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

[redacted]

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

[redacted]

[redacted]

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

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

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

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

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

3.2 Rationale for study design

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

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

Patient population

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

[redacted]

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

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

Screening period

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

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

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

Placebo run-in

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

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

Treatment period

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

Follow-up period

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

[redacted]

at baseline. In one study, QAW039 also demonstrated a reduction in sputum eosinophils in patients with severe asthma.

The potential benefits of QAW039 therapy need to be balanced against its potential risks. Potential side effects of QAW039 include: increased heart rate, non-serious arrhythmia such as palpitations, headache, diarrhea, nausea, vomiting, nasopharyngitis, somnolescence and dizziness. In humans, one major metabolite of QAW039 has been identified which is formed by glucuronidation (acyl glucuronide) and partially binds to plasma proteins. In the literature, in vivo binding of acyl glucuronides to proteins has been reported to be associated with rare idiosyncratic drug reactions (IDRs), although a causal connection of protein adduction to IDRs remains uncertain (Regan et al 2010). There have been no IDRs observed with QAW039 treatment in completed clinical trials as of 31-Jan-2016. Taking QAW039 at the doses used in this study with the cholesterol-lowering drug simvastatin has been shown to cause a small increase in the peak blood level of simvastatin.

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

Patients on doses of simvastatin > 20 mg, doses of atorvastatin >40 mg, doses of pravastatin >40 mg, or doses of pitavastatin >2 mg per day (Elsby et al 2012, Deng et al 2008, Noe et al 2007, and Kalliokoski and Niemi 2009), as well as patients on any statins with high creatine kinase (CK) levels (>2 X ULN (upper limit of normal)) at screening will be excluded from the study. Patients on statin medication who are included in the study will have regular monitoring for relevant symptoms and be subject to discontinuation based on persistent myalgia and/or blood CK levels (Jacobson 2008). Cardiovascular risks will be monitored based on changes in vital signs, ECGs and biochemical parameters. Monitoring of liver function tests (LFT) and renal function will be conducted as described in Appendix 2 and Appendix 3, respectively, of this protocol. Surveillance of adverse events for identification of idiosyncratic drugs will be conducted.

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

4 Population

The study population will include:

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

4.1 Inclusion criteria

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

[redacted]

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

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

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

[redacted]

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

6.5.1 Physical examination

A complete physical examination will be performed at visits specified in the table of assessments (Table 6-1). It will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

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

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

6.5.2 Vital signs

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

6.5.3 Height and weight

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

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

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

6.5.4 Laboratory evaluations

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

Clinically notable laboratory findings are defined in Appendix 1.

6.5.4.1 Hematology

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

[redacted]

6.5.4.2 Clinical chemistry

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

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

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

6.5.4.3 Urinalysis

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

6.5.5 Electrocardiogram (ECG)

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

ECGs must be recorded according to the ECG investigator manual in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is PRO collection first, followed by ECG, and then other study procedures (see Section 6). The Fridericia QT correction formula (QTcF) must be used for clinical decisions.

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

The original trace will be sent electronically for central review directly from the ECG machine. Two 'identical' duplicate print-outs will be generated and kept at the investigator site as source documentation and as back-up for submission to the central laboratory in case of problems with the electronic transmission. Each page of the ECG tracing must be labeled with study number (CQAW039A2317), subject initials (where this is allowed according to local regulations), subject number, date and time, and filed in the study site source documents.

[redacted]

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

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

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

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

Asthma Control Questionnaire (ACQ-5)

In this study, the ACQ-5 will be used to assess improvements in asthma symptom control.

The original ACQ consists of 7 items: 5 items on symptom assessment, 1 item on rescue bronchodilator use, and 1 item on airway caliber (% FEV_1 predicted). The rescue bronchodilator use and % FEV_1 predicted items are not included in the ACQ-5. The ACQ was originally validated in patients with asthma over aged 17 years (Juniper et al 1999, Juniper et al 2006), and is one of several asthma control measures recommended by the GINA Guidelines. The ACQ has been fully validated, including patients aged from 6 to 16 years (Juniper et al 2010) and including a minimal important difference (MID) or smallest change that can be considered clinically important (0.5).

The ACQ-5 will be self-administered at the clinic and only takes a few minutes to complete. Patients will be asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0=no impairment, 6=maximum impairment). The questions are equally weighted and the ACQ-5 score is the mean of the 5 questions: therefore, between 0 (totally controlled) and 6 (severely uncontrolled) (Juniper et al 1999; Juniper et al 2005; Juniper et al 2006).

