NOVARTIS

Global Clinical Development - General Medicine

[QGE031/Ligelizumab]

# Clinical Trial Protocol [CQGE031C2202 / NCT03437278]

## A multicenter, randomized, double-blind, placebo-controlled phase 2b dose-finding study to investigate the efficacy and safety of ligelizumab (QGE031) in adolescent patients with Chronic Spontaneous Urticaria (CSU)

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## List of abbreviations

| [redacted] | [redacted] |
|---|---|
| AC | Adjudication committee |
| ADA | Anti-drug antibodies |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| ALP | Alkaline phosphatase |
| AST | Aspartate aminotransferase |
| BP | Blood pressure |
| B-hCG | Beta Human Chorionic Gonadotropin |
| BUN | Blood urea nitrogen |
| CDLQI | Children Dermatology Life Quality Index |
| CFR | United States Code of Federal Regulations |
| CINDU | Chronic Inducible Urticaria |
| CO | Country Organization |
| CRF | Case Report/Record Form (paper or electronic) |
| CRO | Contract Research Organization |
| CRP | C-reactive protein |
| CSU | Chronic Spontaneous Urticaria |
| DBP | Diastolic blood pressure |
| DMC | Data monitoring committee |
| DSM | Drug supply management |
| EC50 | Concentration of a drug that gives half-maximal response. |
| ECG | Electrocardiogram |
| ECL | electrochemiluminescent |
| EDC | Electronic Data Capture |
| eDiary | Electronic diary |
| eGFR | Estimated glomerular filtration rate |
| ELISA | Enzyme-linked immunosorbent assay |
| EMA | European Medicines Agency |
| Emax | Maximum efficacy |
| EMEA | Europe Middle East ad Africa |
| EOT/TD | End of treatment/Study treatment discontinuation |
| ePRO | Electronic Patient Reported Outcome |
| ER | Exposure-response |
| EU | European Union |
| FAS | Full Analysis set |

[redacted]

| | |
|---|---|
| FcεRII | Low affinity Immunoglobulin E Receptor II |
| [redacted] | [redacted] |
| GCP | Good Clinical Practice |
| G-GT | Gamma-glutamyl transpeptidase |
| H1-AH | H1-antihistamines |
| H2-AH | H2-antihistamines |
| [redacted] | [redacted] |
| HSS | Hives Severity Score |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IgE | Immunoglobulin E |
| IgG | Immunoglobulin G |
| IN | Investigator notification |
| 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) |
| LLOQ | lower limit of quantification |
| LTRA | Leukotriene Receptor Antagonist |
| mAb | Monoclonal antibody |
| MedDRA | Medical dictionary for regulatory activities |
| MoA | Mode of Action or mechanisim of Action |
| M&S | Modelling and Simulation |
| MSD | Meso Scale Discovery |
| NLME | Nonlinear mixed effect |
| PBO | Placebo |
| PCR | Protein to Creatinine Ratio |
| PD | Pharmacodynamics |
| PIP | Pediatric Investigational Plan |

[redacted]

| | |
|---|---|
| PK | Pharmacokinetics |
| PKPD | Pharmacokinetics-pharmacodynamics |
| PRO | Patient Reported Outcome |
| PSD | Premature subject/patient discontinuation |
| PT | Prothrombin time |
| q4w | Every 4 weeks |
| QM | Quality Management |
| QTcF | Fridericia's Correction Formula |
| RAN | Randomized set |
| RBC | Red blood cells |
| REB | Research Ethic Board |
| RES | Reticuloendothelial system |
| SAE | Serious adverse event |
| SAF | Safety set |
| s.c. | Subcutaneous |
| SBP | Systolic blood pressure |
| SMQ | Standardized MedDRA Queries |
| SOP | Standard operating procedure |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |
| TBL | Total bilirubin |
| UAS | Urticaria Activity Score |
| ULN | Upper Limit of Normal |
| UPDD | Urticaria Patient Daily Diary |
| US | United States |
| WBC | White blood cells |
| WHO | World Health Organization |
| WoC | Withdrawal of study consent |
| XS | Third party data |

[redacted]

## Glossary of terms

| | |
|---|---|
| Cohort | A specific group of patients/subjects fulfilling certain criteria |
| Control drug | Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug |
| Dosage | Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day) |
| Electronic Data Capture (EDC) | Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces.<br>EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care. |
| eSource DDE | eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications reduce the use of paper capture source data during clinical visits.<br>eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate. |
| Enrollment | Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol) |
| Investigational drug | The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.” |
| Medication number | A unique identifier on the label of each investigational drug package |
| Part | A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients/subjects with established disease and in those with newly-diagnosed disease. |
| Patient/subject ID | A unique number assigned to each patient upon signing the informed consent |
| Period | The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define |

[redacted]

| | |
|---|---|
| | the study phases and will be used in clinical trial database setup and eventually in analysis |
| Randomization number | A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment |
| Source Data/Document | Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource. |
| Study drug/ treatment | Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy |
| Study Treatment Discontinuation (TD) | When the patient permanently stops taking study treatment prior to the defined study treatment completion date |
| Variable | A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study |
| Withdrawal of study consent (WoC) | Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material |

[redacted]

## Protocol summary

| | |
|---|---|
| **Protocol number** | CQGE031C2202 |
| **Full Title** | A multicenter, randomized, double-blind, placebo-controlled phase 2b dose-finding study to investigate the efficacy and safety of ligelizumab (QGE031) in adolescent patients with Chronic Spontaneous Urticaria (CSU) |
| **Brief title** | A Phase 2b dose-finding study of QGE031 to investigate the efficacy and safety in adolescent patients with Chronic Spontaneous Urticaria (CSU) |
| **Sponsor and Clinical Phase** | Novartis<br>Phase 2b |
| **Investigation type** | Drug |
| **Study type** | Interventional |
| **Purpose and rationale** | This clinical study is designed to evaluate the pharmacokinetics, safety and efficacy of ligelizumab in adolescent patients from 12 to < 18 years of age, with chronic spontaneous urticaria.<br>The study will generate data to be analyzed in a separate modelling and simulation study with the objective of i) estimating the relative potency of ligelizumab in adolescent patients compared with adults and ii) proposing a posology for the future treatment of adolescent patients. |
| **Primary Objective(s)** | To evaluate the efficacy of QGE031 by assessing the change in the Urticaria Activity Score (UAS7) between baseline and Week 24. The primary endpoint will be change in UAS7 from baseline to Week 24. UAS7 is the sum of urticaria activity scores over a seven day period. |
| **Secondary Objectives** | • To evaluate the efficacy of ligelizumab doses with respect to UAS7 change from baseline at each protocol defined study visit<br>• To evaluate the efficacy of ligelizumab doses on complete response in Urticaria Activity Score (UAS7=0), Hives Severity Score (HSS=0), Itch Severity Score (ISS=0) at each protocol defined study visit<br>• To investigate the effects on ISS7 and HSS7 when compared to baseline at each protocol defined study visit<br>• To investigate the pharmacokinetics of ligelizumab<br>• To investigate the Pharmacodynamics of ligelizumab by change in total IgE over time |

[redacted]

| | |
|---|---|
| | • Change from baseline in the Children Dermatology Life Quality Index at each protocol defined study visit<br>• To evaluate the safety (including immunogenicity) and tolerability of ligelizumab. |
| **Study design** | This is a Phase 2b dose-finding, randomized, double-blind, parallel group, placebo controlled multicenter study in adolescent patients |
| **Population** | The study population will consist of approximately 48 adolescent males and females aged ≥ 12 and < 18 years who have been diagnosed with CSU and who remain symptomatic despite treatment with approved doses of H1-antihistamines. |
| **Key Inclusion criteria** | – Parent or legal guardian's written informed consent and child's assent, if appropriate, must be obtained before any study related activity or assessment is performed. Of note, if the subject reaches age of consent (age as per local law) during the study, they will also need to sign the corresponding study ICF (Informed Consent Form) at the next study visit.<br>– Male and female adolescent patients aged ≥ 12 to <18 years at the time of screening.<br>– Diagnosis of CSU refractory to approved doses of H1-antihistamines at the time of randomization, as defined by all of the following:<br>• The presence of itch and hives for at least 6 consecutive weeks at any time prior to enrollment despite current use of non-sedating H1-antihistamines during this time period<br>• UAS7 score (range 0 - 42) ≥ 16 and HSS7 (range 0 - 21) ≥ 8 during 7 days prior to randomization (Day 1)<br>• In-clinic UAS ≥ 4 on at least one of the screening visit days or Day 1 or a medical record of the presence of hives (confirmed and documented by a physician); patients must have been on H1-antihistamines for treatment of CSU at the time of in-clinic UAS at screening visit and/or time of the medical record of hives (for at least 3 days prior to the in-clinic UAS or medical record)<br>• CSU diagnosis for ≥ 6 months<br>– Willing and able to complete a daily symptom eDiary for the duration of the study and adhere to the study visit schedules. |

| | |
|---|---|
| | – Demonstration of compliance with the eDiary: patients should not have had any missing eDiary entries in the 7 days prior to randomization. Re-screening may be considered. |
| **Key Exclusion criteria** | – Clearly defined underlying etiology for chronic urticarias other than CSU. This includes the following:<br>• Inducible urticaria: urticaria factitia, cold-, heat-, solar-, pressure-, delayed pressure-, aquagenic-, cholinergic-, or contact-urticaria<br>• 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)<br>– Any other skin disease associated with chronic itching that might confound the study evaluations and results (e.g. atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis etc.)<br>– Previous exposure to omalizumab<br>– History of anaphylaxis |
| **Study treatment** | • Ligelizumab 120 mg per 1 mL liquid in vial<br>• Placebo 0 mg per 1 mL liquid in vial |
| **Efficacy assessments** | • Hives severity score (HSS)<br>• Itch severity score (ISS)<br>• Weekly Urticaria activity score (UAS7) |
| **Key safety assessments** | Safety evaluations include adverse events, physical examinations, laboratory values, vital signs and ECG |
| Other assessments | • Patient reported outcome ([redacted] CDLQI)<br>• PK/PD [redacted] |
| **Data analysis** | The primary variable is change in UAS7 from baseline to Week 24. UAS7 is the sum of HSS7 and ISS7. The primary variable will be analyzed descriptively in this protocol. In addition UAS7 from this study will be forwarded to a separate cross-study modelling and simulation PKPD analysis study to establish the dose of ligelizumab in the age group to be confirmed in Phase 3.<br>Secondary variables will also be analyzed using descriptive statistics, no formal statistical testing will be applied. |

[redacted]

| | |
|---|---|
| **Key words** | Anti-IgE, chronic spontaneous urticaria, hives severity score, itch severity score, urticaria activity score |

[redacted]

# 1 Introduction

## 1.1 Background

Chronic spontaneous urticaria (CSU) is defined as the spontaneous occurrence of itchy wheals, angioedema or both lasting for at least 6 weeks (Zuberbier et al 2014). The classic description of 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. CSU can be debilitating and is associated with intense itching and has a major impact on patient's well-being, suggested to be comparable to that of severe coronary artery disease (Greaves 2003, Powell et al 2007). The symptoms of urticaria and urticaria associated angioedema adversely affect daily activities and sleep (O'Donnell et al 1997).

