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 eCRF.

Patients who discontinue study treatment will be asked to remain in the study and complete all study visits. Patients withdrawn from study treatment will receive SoC asthma therapy according to investigator judgment.

[redacted]

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule. Data will continue to be collected concerning the patients' condition and changes in concomitant medications, surgeries and procedures, serious and non-serious adverse events, and asthma exacerbations should be recorded in the appropriate eCRF if applicable. If necessary an unscheduled clinical visit may be arranged.

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

If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.10

5.6.3 Withdrawal of informed consent

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

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- Does not allow analysis of already obtained biologic material

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

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

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

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

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

Patients who prematurely discontinue study treatment or withdraw from the study will not be replaced.

5.6.4 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by

[redacted]

documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

5.6.5 Early study termination by the sponsor

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

6 Visit schedule and assessments

Patients/subjects must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who discontinue study treatment before completing the study and accept to remain in the study will return for study visits as described in Section 5.6.2. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

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

Note that the visit schedule for the screening and randomization visits (Visit 1 and Visit 201) for patients completing a prior Phase 3 study of QAW039 will be different from the visit schedule for the screening and randomization visits for patients who have not previously participated in a study of QAW039.

- **For patients completing a prior Phase 3 study of QAW039:** the last visit in the treatment period of the prior study (e.g., Visit 299) will occur on the same day as the screening visit (Visit 1) for Study A2315. The randomization visit (Visit 201) will occur on the following day (i.e., 1 day after Visit 1) so there is no interruption of study treatment and to allow for pre-dose assessments for Study A2315.
- **For patients who have not previously participated in a study of QAW039:** the screening visit (Visit 1) will occur approximately 2 weeks before the randomization visit (Visit 201).

The table below summarizes the screening visit (Visit 1) and randomization visit (Visit 201) timing for patients completing a prior Phase 3 study of QAW039 and for patients who have not previously participated in a study of QAW039.

[redacted]

	Screening (Visit 1)	Randomization (Visit 201)
Patients completing a prior Phase 3 Study of QAW039	Last day of treatment period of prior Phase 3 study (e.g., Visit 299)	Day 1: Visit 1 + 1 day
Patients who have not previously participated in a study of QAW039	Day -14	Day 1: Visit 1 + 14 days

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 prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

Patients will be required to attend the clinic in the morning at approximately the same time for each visit. Patients/subjects will be contacted for safety evaluations during the 30 days following the last administration of study treatment.

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;**
2) **Patient Reported Outcome instruments: ACQ-5 at Visit 1 (new patients);**
3) **Vital signs;**
4) **ECGs;**
5) **Samples for urine/hematology/blood chemistry** (At Visit 1, collect samples prior to spirometry.
6) **Samples for Radioallergosorbant (RAST)/ImmunoCAP test, Total IgE, at certain clinic visit(s)** (At Visit 1, collect samples prior to spirometry.
7) **Spirometry.** Spirometry assessments should be timed so that the Visit 1 spirometry assessment Other tests should be performed as close as possible to those spirometry times.

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

[redacted]

Table 6-1 Assessment schedule

	Screening			Treatment																	Follow-up
				Treatment Epoch 1							Treatment Epoch 2										
Visit Number (Site visits)[1]	1[2, 3]		2	201	202	203	204	205	TD	299[4,5]	301	302	303	304	305	306	307	308	TD	399	401[6]
	NP	PP																			
Treatment Week	-2		1	1	4	13	26	39	TD	52	52	65	78	91	104	117	130	143	TD	156	160
Treatment Day Note: *Visit 2 and 201 will occur on the same day if the patient is randomized	-14	-1	1*	1*	28	91	182	273	TD	364	364	455	546	637	728	819	910	1001	TD	1092	1120
[1]Scheduled clinic visits (starting at Visit1 and thereafter) are to occur in the morning at approximately the same time, so that the specified FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M (±1 hour). [2]For patients who have not previously participated in a study of QAW039: patients experiencing an asthma exacerbation during the Screening Epoch may be re-screened ≥6 weeks after recovery from the exacerbation. [3] For patients completing a prior Phase 3 study of QAW039, Visit 1 will occur on the same day as the last day of treatment in the prior study. [4] For patients continuing into Treatment Epoch 2, Visit 299 and Visit 301 will occur on the same day. [5]For the witnessed dose at Visit 299, patients will take a tablet from the study drug dispensed at Visit 205. [6]Visit 401 will occur after Visit 299 for patients not continuing into Treatment Epoch 2 or after Visit 399 for patients completing Treatment Epoch 2. [†]For patients completing a prior Phase 3 study of QAW039; consult the CRF Completion Guidelines for patient data to be moved from the prior Phase 3 study eCRFs to the Study A2315 eCRFs. [‡]For patients completing a prior Phase 3 study of QAW039, the assessment from the last visit of the Treatment Epoch of the prior Phase 3 study will serve as the Visit 1 assessment for Study A2315. **NP** = New patients not previously participating in a phase 3 study of QAW039; **PP** = patients completing a prior Phase 3 study of QAW039; **TD** = study treatment discontinuation (permanent treatment discontinuation but continue with limited assessments); **(S) =** assessment to be recorded in source documents only; assessment will not be entered into the eCRFs; **V** = Visit;																					
Epoch 1 Informed consent (IC) and assent (if applicable) **Note:** IC and assent (if applicable) may be obtained within 14 days prior to or at V1. **For patients completing a prior phase 3 study of QAW039,** IC and assents (if applicable) for Treatment Epoch 1 may be obtained on the last day of treatment in the prior study's treatment epoch.	X	X																			

	Screening			Treatment																	Follow-up
				Treatment Epoch 1							Treatment Epoch 2										
Visit Number (Site visits)[1]	1[2, 3]		2	201	202	203	204	205	TD	299[4,5]	301	302	303	304	305	306	307	308	TD	399	401[6]
	NP	PP																			
Treatment Week	-2		1	1	4	13	26	39	TD	52	52	65	78	91	104	117	130	143	TD	156	160
Treatment Day Note: *Visit 2 and 201 will occur on the same day if the patient is randomized	-14	-1	1*	1*	28	91	182	273	TD	364	364	455	546	637	728	819	910	1001	TD	1092	1120
[1]Scheduled clinic visits (starting at Visit1 and thereafter) are to occur in the morning at approximately the same time, so that the specified FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M (±1 hour). [2]For patients who have not previously participated in a study of QAW039: patients experiencing an asthma exacerbation during the Screening Epoch may be re-screened ≥6 weeks after recovery from the exacerbation. [3] For patients completing a prior Phase 3 study of QAW039, Visit 1 will occur on the same day as the last day of treatment in the prior study. [4] For patients continuing into Treatment Epoch 2, Visit 299 and Visit 301 will occur on the same day. [5]For the witnessed dose at Visit 299, patients will take a tablet from the study drug dispensed at Visit 205. [6]Visit 401 will occur after Visit 299 for patients not continuing into Treatment Epoch 2 or after Visit 399 for patients completing Treatment Epoch 2. †For patients completing a prior Phase 3 study of QAW039; consult the CRF Completion Guidelines for patient data to be moved from the prior Phase 3 study eCRFs to the Study A2315 eCRFs. ‡For patients completing a prior Phase 3 study of QAW039, the assessment from the last visit of the Treatment Epoch of the prior Phase 3 study will serve as the Visit 1 assessment for Study A2315. **NP** = New patients not previously participating in a phase 3 study of QAW039; **PP** = patients completing a prior Phase 3 study of QAW039; **TD** = study treatment discontinuation (permanent treatment discontinuation but continue with limited assessments); **(S) =** assessment to be recorded in source documents only; assessment will not be entered into the eCRFs; **V** = Visit;																					
Epoch 2 Informed consent (IC) and assent (if applicable)											X										
Ask question on withholding of medication before clinic visits (for details (see Section 5.5.8) **Note:** If the patient has not withheld medications as specified in the protocol before a particular visit, the visit should be rescheduled.	X	X	X		X	X	X	X		X											
Demographics	X	X†, ‡																			
Previous Trial, Site and Subject Identifiers (if applicable)		X†																			

[redacted]

	Screening			Treatment																	Follow-up
				Treatment Epoch 1							Treatment Epoch 2										
Visit Number (Site visits)[1]	1[2, 3]		2	201	202	203	204	205	TD	299[4,5]	301	302	303	304	305	306	307	308	TD	399	401[6]
	NP	PP																			
Treatment Week	-2		1	1	4	13	26	39	TD	52	52	65	78	91	104	117	130	143	TD	156	160
Treatment Day Note: *Visit 2 and 201 will occur on the same day if the patient is randomized	-14	-1	1*	1*	28	91	182	273	TD	364	364	455	546	637	728	819	910	1001	TD	1092	1120
[1]Scheduled clinic visits (starting at Visit1 and thereafter) are to occur in the morning at approximately the same time, so that the specified FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M (±1 hour). [2]For patients who have not previously participated in a study of QAW039: patients experiencing an asthma exacerbation during the Screening Epoch may be re-screened ≥6 weeks after recovery from the exacerbation. [3] For patients completing a prior Phase 3 study of QAW039, Visit 1 will occur on the same day as the last day of treatment in the prior study. [4] For patients continuing into Treatment Epoch 2, Visit 299 and Visit 301 will occur on the same day. [5]For the witnessed dose at Visit 299, patients will take a tablet from the study drug dispensed at Visit 205. [6]Visit 401 will occur after Visit 299 for patients not continuing into Treatment Epoch 2 or after Visit 399 for patients completing Treatment Epoch 2. [†]For patients completing a prior Phase 3 study of QAW039; consult the CRF Completion Guidelines for patient data to be moved from the prior Phase 3 study eCRFs to the Study A2315 eCRFs. [‡]For patients completing a prior Phase 3 study of QAW039, the assessment from the last visit of the Treatment Epoch of the prior Phase 3 study will serve as the Visit 1 assessment for Study A2315. **NP** = New patients not previously participating in a phase 3 study of QAW039; **PP** = patients completing a prior Phase 3 study of QAW039; **TD** = study treatment discontinuation (permanent treatment discontinuation but continue with limited assessments); **(S) =** assessment to be recorded in source documents only; assessment will not be entered into the eCRFs; **V** = Visit;																					
Medical history	X	X[†,‡]																			
Medical History – Protocol solicited events for asthma	X	X[†,‡]																			
Asthma exacerbation history	X																				
Smoking history	X	X[†,‡]																			
Prior/concomitant medication (asthma and non-asthma medications) review	X	X[†,‡]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Inclusion/exclusion criteria	X	X	X																		
Review and record surgeries and procedures	X	X[†,‡]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination (S)	S	S[‡]							S	S									S	S	

[redacted]

