NOVARTIS

Global Clinical Development - General Medicine

QGE031/Ligelizumab

Clinical Trial Protocol CQGE031C2201E1 / NCT02649218

An open label, multicenter, extension study to evaluate the long-term safety of QGE031 240 mg s.c. given every 4 weeks for 52 weeks in Chronic Spontaneous Urticaria patients who completed study CQGE031C2201

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List of abbreviations

[redacted] [redacted]

AC Adjudication committee

ACR Albumin to Creatinine Ratio

[redacted] [redacted]

AE Adverse event

ALT Alanine aminotransferase

AST Aspartate aminotransferase

CFR US Code of Federal Regulations

CIU Chronic Idiopathic Urticaria

CPO Country Pharma Organization

CRF Case Report/Record Form (paper or electronic)

CRO Contract Research Organization

CSU Chronic Spontaneous Urticaria

CTC Common Toxicity Criteria

DBP Diastolic blood pressure

[redacted] [redacted]

DMC Data monitoring committee

DS&E Drug Safety & Epidemiology

ECG Electrocardiogram

EDC Electronic Data Capture

EMA European Medicines Agency

ePRO Electronic Patient Reported Outcome

FcεRII High affinity Immunoglobulin E Receptor II

FcεRI High affinity Immunoglobulin E Receptor I

FDA Food and Drug Administration

GCP Good Clinical Practice

GTL Global trial lead

GWAS Genome-wide association studies

H1-AH H1-antihistamines

H2-AH H2-antihistamines

[redacted]

hCG	Human Chorionic Gonadotropin
hsCRP	High sensitivity C-reactive protein
HSS	Hive Severity Score
IB	Investigator Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IgG	Immunoglobulin G
INR	International Normalized Ratio
IQS	Integrated Quantitative Sciences
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISS	Itch Severity Score
IU	Inducible urticarial
IUD	Intrauterine device
IUS	Intrauterine system
LDH	Lactate dehydrogenase
LFT	Liver function test (raised serum transaminases and/or bilirubin levels)
LTRA	Leukotriene Receptor Antagonist
MedDRA	Medical dictionary for regulatory activities
OC/RDC	Oracle Clinical/Remote Data Capture
PCR	Protein to Creatinine Ratio
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PSW	Premature study withdrawal
q2/4w	Every 2/4 weeks
SAE	Serious adverse event
s.c.	Subcutaneous
SBP	Systolic blood pressure
SUSAR	Suspected Unexpected Serious Adverse Reactions

[redacted]

UAS	Urticaria Activity Score
ULN	Upper Limit of Normal
UPDD	Urticaria Patient Daily Diary
WHO	World Health Organization

[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.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Period	A subdivision of a cross-over study
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
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

[redacted]

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

[redacted]

Protocol summary

Protocol number	**CQGE031C2201E1**
Title	An open label, multicenter, extension study to evaluate the long-term safety of QGE031 240 mg s.c. given every 4 weeks for 52 weeks in patients with Chronic Spontaneous Urticaria who completed study CQGE031C2201
Brief title	A long-term safety study for QGE031 as an add-on therapy for adults with CSU who have completed study CQGE031C2201
Sponsor and Clinical Phase	Novartis Phase 2b, long-term safety study
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate the safety of QGE031 given to CSU patients over a long term treatment period
Primary Objective	The primary objective of this study is to assess the long-term safety of QGE031 (240 mg s.c.) given every 4 weeks for 12 months in patients who completed study CQGE301C2201 by evaluation of: • Incidence and severity of all adverse events • Changes in vital signs, laboratory assessments, and ECGs
Secondary Objectives	To evaluate long-term treatment outcomes of QGE031 in adult patients with CSU by evaluation of: • Sustained remission defined as maintaining UAS7 ≤ 6 over 48 weeks post-treatment follow up epoch among the subjects achieving remission at the end of treatment epoch
Study design	This study is an open label, single arm, long-term safety extension to study CQGE031C2201: a 52 week treatment followed by a 48 week follow up
Population	Adults CSU patients who completed the core study. Approximately 240 patients may enroll into this extension study
Key Inclusion criteria	• Patients who complete study treatment epoch and at least visit 203 in the follow-up epoch in study QGE031C2201 • Present with active disease
Key Exclusion criteria	• New onset of chronic urticaria other than CSU
Investigational and reference therapy	QGE031 240 mg s.c. q4w
Efficacy assessments	• Urticaria Activity Score (UAS7) • Hives Severity Score (HSS7) • Itch Severity Score (ISS7)
Safety assessments	• Incidence and severity of adverse events including serious adverse

	events, adverse events leading to study treatment discontinuation and any events of special interest • Changes in vital signs, laboratory assessments, and ECGs
[redacted]	
Data analysis	Summary statistics will be provided for adverse events, laboratory parameters and efficacy parameters over time. Time to event variables will be summarized by Kaplan-Meier estimates.
Key words	[redacted], chronic spontaneous urticaria, long-term safety

[redacted]

1 Introduction

1.1 Background

Urticaria is a heterogeneous group of diseases characterized by itchy hives and/or angioedema. Chronic urticaria is defined as urticaria that has been continuously or intermittently present for more than 6 weeks (Maurer, et al 2013, Bernstein, et al 2014). Chronic urticaria is then further divided into two subgroups: Chronic Spontaneous Urticaria (CSU) and Inducible Urticaria (IU) the latter including physical urticaria such as heat-, cold-, or pressure-urticaria, and special variants such as cholinergic urticaria. CSU is defined as spontaneous appearance of itchy wheals, angioedema, or both ≥ 6 weeks due to known or unknown causes (Zuberbier, et al 2014). A combination of both the CSU and an inducible form of urticaria is possible, such as the frequently observed combination of asymptomatic dermographic urticaria and CSU.

Previously, all chronic urticaria forms without a known trigger were named "chronic idiopathic urticaria" (CIU). Due to medical progress it is now known that in some of the previously considered "idiopathic" urticaria forms in fact auto-antibodies may be detected. However, the daily fluctuating appearance of the symptoms in this chronic urticaria with auto-antibodies still remains unpredictable and is not induced by a demonstrable trigger, hence appear spontaneously. In order to reflect in the terminology correctly that some of the former "idiopathic" forms in fact may have detectable auto-antibodies, this population is now referred to as chronic spontaneous urticaria (CSU) according to the international guideline (Maurer, et al 2013, Zuberbier, et al 2014). The use of the expression "chronic idiopathic urticaria" in medical practice is no longer recommended. However, this new naming convention is not implemented in all parts of the world and in countries such as the United States and Canada the patient population with chronic urticaria with a non-specific etiology, or unknown triggers is still referred to as chronic idiopathic urticaria (CIU). Following the International Guideline, the disease entity will be referred to as CSU throughout this document for consistency.

The lifetime prevalence of CSU is approximately 1.8%, and 20% of CSU patients still have the disease after 20 years (Greaves 2000, Zuberbier, et al 2010). Affected patients experience frequent pruritic hives with associated erythema and/or episodes of angioedema. Angioedema is reported to be associated with approximately 33-67% of CSU cases (Juhlin 1981, Toubi, et al 2004, Zuberbier, et al 2010, Maurer, et al 2011). The classic skin lesion in urticaria is a wheal and flare with a pale elevated lesion and surrounding erythema, ranging in size from a few millimeters to a few centimeters across, usually occurring in groups and often coalescing to form large confluent lesions. [redacted]

[redacted]

[redacted]

Treatment of CSU is a challenge and non-sedating (second generation) H1-antihistamines (H1-AH) are the mainstay of symptomatic therapy of CSU. While H1-AH at approved doses provide relief for some patients, more than 50% of patients do not respond to H1-AH at regular doses. Even when up-dosing up to fourfold of the approved dose according to the second step of the treatment algorithm of the current International Guideline (Zuberbier, et al 2014), a substantial part of patients do not experience control of urticaria symptoms (Maurer, et al 2011, Marrouche, et al 2014). For patients without disease control at fourfold doses of H1-AH, the third step of the treatment algorithm of the International Guideline foresees the addition of omalizumab, or ciclosporin A, or montelukast to the H1-AH.

The level of evidence for the efficacy of leukotriene receptor antagonists (LTRA) in urticaria is low but best for montelukast which consequently led to only a weak recommendation from experts for this off-label treatment. Short courses (max. 10 days) of systemic corticosteroids can be added to the 3rd level treatment regimens, if exacerbations demand this. Due to the adverse effects associated with chronic systemic corticosteroid exposure, a longer duration of treatment is not advisable. Other treatment options that were previously used such as intravenous immunoglobulin G, dapsone, hydroxychloroquine, H2-antihistamines (H2-AH), methotrexate, and cyclophosphamide, have an unfavorable benefit risk profile or significant side-effect profile and are no longer recommended for therapy of CSU (Kaplan 2002, Powell, et al 2007, Zuberbier, et al 2014). However, given that H2-AH is still used in certain countries, in this protocol, we allow the use of H2-AH as background therapy.

Omalizumab (Xolair®), a humanized monoclonal antibody against human IgE, has recently been approved for the treatment of CSU among subjects whose symptoms cannot be adequately controlled by H1-AHs. [redacted]

[redacted]

[redacted]

The ongoing core study CQGE031C2201 is a dose-range finding, double blind, active and placebo controlled parallel group study to characterize the dose response relationship for QGE031 doses 24, 72 and 240 mg sc q4w administered for 20 weeks with respect to achievement of complete hives response after 12 weeks of treatment. The active comparator in the core study is 300 mg omalizumab administered sc q4w.