The lifetime prevalence of CSU is approximately 1.8%, and 20% of CSU patients still have the disease after 20 years (Zuberbier et al 2010, Greaves 2000). CSU is more common in adults than in children. The pathogenesis of CSU is not fully clear. Up to 50% of CSU cases are associated with histamine-releasing autoantibodies against either the high-affinity IgE receptor (FcεRI) or IgE antibodies; the clinical significance of these autoantibodies is unclear, though there are suggestions that they may be involved in disease pathogenesis (Kaplan 2002, Sabroe and Greaves 2006). It has also been suggested that CSU patients' basophils may have distinct alterations in FcεRIα-mediated degranulation, independent of any potential role of autoantibodies (Eckman et al 2008).

A majority of CSU patients can be treated with $H_1$ antihistamine monotherapy, which is frequently used at doses up to four fold the approved dose (Zuberbier et al 2014). The use of $H_2$ antihistamines and leukotriene receptor antagonist (LTRA) are not as well supported by clinical studies, although they have been recommended in treatment guidelines for patients who were symptomatic despite treatment with $H_1$ antihistamines (Bernstein et al 2014). Systemic corticosteroids are sometimes added to the treatment regimens, however this is not recommended in treatment guidelines for long term treatment as patients are then at risk of adverse effects associated with chronic systemic corticosteroid exposure.

Omalizumab has demonstrated efficacy in patients with CSU and has been approved in several countries including europe (EU), United States (US), Japan and Switzerland as add-on therapy in adult and adolescent patients with symptoms despite treatment with antihistamines. The completed Phase 2 and Phase 3 studies demonstrated that omalizumab improves the signs and symptoms of urticaria (e.g., itch, hives) in patients with CSU who have failed treatment with $H_1$ antihistamines as well as those who have failed treatment with a combination of $H_1$ and $H_2$ antihistamines and a LTRA (Gober et al 2008, Kaplan et al 2008, Maurer et al 2013, Kaplan et al 2013). The primary endpoint, reductions from baseline in mean weekly itch-severity scores (ISS7) and all pre-specified secondary end points (e.g., change from baseline in UAS7 (urticaria activity score over 7 days), weekly score for hive numbers (HSS7), proportion of patients with UAS7 $\leq$6) were dose-responsive. The exact mechanism for how omalizumab does work in CSU patients is still not completely understood. The understanding of the mode of action (MoA) beyond suppression of free-IgE is evolving (Fine and Bernstein 2016, Chang et al 2015).

[redacted]

Revision of recent guidelines for the management of CSU patients confirmed that the therapeutic goal is complete remission of the signs and symptoms (i.e. UAS7 score of 0) (Zuberbier et al 2014); only about 40% of patients were free of symptoms at week 12 with the highest omalizumab dose tested (300 mg) in published Phase 3 studies (Maurer et al 2013, Kaplan et al 2013). Therefore, an unmet medical need exists in the CSU patient population despite the availability of omalizumab (Xolair®).

Whilst the disease is less studied in pediatric patients its understanding in the pediatric population is also starting to evolve (Maurer et al 2017). Urticaria can occur in all age groups. The same disease classification with the distinction of acute and chronic urticaria, the latter distinguishing between CSU and chronic inducible urticaria (CINDU), is currently used to classify urticaria in infants, children and adolescents. Whilst there appears to be no conclusive epidemiologic data in children and adolescents, chronic urticaria may be less common in the pediatric and adolescent population. However, similar as in adults there is an unmet medical need in children. Recent studies indicated low rate of resolution in the pediatric age group of 10% annually suggesting that CSU is a long lasting disease in children as well (Netchiporouk 2017).

Ligelizumab (QGE031) is a humanized monoclonal antibody (mAb) with higher affinity binding to human immunoglobulin E (IgE) than omalizumab. Upon binding, ligelizumab is able to block the interaction of IgE with both the high and low affinity IgE receptors (FcεRI and FcεRII). Ligelizumab is unable to mediate IgE receptor cross-linking and consequently histamine release (i.e. non-anaphylactogenic). When patients receive ligelizumab, circulating IgE is rapidly bound by the anti-IgE antibody and becomes inaccessible to IgE receptors on mast cells and basophils. IgE is necessary for the enhanced expression of the FcεRI seen in atopic patients, and a decrease in FcεRI expression on circulating basophils accompanies ligelizumab treatment. Other potentially beneficial effects from anti-IgE therapy include decreased IgE production, reduced B cell numbers and reduced cytokine production by T cells. Based upon the dose response observed in omalizumab CSU studies (Maurer et al 2013), superior affinity and pharmacodynamic outcomes of ligelizumab compared to omalizumab are anticipated to translate into superior clinical efficacy. Thus the ligelizumab development program in CSU aims to deliver a superior response compared with omalizumab with a similar safety profile in patients not adequately controlled with H1-antihistamines.

Whilst the disease presentation and medical need in adolescents appears to be the same as in adults there remains the question as to whether adolescent patients should receive the same dose as adults, as they do for Xolair®. Consequently, before enrolling adolescents in confirmatory Phase 3 studies, this small study will ascertain whether this age group benefits from ligelizumab and, through administration of two active dose levels and a separate exposure-response data analysis study, determine the relative potency of ligelizumab compared with adults.

## 1.2 Purpose

This clinical study is designed to evaluate the pharmacokinetics, safety and efficacy of ligelizumab in children from 12 to <18 years of age, with chronic spontaneous urticaria.

The study will generate data to be analyzed in a separate modelling and simulation study with the objective of i) estimating the relative potency of ligelizumab in adolescent patients compared with adults and ii) proposing a posology for the future treatment of adolescent patients.

The patient population will be treated with ligelizumab as an add-on therapy to approved doses of H1-antihistamines following the guideline on treatment of CSU (Zuberbier et al 2014).

# 2 Study objectives and endpoints

## 2.1 Objectives and related endpoints

The study data will be forwarded to a separate modelling and simulation study which will utilize exposure (drug concentrations, PK) and UAS7 response data (pharmacodynamics, PD) over the full duration of the clinical study, both whilst on treatment and through follow-up periods (Section 9.5.5).

**Table 2-1 Objectives and related endpoints**

| Objective(s) | Endpoint(s) |
|---|---|
| **Primary Objective** | **Endpoint for primary objective** |
| • Change in the Urticaria Activity Score (UAS7) between baseline and Week 24 | • The primary endpoint will be change in UAS7 from baseline to Week 24. UAS7 is the sum of urticaria activity scores over a seven day period. |
| **Secondary Objective(s)** | **Endpoint(s) for secondary objective(s)** |
| • To evaluate the efficacy of ligelizumab doses 24 mg and 120 mg with respect to UAS7 change from baseline | • UAS7 change from baseline over time (at each protocol defined study visit, in addition to the primary endpoint) |
| • To evaluate the efficacy of ligelizumab doses 24 mg and 120 mg on complete response in Urticaria Activity Score (UAS7=0), Hives Severity Score (HSS=0), Itch Severity Score (ISS=0) | • Rate of complete responders (UAS7=0, HSS7=0, ISS7 =0) over time (at each protocol defined study visit) |

[redacted]

| Objective(s) | Endpoint(s) |
|---|---|
| • To investigate the effects on ISS7 and HSS7 when compared to baseline | • Itch symptom score change from baseline over time (at each protocol defined study visit)<br>• Hives symptom score change from baseline over time (at each protocol defined study visit) |
| • To investigate the pharmacokinetics of ligelizumab | • Model-based estimate of clearance and volume of distribution using at least 7 samples |
| • To investigate the pharmacodynamics of ligelizumab | • Summary statistics of change in Total IgE over time. |
| • Change from baseline in the Children Dermatology Life Quality Index | • Children Dermatology Life Quality Index change from baseline over time (each protocol defined study visit) |
| • To evaluate the safety (including immunogenicity) and tolerability of ligelizumab (doses of 24 mg, 120 mg s.c. every 4 weeks) versus placebo in patients with CSU. | • Adverse events, ECG-intervals and interpretation, vital signs (blood pressure, pulse rate) and clinical laboratory evaluation |

[redacted]