	Screening			Treatment																Follow-up
				Treatment Epoch 1							Treatment Epoch 2									
Visit Number (Site visits)[1]	1[2, 3]		2	201	202	203	204	205	TD	299[4,5]	301	302	303	304	305	306	307	308	TD	399	401[6]
	NP	PP																		
Treatment Week	-2		1	1	4	13	26	39	TD	52	52	65	78	91	104	117	130	143	TD	156	160
Treatment Day Note: *Visit 2 and 201 will occur on the same day if the patient is randomized	-14	-1	1*	1*	28	91	182	273	TD	364	364	455	546	637	728	819	910	1001	TD	1092	1120
[1]Scheduled clinic visits (starting at Visit1 and thereafter) are to occur in the morning at approximately the same time, so that the specified FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M (±1 hour). [2]For patients who have not previously participated in a study of QAW039: patients experiencing an asthma exacerbation during the Screening Epoch may be re-screened ≥6 weeks after recovery from the exacerbation. [3] For patients completing a prior Phase 3 study of QAW039, Visit 1 will occur on the same day as the last day of treatment in the prior study. [4] For patients continuing into Treatment Epoch 2, Visit 299 and Visit 301 will occur on the same day. [5]For the witnessed dose at Visit 299, patients will take a tablet from the study drug dispensed at Visit 205. [6]Visit 401 will occur after Visit 299 for patients not continuing into Treatment Epoch 2 or after Visit 399 for patients completing Treatment Epoch 2. †For patients completing a prior Phase 3 study of QAW039; consult the CRF Completion Guidelines for patient data to be moved from the prior Phase 3 study eCRFs to the Study A2315 eCRFs. ‡For patients completing a prior Phase 3 study of QAW039, the assessment from the last visit of the Treatment Epoch of the prior Phase 3 study will serve as the Visit 1 assessment for Study A2315. **NP** = New patients not previously participating in a phase 3 study of QAW039; **PP** = patients completing a prior Phase 3 study of QAW039; **TD** = study treatment discontinuation (permanent treatment discontinuation but continue with limited assessments); **(S) =** assessment to be recorded in source documents only; assessment will not be entered into the eCRFs; **V** = Visit;																					
Abbreviated physical examination (heart and lung only) (S)			S		S	S	S	S				S	S	S	S	S	S	S			
Height **Note:** Height must be collected using a standard measurement device (such as a stadiometer)	X	X†,‡								X										X	
Weight	X	X†,‡							X	X									X	X	
Vital signs (systolic/diastolic blood pressure, radial pulse [sitting], and body temperature)	X	X†,‡	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Electrocardiogram	X	X†,‡							X										X		

[redacted]

	Screening			Treatment																Follow-up
				Treatment Epoch 1							Treatment Epoch 2									
Visit Number (Site visits)[1]	1[2, 3]		2	201	202	203	204	205	TD	299[4,5]	301	302	303	304	305	306	307	308	TD	399	401[6]
	NP	PP																		
Treatment Week	-2		1	1	4	13	26	39	TD	52	52	65	78	91	104	117	130	143	TD	156	160
Treatment Day Note: *Visit 2 and 201 will occur on the same day if the patient is randomized	-14	-1	1*	1*	28	91	182	273	TD	364	364	455	546	637	728	819	910	1001	TD	1092	1120
[1]Scheduled clinic visits (starting at Visit1 and thereafter) are to occur in the morning at approximately the same time, so that the specified FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M (±1 hour). [2]For patients who have not previously participated in a study of QAW039: patients experiencing an asthma exacerbation during the Screening Epoch may be re-screened ≥6 weeks after recovery from the exacerbation. [3] For patients completing a prior Phase 3 study of QAW039, Visit 1 will occur on the same day as the last day of treatment in the prior study. [4] For patients continuing into Treatment Epoch 2, Visit 299 and Visit 301 will occur on the same day. [5]For the witnessed dose at Visit 299, patients will take a tablet from the study drug dispensed at Visit 205. [6]Visit 401 will occur after Visit 299 for patients not continuing into Treatment Epoch 2 or after Visit 399 for patients completing Treatment Epoch 2. [†]For patients completing a prior Phase 3 study of QAW039; consult the CRF Completion Guidelines for patient data to be moved from the prior Phase 3 study eCRFs to the Study A2315 eCRFs. [‡]For patients completing a prior Phase 3 study of QAW039, the assessment from the last visit of the Treatment Epoch of the prior Phase 3 study will serve as the Visit 1 assessment for Study A2315. **NP** = New patients not previously participating in a phase 3 study of QAW039; **PP** = patients completing a prior Phase 3 study of QAW039; **TD** = study treatment discontinuation (permanent treatment discontinuation but continue with limited assessments); **(S) =** assessment to be recorded in source documents only; assessment will not be entered into the eCRFs; **V** = Visit;																					
Electrocardiogram (Pre-dose)				X	X	X	X	X		X		X	X	X	X	X	X	X		X	
Pregnancy test—serum (women of child bearing potential) **Note:** Pregnancy testing will begin at the first visit a patient is identified as being of child bearing potential and then performed at all subsequent visits.	X																				

[redacted]

	Screening			Treatment																Follow-up
				Treatment Epoch 1							Treatment Epoch 2									
Visit Number (Site visits)[1]	1[2, 3]		2	201	202	203	204	205	TD	299[4,5]	301	302	303	304	305	306	307	308	TD	399	401[6]
	NP	PP																		
Treatment Week	-2		1	1	4	13	26	39	TD	52	52	65	78	91	104	117	130	143	TD	156	160
Treatment Day Note: *Visit 2 and 201 will occur on the same day if the patient is randomized	-14	-1	1*	1*	28	91	182	273	TD	364	364	455	546	637	728	819	910	1001	TD	1092	1120
[1]Scheduled clinic visits (starting at Visit1 and thereafter) are to occur in the morning at approximately the same time, so that the specified FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M (±1 hour). [2]For patients who have not previously participated in a study of QAW039: patients experiencing an asthma exacerbation during the Screening Epoch may be re-screened ≥6 weeks after recovery from the exacerbation. [3] For patients completing a prior Phase 3 study of QAW039, Visit 1 will occur on the same day as the last day of treatment in the prior study. [4] For patients continuing into Treatment Epoch 2, Visit 299 and Visit 301 will occur on the same day. [5]For the witnessed dose at Visit 299, patients will take a tablet from the study drug dispensed at Visit 205. [6]Visit 401 will occur after Visit 299 for patients not continuing into Treatment Epoch 2 or after Visit 399 for patients completing Treatment Epoch 2. [†]For patients completing a prior Phase 3 study of QAW039; consult the CRF Completion Guidelines for patient data to be moved from the prior Phase 3 study eCRFs to the Study A2315 eCRFs. [‡]For patients completing a prior Phase 3 study of QAW039, the assessment from the last visit of the Treatment Epoch of the prior Phase 3 study will serve as the Visit 1 assessment for Study A2315. **NP** = New patients not previously participating in a phase 3 study of QAW039; **PP** = patients completing a prior Phase 3 study of QAW039; **TD** = study treatment discontinuation (permanent treatment discontinuation but continue with limited assessments); **(S) =** assessment to be recorded in source documents only; assessment will not be entered into the eCRFs; **V** = Visit;																					
Pregnancy test—urine (women of child bearing potential) **Note:** Pregnancy testing will begin at the first visit if a patient is identified as being of child bearing potential and then performed at all subsequent visits. A positive urine pregnancy test requires immediate interruption of study medication until serum β-hCG is performed and found to be negative. If positive, the patient must be discontinued from study treatment.		X[†,‡]	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X

[redacted]

	Screening			Treatment																Follow-up
				Treatment Epoch 1							Treatment Epoch 2									
Visit Number (Site visits)[1]	1[2, 3]		2	201	202	203	204	205	TD	299[4,5]	301	302	303	304	305	306	307	308	TD	399	401[6]
	NP	PP																		
Treatment Week	-2		1	1	4	13	26	39	TD	52	52	65	78	91	104	117	130	143	TD	156	160
Treatment Day Note: *Visit 2 and 201 will occur on the same day if the patient is randomized	-14	-1	1*	1*	28	91	182	273	TD	364	364	455	546	637	728	819	910	1001	TD	1092	1120
[1]Scheduled clinic visits (starting at Visit1 and thereafter) are to occur in the morning at approximately the same time, so that the specified FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M (±1 hour). [2]For patients who have not previously participated in a study of QAW039: patients experiencing an asthma exacerbation during the Screening Epoch may be re-screened ≥6 weeks after recovery from the exacerbation. [3] For patients completing a prior Phase 3 study of QAW039, Visit 1 will occur on the same day as the last day of treatment in the prior study. [4] For patients continuing into Treatment Epoch 2, Visit 299 and Visit 301 will occur on the same day. [5]For the witnessed dose at Visit 299, patients will take a tablet from the study drug dispensed at Visit 205. [6]Visit 401 will occur after Visit 299 for patients not continuing into Treatment Epoch 2 or after Visit 399 for patients completing Treatment Epoch 2. †For patients completing a prior Phase 3 study of QAW039; consult the CRF Completion Guidelines for patient data to be moved from the prior Phase 3 study eCRFs to the Study A2315 eCRFs. ‡For patients completing a prior Phase 3 study of QAW039, the assessment from the last visit of the Treatment Epoch of the prior Phase 3 study will serve as the Visit 1 assessment for Study A2315. **NP =** New patients not previously participating in a phase 3 study of QAW039; **PP =** patients completing a prior Phase 3 study of QAW039; **TD =** study treatment discontinuation (permanent treatment discontinuation but continue with limited assessments); **(S) =** assessment to be recorded in source documents only; assessment will not be entered into the eCRFs; **V =** Visit;																					
In countries where monthly pregnancy testing is required for women of child-bearing potential by local laws and regulations: Home Pregnancy testing-urine	Note: These female patients will report the results of monthly home urine pregnancy test as “positive” or “negative” to study site staff as part of a monthly telephone call from the site to the patient between in clinic study visits (S)																			
Urinalysis and urine chemistry (central laboratory)	X	X†,‡		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	

[redacted]

	Screening			Treatment																Follow-up
				Treatment Epoch 1							Treatment Epoch 2									
Visit Number (Site visits)[1]	1[2, 3]		2	201	202	203	204	205	TD	299[4,5]	301	302	303	304	305	306	307	308	TD	399	401[6]
	NP	PP																		
Treatment Week	-2		1	1	4	13	26	39	TD	52	52	65	78	91	104	117	130	143	TD	156	160
Treatment Day Note: *Visit 2 and 201 will occur on the same day if the patient is randomized	-14	-1	1*	1*	28	91	182	273	TD	364	364	455	546	637	728	819	910	1001	TD	1092	1120
[1]Scheduled clinic visits (starting at Visit1 and thereafter) are to occur in the morning at approximately the same time, so that the specified FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M (±1 hour). [2]For patients who have not previously participated in a study of QAW039: patients experiencing an asthma exacerbation during the Screening Epoch may be re-screened ≥6 weeks after recovery from the exacerbation. [3] For patients completing a prior Phase 3 study of QAW039, Visit 1 will occur on the same day as the last day of treatment in the prior study. [4] For patients continuing into Treatment Epoch 2, Visit 299 and Visit 301 will occur on the same day. [5]For the witnessed dose at Visit 299, patients will take a tablet from the study drug dispensed at Visit 205. [6]Visit 401 will occur after Visit 299 for patients not continuing into Treatment Epoch 2 or after Visit 399 for patients completing Treatment Epoch 2. [†]For patients completing a prior Phase 3 study of QAW039; consult the CRF Completion Guidelines for patient data to be moved from the prior Phase 3 study eCRFs to the Study A2315 eCRFs. [‡]For patients completing a prior Phase 3 study of QAW039, the assessment from the last visit of the Treatment Epoch of the prior Phase 3 study will serve as the Visit 1 assessment for Study A2315. **NP =** New patients not previously participating in a phase 3 study of QAW039; **PP =** patients completing a prior Phase 3 study of QAW039; **TD =** study treatment discontinuation (permanent treatment discontinuation but continue with limited assessments); **(S) =** assessment to be recorded in source documents only; assessment will not be entered into the eCRFs; **V =** Visit;																					
Blood for hematology and chemistry. Refer to Section 6.5.4 **Notes:** No fasting requirement prior to blood sampling.	X	X[†,‡]		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Blood for RAST/ImmunoCap test: Only performed for patients who have not previously participated in a prior study of QAW039.	X																				
[redacted]																					

