NOVARTIS

Global Clinical Development - General Medicine

QAW039

Clinical Trial Protocol CQAW039A2307 / NCT02555683

A 52-week, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of QAW039 when added to existing asthma therapy in patients with uncontrolled severe asthma

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List of abbreviations

Abbreviation:	Explanation:
ACQ	Asthma Control Questionnaire
AE(s)	Adverse Event(s)
AHR	Airway Hyper-reactivity Test
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AQLQ+12	Asthma Quality of Life Questionnaire for 12 years and above
AST	Aspartate aminotransferase
ATS/ERS	American Thoracic Society/European Respiratory Society
AUC	Area under the plasma concentration-time curve. The time interval may be specified e.g. AUC_{inf} means the interval 0 to infinity.
b.i.d.	Twice a day
BMI	Body Mass Index
CFR	United States Code of Federal Regulations
CK	Creatine kinase
CPO	Country Pharma Organization
CRO	Contract Research Organization
CRF	Case Report/Record Form (paper or electronic)
CRTh2	Chemoattractant receptor-homologous molecule expressed on Th2
DK-PGD2	13,14-dihydro-15-ketoprostaglandin D2
DP	Prostaglandin D2 receptor
DMC	Data Monitoring Committee
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiography
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
[redacted]	[redacted]
FCT	Film-coated tablet
FDA	Food and Drug Administration
[redacted]	[redacted]
FEV_1	Forced Expiratory Volume in 1 second
[redacted]	[redacted]
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
HbA1c	Hemoglobin A1c; Glycosylated Hemoglobin
hCG	Human Chorionic Gonadotropin
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
IL	Interleukin

[redacted]

Abbreviation:	Explanation:
ImmunoCAP[R]	Specific IgE test
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
LABA	Long-acting Beta-agonist
LAMA	Long-acting muscarinic antagonist
LC-MS/MS	Liquid chromatography–mass spectrometry/mass spectrometry
LFT	Liver Function Test
LLOQ	Lower Limit of Quantification
LTRA	Leukotriene Receptor Antagonist
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of Diet in Renal Disease Study
MID	Minimally Important Difference
MMRM	Mixed Model Repeated Measures
NYHA	New York Heart Association
OC/RDC	Oracle Clinical/Remote Data Capture
OCS	Oral corticosteroids
[redacted]	[redacted]
PGD2	Prostaglandin D2
[redacted]	[redacted]
PK	Pharmacokinetic
PoC	Proof of Concept
PRO	Patient Reported Outcome
p.o.	Oral(ly)
q.d.	Quaque die /once a day
QOL	Quality of life
QTcF	Fridericia QT correction formula
RAST	Radioallergosorbent Test
SABA	Short-acting Beta-agonist
SAE(s)	Serious Adverse Event(s)
SD	Standard Deviation
SoC	Standard of care
SUSAR	Suspected Unexpected Serious Adverse Reactions
TD	Treatment Discontinuation
Th2	T helper type 2 cells
UGT	Uridinediphosphate glucuronosyltransferase
ULN	Upper Limit of Normal

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the drug being tested in the trial
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical Epochs are: screening/recruitment, wash-out, treatment, and follow-up
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.”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* protocol-specified concomitant background therapies when these are standard treatments in that indication
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Premature subject/patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Subject Number	A number assigned to each patient who enrolls into the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

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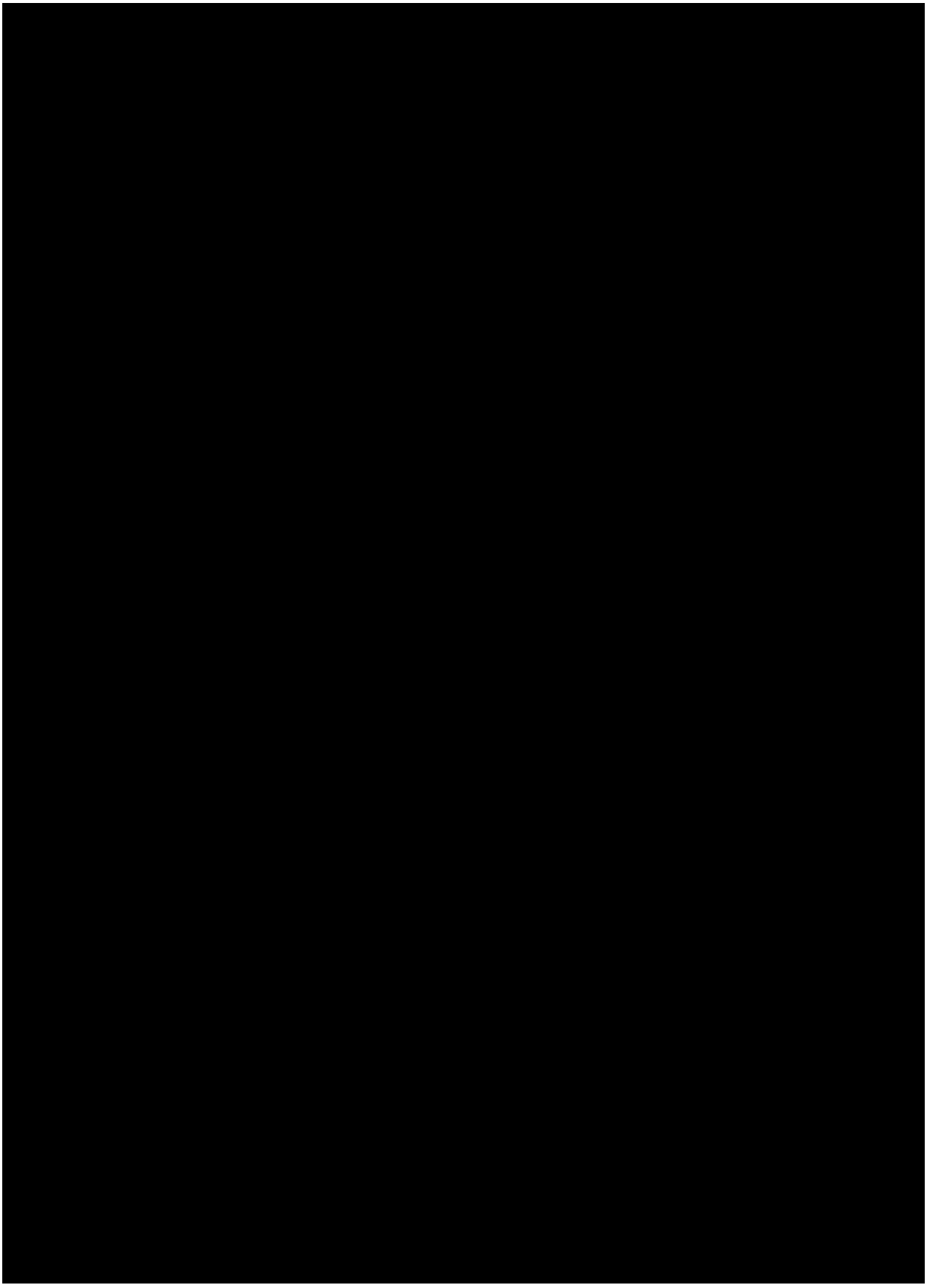