[redacted]

| Objective(s) | Endpoint(s) |
| --- | --- |
| [redacted] | |

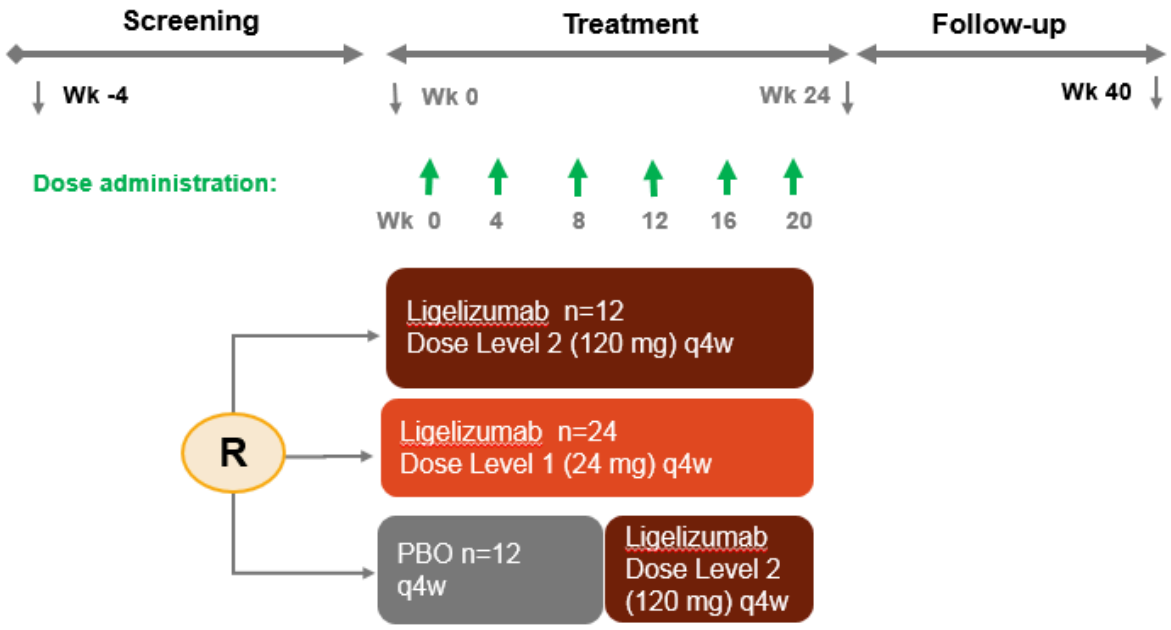
# 3 Investigational plan

## 3.1 Study design

This is a Phase 2b dose-finding, randomized, double-blind, parallel group, placebo controlled multicenter study in adolescent patients. The study design has been agreed with the PDCO (Pediatric Committee (EU)). It consists of 3 distinct study periods, as outlined in Figure 3-1 below. After the screening period (up to 4 weeks), at Day 1 patients are randomized into one of the three treatment arms in 1:2:1 fashion to ligelizumab 120 mg q4w vs. ligelizumab 24 mg q4w vs. placebo. During the 24 weeks of treatment, doses are administered on Day 1 then 4, 8, 12, 16, and 20 weeks after randomization. Subjects randomized to placebo will receive placebo on Day 1, Weeks 4 and 8; thereafter they will receive 120 mg ligelizumab on Week 12, 16 and 20 such that the same number of patients will, by the end of the study, receive 120 mg as 24 mg. Safety is assessed every 4 weeks; efficacy is primarily assessed using daily itch and hives scores summed into the weekly UAS7. The treatment period (24 weeks) is followed by a follow-up period of 16 weeks to a maximum of Week 40.

[redacted]

**Figure 3-1 Study design**




R: Randomization

## Screening

Patients will have up to 4 weeks for screening to establish eligibility for the study. Patients will be required to attend two visits during the screening period: at Day −28 and Day −7. The Day-7 can be brought forward depending on the availability of all laboratory results and the adherence to wash-outs related to non-allowed medication. Only in exceptional circumstances, when information concerning eligibility is outstanding (e.g. pending laboratory data), will an extended screening period be permitted.

For certain Inclusion/Exclusion criteria, re-screening may be allowed for patients who fail initial screening (see Section 4.1 and 4.2). Only one re-screening will be allowed. If a patient rescreens for the study, the patient and their legal guardian (where applicable) must sign a new informed consent and child's assent and he/she will be issued a new subject number. Informed consent for a rescreened patient must be obtained prior to performing any study-related assessments or collecting any data for the screening visit.

## Double-blind treatment period

On Day 1, eligible patients will be randomly assigned to receive ligelizumab 24 mg, 120 mg or placebo s.c. q4w during the 24-week double-blind treatment period. It is planned to allocate approximately 12 patients to the ligelizumab 120 mg q4w, 24 patients to the ligelizumab 24 mg q4w and 12 patients to the placebo arm q4w. Patients are expected to attend all site visits based on the assessment schedule (Table 6-1).

The last dose of study drug during the treatment period will be administered at the Day 141 (Week 20) study visit. As background medication, all patients in this study will continue to receive H1-antihistamines. Patients should remain on a stable treatment regimen throughout the study.

### Post-treatment follow-up period

After the completion of the double-blind treatment period, patients will enter a post-treatment follow-up period to allow for further characterization of the PK and response to ligelizumab as the drug washes out, collection of additional efficacy and safety data (e.g. relapse), and evaluation of the presence of anti-drug antibodies (ADAs). The follow-up period is 16 weeks with the last follow-up visit at day 281 (Week 40) corresponding to 20 weeks after the last treatment dose. No investigational treatment will be given during the post-treatment follow-up period, [redacted]. Patients will be required to visit the study center every four weeks during post-treatment period.

[redacted]

## 3.2 Rationale for study design

The study uses a placebo-controlled parallel-group design to allow the assessment of the treatment effects in an unbiased fashion and to account for placebo effects. The duration of the placebo treatment is restricted to twelve weeks to reduce the time adolescents are having symptoms that would require a more effective treatment. Patients having received placebo will be rolled over to the 120 mg ligelizumab arm to collect further safety and efficacy data and give them an opportunity for a pronounced symptom improvement upon continuation of the study.

[redacted]

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

[redacted]

[redacted]

[redacted]

## 3.4 Rationale for choice of comparator

The comparator treatment in this study is placebo.

Placebo is used in this study for the following reasons:

- to allow blinding of investigators and patients to their treatment and thereby minimize bias in the evaluation of safety and efficacy assessments,
- to allow assessment of the improvement in terms of CSU control for patients with disease not controlled by background medication who are treated with ligelizumab, in comparison to those continuing solely on background medication, and
- to allow the assessment of safety of ligelizumab on top of background medication compared to background medication alone

All patients, regardless of the treatment arm they are randomized to, will receive standard of care antihistamine therapy (approved doses) as background medication. [redacted] Although the signs and symptoms of CSU are burdensome to patients, placebo trials have been safely and successfully conducted in this indication (Kaplan et al 2013, Maurer et al 2013). Administration of placebo has been limited to 12 weeks while still allowing statistical comparison and maintenance of blinding to active versus placebo treatment. Patients having received placebo will be rolled over to the 120 mg ligelizumab arm to collect further safety and efficacy data and give them an opportunity for a pronounced symptom improvement upon continuation of the study. Patients have been allocated across the treatment arms according to the number needed to satisfy data requirements for optimal modeling and the number of placebo used has been kept to the minimum that still allows a meaningful analysis from the study data.

[redacted]

**Table 3-1 Number of study drug administrations**

| Treatment | Ligelizumab 120 mg arm | Ligelizumab 24 mg arm | Placebo/ligelizumab arm | |
|---|---|---|---|---|
| | | | Placebo period | Ligelizumab period (120 mg dose) |
| Ligelizumab 120 mg/mL liquid in vial | 1 x 1.0 mL | 1 x 0.2 mL | 0 | 1 x 1.0 mL |
| QGE031 Placebo 0 mg/mL liquid in vial | 0 | 0 | 1 x 1 mL | 0 |
| Total # of injections | 1 | 1 | 1 | 1 |
| Total volume injected | 1 mL | 0.2 mL | 1 mL | 1 mL |

## 3.5 Purpose and timing of interim analyses/design adaptations

No interim analysis is planned at the time of writing of this protocol, but may be added in case there is a need to provide information to health authorities, or to support program milestones.

## 3.6 Risks and benefits

This study is investigating the exposure-response of ligelizumab in adolescent patients with Chronic Spontaneous Urticaria. This will allow to identify the best dose regimen that is used in adolescent patients. At the point of enrollment of adolescents substantial safety data supporting the safe use of ligelizumab has been collected in adult patient population. [redacted] Overall ligelizumab is an investigational drug considered to be safe and well tolerated.

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

### Potential risks for study participants

[redacted]

[redacted]

[redacted]

[redacted]

**Blood sampling and volumes**

Blood volumes taken on single visit days and during the whole trial will be kept to a minimum to allow analyses of the key parameters specified for determining safety and pharmacodynamics effects and also to keep within the limits of health authority recommendations (EMA 2017).

## Possible benefits for the study participants

In a Phase 2b study in adults, ligelizumab was very effective for the treatment of CSU. In comparison to omalizumab, another effective IgE targeted antibody, ligelizumab was superior in suppressing the cardinal symptoms of CSU, hives and itch and led to freedom of symptoms in a higher percentage of patients than with omalizumab. Patients that receive a dose of 120 mg in the current study could be expected to achieve such a response. Also the patients who receive placebo in the first part of the study and who will receive 120 mg ligelizumab from week 12 onwards could expect a response as seen in adult patients with CSU. Whilst the patients who receive the lower dose of 24 mg may not achieve the same degree of symptom control as those who receive a 120 mg dose, they are, based on adult clinical data, expected to have a partial response. Note it is essential for the scientific integrity of the study that the lower dose (24 mg) is not fully effective as otherwise no dose-response analysis can be executed for the adolescent patient population. While all patients in the current study could achieve amelioration of their symptoms during the course of the study, it should however be noted that there may be patients who do not respond to ligelizumab treatment at all.

[redacted]

# 4 Population

The study population will consist of approximately 48 adolescent males and females aged ≥ 12 and < 18 years who have been diagnosed with CSU and who remain symptomatic despite treatment with approved doses of H1-antihistamines.

It is anticipated that approximately 100 patients need to be screened in order to randomize approximately 48 into the 3 treatment arms due to an estimated screening failure rate of approximately 50% (see Figure 3-1).