[redacted]

	Screening			Treatment																Follow-up
				Treatment Epoch 1							Treatment Epoch 2									
Visit Number (Site visits)[1]	1[2, 3]		2	201	202	203	204	205	TD	299[4,5]	301	302	303	304	305	306	307	308	TD	399	401[6]
	NP	PP																		
Treatment Week	-2		1	1	4	13	26	39	TD	52	52	65	78	91	104	117	130	143	TD	156	160
Treatment Day Note: *Visit 2 and 201 will occur on the same day if the patient is randomized	-14	-1	1*	1*	28	91	182	273	TD	364	364	455	546	637	728	819	910	1001	TD	1092	1120
[1]Scheduled clinic visits (starting at Visit1 and thereafter) are to occur in the morning at approximately the same time, so that the specified FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M (±1 hour). [2]For patients who have not previously participated in a study of QAW039: patients experiencing an asthma exacerbation during the Screening Epoch may be re-screened ≥6 weeks after recovery from the exacerbation. [3] For patients completing a prior Phase 3 study of QAW039, Visit 1 will occur on the same day as the last day of treatment in the prior study. [4] For patients continuing into Treatment Epoch 2, Visit 299 and Visit 301 will occur on the same day. [5]For the witnessed dose at Visit 299, patients will take a tablet from the study drug dispensed at Visit 205. [6]Visit 401 will occur after Visit 299 for patients not continuing into Treatment Epoch 2 or after Visit 399 for patients completing Treatment Epoch 2. [†]For patients completing a prior Phase 3 study of QAW039; consult the CRF Completion Guidelines for patient data to be moved from the prior Phase 3 study eCRFs to the Study A2315 eCRFs. [‡]For patients completing a prior Phase 3 study of QAW039, the assessment from the last visit of the Treatment Epoch of the prior Phase 3 study will serve as the Visit 1 assessment for Study A2315. **NP =** New patients not previously participating in a phase 3 study of QAW039; **PP =** patients completing a prior Phase 3 study of QAW039; **TD =** study treatment discontinuation (permanent treatment discontinuation but continue with limited assessments); **(S) =** assessment to be recorded in source documents only; assessment will not be entered into the eCRFs; **V =** Visit;																					
Review Visit 1 laboratory results or laboratory results from previous study if applicable (chemistry, hematology, hemoglobin HbA1c, RAST/ImmunoCAP, urine chemistry and urinalysis as applicable). **Note:** If results for one of the laboratory tests is missing, obtain a repeat for the missing result.			X																	

[redacted]

	Screening			Treatment																	Follow-up
				Treatment Epoch 1							Treatment Epoch 2										
Visit Number (Site visits)[1]	1[2, 3]		2	201	202	203	204	205	TD	299[4,5]	301	302	303	304	305	306	307	308	TD	399	401[6]
	NP	PP																			
Treatment Week	-2		1	1	4	13	26	39	TD	52	52	65	78	91	104	117	130	143	TD	156	160
Treatment Day Note: *Visit 2 and 201 will occur on the same day if the patient is randomized	-14	-1	1*	1*	28	91	182	273	TD	364	364	455	546	637	728	819	910	1001	TD	1092	1120

[1]Scheduled clinic visits (starting at Visit1 and thereafter) are to occur in the morning at approximately the same time, so that the specified FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M (±1 hour).
[2]For patients who have not previously participated in a study of QAW039: patients experiencing an asthma exacerbation during the Screening Epoch may be re-screened ≥6 weeks after recovery from the exacerbation.
[3] For patients completing a prior Phase 3 study of QAW039, Visit 1 will occur on the same day as the last day of treatment in the prior study.
[4] For patients continuing into Treatment Epoch 2, Visit 299 and Visit 301 will occur on the same day.
[5]For the witnessed dose at Visit 299, patients will take a tablet from the study drug dispensed at Visit 205.
[6]Visit 401 will occur after Visit 299 for patients not continuing into Treatment Epoch 2 or after Visit 399 for patients completing Treatment Epoch 2.
[†]For patients completing a prior Phase 3 study of QAW039; consult the CRF Completion Guidelines for patient data to be moved from the prior Phase 3 study eCRFs to the Study A2315 eCRFs.
[‡]For patients completing a prior Phase 3 study of QAW039, the assessment from the last visit of the Treatment Epoch of the prior Phase 3 study will serve as the Visit 1 assessment for Study A2315.
NP = New patients not previously participating in a phase 3 study of QAW039; **PP** = patients completing a prior Phase 3 study of QAW039; **TD** = study treatment discontinuation (permanent treatment discontinuation but continue with limited assessments); **(S) =** assessment to be recorded in source documents only; assessment will not be entered into the eCRFs; **V** = Visit;

Parasitic screening **Notes:** Only for patients who HAVE NOT PREVIOUSLY PARTICIPATED IN A PHASE 3 STUDY OF QAW039. Only if **required by** health authority and/or ethics committee/institutional review board. Sites should use local laboratories.	S																				
Serious adverse event recording	X	X[†,‡]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event recording	X	X[†,‡]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Record deaths	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver events monitoring	X	X[†,‡]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[redacted]

	Screening			Treatment																	Follow-up
				Treatment Epoch 1							Treatment Epoch 2										
Visit Number (Site visits)[1]	1[2, 3]		2	201	202	203	204	205	TD	299[4,5]	301	302	303	304	305	306	307	308	TD	399	401[6]
	NP	PP																			
Treatment Week	-2		1	1	4	13	26	39	TD	52	52	65	78	91	104	117	130	143	TD	156	160
Treatment Day Note: *Visit 2 and 201 will occur on the same day if the patient is randomized	-14	-1	1*	1*	28	91	182	273	TD	364	364	455	546	637	728	819	910	1001	TD	1092	1120
[1]Scheduled clinic visits (starting at Visit1 and thereafter) are to occur in the morning at approximately the same time, so that the specified FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M (±1 hour). [2]For patients who have not previously participated in a study of QAW039: patients experiencing an asthma exacerbation during the Screening Epoch may be re-screened ≥6 weeks after recovery from the exacerbation. [3] For patients completing a prior Phase 3 study of QAW039, Visit 1 will occur on the same day as the last day of treatment in the prior study. [4] For patients continuing into Treatment Epoch 2, Visit 299 and Visit 301 will occur on the same day. [5]For the witnessed dose at Visit 299, patients will take a tablet from the study drug dispensed at Visit 205. [6]Visit 401 will occur after Visit 299 for patients not continuing into Treatment Epoch 2 or after Visit 399 for patients completing Treatment Epoch 2. [†]For patients completing a prior Phase 3 study of QAW039; consult the CRF Completion Guidelines for patient data to be moved from the prior Phase 3 study eCRFs to the Study A2315 eCRFs. [‡]For patients completing a prior Phase 3 study of QAW039, the assessment from the last visit of the Treatment Epoch of the prior Phase 3 study will serve as the Visit 1 assessment for Study A2315. **NP** = New patients not previously participating in a phase 3 study of QAW039; **PP** = patients completing a prior Phase 3 study of QAW039; **TD** = study treatment discontinuation (permanent treatment discontinuation but continue with limited assessments); **(S) =** assessment to be recorded in source documents only; assessment will not be entered into the eCRFs; **V** = Visit;																					
Renal events monitoring	X	X[†,‡]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Asthma exacerbation recording **Note:** 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 organized.	X	X[†,‡]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[redacted]

	Screening			Treatment																Follow-up
				Treatment Epoch 1							Treatment Epoch 2									
Visit Number (Site visits)[1]	1[2, 3]		2	201	202	203	204	205	TD	299[4,5]	301	302	303	304	305	306	307	308	TD	399	401[6]
	NP	PP																		
Treatment Week	-2		1	1	4	13	26	39	TD	52	52	65	78	91	104	117	130	143	TD	156	160
Treatment Day Note: *Visit 2 and 201 will occur on the same day if the patient is randomized	-14	-1	1*	1*	28	91	182	273	TD	364	364	455	546	637	728	819	910	1001	TD	1092	1120
[1]Scheduled clinic visits (starting at Visit1 and thereafter) are to occur in the morning at approximately the same time, so that the specified FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M (±1 hour). [2]For patients who have not previously participated in a study of QAW039: patients experiencing an asthma exacerbation during the Screening Epoch may be re-screened ≥6 weeks after recovery from the exacerbation. [3] For patients completing a prior Phase 3 study of QAW039, Visit 1 will occur on the same day as the last day of treatment in the prior study. [4] For patients continuing into Treatment Epoch 2, Visit 299 and Visit 301 will occur on the same day. [5]For the witnessed dose at Visit 299, patients will take a tablet from the study drug dispensed at Visit 205. [6]Visit 401 will occur after Visit 299 for patients not continuing into Treatment Epoch 2 or after Visit 399 for patients completing Treatment Epoch 2. [†]For patients completing a prior Phase 3 study of QAW039; consult the CRF Completion Guidelines for patient data to be moved from the prior Phase 3 study eCRFs to the Study A2315 eCRFs. [‡]For patients completing a prior Phase 3 study of QAW039, the assessment from the last visit of the Treatment Epoch of the prior Phase 3 study will serve as the Visit 1 assessment for Study A2315. **NP =** New patients not previously participating in a phase 3 study of QAW039; **PP =** patients completing a prior Phase 3 study of QAW039; **TD =** study treatment discontinuation (permanent treatment discontinuation but continue with limited assessments); **(S) =** assessment to be recorded in source documents only; assessment will not be entered into the eCRFs; **V =** Visit;																					
Spirometry (centralized) To be performed prior to reversibility test if reversibility test is required. **Note:** This spirometry assessment must be performed between 6:00 AM and 10:00 AM (±1 hour).	X								X											

[redacted]

	Screening			Treatment																Follow-up
				Treatment Epoch 1							Treatment Epoch 2									
Visit Number (Site visits)[1]	1[2, 3]		2	201	202	203	204	205	TD	299[4,5]	301	302	303	304	305	306	307	308	TD	399	401[6]
	NP	PP																		
Treatment Week	-2		1	1	4	13	26	39	TD	52	52	65	78	91	104	117	130	143	TD	156	160
Treatment Day Note: *Visit 2 and 201 will occur on the same day if the patient is randomized	-14	-1	1*	1*	28	91	182	273	TD	364	364	455	546	637	728	819	910	1001	TD	1092	1120

[1]Scheduled clinic visits (starting at Visit1 and thereafter) are to occur in the morning at approximately the same time, so that the specified FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M (±1 hour).