As an open-label extension to study CQGE031C2201, study CQGE031C2201E1 will assess the long-term safety and tolerability as well as explore long-term efficacy of QGE031 during 52-week treatment and 48-week post-treatment follow-up among patients who completed CQGE031C2201. For those subjects who received placebo or lower doses of QGE031 in the core study, this study presents a chance to be treated with a higher dose of QGE031 240 mg. In addition, this study also provides an opportunity to collect safety and efficacy data related to re-treatment with QGE031.

1.2 Purpose

The purpose of this study is to evaluate long-term safety as well as efficacy outcome of QGE031 240 mg sc administered every 4 weeks for 12 months in patients with chronic spontaneous urticaria (CSU) who completed the CQGE031C2201 study. Safety and efficacy assessments will be conducted during the treatment epoch and the 48-week post-treatment epoch and the latter allows an assessment of sustained remission among responders. The efficacy of retreatment among subjects who were exposed to different dose levels of QGE031 in the core study will also be assessed. In this study, QGE031 is administered as an add-on therapy to H1-AH alone at approved or increased doses or in combination with H2-AH and/or a LTRA.

2 Study objectives

2.1 Primary objective(s)

The primary objective of this study is to assess the long-term safety of QGE031 in adult CSU patients who completed the core study CQGE031C2201 using the following evaluations:

- Incidence and severity of non-serious and serious adverse events including any events of special interest
- Changes in vital signs, laboratory assessments, and ECGs

2.2 Secondary objectives

The secondary objective of this study is to assess the long-term efficacy of QGE031 in adult CSU patients who completed the CQGE031C2201 study using the following evaluations:

- Sustained remission defined as maintaining UAS7 $\leq$ 6 over 48 weeks post-treatment follow up epoch among the subjects achieving remission at the end of treatment epoch

[redacted]

[redacted]

3 Investigational plan

3.1 Study design

This study is an open label, single arm, long-term safety extension for all patients who completed the core study CQGE031C2201 and fulfil the enrollment criteria for the extension study.

Among the 360 patients expected to participate in the core study, it is estimated that approximately 240 subjects may enroll in this extension study. Enrollment criteria require subjects to complete the treatment epoch and atleast visit 201 - 203 in the follow-up epoch in study CQGE031C2201 and present with active disease, as defined by UAS7≥12. The study consists of two epochs: open-label treatment and post-treatment follow up epoch. At or after visit 203, when the subjects become eligible to enroll in this extension study, they will complete all assessments associated with Visit 206 as a part of core study completion. The treatment epoch of this extension study will consist of 52 weeks of QGE031 240 mg s.c. at 4-week intervals. During the post-treatment follow-up epoch, the patients will be followed at 12-week intervals for 48 weeks. See Figure 3-1 for study design.

As in the core study, patients will continue using their background medication i.e H1-AH at approved or increased doses alone or in combination with H2-AH and/or a LTRA.

Open-label study Treatment Epoch:

- Visit 301 - 313
- This treatment epoch consists of 52 weeks of open label treatment with QGE031 240mg sc every 4 weeks.
- All lab assessments done as a part of end of core study visit (Visit 206) will be used to determine eligibility to enroll into the extension study.

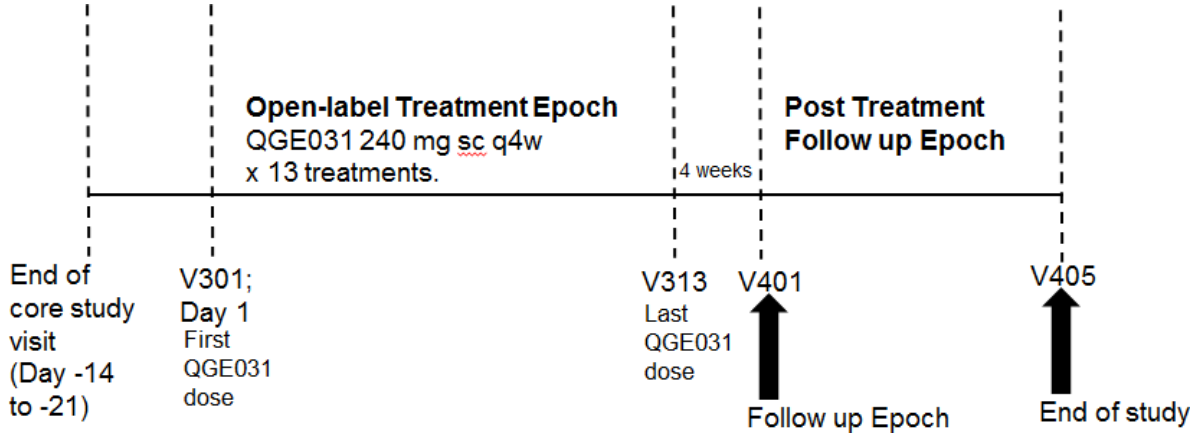
[redacted]

- The informed consent will be signed at visit 206
- The subjects will continue to complete eDiary assessments between visits 206 and 301
- Visit 301 should occur approximately 14 - 21 days after visit 206 core study assessments. Only in exceptional circumstances, when information concerning eligibility is outstanding (e.g., pending laboratory data), visit 301 can be extended.
- Subjects relevant medical conditions and concomitant medications will be reviewed at visits 206
- Subjects receive their first dose of QGE031 at visit 301 and last dose of QGE031 at visit 313

Post-treatment follow-up Epoch:

- Visit 401 – 405
- 48 weeks of post-treatment follow up consisting of visits every 12 weeks.
- No study treatment will be given during the post-treatment follow-up epoch; however, patients are allowed to take background medication and rescue medication. If a subject relapses i.e. develops symptoms with an UAS7 ≥12, the investigator should be contacted for an ad-hoc visit to consider treatment with standard of care or other therapy.

Figure 3-1 Study design



3.2 Rationale of study design

An open-label study design was chosen to obtain information on the long-term safety and efficacy of QGE031 (240 mg) given s.c. q4w for 52 weeks in patients with chronic spontaneous urticaria patients completing study CQGE031C2201. An open-label design avoids exposing patients to placebo for an extended period of time and administration of QGE031 240 mg allows for maximum exposure to the study drug. The 48-week post-treatment follow-up epoch will assess safety following treatment discontinuation, as well as to evaluate [redacted] including sustained remission.

[redacted]

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

Given that the primary goal of this study is to assess the long-term safety of QGE031 in chronic spontaneous urticaria patients, the highest dose tested in the core study - 240 mg QGE031 administered sc q4w for 52 weeks is used for this extension study.

[redacted]

The subcutaneous (s.c.) route of administration is selected since this is the route of administration in the core study, favorable bioavailability demonstrated with QGE031 in previous studies and its ease for both patients and caregivers.

3.4 Rationale for choice of comparator

Not applicable.

3.5 Purpose and timing of interim analyses/design adaptations

An interim analysis of safety and efficacy data will be performed at the end of open-label treatment epoch to collect information that might be relevant for the planning of other trials. Of note, the study procedures will not be modified as a result of this interim analysis.

3.6 Risks and benefits

The inclusion and exclusion criteria are selected to enroll patients with CSU most likely to benefit from participating in the study and are consistent with the criteria used in the core study CQGE031C2201. The overall risk to patients will be minimized by compliance with the inclusion/exclusion criteria and clinical monitoring.

[redacted]

The investigators will provide the patient with written instructions to contact them if symptoms of CSU worsen. Investigators will be instructed on acceptable treatments for worsening CSU to allow patients to continue on the study.

Other treatment alternatives to QGE031 for patients that have failed the standard treatment with H1-AH at approved or increased doses include omalizumab and immunosuppressive agents such as cyclosporine A, or repeated exposure to oral glucocorticoids. There are potential adverse effects associated with both of these alternatives. Omalizumab is an approved therapy for treatment of CSU refractory to standard of care treatment, and exhibits a favorable benefit-risk profile. It is a recombinant humanized IgG1 monoclonal antibody that binds to IgE-specific epitopes within the C3 (FcεRI binding) region of the IgE molecule and is indicated in many countries for the treatment of CSU refractory to standard therapy.

QGE031, although similar in principle to omalizumab, is still in clinical development. The risks associated with QGE031 are not fully characterized; however it is expected that the risk will be similar to Xolair. As of 31-Jan 2015, approximately 390 patients have been exposed to QGE031 across 8 studies (up to 6 SC administrations of 280 mg q2w and a single IV administration of 10 mg/kg). About 115 patients have completed 16 weeks treatment in the ongoing CQGE031B2201 asthma study [redacted] and have entered into the one year open label extension study (QGE031 dose 240 mg sc q4w). In all the completed and currently ongoing clinical studies with QGE031, no deaths related to QGE031 have been reported. QGE031 administration has been safe and well-tolerated with the most commonly reported adverse events being procedure-related adverse events, such as injection-site pain, swelling, bruising, or redness and other hypersensitivity reactions (e.g. rash, swelling of throat and/or tongue) including anaphylaxis.