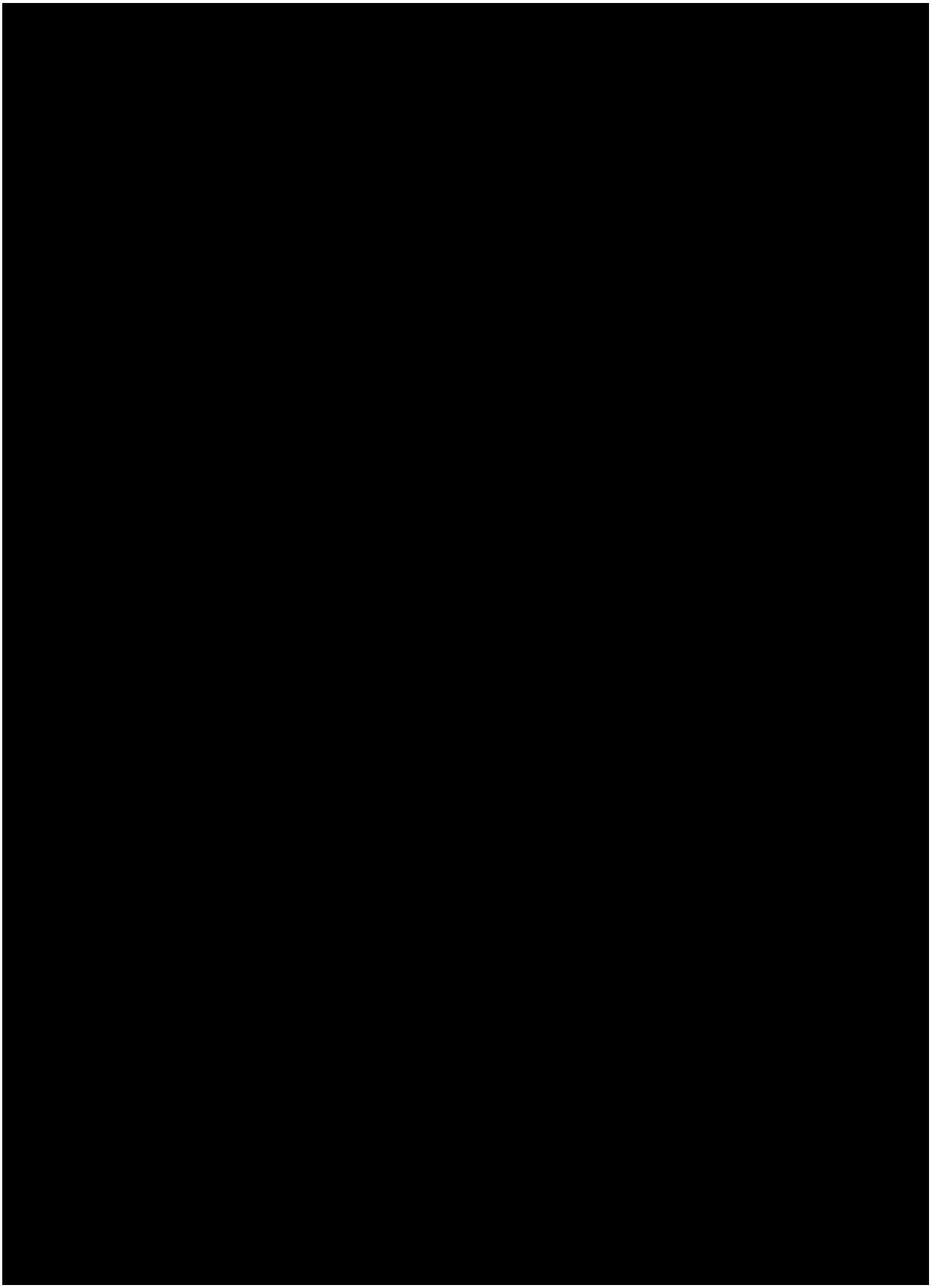

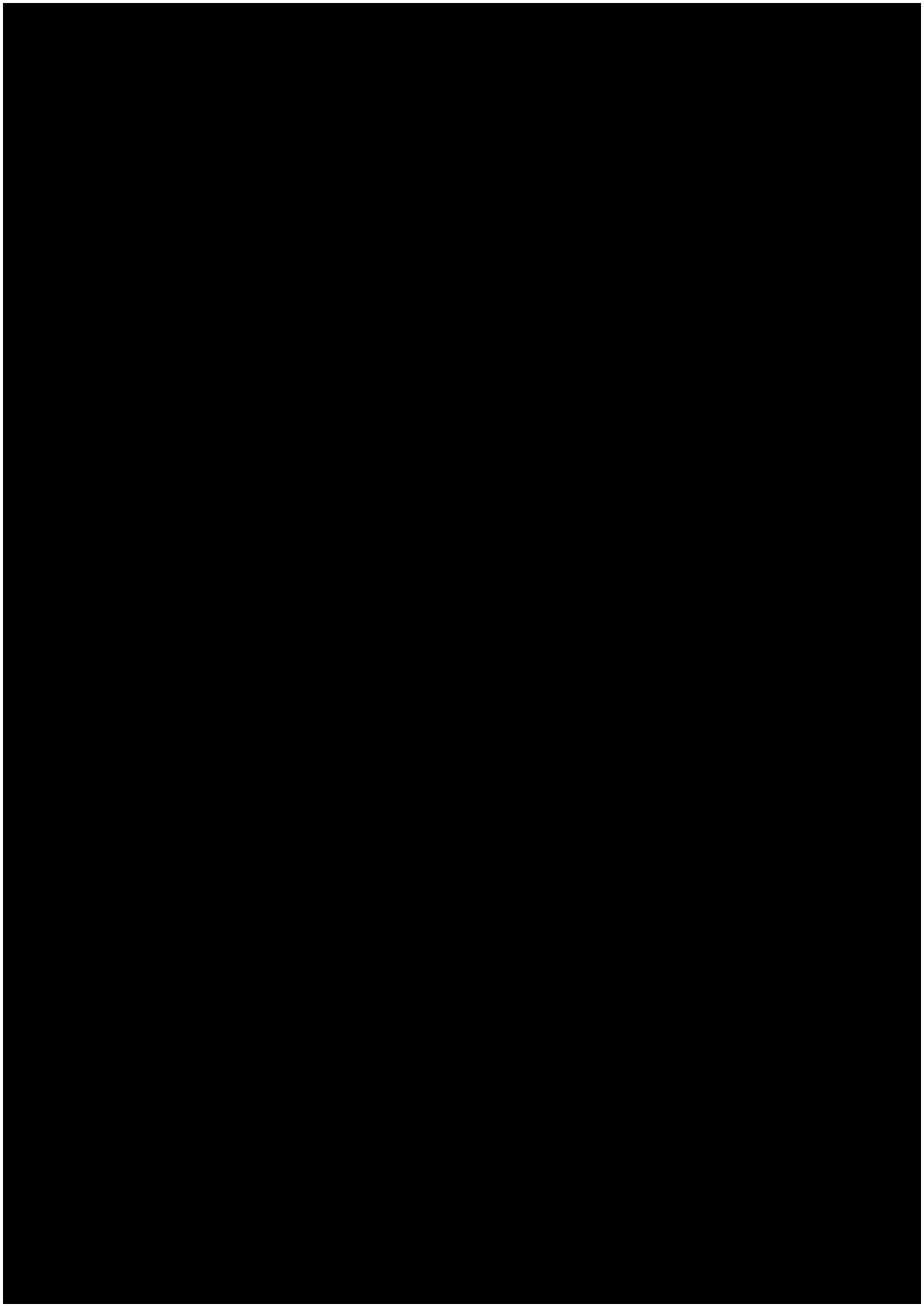

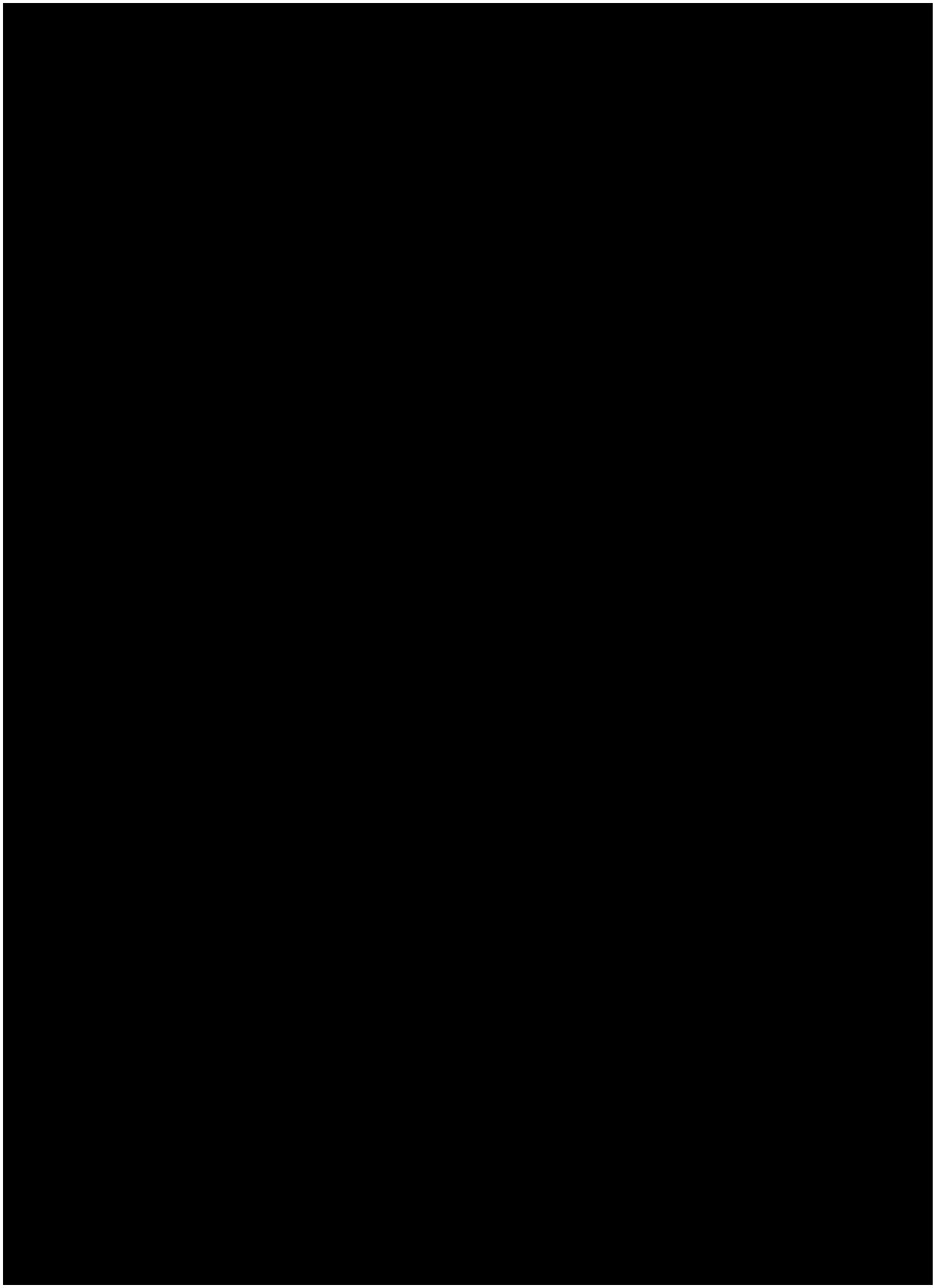

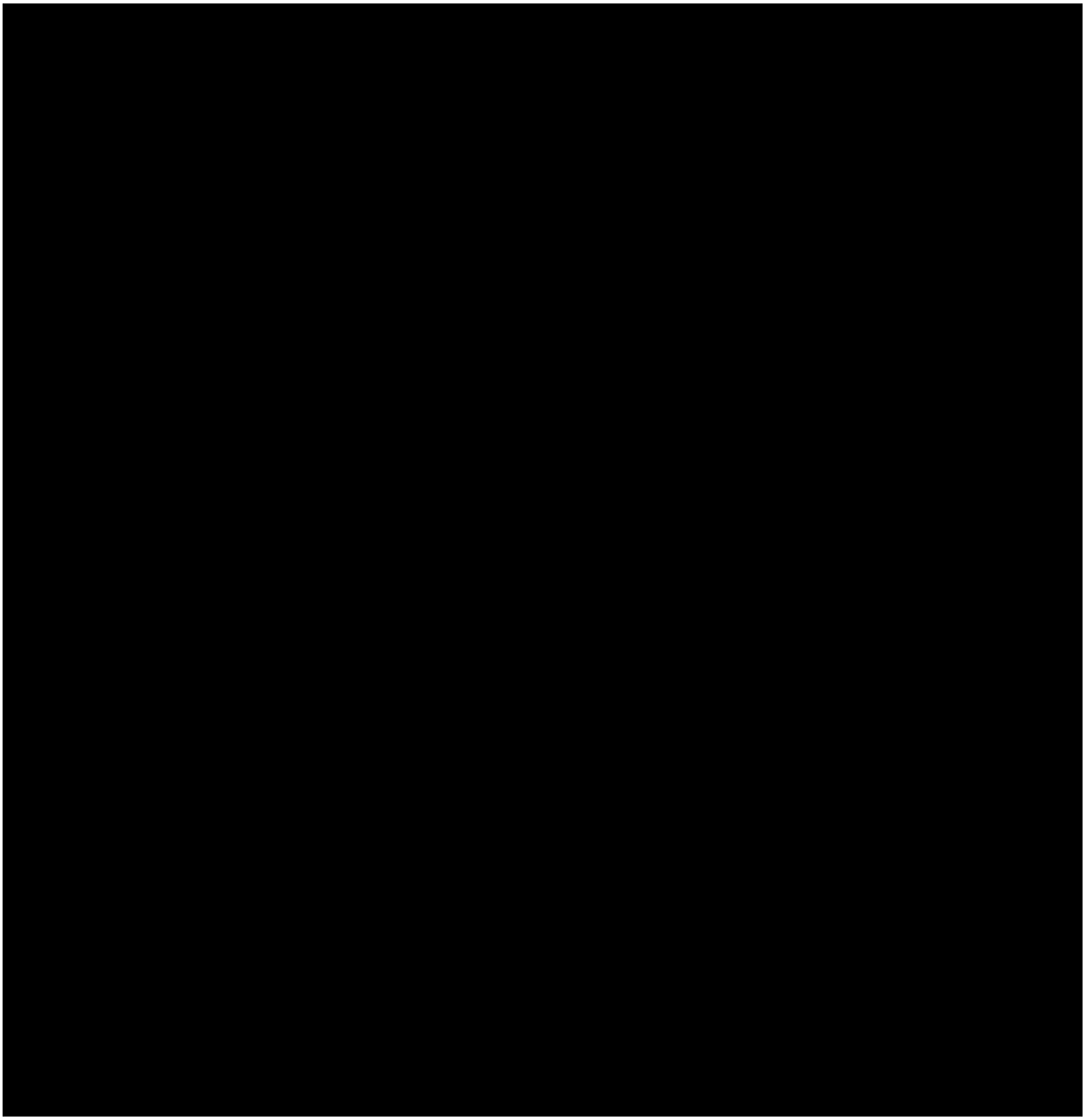

Protocol summary

Protocol number	CQAW039A2307
Title	A 52-week, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of QAW039 when added to existing asthma therapy in patients with uncontrolled severe asthma.
Brief title	Study of efficacy and safety of QAW039 in male and female patients (≥12 years) with severe asthma inadequately controlled with standard of care asthma treatment.
Sponsor and Clinical Phase	Novartis, Phase III.
Investigation type	Drug.
Study type	Interventional.
Purpose and rationale	The overall purpose of this study is to determine the efficacy and safety of QAW039 (150 mg and 450 mg once daily), compared with placebo, when added to GINA steps 4 and 5 standard-of-care (SoC) asthma therapy (GINA 2016), in patients with inadequately controlled severe asthma and high eosinophil counts (eosinophil count at Visit 1 ≥250 cells/µl). Inadequate control is defined as partly controlled or uncontrolled asthma (GINA 2016). The study will also determine the efficacy and safety of QAW039 (150 mg and 450 mg once daily), compared with placebo, in the overall study population. The rationale for this approach is to determine whether QAW039 reduces the rate of moderate-to-severe asthma exacerbations in the subset of patients with severe asthma and high eosinophil counts (≥250 cells/µl) as well as in the overall study population regardless of eosinophil counts.
Primary Objectives	In patients with severe asthma and high eosinophil counts (≥250 cells/µl) receiving SoC asthma therapy, to demonstrate the efficacy (as measured by rate of moderate-to-severe asthma exacerbations) of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, at the end of the 52-week active-treatment epoch. In patients with severe asthma receiving SoC asthma therapy, to demonstrate the efficacy (as measured by rate of moderate-to-severe asthma exacerbations) of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, at the end of the 52-week active-treatment epoch.
Secondary Objectives	In patients with severe asthma and high eosinophil counts (≥250 cells/µl) receiving SoC asthma therapy: • To demonstrate the efficacy of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, with respect to change from baseline in Asthma Quality of Life Questionnaire (AQLQ+12) scores at the end of the 52-week active-treatment epoch. • To demonstrate the efficacy of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, with respect to change from baseline in Asthma Control Questionnaire-5 (ACQ-5)

[redacted]

	score at the end of the 52-week active-treatment epoch. • To demonstrate the efficacy of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, with respect to change from baseline in pre-dose FEV1 at the end of the 52-week active-treatment epoch. • To assess the safety of QAW039 (150 mg and 450 mg once daily), compared with placebo, with respect to adverse events, electrocardiograms (ECGs), vitals sign, laboratory tests and hypersensitivity reactions. In all patients with severe asthma receiving SoC asthma therapy: • To demonstrate the efficacy of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, with respect to change from baseline in Asthma Quality of Life Questionnaire (AQLQ+12) scores at the end of the 52-week active-treatment epoch. • To demonstrate the efficacy of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, with respect to change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at the end of the 52-week active-treatment epoch. • To demonstrate the efficacy of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, with respect to change from baseline in pre-dose FEV1 at the end of the 52-week active-treatment epoch. • To assess the safety of QAW039 (150 mg and 450 mg once daily), compared with placebo, with respect to adverse events, electrocardiograms (ECGs), vitals sign, laboratory tests and hypersensitivity reactions.
Study design	This study uses a randomized, multicenter, double-blind, placebo-controlled parallel-group study design in which QAW039 or placebo is added to GINA steps 4 and 5 asthma therapy. The study will include: • a Screening epoch of up to 2 weeks to assess eligibility; • a Run-in epoch of approximately 2 weeks and a maximum of 6 weeks to collect baseline data for efficacy variables and compliance with the Electronic Peak Flow/ eDiary device (if a patient experiences an asthma exacerbation during the run-in epoch, the run-in epoch must be extended to 6 weeks to permit for resolution of the asthma exacerbation before randomization. The run-in epoch should only be extended beyond 2 weeks (+/- 5 days) for an asthma exacerbation.); • a Treatment epoch of 52 weeks; • a Follow-up epoch of 4 weeks, investigational and drug-free, following the last dose of study drug.
Population	The study population will include approximately 846 males and females aged ≥12 years with inadequately controlled severe asthma (partly controlled or uncontrolled asthma on treatment at GINA steps 4 and 5). Approximately 15% of the patients will be adolescents (aged ≥12 to <18 years). Approximately two thirds of randomized patients will have a blood eosinophil count ≥ 250 cells/µl and one third a blood eosinophil count < 250 cells/µl.
Inclusion criteria	• Written informed consent and assent (if applicable) must be obtained within 14 days prior to or at Visit 1 before any assessment is

[redacted]

performed including any adjustment to asthma medication.

- Male and female patients aged ≥12 years (or ≥ lower age limit allowed by health authority and/or ethics committee/institutional review board approvals).
- Patients must have a diagnosis of asthma (according to GINA 2016) for a period of at least 24 months prior to Visit 1.
- Patients have been treated with:
  - Medium or high-dose inhaled corticosteroids (ICS) plus long-acting beta agonist (LABA), or
  - Medium or high-dose ICS plus leukotriene receptor antagonist (LTRA), or
  - Medium or high-dose ICS plus theophylline, or
  - Medium or high-dose ICS plus Long-acting muscarinic antagonist (LAMA), or
  - Medium or high-dose ICS plus LABA plus LAMA, or
  - Medium or high-dose ICS plus LABA plus LTRA, or
  - Medium or high-dose ICS plus LABA plus theophylline,

  with or without maintenance oral corticosteroids for at least 3 months prior to Visit 1. The doses must have been stable for at least 4 weeks prior to Visit 1.
    - See GINA 2016 for the definition of medium and high-dose ICS (Appendix 7 contains the estimated equivalence of inhaled corticosteroids per GINA 2016).
- For patients aged ≥18 years, FEV1 of ≤80% 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.
- Demonstration of inadequate control of asthma based on an ACQ score ≥1.5 at Visit 1.
- A history of 2 or more asthma exacerbations within the 12 months prior to Visit 1 that required either:
  - Treatment with systemic corticosteroids (tablets, suspension or injection)

    OR
  - Hospitalization (defined as an inpatient stay or >24-hour stay in an observation area in the emergency room of other equivalent facility.
- 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 Visit 1. If reversibility is not demonstrated at Visit 1*, the following historical information may be used:
    - Documented evidence of reversibility that was performed according to ATS/ERS guidelines (ATS/ERS 2005) within the 2 years prior to Visit 1. Where a patient is assessed as

[redacted]

	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-reactivity (AHR) test result within the 2 years prior to or at Visit 101, 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. *NOTE: If reversibility is not demonstrated at Visit 1 and documented evidence for one of the other criteria for a clinical diagnosis of asthma is not met, then the reversibility test may be repeated at Visit 101.
Key exclusion criteria	• Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days until the expected pharmacodynamic effect has returned to baseline, whichever is longer. • Patients who have participated in another trial of QAW039 (i.e. patient received study medication [active (QAW039), placebo or other]. • Patients with a resting QTcF (Fridericia) ≥450 msec (male) or ≥460 msec (female) at Visit 1 or at Visit 101. • Patients with a history of malignancy of any organ, treated or untreated, whether or not there is evidence of local recurrence of metastases, with the exception of local basal cell carcinoma of the skin. • 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. • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment. • Patients who have a clinically significant laboratory abnormality at the Visit 1 laboratory test. • Patients with serious co-morbidities including, but not limited to, neurodegenerative diseases, rheumatoid arthritis and other autoimmune diseases. • Patients on >20 mg of simvastatin, > 40 mg of atorvastatin, >40 mg of pravastatin, or >2 mg of pitavastatin. Statin doses less than or equal to these doses as well as other statins will be permitted during the study. • Patients on any statin therapy with a CK level >2 X ULN at Visit 1. • Patients with a history of conditions other than asthma that could result in elevated eosinophils (e.g., hypereosinophilic syndromes, Churg-Strauss Syndrome, eosinophilic esophagitis). Patients with known parasitic infestation within 6 months prior to Visit 1 are also excluded.
Investigational and reference therapy	• QAW039 150 mg once daily • QAW039 450 mg once daily • Placebo to QAW039 once daily

[redacted]

Efficacy assessments	• Asthma exacerbations • Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12) • Asthma Control Questionnaire (ACQ-5) • Spirometry (Pre-dose FEV1)
Safety assessments	• History and physical examination • Vital signs • Hematology • Blood chemistry including liver function tests, 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) • Urinalysis • Pregnancy test (females of childbearing potential) • ECG • Adverse events including serious adverse events
[redacted]	
Data analysis	The primary variable for this study is the number of moderate-to-severe asthma exacerbations experienced by each patient per patient year of follow-up. The primary variable will be analyzed using a negative binomial regression model with the natural logarithm of the duration of follow-up as an offset variable, treatment group, randomization strata and region as fixed class effects, as well as the natural logarithm of the number of asthma exacerbations in the 12 months prior to screening and the baseline pre-dose FEV1 as continuous linear covariates. Missing data will be imputed assuming no further treatment effect versus placebo for QAW039 patients that discontinue treatment and are lost to follow-up due to (or following a treatment discontinuation due to) lack of efficacy, adverse events or death. In contrast a continued treatment effect for QAW039 patients being lost to follow-up for reasons likely to be unrelated to study treatment (e.g. lost to follow-up, withdrew consent) will be imputed. The superiority of QAW039 over placebo will be considered confirmed if at least one of the four primary null hypotheses regarding the exacerbation rates is rejected in favor of the respective two-sided superiority alternative hypothesis. The familywise type I error rate will be controlled at the two-sided 5% level across the primary and key secondary null hypotheses using a closed testing procedure. In this closed testing procedure the primary null hypotheses about exacerbations for each dose and population act as gatekeepers for the key secondary null hypotheses for the same dose and population. 188 patients per arm in the subpopulation with blood eosinophils ≥ 250 cells/µl and 282 patients per arm in the overall population corresponding

[redacted]

	to a total sample size of 846 patients provide greater than 80% power for demonstrating the superiority of each dose of QAW039 compared to placebo in the subpopulation with blood eosinophils ≥ 250 cells/µl and overall population. Treatment discontinuation rate of 15% by 1 year is assumed in the active treatment groups and the placebo group. No further treatment effect versus placebo has been assumed during the off-treatment period. Additionally, the planned sample size will give 80% power for FEV1 for each dose in the subpopulation at the resulting local two-sided significance level of 1.625% and 90% power for each dose in the overall population at the resulting local two-sided significance level of 0.698% once the respective primary null hypothesis has been rejected. It was assumed that QAW039 achieves a difference of 150 mL against placebo in FEV1 after 52 weeks for patients that remain on treatment. A SD of 380 mL was assumed for FEV1. The key secondary variables of this trial are AQLQ+12, ACQ-5 and average of the two pre-dose FEV1 assessments at the end of the 52 week treatment period. For each key secondary variable, QAW039 dose and population the null hypothesis that the difference to placebo at week 52 is zero will be tested versus the two-sided alternative hypothesis that the treatment difference at week 52 $\neq$ 0 using analysis of covariance. Prior to analysis, missing values for key secondary variables will be imputed in a similar manner as for the primary variable. Safety summaries will be primarily based on on-treatment data for the safety set with selected tables also presented for the all data after the first intake of study drug, while all databased safety data will be listed.
Key words	Efficacy and 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 estimates that 15 million disability–adjusted life years are lost annually due to asthma, representing 1% of the total global burden. Annual worldwide deaths have been estimated at 250,000 (Masoli, et al 2004). Uncontrolled asthma has a prevalence of greater than 6 million patients worldwide.

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 can predominate 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 and a number of biologic therapies (including anti-IL-5, anti-IL-5R, anti-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, et al 2005; Nair, et al 2009). Consequently, there remains a need for well tolerated, easily-administered, anti-inflammatory therapies with the capability of suppressing 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 (PDG_2) which is one of the major prostanoid inflammatory mediators identified in asthma. 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 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 Study CQAW039A2208: a randomized, placebo-controlled, 12-week sputum study of QAW039 (225 mg BID), compared with placebo, in patients with severe eosinophilic asthma. In this study, QAW039 demonstrated a fall in sputum eosinophils of 71% (geometric mean) after 12 weeks treatment.

Given published results with other asthma therapies in which a reduction in sputum eosinophils is associated with a reduction in asthma exacerbations (Haldar, et al 2009; Pavord,

[redacted]

et al 2012), and the observed reduction in sputum eosinophils in Study CQAW039A2208, it is postulated QAW039 will reduce the rate of asthma exacerbations.

1.2 Purpose

The overall purpose of this study is to determine the efficacy and safety of QAW039 (150 mg and 450 mg once daily), compared with placebo, when added to GINA steps 4 and 5 standard-of-care (SoC) asthma therapy (GINA 2016)[†], in patients with inadequately controlled severe asthma and high eosinophil counts (eosinophil count at Visit 1 ≥250 cells/ µl). Inadequate control is defined as partly controlled or uncontrolled asthma (GINA 2016).

The study will also determine the efficacy and safety of QAW039 (150 mg and 450 mg once daily), compared with placebo, in the overall study population.

This approach will permit the determination of the effect of QAW039 in reducing asthma exacerbations in the subset of patients with severe asthma and high eosinophil counts as well as in the overall study population regardless of eosinophil counts.

[†]Medium or high-dose ICS plus a second controller and/or systemic corticosteroids.

2 Study objectives

2.1 Primary objective(s)

- In patients with severe asthma and high eosinophil counts (≥250 cells/µl) receiving SoC asthma therapy, to demonstrate the efficacy (as measured by rate of moderate-to-severe asthma exacerbations) of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, at the end of the 52-week active-treatment epoch.
- In all patients with severe asthma receiving SoC asthma therapy, to demonstrate the efficacy (as measured by rate of moderate-to-severe asthma exacerbations) of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, at the end of the 52-week active-treatment epoch.

2.2 Secondary objectives

In patients with severe asthma and high eosinophil counts (≥250 cells/µl) receiving SoC asthma therapy:

- To demonstrate the efficacy of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, with respect to change from baseline in Asthma Quality of Life Questionnaire (AQLQ+12) scores at the end of the 52-week active-treatment epoch.
- To demonstrate the efficacy of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, with respect to change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at the end of the 52-week active-treatment epoch.
- To demonstrate the efficacy of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, with respect to change from baseline in pre-dose FEV1 at the end of the 52-week active-treatment epoch.

[redacted]

- To assess the safety of QAW039 (150 mg and 450 mg once daily), compared with placebo, with respect to adverse events, electrocardiograms (ECGs), vitals sign, laboratory tests and hypersensitivity reactions.

In all patients with severe asthma receiving SoC asthma therapy:

- To demonstrate the efficacy of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, with respect to change from baseline in Asthma Quality of Life Questionnaire (AQLQ+12) scores at the end of the 52-week active-treatment epoch.
- To demonstrate the efficacy of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, with respect to change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at the end of the 52-week active-treatment epoch.
- To demonstrate the efficacy of at least one dose level of QAW039 (150 mg or 450 mg once daily), compared with placebo, with respect to change from baseline in pre-dose FEV1 at the end of the 52-week active-treatment epoch.
- To assess the safety of QAW039 (150 mg and 450 mg once daily), compared with placebo, with respect to adverse events, electrocardiograms (ECGs), vitals sign, laboratory tests and hypersensitivity reactions.

[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 GINA steps 4 and 5 asthma therapy (Figure 3-1).

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 101 (See Section 5.5.8). Approximately 2400 patients will be screened to randomize 846 patients into this study.

The study will include:

- a Screening epoch of up to 2 weeks to assess eligibility;
- a Run-in epoch of approximately 2 weeks and a maximum of 6 weeks to collect baseline data for efficacy variables and compliance with the Electronic Peak Flow/ eDiary device (if a patient experiences an asthma exacerbation during the run-in epoch, the run-in epoch must be extended to 6 weeks to permit for resolution of the asthma exacerbation before randomization. The run-in epoch should only be extended beyond 2 weeks (+/- 5 days) for an asthma exacerbation.);
- a Treatment epoch of 52 weeks;
- a Follow-up epoch of 4 weeks, investigational and drug-free, following the last dose of study drug. **Note:** the follow-up epoch applies to all patients **except** those patients who enter the safety study directly after Visit 299.