[2]For patients who have not previously participated in a study of QAW039: patients experiencing an asthma exacerbation during the Screening Epoch may be re-screened ≥6 weeks after recovery from the exacerbation.

[3] For patients completing a prior Phase 3 study of QAW039, Visit 1 will occur on the same day as the last day of treatment in the prior study.

[4] For patients continuing into Treatment Epoch 2, Visit 299 and Visit 301 will occur on the same day.

[5]For the witnessed dose at Visit 299, patients will take a tablet from the study drug dispensed at Visit 205.

[6]Visit 401 will occur after Visit 299 for patients not continuing into Treatment Epoch 2 or after Visit 399 for patients completing Treatment Epoch 2.

[†]For patients completing a prior Phase 3 study of QAW039; consult the CRF Completion Guidelines for patient data to be moved from the prior Phase 3 study eCRFs to the Study A2315 eCRFs.

[‡]For patients completing a prior Phase 3 study of QAW039, the assessment from the last visit of the Treatment Epoch of the prior Phase 3 study will serve as the Visit 1 assessment for Study A2315.

NP = New patients not previously participating in a phase 3 study of QAW039; **PP =** patients completing a prior Phase 3 study of QAW039; **TD =** study treatment discontinuation (permanent treatment discontinuation but continue with limited assessments); **(S) =** assessment to be recorded in source documents only; assessment will not be entered into the eCRFs; **V =** Visit;

[redacted]

[redacted]

	Screening			Treatment																Follow-up
				Treatment Epoch 1							Treatment Epoch 2									
Visit Number (Site visits)[1]	1[2, 3]		2	201	202	203	204	205	TD	299[4,5]	301	302	303	304	305	306	307	308	TD	399	401[6]
	NP	PP																		
Treatment Week	-2		1	1	4	13	26	39	TD	52	52	65	78	91	104	117	130	143	TD	156	160
Treatment Day Note: *Visit 2 and 201 will occur on the same day if the patient is randomized	-14	-1	1*	1*	28	91	182	273	TD	364	364	455	546	637	728	819	910	1001	TD	1092	1120

[1]Scheduled clinic visits (starting at Visit1 and thereafter) are to occur in the morning at approximately the same time, so that the specified FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M (±1 hour).

[2]For patients who have not previously participated in a study of QAW039: patients experiencing an asthma exacerbation during the Screening Epoch may be re-screened ≥6 weeks after recovery from the exacerbation.

[3] For patients completing a prior Phase 3 study of QAW039, Visit 1 will occur on the same day as the last day of treatment in the prior study.

[4] For patients continuing into Treatment Epoch 2, Visit 299 and Visit 301 will occur on the same day.

[5]For the witnessed dose at Visit 299, patients will take a tablet from the study drug dispensed at Visit 205.

[6]Visit 401 will occur after Visit 299 for patients not continuing into Treatment Epoch 2 or after Visit 399 for patients completing Treatment Epoch 2.

[†]For patients completing a prior Phase 3 study of QAW039; consult the CRF Completion Guidelines for patient data to be moved from the prior Phase 3 study eCRFs to the Study A2315 eCRFs.

[‡]For patients completing a prior Phase 3 study of QAW039, the assessment from the last visit of the Treatment Epoch of the prior Phase 3 study will serve as the Visit 1 assessment for Study A2315.

NP = New patients not previously participating in a phase 3 study of QAW039; **PP =** patients completing a prior Phase 3 study of QAW039; **TD =** study treatment discontinuation (permanent treatment discontinuation but continue with limited assessments); **(S) =** assessment to be recorded in source documents only; assessment will not be entered into the eCRFs; **V =** Visit;

[redacted]

[redacted]

	Screening			Treatment																	Follow-up
				Treatment Epoch 1							Treatment Epoch 2										
Visit Number (Site visits)[1]	1[2, 3]		2	201	202	203	204	205	TD	299[4,5]	301	302	303	304	305	306	307	308	TD	399	401[6]
	NP	PP																			
Treatment Week	-2		1	1	4	13	26	39	TD	52	52	65	78	91	104	117	130	143	TD	156	160
Treatment Day Note: *Visit 2 and 201 will occur on the same day if the patient is randomized	-14	-1	1*	1*	28	91	182	273	TD	364	364	455	546	637	728	819	910	1001	TD	1092	1120
[1]Scheduled clinic visits (starting at Visit1 and thereafter) are to occur in the morning at approximately the same time, so that the specified FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M (±1 hour). [2]For patients who have not previously participated in a study of QAW039: patients experiencing an asthma exacerbation during the Screening Epoch may be re-screened ≥6 weeks after recovery from the exacerbation. [3] For patients completing a prior Phase 3 study of QAW039, Visit 1 will occur on the same day as the last day of treatment in the prior study. [4] For patients continuing into Treatment Epoch 2, Visit 299 and Visit 301 will occur on the same day. [5]For the witnessed dose at Visit 299, patients will take a tablet from the study drug dispensed at Visit 205. [6]Visit 401 will occur after Visit 299 for patients not continuing into Treatment Epoch 2 or after Visit 399 for patients completing Treatment Epoch 2. †For patients completing a prior Phase 3 study of QAW039; consult the CRF Completion Guidelines for patient data to be moved from the prior Phase 3 study eCRFs to the Study A2315 eCRFs. ‡For patients completing a prior Phase 3 study of QAW039, the assessment from the last visit of the Treatment Epoch of the prior Phase 3 study will serve as the Visit 1 assessment for Study A2315. **NP** = New patients not previously participating in a phase 3 study of QAW039; **PP** = patients completing a prior Phase 3 study of QAW039; **TD** = study treatment discontinuation (permanent treatment discontinuation but continue with limited assessments); **(S) =** assessment to be recorded in source documents only; assessment will not be entered into the eCRFs; **V** = Visit;																					
Reversibility test (spirometry after administration of SABA) **Notes:** If reversibility is not demonstrated at Visit 1, historical information demonstrating reversibility may be used.	X																				
Contact IRT (S)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomize patient through IRT (S)				X																	

[redacted]

	Screening			Treatment																	Follow-up
				Treatment Epoch 1							Treatment Epoch 2										
Visit Number (Site visits)[1]	1[2, 3]		2	201	202	203	204	205	TD	299[4,5]	301	302	303	304	305	306	307	308	TD	399	401[6]
	NP	PP																			
Treatment Week	-2		1	1	4	13	26	39	TD	52	52	65	78	91	104	117	130	143	TD	156	160
Treatment Day Note: *Visit 2 and 201 will occur on the same day if the patient is randomized	-14	-1	1*	1*	28	91	182	273	TD	364	364	455	546	637	728	819	910	1001	TD	1092	1120
[1]Scheduled clinic visits (starting at Visit1 and thereafter) are to occur in the morning at approximately the same time, so that the specified FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M (±1 hour). [2]For patients who have not previously participated in a study of QAW039: patients experiencing an asthma exacerbation during the Screening Epoch may be re-screened ≥6 weeks after recovery from the exacerbation. [3] For patients completing a prior Phase 3 study of QAW039, Visit 1 will occur on the same day as the last day of treatment in the prior study. [4] For patients continuing into Treatment Epoch 2, Visit 299 and Visit 301 will occur on the same day. [5]For the witnessed dose at Visit 299, patients will take a tablet from the study drug dispensed at Visit 205. [6]Visit 401 will occur after Visit 299 for patients not continuing into Treatment Epoch 2 or after Visit 399 for patients completing Treatment Epoch 2. [†]For patients completing a prior Phase 3 study of QAW039; consult the CRF Completion Guidelines for patient data to be moved from the prior Phase 3 study eCRFs to the Study A2315 eCRFs. [‡]For patients completing a prior Phase 3 study of QAW039, the assessment from the last visit of the Treatment Epoch of the prior Phase 3 study will serve as the Visit 1 assessment for Study A2315. **NP** = New patients not previously participating in a phase 3 study of QAW039; **PP** = patients completing a prior Phase 3 study of QAW039; **TD** = study treatment discontinuation (permanent treatment discontinuation but continue with limited assessments); **(S) =** assessment to be recorded in source documents only; assessment will not be entered into the eCRFs; **V** = Visit;																					
ACQ-5 in clinic **Note:** Only for patients who HAVE NOT PREVIOUSLY PARTICIPATED IN A PHASE 3 STUDY OF QAW039.	X																				
Dispense rescue SABA to be used on an as-needed basis (S)	S	S		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S			
Return and assess rescue SABA (to be used on an as-needed basis) (S)				S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	

[redacted]

	Screening			Treatment																Follow-up
				Treatment Epoch 1							Treatment Epoch 2									
Visit Number (Site visits)[1]	1[2, 3]		2	201	202	203	204	205	TD	299[4,5]	301	302	303	304	305	306	307	308	TD	399	401[6]
	NP	PP																		
Treatment Week	-2		1	1	4	13	26	39	TD	52	52	65	78	91	104	117	130	143	TD	156	160
Treatment Day Note: *Visit 2 and 201 will occur on the same day if the patient is randomized	-14	-1	1*	1*	28	91	182	273	TD	364	364	455	546	637	728	819	910	1001	TD	1092	1120
[1]Scheduled clinic visits (starting at Visit1 and thereafter) are to occur in the morning at approximately the same time, so that the specified FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M (±1 hour). [2]For patients who have not previously participated in a study of QAW039: patients experiencing an asthma exacerbation during the Screening Epoch may be re-screened ≥6 weeks after recovery from the exacerbation. [3] For patients completing a prior Phase 3 study of QAW039, Visit 1 will occur on the same day as the last day of treatment in the prior study. [4] For patients continuing into Treatment Epoch 2, Visit 299 and Visit 301 will occur on the same day. [5]For the witnessed dose at Visit 299, patients will take a tablet from the study drug dispensed at Visit 205. [6]Visit 401 will occur after Visit 299 for patients not continuing into Treatment Epoch 2 or after Visit 399 for patients completing Treatment Epoch 2. [†]For patients completing a prior Phase 3 study of QAW039; consult the CRF Completion Guidelines for patient data to be moved from the prior Phase 3 study eCRFs to the Study A2315 eCRFs. [‡]For patients completing a prior Phase 3 study of QAW039, the assessment from the last visit of the Treatment Epoch of the prior Phase 3 study will serve as the Visit 1 assessment for Study A2315. **NP** = New patients not previously participating in a phase 3 study of QAW039; **PP** = patients completing a prior Phase 3 study of QAW039; **TD** = study treatment discontinuation (permanent treatment discontinuation but continue with limited assessments); **(S) =** assessment to be recorded in source documents only; assessment will not be entered into the eCRFs; **V** = Visit;																					
Dispense study drug **Note:** Study drug dispensed at Visit 201 will be re-dispensed at Visit 202 as kits are provided for 13 weeks of treatment.				X	X	X	X	X			X	X	X	X	X	X	X	X			
Return and assess compliance with study drug (count tablets in returned bottles) (S)						S	S	S	S	S		S	S	S	S	S	S	S	S	S	
Patient to bring all bottles of study medication to clinic					X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	

[redacted]