## 4.1 Inclusion criteria

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

1. Parent or legal guardian's written informed consent and child's assent, if appropriate, must be obtained before any study related activity or assessment is performed. Of note, if the subject reaches age of consent (age as per local law) during the study, they will also need to sign the corresponding study ICF (Informed Consent Form) at the next study visit.
2. Male and female adolescent patients aged ≥ 12 to < 18 years at the time of screening.
3. Diagnosis of CSU refractory to approved doses of H1-antihistamines at the time of randomization, as defined by all of the following:
   - The presence of itch and hives for at least 6 consecutive weeks at any time prior to enrollment despite current use of non-sedating H1-antihistamines during this time period
   - UAS7 score (range 0 - 42) ≥ 16 and HSS7 (range 0 - 21) ≥ 8 during 7 days prior to randomization (Day 1)
   - In-clinic UAS ≥ 4 on at least one of the screening visit days or Day 1 or a medical record of the presence of hives (confirmed and documented by a physician); patients must have been on H1-antihistamines for treatment of CSU at the time of in-clinic UAS at screening visit and/or time of the medical record of hives (for at least 3 days prior to the in-clinic UAS or medical record)
   - CSU diagnosis for ≥ 6 months
4. Willing and able to complete a daily symptom e-Diary for the duration of the study and adhere to the study visit schedules.
5. Demonstration of compliance with the eDiary: patients should not have had any missing eDiary entries in the 7 days prior to randomization. Re-screening may be considered.

## 4.2 Exclusion criteria

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

[redacted]

1. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of the other investigational drugs prior to Visit 1, whichever is longer.
2. History of hypersensitivity to any of the study drugs or its components, or to drugs of similar chemical classes (i.e. to murine, chimeric, or human antibodies).
3. Clearly defined underlying etiology for chronic urticarias other than CSU. This includes the following:
   - Inducible urticaria: urticaria factitia, cold-, heat-, solar-, pressure-, delayed pressure-, aquagenic-, cholinergic-, or contact-urticaria
   - 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. Patients with a stool examination positive for ova or parasites (at screening); re-screening may be considered if absence of persisting infection has been demonstrated in repeat stool examinations.
5. Any other skin disease associated with chronic itching that might confound the study evaluations and results (e.g. atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis etc.)
6. Previous exposure to ligelizumab
7. Previous exposure to omalizumab
8. History or evidence of ongoing alcohol or drug abuse, within the last 6 months prior to randomization
9. Inability to comply with study and follow-up procedures
10. Use of prohibited treatment detailed in protocol (Table 5-1)
11. Contraindications to or hypersensitivity to fexofenadine, loratadine, cetirizine, rupatadine, bilastine or epinephrine or any of the ingredients
12. History of anaphylaxis
13. History of malignancy of any organ system within the past 5 years (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)
14. Presence of clinically significant cardiovascular (e.g. congenital heart diseases with significant persistent cardiac damage), 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 or compromise the safety of the patients, interfere with evaluation or interpretation of the study results, or preclude completion of the study

[redacted]

15. Medical examination or laboratory findings that suggest the possibility of decompensation of co-existing conditions for the duration of the study. Any items that are cause for uncertainty will be reviewed with the investigator
16. 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 1.5 x upper limit of normal (ULN) at Visit 1
17. History or presence of renal disease and/or estimated glomerular filtration (eGFR) rate of <35ml/min as calculated by the Schwartz formula at Visit 1
18. Platelets < 100 000/µL at Visit 1
19. History of long QT syndrome or whose QTcF (Fridericia) measured at Visit 1 is prolonged (> 450 ms for males or > 460 ms for females) and confirmed by a central assessor (these patients should not be re-screened).
20. Pregnant or nursing (lactating) females, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive B-hCG laboratory test
21. Women of child-bearing potential, defined as all females physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study medication and up to 20 weeks (5 times the terminal half-life) after stopping medication. Effective contraception methods include:
    - Total abstinence (when this is in line with the lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
    - Barrier methods of contraception:
        - Male or female condom with or without spermicide
        - Cap, diaphragm, or sponge with spermicide
    - 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.

[redacted]

# 5 Treatment

## 5.1 Study treatment

### 5.1.1 Investigational and control drugs

- Ligelizumab 120 mg per 1 mL liquid in vial
- Placebo 0 mg per 1 mL liquid in vial

During the 24 weeks of the treatment period, study drugs will be administered as per Table 3-1 at the clinic.

Novartis Drug Supply Management (DSM) will provide these investigational products as open-label patient-specific supplies.

The investigational products will be supplied as a liquid in vial dosage form.

### 5.1.2 Additional treatment

No other additional treatment beyond investigational treatment (ligelizumab, placebo) is requested for this trial. Patients will continue to use their background medication (standard of care) with a stable regimen during the study.

[redacted]

## 5.2 Treatment arms

Patients will be assigned to one of the following three treatment arms in a ratio of 1:2:1.

A. Ligelizumab 120 mg: 1 injection of ligelizumab (1mL) every 4 weeks from Day 1 to Week 20 (inclusive)

B. Ligelizumab 24 mg: 1 injection of ligelizumab (0.2mL) every 4 weeks from Day 1 to Week 20 (inclusive)

C. Placebo 0 mg: 1 injection of placebo (1 mL) at Day 1, Week 4, Week 8; followed by the same treatment as in Treatment A from week 12 onwards to week 20 (inclusive)

## 5.3 Treatment assignment and randomization

At Day 1, all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will inform the independent unblinded site personnel (pharmacist or authorized delegate) to contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the package of investigational treatment to be dispensed to the

[redacted]

patient and will specify the volume of dose. The randomization number will not be communicated to the caller.

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

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

## 5.4 Treatment blinding

Patients, investigator staff and personnel performing the study assessments will remain blinded to the identity of the treatment from the time of randomization until final database lock. Data managers, programmers, statisticians, pharmacometricians and clinical experts of the Novartis trial team will also remain blinded until final database lock. An unblinded study monitor will visit the study site to monitor study drug related administration (see Section 8.1)

The following measures will be applied to keep the patient and study personnel blinded despite differences of the investigational treatments in appearance, viscosity and volume:

The study drug must be prepared by an independent unblinded pharmacist (or authorized delegate) and administered by an independent unblinded administrator. If an unblinded pharmacist is not available preparation and administration of drug may also be performed by a single independent unblinded site person if he/she is authorized to do both. Any site staff involved in the preparation and / or administration of study drug must not be involved in any of the study assessments.

- Preparation of the investigational drug must be done in a separate space/room where patients and study personnel have no access.
- To blind the liquid volume in the syringe, the syringe must be covered by a strip of opaque tape. The differences in length of the syringe plunger, related to the differences in the volume, should also be covered by the way of administration (see pharmacist manual).
- The independent unblinded authorized site persons (pharmacist/administrator) should not communicate the appearance, the volume and any perceived sensation associated with the administration of the investigational drug.

The procedural details relating to treatment blinding and unblinded drug administration will be described in the Pharmacist Manual which will be provided separately.

1. Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions:

[redacted]

- Bioanalyst (PK): to enable identification of samples from the ligelizumab treatment arms of the study to facilitate bioanalysis.
- Independent personnel (external to Novartis) involved in monitoring anaphylaxis and pre-malignancy/malignancy events (Adjudication Committee members) if such events would occur.

Unblinding during the conduct of the trial will only occur in the case of patient emergencies (Section 5.5.9). The patients, investigator staff and persons performing the assessments will remain blinded until after final database lock.

Health authorities will be granted access to unblinded data if needed.

The appropriate personnel from the study site and Novartis will assess whether study treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason. Study treatment must be discontinued after emergency unblinding.

## 5.5 Treating the patient

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

### 5.5.1 Patient numbering

Each patient is uniquely identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each patient is numbered uniquely across the entire database.

Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number available in the electronic data capture (EDC) system. 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.

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 appropriate CRF.

### 5.5.2 Dispensing the study drug

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

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the “3” treatment arms and a specific visit or dose/dose level. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient’s unique subject number.

[redacted]

### 5.5.3 Handling of study and additional treatment

#### 5.5.3.1 Handling of study treatment

Study treatment must be received by an independent unblinded designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the unblinded designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) Quality Assurance.

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

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

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

#### 5.5.3.2 Handling of additional treatment

The [redacted] concomitant medication allowed in the trial is described in Sections 5.5.6 and 5.5.7.

### 5.5.4 Instructions for prescribing and taking study treatment

The independent study drug administrator will administer the study treatment to the patient during the study visit without engaging in any unnecessary interactions that may have the potential to unblind the patient or any of the study site personnel. All study treatments will be administered at the hospital/clinic.

The injection 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 injection is administered subcutaneously after aspiration of the plunger of the syringe. If blood appears at the hub or blood is withdrawn into a syringe, the needle is removed without administration of the dose and the injection site is changed.

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

Patients will remain on-site for observation for a period of 2 h post-dose for all study drug administration visits. 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

[redacted]

Committees Joint task Force (Cox 2007) for the anti-IgE therapy currently available (omalizumab). As described in the Investigator's Brochure (IB), the site needs to ensure readiness to react to anaphylactic events (e.g. have available injectable epinephrine, antihistamine, corticosteroids, intravenous supplies, oxygen, an oral airway, Ambu bag, and the ability to transport a patient rapidly to an emergency department/hospital).

The dosing schedule for individual patients will be the same within a treatment arm and will be assigned at randomization (Day 1).

All study drug dosages prescribed and dispensed to the patient and all dose changes or missed administrations during the study must be recorded on the appropriate CRF page.

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

### 5.5.5 Permitted dose adjustments and interruptions of study treatment

Study drug dose adjustments and interruptions are not permitted.

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

[redacted]

### 5.5.7 Concomitant medication

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

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started. Approved doses of continuous H1-antihistamine therapy provided as concomitant medication should be kept stable during the study duration.

[redacted]

### 5.5.8 Prohibited medication

Use of the class of treatments displayed in Table 5-1 is NOT allowed after start of first screening visit. The minimum required period without prohibited treatment before the first screening visit (Visit 1) 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.