One case of anaphylaxis has been observed with QGE031 in study CQGE031B2201E1 as of 31 July 2015. The risk of significant hypersensitivity reactions is mitigated by administering study medication only at the study site and observing patients for extended period after administration at the study site. (please refer to the Investigator Brochure (IB) for the complete safety summary). In addition, epinephrine is provided to the study participants in case needed.

Although the clinical benefits and safety profile of QGE031 in patients with CSU have not yet been established, given the similar mode of action as omalizumab, the benefit to the patient from study participation is that treatment with QGE031 will likely improve itch, hives and angioedema. The risk for patients participating in this study includes the potential for known safety issues such as hypersensitivity reactions including anaphylaxis, as well as for any unknown safety effects that could occur.

4 Population

The study population will consist of male and female adult patients (≥18 years old, ≤ 75 years old at the time of enrollment into the core study). All patients who received either various doses of QGE031 or Xolair or placebo in the core study and present active disease defined as UAS ≥ 12 at visit 203 or subsequent visits of the follow-up epoch of the core study will be offered the possibility to enter this study. Among 360 patients expected to participate in the

[redacted]

core CQGE031C2201 study, approximately 240 are estimated to enroll into this extension study.

4.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed.
2. Patients who complete the treatment epoch in study CQGE031C2201 and complete at least Visit 203 (Week 32 of the follow-up epoch, ≥16 weeks after last injection) and present with active disease as defined by UAS7 ≥12.
3. Patients must not have any missing eDiary entries in the 7 days prior to Visit 301 (patients are allowed to repeat until this criterion is met).
4. Willing and able to complete a daily symptom eDiary for the duration of the study and adhere to the study visit schedules.

4.2 Exclusion criteria

As in the core study CQGE031C2201, 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 at the time of enrollment into the extension study or within 30 days or 5-half-lives prior to visit 206, whichever is longer
2. Patients with a stool examination positive for ova and parasites (stool sample taken at visit 206).
3. New onset or signs and symptoms of any form of chronic urticaria other than CSU during the follow-up epoch of study CQGE031C2201. This includes the following:
   - Inducible urticaria: urticaria factitia, cold, heat, solar, pressure, delayed pressure, aquagenic, cholinergic, or contact urticarial per investigator's evaluation
   - Diseases with possible symptoms of urticaria or angioedema such as urticarial vasculitis, erythema multiforme, cutaneous mastocytosis (urticaria pigmentosa), and hereditary or acquired angioedema (e.g., due to C1 inhibitor deficiency)
4. Any other skin disease associated with chronic itching that might confound the study evaluations and results (e.g. atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus etc.)
5. Onset or ongoing alcohol or drug abuse, within the last 6 months
6. Unable to comply with study and follow-up procedures during the entire treatment and follow-up period
7. Use of prohibited treatment as detailed in protocol (Table 5-1)
8. Hypersensitivity to any of the study drugs i.e. QGE031, fexofenadine, loratidine, cetirizine, or epinephrine or any of the ingredients or its components, or to drugs of similar chemical classes (i.e. to murine, chimeric, or human antibodies)
9. History of anaphylactic shock

[redacted]

10. Onset of malignancy of any organ system within the past 1 year (except for basal cell carcinoma or actinic keratoses or Bowen disease (carcinoma in situ) that have been treated with no evidence of recurrence in the past 12 weeks; carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed)
11. Onset of clinically significant cardiovascular (such as but not limited to myocardial infarction, unstable ischemic heart disease, NYHA Class III/IV left ventricular failure arrhythmia, uncontrolled hypertension within 12 months prior to visit 206), neurological, psychiatric, metabolic, or other pathological conditions such as but not limited to cerebrovascular disease, neurodegenerative diseases, or other neurological disease, uncontrolled hypo- and hyperthyroidism and other autoimmune diseases, hypokalemia, hyperadrenergic state, or ophthalmologic disorder that could interfere with the compromise the safety of the patients, interfere with evaluation or interpretation of the study results, or preclude completion of the study
12. Medical examination or laboratory findings that suggest the possibility of decompensation of co-existing conditions for the duration of this study. Any items that are cause for uncertainty will be reviewed with the investigator
13. History or current treatment for hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis or hepatic failure or AST/ALT levels or INR of more than 1.5x upper limit of normal (ULN)
14. History of renal disease or creatinine level above 1.5x ULN at visit 206
15. Platelets < 100,000/µL at visit 206
16. Long QT syndrome or whose QTcF (Fridericia) measured at end of core study visit (Visit 206) is prolonged (> 450 ms for males or > 460 ms for females) and confirmed by a central assessor (ECG measurement should not be repeated in these patients to confirm eligibility)
17. 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
18. 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. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 m prior to screening in core study). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Barrier methods of contraception:
        - Male or female condom with or without spermicide
        - Cap, diaphragm, or sponge with spermicide

[redacted]

- 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.

Note: 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 atleast 6 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.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Study treatment

The following will be prepared by Novartis and supplied to the Investigative site as open-label medication of liquid formulation vials:

- QGE031 120mg/mL solution for subcutaneous injection is provided in 2mL glass vials each containing 1mL QGE031 solution at 120mg/mL. [redacted] The solution is clear to opalescent, colorless to yellowish in 2mL glass vials with rubber stopper and aluminum flip-off cap and is ready-to-use for subcutaneous injection.

5.1.2 Additional study treatment

No additional treatment beyond study treatment is requested for this trial.

Patients will continue to use their background medication i.e H1-AH at approved or increased doses alone or in combination with H2-AH and/or a LTRA (standard of care) with a stable regimen during the study.

5.2 Treatment arms

Patients will all be treated with QGE031 240 mg sc q 4 weeks for 52 weeks (13 treatments) in this open label study.

5.3 Treatment assignment, randomization

This is a single-arm study and all patients will receive QGE031 treatment.

At Visit 301, all eligible patients will be enrolled via Interactive Response Technology (IRT). The investigator or his/her delegate will contact the IRT system after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a unique medication

[redacted]

number for the first package of study treatment (QGE031) to be dispensed to the patient. There will be no randomization.

5.4 Treatment blinding

In this extension study, treatment is open-label; patients, investigator staff, persons performing the assessments, the sponsor and data analysts will know that all patients receive QGE031 q4w.

Randomization/treatment assignment data from the study CQGE031C2201 will be kept strictly confidential and will not be unblinded to the extension study sites at least until the core study CQGE031C2201 is fully completed. The site staff including the unblinded pharmacist who prepared the study treatment in the core study CQGE031C2201 must ensure that blinding for the core study is strictly maintained. To avoid any biased assessments in the extension study, the unblinded pharmacist or designee from the core study cannot be involved in the extension study other than to prepare and/or administer the open-label QGE031 in the extension study.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient was uniquely identified by a Subject Number in the core study CQGE031C2201, which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. In this extension study, the subject numbers will remain the same as assigned during the core study CQGE031C2201; no new subject numbers will be assigned.

The same RDC database will be used for both the core and the extension study. Study visits related to the extension study will become available once the patient has completed the core study and the site has indicated in the eCRFs that the patient will continue into the extension study.

Upon signing the informed consent for the extension study, 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 system.

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 Treatment Epoch Disposition form.

5.5.2 Dispensing the investigational treatment

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

All patients will receive QGE031 240mg (2 vials) at each study drug administration and supplies will be provided in 2 boxes (1 vial in one box). Each vial is 120mg/1ml. The investigational treatment packaging has a 2-part label. A unique medication number is printed on each part of this label. Investigator staff will identify the investigational treatment package(s) to dispense to the patient by contacting the IRT and obtaining the medication

[redacted]

number. Immediately before dispensing the medication 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

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 or remotely and at the completion of the trial. Patients will be asked to return all unused investigational treatment and packaging throughout, 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

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

All study drug administrations can be done in an outpatient ambulatory clinic setting. Study drug will be administered by a pharmacist or designee. Blinded personnel involved in core study can prepare and administer drug in this extension study. Subjects will remain on-site for observation for a period of 2 hours for the first 3 study drug administrations (Visit 301, 302 and 303) and 30 minutes for subsequent drug administration visits (304 to 313). This observation period follows the recommendation suggested by the National Heart, Lung, and Blood Institute and by The American Academy of Allergy, Asthma& Immunology and the American College of Allergy, Asthma and Immunology Executive Committees Joint Task Force (Cox et al 2007) for the anti IgE therapy currently available (omalizumab).

Two injections are required to administer the dose of 240 mg. The injections can be administered in the deltoid region on the right and/or left arm, and/or on the right and/or left thigh, or the abdomen as preferred by patient and/or site. The injections are administered

[redacted]

subcutaneously after aspiration of the plunger of the syringe. If blood appears at his hub or blood is withdrawn into a syringe, the needle is removed without administration of the dose and the injection site is changed. Each injection must be administered at a different site (e.g., right arm and left thigh).

The guidelines for the preparation and administration of study medication are described in the pharmacist manual.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study drug dose adjustments are not permitted. Study drug interruption is only permitted if the investigator considers an interruption necessary for the treatment of an adverse event. An interruption of two (2) consecutive study drug administrations or three or more administrations in total should be discussed with Novartis or delegate regarding the patient's eligibility to continue investigational treatment.

Any missed or altered study drug administrations must be recorded on the Dosage Administration Record CRF in order to reconstruct an accurate dosing history for each patient.