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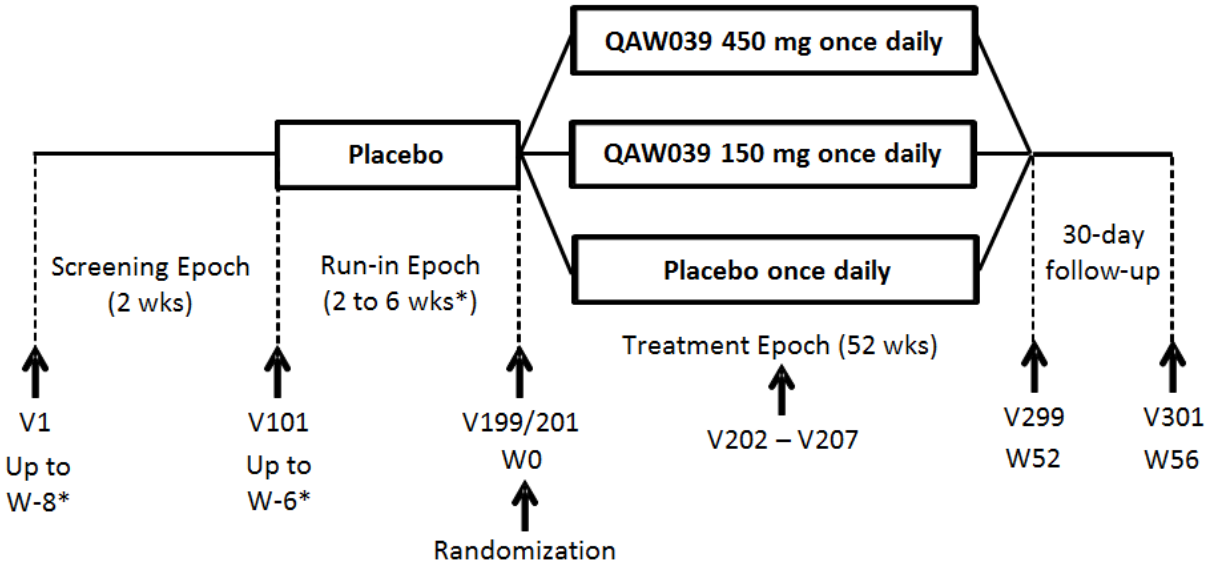
Figure 3-1 Study design



*flexible Run-in Epoch (2 to 6 weeks) to accommodate subjects with asthma exacerbations

Upon completion of the run-in epoch, all patients who met the eligibility criteria will be randomized to 1 of 3 treatments (QAW039 [150 mg or 450 mg once daily] or placebo once daily) in a ratio of 1:1:1. Randomized patients will stratified according to their peripheral blood eosinophil counts (<250 cells/µl or ≥250 cells/µl), patient age (<18 years or ≥18 years), and their baseline use or non-use of oral corticosteroids as part of their SoC asthma therapy at Visit 1. Clinic visits will be scheduled approximately 4 weeks after randomization and then at approximately 8-week intervals during the active-treatment epoch. Phone calls will occur at specified time points between visits occurring at 8-week intervals (see schedule of assessments Table 6-1). 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 (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, patients who successfully complete 52 weeks of treatment in this study (Study A2307) 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.

Note:

Patients experiencing an asthma exacerbation during the run-in epoch should receive treatment for their exacerbation, and remain in the run-in epoch until the subject has returned to their baseline asthma status for at least 2 weeks (2 weeks=14 days). If patients do not return to their baseline status for at least 2 weeks prior to Visit 199, patients will not be eligible for randomization and will be designated a run-in failure.

In addition to periodic unblinded safety reviews by an independent Data Monitoring Committee, a single futility interim analysis is planned as described in Section 3.5.

[redacted]

3.2 Rationale of study design

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 inadequately controlled severe asthma otherwise treated according to GINA 2016 (steps 4 and 5) guidelines. According to 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 symptomatic and objective parameters of asthma control (symptomatic parameters: daytime and nighttime asthma symptoms, SABA use, quality of life, Asthma Control Questionnaire [ACQ] scores; objective: lung function [FEV1, peak flow]) and future risk (moderate-to-severe asthma exacerbations, longitudinal lung function) in patients at the end of 52 weeks of therapy.

Patient population

The overall purpose of this study is to determine the efficacy and safety of QAW039 (150 mg and 450 mg once daily), compared with placebo, when added to GINA steps 4 and 5 standard-of-care (SoC) asthma therapy (GINA 2016), in patients with inadequately controlled severe asthma and high eosinophil counts (eosinophil count at Visit 1 ≥250 cells/µl). The study will also determine the efficacy and safety of QAW039 (150 mg and 450 mg once daily), compared with placebo, in the overall study population.

A prior study of QAW039 (Study CQAW039A2208) demonstrated QAW039 (225 mg BID), compared with placebo, caused a reduction in sputum eosinophils in patients with severe eosinophilic asthma. Given published results with other asthma therapies in which a reduction in sputum eosinophils is associated with a reduction in asthma exacerbations (Haldar, et al 2009; Pavord, et al 2012), and the observed reduction in sputum eosinophils in Study CQAW039A2208, it is postulated QAW039 will reduce the rate of asthma exacerbations. Further, recent published results of the MENSA study (Ortega, et al 2014), in which the included patient population is similar to that proposed for the current study of QAW039, suggest patients with severe asthma, particularly those with severe eosinophilic asthma, are at risk for recurrent asthma exacerbations. Taken together, the patient population for the current study is appropriate to evaluate the effect of QAW039 on reduction in rate of asthma exacerbations when patients stratified by eosinophil counts.

Screening epoch

The screening epoch 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.

Run-in epoch

The run-in epoch allows for patients to become familiar with administration of investigational treatment, to determine patient's level of asthma control based on ACQ score (for eligibility), and to collect baseline data for all efficacy variables. This epoch will also assess patients' compliance with an Electronic Peak Flow/ eDiary device and treatment.

[redacted]

Treatment epoch

During this epoch oral QAW039 (150 mg and 450 mg) or placebo (1:1:1) will be administered once daily for 52 weeks, with the last dose given at Week 52 and final assessment for the treatment period at week 52. A 52-week study duration is necessary to minimize the impact of the seasonal variation on the primary endpoint, the rate of asthma exacerbations. Since one of the secondary endpoints is predose 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 predose FEV1 prior to dosing.

Follow-up epoch

The 4 week wash out epoch will monitor the safety and tolerability profile after the last dose of study drug. **Note:** the follow-up epoch applies to all patients **except** those patients who enter the safety study directly after Visit 299.

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

QAW039 will be administered at doses of 150 mg and 450 mg once daily as oral film-coated tablets (FCTs) in this study.

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

- At a dose of 450 mg once daily, >98% receptor occupancy is expected for the entire dosing interval in a "typical patient" at steady state allowing inhibition of eosinophil migration over the entire treatment interval.
- A 500 mg once daily dose of QAW039 was efficacious on the endpoint of pre-dose FEV1 in a sub-set of patients with percent predicted FEV1 <70% at baseline in Study CQAW039A2201 (proof-of-concept study). A 450 mg total daily dose was also efficacious on the endpoint of pre-dose FEV1 in study CQAW039A2206.
- A total daily dose of 450 mg (225 mg twice daily) was evaluated in Study CQAW039A2208 in patients with severe asthma as add-on to SoC asthma therapy. In this study, 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 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 2012; 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 refractory 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 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 ½ 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.

[redacted]

3.4 Rationale for choice of comparator

All patients in this study will continue to receive their asthma medications as background treatment. QAW039 or placebo will be administered as add-on therapy.

The use of placebo will permit the assessment of improvement in terms of incidence of moderate-to-severe asthma exacerbations for patients with uncontrolled disease who are treated with QAW039, in comparison to those continuing solely on existing SoC asthma therapy. Additionally, the use of placebo will permit a controlled evaluation of the safety of QAW039 in these patients.

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

3.5 Purpose and timing of interim analyses/design adaptations

An independent Data Monitoring Committee (see Section 8.3) will conduct periodic unblinded safety reviews of the accumulating data (including specific safety summaries for adolescent participants) from this trial and other Phase III trials of the QAW039 asthma development program to ensure safety of trial participants.

In addition, a single interim analysis for futility will be conducted to assess whether the study should be stopped for futility or safety, or whether treatment in one or more QAW039 dose groups should be discontinued for safety reasons. There will be no stopping for demonstrated efficacy prior to the completion of the study at either the unblinded safety reviews or the futility interim analysis, because a sufficiently large safety dataset is needed in addition to efficacy data. Therefore, no statistical adjustment will be made to the final analysis.

This interim analysis for futility will occur when approximately 200 patient-years of follow-up data have accumulated. The timing of the futility interim analysis may be modified based on the progress of recruitment, the logistics of arranging DMC meetings, the data accrual in other QAW039 asthma Phase III trials and additional external data that might become available.

3.6 Risks and benefits

QAW039 is a potent and highly selective oral CRTh2 receptor antagonist being developed as a potential therapy treatment 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.

QAW039 is at least 300-fold selective for the CRTh2 receptor compared to other available prostanoid receptors and to cyclooxygenase-1 and cyclooxygenase-2, and it has been demonstrated to be a potent *in vitro* inhibitor of human whole blood eosinophil activation and induction of Th-2 cytokines. After oral dosing in rats, QAW039 inhibited pulmonary eosinophilia induced by the PGD_2 metabolite DK-PGD_2.

The potential benefits of QAW039 therapy need to be balanced against its potential risks. The risk to patients in this study will be minimized by compliance with the inclusion/exclusion

[redacted]

criteria and close clinical monitoring. All patients will remain on the background SoC asthma therapy they were taking at screening throughout the study. Furthermore, patients will be instructed how to react to worsening of asthma symptoms so patients can be managed appropriately.

The overall clinical experience with QAW039 includes 12 studies: 10 (6 in healthy volunteers and 4 in patients) have completed and 2 (in patients) are ongoing. The completed phase 2 studies consist of 3 in patients with asthma and 1 in patients with allergic rhinitis. The ongoing phase 2 studies include one study in patients with asthma (CQAW039A2214) and 1 study in patients with atopic dermatitis (CQAW039X2201).

As of January 2015, over 1300 subjects have been exposed to QAW039 in the clinical program. In the completed studies of QAW039, 1239 subjects (175 healthy volunteers and 1064 patients with asthma or allergic rhinitis) received QAW039, 342 subjects received placebo, and 359 subjects received other treatment (rosuvastatin, simvastatin or montelukast).

QAW039 has been well tolerated in populations studied to date at total daily doses up to 500 mg given for up to 12 weeks. In the 10 completed studies, 16 patients reported 17 serious adverse events (SAEs), no deaths due to SAEs were reported, and 5 discontinuations due to SAEs were reported. Of the 16 patients reporting SAEs, 12 patients reported 13 events, 2 patients reported 2 events and 2 patients reported 2 events in the QAW039, placebo, and montelukast treatment groups, respectively. There were no SAEs with a suspected causal relationship to QAW039. There have been no adverse events of idiopathic drug reactions.

Overall, the safety profile of QAW039 has been favorable across studies.

Three Phase 2 studies in patients with asthma demonstrated the effect of QAW039 across the range of asthma severities (mild to severe). Below is a summary of efficacy data from these 3 completed studies in asthma. For detailed information on the studies described below, please refer to the Investigators Brochure.

Study A2201 (proof-of-concept [PoC] study)

Study A2201 was a PoC study in 170 corticosteroid-free, atopic, asthmatic patients uncontrolled on as needed β-agonist medication who were randomized (1:1) to receive QAW039 500 mg or matching placebo for 28 days. The primary objective was to assess the efficacy of QAW039, compared with placebo, as measured by trough FEV1 after 28 days of treatment. Overall benefit for QAW039 treatment was not demonstrated in the entire study population (patients with percent predicted FEV_1 of 60% to 85% at baseline) compared with placebo treatment. Benefit occurred only in those patients with more severe baseline airflow obstruction (FEV_1 < 70% predicted). Results from Study A2201 demonstrated 4 weeks of treatment with QAW039 (500 mg q.d.) improved both lung function (FEV_1: 207 ml > placebo group, p=0.002, 1-sided test) and control of asthma symptoms (ACQ: 0.41 points < placebo group, p=0.009, 1-sided test) in the subset of patients with moderate airflow obstruction at baseline (FEV_1 < 70% predicted) who were inadequately controlled on reliever medication alone.

Study A2206 (dose-ranging study)

Study A2206 was a randomized, placebo-controlled, multi-center, dose-ranging study in patients with moderate-to-severe allergic asthma inadequately controlled by ICS therapy.

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Patients who satisfied selection criteria were randomized to 1 of 15 treatment arms (13 QAW039 treatment arms, 1 montelukast positive control arm and 1 placebo arm) for 12 weeks followed by a single-blind, placebo wash-out period for 4 weeks. The primary objective of the study was to assess the efficacy of QAW039, compared with placebo, as measured by trough FEV1 after 12 weeks of treatment. A total 1058 patients were randomized to the following treatment groups: 139 patients to montelukast, 137 patients to placebo and 782 patients to QAW039. The study achieved its primary endpoint by demonstrating a clinically and statistically significant improvement (0.112 L; p=0.0035) in trough FEV1 after 12 weeks therapy with QAW039, compared with placebo, in a population of moderate-to-severe, persistent, atopic asthmatics with a predicted baseline, pre-bronchodilator FEV1 of 40% to 80% of the predicted value who were uncontrolled on low dose ICS.

Results showed the greatest differences from placebo occurred at doses of 75 mg twice daily and 150 mg once daily. These doses were towards the middle of the 1 mg to 450 mg dose range tested. There appeared to be little difference between once daily and twice daily dosing. There were no significant changes compared with placebo in ACQ, AQLQ or Juniper asthma control diary scores across the study population either for QAW039 or the positive control, montelukast. Examination of sub-groups did not provide evidence of increased efficacy for QAW039, compared with placebo, in terms of FEV1.

Study A2208

Study A2208 was a single site, double-blind, placebo-controlled study to determine whether, in patients with sputum eosinophilia (≥ 2%) and persistent, moderate-to-severe asthma, 12 weeks of treatment with QAW039 at a dose of 225 mg twice daily, compared with placebo, on top of SoC asthma treatment would reduce levels of eosinophils in induced sputum. In addition to measurements of changes in sputum eosinophilia (primary endpoint) and ACQ (secondary endpoint), a very wide range of lung function, patient reported outcome, imaging, histological, proteomic and transcriptional endpoints were also measured.

A total of 61 patients were randomized and 55 patients completed their assigned double-blind treatment period. The primary endpoint of the study was achieved. The level of sputum eosinophilia decreased by 71% (geometric mean) from baseline after 12 weeks treatment with QAW039. This fall was significantly different from the change observed in placebo-treated patients (p=0.0007). QAW039 led to clinically and statistically relevant asthma control (as measured by the ACQ test) in patients uncontrolled at baseline (i.e. baseline ACQ7≥1.5), with the ACQ7 improving by 0.58 points (p=0.0473) in the per-protocol population. In the overall population, the ACQ7 score improved by 0.40 points (p=0.0843). There was a clinically (0.5 point) and statistically significant improvement in QoL, as measured by the AQLQ overall score, after 12 weeks treatment with QAW039 in comparison to placebo (treatment difference = 0.593 point; p=0.0080). The proportion of patients experiencing a moderate or severe asthma exacerbation was similar across the two treatment groups (7 in the QAW039 group and 6 in the placebo group). This finding was not surprising given the study was small and of limited duration and, therefore, was not designed to detect an effect on this endpoint. Numerical increases were seen in pre-bronchodilator FEV1 in QAW039-treated patients regardless of whether absolute volume or % change was considered. The greatest increases were observed in those per protocol-treated patients whose predicted FEV1 was <70% at baseline (190 mL and 13.409% for volume and % change, respectively). However, none of

[redacted]

these results were statistically significant. Given the results with other therapies (a reduction in sputum eosinophils is associated with a reduction in asthma exacerbations), and the observed reduction in sputum eosinophil numbers in the prior study of QAW039, it is postulated QAW039 will reduce the rate of asthma exacerbations in the current study. Therefore, the main purpose of the current study is to definitively demonstrate the effect of QAW039 on reduction in the rate of moderate-to-severe asthma exacerbations.

Cardiovascular risks:

Transient, increases in heart rate were observed in a cardiovascular safety pharmacology study in dogs. These changes were not associated with any significant alterations in blood pressure, ECG interval duration, morphology or rhythm or any structural changes in cardiac tissues. No cardiac findings have been identified in the healthy volunteer and patient studies completed to date apart from an observed imbalance in the frequency of post-randomization cardiac adverse events in study CQAW039A2206 with a higher incidence in the QAW039 treatment group (1.7%) compared with either placebo (0.7%) or montelukast (0%) treated patients. The cardiac events comprised a number of different non-serious arrhythmias and one serious adverse event of pericarditis not suspected to be related to study drug by the investigator. Three of the events in the QAW039 treatment groups occurred during the washout period and 9 resolved on treatment. Based on the inability to identify discernable trends with QAW039 dose, regimen, time-of-onset, patient age and gender, concomitant medication, event type and following detail ECG review, it was considered that these were most probably coincidental events without a causal association to study drug.

A formal QTc study has not been completed for QAW039. Monitoring for changes in vital signs, ECGs and biochemical parameters will be conducted.

Liver toxicity:

Dose-dependent increases in liver weights with concomitant hepatocellular hypertrophy were the primary findings during 2- and 13-week toxicity studies in mice. These changes were considered to be a species-specific adaptive metabolic response with no relevance for humans. Liver toxicity findings have not been identified in the healthy volunteer and patient studies completed to date. Monitoring of liver function tests will be conducted as described in Appendix 2 of this protocol.

Potential risk of idiosyncratic drug reactions

CCN362 is an acylglucuronide metabolite of QAW039 and its potential to covalently bind to plasma proteins, such as albumin, was demonstrated in the human ADME (Absorption, distribution, metabolism, and excretion) study of QAW039 (CQAW039A2104). 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. Surveillance of adverse events for identification of IDRs will be conducted.

[redacted]

Drug-drug interactions

QAW039 and CCN362 did not show any relevant inhibition or induction of the cytochrome P450 isoenzymes or inhibition of ubiquitous efflux transporters. The most potent in vitro inhibition by QAW039 was found for OATP1B1, but clinically only a small impact was observed at 450 mg/day (~2-fold increase in Cmax of simvastatin acid and rosuvastatin without change in AUC). Based on these data, as well as recommendations in the simvastatin label, simvastatin doses of > 20 mg per day should not be co-administered with QAW039; no relevant impact on the disposition of other co-medications are expected with QAW039 dosed up to 450 mg/day. Patients on doses of simvastatin >20 mg, doses of atorvastatin >40 mg, doses of pravastatin >40mg, 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 (Visit 1) will be excluded from the study (see Section 4.2). Furthermore, 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 blood CK levels (Jacobson 2008) as described in Section 5.5.10.