**Table 5-1 Prohibited treatment**

| **Medication** | **Minimum required period without medications before Visit 1** |
|---|---|
| Anti-IgE therapy | no prior use allowed |
| Routine (daily or every other day during more than one consecutive day /month) doses of systemic corticosteroids | 30 days |
| Beta-blocker therapy | 7 days |
| Leukotriene antagonists | Stop at visit 1 |
| H2-antihistamines | Stop at visit 1 |
| H1-antistamines with sedative effects | Stop at visit 1 |
| Constant use of H1-antihistamines at dose levels that are not labeled (approved) | Stop at visit 1 |
| Routine (daily or every other day during 5 or more consecutive days) doses of hydroxychloroquine | 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 |
| Inactivated virus vaccination | 48 hours prior to Visit 110, 120, 130, 140, 150 and 160, |
| Live attenuated vaccine | 30 days |

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.

The table is not considered all inclusive. Medication should be assessed for adherence to the indication and other inclusion/exclusion criteria.

[redacted]

### 5.5.9 Emergency breaking of assigned treatment code

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

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- subject number

In addition, oral and written information to the patient must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time. The appropriate personnel from the site and Novartis will assess whether investigational treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

Patients who discontinue investigational treatment should NOT be considered withdrawn from the study. They will be expected to perform the Visit 170 End of treatment/Study treatment discontinuation (EOT/TD) assessments four weeks after their last dose and will be expected to perform all follow-up assessments (Visit 180-210). 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 also contact the IRT to register the patient's discontinuation from investigational treatment.

## 5.6 Study completion and discontinuation

### 5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol. The investigator must call or logon to the IRT system to record the patient completion. No post-study treatment is planned for this trial.

### 5.6.2 Discontinuation of study treatment

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

[redacted]

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

Investigational treatment must be discontinued under the following circumstances:

- Patient/guardian wish
- Pregnancy (see Section 6.5.6 and Section 7.6)
- Any situation in which study participation might result in a safety risk to the patient
- Adverse events for which continued exposure to the study drug would be detrimental
- Abnormal renal laboratory results requiring discontinuation (for guidance under which conditions a study drug discontinuation needs to be considered see Appendix 3)
- Abnormal liver laboratory results requiring discontinuation (for further guidance under which conditions study drug discontinuation should be considered see Appendix 2)
- Platelets < 75000/µL
- Unblinding of study treatment other than to authorized personnel (see Section 5.4) for any reason
- 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 6.
    - Lower or upper respiratory organs: Respiratory failure with or without loss of consciousness
    - Or cardiovascular system: Hypotension with or without loss of consciousness
- Requirement of emergency use of epinephrine (or a similar emergency intervention) due to anaphylactic or anaphylactoid reaction
- Any other protocol deviation that results in a significant risk to the patient's safety

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

Patients who discontinue investigational treatment should NOT be considered withdrawn from the study. They will be expected to perform the end of treatment/study treatment discontinuation visit (EOT/TD) and all follow up visits. 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 and their legal guardians.

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

[redacted]

If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.9

### 5.6.3 Withdrawal of informed consent

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

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- Does not allow analysis of already obtained biologic material

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

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

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

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment table below.

### 5.6.4 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her planned end of study visit has passed.

### 5.6.5 Early study termination by the sponsor

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

[redacted]

# 6 Visit schedule and assessments

Table 6-1 lists all of the assessments.

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

All patients who complete the treatment period will be expected to attend all follow-up visits (Week 28 – Week 40). Patients who withdraw early will be contacted for safety evaluations every 4 weeks following their last study drug administration until 20 weeks post withdrawal. Documentation of attempts to contact the patient should be recorded in the source documentation.

[redacted]

**Table 6-1 Assessment schedule**

| Period | Screening | | Double-blind Treatment | | | | | | | Post-treatment Follow-Up | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 1 | 2 | 110 | 120 | 130 | 140 | 150 | 160 | 170 or 1998 (EOT/ TD) | 180 | 190 | 200 | 210 or 1999 (EOS/P SD) |
| Day | -28 to -14 | -7 | 1 | 29 | 57 | 85 | 113 | 141 | 169 | 197 | 225 | 253 | 281 |
| Week (R = randomization week) | -4 to -2 | -1 | R | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 |
| Obtain Informed Consent | X | | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | X | | | | | | | | | | |
| Demographic data | X | | | | | | | | | | | | |
| Relevant medical history | X | | | | | | | | | | | | |
| Family malignancy history – only to be completed if patient develops a malignancy event | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Prior urticaria treatment | X | | | | | | | | | | | | |
| Prior and Concomitant medication usage | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Surgery and procedures | X | X | X | X | X | X | X | X | X | X | X | X | X |

[redacted]

| Period | Screening | | Double-blind Treatment | | | | | | | Post-treatment Follow-Up | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 1 | 2 | 110 | 120 | 130 | 140 | 150 | 160 | 170 or 1998 (EOT/ TD) | 180 | 190 | 200 | 210 or 1999 (EOS/P SD) |
| Day | -28 to -14 | -7 | 1 | 29 | 57 | 85 | 113 | 141 | 169 | 197 | 225 | 253 | 281 |
| Week (R = randomization week) | -4 to -2 | -1 | R | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 |
| Re-screening (re-screening CRF should be recorded if the patient is re-screened) | X | | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | | |
| Study drug/placebo administration | | | X | X | X | X | X | X | | | | | |
| Randomization | | | XS | | | | | | | | | | |
| Contact IRT | XS | | XS | XS | XS | XS | XS | XS | XS | | | | XS |
| In-clinic assessment of UAS and check of medical record for hives | X | X | X | | | | | | | | | | |
| **ePROs** should be completed prior to any other assessment | | | | | | | | | | | | | |
| Dispense Patients' e-Diary | S | | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | | |

| Period | | Screening | | Double-blind Treatment | | | | | | | Post-treatment Follow-Up | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | 1 | 2 | 110 | 120 | 130 | 140 | 150 | 160 | 170 or 1998 (EOT/ TD) | 180 | 190 | 200 | 210 or 1999 (EOS/P SD) |
| Day | | -28 to -14 | -7 | 1 | 29 | 57 | 85 | 113 | 141 | 169 | 197 | 225 | 253 | 281 |
| Week (R = randomization week) | | -4 to -2 | -1 | R | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 |
| Patients' e-Diary (download and review) Includes the urticaria patient daily diary (UPDD) [redacted] | | | XS | XS | XS | XS | XS | XS | XS | XS | XS | XS | XS | XS |
| CDLQI (Children Dermatology Life Quality Index) | | | | XS | XS | XS | XS | XS | XS | XS | XS | XS | XS | XS |
| **Laboratory tests** | | | | | | | | | | | | | | |
| Stool ova and parasite evaluation; if clinical signs or symptoms of parasitosis develop at any time prior to the last study drug administration, additional assessments for parasitic conditions will be performed | | X | | | | | | | | | | | | X |
| | Hematology (plus INR at all visits except Day -7, | XS | | XS | XS | XS | XS | XS | XS | XS | XS | XS | XS | XS |

[redacted]

| Period | | Screening | | Double-blind Treatment | | | | | | | Post-treatment Follow-Up | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | 1 | 2 | 110 | 120 | 130 | 140 | 150 | 160 | 170 or 1998 (EOT/ TD) | 180 | 190 | 200 | 210 or 1999 (EOS/P SD) |
| Day | | -28 to -14 | -7 | 1 | 29 | 57 | 85 | 113 | 141 | 169 | 197 | 225 | 253 | 281 |
| Week (R = randomization week) | | -4 to -2 | -1 | R | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 |
| Blood sampling | Day 1, Week 24 and Week 40) | | | | | | | | | | | | | |
| | Clinical chemistry including Bilirubin (all indicated visits), [redacted] | XS | | XS | XS | XS | XS | XS | XS | XS | XS | XS | XS | XS |
| | Serum pregnancy B-hCG test (for females of child bearing potential) | XS | | | | | | | | | | | | XS |
| | PK (ligelizumab)[1] | | | XS | XS | XS | XS | XS | XS | XS | | XS | | XS |
| | PD (total IgE)[1] | | | XS | XS | XS | XS | XS | XS | XS | | XS | | XS |
| | Anti-Drug/ligelizumab antibodies (ADA)[1] | | | XS | | XS | | XS | | XS | | XS | | XS |

[redacted]

| Period | | Screening | | Double-blind Treatment | | | | | | | Post-treatment Follow-Up | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | 1 | 2 | 110 | 120 | 130 | 140 | 150 | 160 | 170 or 1998 (EOT/ TD) | 180 | 190 | 200 | 210 or 1999 (EOS/P SD) |
| Day | | -28 to -14 | -7 | 1 | 29 | 57 | 85 | 113 | 141 | 169 | 197 | 225 | 253 | 281 |
| Week (R = randomization week) | | -4 to -2 | -1 | R | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 |
| [redacted] | | | | | | | | | | | | | | |
| Urine samplin g | Urinalysis<br>When a dipstick evaluation is abnormal, e.g. positive for WBC and/or blood, a microscopic examination including RBC and WBC | | XS | | XS | | XS | | | XS | | | | XS |

[redacted]

| Period | | Screening | | Double-blind Treatment | | | | | | | Post-treatment Follow-Up | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | 1 | 2 | 110 | 120 | 130 | 140 | 150 | 160 | 170 or 1998 (EOT/ TD) | 180 | 190 | 200 | 210 or 1999 (EOS/P SD) |
| Day | | -28 to -14 | -7 | 1 | 29 | 57 | 85 | 113 | 141 | 169 | 197 | 225 | 253 | 281 |
| Week (R = randomization week) | | -4 to -2 | -1 | R | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 |
| | should be done by central lab | | | | | | | | | | | | | |
| | Urine Pregnancy Test if positive to be confirmed by serum B-hCG , should be done be central lab | S | S | S | S | S | S | S | S | S | S | S | S | S |
| **Safety** | | | | | | | | | | | | | | |
| Physical Exam<br>(Physical exam between Day -28 to Day -14 is a complete exam but subsequent physical exams maybe limited to a short exam) | | S | S | S | S | S | S | S | S | S | S | S | S | S |
| Vital signs | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Height and Weight (at Visits 170 and 210 only body weight will be measured) | | X | | | | | | | | X | | | | X |