5.5.6 Rescue medication

Fexofenadine, loratadine, and cetirizine (H1-AH), in addition to being used as background medication will be allowed as rescue medication and used on an as needed basis during treatment and follow-up epochs. The selection of any one rescue medication should be made once for an individual patient. A switch of the rescue medication for an individual patient or between the core and extension study is not permitted. The patients will use the rescue medication at the indicated dose. If required for symptomatic relief, patients may take up to 4x the approved dose of the rescue medication, depending on local clinical practice and guideline. H1-AH rescue medication will be sourced locally.

[redacted]

As an additional safety precaution for the treatment of anaphylactic reactions, patients will be supplied with epinephrine, either via an auto-injector (if available) or as per other local standard of care. The investigator will train the patients on how to detect such reactions and how to use epinephrine. After any use of epinephrine, patients will need to seek immediate medical attention to ensure that the initial reaction has been successfully controlled and/or to trigger additional therapeutic steps.

The use of epinephrine will be recorded on the concomitant medication CRF page.

5.5.7 Concomitant treatment

This study requires concurrent use of H1-AH alone (at approved doses as per local health authority guidance or at increased doses up to four-fold) or in combination with H2-AH and/or LTRA (montelukast, zafirlukast, pranlukast) as background medication.

[redacted]

It is recommended that patients should remain on a stable treatment regimen (H1-AH alone or in combination with H2-AH and/or LTRA) throughout the study.

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 on the respective CRF pages.

5.5.8 Prohibited Treatment

Consistent with the core study CQGE031C2201, the use of the treatments displayed in Table 5-1 is NOT allowed after the start of study treatment. The minimum required period without prohibited treatment before Visit 206 is listed in Table 5-1 as well. Each concomitant drug must be individually assessed against all exclusion criteria and the table below to see if it is allowed. If in doubt, the investigator should contact Novartis or delegate before randomizing a patient or allowing a new medication to be started. If the prohibited treatment was used during the study for any indication, the patient must discontinue use of the prohibited treatment if he/she wishes to continue in the study. If the patient received a live virus vaccination during the study, the patient must discontinue study treatment

Table 5-1 Prohibited Treatment

Medication	Minimum required period without medication before Visit 301
Beta-blocker therapy	7 days
Routine (daily or every other day during 5 or more consecutive days) doses of systemic corticosteroids	30 days
Routine (daily or every other day during 5 or more consecutive days) doses of hydrochloroquine	30 days
Routine (daily or every other day during 5 or more consecutive days) doses of methotrexate, cyclosporine A, cyclophosphamide, tacrolimus and mycophenolate mofetil)	30 days
Intravenous immunoglobulin G	30 days
Plasmapheresis	30 days
Regular (daily or every other day) doxepin (oral)	14 days
Inactive vaccination	48 hours prior to any visit
Live attenuated vaccine	30 days

5.5.9 Emergency breaking of assigned treatment code

Not applicable

[redacted]

5.6 Study completion and discontinuation

5.6.1 Study completion and post study treatment

Study completion for individual patients will be when he/she has completed the extension study 52 weeks of treatment and the full follow-up epoch up to and including Visit 405.

Treatment completion will be when the patient completed the full 52-week treatment epoch. If patients relapse during the follow-up epoch of the extension study as defined by a UAS7 ≥ 12, they will be allowed to exit the study if desired and receive conventional therapy at the discretion of the investigator.

Completion of the study will be considered when all patients will have completed 52 weeks of treatment epoch and the full follow up epoch or have prematurely withdrawn from the study.

Information on the subject's completion or discontinuation of the study and the reason for discontinuation of the study will be recorded on the appropriate Study Epoch Completion eCRF page.

When the patient has completed all scheduled study assessments, the investigator must call or logon to the IRT system to record the patient completion as per above completion definitions.

The following is recommended for initiating other treatment outside or post study:

- A wash-out of QGE031 of at least 4 months is advised prior to commencing Xolair® treatment

5.6.2 Discontinuation of study treatment

Patients may voluntarily discontinue study treatment for any reason at any time.

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

As in study CQGE031C2201E1, study treatment must be discontinued under the following circumstances:

- Adverse events for which continued exposure to the study drug would be detrimental
- Abnormal renal laboratory results requiring discontinuation (see Section 7.4)
- Abnormal liver laboratory results requiring discontinuation (see Appendix 2)
- Platelets < 75000/ µL
- Pregnancy
- If a patient develops a medical condition that requires use of prohibited treatment as per Section 5.5.8, or if patient exhibits a behavior of non-compliance regarding prohibited medications
- Patient received a live virus vaccination during the study
- If a patient experiences an unexpected hypersensitivity reaction of grade 4, as defined by the World Allergy Organization Grading System (Cox 2010), see Appendix 3
    - Lower or upper respiratory: Respiratory failure with or without loss of consciousness

[redacted]

- Or cardiovascular: Hypotension with or without loss of consciousness

- Emergency use of epinephrine due to anaphylactic or anaphylactoid reaction
- Any protocol deviation that results in a significant risk to the patient's safety

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They will be expected to perform the Visit 313 (PSW) assessments four weeks after their last dose (except receiving study drug as a part of visit 313) and will be expected to perform all follow-up assessments (Visit 401-405). If they fail to return for these assessments for unknown reasons, every effort (e.g., telephone, e-mail, letter) should be made to contact them.

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. This care may include initiating another treatment outside of the study as deemed appropriate by the investigator

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

5.6.3 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.

5.6.4 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to 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 (Visit 405) would have occurred.

5.6.5 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.

[redacted]

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.

Given that this is a safety extension study to the core CQGE031C2201 study, if the core study is terminated for any reason including the outcome of interim analysis or the program is terminated, then the current study will also be terminated.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments. All data obtained from the assessments listed in Table 6-1 must be supported in the patient's source documentation. The table indicates which data are entered into the CRF from the source data (D), remain in the source documents only (S) or are loaded into the database from separate source documents, i.e. outside vendors (DS).

Patients should be seen for all visits on the designated day or as close to it as possible. The patient should be instructed to contact the investigator if he/she is unable for any reason to attend the visit as planned and the visit should be rescheduled as close as possible to the original date.

All patients who complete the treatment epoch will be expected to attend all follow-up visits (Visits 401-405). Patients who withdraw early will also be contacted every 4 weeks following final study drug administration until 12 weeks post withdrawal. Documentation of attempts to contact the patient should be recorded in the source documentation.

Table 6-1 Assessment Schedule

Epoch	Core study *, 1, a	Treatment Epoch													Post-treatment follow up epoch				
Visit	**206**	**301**	**302**	**303**	**304**	**305**	**306**	**307**	**308**	**309**	**310**	**311**	**312**	**313 PSW**	**401**	**402**	**403**	**404**	**405 PSW**
Week	**-3/-2**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**64**	**76**	**88**	**100**
Day	**-21/-14**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**449**	**533**	**617**	**701**
Obtain informed consent	D	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion/ Exclusion Criteria	D	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Relevant Medical history	D	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Family Malignancy history	D	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ongoing Concomitant medication usage	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D
Surgery and procedures	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D
Dispense H1-AH rescue medication	-	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Rescue medication usage	-	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D
Dispense epinephrine	-	S	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Study drug administration	-	D	D	D	D	D	D	D	D	D	D	D	D	D	-	-	-	-	-
Contact IRT	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	-	-	-	-	DS

[redacted]

Epoch		Core study *, 1, a	Treatment Epoch													Post-treatment follow up epoch				
Visit		**206**	**301**	**302**	**303**	**304**	**305**	**306**	**307**	**308**	**309**	**310**	**311**	**312**	**313 PSW**	**401**	**402**	**403**	**404**	**405 PSW**
Week		**-3/-2**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**64**	**76**	**88**	**100**
Day		**-21/-14**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**449**	**533**	**617**	**701**
Patient eDiary																				
UPDD		DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS
[redacted]																				
Laboratory tests/ Safety																				
Stool ova and parasite evaluation		DS	-	-	-	-	-	-	-	-	-	-	-	-	-	DS	-	-	-	-
Blood sample	Hematology	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS
	Clinical Chemistry including bilirubin, hsCRP	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS	DS
	[redacted]																			

[redacted]

Epoch		Core study *, 1, a	Treatment Epoch													Post-treatment follow up epoch				
Visit		**206**	**301**	**302**	**303**	**304**	**305**	**306**	**307**	**308**	**309**	**310**	**311**	**312**	**313 PSW**	**401**	**402**	**403**	**404**	**405 PSW**
Week		**-3/-2**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**64**	**76**	**88**	**100**
Day		**-21/-14**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**449**	**533**	**617**	**701**
[redacted]																				
Urine sample	Urinalysis dipstick (if abnormal submit sample to central lab)	D	D	-	-	-	D	-	-	-	D	-	-	-	D	-	-	D	-	D
	Pregnancy test	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D
	[redacted]																			
Physical Exam		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Vital signs		D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D
Weight		D	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	D
ECG		D	-	-	-	-	-	-	-	-	-	-	-	-	D	-	-	-	-	D
Adverse events		D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D
Liver safety monitoring		D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D
Renal safety monitoring		D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D

[redacted]

Epoch	Core study *, 1, a	Treatment Epoch													Post-treatment follow up epoch				
Visit	**206**	**301**	**302**	**303**	**304**	**305**	**306**	**307**	**308**	**309**	**310**	**311**	**312**	**313 PSW**	**401**	**402**	**403**	**404**	**405 PSW**
Week	**-3/-2**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**64**	**76**	**88**	**100**
Day	**-21/-14**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**449**	**533**	**617**	**701**
Others																			
Screening epoch completion form		D																	
Treatment epoch completion form															D				
Post treatment follow up epoch completion form																			D

*Visit 301 can occur approximately 14 to 21 days after visit 206 of the core study.