4 Population

The study population will include approximately 846 males and females aged ≥12 years with inadequately controlled severe asthma (partly controlled or uncontrolled asthma on treatment at GINA steps 4 and 5). Approximately 15% of the patients will be adolescents (aged ≥12 to <18 years).

Patients will be stratified based on blood eosinophil counts at Visit 1, so that approximately two thirds of randomized patients will have a blood eosinophil count ≥ 250 cells/µl and one third a blood eosinophil count < 250 cells/µl at Visit 1. It is anticipated at least 2400 patients will need to be screened to randomize approximately 846 patients into the study. It is estimated that approximately 15% of patients will discontinue their investigational treatment during the treatment epoch; these patients will not be replaced.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill **all** of the following criteria:

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 aged ≥12 years (or ≥ lower age limit allowed by health authority and/or ethics committee/institutional review board approvals).
3. Patients must have a diagnosis of asthma (according to GINA 2016) for a period of at least 24 months prior to Visit 1.
4. Patients have been treated with:
   - Medium or high-dose ICS plus long-acting beta agonist (LABA), or
   - Medium or high-dose ICS plus leukotriene receptor antagonist (LTRA), or
   - Medium or high-dose ICS plus theophylline, or
   - Medium or high-dose ICS plus long-acting muscarinic antagonist (LAMA), or
   - Medium or high-dose ICS plus LABA plus LAMA, or

- Medium or high-dose ICS plus LABA plus LTRA, or
- Medium or high-dose ICS plus LABA plus theophylline,

with or without maintenance oral corticosteroids for at least 3 months prior to Visit 1. The doses must have been stable for at least 4 weeks prior to Visit 1.

  - See GINA 2016 for the definition of medium and high-dose ICS (Appendix 7 contains the estimated equivalence of inhaled corticosteroids per GINA 2016).

5. For patients aged ≥18 years, FEV1 of ≤80% 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:

   - 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 once daily ≥ 24 hours;
   - LAMAs ≥ 24 hours.

6. Demonstration of inadequate control of asthma based on an ACQ score ≥1.5 at Visit 1.
7. A history of 2 or more asthma exacerbations within the 12 months prior to Visit 1 that required either:

   - Treatment with systemic corticosteroids (tablets, suspension or injection).

   OR

   - Hospitalization (defined as an inpatient stay or >24-hour stay in an observation area in the emergency room of other equivalent facility.

   NOTES:

   - For subjects receiving maintenance OCS, the OCS treatment for exacerbations must have been at least a 2-fold or greater increase in the dose of OCS.
   - The start of the second exacerbation episode must have been at least 7 days after the end of the first exacerbation episode.
   - Investigators must use appropriate means to ensure the accuracy of the patient's exacerbation history (patient history at Visit 1 documented in source notes, pharmacy records, hospital records, or chart records are acceptable).

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

   - An increase of ≥12% and ≥200 ml in FEV_1 approximately10 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 that was performed according to ATS/ERS guidelines (ATS/ERS 2005) within the 2 years prior to Visit 1. Where a patient is assessed as eligible based on historical evidence of

[redacted]

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-reactivity (AHR) test result within the 2 years prior to or at Visit 101, 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.

*NOTE: If reversibility is not demonstrated at Visit 1 and documented evidence for one of the other criteria for a clinical diagnosis of asthma is not met, then the reversibility test may be repeated at Visit 101.

4.2 Exclusion criteria

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

1. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
2. Patients who have participated in another trial of QAW039 (i.e. patient received study medication [active (QAW039), placebo or other].
3. History of hypersensitivity to any ingredients of the study drugs or to drugs related to QAW039.
4. Patients who, in the judgment of the investigator have a clinically significant ECG abnormality such as (but not limited to) sustained ventricular tachycardia, or clinically significant second or third degree AV block without a pacemaker.
5. Patients with a history of familial long QT syndrome or known family history of Torsades de Pointes.
6. Patients with a resting QTcF (Fridericia) ≥450 msec (male) or ≥460 msec (female) at Visit 1 or at Visit 101.
7. Patients receiving any medications or other agents known to prolong the QT interval.
8. Patients with a history of malignancy of any organ, treated or untreated, whether or not there is evidence of local recurrence of metastases, with the exception of local basal cell carcinoma of the skin.
9. 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.
10. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment. Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject) if allowed as effective method of contraception by local regulations. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

[redacted]

- 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 should be the sole partner for that subject
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) if allowed as effective 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
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)

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

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.

11. 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.)*.
12. Patients who have had an asthma attack/exacerbation requiring systemic corticosteroids hospitalization or emergency room visit within 6 weeks prior to Visit 1. If patients experience an asthma attack/exacerbation requiring systemic corticosteroids, hospitalization or emergency room visit during screening, they may be rescreened once, 6 weeks after recovery from the exacerbation.
13. Patients who have had a respiratory tract infection or asthma worsening within 4 weeks of Visit 1. Patients who experience a respiratory tract infection of asthma worsening during screening may be re-screened after 4 weeks after recovery from their respiratory tract infection or asthma worsening.
14. Patients with any chronic condition of the respiratory tract which in the opinion of the investigator may interfere with study evaluation or optimal participation in the study.
15. Patients with a history of chronic lung disease other than asthma, including (but not limited to) chronic obstructive pulmonary disease, bronchiectasis, (non-clinically significant bronchiectasis may be allowed provided recent [within 3 months prior to Visit 101] CT scan proof is available), sarcoidosis, interstitial lung disease, cystic fibrosis, and tuberculosis.
16. Patients with uncontrolled diabetes having an HbA1c test result ≥8% at the Visit 1 laboratory test.

[redacted]

17. 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 m^2
18. Patients who in the judgment of the investigator have a clinically significant condition such as (but not limited to) unstable ischemic heart disease, 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.
19. Patients with a history of myocardial infarction within 12 months of Visit 1.
20. Patients with serious co-morbidities including, but not limited to, neurodegenerative diseases, rheumatoid arthritis and other autoimmune diseases.
21. Patients with a history of alcohol or drug abuse within 12 months prior to Visit 1.
22. Patients with a weight <30 kg.
23. Patients receiving any medications in the classes listed in Table 5-3 should be excluded unless they meet the criteria as specified in Table 5-3.
24. Patients receiving medications in the classes listed in Table 5-1 should be excluded unless the medication has been stabilized for the specified period and the stated conditions have been met.
25. 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.
26. Patients with a known history of non-compliance to medication or who are unable or unwilling to complete an electronic patient diary or who are unable or unwilling to use Electronic Peak Flow with eDiary device or who are unable to demonstrate good eDiary compliance (defined as >75% for eDiary compliance) during the run-in epoch.
27. Inability to comply with all study requirements and demonstrate good medication compliance (>=80% compliance rate) during the treatment run-in epoch.
28. 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.
29. Patients with a history of being unable to swallow tablets.
30. Patients who have received methotrexate, oral gold, troleandomycin, cyclosporine azathioprine or any experimental anti-inflammatory therapies within 6 months of Visit 101.
31. 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 101.
32. 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.

[redacted]

33. Patients with a history of immunodeficiency disease or hepatitis B or hepatitis C.
34. 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.
35. Patients on any statin therapy with a CK level >2 X ULN at Visit 1.
36. 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]).
37. No person directly associated with the administration of the study is allowed to participate as a study subject.
38. No family member of the investigational study staff is allowed to participate in this study.
39. History of lactose or milk sensitivity.
40. Patients with a history of conditions other than asthma that could result in elevated eosinophils (e.g., hypereosinophilic syndromes, Churg-Strauss Syndrome, eosinophilic esophagitis). Patients with known parasitic infestation within 6 months prior to Visit 1 are also excluded.
41. 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 (Center for Disease Control and Prevention, 2000) if local growth charts are not available).

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

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

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

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

- Name: QAW039 placebo
- Formulation: tablet

Unit dose: matching placebo to QAW039 150 mg, matching placebo to QAW039 450 mg

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

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

[redacted]

5.1.2 Additional study treatment

No additional maintenance asthma treatment beyond investigational treatment is requested for this trial.

All patients will be provided with short-acting β_2-agonists (SABAs) (salbutamol/albuterol/other SABA) which they will be instructed to use throughout the study as rescue medication on an 'as needed basis.'

Short-acting β_2-agonists 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

During the run-in epoch, all patients will receive 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 assigned to one of three treatment arms as follows in a 1:1:1 ratio in the treatment epoch:

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

Patients will be instructed to take their investigational treatment (QAW039 or placebo) once daily in the morning without regard to time of food intake.

5.3 Treatment assignment, randomization

At Visit 201, all eligible patients will be randomized via Interactive Response Technology (IRT) to 1 of the 3 treatment arms (QAW039 150 mg or 450 mg once daily or placebo once daily) in a 1:1:1 fashion within each of the randomization strata (peripheral blood eosinophil counts at Visit 1(<250 cells/μl or ≥250 cells/μl), patient age (<18 years or ≥18 years), and their use or non-use of oral corticosteroids as part of their SoC asthma therapy) by IRT. 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 packages of investigational treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

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

[redacted]

Randomization will be stratified by peripheral blood eosinophil counts at Visit 1 (<250 cells/μl or ≥250 cells/μl), patient age (<18 years or ≥18 years), and patient use or non-use of oral corticosteroids as part of their SoC asthma therapy. Treatment randomization will be stratified at the regional level.

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 will be reviewed and approved by a member of the Novartis Randomization Group.

5.4 Treatment blinding

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

Patients, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone involved in the study [redacted] (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 the doses, a double-dummy design will be used.

Unblinding should only occur in the case of patient emergencies and at the conclusion of the study. In addition, the independent DMC will be unblinded for the purpose of safety reviews and at the time of the futility interim analysis.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Subject Number will not be reused. If a patient is re-screened they will be assigned a new subject number.

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 should select the CRF book with a matching Subject Number from the 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 Epoch Study Disposition CRF.

5.5.2 Dispensing the investigational treatment

[redacted]

Each study site will be supplied by Novartis with investigational treatment in packaging of identical appearance.

The investigational treatment packaging has a 2-part label.

A unique randomization medication number is printed on each part of this label which corresponds to the study epoch and/or treatment arm the patient is assigned to.

Investigator staff will identify the investigational treatment 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 treatment

5.5.3.1 Handling of investigational treatment

The investigational treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all investigational treatment should 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 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 investigational 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 investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial. Patients will be asked to return all unused investigational treatment and packaging at the end of the study or at the time of discontinuation of investigational treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused investigational 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 other study treatment

No applicable.

5.5.4 Instructions for prescribing and taking study treatment

Study treatment will be single-blind during the run-in and double-blind, double-dummy, and placebo-controlled after randomization. At clinic visits, patients will receive a witnessed dose of study medication. These in-clinic witnessed doses will be given after the completion of all pre-dose assessments (see Section 6) and should be given at approximately the same time at each clinic visit. Between clinic visits, patients will take study medication once daily in the

[redacted]

morning. Patients will be instructed to take their study medication at approximately the same time each morning.

At Visit 101, all eligible patients will be given oral placebo to QAW039 for a run-in epoch of 2 weeks and will be instructed on the intake of the investigational treatment. **In order to maintain the blind from the patient's point of view, investigators should not divulge information regarding the fact that all individuals will be assigned to placebo during the run-in epoch**. If a patient experiences an asthma exacerbation during the run-in epoch, the run-in epoch must be extended up to 6 weeks to permit for resolution of the asthma exacerbation before randomization. The run-in epoch should only be extended beyond 2 weeks (+/- 5 days) for an asthma exacerbation. At Visit 201, patients will be randomized and stratified according to their peripheral blood eosinophil counts (<250 cells/µl or ≥250 cells/µl), patient age (<18 years or ≥18 years), and their baseline use or non-use of oral corticosteroids as part of their SoC asthma therapy at Visit 1. Each randomized patient will then enter a 52-week treatment epoch where they will receive one of the following 3 treatments: (i) QAW039 150 mg once daily or (ii) QAW039 450 mg once daily or (iii) placebo once daily given on top of their individual background asthma treatment. The investigational treatment will be dispensed in medication packs (bottles) at each site visit during the treatment epoch 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

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

The investigator should instruct the patient to take the investigational treatment exactly as prescribed in order to ensure compliance. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the investigational treatment as prescribed.

5.5.5 Permitted dose adjustments and interruptions of study treatment

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 adverse event.

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

5.5.6 Rescue medication

At Visit 1 all patients will be provided with a SABA (such as salbutamol [100 mcg or albuterol 90 mcg]) which they will be instructed to use throughout the study as rescue medication on an 'as needed basis'. Patients will be advised that between visits they can take their rescue medication for symptoms of asthma. Rescue medication (i.e., SABAs) will either be supplied to the investigator sites locally by the Novartis CPO or provided by the study center and reimbursed by Novartis.

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

[redacted]

To standardize measurements, patients will be instructed not to use their rescue medication upon rising in the morning on days requiring spirometric assessments indicated in Table 6-1, unless absolutely necessary. If rescue medication is taken within 6 hours prior to spirometry, this information will be recorded by the study site staff using the equipment provided by the central spirometry vendor. Additionally, if rescue medication is taken within 6 hours prior to spirometry at any of the scheduled visits, the visit should be rescheduled to the next possible day.

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

Unless clinically indicated, the type of rescue medication (i.e., SABA) a patient uses, the device used to deliver the medication (e.g. dry powder or 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 CRF after the start of study drug.

5.5.7 Background therapy

All patients will remain on the incoming SoC asthma therapy they were taking at the screening visit (Visit 1) throughout the study. No dosage adjustments of the patient's incoming SoC therapy will be permitted during the study. Short bursts of rescue systemic corticosteroids are allowed for treatment of asthma exacerbations, as clinically indicated (see Section 6.4.1). The duration of a burst of rescue systemic corticosteroids should be approximately 3 to 10 days, and be of the shortest time needed to allow symptom control.

5.5.8 Concomitant treatment

The medications in Table 5-1 are only permitted under the circumstances given. This table is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria.

Table 5-1 Medications allowed under certain conditions

Class of medication	Condition
Inhaled corticosteroids (ICS)**	Medium or high-dose* daily or equivalent. 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 a LABA or an alternate therapy (LTRA or theophylline or LAMA) or with LABA/LAMA or with LABA/LTRA or with LABA/theophylline.
Long-acting inhaled β-2 agonists (LABAs)**	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 medium or high-dose* ICS.
Fixed dose combinations of ICS and LABA (FDC)**	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)**	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 medium or high-dose* ICS.
Theophylline**	Used for at least 3 months prior to Visit 1 and stable for at least 4 weeks prior to Visit 1.

[redacted]

	Must be taken with medium or high-dose* ICS.
Long-acting muscarinic antagonists (LAMAs)**	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 medium or high-dose* ICS.
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. Short bursts of rescue systemic corticosteroids are allowed for treatment of asthma exacerbations, as clinically indicated. The duration of a burst of rescue systemic corticosteroids should be approximately 3 to 10 days, and be of the shortest time needed to allow symptom control.
Short-acting β_2-agonist (SABAs)	Rescue medication to be taken as needed.
Maintenance immunotherapy for allergies	Stable dose for at least 3 months prior to screening and the dose remains stable throughout the study.
Inactivated influenza vaccine, pneumococcal vaccination or any other inactivated vaccine	Not administered within 48 h prior to a study visit.
Topical corticosteroids for treatment of eczema	Recommended doses and dosage regimens
Antihistamines (e.g., loratadine, cetirizine)	Recommended doses and dosage regimens
Nasal anticholinergics Nasal corticosteroids Nasal or ophthalmological preparations of nedocromil Nasal or ophthalmological preparations of antihistamines	Treatment regimen has been stable for at least 1 month prior to screening (Visit 1). In the case of as needed use, providing an established pattern of use has been documented.

*See GINA 2016 for definition of medium and high-dose ICS.

**See Section 4.1 (inclusion criterion 4) for permitted combinations of therapy.

Table 5-2 indicates the wash-out periods for allowed asthma medications prior to spirometry assessments. See Appendix Spirometry Guidance for more details.

Table 5-2 Medications to be withheld prior to spirometry

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

[redacted]

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

5.5.9 Prohibited Treatment

Use of the treatments displayed in Table 5-3 is NOT allowed after the start of study (i.e., after Visit 101). Each concomitant drug must be individually assessed against all exclusion criteria and the tables below to see if it is allowed. If in doubt, the investigator should contact the Novartis medical monitor or designee before randomizing a patient or allowing a new medication to be started. This table is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria.

These medications are also prohibited if administered for other indications.

Table 5-3 Prohibited medications

Class of medication	Minimum cessation prior to run-in (Visit 101)
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 short-acting β_2 agonists and short-acting anticholinergics	8 hours
Systemic mast cell stabilizers (e.g. cromoglycate, nedocromil, ketotifen)	7 days
Monoclonal antibodies, investigational or approved, for the treatment of asthma (e.g., omalizumab)	5 months
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	6 months

5.5.10 Discontinuation of study treatment

Patients may voluntarily discontinue active study medication (refuse study treatment but continue with study participation) at any time. **Patients who wish to discontinue active study medication 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 judgement.**

[redacted]

The investigator should discontinue study treatment for a given patient if, on balance, he/she believes that continuation of study treatment would be detrimental to the patient's well-being.

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

- Withdrawal of informed consent (and the investigator must prematurely withdraw the patient from the study);
- Pregnancy;
- Female subjects non-compliant with the chosen effective method of contraception during the study: The investigator must provide appropriate advice on the continued use of effective contraception for at least one week (at least 5 half-lives of QAW039) after study drug discontinuation and follow up with the subject as appropriate at least to the end of this period;
- Any protocol deviation that results in a significant risk to the patient's safety;
- Liver laboratory test abnormality / event (see 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 (Appendix 2);
- Premature unblinding of study treatment for a patient for any reason;
- Total white blood cell count <1000 cells/μL;
- If patients on statin therapy complain of persistent muscle pain without any obvious cause for greater than 3 days accompanied by increase in CK levels >10xULN or persistent intolerable muscle pain regardless of the accompanying CK level;
- If a patient develops a medical condition that requires consistent use of prohibited treatment as per Section 5.5.9 or if patient exhibits a behavior of non-compliance regarding prohibited medication.

The appropriate personnel from the site and Novartis will assess whether investigational treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

Patients who discontinue investigational treatment should NOT be considered withdrawn from the study. If premature discontinuation of investigational treatment occurs for any reason the patient should continue attending the remaining study visits while off investigational treatment. The patient should return to the clinic as soon as possible for an investigational treatment discontinuation visit (TD). At this visit, the assessments listed under UNSCHEDULED-TD in Table 6-1 should be completed and recorded in the eCRF. The investigator and study staff must discuss with the patient, the patient's continued participation in the study and request patients to continue attending study visits according to the study visit schedule with all assessments (except study drug related assessments such as compliance checks) completed up to Visit 299. If the patient cannot or is unwilling to attend any further visit(s), the site staff should maintain regular phone contact with the patient, or with a person pre-designated by the patient. This phone contact should preferably be done according to the study visit schedule. Data will continue to be collected concerning the patients' condition and changes in concomitant medications, surgeries and procedures, serious and non-serious

[redacted]

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 investigational treatment

5.5.11 Discontinuation from study

Patients will only be discontinued from the study if they withdraw consent, die during the study or are lost to follow-up (see Section 5.5.13**).**

5.5.12 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only 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.