[redacted]

| Period | Screening | | Double-blind Treatment | | | | | | | Post-treatment Follow-Up | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 1 | 2 | 110 | 120 | 130 | 140 | 150 | 160 | 170 or 1998 (EOT/ TD) | 180 | 190 | 200 | 210 or 1999 (EOS/P SD) |
| Day | -28 to -14 | -7 | 1 | 29 | 57 | 85 | 113 | 141 | 169 | 197 | 225 | 253 | 281 |
| Week (R = randomization week) | -4 to -2 | -1 | R | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 |
| ECG (three ECG measurements to be taken at approximately 1 minute intervals at Visit 1 and 170, all other visits a single ECG measurement will be recorded) | XS | | | | XS | | | | XS | | | | XS |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Others** | | | | | | | | | | | | | |
| Study disposition | | | | | | | | | X | | | | X |

EOT/TD = End of treatment / Study treatment discontinuation; EOS / PSD = End of Study / Premature subject/patient discontinuation
X = assessment to be recorded on clinical data base
S = assessment to be recorded on source documentation only
XS =third party data

[1] all samples to be taken pre-dose on dosing days

[redacted]

## 6.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the next period will have reason for not being treated, demographics, 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 to be collected on all patients include age, sex, race, ethnicity. Relevant medical history/current medical condition present before signing the informed consent will be captured. Where possible, diagnoses, and not symptoms, will be recorded. In addition, data on patient's family history on malignancies is collected on the respective CRF page for those patients who during the trial experience an event related to any malignancies.

## *6.3* Treatment exposure and compliance

Patients will receive one subcutaneous injection every 4 weeks at six visits during the double-blind treatment period. Compliance is assured as study drug needs to be administered by independent unblinded study personnel via subcutaneous injection at the site. Administration of study drug should be recorded in the source documents and the corresponding CRF for each administration.

## 6.4 Efficacy

The efficacy assessments consist of Patient Reported Outcomes (PROs) that have been reported in the patient eDiary. The following efficacy variables will be assessed during the study:

- Hives severity score (HSS)
- Itch severity score (ISS)
- Weekly Urticaria Activity score (UAS7)
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Angioedema occurrence
- Number of calls to doctor or nurse

### 6.4.1 eDiary assessments for patient reported outcomes

All patients will be provided with a handheld electronic device (eDiary) that consists of the Urticaria Patient Daily Diary (UPDD), [redacted] and the Children Dermatology Life Quality Index (CDLQI)

[redacted]

The patients will receive clear instructions on the completion of the eDiary twice daily or once daily depending on the questions. Sites and patients will receive appropriate training and guidance on the use of the eDiary device.

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

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

#### 6.4.1.1 Urticaria Patient Daily Diary (UPDD)

UPDD includes UAS7 (itch and hives) for clinical symptoms, [redacted] angioedema occurrence and its management (Appendix 3).

##### 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 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.

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 (7-12/12 hours) |
| 3 | Severe (>12 hives/12 hours) |

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 at least 4 non-missing daily scores within the 7 days prior to the 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 diary score, multiplied by 7.

[redacted]

- If there are less than 4 non-missing daily scores within the prior 7 days, then the weekly score is missing for the week.

#### 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 diary 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) |

#### 6.4.1.1.3 The 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.

[redacted]

[redacted]

[redacted]

6.4.1.1.7 Angioedema occurrence

**Table 6-6 Actions/treatments for Angioedema**

| Score | Action/treatments |
|---|---|
| 0 | Did nothing |
| 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 |

[redacted]

#### 6.4.1.1.8 Number of calls to doctor or nurse

The number of calls to doctor, nurse or nurse practitioner because of the patient's skin condition will be recorded once daily in the eDiary by the patient.

[redacted]

### 6.4.2 Children Dermatology Life Quality Index (CDLQI)

The Children Dermatology Life Quality Index questionnaire is designed for use in children, i.e patients from age 4 to age 16. It will also be deployed to any 17 year olds participating in this trial. It is a 10-item dermatology-specific health-related quality of life measure. Patients rate their dermatology symptoms as well as the impact of their skin condition on various aspects of their lives. An overall score will be calculated as well as for the following domains: Symptoms and Feelings, Leisure, School or Holidays, Personal Relationships, Sleep, Treatment. The patient will complete this questionnaire on the eDiary at the hospital/clinic as per the assessment schedule in Table 6-1.

### 6.4.3 Other assessments: In-clinic assessment of UAS

The UAS will be recorded by the Investigator at the site by rating the patient's number of urticaria lesion (hives) and interviewing the patient for the assessment of pruritus reflective of the patient's condition over the 12 hours prior to the visit (Table 6-7).

**Table 6-7 In-clinic UAS**

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

### 6.4.4 Appropriateness of efficacy assessments

The main CSU symptoms are hives and intense itch, therefore, it is appropriate to evaluate clinical response through use of the UAS, a composite endpoint that measures both of these symptoms.

In the past literature 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, hives are

[redacted]

more objective since they can be counted on the body and thus are more easily quantifiable, whereas the itch is a subjective, non-specific sensation which could be of different origin.

Thus, in this study, the primary efficacy endpoint will be the combination of both weekly hives and itch severity as covered by the UAS7 score. In addition each symptom score component (i.e. itch and hives score during the last seven days, ISS7 and HSS7 are analyzed as secondary endpoints.

Disease recurrence after study drug is withdrawn will be measured during the post-treatment follow-up period. For all patients, symptom scores will be measured during both the treatment and post-treatment follow-up periods. The assessment of onset and offset of effect is also important to inform the model based analysis that is planned based on the data set collected in this study.

## 6.5 Safety

Main safety and tolerability assessments include:

- AEs and SAEs. AEs leading to treatment discontinuation; Events of special interest are injection site reactions, 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.

A short physical exam will include the examination of general appearance and vital signs (see section 6.5.2). A short physical exam will be at all visits starting from the first screening visit except where a complete physical examination is required (see Table 6.1).

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after signing the informed consent 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 blood pressure 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 using a validated device with an appropriately sized cuff. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

[redacted]

Clinically notable vital signs are defined in Appendix 1

### 6.5.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

### 6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens detailed in this section unless noted otherwise. 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 (RBC) count, white blood cell (WBC) 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 [redacted] 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

A midstream urine sample (approximately 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments. If possible, a morning sample should be used to eliminate benign orthostatic (postural) proteinuria. Semi-quantitative “dipstick” evaluation for specific gravity, glucose, protein, bilirubin, ketones, leukocytes and blood will be performed at site. 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 microscopic examination including RBC and WBC. Details on collection of urine for analysis by central laboratory are provided to investigators in the laboratory manual.

#### 6.5.4.4 Assessment of parasitic infections

Reduction in IgE levels may confer increased susceptibility to parasitic infections. The evidence of risk of acquiring or activating infections with helminthes is not confirmed and suspected to be low after treatment with anti-IgE such as ligelizumab and Omalizumab.

As indicated in Section 4.2 (exclusion criteria), all patients will need to have a stool sample collected at screening.

In case the patient is unable to provide a stool sample, they should take a sample pot home to bring or send in a stool sample as soon as possible after the visit, preferably the day after.

[redacted]

Stool samples and additional assessment for parasitic disease will be examined for ova and parasites by the central laboratory. Negative tests must be documented before initiation of dosing.

If diarrhea or other clinical symptoms or signs of helminth infection develop at any time prior to the last study drug administration, additional assessments for parasitic conditions need to be performed.

A stool sample will also be collected at the end of study visit (EOS).

### 6.5.5 Electrocardiogram (ECG)

Standard 12 lead ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia 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 1 and 170; single ECGs will be recorded at all other visits where ECG is assessed. For each ECG performed, original traces and identical duplicate traces will be produced. The original trace will be sent electronically to the Contract Research Organization (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 patient's number, the date and actual time of the tracing, and Study Code (CQGE031C2202) must appear on each page of the ECG tracing. 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/AE CRF page, as appropriate. 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.

### 6.5.6 Pregnancy and assessments of fertility

Females of child-bearing potential are defined as all females physiologically capable of becoming pregnant. This includes female adolescent patients who have had their menarche or who experience their menarche during the study.

A urine pregnancy test and a serum B-hCG will be performed for all females of child-bearing potential according to the schedule in Table 6-1. A positive urine pregnancy test requires immediate interruption of study medication until serum B-hCG is performed and found to be negative. If positive, the patient must be discontinued from the investigational treatment. However, a patient may choose to remain in the study should she become pregnant, and be followed according to the protocol-defined study visits. Additional pregnancy tests may be performed at the investigator's discretion during the study.

All female adolescents and their parents/caregivers should be informed about the potential risks of pregnancy and the need to prevent pregnancy during the study.

Urine pregnancy test kits will be provided to the sites by the Central Lab.

[redacted]

### 6.5.7 Anaphylaxis assessment

An adjudication committee (AC) will be put in place to determine whether cases identified through a search algorithm based on the Standardized MedDRA Queries (SMQ) 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 cardiovascular events

An AC will be put 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

In addition to standard safety assessments that are commonly used in to assess the safety of patient populations, events of special interest that might possibly related to the mode of action of ligelizumab such as anaphylaxis, malignancies, and cardio-cerebrovascular events will be monitored and will be adjudicated by expert adjudication committees.

## 6.6 Other assessments

### 6.6.1 Resource utilization

Healthcare utilization (calling a doctor, nurse, or nurse practitioner) will be reported by the patient in the daily diary. The action(s) taken by the patient in response to their angioedema will be also reported in the daily diary.

### 6.6.2 Pharmacokinetics/Pharmacodynamics

PK (ligelizumab) and PD (total IgE (free IgE plus IgE bound to ligelizumab)) will be measured in serum every 4 weeks during the treatment period and at selected visits during washout. A single blood collection will account for ligelizumab and total IgE. Where sample collections coincide with dosage administration then the blood sample must be taken immediately before the dose is administered.