1: Patients who become eligible to enroll into the extension study at or after visit 203 of the core study must complete all lab assessments related to the end of core study (visit 206). The current version of the core protocol is to be referred regarding assessments related to visit 206.

[a] Subjects must complete all assessments associated with visit 206 as a part of core study to determine eligibility for enrollment into the extension study. The informed consent must be signed at visit 206. Subjects will continue using eDiary between visit 206 and 301.

[redacted]

PSW = Premature subject/patient withdrawal. Patients who discontinue study treatment will be expected to perform the Visit 313 (PSW) assessments (except receive the study drug dose associated with visit 313) four weeks after their last dose and will be expected to perform all follow-up assessments (Visit 401-405). If they fail to return for these assessments for unknown reasons, every effort (e.g., telephone, e-mail, letter) should be made to contact them.

S = assessment to be recorded on clinical data base,

D= assessment to be recorded on the CRF based on source documentation,

DS=assessment to be loaded into the database from separate source documents i.e. outside vendors

[redacted]

6.1 Information to be collected on screen/ roll-over failures

All patients who have signed informed consent but are not administered study drug will have the study phase completion page for the screening epoch, patient visit dates, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data including date of birth, age, sex, race and ethnicity that was collected as a part of the core study will be used for this extension study. Relevant medical history/ medical condition will be reviewed at Visit 206 prior to signing the informed consent. Data on patient's family history on malignancies will also be collected at Visit 206 on the respective CRF page.

6.3 Treatment exposure and compliance

Patients will receive two subcutaneous injections every 4 weeks at 13 visits during the open label treatment epoch.

Compliance is assured as study drug needs to be administered by study personnel every 4 weeks via subcutaneous injection. Administration of study drug, date, time and injection site will be recorded in the source documents and on the Drug Administration Record eCRF for each injection.

6.4 Efficacy

A number of efficacy variables will be assessed during the study. Efficacy will be assessed for each patient individually based on the baseline data collected between Visit 206 and Visit 301.

6.4.1 eDiary Assesments

All patients will be provided with an electronic device (eDiary). Similar to the core study, the eDiary will consist of two components: Urticaria Patient Daily Diary (UPDD) [redacted]. The patients will receive clear instructions on the completion of the eDiary twice daily or once daily depending on the questions. The patients will continue using the eDiary between visit 206 and 301.

6.4.1.1 Urticaria Patient Daily Diary (UPDD)

UPDD includes UAS7 (itch and hives) for clinical symptoms, use of rescue medication, sleep and activity interference, angioedema occurrence and its management, and number of calls

6.4.1.1.1 Hives severity score (HSS)

The wheals (hives) severity score, defined by number of hives, will be recorded by the patient twice daily in their eDiary, on a scale of 0 (none) to 3 (intense/severe) (see Table 6-2). A

[redacted]

weekly score (HSS7) is derived by adding up the average daily scores of the 7 days preceding the visit. The possible range of the weekly score is therefore 0 - 21.

When either the morning or evening score is missing, the non-missing score for that day (morning or evening) will be used as the daily score. When one or more of the daily scores are missing, the following principles will be applied to handle the missing data:

If a patient has atleast 4 non-missing daily scores within the 7 days prior to study visit, the weekly score is calculated as the sum of the available ediary scores in that week, divided by the number of days that have a non-missing ediary score, multiplied by 7. If there are less than 4 non-missing daily scores within the prior 7 days, then the weekly score is missing for the week.

Complete hives response is defined as HSS7 = 0.

Table 6-2 Hives Severity Score

Score	Wheals (Hives)
0	None
1	Mild (1-6 hives/ 12 hours)
2	Moderate (7-12 hives/ 12 hours)
3	Severe (> 12 hives/ 12 hours)

6.4.1.1.2 Itch Severity Score (ISS)

The severity of the itch will be recorded by the patient twice daily in their ediary, on a scale of 0 (none) to 3 (intense/severe) (see Table 6-3). A weekly score (ISS7) is derived by adding up the average daily scores of the 7 days preceding the visit. The possible range of the weekly score is therefore 0 - 21. Partially missing ediary entries will be handled in the same way as described for the hives severity score.

Complete itch response is defined as ISS7 = 0.

Table 6-3 Itch Severity Score

Score	Pruritus (Itch)
0	None
1	Mild (minimal awareness, easily tolerated)
2	Moderate (definite awareness, bothersome but tolerable)
3	Severe (difficult to tolerate)

[redacted]

6.4.1.1.3 Weekly Urticaria Activity Score (UAS7)

The UAS7 is the sum of the HSS7 score and the ISS7 score. The possible range of the weekly UAS7 score is 0 - 42. Complete UAS7 response is defined as UAS7 = 0. Clinical remission is defined as UAS7 ≤ 6, and the status of "remission" and "sustained remission" will be assessed during treatment and post-treatment epoch, respectively. Clinical relapse is defined as UAS7≥12.

[redacted]

[redacted]

6.4.3 Appropriateness of efficacy assessments

In the past literature it has been noted that assessment of itch is the symptom of greatest concern to patients, with greatest impact on their quality of life (Mathias, et al 2010). However, based on the current experts' feedback, the hives are more objective and specific to underlying condition being studied, whereas the itch is very subjective, non-specific and can be of different origin.

Disease recurrence after study drug is withdrawn will be measured during the post-treatment follow-up epoch. For all patients, symptom scores will be measured during both the treatment and post-treatment follow-up epochs.

6.5 Safety

Main safety and tolerability assessments include:

- AEs and SAEs, including AEs leading to treatment discontinuation and events of interest such as anaphylaxis, pre-malignancy/malignancy, cardio-cerebrovascular events
- Physical examination
- Vital signs
- Laboratory evaluations
- ECG

6.5.1 Physical examination

A complete physical examination 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 at Visit 301.

A short physical exam will include the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse). A short physical exam will be at all visits starting from Visit 302.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings made after first administration of investigational drug which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the CRF.

6.5.2 Vital signs

Vital signs include BP and pulse measurements. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON,

[redacted]

with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 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.

Clinically notable vital signs are defined in Appendix 1.

6.5.3 Height and weight

Body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured. Height will be taken from the baseline assessment in the core study and will not be repeated for the extension study.

6.5.4 Laboratory evaluations

A central laboratory will be used to analyze and report blood chemistry/hematology, urine (if abnormal dip stick at site), and any stool samples. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Appendix 1.

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured. Also coagulation will be assessed by International Normalized Ratio (INR).

6.5.4.2 Clinical chemistry

Albumin, total bilirubin, alkaline phosphatase, AST, ALT, chloride, calcium, sodium, potassium, magnesium, LDH, creatinine, inorganic phosphorus, urea/BUN, uric acid and hs-CRP will be measured. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

6.5.4.3 Urinalysis

Semi-quantitative “dipstick” evaluation will be performed at site including but not limited to specific gravity, glucose, protein, bilirubin, ketones, leukocytes and blood. Only when a dipstick evaluation is abnormal, e.g. positive for WBC and/or blood, a urine sample needs to be sent to the Central Lab for further examination including but not limited to RBC and WBC. Please refer to Section 7.4 and Table 7-1 for, specific actions and assessments needed in case of any abnormal findings related to renal function.

Dipsticks will be provided to the sites by the Central Lab.

[redacted]

6.5.4.4 Assessment of parasitic infections

[redacted]

All subjects will have a stool sample collected at Visit 206 and 401. In case the patient is unable to provide a stool sample they should take the sample pot home to bring in a stool sample as soon as possible after the visit, preferable the day after. Stool samples and additional assessment for parasitic disease will be examined for ova and parasites by the central laboratory. Negative test results must be documented before initiation of study treatment. In case diarrhea develops at any time prior to the last dose of study drug administration, additional assessments for parasitic infections would be performed and study treatment would not be resumed until results are obtained.

6.5.5 Electrocardiogram (ECG)

Standard 12 lead ECGs must be performed only after subjects have been resting in the supine position for at least 10 minutes. The preferred sequence of cardiovascular data collection during study visits is to perform the ECG prior to vital signs, and blood sampling. The Fridericia's QT correction formula (QTcF) should be used for clinical decisions.

Triplicate ECGs (3 ECG measurements taken at approximately 1 min intervals) will be recorded at Visits 206, 313 and 405. For patients whose ECG is abnormal at Visit 206 due to technical/mechanical faults, a repeat ECG may be performed. All electrocardiograms must be performed using a 12 standard lead. For those patients who prematurely discontinue from the study, an ECG tracing will be taken at Visit 405.

For each ECG performed original traces and identical duplicate traces will be produced. The original trace will be sent electronically to the CRO directly from the provided 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 vendor in case of problems with the electronic transmission. The 'identical' duplicates kept at the investigator site will be dated and signed and will be archived at the study site. The subject's number, subject initials, the date, actual time of the tracing, and Study Code (CQGE031C2201E1) must appear on each page of the ECG tracing.