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

[redacted]

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

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

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

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

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

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

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

[redacted]

7.2.2 SAE reporting

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

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

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

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology (DS&E) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with European Union (EU) Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

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

7.3 Liver safety monitoring

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

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

[redacted]

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

9.4.3 Handling of missing values/censoring/discontinuations

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

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

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

9.4.4 Supportive analyses

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

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

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

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

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

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

[redacted]

Table 9-2 Power simulations for secondary variables

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

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

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

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

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

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

[redacted]

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

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

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

[redacted]

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]

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

SELF-ADMINISTERED DATE: _____

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

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

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

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

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

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

[redacted]

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

[redacted]

3 Investigational plan

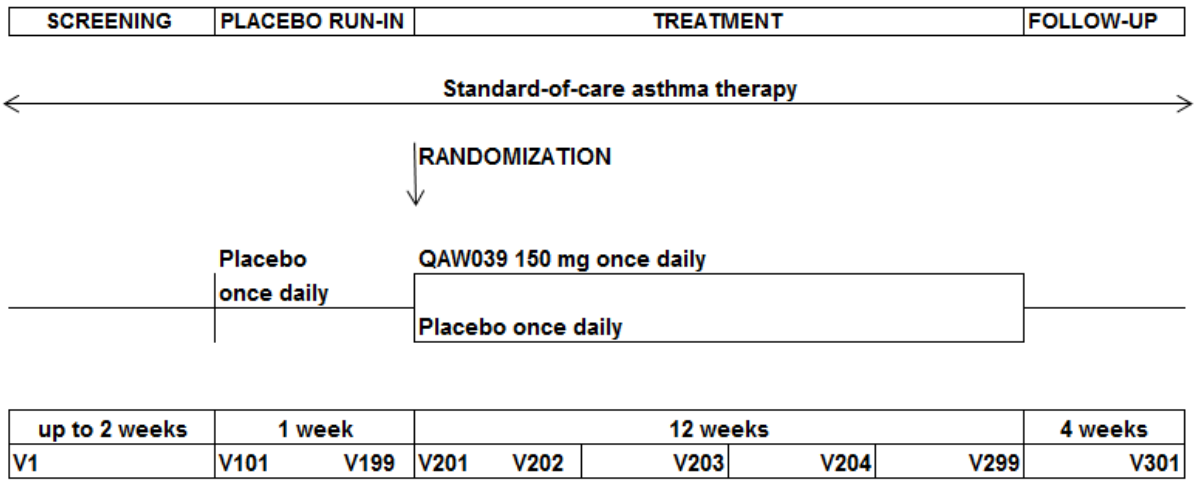
3.1 Study design

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

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

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

Figure 3-1 Study design



The investigator must provide appropriate advice on the continued use of effective contraception for at least one week (at least 5 half-lives of QAW039) after the last dose of study drug and follow up with the subject as appropriate.

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

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

3.4 Rationale for choice of comparator

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

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

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.6 Risks and benefits

QAW039 is a potent and highly selective oral DP2 antagonist being developed as a potential therapy for patients with severe asthma. DP2 is a receptor for PGD_2 which mediates the activation and migration of T helper 2 (Th-2) cells and eosinophils, some of the key inflammatory cell types in asthma. Recruitment of these cells into the lung is partly responsible for the intermittent airway obstruction which leads to wheezing and shortness of breath characteristic of asthma.

The overall clinical experience with QAW039 includes 15 studies: 11 (six in healthy volunteers and five in patients) have completed and four (three in patients and one in healthy volunteers) are ongoing. The completed phase 2 studies consist of three in patients with asthma, one in patients with allergic rhinitis and one in patients with atopic dermatitis (Refer to the Investigator's Brochure (IB) for information on the studies of QAW039). As of 31-Jan-2016, >1400 patients have been exposed to QAW039.

Three Phase 2 studies in patients with asthma evaluated the effect of QAW039 across the range of asthma severities (mild to severe). In these studies, QAW039 demonstrated an effect on lung function (FEV1) in patients with moderate-to-severe asthma, and an improvement in quality of life scores and asthma control questionnaire scores in severe patients uncontrolled

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

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

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

[redacted]

Table 6-1 Assessment schedule

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

[redacted]

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

[redacted]

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

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

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

6.5.6 Pregnancy and assessments of fertility

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

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

6.5.7 Appropriateness of safety measurements

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

6.6 Other assessments

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

6.6.1 Clinical Outcome Assessments (COAs)

6.6.1.1 Patient Reported Outcomes (PRO)

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

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

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

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

[redacted]

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

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

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

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

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

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

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

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

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

7.2 Serious adverse events

7.2.1 Definition of SAE

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

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

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

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

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

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

[redacted]

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

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

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

For the liver laboratory trigger:

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

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

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

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

For the liver events:

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

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

7.4 Renal safety monitoring

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

- Serum event:
  - Confirmed (after ≥24 hours) increase in serum creatinine (sCr) of ≥25% compared to baseline during normal hydration status.
- Urine event
  - Albumin-creatinine ratio (ACR) ≥1g/g or ≥100 mg/mmol.

[redacted]

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

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

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

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

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

Subgroups

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

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

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

[redacted]

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

10.3 Responsibilities of the investigator and IRB/IEC

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

10.4 Publication of study protocol and results

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

10.5 Quality Control and Quality Assurance

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

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

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

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any

[redacted]

15 Appendix 3: Specific Renal Alert Criteria and Actions

Table 15-1 Specific Renal Alert Criteria and Actions

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

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

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

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

SELF-ADMINISTERED
(≥12 years)

For further information:

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

APRIL 2008

[redacted]

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

SELF-ADMINISTERED DATE: _____

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

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

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

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

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

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

[redacted]