Serum IgE levels will also be assessed prior to study drug administration at randomization visit (Visit 110).

**Blood collection and processing**

All blood samples will be taken from the contra-lateral arm of the injection by either direct venipuncture or an indwelling cannula inserted in a forearm vein. All samples will be given a

[redacted]

unique sample number (as listed in Appendix 5). The actual sample collection date and time will be entered on the PK blood collection page of the CRF.

Detailed instructions for blood sample collection, processing, storage and shipment are provided in the lab manual and flow charts prepared by the Central Laboratory.

[redacted]

**Pharmacokinetic calculations**

Due to the sparse nature of PK sampling in this study conventional non-compartmental analysis will not be conducted. Instead the data from this study will be added to a pooled dataset from different studies and analyzed with nonlinear mixed effect models based analysis (NLME) (see Section 9.5.5)

Further details on sample collection, numbering, processing and shipment can be found in the Laboratory Manual

[redacted]

[redacted]

# 7 Safety monitoring

## 7.1 Adverse events

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

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

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

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 7.2):

1. The severity grade.
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be ‘Not suspected’. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.

[redacted]

4. whether it constitutes a SAE (see Section 7.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment.

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

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn

6. its outcome i.e., its recovery status or whether it was fatal

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

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

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

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

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

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subjects with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

## 7.2 Serious adverse events

### 7.2.1 Definition of SAE

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

- fatal
- life-threatening

[redacted]

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

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

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

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

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

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

### 7.2.2 SAE reporting

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

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a

[redacted]

different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

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

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

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

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

## 7.3 Liver safety monitoring

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

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

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

Please refer to Table 13.1 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 13.1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 13.2. Repeat liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

[redacted]

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event

These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

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

## 7.4 Renal safety monitoring

Routine renal safety monitoring includes the assessment of creatinine, BUN, urine dipstick measurements. eGFR will be calculated using the Schwartz formula. For diagnosis and actions related to renal adverse events please refer to Appendix 3.

## 7.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the appropriate CRF, 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.

[redacted]

**Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse**

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

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

## 7.6 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The newborn will be followed up to 3 months after the birth to collect any information on any development issue that would not be seen at birth.

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

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

## 7.7 Other safety assessments

### 7.7.1 Immunogenicity assessments

The presence of anti-QGE031 antibodies will be determined in samples collected prior to the first dose and on Week 8, 16, 24, 32 and 40.

The presence of anti-QGE031 antibodies will be assayed using a MSD-based homogenous bridging assay. In this assay anti-QGE031 antibodies are captured in solution by combination of biotinylated and ruthenium-labeled forms of ligelizumab. Formed complex is subsequently detected by the ECL using streptavidin coated plates (MSD). Interference of endogenous IgE will be minimized by pre-treatment with an anti-IgE antibody coupled to magnetic beads to remove IgE and interference with ligelizumab will be minimized by an acid-treatment step to disrupt pre-existing anti-QGE031-QGE031 complexes. The detailed method to assess immunogenicity will be described in the bioanalytical raw data of the study and in the bioanalytical data report.

[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 data capture requirements (i.e. eSource DDE or eCRFs) 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 data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs. 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 data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients/subjects will be disclosed.

## 8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

[redacted]

## 8.3 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

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. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis personnel (or designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

## 8.4 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify or terminate a trial.

Specific details regarding composition, responsibilities, data monitoring and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

[redacted]

## 8.5 Adjudication Committee

The role of the Adjudication Committee (AC) is to ensure that all treatment outcomes are judged uniformly, using standard criteria and processes. The AC will be composed of clinical experts to evaluate disease progression and harmonize endpoint assessment criteria using data provided by the sponsor.

All personnel involved in the adjudication process will remain blinded to treatment allocation throughout the trial. Specific details regarding endpoint definitions can be found in the adjudication charter.

# 9 Data analysis

The analysis will be conducted on all patient data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

## 9.1 Analysis sets

The randomized set (RAN), which comprises all randomized patients, regardless of whether or not they actually received study medication, will be used for summaries of patient disposition and analysis sets.

The Full Analysis set (FAS) comprises all patients to whom study treatment has been assigned. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization. FAS will be used for all efficacy variables, unless otherwise stated.

The safety set (SAF) will include all patients who received at least one dose of study drug whether or not being randomized. Patients will be analyzed according to the treatment they received. The safety set will be used in the analysis of all safety variables.

Note that the FAS and safety set are the same except that the safety set allows the inclusion of non-randomized patients who receive study drug in error. Also the FAS assigns randomized treatment and the safety set assigns received treatment.

## 9.2 Patient demographics and other baseline characteristics

Demographics and baseline characteristics will be summarized using the safety set including disease characteristics, prior and background medications to treat urticaria, and relevant medical histories.

## 9.3 Treatments

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

Concomitant medications will be summarized by treatment 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. [redacted]

## 9.4 Analysis of the primary variables

The primary variable will be analyzed descriptively in this protocol. In addition UAS7 from this study will be forwarded to a separate cross-study modelling and simulation PKPD analysis study (outlined in Section 9.5.5).

### 9.4.1 Primary Variables

The primary variable is change in UAS7 from baseline to Week 24. UAS7 is the sum of HSS7 and ISS7 as described in Section 6.4.1.

### 9.4.2 Statistical model, hypothesis, and method of analysis

No formal statistical testing will be applied for the primary variable.

The primary variable will be summarized by treatment group in FAS, using descriptive statistics, which include arithmetic mean, standard deviation, minimum, maximum and median. The mean of the change from baseline by treatment group will be shown descriptively with 95% confidence intervals based on the t-distribution.

### 9.4.3 Handling of missing values/censoring/discontinuations

As the primary analysis is to summarize the data descriptively, no imputation for the missing UAS7 will be applied. If ISS7 or HSS7 is missing, UAS7 will also be missing.

To calculate ISS7/HSS7 score from daily score, missing daily score will be handled according to the rule described in Section 6.4.1.

### 9.4.4 Sensitivity analyses

No sensitivity analysis is planned for the primary variable, as no statistical model is used.

## 9.5 Analysis of secondary [redacted]variables

### 9.5.1 Efficacy variables

Table 9-1 shows the list of efficacy variables. Unless otherwise specified, all efficacy variables will be analyzed in FAS. Summary tables will be presented by treatment group and visit (as applicable), using descriptive statistics, which include absolute and relative frequencies for categorical variables and arithmetic mean, standard deviation, minimum, maximum, median for continuous variables. Mean differences of the change from baseline in UAS7, HSS7 and ISS7 between groups will be shown descriptively with 95% confidence intervals based on two-sample t-test. All analyses are shown descriptively and no formal statistical testing will be applied.

[redacted]

**Table 9-1 Secondary [redacted] efficacy variables**

| Domain | Variable | Treatment period: Weeks 12 and 24 | Follow-up period: Week 40 |
|---|---|---|---|
| Clinical symptoms: total | Complete UAS7 response (UAS7 = 0) | Y | Y |
| | Change from Baseline in Urticaria Activity Score (UAS7) | Y | Y |
| | Number of patients who have relapse (UAS7>=12) after achieving UAS7<=6 | Y | Y |
| Clinical symptoms: hives | Complete hives response (HSS7 = 0) | Y | Y |
| | Change from Baseline in HSS7 | Y | Y |
| Clinical symptoms: itch | Complete itch response (ISS7 = 0) | Y | Y |
| | Change from Baseline in Itch Severity Score (ISS7) | Y | Y |
| Clinical symptoms: angioedema | Number of days with angioedema according to the patient diary | Y | Y |
| [redacted] | | | |
| Quality of life: CDLQI | Absolute and percentage change from baseline in total Children Dermatology life Quality Index (CDLQI) score | Y | Y |
| | CDLQI individual domain scores | Y | Y |
| | Achievement of CDLQI =0 or 1 | Y | Y |
| [redacted] | | | |

Y: yes, N: no

[redacted]

### 9.5.2 Safety variables

All safety variables will be analyzed by Safety Set (SAF).

#### Adverse events

All adverse events which start after the first dose of study medication and within 16 weeks of the last dose will be considered as a treatment emergent adverse event. 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. For the patients in the placebo arm, adverse events after switching to ligelizumab will be summarized separately.

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 newly detected 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]

### Anti-QGE031 antibody

A summary of anti-QGE031 antibodies will be provided.

### Vital signs

Vital signs (i.e. blood pressure and pulse rate) 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.

## 9.5.3 Pharmacokinetics

PK data will be summarized descriptively and will be analyzed separately as part of the PK/PD analysis.

[redacted]

## 9.5.5 PK/PD

PKPD modelling will be conducted in a separate modelling and simulation (M&S) study as the data from this study, QGE031C2202, will be only one part of a pool from both adolescent and adult patients. [redacted]

[redacted]

[redacted]

## 9.7 Interim analyses

No interim analyses is planned at the time of writing of this protocol, but may be added in case there is a need to provide information to health authorities, or to support program milestones. In addition the DMC will receive on a regular basis safety information from the ongoing study.

## 9.8 Sample size calculation

The expected half-width of 95% confidence intervals for the change from baseline in UAS7 for each group is 5.2, assuming 24 patients in ligelizumab 24 mg arm and SD=13. If the mean change from baseline in UAS7 for ligelizumab group is -22.0 (based on C2201 adult study), the 95% confidence interval of the mean change from baseline in UAS7 will be (-27.2, -16.8).

[redacted]

# 10 Ethical considerations

## 10.1 Regulatory and ethical compliance

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

## 10.2 Informed consent procedures

Eligible patients may only be included in the study after the patient or a parent or legal guardian provides written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent. 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 (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must 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.

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

## 10.3 Responsibilities of the investigator and IRB/IEC

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

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol,

[redacted]

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

## 10.4 Publication of study protocol and results

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

## 10.5 Quality Control and Quality Assurance

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

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

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

# 11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients/subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

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

[redacted]

## 11.1 Protocol amendments

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

[redacted]

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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 laboratory values for hepatotoxicity.