	Screening			Treatment																Follow-up
				Treatment Epoch 1							Treatment Epoch 2									
Visit Number (Site visits)[1]	1[2, 3]		2	201	202	203	204	205	TD	299[4,5]	301	302	303	304	305	306	307	308	TD	399	401[6]
	NP	PP																		
Treatment Week	-2		1	1	4	13	26	39	TD	52	52	65	78	91	104	117	130	143	TD	156	160
Treatment Day Note: *Visit 2 and 201 will occur on the same day if the patient is randomized	-14	-1	1*	1*	28	91	182	273	TD	364	364	455	546	637	728	819	910	1001	TD	1092	1120
[1]Scheduled clinic visits (starting at Visit1 and thereafter) are to occur in the morning at approximately the same time, so that the specified FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M (±1 hour). [2]For patients who have not previously participated in a study of QAW039: patients experiencing an asthma exacerbation during the Screening Epoch may be re-screened ≥6 weeks after recovery from the exacerbation. [3] For patients completing a prior Phase 3 study of QAW039, Visit 1 will occur on the same day as the last day of treatment in the prior study. [4] For patients continuing into Treatment Epoch 2, Visit 299 and Visit 301 will occur on the same day. [5]For the witnessed dose at Visit 299, patients will take a tablet from the study drug dispensed at Visit 205. [6]Visit 401 will occur after Visit 299 for patients not continuing into Treatment Epoch 2 or after Visit 399 for patients completing Treatment Epoch 2. †For patients completing a prior Phase 3 study of QAW039; consult the CRF Completion Guidelines for patient data to be moved from the prior Phase 3 study eCRFs to the Study A2315 eCRFs. ‡For patients completing a prior Phase 3 study of QAW039, the assessment from the last visit of the Treatment Epoch of the prior Phase 3 study will serve as the Visit 1 assessment for Study A2315. **NP** = New patients not previously participating in a phase 3 study of QAW039; **PP** = patients completing a prior Phase 3 study of QAW039; **TD** = study treatment discontinuation (permanent treatment discontinuation but continue with limited assessments); **(S) =** assessment to be recorded in source documents only; assessment will not be entered into the eCRFs; **V** = Visit;																				
In-clinic witnessed study drug intake **Note:** Complete Dose administration record (DAR) – at site visit.				X	X	X	X	X		X		X	X	X	X	X	X	X		X	
Complete Dose administration record - Summary page				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Screening Phase Disposition page (screening)			X																		
Study Phase Completion page										X										X	
End of Study Treatment page										X										X	

[redacted]

	Screening			Treatment																Follow-up
				Treatment Epoch 1							Treatment Epoch 2									
Visit Number (Site visits)[1]	1[2, 3]		2	201	202	203	204	205	TD	299[4,5]	301	302	303	304	305	306	307	308	TD	399	401[6]
	NP	PP																		
Treatment Week	-2		1	1	4	13	26	39	TD	52	52	65	78	91	104	117	130	143	TD	156	160
Treatment Day Note: *Visit 2 and 201 will occur on the same day if the patient is randomized	-14	-1	1*	1*	28	91	182	273	TD	364	364	455	546	637	728	819	910	1001	TD	1092	1120
[1]Scheduled clinic visits (starting at Visit1 and thereafter) are to occur in the morning at approximately the same time, so that the specified FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M (±1 hour). [2]For patients who have not previously participated in a study of QAW039: patients experiencing an asthma exacerbation during the Screening Epoch may be re-screened ≥6 weeks after recovery from the exacerbation. [3] For patients completing a prior Phase 3 study of QAW039, Visit 1 will occur on the same day as the last day of treatment in the prior study. [4] For patients continuing into Treatment Epoch 2, Visit 299 and Visit 301 will occur on the same day. [5]For the witnessed dose at Visit 299, patients will take a tablet from the study drug dispensed at Visit 205. [6]Visit 401 will occur after Visit 299 for patients not continuing into Treatment Epoch 2 or after Visit 399 for patients completing Treatment Epoch 2. †For patients completing a prior Phase 3 study of QAW039; consult the CRF Completion Guidelines for patient data to be moved from the prior Phase 3 study eCRFs to the Study A2315 eCRFs. ‡For patients completing a prior Phase 3 study of QAW039, the assessment from the last visit of the Treatment Epoch of the prior Phase 3 study will serve as the Visit 1 assessment for Study A2315. **NP =** New patients not previously participating in a phase 3 study of QAW039; **PP =** patients completing a prior Phase 3 study of QAW039; **TD =** study treatment discontinuation (permanent treatment discontinuation but continue with limited assessments); **(S) =** assessment to be recorded in source documents only; assessment will not be entered into the eCRFs; **V =** Visit;																				
Follow-up Phase Completion page (follow-up)																				X

[redacted]

	Screening			Treatment																Follow-up
				Treatment Epoch 1							Treatment Epoch 2									
Visit Number (Site visits)[1]	1[2, 3]		2	201	202	203	204	205	TD	299[4,5]	301	302	303	304	305	306	307	308	TD	399	401[6]
	NP	PP																		
Treatment Week	-2		1	1	4	13	26	39	TD	52	52	65	78	91	104	117	130	143	TD	156	160
Treatment Day Note: *Visit 2 and 201 will occur on the same day if the patient is randomized	-14	-1	1*	1*	28	91	182	273	TD	364	364	455	546	637	728	819	910	1001	TD	1092	1120
[1]Scheduled clinic visits (starting at Visit1 and thereafter) are to occur in the morning at approximately the same time, so that the specified FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M (±1 hour). [2]For patients who have not previously participated in a study of QAW039: patients experiencing an asthma exacerbation during the Screening Epoch may be re-screened ≥6 weeks after recovery from the exacerbation. [3] For patients completing a prior Phase 3 study of QAW039, Visit 1 will occur on the same day as the last day of treatment in the prior study. [4] For patients continuing into Treatment Epoch 2, Visit 299 and Visit 301 will occur on the same day. [5]For the witnessed dose at Visit 299, patients will take a tablet from the study drug dispensed at Visit 205. [6]Visit 401 will occur after Visit 299 for patients not continuing into Treatment Epoch 2 or after Visit 399 for patients completing Treatment Epoch 2. [†]For patients completing a prior Phase 3 study of QAW039; consult the CRF Completion Guidelines for patient data to be moved from the prior Phase 3 study eCRFs to the Study A2315 eCRFs. [‡]For patients completing a prior Phase 3 study of QAW039, the assessment from the last visit of the Treatment Epoch of the prior Phase 3 study will serve as the Visit 1 assessment for Study A2315. **NP** = New patients not previously participating in a phase 3 study of QAW039; **PP** = patients completing a prior Phase 3 study of QAW039; **TD** = study treatment discontinuation (permanent treatment discontinuation but continue with limited assessments); **(S) =** assessment to be recorded in source documents only; assessment will not be entered into the eCRFs; **V** = Visit;																					
Re-screening of patient Note: Re-screening of patients who have not previously participated in a study of QAW039 is permitted once. If a patient is re-screened, a new informed consent (and assent if applicable) must be obtained for the study as outlined in the assessment schedule above. Patients completing a prior Phase 3 study of QAW039 may not be re-screened.	X																			

[redacted]

	Screening			Treatment																	Follow-up
				Treatment Epoch 1							Treatment Epoch 2										
Visit Number (Site visits)[1]	1[2, 3]		2	201	202	203	204	205	TD	299[4,5]	301	302	303	304	305	306	307	308	TD	399	401[6]
	NP	PP																			
Treatment Week	-2		1	1	4	13	26	39	TD	52	52	65	78	91	104	117	130	143	TD	156	160
Treatment Day Note: *Visit 2 and 201 will occur on the same day if the patient is randomized	-14	-1	1*	1*	28	91	182	273	TD	364	364	455	546	637	728	819	910	1001	TD	1092	1120
[1]Scheduled clinic visits (starting at Visit1 and thereafter) are to occur in the morning at approximately the same time, so that the specified FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M (±1 hour). [2]For patients who have not previously participated in a study of QAW039: patients experiencing an asthma exacerbation during the Screening Epoch may be re-screened ≥6 weeks after recovery from the exacerbation. [3] For patients completing a prior Phase 3 study of QAW039, Visit 1 will occur on the same day as the last day of treatment in the prior study. [4] For patients continuing into Treatment Epoch 2, Visit 299 and Visit 301 will occur on the same day. [5]For the witnessed dose at Visit 299, patients will take a tablet from the study drug dispensed at Visit 205. [6]Visit 401 will occur after Visit 299 for patients not continuing into Treatment Epoch 2 or after Visit 399 for patients completing Treatment Epoch 2. [†]For patients completing a prior Phase 3 study of QAW039; consult the CRF Completion Guidelines for patient data to be moved from the prior Phase 3 study eCRFs to the Study A2315 eCRFs. [‡]For patients completing a prior Phase 3 study of QAW039, the assessment from the last visit of the Treatment Epoch of the prior Phase 3 study will serve as the Visit 1 assessment for Study A2315. **NP** = New patients not previously participating in a phase 3 study of QAW039; **PP** = patients completing a prior Phase 3 study of QAW039; **TD** = study treatment discontinuation (permanent treatment discontinuation but continue with limited assessments); **(S) =** assessment to be recorded in source documents only; assessment will not be entered into the eCRFs; **V** = Visit;																					
Withdrawal of informed consent	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Appointment for next clinic visit (S)	S	S		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	
Dispense patient card (S)	S	S																			
Collect patient card (S)																					S

[redacted]

6.1 Information to be collected on screening failures

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

All AEs **occurring after informed consent is signed** should be recorded on the Adverse Event CRF.

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

6.2 Patient demographics/other baseline characteristics

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 Y/N (RAST/ImmunoCap)
- Smoking history
- Reversibility (demonstrated or historical)
- FEV1
- OCS use Y/N
- Participation in a prior Phase 3 study of QAW039
- [redacted]
- Relevant medical history/current medical condition present before signing informed consent. Where possible, diagnoses and not symptoms will be recorded.

6.3 Treatment exposure and compliance

Study drug compliance will be assessed by the investigator and/or center personnel at designated visits by recording tablet counts from the previously dispensed bottles.

The total number of doses of study drug administered since the last dispensing visit will be recorded in the Dosage Administration Record eCRF.

[redacted]

All doses of study drug taken at the clinic visits should be from the newly assigned medication kits, **except at Visit 202 and Visit 299 when the medication returned by the patient should be used**.

6.4 Efficacy

6.4.1 Spirometry (FEV1)

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. Spirometry will be performed between 6:00 AM and 10:00 AM (±1 hour), [redacted]

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

Please refer to the Spirometry Guidance, in Appendix 4, for full details on scheduling and performing spirometry. Reversibility testing must be conducted in the morning.

6.4.2 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.

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

Patients who have not previously participated in a study of QAW039 may be rescreened once. If a patient who has not previously participated in a study of QAW039 experiences an asthma exacerbation requiring systemic corticosteroids, hospitalization, or emergency room visit during the Screening Period, rescreening of the patient should occur ≥6 weeks after recovery

[redacted]

from the asthma exacerbation. Patients completing a prior Phase 3 study of QAW039 may not be re-screened.

6.4.3 Appropriateness of efficacy assessments

The measures 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:

- Vital signs
- History and physical examinations
- 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, γ-GT, alkaline phosphatase, lactose dehydrogenase (LDH), CK, iron, uric acid, cholesterol, triglycerides
  - amylase, lipase
  - High reactive C-reactive protein (hsCRP)
  - CK-MB and Troponin-I (in response to CK results outside of the normal range)
  - Glycated hemoglobin (HbA1c) (collected at Visit 1 for new patients only)
- Urinalysis and urine chemistry
- Pregnancy test (females of childbearing potential)
- ECG
- AEs including SAEs

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 overview safety during the study. See Section 8.4 for details.