If a patient withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information. Investigational treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

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.

5.5.13 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until his/her scheduled end of study visit would have occurred.

5.5.14 Emergency breaking of assigned treatment code

Emergency treatment code breaks should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study drug 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 Novartis that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable, redundant procedure in place to allow access to the IRT code break card at any time in case of emergency. The investigator will provide the protocol number, investigational treatment name if available, patient number as well as oral and written information to the patient on how to contact his/her backup in cases of emergency when he/she is unavailable to ensure that un-blinding can be performed at any time in the case of emergency. Study drug must be discontinued after emergency unblinding. Study drug must also be discontinued for any patient whose treatment code has been inadvertently broken or for any other non-emergency reason.

5.5.15 Study completion and post-study treatment

Study completion for a patient will occur after he/she has completed 52 weeks of treatment (through to Visit 299) or they have prematurely withdrawn. Completion of the study will be when all randomized patients have completed 52 weeks of treatment and the post-treatment follow-up visit.

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

A Safety Study of QAW039 is planned. At sites participating in the Safety Study, patients who successfully complete 52 weeks of treatment in this study (Study A2307) may be offered participation in the Safety Study; patient participation in the Safety Study will be optional. Patients not entering the safety study will complete the follow-up epoch and will not be given further access to study drug because the risk/benefit ratio will not yet have been substantiated and there are already other marketed therapeutic alternatives available to treat these patients. At the time of study completion or early termination, all patients will be placed on the appropriate asthma treatment as prescribed by the investigator.

The investigator must provide appropriate advice on the continued use of effective contraception for at least one week (at least 5 half-lives of QAW039) after the study completion (V299) 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.

5.5.16 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated for 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

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

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

[redacted]

Patients should be seen for all visits as close as possible to the visit date. In case a treatment visit cannot occur as scheduled in the protocol, visits should be scheduled according to the specified visit window in the schedule of assessments.

Patients, who discontinue study treatment before completing the study and will accept to remain in the study, will return for study visits as described in Section 5.5.10. If they fail to return for these assessments for unknown reasons, every effort should be made to contact them as specified in Section 5.5.10. At the very least, patients should be asked if they can be contacted by phone by study personnel at the date they would have been scheduled to end the follow up epoch (4 weeks after premature drug discontinuation) to ask about concomitant medication use, surgery and procedures, SAEs, AEs and asthma exacerbations.

Patients will be required to attend the clinic in the morning at approximately the same time, so that pre-dose FEV1 assessments can be performed between 6:00 A.M. and 10:00 A.M. (+/- 1 hour). [redacted] At certain clinic visits, measurements will be collected 2 hours post dosing; these measurements should be accounted for when scheduling clinic visits.

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 to be completed in the following order: ACQ-5, AQLQ+12,** [redacted] **at certain clinic visits;**
3) **Vital signs;**
4) **ECGs;**
5) **Samples for urine/hematology/blood chemistry** (At Visit 1 collect samples prior to spirometry. At all other visits, collect samples prior to the 1st pre-dose spirometry [which is the -45 min pre-dose spirometry] or between the 1st and 2nd pre-dose spirometry measurements.);
6) **Samples for RAST/ImmunoCAP test, Total IgE, at certain clinic visit(s)** (At Visit 1 collect samples prior to spirometry. At all other visits, collect samples prior to the 1st pre-dose spirometry [which is the -45 min pre-dose spirometry] or between the 1st and 2nd pre-dose spirometry measurements.);

[redacted]

9) **Spirometry assessments should be timed so that the Visit 1 spirometry assessment and all pre-dose spirometry assessments (i.e., FEV1 measurements) during the run-in epoch and treatment epoch are performed between 6:00 A.M. and 10:00 A.M. (+/- 1 hour)**. Other tests should be performed as close as possible to those spirometry times. During the run-in epoch and treatment epoch, two pre-dose spirometry assessments should be performed as follows:

[redacted]

- **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**.**

10) **Reversibility at certain visits** (spirometry after administration of SABA) may be performed after 10:00 A.M. (+/- 1 hour);
11) **In-clinic witnessed dosing of study drug;**
12) **ECGs (2 hour post-dose) at certain clinic visits;**

[redacted]

[redacted]

Table 6-1 Assessment schedule

	Screen	Run-in		Treatment															Follow-up
Visit Number (Site visits)[1]	1	101	199	201	202		203		204		205		206		207		UNSCHEDULED-TD	299	301
Telephone Call (TC)[2] **Note:** TC in-between site visits						TC1		TC2		TC3		TC4		TC5		TC6			
Treatment Week	-4	-2[3]	1	1	4	8	12	16	20	24	28	32	36	40	44	48	TD	52	56
Treatment Day **Note:** *V199 and 201 will occur on the same day if the patient is randomized.	-28	-14[3]	1*	1*	28	56	84	112	140	168	196	224	252	280	308	336	TD	364	392
Visit Window (Days)	NA	+/-7	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	NA	+/-5	+/-5
[1]Scheduled clinic visits (starting at Visit101 and thereafter) are to occur in the morning at approximately the same time, so that the -45 min and -15 min pre-dose FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M. (+/- 1 hour). [2]Scheduled telephone calls (TCs) will be conducted to check the patients' condition (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. [3]For patients experiencing an asthma exacerbation during the run-in epoch, the run-in may be extended up to 6 weeks. [4]The follow-up epoch applies to all patients except those patients who enter the safety study directly after Visit 299. **TD** = investigational 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																			
Informed consent and assent (if applicable) **Note:** ICF must be obtained within 14 days prior to or on V1.	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 must be rescheduled.	X	X	X		X		X		X		X		X		X		X	X	
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		X		X		X	X	
Inclusion/exclusion criteria	X	X	X																

[redacted]

	Screen	Run-in		Treatment															Follow-up
Visit Number (Site visits)[1]	1	101	199	201	202		203		204		205		206		207		UNSCHEDULED-TD	299	301
Telephone Call (TC)[2] **Note:** TC in-between site visits						TC1		TC2		TC3		TC4		TC5		TC6			
Treatment Week	-4	-2[3]	1	1	4	8	12	16	20	24	28	32	36	40	44	48	TD	52	56
Treatment Day **Note:** *V199 and 201 will occur on the same day if the patient is randomized.	-28	-14[3]	1*	1*	28	56	84	112	140	168	196	224	252	280	308	336	TD	364	392
Visit Window (Days)	NA	+/-7	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	NA	+/-5	+/-5
[1]Scheduled clinic visits (starting at Visit101 and thereafter) are to occur in the morning at approximately the same time, so that the -45 min and -15 min pre-dose FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M. (+/- 1 hour). [2]Scheduled telephone calls (TCs) will be conducted to check the patients' condition (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. [3]For patients experiencing an asthma exacerbation during the run-in epoch, the run-in may be extended up to 6 weeks. [4]The follow-up epoch applies to all patients except those patients who enter the safety study directly after Visit 299. **TD** = investigational 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 and record surgeries and procedures	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination **(S)**	X																X	X	
Abbreviated physical examination (heart and lung only) **(S)**		X	X		X		X		X		X		X		X				
Height **Note:** Height must be collected using a standard measurement device (such as a stadiometer)	X																	X	
Weight	X		X														X	X	
Parasitic screening **(S)** **Note:** Only if **required by** health authority and/or ethics committee/institutional review board. Sites should use local laboratories.	X																		
Vital signs (systolic/diastolic blood pressure, radial pulse (sitting), and body temperature)	X	X	X		X		X		X		X		X		X		X	X	
Electrocardiograms	X																X		
Electrocardiograms (Pre-dose)		X		X	X		X		X		X		X		X			X	
Electrocardiograms (2h-post dose)				X	X						X							X	

[redacted]

	Screen	Run-in		Treatment															Follow-up
Visit Number (Site visits)[1]	1	101	199	201	202		203		204		205		206		207		UNSCHEDULED-TD	299	301
Telephone Call (TC)[2] **Note:** TC in-between site visits						TC1		TC2		TC3		TC4		TC5		TC6			
Treatment Week	-4	-2[3]	1	1	4	8	12	16	20	24	28	32	36	40	44	48	TD	52	56
Treatment Day **Note:** *V199 and 201 will occur on the same day if the patient is randomized.	-28	-14[3]	1*	1*	28	56	84	112	140	168	196	224	252	280	308	336	TD	364	392
Visit Window (Days)	NA	+/-7	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	NA	+/-5	+/-5
[1]Scheduled clinic visits (starting at Visit101 and thereafter) are to occur in the morning at approximately the same time, so that the -45 min and -15 min pre-dose FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M. (+/- 1 hour). [2]Scheduled telephone calls (TCs) will be conducted to check the patients' condition (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. [3]For patients experiencing an asthma exacerbation during the run-in epoch, the run-in may be extended up to 6 weeks. [4]The follow-up epoch applies to all patients except those patients who enter the safety study directly after Visit 299. **TD =** investigational 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—serum (women of child bearing potential) **Note:** Pregnancy testing will begin at Visit 1 if a patient is identified as being of child bearing potential	X																		
Pregnancy test—urine (women of child bearing potential) **Notes:** 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 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
In countries where monthly pregnancy testing is required for women of child-bearing potential by local laws or regulations: Home Pregnancy testing- urine **Note:** at telephone visits **(S)**						X		X		X		X		X		X			
Urinalysis and urine chemistry (central laboratory)	X			X	X		X		X		X		X		X		X	X	

[redacted]

	Screen	Run-in		Treatment														Follow-up
Visit Number (Site visits)[1]	1	101	199	201	202		203		204		205		206		207		UNSCHEDULED-TD	299	301
Telephone Call (TC)[2] **Note:** TC in-between site visits						TC1		TC2		TC3		TC4		TC5		TC6			
Treatment Week	-4	-2[3]	1	1	4	8	12	16	20	24	28	32	36	40	44	48	TD	52	56
Treatment Day **Note:** *V199 and 201 will occur on the same day if the patient is randomized.	-28	-14[3]	1*	1*	28	56	84	112	140	168	196	224	252	280	308	336	TD	364	392
Visit Window (Days)	NA	+/-7	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	NA	+/-5	+/-5
[1]Scheduled clinic visits (starting at Visit101 and thereafter) are to occur in the morning at approximately the same time, so that the -45 min and -15 min pre-dose FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M. (+/- 1 hour). [2]Scheduled telephone calls (TCs) will be conducted to check the patients' condition (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. [3]For patients experiencing an asthma exacerbation during the run-in epoch, the run-in may be extended up to 6 weeks. [4]The follow-up epoch applies to all patients except those patients who enter the safety study directly after Visit 299. **TD** = investigational 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 (central laboratory) **Notes:** No fasting requirement prior to blood sampling.	X			X	X		X		X		X		X		X		X	X	
[redacted]																			
Blood for RAST/ImmunoCAP test (central laboratory)	X																		
Blood sample for IgE				X													X	X	
Review Visit 1 laboratory results (chemistry, hematology, HbA1c, RAST/ImmunoCAP, IgE, urine chemistry and urinalysis). **(S)** **Note:** If results for chemistry, hematology, HbA1c, RAST/ImmunoCAP, IgE, urine chemistry and urinalysis are missing, obtain a repeat for the missing result.		X																	
Telephone contact with patient **(S)**						X		X		X		X		X		X			
Serious adverse event recording	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	

[redacted]

	Screen	Run-in		Treatment															Follow-up
Visit Number (Site visits)[1]	1	101	199	201	202		203		204		205		206		207		UNSCHEDULED-TD	299	301
Telephone Call (TC)[2] **Note:** TC in-between site visits						TC1		TC2		TC3		TC4		TC5		TC6			
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Treatment Day **Note:** *V199 and 201 will occur on the same day if the patient is randomized.	-28	-14[3]	1*	1*	28	56	84	112	140	168	196	224	252	280	308	336	TD	364	392
Visit Window (Days)	NA	+/-7	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	NA	+/-5	+/-5
[1]Scheduled clinic visits (starting at Visit101 and thereafter) are to occur in the morning at approximately the same time, so that the -45 min and -15 min pre-dose FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M. (+/- 1 hour). [2]Scheduled telephone calls (TCs) will be conducted to check the patients' condition (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. [3]For patients experiencing an asthma exacerbation during the run-in epoch, the run-in may be extended up to 6 weeks. [4]The follow-up epoch applies to all patients except those patients who enter the safety study directly after Visit 299. **TD =** investigational 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																			
Record deaths	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	
Renal events monitoring	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	
Spirometry (centralized) [£]To be performed prior to reversibility test.	X[£]																X		
1st Pre-dose Spirometry (centralized) - 45 min pre-dose **Note:** To be performed approximately. 45 min prior to in-clinic witnessed study drug administration.		X		X	X		X		X		X		X		X			X	
2nd pre-dose Spirometry (centralized) - 15 min pre-dose **Note:** To be performed approximately. 15 min prior to in-clinic witnessed study drug administration. [£]To be performed prior to reversibility test.		X[£]		X[£]	X[£]		X		X		X[£]		X		X			X[£]	

[redacted]

	Screen	Run-in		Treatment															Follow-up
Visit Number (Site visits)[1]	1	101	199	201	202		203		204		205		206		207		UNSCHEDULED-TD	299	301
Telephone Call (TC)[2] **Note:** TC in-between site visits						TC1		TC2		TC3		TC4		TC5		TC6			
Treatment Week	-4	-2[3]	1	1	4	8	12	16	20	24	28	32	36	40	44	48	TD	52	56
Treatment Day **Note:** *V199 and 201 will occur on the same day if the patient is randomized.	-28	-14[3]	1*	1*	28	56	84	112	140	168	196	224	252	280	308	336	TD	364	392
Visit Window (Days)	NA	+/-7	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	NA	+/-5	+/-5
[1]Scheduled clinic visits (starting at Visit101 and thereafter) are to occur in the morning at approximately the same time, so that the -45 min and -15 min pre-dose FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M. (+/- 1 hour). [2]Scheduled telephone calls (TCs) will be conducted to check the patients' condition (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. [3]For patients experiencing an asthma exacerbation during the run-in epoch, the run-in may be extended up to 6 weeks. [4]The follow-up epoch applies to all patients except those patients who enter the safety study directly after Visit 299. **TD =** investigational 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 / Post-bronchodilator FEV1 (spirometry after administration of short-acting β-agonist [SABA]) **Notes:** **If reversibility is not demonstrated at Visit 1 and documented evidence for one of the other criteria for a clinical diagnosis of asthma is not met, then the reversibility test may be repeated at Visit 101. [α]To be performed prior to in-clinic witnessed study drug administration. [ß]To be performed after the second pre-dose spirometry (may be performed after 10:00 AM (+/- 1 hour)).	X	X**,α,ß		X[α,ß]	X[α,ß]						X[α,ß]							X[α,ß]	
Airway hyper-reactivity test ***optional test if reversibility is not met at V1.		X***																	
[redacted]																			

[redacted]

	Screen	Run-in		Treatment															Follow-up
Visit Number (Site visits)[1]	1	101	199	201	202		203		204		205		206		207		UNSCHEDULED-TD	299	301
Telephone Call (TC)[2] **Note:** TC in-between site visits						TC1		TC2		TC3		TC4		TC5		TC6			
Treatment Week	-4	-2[3]	1	1	4	8	12	16	20	24	28	32	36	40	44	48	TD	52	56
Treatment Day **Note:** *V199 and 201 will occur on the same day if the patient is randomized.	-28	-14[3]	1*	1*	28	56	84	112	140	168	196	224	252	280	308	336	TD	364	392
Visit Window (Days)	NA	+/-7	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	NA	+/-5	+/-5
[1]Scheduled clinic visits (starting at Visit101 and thereafter) are to occur in the morning at approximately the same time, so that the -45 min and -15 min pre-dose FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M. (+/- 1 hour). [2]Scheduled telephone calls (TCs) will be conducted to check the patients' condition (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. [3]For patients experiencing an asthma exacerbation during the run-in epoch, the run-in may be extended up to 6 weeks. [4]The follow-up epoch applies to all patients except those patients who enter the safety study directly after Visit 299. **TD** = investigational 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																			
Train and assess patient's ability to use eDiary, [redacted] and dispense eDiary, [redacted] **(S)**	X																		
Review eDiary [redacted] compliance prior to randomizing the patient **(S)**		X	X																
Review eDiary [redacted] entries **(S)**					X		X		X		X		X		X		X	X	
Contact IRT **(S)**	X	X	X	X	X		X		X		X		X		X		X	X	X
Randomize patient through IRT **(S)**				X															
ACQ-5 in clinic	X	X	X		X		X		X		X		X		X		X	X	
AQLQ+12 in clinic		X	X		X		X		X		X		X		X		X	X	
[redacted]																			
Dispense study drug **(S)** **Note:** The patients will be instructed to take their investigational treatment in the morning		X		X	X		X		X		X		X		X				

[redacted]

	Screen	Run-in		Treatment															Follow-up
Visit Number (Site visits)[1]	1	101	199	201	202		203		204		205		206		207		UNSCHEDULED-TD	299	301
Telephone Call (TC)[2] **Note:** TC in-between site visits						TC1		TC2		TC3		TC4		TC5		TC6			
Treatment Week	-4	-2[3]	1	1	4	8	12	16	20	24	28	32	36	40	44	48	TD	52	56
Treatment Day **Note:** *V199 and 201 will occur on the same day if the patient is randomized.	-28	-14[3]	1*	1*	28	56	84	112	140	168	196	224	252	280	308	336	TD	364	392
Visit Window (Days)	NA	+/-7	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	NA	+/-5	+/-5
[1]Scheduled clinic visits (starting at Visit101 and thereafter) are to occur in the morning at approximately the same time, so that the -45 min and -15 min pre-dose FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M. (+/- 1 hour). [2]Scheduled telephone calls (TCs) will be conducted to check the patients' condition (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. [3]For patients experiencing an asthma exacerbation during the run-in epoch, the run-in may be extended up to 6 weeks. [4]The follow-up epoch applies to all patients except those patients who enter the safety study directly after Visit 299. **TD** = investigational 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																			
Return and assess compliance with study drug (count tablets in returned bottles) **(S)**			X		X		X		X		X		X		X		X	X	
In-clinic witnessed study drug intake **Note** Complete Dose administration record (DAR) – at site visit		X		X	X		X		X		X		X		X			X	
Complete Dose administration record - Summary page			X		X		X		X		X		X		X		X	X	
Complete Study Disposition page (screening)	X																		
Complete Study Disposition page (run-in) **Note:** [$]V101 Disposition is only present if patient is a run-in failure.		X[$]	X																
Complete Study Disposition page (end of treatment)																		X	
Complete Study Disposition page (follow-up)																			X
Withdrawal of informed consent	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Re-screening of patient **Notes:** Re-screening of patients is permitted once. Once a patient enters the run-in epoch, the patient may not be re-screened. 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.	X																		
Appointment for next clinic visit **(S)**	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[redacted]

	Screen	Run-in		Treatment															Follow-up
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Telephone Call (TC)[2] **Note:** TC in-between site visits						TC1		TC2		TC3		TC4		TC5		TC6			
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Treatment Day **Note:** *V199 and 201 will occur on the same day if the patient is randomized.	-28	-14[3]	1*	1*	28	56	84	112	140	168	196	224	252	280	308	336	TD	364	392
Visit Window (Days)	NA	+/-7	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	+/-5	NA	+/-5	+/-5
[1]Scheduled clinic visits (starting at Visit101 and thereafter) are to occur in the morning at approximately the same time, so that the -45 min and -15 min pre-dose FEV1 assessments can be performed between 06:00 A.M. and 10:00 A.M. (+/- 1 hour). [2]Scheduled telephone calls (TCs) will be conducted to check the patients' condition (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. [3]For patients experiencing an asthma exacerbation during the run-in epoch, the run-in may be extended up to 6 weeks. [4]The follow-up epoch applies to all patients except those patients who enter the safety study directly after Visit 299. **TD** = investigational 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 patient card **(S)**	X																		
Collect patient card **(S)**																		X For patients participating in the safety study	X
For sites participating in the Safety Study, discuss optional patient participation in the Safety Study.																		X	

[redacted]

6.1 Information to be collected on screening failures and run-in failures

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

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

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

6.2 Patient demographics/other baseline characteristics

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
- Baseline ACQ
- [redacted]
- Blood eosinophil counts at Visit 1 and baseline
- Relevant medical history/current medical condition present before signing informed consent. Where possible, diagnoses and not symptoms will be recorded.