Full details of all procedures relating to the ECG collection and reporting will be contained in an investigator manual to be provided by the CRO to each investigator site.

Clinically significant ECG findings prior to dosing with investigational treatment must be discussed with the sponsor.

Clinically significant abnormalities should be recorded on the relevant section of the medical history/Current medical conditions if present at visit 206 or on the AE eCRF page as appropriate.

[redacted]

6.5.6 Pregnancy

Women of child-bearing potential only will have a urine pregnancy test at the visits specified in Table 6-1. A positive urine pregnancy test requires a serum sample to be sent to the Central Lab and, during treatment epoch, 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 drug but remain on the trial for the safety evaluation. Urine pregnancy test kits will be provided to the sites by the Central Lab.

6.5.7 Anaphylaxis assessment

An adjudication committee (AC) is in place to determine whether cases identified through a search algorithm based on the Standardized MedDRA Queries of hypersensitivity may represent cases of anaphylaxis. Further details regarding the AC will be documented in the AC charter. See Section 8.5 for details.

6.5.8 Assessment of cardio-cerebrovascular events

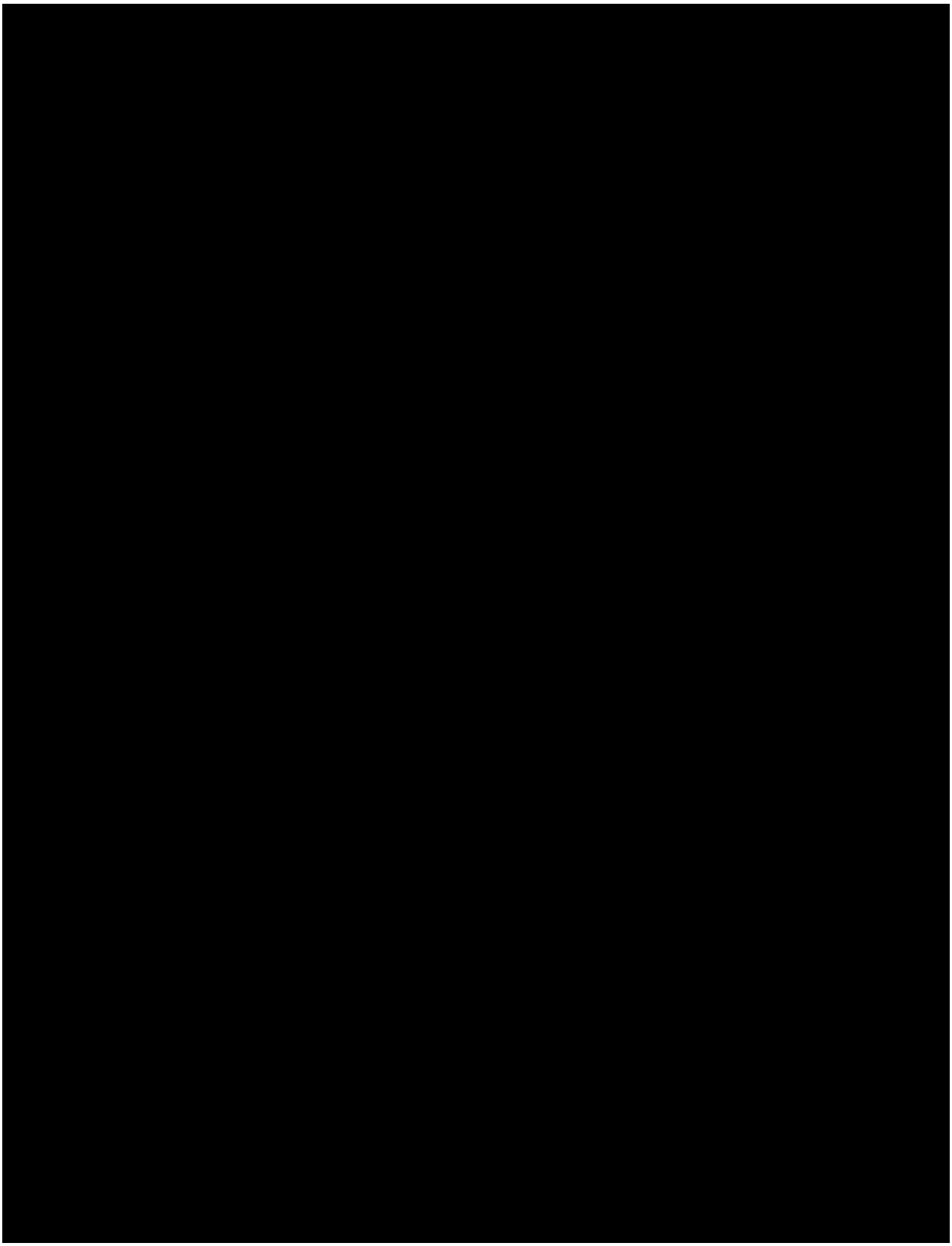
An AC is in place to review all cases identified through a search algorithm based on the Standardized MedDRA Queries of cardio-cerebrovascular events. The clinical presentation and association of these events with pre-existing risk factors will be part of the assessment. See Section 8.5 for details.

6.5.9 Assessment of pre-malignancies and malignancies

An AC will be put in place to review all cases identified through a search algorithm based on the Standardized MedDRA Queries of pre-malignancies and malignancies. The clinical presentation and association of these events with pre-existing risk factors will be part of the assessment. See Section 8.5 for details.

6.5.10 Appropriateness of safety measurements

Events of special interest such as suspected anaphylaxis, neoplastic events, and cardiovascular events will be monitored and will be adjudicated by expert adjudication committees.



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 patient or clinical investigation patient 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 an investigational product.

For all patients who have signed informed consent and are entered into the next epoch (Extension 1 Treatment epoch) of the study, all adverse events occurring after informed consent is signed will be recorded on the Adverse Event CRF.

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 and will be described in the laboratory manual.

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 investigational treatment (no/yes), or
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
- whether it constitutes a SAE (see Section 7.2.1 for definition of SAE)
- action taken regarding investigational treatment.

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

- no action taken (i.e. further observation only)
- investigational treatment dosage adjusted/temporarily interrupted
- investigational treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) 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.

7.2 Serious adverse events

7.2.1 Definition of SAE

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

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

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

[redacted]

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit (Visit 405) must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day 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 (either initial or follow-up information) is collected and recorded in English on the paper Serious Adverse Event Report Form or the electronic Serious Adverse Event Form within the Oracle Clinical/Remote Data Capture (OC/RDC) system (where available). The investigator must assess the relationship to each specific component of the study treatment (if the study treatment consists of several components).

SAEs (initial and follow-up) that are recorded on the paper SAE form should be faxed within 24 hours of awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

SAEs (initial and follow-up) that are recorded electronically in the OC/RDC system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to Novartis Drug Safety & Epidemiology immediately after investigator signature or 24 hours after entry, whichever occurs first.

Follow-up information provided should describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

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 investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and

[redacted]

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 13-1 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 13-1 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 13-2 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.

[redacted]

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 renal adverse events 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:
   - New onset (≥ 1+) proteinuria, hematuria or glucosuria; or
   - Doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable).

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	
New dipstick proteinuria ≥ 1+	Confirm value after 24-48h
Albumin- or Protein-creatinine ratio increase ≥ 2-fold	Perform urine microscopy
Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol	Consider drug interruption/discontinuation
Protein-creatinine ratio (PCR) ≥ 150 mg/g or >15 mg/mmol	
New dipstick glucosuria ≥ 1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria ≥ 1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
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.	

7.5 Reporting of study treatment errors including misuse/ abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of study drug while under the control of a healthcare professional, patient or consumer

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

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

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

Table 7-2 Reporting of study treatment errors

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

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 study treatment.

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

7.7 Prospective suicidality assessment

All SAEs relating to suicidal behavior should be reviewed by the Safety Management Team or early project teams.

[redacted]

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and 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 eCRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment. The study monitor will also ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data and identify risks and trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the 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 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. Data from both the core study (CQGE031C2201) and extension study (CQGE031C2201E1) will be entered into the same database.

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

[redacted]

8.3 Database management and quality control

Novartis staff or CRO working on behalf of Novartis review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

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

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

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

Diary data will be entered into an electronic diary by the patient. 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).

Data about study treatment administered to the patient 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).

The occurrence of relevant protocol deviations will be determined. Prior to the final analysis, after these actions have been completed and the database has been declared to be complete, it will be locked. Data cleaning and determination of protocol deviations will also be performed on an ongoing basis, with particular effort before the planned interim analyses. However, sites are able to change data until the final database lock. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee

A DMC is not required.

8.5 Adjudication Committees

To enhance the safety assessment, more specifically relative to anaphylactic events, neoplastic events and major cardio-cerebrovascular events, three independent panels of experts external to Novartis will provide independent reviews of potentially identified events in a blinded manner and adjudicated on a regular basis.

All the details of the adjudication processes including the committee members are included in the adjudication committee charters.

[redacted]

9 Data analysis

9.1 Analysis sets

Safety Set (SS): The SS consists of all patients who received at least one dose of open-label study drug during this open-label study and who had at least one post-baseline (Visit 301) safety assessment.

All safety and efficacy analyses will be performed on the safety analysis set and for the total population (not broken down by treatment) unless otherwise specified.