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 specified in Table 6-1. The abbreviated physical examination will include examination of the lungs and heart.

[redacted]

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 blood pressure, pulse rate, and body temperature.

After the patient has been sitting for ten minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured once using an automated validated device, e.g. OMRON, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

The patient's condition must be monitored to rule out any clinically relevant arrhythmia or tachycardia.

6.5.3 Height and weight

Height in centimeters (cm) will be measured at visits specified in the table of assessments (Table 6-1). Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at visits specified in the table of assessments (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, volume of samples, 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 at visits specified in the table of assessments (Table 6-1). Other reflex testing will be performed as outlined in the laboratory manual.

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 for new

[redacted]

patients only) and immunoglobulins (IgE, 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 should be followed until the values return to within the normal ranges or until a clinical explanation is identified, even after study medication has discontinued.

6.5.4.3 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 17-1 "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.

Three ECGs must be recorded after 10 minutes of rest 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) should be used for clinical decisions.

Triplicate 12 lead ECGs are to be collected with ECG machines supplied by the core laboratory.

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 should be labeled with study number (CQAW039A2315), subject initials (where this is allowed according to local regulations), subject number, date and time, and filed in the study site source documents.

For any ECGs with subject safety concerns, two additional ECGs should be performed to confirm the safety finding and copies forwarded to the central ECG laboratory for assessment. The final ECG assessments will be those provided by the ECG overreaders of the central ECG core laboratory. Clinically significant ECG findings prior to dosing with investigational treatment must be discussed with the Novartis responsible person or designee.

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

[redacted]

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 when a patient is identified as being of child bearing potential.

For patients completing a prior phase 3 study of QAW039, the urine pregnancy test from Visit 299 of the previous study will serve as the required Visit 1 pregnancy test for Study A2315. There will be a urine pregnancy test at all other site visits (except Visit 201, since Visit 2 and 201 should occur on the same day.

In countries where monthly pregnancy testing is required for women of child-bearing potential, these patients will perform home urine pregnancy testing monthly as instructed by the study site. These female patients will report the results of their home urine pregnancy test as "positive" or "negative" to study site staff via a monthly telephone call made by the study staff to the patient. The results will be recorded in source documents.

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 treatment 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

6.6.1 Clinical Outcome Assessments (COAs)

Asthma Control Questionnaire (ACQ)

The study coordinator should be familiar with the instrument and the associated user guides and training materials provided.

In this study, the ACQ-5 will be used to assess asthma symptom control as an inclusion criterion for patients who have not previously participated in a study of QAW039.

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 (see Appendix 6) 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

[redacted]

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 completed by patients who have not previously participated in a study of QAW039 at Visit 1 (See Table 6-1). The questionnaire should be completed before any other assessments (see Section 6). The appropriate language version(s) of the questionnaire will be used in each participating country.

Patients should complete the questionnaire in a quiet area and are allowed to ask questions; however, the site staff should take care not to influence the patient's response. In response to a question, patients should be instructed to provide the truest or best response for them.

Missing data should be avoided; therefore, the study coordinator will check the questionnaire for completeness before the patient leaves the clinic, and if necessary, encourage the patient to complete any missing responses. The original questionnaire will be kept with the patient's file as the source document.

Completed questionnaires will be reviewed by the investigator for responses which may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaire 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. Investigators should not encourage the patients to change the responses reported in the completed questionnaires.

[redacted]

7 Safety monitoring

7.1 Adverse events

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

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

Adverse events should 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

[redacted]

- its relationship to the study treatment (no/yes), or its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should 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 should be treated appropriately. Treatment may include one or more of the following:

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

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

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

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

Adverse events of special interest are being evaluated in this study population. Definitions are provided in Appendix 3.

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:

[redacted]

- 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 (see 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 (see Annex IV, ICH-E2D Guideline).

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

7.2.2 SAE reporting

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

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

[redacted]

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

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study 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.

7.3 Liver safety monitoring

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

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

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

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

Every liver laboratory trigger or liver event as defined in Table 14-1 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.

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

[redacted]

a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event must be reported on the Liver CRF pages.

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

For the liver events:

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

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

7.4 Renal safety monitoring

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

- Serum event:
  - confirmed (after ≥24h) increase in serum creatinine of ≥25% compared to baseline during normal hydration status
- Urine event
  - Albumin-creatinine ratio (ACR) ≥1g/g or ≥100 mg/mmol;
  - Protein-creatinine ratio (PCR)≥1g/g or ≥100 mg/mmol

Every renal laboratory trigger or renal event as defined in Table 17-1 should be followed up by the investigator or designated personnel at the trial site as summarized in Appendix 5.

7.5 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 is provided in Appendix 3.

[redacted]

Events with potential to be IDRs will be identified thorough a pre-specified search algorithm based on the Standardized MedDRA Queries as described in the study analysis plan. These events will be reviewed by the DMC on a regular basis.

7.6 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 Medicines Agency definition).

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

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

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

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

7.7 Pregnancy reporting

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

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

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

[redacted]

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and 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 entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis Clinical Research Associate (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 CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients/subjects will be disclosed.

8.2 Data collection

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

[redacted]

8.3 Database management and quality control

Novartis staff [or 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. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

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

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

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

Centralized spirometry readings will be processed centrally and the results will be sent electronically to Novartis (or a 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.

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, (DMC) will review safety data (including specific safety summaries for adolescent participants) from this study and other Phase 3 studies in the QAW039 asthma development program. The DMC consists 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 blinded to the interim results as described in Section 5.4. Based on the safety implications of the data, the DMC may recommend modification or termination of the study. There will be no stopping for demonstrated efficacy prior to the completion of the study, because the primary purpose of the study is the assessment of long-term safety.

[redacted]

Therefore, no statistical adjustment will be made to the final analysis due to safety DMC reviews of the data. Full details on procedures for the DMC are specified in the DMC charter.

The charter for the Data Monitoring Committee (DMC) is available as a separate document. The DMC is the autonomous data and safety advisory group for Novartis. Novartis is described as the "Sponsor" in the charter, though the Sponsor of the study in any particular country may in fact be an affiliate of this entity.

The DMC charter defines:

1. the membership of the DMC
2. responsibilities of the DMC and Novartis
3. responsibilities of independent biostatistician and programmer
4. the relationship of the DMC with other study components and data flow
5. the purpose and timing of DMC meetings
6. procedures for ensuring proper confidentiality, addressing conflict of interest, and ensuring proper communication

The charter will comply with Novartis standard operating procedures and is in accordance with the FDA guidance (FDA 2006) and CHMP guidelines (CHMP 2006) on DMCs. If significant safety issues arise in between scheduled meetings, ad-hoc meetings will be scheduled to review the data.

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 reporting at the end of Treatment Period 1 will be solely based on all Treatment Period 1 data while the reporting at the end of Treatment Period 2 will be based on all the data from both Treatment Period 1 and Treatment Period 2. Analyses combining data from prior studies of QAW039 will not be a part of the clinical study report but may be presented as a part of the separate pooled analyses.

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 during this study. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.

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

[redacted]

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

Note that the set of patients included in the FAS and SAF are the same except that the SAF allows the inclusion of non-randomized patients who receive study drug in error.

Major protocol deviations will be defined in the data handling plan prior to database lock and the un-blinding of the study and will be listed.

9.2 Patient demographics and other baseline characteristics

Baseline age will be defined as the age of the patient at study entry in Study A2315. For all other variables in patients completing a prior phase 3 study of QAW039, the baseline value from the prior study will be used as the baseline value for this study (Study A2315). For all variables in patients who have not previously participated in a study of QAW039, the last pre-treatment assessment in the current study (Study A2315) will be used as the baseline value.

Patient demographics and baseline characteristics including age, sex, race, ethnicity, height, weight, body mass index (BMI), relevant medical history, smoking history, asthma duration, background therapies, pre- and post-bronchodilator FEV1, percent predicted FEV1, [redacted], number of exacerbations in the previous year prior to screening will be summarized by treatment group for the FAS. Categorizations of age will include at least the categories of <18 years of age and ≥18 years of age.

9.3 Treatments

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

Medications started prior to study drug, taken concomitantly, and started following last study drug dose (if applicable) will be summarized by treatment group in separate tables for 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 pharmacological (ATC) class and preferred term. More than one ATC class per medication is possible and the medication will be reported under all applicable classes.

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

Compliance with study medication over the entire study will be summarized as the percentage of days with study medication 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 on the SAF.

[redacted]

9.4.1 Variables

The primary variables for the study are:

- Time-to-first treatment emergent AE;
- Time-to-first treatment emergent SAE; and
- Time-to-first treatment emergent AE leading to discontinuation from study treatment.

Adverse events (including asthma exacerbations), starting on or after the time of the first intake of study drug and until the day after the last intake of study drug will be classified as treatment emergent AEs. Any AEs that started during the study after informed consent and before the time of the first intake of study drug will be classified as a prior AE and not classified as treatment emergent AE. The time-to-first treatment emergent AE will be defined as the time to the occurrence of an AE from the treatment start date, and will be computed as time to AE=AE start date-treatment start date+1 day. Treatment emergent SAEs and AEs leading to discontinuation from study treatment will be defined in a similar manner.

9.4.2 Statistical model, hypothesis, and method of analysis

The time-to-first treatment emergent AE will be considered from the start of Study A2315 only and the clinical study report will be based solely on the data from Study A2315.

The primary variable will be analyzed by a Cox regression model stratified by randomization stratum (but not by region):

- patients on QAW039 150 mg once daily treatment in Studies QAW039A2307 and QAW039A2314,
- patients on QAW039 450 mg once daily treatment in Studies QAW039A2307 and QAW039A2314,
- patients on placebo in Studies QAW039A2307 and QAW039A2314,
- patients on QAW039 150 mg once daily treatment in Studies QAW039A2316 and QAW039A2317,
- patients on placebo in Studies QAW039A2316 and QAW039A2317,
- patients who have not previously participated in a study of QAW039,

and treatment group, severity of asthma (GINA treatment steps 3, 4 and 5), and region as fixed class effects.

Hazard ratios comparing QAW039 450 mg once daily, QAW039 150 mg, once daily, and placebo treatments with regard to time to first treatment emergent AEs and their corresponding 95% profile likelihood confidence intervals will be presented. The other primary variables, treatment emergent SAEs and AEs leading to study treatment discontinuation, will be analyzed in a similar fashion.

The detailed statistical analysis plan will pre-specify how strata would be pooled for analysis purposes, if this is necessary.

The same analyses will be performed based on the Treatment Period 1 data and based on the entirety of the study (Treatment Period 1 and Treatment Period 2 combined). A multiplicity adjustment for these two separate assessments is not foreseen.