[redacted]

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.

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

6.4 Efficacy

6.4.1 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.

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

6.4.2 Asthma Control Questionnaire (ACQ-5)

In this study, the ACQ-5 will be used to assess improvements in asthma symptom control. The ACQ-5 will be collected in an electronic format.

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 1999, 2006), and

[redacted]

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 2010) and including a minimal important difference (MID) or smallest change that can be considered clinically important (0.5).

The ACQ-5 (see Appendix 8) 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 completed by patients at the visits specified in the table of assessments (See Table 6-1). The questionnaire should 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 should be used by a particular patient throughout the study.

The study coordinator should be familiar with the instrument and the associated user guides and training materials provided. 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. At later visits patients are not allowed to review their previous responses.

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.

6.4.3 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 will be collected in an electronic format.

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 9).

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

[redacted]

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 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 should be used by a particular patient throughout the study.

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

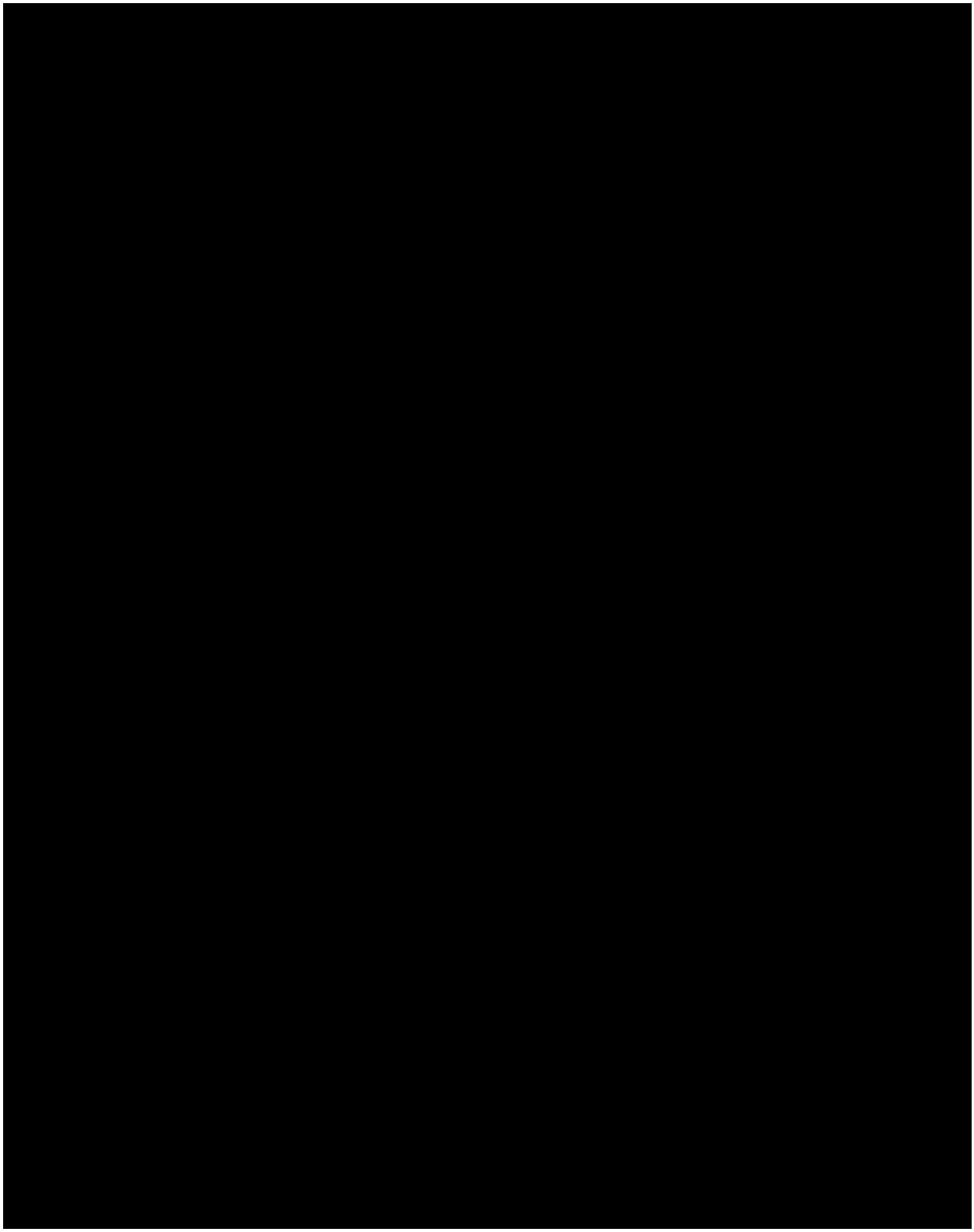
Missing data should be avoided, therefore, the study coordinator will check the questionnaire for completeness before the patient leaves the clinic, and if necessary, encourage the patient to complete any missing responses. At later visits patients are not allowed to review their previous responses.

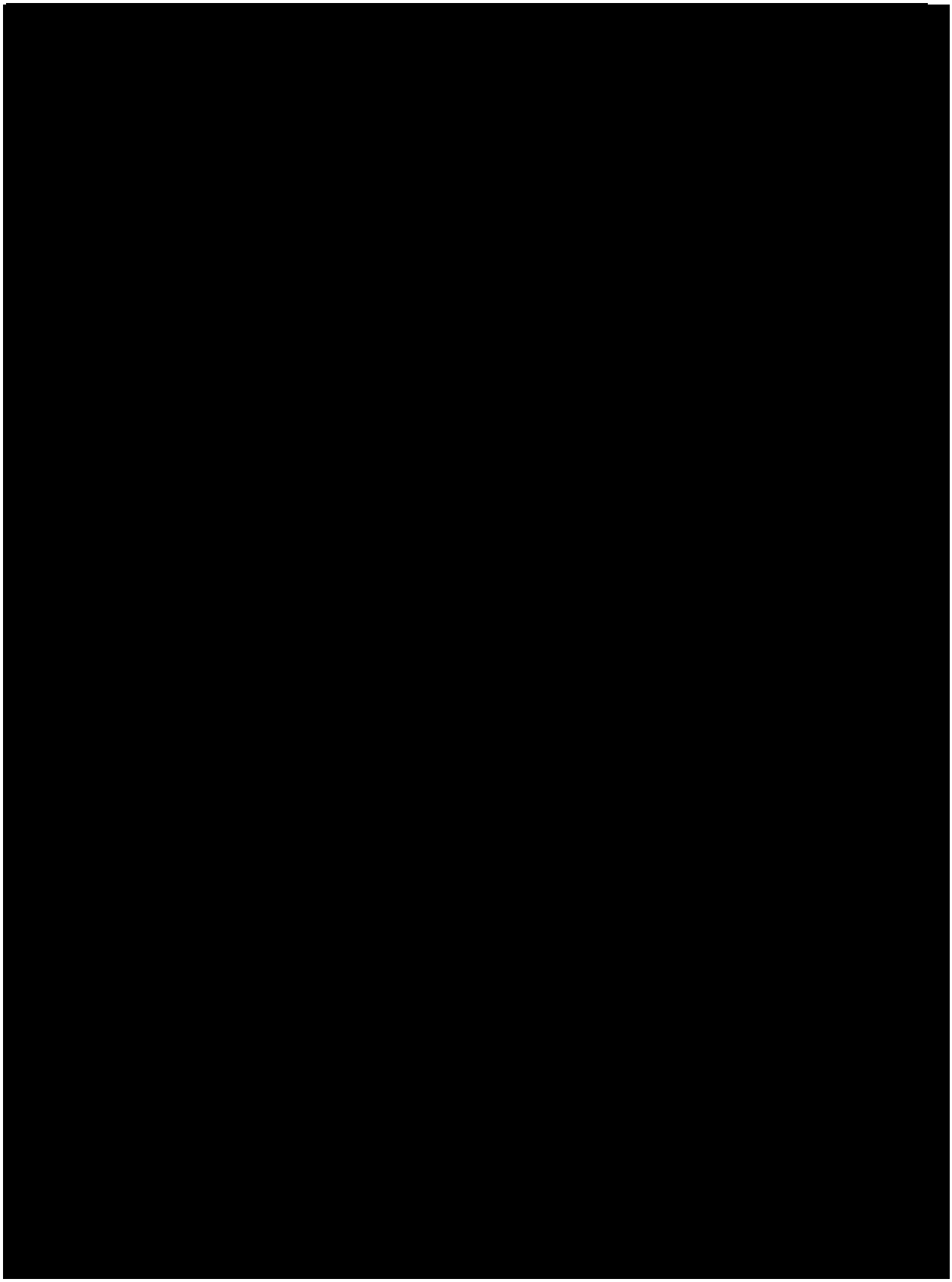
Completed questionnaires will be reviewed by the investigator for responses which may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaire but also for any unsolicited comments written by the patient. If AEs or SAEs are confirmed 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.

The PROs ACQ, AQLQ+12, [redacted] questionnaires should always be completed before any other assessments and in the above order (see Section 6).

[redacted]

[redacted]





[redacted]

6.4.8 Spirometry (FEV1 [redacted])

All clinic visits must occur in the morning. Please refer to Section 6 and Table 6-1 for full details of the scheduling of spirometry measurements.

Equipment for spirometry assessments will be provided to all study sites by a Central Spirometry vendor, and 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 5, for full details on scheduling and performing spirometry. Reversibility testing must be conducted in the morning.

6.4.9 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:

- History and physical examination
- Vital signs
- Hematology
- Blood chemistry including but not limited to

[redacted]

- Liver function tests: ALT, AST, total bilirubin
- Metabolic panel: sodium, potassium, chloride, bicarbonate, BUN/urea, creatinine, glucose, calcium, phosphorus, magnesium, total protein, albumin, γ-GT, alkaline phosphatase, LDH, CK, iron, uric acid, cholesterol, triglycerides
- amylase, lipase
- hsCRP
- CK-MB and Troponin-I (in response to CK results outside of the normal range)
- HbA1c (collected at Visit 1 only)

- Urinalysis and urine chemistry.
- Pregnancy test (females of childbearing potential)
- ECG
- Adverse events including serious adverse events

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

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

A Data Monitoring Committee will be set up to overview safety. See Section 8.3 for details.

6.5.1 Physical examination

A complete physical examination will be performed at Visits 1 and 299 (and UNSECHEDULED-TD if a patient discontinues investigational treatment but continues with study participation). It will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Abbreviated physical examinations will be performed at visits 101 to 207 (except Visit 201, since Visit 199 and 201 should occur on the same day). It 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 assessed at every visit (except Visit 201, since Visit 199 and 201 should occur on the same day). 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 three times using an

[redacted]

automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 to 2 minute intervals and the mean of the three measurements will be used. 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.

Clinically notable vital signs are defined in Appendix 1.

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.

Details on 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.

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) and immunoglobulins (IgE, RAST/ImmunoCAP test), will be measured according to the assessment schedule in Table 6-1. Other reflex testing will be performed as outlined in the laboratory manual.

If the total bilirubin concentration is increased 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.

[redacted]

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 7-1 "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 Visits 1 and 101 an ECG will be measured to test for eligibility for trial inclusion.

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. 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 should be labeled with study number (CQAW039A2307), 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 central cardiologist ECG overreaders of the central vendor. 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.

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 of child bearing potential will have a serum pregnancy test at Visits 1 and a urine pregnancy test at all other site visits (except visit 201, since Visit 199 and 201 should occur on the same day).

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

[redacted]

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

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

6.5.7 Appropriateness of safety measurements

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

6.6 Other assessments

[redacted]

[redacted]

6.6.4 Airways hyper-reactivity test

An airways hyper-reactivity (AHR) test should be performed at Visit 101 if reversibility is not demonstrated at screening (Visit 1) and documented evidence for one of the other criteria for a clinical diagnosis of asthma is not met (see Section 4.1). A positive result is defined as a provoked fall in FEV_1 of 20% (PC20) 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.

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. 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
- 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 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 study 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)
- study treatment dosage increased/reduced
- study treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- non-drug therapy given
- patient hospitalized/patient’s hospitalization prolonged

[redacted]

- 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) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

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 of IDRs 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:

- 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 under study
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

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

[redacted]

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

All AEs (serious and non-serious) are captured on the CRF, SAEs also require individual reporting to DS&E as per Section 7.2.2.

7.2.2 SAE reporting

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

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

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 investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same

[redacted]

investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

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:

- 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 LFT within the next week to confirm elevation.

These LFT repeats should 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 should 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 should 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 should be recorded on appropriate CRF pages, including the liver event overview CRF pages.

7.4 Renal safety monitoring

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

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

1. Serum event:

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

2. Urine event:

- urinary albumin-creatinine ratio (ACR) ≥ 1 g/g or ≥ 100 mg/mmol
- urinary protein-creatinine ratio (PCR) ≥ 1 g/g or ≥ 100 mg/mmol

Every renal laboratory trigger or renal event as defined in Table 7-1 should be followed up by the investigator or designated personnel at the trial site as summarized below.

Table 7-1 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 drug 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 drug interruption / discontinuation
For all renal events:	
1. Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed 2. 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.	

[redacted]

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 are provided in Appendix 3

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

7.6 Pregnancy reporting

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

Pregnancy should be recorded 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 investigational treatment.

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

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 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 CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for

site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each 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 will be disclosed.

8.2 Database management and quality control

Novartis staff, or a 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).

Diary data will be entered into an electronic diary by the patient. The system will be supplied by a vendor(s), who will also manage the database. The database 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).

[redacted]

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.

8.3 Data Monitoring Committee

An independent, external data monitoring committee (DMC) will be set up to review safety data (including specific safety summaries for adolescent participants) from this trial and other Phase III trials in the QAW039 asthma development program, as well as to conduct the planned single interim analysis for futility as described in Section 3.5 and Section 9.6. The DMC will consist of a group of experts independent of the sponsor, analyses for the DMC will be prepared by individuals independent of the sponsor and sponsor personnel will remain fully blinded to the interim results until the final clinical database lock as described in Section 5.4. Based on the safety implications of the data, the DMC may recommend modification or termination of the study. There will be no stopping for demonstrated efficacy prior to the completion of the study at either the unblinded safety reviews or the futility interim analysis, because a sufficiently large safety dataset is needed in addition to efficacy data. Therefore, no statistical adjustment will be made to the final analysis. Full details on procedures, the DMC and futility criteria will be specified in a DMC charter.

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

The purpose of the DMC charter is to define:

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 trial 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.

[redacted]

8.4 Data collection

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be given access to the system until they have been trained.

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

8.5 Adjudication Committee

Not required.

9 Data analysis

9.1 Analysis sets

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

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

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

The per-protocol set (PPS) will include all patients in the FAS without any major protocol deviations such as violation of major entry criteria. Patients may also be considered censored for the PPS analysis at the time of major post-baseline protocol deviations. Major protocol deviations will be defined in the data handling plan prior to database lock and the un-blinding of the study. Patients will be analyzed according to the treatment they received.

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

[redacted]

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

[redacted]

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.

9.2 Patient demographics and other baseline characteristics

Patient demographics and baseline characteristics measured before randomization including age (calculated from date of birth to date of Visit 1), sex, race, ethnicity, height, weight, body mass index (BMI), relevant medical history, including smoking history, asthma duration, use of long-acting beta-agonists, use of oral corticosteroids, pre- [redacted] FEV1, percent predicted FEV1, ACQ score, blood eosinophil count, number of exacerbations in the previous year [redacted] will be summarized by treatment group for the FAS. Categorizations of age will include at least the categories of <18, 18 to <65, 65-74, 75-84 and ≥85 years of age.

Blood eosinophil counts will also be summarized for the SCR.

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 and stopped prior to study drug, taken concomitantly, and started following last study drug dose (if applicable) will be summarized by treatment group in separate tables in the SAF. Concomitant therapies will be recorded, listed and summarized separately for asthma related medications / non-drug therapies and other medications. Concomitant asthma related medications will be summarized by pre-defined category. Concomitant medications not related to asthma will be summarized by 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.

Short acting β_2-agonist usage (number of puffs) during the screening epoch will be summarized.

Usage of asthma medication (e.g. LABA, ICS) at baseline will be summarized. Usage of oral corticosteroids (OCS) 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 according the intention to treat principle.

9.4.1 Variable(s)

The primary variable for this study is the number of moderate-to-severe asthma exacerbations as defined in Section 6.4.1 experienced by each patient per patient year of follow-up. The start date of a moderate-to-severe asthma exacerbation recorded in the CRF is defined as the first day of 'rescue' systemic corticosteroid use, or the date of death if no rescue corticosteroids were taken prior to an asthma related death. Further asthma exacerbations will only be considered additional events, if the start date of the next episode is at least 7 days after the end

[redacted]

of the previous exacerbation episode. The end of an exacerbation is defined as the last day of systemic corticosteroid use.

The key secondary variables are AQLQ+12, ACQ-5 and pre-dose FEV1 at the end of the 52 week treatment period. Their definition and analysis is described in Section 9.5.

9.4.2 Statistical model, hypothesis, and method of analysis

Primary null hypotheses

The trial will be considered positive, if one or more of the two QAW039 doses demonstrate a statistically significant reduction in the rate of moderate-to-severe asthma exacerbations. As described below, the two doses will be tested in parallel and each dose may achieve statistically significant results irrespective of the results achieved by the other dose.