9.2 Patient demographics and other baseline characteristics

Demographic and background information will be summarized and be presented based on the Safety Set. Medical history/current medical condition before the start of open-label extension study will be summarized by system organ class and preferred term according to MedDRA dictionary.

9.3 Treatments

The number of patients and the length of time (in days) exposed to study drug will be summarized by treatment for the safety set.

Concomitant medications will be summarized for the safety set separated for urticaria related background medications and non-urticaria related medications. Urticaria related background medications will be summarized by pre-specified categories (including dose) and preferred term. Non-urticaria related concomitant medications will be summarized by preferred term. Use of rescue medication will be summarized as well.

9.4 Analysis of the primary variable(s)

Descriptive safety analyses will be conducted using the Safety Set.

9.4.1 Variable(s)

The primary objective of this study is to obtain additional data on the long-term safety and tolerability of QGE031 for 12 months of treatment in CSU patients.

The primary variables are: for AEs/SAEs, ECGs, laboratory assessments, vital signs data and events of special interest such as hypersensitivity reactions, anaphylaxis, cardio-cerebrovascular events, and pre- and malignancies.

Baseline for the safety analysis is the last visit (Visit 206) of the core study CQGE031C2201, except for parameters which are newly assessed at Visit 301, in which case Visit 301 is the baseline visit.

Adverse events

All adverse events which start after the first dose of study medication in the extension study and within 52 weeks of the last dose will be considered as a treatment emergent adverse event.

[redacted]

Treatment emergent adverse events may be presented in 2 sub-groups; those which started after first study drug dose and within 4 weeks after the last dose and those which started more than 4 weeks after the last dose. Adverse events that started during the follow-up epoch of the core study will be reported and analyzed in the core study and will not be included in tables of the extension study unless they become more severe. They will, however, be included in listings with additional collected information (e.g., outcome) as applicable. Adverse events that started in the core study but became more severe in the extension study will be reported and analyzed as new events.

Treatment emergent adverse events with the number and percentage of patients having any adverse event overall, by system organ class and preferred term will be provided for:

- All adverse events
- Adverse events by maximum severity
- Adverse events suspected by the investigator as study drug-related
- Serious adverse events
- Adverse events leading to permanent discontinuation of study drug

AEs of Special Interest

Hypersensitivity assessment

All hypersensitivity reactions that are possible cases of anaphylaxis will be adjudicated by independent committee. The adjudicated hypersensitivity reactions will be summarized by preferred term and severity.

Cardio- and Cerebrovascular events

All cardio- and cerebrovascular events will be adjudicated by independent committee and summarized by preferred term and severity.

Malignancies

Frequency of adjudicated malignancies whether newly detected or worsening of existing malignancies will be reported.

Laboratory data

The following analyses will be performed, where appropriate, for measurements of urinalysis, hematology and blood chemistry tests:

Standard descriptive statistics for values measured at baseline and post-baseline visits including changes from baseline, shift tables relative to the normal ranges between baseline and post-baseline visits, number (and percentage) of patients with clinically notable changes for selected tests.

[redacted]

Vital signs

Vital signs (i.e. blood pressure, pulse rate and) will be summarized with standard descriptive statistics of raw data and changes from baseline for each visit separately. The numbers of patients with vital signs meeting the definition of notably abnormal will be presented by parameter.

ECG

ECG data will be summarized by treatment and visit. Changes from baseline will be summarized.

Notable QTc values and change from baseline will be summarized. A notable value is defined as a QTc interval of greater than 450 ms. The categories used for the change (increase) in QTc are - less than 30 ms, 30 to 60 ms and greater than 60 ms.

The Fredricia QT correction formula (QTcF) will be used for clinical decisions.

9.4.2 Statistical model, hypothesis, and method of analysis

No hypotheses will be tested.

Adverse events will be summarized by presenting the number and percentage of patients having any AE by primary system organ class and/or preferred term. AE by severity, drug related AEs, AEs leading to premature discontinuation of study drug, death and serious AEs will be presented in a similar format as all AEs.

AEs related to potential anaphylaxis will be summarized separately.

Laboratory and vital sign data will be summarized by presenting summary statistics of values and change from baseline by visit, and by presenting frequency of patients with clinically notable changes.

ECG intervals will be summarized by presenting summary statistics for change from baseline values by visit. Count and frequency of clinically notable ECG abnormalities or changes will be presented. The (uncorrected) QT interval will be corrected according to the Fridericia's formulae.

Laboratory data, vital sign data and ECG data will be listed with abnormal value flagged based on normal ranges or clinically notable ranges.

Other safety data will be summarized and listed as appropriate.

9.4.3 Handling of missing values/censoring/discontinuations

All available data for the endpoints outlined in Section 9.4.1 will be reported. Missing data will not be imputed.

9.4.4 Supportive analyses

The analysis of subgroups of patients for safety parameters is not foreseen. If deemed necessary based on, for example, results obtained in the core study, such subgroups may be predefined and specified in the statistical analysis plan.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

Secondary efficacy variables will be summarized by visit with descriptive statistics, which include absolute and relative frequencies for categorical variables and arithmetic mean, standard deviation, minimum, maximum, median and first and third quartile for continuous variables. Baseline measurements are those taken in the week preceding the first dose administered in the extension study. Time to event variables will be summarized using Kaplan-Meier estimates.

Table 9-1 Secondary [redacted] efficacy variables

Domain	Variable	Analyzed in treatment epoch	Analyzed in follow-up epoch
Clinical symptoms: total	Complete UAS7 response (UAS7 = 0)	Y	Y
	Change from Baseline in Urticaria Activity Score (UAS7)	Y	Y
	Time to achievement of complete UAS7 response	Y	N
	Time to loss of complete UAS7 response for patients having achieved complete UAS7 response at Week 52	N	Y
	[redacted]		
Clinical symptoms: hives	Complete hives response (HSS7 = 0)	Y	Y
	Change from Baseline in HSS7	Y	Y
	Time to achievement of complete hives response	Y	N
	Time to loss of complete hives response for patients having achieved complete hives response at Week 52	N	Y
Clinical symptoms: itch	Complete itch response (ISS7 = 0)	Y	Y
	Change from Baseline in Itch Severity Score (ISS7)	Y	Y
[redacted]			

[redacted]

Domain	Variable	Analyzed in treatment epoch	Analyzed in follow-up epoch
[redacted]			

Y: yes, N: no

Achievement of UAS7=0 response, HSS7 = 0 response and ISS7 = 0 response will also been summarized by treatment received in the core study, and by response status achieved at week 20 of the core study.

9.5.2 Safety variables

See section 9.4.

[redacted]

[redacted]

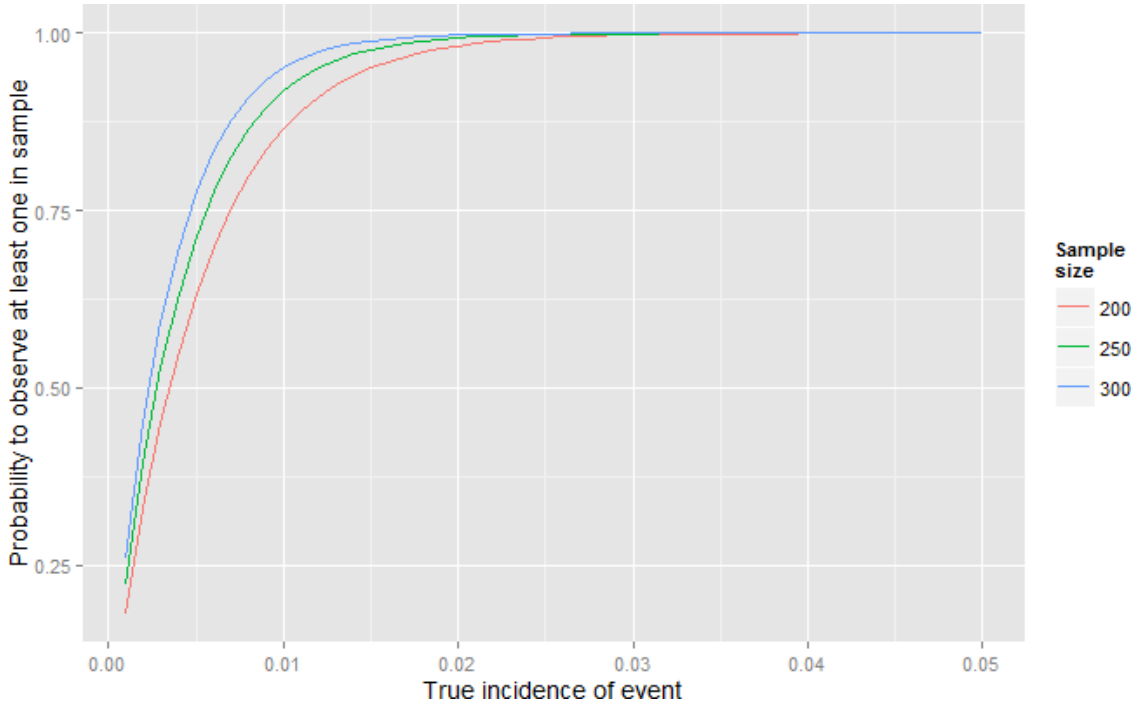
9.6 Interim analyses

An interim summary of safety and efficacy data will be prepared when all patients have completed the treatment epoch. In particular, the summary will include baseline characteristics, adverse events, safety laboratory data and the weekly symptom scores and derived responder status. Additional parameters may be added as deemed necessary and will be defined in more detail in an interim analysis plan. Study procedures will not be modified as a result of this interim analysis.