[redacted]

Summary statistics for the primary variable

The primary variables will be summarized for the SAF by treatment group in terms of the number of patients experiencing a treatment emergent AE, as well as the exposure-adjusted incidence rate (patients with treatment emergent AEs per patient year of follow-up to first event [AE or censoring]). The duration of on-treatment follow-up in years will be calculated for each patient as (treatment end date - treatment start date + 2 days)/365.25 without taking into account treatment interruptions. Summaries of the other primary variables, treatment emergent SAEs and AEs leading to study treatment discontinuation, will be similarly presented. Additionally, incidence rates may be compared with epidemiological background rates in appropriately matched populations.

Estimates of the cumulative incidence of the primary outcomes will be displayed graphically for the SAF.

9.4.3 Handling of missing values/censoring/discontinuations

Patients that do not experience a treatment emergent AE prior to study end or the day after treatment discontinuation will be considered censored at the time of study end or the day after the last intake of study drug. For the analysis of the 52-week data from Treatment Period 1, patients without a treatment emergent AE during Treatment Period 1 will be considered censored on the day after their last intake of study drug in Treatment Period 1 or on the day of the completion visit (Visit 299) in Treatment Period 1, if the patient continued into Treatment Period 2.

The primary Cox regression model will implicitly impute the censored data under the assumption of independent censoring (conditional on the baseline covariates). That is, a censored patient is assumed to be no more or less likely to experience an event in any future time interval than other patients in the same stratum that continue to be at risk for a first event and that have the same model covariates. The implied assumption of a continued treatment effect after treatment discontinuation is considered conservative for the purpose of the evaluation of safety outcomes that are assumed to be more likely to occur while active treatment is ongoing. The sensitivity analyses described in Section 9.4.4 will evaluate the impact of these assumptions on the trial conclusions.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The primary and secondary objectives of the study are based on safety variables and hence no efficacy variables are stated in this section.

9.5.2 Safety variables

All safety data will be summarized for the SAF.

Safety summaries will be primarily based on on-treatment data with selected tables also presented for the all data after the first intake of study drug, while all data based safety data will be listed.

Secondary safety endpoints

The secondary endpoint of the rate of patients with at least one treatment emergent AE by primary system organ class will be presented descriptively and analyzed using a Cox regression model in a similar manner as the primary endpoint. A supportive analysis on the rate of patients with at least one AE by primary system organ class will be conducted similarly including all AEs starting on or after the time of the first intake of study drug (i.e., treatment emergent AEs and AEs occurring during the post-treatment follow-up).

The secondary endpoint of the rate of treatment emergent patient deaths and patient hospitalizations (any visit to the hospital requiring an overnight stay or an emergency room visit greater than 24 hours) due to an asthma exacerbation will be analyzed using a negative binomial regression model. The model will include randomization stratum (as in the analysis on primary endpoint), treatment group, severity of asthma (GINA steps 3, 4 and 5), and region as fixed class effects, with the natural logarithm of the duration of on-treatment follow-up in years as an offset variable. The duration of on-treatment follow-up in years will be calculated

for each patient as (treatment end date - treatment start date + 2 days)/365.25 without taking into account treatment interruptions. A supportive analysis of the rate of patient deaths and patient hospitalizations due to asthma exacerbations treatment emergent and after treatment discontinuation will be conducted similarly with the natural logarithm of the duration of follow-up in years as an offset variable.

In addition to the inferential analysis, summary statistics on the secondary safety variables will be presented as described below.

Adverse events

Adverse events after informed consent including asthma exacerbations will be summarized and listed. Summaries will include the number of patients with an event, exposure-adjusted incidence rates (patients with an event per patient year of follow-up to first event or censoring) and the percentage of patients with an event.

The following treatment emergent AE 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 AEs by system organ class and preferred term,
- SAEs by system organ class and preferred term, and
- AEs leading to permanent discontinuation of study-drug by system organ class and preferred term.

Additionally, summaries including both treatment emergent and post-treatment discontinuation events will be produced for AEs and SAEs by system organ class and preferred term. Similarly, summaries will also be presented on patient deaths and patient hospitalizations (any visit to the hospital requiring an overnight stay or an emergency room visit greater than 24 hours) due to an asthma exacerbation.

The number and percentage of patients with treatment emergent AEs of special interest (e.g., IDRs), will be summarized for each type of event with a break-down for each type of event by SMQ (when applicable) and preferred term. Time-to-first-event analyses using Kaplan-Meier plots and Cox regressions with the same model terms as the primary efficacy analysis model will be reported for each type of event, as well as incidence for recurrent events per patient-year of follow-up. The strategy for identifying these events will be defined in the detailed statistical analysis plan for this study.

Vital signs

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

[redacted]

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

Electrocardiogram (ECG)

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

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

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

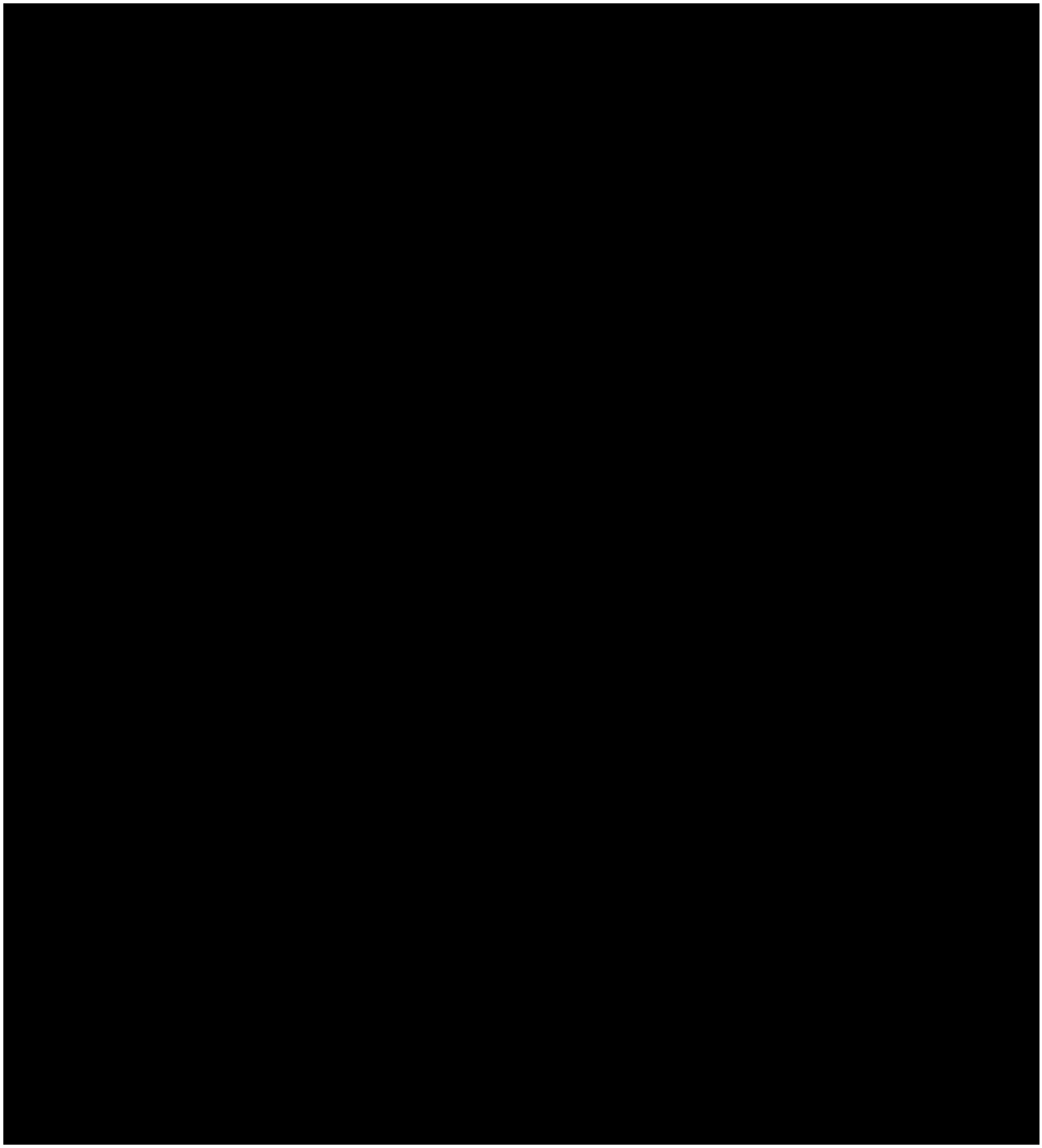
Laboratory data

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

Shift tables relative to the normal reference ranges will be used to summarize the on-treatment change from baseline to post-baseline for each laboratory parameter. For each on-treatment 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 on-treatment 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 on-treatment value meeting the clinically notable criteria will be counted under the applicable criteria.

[redacted]



9.7 Interim analyses

As described in Section 3.5, periodic unblinded safety reviews by the DMC (see Section 8.4) using data (including specific safety summaries for adolescent participants) from this study and other Phase 3 studies in the QAW039 asthma development program will be conducted. No stopping for demonstrated efficacy or safety prior to the completion of the study is foreseen, because the purpose of the study is to assess long-term safety. Thus, no statistical adjustment will be made to any of the interim analyses or the analysis after all patients have

completed the study. No adjustment is foreseen to account for these two reporting times. To support the worldwide registration of QAW039 and to address health authority requests, interim analyses are foreseen and the results may be submitted to health authorities. Interim analyses will focus on presentation of safety data, including partial data for patients ongoing in the study; analyses on efficacy endpoints will not be performed. After all patients have completed or discontinued Treatment Period 1, a report based on Treatment Period 1 data will be produced and results may be published.

9.8 Sample size calculation

Approximately 1000 patients are expected to complete prior QAW039 Phase 3 studies and join the current Study A2315, based on the following assumptions.

- In the prior QAW039 Phase 3 studies, 85% of randomized patients are expected to complete the prior study and eligible for participation in the current study.
- It is estimated that 50% of those eligible patients from Studies A2307 and A2314 will enter in the current study.
- It is estimated that 25% of those eligible patients from Studies A2316 and A2317 will enter in the current study.

New patients (i.e., patients who have not previously participated in a study of QAW039) will also be recruited according to local regulatory requirements in certain countries. It is currently anticipated that approximately 570 newly recruited patients will be enrolled in the current study. Thus, the anticipated total sample size of this study is approximately 1,570 patients. This number of patients participating in the safety study will ensure 6-month exposure for each QAW039 dose clearly across the whole Phase 3 program in excess of the 300 to 600 patients (as well as in excess of 100 patients exposed for at least 1 year) suggested by ICH E1 at the time of the first regulatory submission for QAW039. The number of new patients and total patients may be subject to change depending on the actual participation of patients from prior QAW039 Phase 3 studies, the actual dropout rate in the current study and the local regulatory requirements.

While no formal hypothesis testing is foreseen for the primary safety objectives, if both QAW039 doses have a 50% relative hazard increase for treatment emergent events, compared with placebo, then there will be approximately > 99%, 94% and 38% power that the two-sided 95% confidence interval not adjusted for multiplicity for one of the two QAW039 doses would exclude no effect for the primary safety variables of time-to-first treatment emergent AE, time-to-first treatment emergent SAE, and time-to-first treatment emergent AE leading to study treatment discontinuation analyzed across Treatment Period 1 and Treatment 2 combined, respectively. The power was estimated using 10,000 simulations based on 1,570 patients being randomized into the current study. In addition, the sensitivity of the power is further assessed for different scenarios of sample size (1470 patients and 1670 patients).This power will be higher, if more patients are randomized (e.g., due to additional new patients being enrolled) or more patients completing prior Phase 3 studies of QAW039 elect to participate in the current study.