The primary null hypotheses are:

- $H_{0\ 450\ \text{eosinophil subgroup}}$: relative risk ratio for the QAW039 450 mg QD group versus placebo in patients with eosinophil count ≥ 250 cells/µl = 1,
- $H_{0\ 150\ \text{eosinophil subgroup}}$: relative risk ratio for the QAW039 150 mg QD versus placebo in patients with eosinophil count ≥ 250 cells/µl = 1,
- $H_{0\ 450\ \text{overall}}$: relative risk ratio for the QAW039 450 mg QD versus placebo in the overall study population = 1 and
- $H_{0\ 150\ \text{overall}}$: relative risk ratio for the QAW039 150 mg QD versus placebo in the overall study population = 1.

The primary alternate hypotheses are:

- $H_{A\ 450\ \text{eosinophil subgroup}}$: relative risk ratio for the QAW039 450 mg QD group versus placebo in patients with eosinophil count ≥ 250 cells/µl ≠ 1,
- $H_{A\ 150\ \text{eosinophil subgroup}}$: relative risk ratio for the QAW039 150 mg QD group versus placebo in patients with eosinophil count ≥ 250 cells/µl ≠ 1,
- $H_{A\ 450\ \text{overall}}$: relative risk ratio for the QAW039 450 mg QD group versus placebo in the overall study population ≠ 1 and
- $H_{A\ 150\ \text{overall}}$: relative risk ratio for the QAW039 150 mg QD group versus placebo in the overall study population ≠ 1.

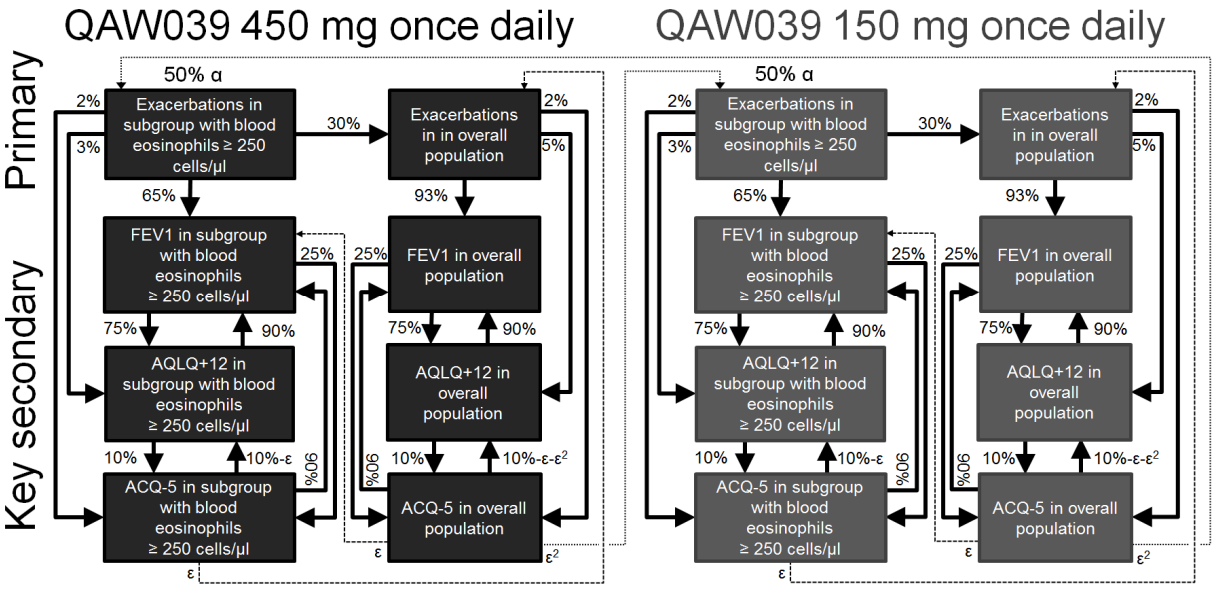
The superiority of QAW039 over placebo will be considered confirmed if at least one of the four primary null hypotheses is rejected in favor of the respective two-sided alternative hypotheses.

Familywise type I error rate control

The familywise type I error rate will be controlled at the two-sided 5% level across the primary and key secondary null hypotheses using the closed testing procedure specified by Figure 9-1 using the graphical method of Bretz, et al 2009. In this closed testing procedure the primary null hypothesis about exacerbations in the subset of patients with eosinophil count ≥ 250 cells/µl for each dose acts as a gatekeeper for the other null hypotheses for the same dose.

[redacted]

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



Vertices with associated weights denote the individual null hypotheses and their local significance levels (initially α is split 50%:50% across the primary null hypotheses regarding the subgroup with blood eosinophils ≥ 250 cells/µl for the 2 QAW039 doses). Directed edges between the vertices specify how the local significance levels are propagated in case of significant results. Dotted Dashed edges with a weight of ε indicate that the local significance level from the key secondary null hypotheses of a dose will only be propagated to the other population for the same dose, once all key secondary null hypotheses for a dose and population have been rejected. Dotted edges with a weight of ε^2 (much smaller than ε) indicate that the local significance level from the key secondary null hypotheses of a dose will only be propagated to the other dose, once all key secondary null hypotheses for a dose have been rejected.

Initially, 50% of the alpha is assigned to each of the primary null hypotheses regarding the subgroup with blood eosinophils ≥ 250 cells/µl for the QAW039 450 mg QD and QAW039 150 mg QD doses, respectively.

Once this first primary null hypothesis for a dose has been rejected, the alpha will be distributed to the other primary null hypothesis regarding the overall population for the same dose and the key secondary null hypotheses regarding the subgroup with blood eosinophils ≥ 250 cells/µl for that same dose. If the null hypothesis regarding the primary endpoint for the overall population is rejected for a dose, then alpha is reassigned to the key secondary null hypotheses regarding the overall population for that dose. Alpha will only be reassigned from the set of null hypotheses for a dose to the null hypotheses for the other dose once all null hypotheses for the dose to which the alpha was originally assigned have been rejected.

Once the primary null hypothesis for a dose and population has been rejected, all key secondary null hypothesis for that dose and population are tested and can be rejected irrespective of whether the other key secondary null hypotheses for that dose and population can be rejected. However, FEV1 will be initially given the highest local significance level due to its regulatory importance.

[redacted]

Statistical model for primary variable

These hypothesis tests, as well as point estimates and confidence intervals will be based on a negative binomial regression model with the natural logarithm of the duration of follow-up in years as an offset variable (Keene, et al 2007; Keene, et al 2008), treatment group, randomization stratum (use or non-use of oral corticosteroids as part of SoC asthma therapy, patient age at Visit 1 [<18 years or ≥18 years], and when analyzing the overall population, peripheral blood eosinophil counts at Visit 1 [<250 cells/µl or ≥250 cells/µl]) and region as a fixed class effects, the natural logarithm of the number of asthma exacerbations (requiring treatment with oral or systemic corticosteroids) in the 12 months prior to screening and the baseline pre-dose FEV1 as a continuous linear covariate. Note that the duration of follow-up will be the planned duration of follow-up for all patients, because any missing data will be imputed as described in Section 9.4.3. The inclusion of the offset is nevertheless useful to make regression coefficients easier to interpret. Should despite the inclusion criteria a patient with no exacerbations requiring treatment with oral or systemic corticosteroids in the 12 months prior to screening be included in the trial, such a patient will be considered to have had 0.5 such exacerbations.

A negative binomial model will be used, because patient heterogeneity beyond that captured by the available patient-level covariates is expected. This can lead to over dispersed cumulative counts and zero inflation. A negative binomial model can better capture such heterogeneity than a Poisson model and can be seen as a Poisson model with the intensity distributed across patients according to a Gamma distribution (Keene, et al 2007).

Summary statistics for the primary variable

The primary variable will be summarized by treatment group in terms of the mean rate (events per patient year of follow-up) overall and for different time intervals, the distribution of patients by number of exacerbations and using plots of Nelson's (1995) nonparametric estimate of the mean cumulative function. The components of the composite primary endpoint will be summarized.

9.4.3 Handling of missing values/censoring/discontinuations

Despite all attempt to ensure complete follow-up for all patients, some patients may not be followed for exacerbations for the whole planned study duration. Missing data will be imputed using a multiple imputation approach similar to the “missing at random and jump to reference” approach described by Keene et al. (2014).

The first step in implementing this approach is fitting a Bayesian negative multinomial model with non-informative priors to the data. This model will distinguish on- and off-treatment data for the QAW039 group and assume that the same event rate as in the placebo group applies after QAW039 discontinuation. The model will include the same covariates as the primary model, as well as a log length of follow-up offset variable. Missing data on exacerbations in both treatment groups will then be imputed by simulation using independent pseudorandom draws from the posterior for the parameters of this model in the conditional distribution of the missing data given the observed data as described by Keene et al. (2014). The imputation will use a mixture of the jump to reference and the missing at random approaches (Keene et al. 2014) and will distinguish the following two cases:

[redacted]

1. No further treatment effect versus placebo will be imputed for QAW039 patients that discontinue treatment and are lost to follow-up due to (or following a treatment discontinuation due to) lack of efficacy, adverse events or death.
2. A continued treatment effect for QAW039 patients being lost to follow-up for reasons likely to be unrelated to study treatment (e.g. lost to follow-up, withdrew consent) will be assumed.

A large number of imputed datasets will be created, with their number chosen based on computational feasibility, but at least 1,000 based on the recommendation of Keene et al. (2014). Each dataset will be analyzed using the model described in Section 9.4.2 and the results will be combined on the log-scale using Rubin's rule (Barnard and Rubin 1999). Regression coefficients and their confidence intervals will then be exponentiated to obtain rates and risk ratios.

9.4.4 Supportive analyses

The primary and the key 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.

If feasible retrieved data after the discontinuation of treatment (retrieved drop-out) will be used to impute missing post-treatment discontinuation data as a sensitivity analysis. While retrieved drop-outs may be a particularly suitable basis for imputing data for non-retrieved drop-outs, this analysis may not be feasible or may require simplification of the imputation model, because observed post-treatment discontinuation data may be sparse.

An on-treatment analysis will also be conducted. In this analysis all moderate-to-severe asthma exacerbations as defined in Section 6.4.1 will be counted, if the start date of the exacerbation is on or after the first day of treatment with double-blind study medication, but before or on the day after the last day of treatment with double-blind study medication. In this analysis a negative binomial regression model with the natural logarithm of the duration of on-treatment follow-up in years as an offset variable will be used. The duration of on-treatment follow-up in years will be calculated for each patient as (treatment end date - treatment start date + 1 day)/365.25 without taking into account treatment interruptions. Such a negative binomial model assumes that missing data after censoring either due to losses to follow-up or the end of treatment are missing at random conditional on the baseline covariates and the preceding data on events per follow-up time included in the analysis (Cook and Lawless 2007). Under this assumption the model implicitly imputes the missing data and the data censored at the end of treatment assuming a hypothetical situation of continued treatment with an unchanged on-treatment event rate for the patient (Committee for Medicinal Products for Human Use 2010). This analysis and missing data handling approach is in-line with the recently completed MENSA exacerbation trial for the monoclonal anti-interleukin-5 antibody mepolizumab in a similar population (Ortega, et al 2014). It is therefore the most appropriate analysis for a comparison of the results of the present trial to the MENSA trial.

In a tipping point analysis it will be explored by how much the event rate post-discontinuation would have had to increase (or continuous outcomes to worsen) in the primary and key secondary analyses in order to change the trial conclusions.

[redacted]

As a worst reasonable case analysis a disappearing treatment effect for all patients that are lost-to-follow-up will be used (jump-to-reference). This is a sensitivity analysis for the effect of assuming a continued treatment effect for patients withdrawing from the study for reasons considered to be likely unrelated to study therapy (see Section 9.4.3)

In a further rank-based sensitivity analysis for the primary endpoint withdrawal from the trial and death will be directly treated as negative trial outcomes for patients. Patients that completed the trial will be ranked as having had a more favorable outcome than patients that withdrew from the trial, who will in turn be ranked as having had a more favorable outcome than patients that died. Within each of these categories patients will be ranked according to (number of exacerbations + 0.5)/patient years of follow-up. Compared to solely ranking patients according to the number of exacerbations or solely according to the duration of follow-up, this ensures that patients lost to follow-up very early in the trial without experiencing any exacerbations will not be ranked more favorably than patients that nearly completed the trial and only had 1, or 2 exacerbations, while also ensuring that a patient with 10 exacerbations that was lost to follow-up after 11 months and 1 day is not ranked as having a more favorable outcome than a patient with 0 exacerbations that was lost to follow-up after 11 months. A Wilcoxon rank-sum test stratified by randomization stratum will be used to analyze the ranked data.

Supportive analyses will also explore whether allowing the possibility of declining or increasing exacerbation rates over time affects study conclusions.

Time to first asthma exacerbation and mean duration of asthma exacerbations will also be analyzed.

The absolute difference in the rates of moderate to severe asthma exacerbation rates per patient year and resulting number of patients that needs to be treated for 1 year to prevent one exacerbation will also be reported with confidence intervals.

For comparison to historical study results, data for the key secondary endpoints using last-observation-carried-forward will also be provided.

Subgroups

The primary and key 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, OCS use/GINA step, baseline FEV1 tertiles, ACQ tertiles, as well as blood eosinophil counts).

Relationship of efficacy and baseline eosinophil levels

In addition to subgroup analyses with different baseline eosinophil levels, the functional relationship between the treatment effect and baseline blood eosinophil levels as a continuous covariate will be investigated for the primary and key secondary variables.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The key secondary variables of this trial are the mean of the two pre-dose FEV1 assessments at the week 52 visit, AQLQ+12 and ACQ-5 at the end of the 52 week treatment period. Data

[redacted]

from the preceding visits will be used primarily to describe the onset of action and for missing data imputation.

The key secondary variables of AQLQ+12, ACQ-5 and pre-dose FEV1 will be analyzed using an analysis of covariance (ANCOVA) model with factors for treatment group, randomization stratum and region, as well as the baseline AQLQ+12, baseline ACQ-5 and baseline pre-bronchodilator FEV1 as continuous linear covariates.

The null hypothesis will be tested for each dose group, each population (subgroup with peripheral blood eosinophil counts at Visit 1 ≥250 cells/µl or overall population) and each key secondary variable using this model versus the two-sided alternative hypotheses

For each key secondary endpoint, each QAW039 dose and each population the null hypothesis is that the treatment difference compared to placebo at the week 52 visit = 0, while the alternative hypothesis is that the treatment difference to placebo at the week 52 visit ≠ 0.

This model will be fitted to each of multiple imputations generated using the jump-to-reference approach described by Carpenter et al. (2013). In a similar manner to the primary analysis a continued treatment effect will be imputed for QAW039 patients with intermittent missing data and those QAW039 patients discontinuing double-blind study medication due to reasons likely to be unrelated to study medication (see Section 9.4.3). For all other QAW039 patients with missing data and placebo patients with missing data imputation will be based on the placebo group. 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.

The test for the key secondary variables AQLQ+12, ACQ-5 and pre-dose FEV1 in patients with eosinophil count ≥ 250 cells/µl and for the overall population for each dose will be performed, if the primary null hypothesis has been rejected for the same dose for patients with eosinophil count ≥ 250 cells/µl and for the overall population, respectively. The local significance level for each secondary null hypothesis will be determined based on the closed testing procedure specified by Figure 9-1.

Sensitivity analyses for the key secondary endpoints

A range of sensitivity analyses for the key secondary endpoints similar to those described in Section 9.4.3 and Section 9.4.4 will be conducted. Further supportive analyses will look at the treatment effect separately for each visit.

Additionally, a mixed model for repeated measures (MMRM) with an unstructured covariance structure will be fitted for secondary variables to evaluate the average treatment effect during weeks 12 to 52 of the trial. These MMRMs will include treatment group, visit, randomization stratum and region as fixed class effects, and the baseline AQLQ+12, baseline ACQ-5 and baseline pre-bronchodilator FEV1 as continuous linear covariates. Treatment group by week 4 visit and baseline value by visit interactions will also be included in the model. This average effect will be both investigated using the main data imputation approach, as well as in an on-treatment analysis. Note that the supportive on-treatment analysis for the on-treatment values (from start of double-blind study medication to the day after the last day of treatment) will use a MMRM with an unstructured covariance structure. This model implicitly imputes unrecorded values and the data censored at the end of treatment assuming a hypothetical situation of continued treatment with an unchanged on-treatment effect that is constant across

the week 12 to 52 visits for patients in a similar manner as the on-treatment analysis using a negative binomial model described in Section 9.4.4.

An analysis of percent change from baseline in pre-dose FEV1 will also be performed. For this analysis pre-dose FEV1 and its baseline will be log-transformed for analysis and results will be back-transformed to obtain geometric means and ratios of geometric means to allow an interpretation as percent change from baseline.

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

The 32 items in the AQLQ+12 are divided into 4 domain-specific scores and a total score as follows:

- Symptoms = Mean of Items 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30 (12 items)
- Activity limitation = Mean of Items 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32 (11 items)
- Emotional function = Mean of Items 7, 13, 15, 21, 27 (5 items)
- Environmental Stimuli = Mean of Items 9, 17, 23, 26 (4 items)
- Overall Score = Mean of Items 1 to 32 (32 items)

Each item of the AQLQ+12 is equally weighted and scored along a 7-point scale, where 1 indicates maximal impairment and 7 indicates no impairment. Thus, higher scores indicate better asthma-related HRQOL. There is a mean score calculated for each of the four domains, as well as an overall quality-of-life score, which is the mean score of all 32 items. The resultant overall scores will be between 1 and 7.

The developer suggests no more than 10% of missing data. This means no more than 3 missing responses for the overall score and no more than 1 missing response per domain. For the symptoms and activity domain scores, one missing value per domain is allowed. For the emotional function and environmental stimuli domain scores, no missing values are allowed. If these limits for missing questions are exceeded, the variable will be considered missing and will be imputed as described in Section 9.5.1.

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

9.5.1.2 Pre-dose FEV1

The baseline measurement is defined as the mean of the pre-bronchodilator FEV1 values taken at the last visit in the clinic prior to first dose of study drug.

If the pre-dose FEV1 is taken within 6 hours of SABA use, or within 12 hours of twice-daily LABA (including fixed dose combinations of LABA and ICS) use, or 24 hours of once-daily LABA (including fixed dose combinations of LABA and ICS) use, or 24 hours of once-daily LAMA use, then the individual FEV1 value is set to missing.

9.5.1.3 Asthma Control Questionnaire (ACQ-5)

The ACQ measures asthma symptom control and consists of 7 items. It includes the 5 most important symptoms, 1 about rescue bronchodilator use and 1 about airway calibre (FEV1 %

[redacted]

predicted pre-bronchodilator). Patients will be asked to recall their experiences during the past one week and to response items 1-6 (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheeze, and rescue short-acting β2-agonist use) on a 7-point scale (0 – totally controlled, 6 – extremely poorly controlled). The ACQ-5 score calculated based on the 5 questions of the 5 most important symptoms. The5 questions of the ACQ-5 are equally weighted. The ACQ-5 score is the mean of the responses to the 5 questions. The resultant score will be between 0 and 6.

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

9.5.2 Safety variables

All safety data will be summarized for the safety set.