9.7 Sample size calculation

It is expected that approximately 240 patients will enter the extension study**.** The following graph shows the binomial probability of observing at least one event for a range of true incidences from 0.001 (0.1%) to 0.05 (5%) in samples of 200, 250 and 300 patients**.**

Figure 9-1 Probability of observing adverse events with given incidence



[redacted]

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 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.

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 Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an

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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.

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 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. **Only amendments that are required for patient safety may be implemented prior to IRB/IEC approv**al. 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, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days or less, if required by local regulations.

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[redacted]

13 Appendices

13.1 Appendix 1: Clinically notable laboratory values and vital signs

Refer to Appendix 2 for clinically notable serum blood chemistry tests for hepatotoxicity.

The following specific criteria have been identified for this study:

- AST, ALT or INR above 1.5x ULN
- Creatinine above ULN
- Platelets <75,000µL.
- Stool test result positive for ova or parasites

Any patient that has AST, ALT, INR or creatinine levels above the limits specified above or a stool test result positive for ova or parasites at Visit 206, should be excluded from the study.

Any patients that have AST, ALT, INR or creatinine levels above the limits specified above, after the patient has started treatment in the extension study, should have regular laboratory assessments to monitor those laboratory parameters, until they return to baseline values (or within normal range), or the investigator indicates that post baseline values are sufficiently close to baseline that no further follow-up is warranted for patient safety.

Any patients that have platelets <75,000µL after the patient has started treatment should be discontinued from study drug.

For all other laboratory assessments, the Central Laboratory will flag laboratory values falling outside of the normal ranges on the Central Laboratory Report (which the investigator should review and sign-off) and the investigator will report any values considered clinically significant in the eCRF.

Notable values for vital signs and change from baseline will be summarized. A notable value is defined as follows: heart rate of <40 and >90 bpm; systolic blood pressure of <90 and >140 mmHg; diastolic blood pressure of <65 and >90 mmHg.

For ECGs a notable QTc value is defined as a QTc (Fridericia's) interval of greater than 450 ms for males and > 460 for females – all such ECGs require assessment for clinical relevance by the Investigator. Patients with a heart rate of >100 bpm measured on 2 occasions, approximately 10 minutes apart, while resting, should be discontinued from study treatment.

[redacted]

13.2 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 13-1 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 x ULN ALP > 2 x ULN (in the absence of known bone pathology) TBL > 2 x ULN (in the absence of known Gilbert syndrome) ALT or AST > 3 x ULN and INR > 1.5 Potential Hy's Law cases (defined as ALT or AST > 3 x ULN and TBL > 2 x ULN [mainly conjugated fraction] without notable increase in ALP to > 2 x ULN) Any clinical event of jaundice (or equivalent term) ALT or AST > 3 x ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia Any adverse event potentially indicative of a liver toxicity *

Table 13-2 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 x 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 x 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)

[redacted]

Criteria	Actions required	Follow-up monitoring
> 5 to ≤ 8 x ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for *more than 2 weeks*, discontinue the study drug • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 x 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 x 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
ALP (isolated)		
> 2 x 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 x 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 x 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	• Consider study drug	Investigator discretion

[redacted]

Criteria	Actions required	Follow-up monitoring
a liver toxicity*	interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	

*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

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

13.3 Appendix 3 World Allergy Organization Grading System

World Allergy Organization subcutaneous immunotherapy systemic reaction grading system

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptom(s)/sign(s) of 1 organ system present Cutaneous Generalized pruritus, urticaria, flushing, or sensation of heat or warmth **or** Angioedema (not laryngeal, tongue or uvular) **or** Upper respiratory Rhinitis - (eg, sneezing, rhinorrhea, nasal pruritus and/ or nasal congestion) **or** Throat-clearing (itchy throat) **or** Cough perceived to originate in the upper airway, not the lung, larynx, or trachea **or** Conjunctival Erythema, pruritus or tearing Other Nausea, metallic taste, or headache	*Symptom(s)/sign(s) of more than 1 organ system present* **or** Lower respiratory Asthma: cough, wheezing, shortness of breath (eg, less than 40% PEF or FEV1 drop, responding to an inhaled bronchodilator) **or** Gastrointestinal Abdominal cramps, vomiting, or diarrhea **or** Other Uterine cramps	Lower respiratory Asthma (eg, 40% PEF or FEV1 drop NOT responding to an inhaled bronchodilator) **or** Upper respiratory Laryngeal, uvula, or tongue edema with or without stridor	Lower or upper respiratory Respiratory failure with or without loss of consciousness **or** Cardiovascular Hypotension with or without loss of consciousness	Death

Source: Cox 2010

[redacted]

13.4 Appendix 4 Blood log

Sample	Sample type	Visit																	
		206*	301	302	303	304	305	306	307	308	309	310	311	312	313	401	402	403	404	405
		Day																		
		-21/-14	1	29	57	85	113	141	169	197	225	253	281	309	337	365	421	477	533	701
Chemistry	Serum 1.5mL	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Haem+ PT(INR)	Blood 4.5+2mL	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
[redacted]																				
Total blood volume for labs/ [redacted] per visit		16.1	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
[redacted]																				

[redacted]

Sample	Sample type	Visit																	
		206*	301	302	303	304	305	306	307	308	309	310	311	312	313	401	402	403	404	405
		Day																		
		-21/-14	1	29	57	85	113	141	169	197	225	253	281	309	337	365	421	477	533	701
[redacted]																				
Total blood Volume/ visit		26.1	10	10	10	10	10	10	20	10	10	10	10	10	20	10	16	10	16	20

Total blood volume from Visit 301 - 405	222 mL

*: Blood volume from assessments done as a part of Visit 206 not included in Total blood volume for this extension study

[redacted]

13.5 Appendix 5 ePRO tools

Samples of questionnaire provided here are for illustrative purposes only. The text format and wording might slightly vary.

Patient Diary: Urticaria Patient Daily Diary (UPDD)

General Instructions

Please answer each question to the best of your ability.

There are no right or wrong answers.

For each question, please choose the response that describes your experience.

Please pay close attention to the timeframe of interest. Some questions ask about the **past 12 hours**, while others ask about the **past 24 hours**.

Instructions for Counting the Number of Hives

Count each hive separately even if you have more than one hive grouped together with other hives.

Today's Date day month year

Please complete this section every morning throughout the duration of the study.
(Please circle only one response.)

1. Thinking about the **past 12 hours**, please record the severity of itch and the number of hives you may have had associated with your skin condition. **Please count each hive separately** even if you have more than one hive grouped together with other hives.

Itch (severity)

0 = none

1 = mild

2 = moderate

3 = severe

Hives (number)

0 = none

1 = between 1 and 6 hives

2 = between 7 and 12 hives

3 = greater than 12 hives

[redacted]

Today's Date day month year

Please complete this section <u>every evening</u> throughout the duration of the study.
(Please circle only one response.)

2. Thinking about the **<u>past 12 hours</u>**, please record the severity of itch and the number of hives you may have had associated with your skin condition. **<u>Please count each hive separately</u>** even if you have more than one hive grouped together with other hives.

Itch (severity)

0 = none

1 = mild

2 = moderate

3 = severe

Hives (number)

0 = none

1 = between 1 and 6 hives

2 = between 7 and 12 hives

3 = greater than 12 hives

Today's Date day month year

Please complete this section <u>once each day</u> throughout the duration of the study (preferably at the same time each day).

(Please circle only one response.)

3. Please rate how much your hives or itch interfered with your sleep during the **<u>past 24 hours</u>**.

0 = No interference

1 = Mild, little interference with sleep

2 = Moderate, awoke occasionally, some interference with sleep

3 = Substantial, woke up often, severe interference with sleep

4. Please rate how much your hives or itch interfered with your daily activities during **<u>the past 24 hours</u>**. This could include work, school, sports, hobbies, and activities with friends and family.

0 = No interference

1 = Mild, little interference with daily activities

2 = Moderate, some interference with daily activities

3 = Substantial, severe interference with daily activities

[redacted]

These next questions are about your symptoms and how you managed them during the past 24 hours.

5. During the **past 24 hours**, how many tablets of rescue medication did you use in order to control symptoms of your skin condition such as itch or hives?

   ☐

   The maximum number of tablets per day should be according to your doctor's recommendation.

6a. During the **past 24 hours**, did you have any rapid swelling on your face, (especially your eyelids or lips), inside your mouth (including your throat or tongue), or elsewhere on your body? This rapid swelling, also called angioedema, is at a deeper level under your skin than hives.

   0 = No **(GO TO Question 7)**

   1 = Yes

6b. If Yes, how did you treat this rapid swelling? **(Circle all that apply.)**

   0 = Did nothing **(GO TO Question 7)**

   1 = Took some prescription or non-prescription medication

   2 = Called my doctor, nurse or nurse practitioner

   3 = Went to see my doctor, nurse or nurse practitioner

   4 = Went to the emergency room at the hospital

   5 = Was hospitalized

7. During the **past 24 hours**, did you or someone else call your doctor, nurse or nurse practitioner because of your skin condition?

   0 = No

   1 = Yes

[redacted]