[redacted]

The underlying assumptions for the power simulations were an exponential censoring rate in the placebo group of 0.22 and of 0.16 in the QAW039 treatment groups. The assumptions on the exponential event rate in each treatment group are shown in Table 9-1. These assumptions are based on the, DREAM (Pavord et al. 2012) and MENSA (Ortega et al. 2014) trials, as well as a QAW039 Phase 2 study in moderate-to-severe asthma. The detailed power calculations are shown in the Table 9-2 and Table 9-3.

Table 9-1 Assumed placebo event rates for power calculations

Endpoint	Previous study patients were enrolled in or new patients	Assumed exponential event rate (per patient-year)
Rate of AEs	QAW039A2316/ QAW039A2317	3.01
	QAW039A2307/ QAW039A2314	2.86
	New patients	2.86
Rate of SAEs	QAW039A2316/ QAW039A2317	0.07
	QAW039A2307/ QAW039A2314	0.24
	New patients	0.24
Rate of AEs leading to study treatment discontinuation	QAW039A2316/ QAW039A2317	0.03
	QAW039A2307/ QAW039A2314	0.03
	New patients	0.03

Table 9-2 Power (%) for a non-multiplicity adjusted confidence interval to exclude no-difference versus placebo for the primary safety variables

Primary Endpoint	Treatment Period	QAW039 150 mg versus placebo	QAW39 450 mg versus placebo	Both QAW039 150 mg and 450 mg versus placebo	One of the two QAW039 doses versus placebo
Time-to-first AE	1	>99	>99	>99	>99
	1 & 2	>99	>99	>99	>99
Time-to-first SAE	1	65	65	54	76
	1 & 2	89	89	84	94
Time-to-first AE leading to study treatment discontinuation	1	16	16	9	22
	1 & 2	29	28	19	38

Power results are based on the sample size of 1570 randomized patients (1000 rollover patients plus 570 new patients).
Simulations were performed in SAS 9.4.

Table 9-3 power (%) for a non-multiplicity adjusted confidence interval to exclude no-difference versus placebo for the primary safety variables based on different sample size scenarios

Primary Endpoint	Treatment Period	QAW039 150 mg versus placebo	QAW39 450 mg versus placebo	Both QAW039 150 mg and 450 mg versus placebo	One of the two QAW039 doses versus placebo
Time-to-first AE	1	>99	>99	>99	>99
		>99	>99	>99	>99
	1 & 2	>99	>99	>99	>99
		>99	>99	>99	>99
Time-to-first SAE	1	62	62	50	73
		68	68	57	79
	1 & 2	87	87	81	93
		92	91	87	96
Time-to-first AE leading to study treatment discontinuation	1	14	14	8	21
		17	16	10	23
	1 & 2	27	27	17	36
		30	30	20	40

Power results in the upper rows are based on the sample size of 1470 randomized patients (1000 rollover patients plus 470 new patients).
Power results in the lower rows are based on the sample size of 1670 randomized patients (1000 rollover patients plus 670 new patients).
Simulations were performed in SAS 9.4.

[redacted]

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

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

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.

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

10.3 Responsibilities of the investigator and IRB/IEC

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

[redacted]

page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

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

10.5 Quality Control and Quality Assurance

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

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

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal 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/subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

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

11.1 Protocol Amendments

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

hazard to patients/subjects may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

12 References

References are available upon request.

ATS (2000) Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. Am J Respir Crit Care Med; 162: 2341-51.

ATS/ERS (2005) Recommendations for Standardized Procedures for Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide. AJRCCM; 171: 912-930.

Castro M, Mathur S, Hargreave F et al (2011) Reslizumab for poorly controlled, eosinophilic asthma. Am J Resp Crit Care Med; 184: 1125-1132.

Castro M, Zangrilli J, Wechsler ME et al. (2015) Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two, multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med; Published Online: 23 February 2015.

Cdc.gov, (2000). *Growth Charts - Homepage*. [online] Available at: http://www.cdc.gov/growthcharts/ [Accessed 26 Feb. 2016].

Chevalier E, Stock J, Fisher T et al. (2005) Cutting edge: chemoattractant receptor-homologous molecule expressed on Th2 cells plays a restricting role on IL-5 production and eosinophil recruitment. J Immunol; 175: 2056–2060.

Chung KF, Wenzel S, Brozek J et al. (2014) International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J; 43:343.

Deng JW, Song IS, Shin HJ et al (2008) The effect of SLC01B1*15 in the disposition of pravastatin and pitavastatin is substrate dependent: the contribution of transporting activity changes by SLC01B1*15. Pharmacogenetics and Genomics; 18(5): 424-433.

Elsby R, Hilgendorf C, and Fenner K (2012) Understanding the critical disposition pathways of statins to assess drug-drug interaction risk during drug development: it's not just about OATP1B1. Clin Pharmacol and Ther; 92: 585-598.

Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2016. Available from http://www.ginasthma.org/.

Haldar P, Brightling CE, Hargadon B et al. (2009) Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med; 360(10):973-84.

Jacobson TA (2008) Toward "pain-fee" statin prescribing: clinical algorithm for diagnosis and management of myalgia. Mayo Clin Proc; 83: 687-700.

[redacted]

Juniper EF, O'Byrne PM, Guyatt GH et al. (1999) Development and validation of the questionnaire to measure asthma control. Eur Resp J; 14: 902-907.

Juniper EF, Svensson K, Moerk AC, Ståhl E (2005) Modification of the Asthma Quality of Life Questionnaire (standardised) in patients 12 years and older. Health and Quality of Life Outcomes. Health Qual of Life Outcomes; 3: 58.

Juniper EF, Bousquet J, Abetz L et al., GOAL Committee (2006) Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med; 100: 616- 621.

Juniper EF, Gruffydd-Jones K, Ward S, Svensson K (2010) Validation, measurement properties and interpretation of the Asthma Control Questionnaire in children. Eur Respir J; 36: 1410-1416.

Kalliokoski A and Niemi M (2009) Impact of OATP transporters on pharmacokinetics. B J P; 158: 693-705.

[redacted]

Masoli M, Fabian D, Holt S et al. (2004) The global burden of asthma: executive summary of the GINA Dissemination Committee Report. Allergy; 59: 469-478.

Nair P, Pizzichini MM, Kjarsgaard M et al (2009) Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Engl J Med; 360(10):985-93.

[redacted]

Noe J, Portmann R, Brun ME et al (2007) Substrate-dependent drug-drug interactions between gemfibrozil, fluvastatin, and other organic anion-transporting peptide (OATP) substrates on OATP1B1, OATP2B1, and OATP1B3. Drug Metab Dispos 35(8): 1308-1314.

Nowak RM, Parker JM, Silverman RA et al (2015) A randomized trial of benralizumab, an antiinterleukin 5 receptor α monoclonal antibody, after acute asthma. Am J Emergency Med; 33:14-20.

Ortega H, Liu MC, Pavord ID et al. (2014) Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med; 371(13): 1198-1207.

Pavord ID, Korn S, Howarth P et al. (2012) Mepolizumab for severe eosinophilic asthma (DREAM): a multicenter, double-blind, placebo-controlled trial. Lancet; 380: 651-659.

Reddel HK, Taylor DR, Bateman ED et al. (2009) An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med; 180: 59-99.

Regan SL, Maggs JL, Hammond TG et al (2010) Acyl glucuronides: the good, the bad and the ugly. Biopharm Drug Dispos; 31:367-95.

[redacted]

Takaku Y, Soma T, Nishihara F et al. (2013) Omalizumab attenuates airway inflammation and interleukin-5 production by mononuclear cells in patients with severe allergic asthma. Int Arch Allergy Immunol; 161 Suppl 2:107-17.

Wenzel S (2005) Severe asthma in adults. Am J Respir Crit Care Med; 172(2):149-60. Epub 2005 Apr 22.

Wenzel S, Ford L, Pearlman D (2013) Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med; 368(26): 2455-66.

[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 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 5 for specific renal alert Criteria and actions

For 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 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
TBL: total bilirubin; ULN: upper limit of normal

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

Criteria	**Actions required**	**Follow-up monitoring**
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • 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)

[redacted]

Criteria	Actions required	Follow-up monitoring
> 3 × ULN accompanied by symptoms[b]	• 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 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.

[redacted]

15 Appendix 3: List of IDRs for investigators

Table 15-1 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]

16 Appendix 4: 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 FVC tracings. All spirometry values should be reported at BTPS by the method established by the manufacturer.

Calibration

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

Preparing the test subject

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

- Coffee, tea, chocolate, cola and other caffeine-containing beverages and foods and ice-cold beverages for 4 hours prior to spirometry
- Alcohol for 4 hours prior to spirometry
- Strenuous activity for 12 hours prior to spirometry
- 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.

[redacted]

Acceptability

An acceptable maneuver has the following characteristics:

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

Repeatability

The 2 largest FVC and 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 at Visit 1, patient may be rescreened or allow one spirometry retest.

Recording of data

The greatest FEV_1 and FVC from any of the acceptable curves are recorded. (The greatest FEV_1 and FVC may not necessarily result from the same acceptable curve).

Predicted normal

For all subjects, this study will utilize the global lung function 2012 spirometric prediction 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 a witheld period as indicated in Table 5-2.

Administer 400µg of salbutamol/albuterol (or equivalent) following the completion of the pre-bronchodilator assessment*. Post-bronchodilator spirometry assessment is then performed approximately 10 to 15 minutes after administration of the salbumatol/albuterol.

Reversibility is calculated as:

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

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

[redacted]

[redacted]

16.1 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]

17 Appendix 5: Specific Renal Alert Criteria and Actions

Table 17-1 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.	

18 Appendix 6: Asthma Control Questionnaire

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

December 2002

SYMPTOMS ONLY MODIFIED 30 JAN 04 NORTH AMERICAN ENGLISH

[redacted]

ASTHMA CONTROL QUESTIONNAIRE© Page 1 of 1

Please answer questions 1 - 5

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

1.	On average, during the past week, how often were you **woken by your asthma** during the night?	0 Never 1 Hardly ever 2 A few times 3 Several times 4 Many times 5 A great many times 6 Unable to sleep because of asthma
2.	On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?	0 No symptoms 1 Very mild symptoms 2 Mild symptoms 3 Moderate symptoms 4 Quite severe symptoms 5 Severe symptoms 6 Very severe symptoms
3.	In general, during the past week, how **limited were you in your activities** because of your asthma?	0 Not limited at all 1 Very slightly limited 2 Slightly limited 3 Moderately limited 4 Very limited 5 Extremely limited 6 Totally limited
4.	In general, during the past week, how much **shortness of breath** did you experience because of your asthma?	0 None 1 A very little 2 A little 3 A moderate amount 4 Quite a lot 5 A great deal 6 A very great deal
5.	In general, during the past week, how much of the time did you **wheeze**?	0 Not at all 1 Hardly any of the time 2 A little of the time 3 A moderate amount of the time 4 A lot of the time 5 Most of the time 6 All the time

SYMPTOMS ONLY MODIFIED 30 JAN 04 NORTH AMERICAN ENGLISH

[redacted]