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 databased safety data will be listed.

Unless otherwise specified, all safety summaries will be provided for patients with eosinophil count ≥ 250 cells/µl, for patients with eosinophil count < 250 cells/µl and for the overall study population.

Adverse events

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

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

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

discontinuation events will be produced for adverse events and serious adverse events by system organ class and preferred term.

The number and percentage of patients with treatment emergent adverse events of special interest (e.g. IDRs), as well as cardiac events 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 regression 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 trial.

Vital signs

On-treatment data from the vital signs (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) can 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.

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, schedule 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: ventricular rate, 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.

9.6 Interim analyses

As described in Section 3.5, a single futility interim analysis will be conducted in addition to periodic unblinded safety reviews by the DMC (see Section 8.3) using data (including specific safety summaries for adolescent participants) from this trial and other Phase III trials in the QAW039 asthma development program. No stopping for demonstrated efficacy prior to the completion of the study is foreseen at either the unblinded safety reviews or the futility interim analysis, because a sufficiently large safety dataset is needed in addition to efficacy data and thus, no statistical adjustment will be made to the final analysis.

9.7 Sample size calculation

To be conservative a mean placebo event rate of 1.5 events per patient year of follow-up has been assumed for this study; this is a slightly lower rate than the 1.75 events per patient-year observed in the placebo group of the MENSA trial (Ortega, et al 2014) and the same event rate as assumed for the DREAM trial, although the actual DREAM placebo event rate was 2.4 events per patient year of follow-up (Pavord, et al 2012). A 40% reduction in the rate of asthma exacerbations per year in the QAW039 treatment compared to placebo has been assumed for the subgroup with high eosinophils $\geq$ 250 cells/µl for this study; this is considered to be highly clinically relevant and at the same time realistic based on the DREAM and MENSA trials conducted in similar patient populations. In the DREAM trial 75 mg mepolizumab reduced the number of asthma exacerbations per patient per year by 48%,

250mg mepolizumab by 39% and 750mg mepolizumab by 52% compared with placebo. In the MENSA trial intravenous mepolizumab reduced the number of asthma exacerbations per patient per year by 47% and subcutaneous mepolizumab by 53% compared with placebo. These relative risk reductions were taken into account, because the observed reduction in sputum eosinophils with QAW039 in Study CQAW039A2208 were similar to those observed with mepolizumab (Haldar, et al 2009; Pavord, et al 2012). On this basis it is postulated QAW039 may reduce the rate of asthma exacerbations to a similar extent as mepolizumab. For the subgroup with eosinophils < 250 cells/µl a lesser relative risk reduction of 30% was assumed. However, it should be noted that the trial may produce a significant result with a smaller reduction in exacerbations than that assumed for power calculations and that such a reduction could still be considered clinically relevant.

As reported in online supplementary material for the MENSA publication the negative binomial dispersion parameter for the exacerbation rates was estimated to be 0.8 in the DREAM trial. In the DREAM trial approximately 15% of patients in the mepolizumab arms and 20% of patients in the placebo arm were lost to follow-up by the end of the 1-year trial, while in the 32 week MENSA trial only 6 to 8% of patients were lost across groups. Therefore, a constant exponential hazard rate over time for treatment discontinuation is assumed with 15% of patients off treatment by 1 year in the active treatment groups and the placebo group. No further treatment effect versus placebo has been assumed during the off-treatment, i.e. a mean event rate of 1.5 events per patient year has been assumed for patients after treatment discontinuation in both the QAW039 and placebo groups.

A 1:1:1 randomization was used, even though the power to demonstrate the superiority of at least one arm versus placebo would likely have been higher with an increased assignment to the placebo group, in order to not reduce the amount of efficacy and safety information for each QAW039 dose group.

Negative binomial counts were simulated based on the assumptions above and the testing procedure in Figure 9-1 was applied to each simulation result. For the purpose of evaluating the power for the primary trial objectives, it was assumed that none of the key secondary null hypotheses would be rejected.

For this study a two-sided significance level of 5% is used for testing. As shown in Table 9-1 188 patients per arm in the subpopulation with blood eosinophils ≥ 250 cells/µl and 282 patients per arm in the overall population corresponding to a total sample size of 846 patients provide greater than 80% power for demonstrating the superiority of each dose of QAW039 compared to placebo in the subpopulation with blood eosinophils ≥ 250 cells/µl and overall population under the described assumptions.

[redacted]

Table 9-1 Power for the primary variable

True relative risk reduction Upper row: Subpopulation Lower row: Other population		Power (%) Upper row: Subpopulation Lower row: Overall population			
450 mg (%)	150 mg (%)	450 mg	150 mg	At least one dose significant	All doses Significant
40	**40**	**89%**	**89%**	**96%**	**82%**
30	**30**	**84%**	**84%**	**93%**	**75%**
40	40	89%	89%	96%	82%
20	20	76%	76%	88%	64%
40	40	89%	89%	96%	82%
0	0	49%	49%	66%	32%

Subpopulation means the subpopulation with blood eosinophils ≥ 250 cells/µl, while other population refers to the subpopulation with blood eosinophils < 250 cells/µl. Power results are based on 100,000 simulated trials per scenario. Only results for primary endpoints were simulated. For the purpose of evaluating the power for the primary trial objectives, it was assumed that none of the key secondary null hypotheses would be rejected. All simulations were performed in SAS 9.4.

If statistical significance is achieved in the primary test, the test for the key secondary variables pre-dose FEV1, AQLQ+12 and ACQ-5 will be performed. The local significance level for each secondary null hypothesis will be determined based on the closed testing procedure shown in Figure 9-1. For the power for each key secondary variable in the subpopulation with blood eosinophils ≥250 cells/µl and overall population, it was conservatively assumed that only the null hypothesis for the primary endpoint for the respective dose in the subpopulation and overall population would be rejected. For AQLQ+12 and ACQ5 the power was additionally calculated conditional on both the null hypothesis for the primary endpoint and pre-dose FEV1 for the respective dose in the subpopulation and overall population having been rejected. The power for each key secondary endpoint is shown in Table 9-2. However, note that the power for the key secondary endpoints will be higher once the null hypotheses relating to other key secondary variables or other doses have been rejected. For the power calculation of secondary endpoints no further treatment effect versus placebo has been assumed for patients with treatment discontinuation.

It was assumed that QAW039 achieves a difference of 150 mL against placebo in FEV1 after 52 weeks for patients that remain on treatment. A SD of 380 mL was assumed for the analysis in FEV1. Given a 15% treatment discontinuation rate by week 52, the planned sample size will give 80% power for each dose in the subpopulation at the resulting local two-sided significance level of 1.625% and 90% power for each dose in the overall population at the resulting local two-sided significance level of 0.698%.

Assuming a clinically important true improvement of at least 0.5 in AQLQ+12 after 52 weeks treatment for patients that remain on treatment, a standard deviation (SD) of 1 and 15% treatment discontinuation rate by week 52, the planned sample size per arm will provide 76% power for each dose in the subpopulation with blood eosinophils ≥ 250 cells/µl at the resulting local two sided significance level of 0.075% and 93% power for each dose in the overall

[redacted]

population at the resulting local two-sided significance level of 0.038% after the respective primary null hypothesis has been rejected.

Assuming a difference of 0.5 against placebo in ACQ-5 after 52 weeks for patients without treatment discontinuation, a SD of 1.1, and a 15% treatment discontinuation rate by week 52, the planned sample size will give 59% power for each dose in the subpopulation at the resulting local two-sided significance level of 0.05% and 78% power for each dose in the overall population at the resulting two-sided local significance level of 0.015% after the respective primary null hypothesis has been rejected.

Table 9-2 Power of each dose for the analyses of key secondary variables

		Pre-dose FEV1	AQLQ+12	ACQ-5
Difference of effect (δ) for patients without treatment discontinuation		150 mL	0.5	0.5
SD (σ)		380 mL	1	1.1
Treatment discontinuation rate		15%	15%	15%
Subpopulation	Local two-sided significance level	1.625%	0.075%* 1.294%†	0.05%* 0.456%†
	Power	80%	76%* 95%†	59%* 81%†
Overall population	Local two-sided significance level	0.698%	0.038%* 0.561%†	0.015%* 0.189%†
	Power	90%	93%* 99%†	78%* 93%†

Subpopulation means the subpopulation with blood eosinophils ≥ 250 cells/µl.

* For local two-sided significance level and power in AQLQ+12 and ACQ5 the upper row shows the value when only the null hypothesis for the primary endpoint for the respective dose in the subpopulation and overall population have been rejected.

† The lower row shows the value when both the null hypothesis for the primary endpoint and pre-dose FEV1 for the respective dose in the subpopulation and overall population have been rejected.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented 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 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 should be

informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should 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 (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

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 should 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 should not be entered in the study.

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or Ethics Committee approval will be obtained.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution should 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

Novartis assures that 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

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.

[redacted]

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 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 should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

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. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol Amendments

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

12 References

References are available upon request.

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.

Barnard J, Rubin D (1999) Small-sample degrees of freedom with multiple imputation. Biometrika; 86:948–955.

Bretz F, Maurer W, Brannath W et al. (2009) A graphical approach to sequentially rejective multiple test procedures. Statistics in Medicine; 28(4): 586-604.

Carpenter JR, Roger JH and Kenward MG (2013) Analysis of Longitudinal Trials with Protocol Deviation: A Framework for Relevant, Accessible Assumptions, and Inference via Multiple Imputation. Journal of Biopharmaceutical Statistics, 23:6, 1352-1371

[redacted]

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 blood eosinophil counts from two, multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med; Published Online: 23 February 2015.

Center for Disease Control and Prevention (Cdc.gov) (2000). Growth Charts - Homepage. Available from: http://www.cdc.gov/growthcharts/.

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.

Cook, Richard J., and Jerald F. Lawless. The statistical analysis of recurrent events. Springer, 2007.

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.

Hurst H, Bolton J. (2004) Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther; 27:26-35.

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

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]

Keene, O. N., Jones, M. R., Lane, P. W., & Anderson, J. (2007) Analysis of exacerbation rates in asthma and chronic obstructive pulmonary disease: example from the TRISTAN study. Pharmaceutical statistics; 6(2): 89-97.

Keene ON, Calverley PM, Jones PW, Vestbo J, Anderson JA (2008) Statistical analysis of exacerbation rates in COPD: TRISTAN and ISOLDE revisited. Eur Respir J; 32: 17–24.

Keene ON, Roger JH, Hartley BF and Kenward MG (2014) Missing data sensitivity analysis for recurrent event data using controlled imputation. Pharmaceut. Statist.; 13: 258–264

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.

Nelson, W (1995) Confidence Limits for Recurrence Data—Applied to Cost or Number of Product Repairs. Technometrics; 37: 147–157.

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.

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

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.

Woodruff PG, Modrek B, Choy DF et al. (2009) T-helper type 2-driven inflammation defines major subphenotypes of asthma. Am J Respir Crit Care Med; 180(5):388-95.

[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.

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 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)
ALT or AST		
> 8 × ULN	• 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)
> 3 × ULN and INR > 1.5	• 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)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator

[redacted]

Criteria	Actions required	Follow-up monitoring
	• If elevation persists for *more than 2 weeks*, discontinue the study drug • Establish causality • Complete liver CRF	discretion)
> 3 × ULN accompanied by symptoms[b]	• 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)
> 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 drug 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 drug 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]

Refer to Section 5.5.10 for additional guidance on study treatment discontinuation due to liver laboratory abnormality / liver event, and to Section 7.3 for guidance on liver safety monitoring.

[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: Blood collection logs

Table 16-1 Time schedule for blood sampling for safety, Total IgE and RAST/ImmunoCAP test

Analyte	Blood sample volume	Visits with blood sample collection									
		Visit 1	Visit 201	Visit 202	Visit 203	Visit 204	Visit 205	Visit 206	Visit 207	Visit 299	Visit UNSCHEDULED-TD*
Clinical chemistry and troponin, CK-MB (for reflex testing if needed) Note: At V1, includes serum pregnancy test	5.0 mL	x	x	x	x	x	x	x	x	x	x*
Haematology	2.0 mL		x	x	x	x	x	x	x	x	x*
Haematology, HbA1c	3.0 mL	x									
Total IgE	1.25 mL		x							x	x*
Specific IgE (RAST/ImmunoCAP test)	2.5 ml	x									
Total blood volume per patient (mL) each visit		10.50	8.25	7.00	7.00	7.00	7.00	7.00	7.00	8.25	8.25
Estimated total blood volume per patient (mL)		69.0									77.25*

*For patients who discontinue study drug early and remain in the study (see Section 5.5.10), extra blood samples must be taken at the UNSCHEDULED-TD visit.

[redacted]

17 Appendix 5: Spirometry Guidance

Equipment

Spirometers must meet the specifications and performance criteria recommended in the American Thoracic Society (ATS)/European Respiratory Society (ERS) Standardization of Spirometry[1]. Spirometers must have the capacity to print [redacted] 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.

[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 [redacted] FEV_1 values from 3 acceptable maneuvers should not vary by more than 0.150 L.
If patient does not meet the repeatability or acceptability criteria during the screening epoch, patient may be rescreened once or allow one spirometry retest.

Recording of data

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

Predicted normal

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

Reversibility

All reversibility evaluations should follow the recommendations of the ATS/ERS Task force: Standardization of Lung Function Testing[1]. A pre-bronchodilator spirometry* assessment should be performed after withholding of specified medications as specified in Table 5-2 "Medications to be withheld prior to spirometry".

Administer 400µg of salbutamol/albuterol (or equivalent) following the completion of the pre-bronchodilator assessment*. [redacted]

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

*NOTE: At visits with two pre-dose spirometry assessments (please see Table 6-1 for schedule of assessments) the FEV_1 from the 2nd pre-dose spirometry assessment (performed

[redacted]

approximately 15 min prior to in-clinic witnessed study drug administration) should be used for FEV1 (pre-bronchodilator).

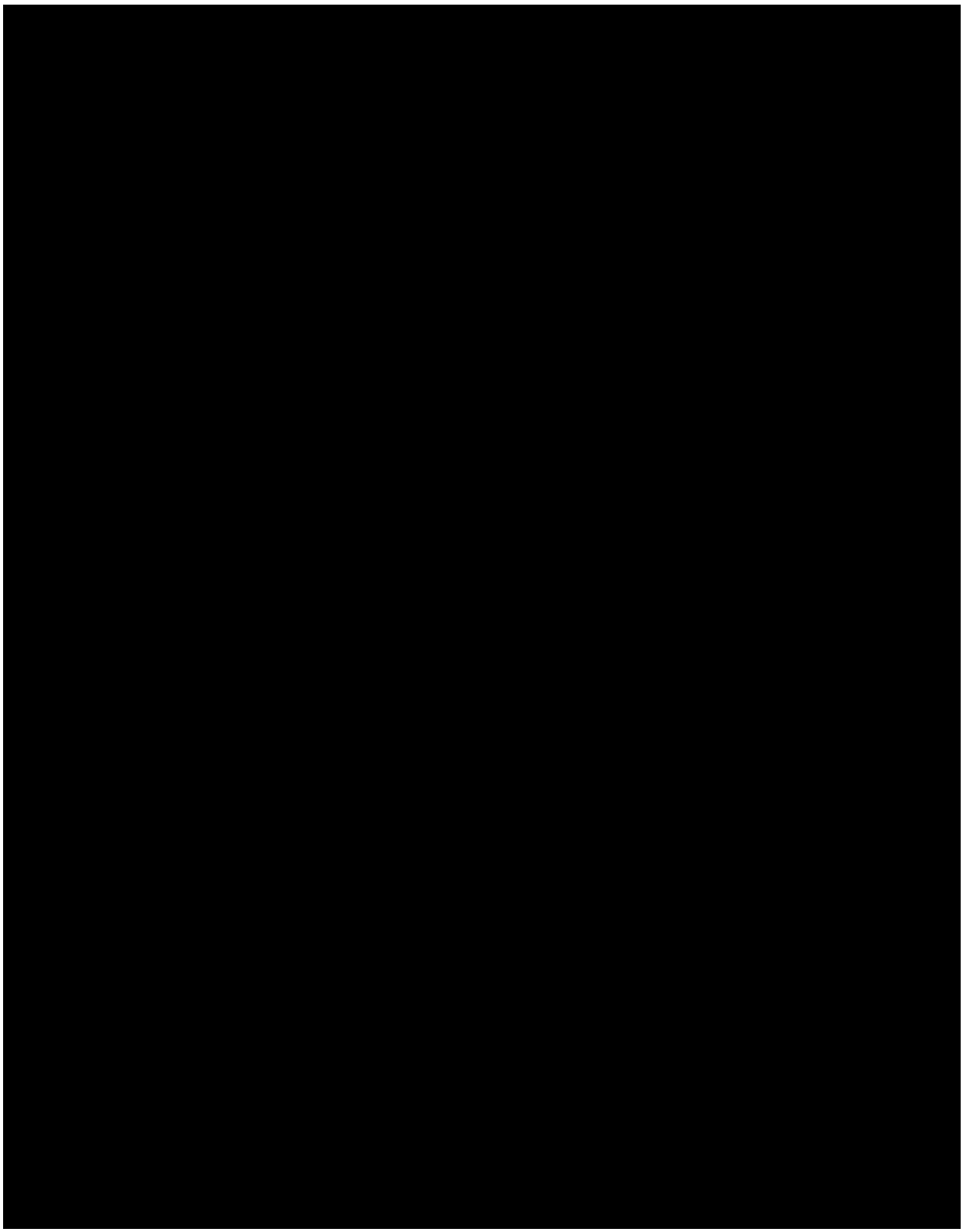
17.1 References for appendix

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

[2]Quanjer PH, Stanojevic S, Cole TJ, Baur X, L Hall GL, Culver B, Enright PL, Hankinson JL, Zheng J, Stocks J and the ERS Global Lung Function Initiative (2012) Multi ethnic reference values for spirometry for the 3-95 year age range: the global lung function 2012 equations. Report of the Global Lung Function Initiative (GLI), ERS Task Force to establish improved Lung Function Reference Values. Eur Resp J; 40:1324-1343.

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

[redacted]



19 Appendix 7: Estimated Equivalence of Inhaled Corticosteroids

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

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

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

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For the purposes of calculating total daily dose for the study, if the table has the medication dose listed by DPI, but not by MDI, then use the DPI classification as the reference and vice versa (i.e., if the table has the medication dose listed by MDI, but not by DPI, then use the MDI classification).

[redacted]

20 Appendix 8: 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:

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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]

21 Appendix 9: Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12)

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

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

SELF-ADMINISTERED
(≥12 years)

For further information:

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APRIL 2008

[redacted]

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

SELF-ADMINISTERED DATE: _____

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

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

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

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

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

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

[redacted]

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

SELF-ADMINISTERED DATE: _____

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

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

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

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

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

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

[redacted]

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

SELF-ADMINISTERED DATE: _____

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

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

[redacted]

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

SELF-ADMINISTERED DATE: _____

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

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

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

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

[redacted]

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID _____

SELF-ADMINISTERED DATE_____

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

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

DOMAIN CODE:

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

[redacted]