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

[redacted]

Objective(s)	Endpoint(s)
[redacted]	

3 Investigational plan

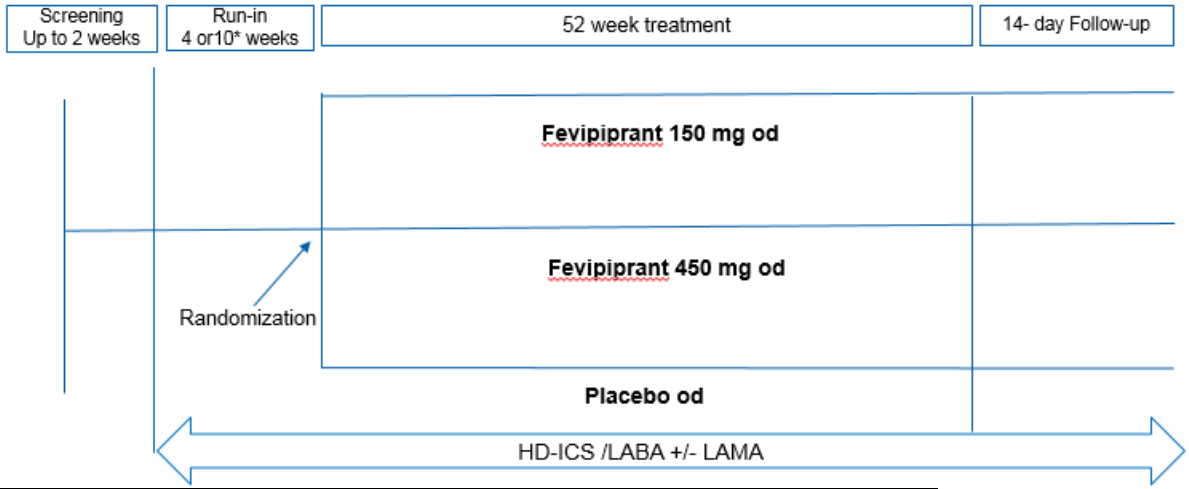
3.1 Study design

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

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

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

Figure 3-1 Study design



[redacted]

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

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

3.2 Rationale for study design

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

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

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

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

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

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

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

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

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

[redacted]

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

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

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

3.4 Rationale for choice of comparator

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

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

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

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

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

[redacted]

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

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

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

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

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

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

4 Population

4.1 Inclusion criteria

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

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

[redacted]

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

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

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

[redacted]

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

[redacted]

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

6.4.2.1 Asthma Quality of Life Questionnaire (AQLQ+12)

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

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

6.4.2.2 Asthma Control Questionnaire (ACQ-5)

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

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

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

6.4.3 eDiary

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

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

[redacted]

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

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

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

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

6.5.1 Medical history and physical examination

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

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

6.5.2 Asthma Exacerbations

The following definitions of exacerbations are used in this study.

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

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

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

[redacted]

6.5.5.1 Hematology

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

6.5.5.2 Clinical chemistry

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

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

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

6.5.5.3 Urinalysis

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

6.5.6 Electrocardiogram (ECG)

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

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

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

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

[redacted]

[redacted]

6.6.3 Pharmacokinetics

Not applicable.

6.6.4 Spirometry

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

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

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

6.6.5 Other biomarkers

Not applicable.

7 Safety monitoring

7.1 Adverse events

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

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

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

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by

[redacted]

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

Adverse events must be recorded under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 7.2.1)

1. The severity grade
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 7.2.1 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment
6. All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose Reduced/increased
   - Drug interrupted/withdrawn
7. its outcome i.e., its recovery status or whether it was fatal

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

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

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

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

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

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

[redacted]

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

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

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

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

7.3 Liver safety monitoring

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

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

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

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

[redacted]

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

9.4.3 Handling of missing values/censoring/discontinuations

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

9.4.4 Sensitivity analyses

The details on sensitivity analysis will be provided in SAP.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

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

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

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

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

Asthma Quality of Life Questionnaire (AQLQ+12)

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

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

[redacted]

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

[redacted]

ASTHMA CONTROL QUESTIONNAIRE© Page 1 of 1

Please answer questions 1 - 5

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

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

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

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

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

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

SYMPTOMS ONLY MODIFIED 30 JAN 04 NORTH AMERICAN ENGLISH

[redacted]

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

SELF-ADMINISTERED DATE: _____

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

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

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

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

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

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

[redacted]

Glossary of terms

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

[redacted]

3.5 Purpose and timing of interim analyses/design adaptations

Flexible scenario

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

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

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

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

3.6 Risks and benefits

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

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

[redacted]

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

4.2 Exclusion criteria

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

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

[redacted]

Table 6-1 Assessment Schedule

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

[redacted]

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

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

[redacted]

6.4.3.1 Daily Symptom Scores

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

Symptom diary scale questions

Table 6-2 Daytime symptom diary scale questions

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

Table 6-3 Nocturnal diary scale question

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

6.4.3.2 Number of inhalations of Rescue Medication

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

6.4.3.3 Peak expiratory flow (PEF)

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

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

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

[redacted]

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

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

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

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

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

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

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

6.5.3 Vital signs

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

6.5.4 Height and weight

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

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

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

6.5.5 Laboratory evaluations

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

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

[redacted]

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

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

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

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

6.5.7 Pregnancy

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

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

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

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

6.5.8 Appropriateness of safety assessments

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

6.6 Other assessments

Not applicable

6.6.1 Clinical Outcome Assessments (COAs)

Please refer to Section 6.4.2

[redacted]

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subjects with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 13.

7.2 Serious adverse events

7.2.1 Definition of SAE

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

- fatal
- life-threatening

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

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

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

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

[redacted]

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

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
- These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF

7.4 Renal safety monitoring

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

Serum event:

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

Urine event:

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

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

7.5 Reporting of study treatment errors including misuse/abuse

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

[redacted]

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

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

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

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

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

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

Asthma Control Questionnaire (ACQ-5)

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

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

[redacted]

Criteria	Actions required	Follow-up monitoring
	• If elevation is confirmed, initiate close observation of the patient	Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Investigator discretion

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

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

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

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

[redacted]

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

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

SELF-ADMINISTERED

(≥12 years)

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APRIL 2008

[redacted]

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

SELF-ADMINISTERED DATE: _____

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

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

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

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

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

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

[redacted]