Refer to Section 7.4 for clinically notable laboratory values for nephrotoxicity.

The following other specific criteria have been identified for this study:

- Platelets < 75 000/μL

Any patient who have platelets <75 000/μL after being randomized should discontinue study treatment.

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 CRF.

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 or greater than 460 ms for females – all such ECGs will be flagged by the Central CRO's cardiologist and require assessment for clinical relevance by the investigator.

[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<br>• 1.5 x ULN < TBL ≤ 2 x ULN |
| LIVER EVENTS | • ALT or AST > 5 × ULN<br>• ALP > 2 × ULN (in the absence of known bone pathology)<br>• TBL > 2 × ULN (in the absence of known Gilbert syndrome)<br>• ALT or AST > 3 × ULN and INR > 1.5<br>• Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)<br>• Any clinical event of jaundice (or equivalent term)<br>• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia<br>• Any adverse event potentially indicative of a liver toxicity* |

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

**Table 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 treatment immediately<br>• Hospitalize, if clinically appropriate<br>• Establish causality<br>• Record liver events to the appropriate CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| **ALT or AST** | | |
| > 8 × ULN | • Discontinue the study treatment immediately<br>• Hospitalize if clinically appropriate<br>• Establish causality<br>• Record liver events to the appropriate CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| > 3 × ULN and INR > 1.5 | • Discontinue the study treatment immediately<br>• Hospitalize, if clinically appropriate<br>• Establish causality<br>• Record liver events to the appropriate CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| > 5 to ≤ 8 × ULN | • Repeat LFT within 48 hours<br>• If elevation persists, continue follow-up monitoring<br>• If elevation persists for more than 2 weeks, discontinue the study drug | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) |

[redacted]

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

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

Alb: albumin, γGT : Gamma Glutamyl Transferase, LFT: Liver function tests

[redacted]

## 13.3 Appendix 3: Specific Renal Alert Criteria and Diagnosis

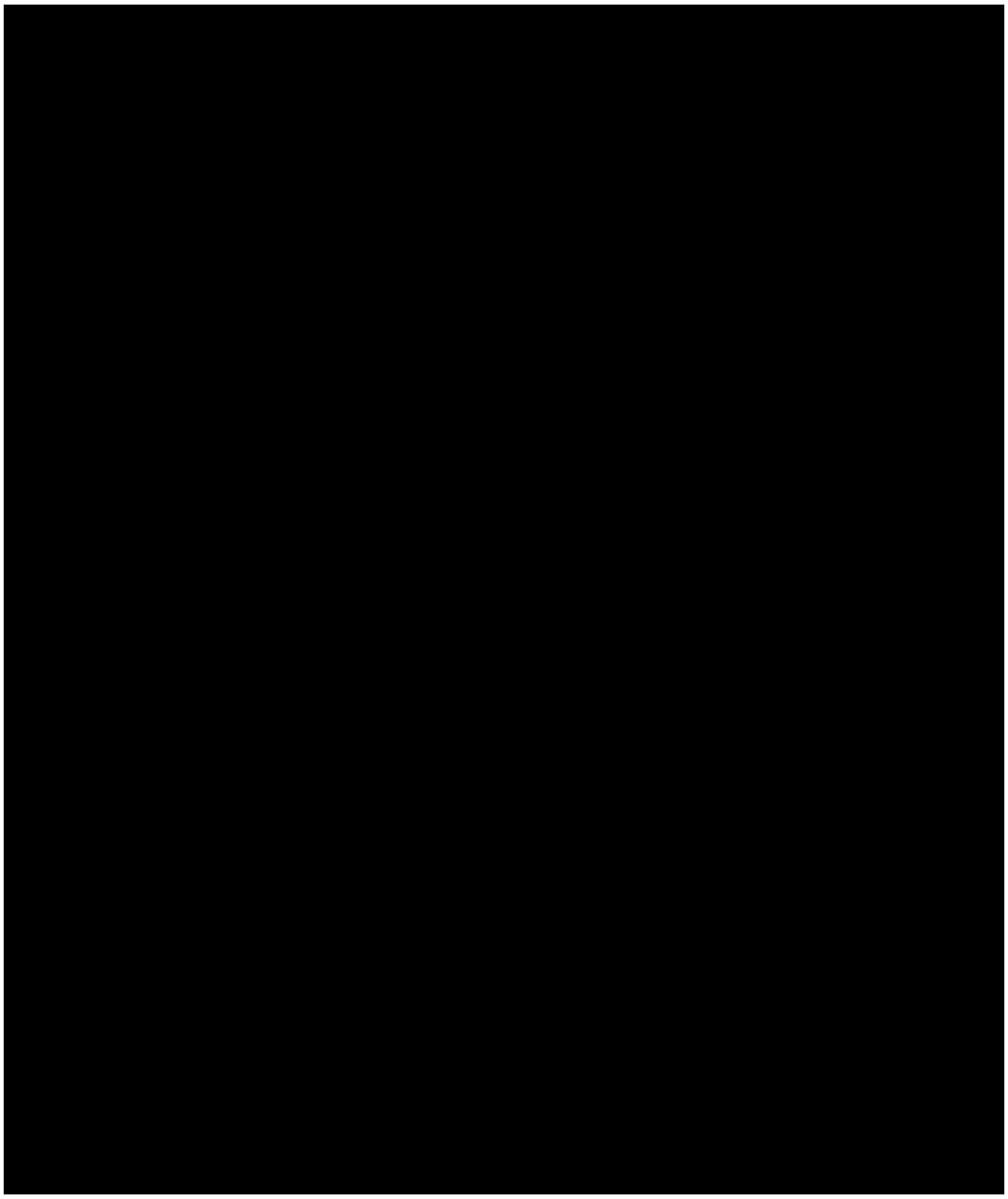
Ligelizumab is not a drug that has shown an increased risk for drug induced renal toxicity so far. However, when suspecting a drug induced renal event which could be related to the study medication please contact Novartis and do not continue to administer ligelizumab.

**Table 13-3 Specific Renal Alert Criteria and Diagnosis**

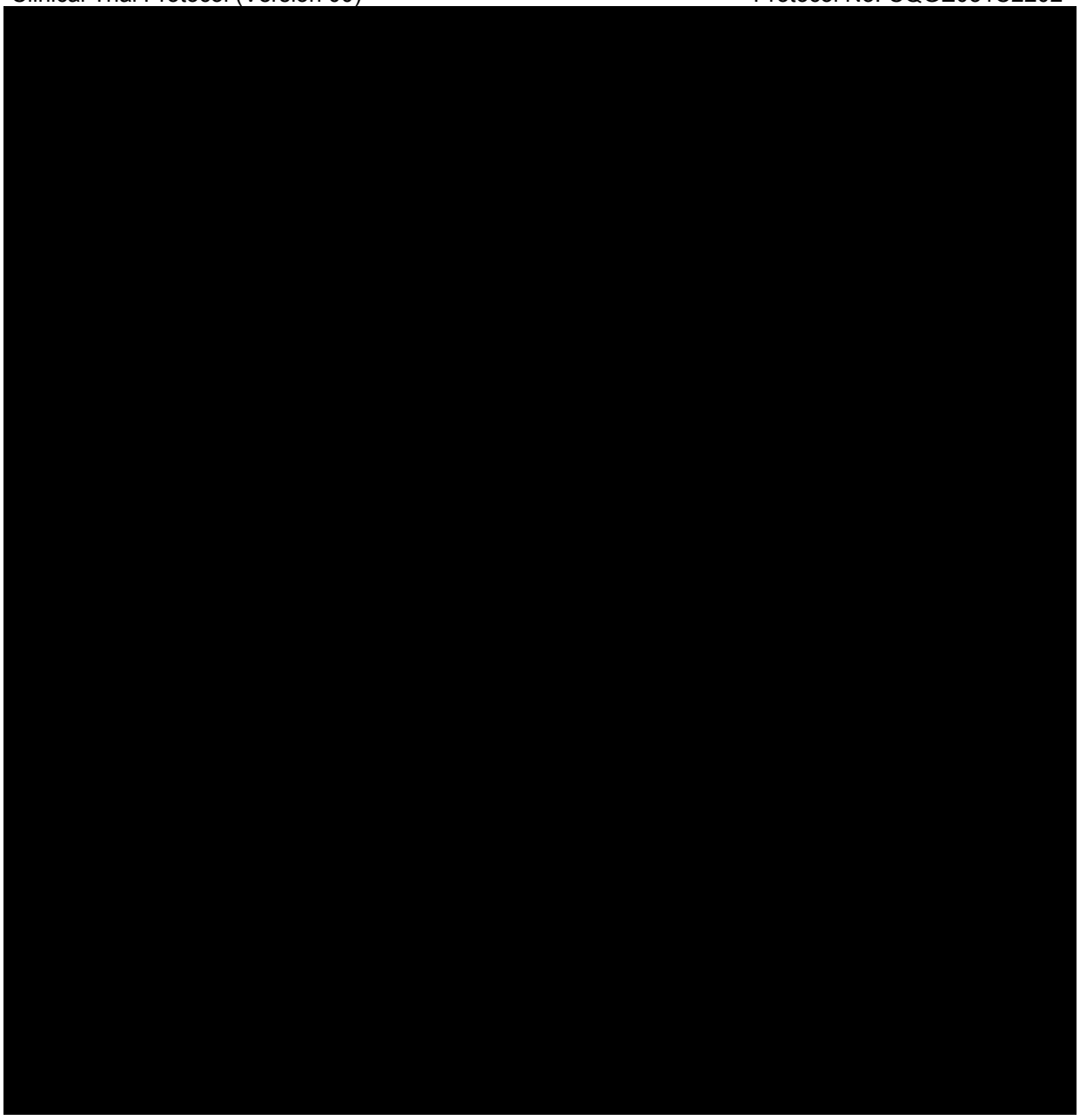
| | |
|---|---|
| **Serum Event** | |
| 25% decrease in eGFR and eGFR ≤ 90ml/min/1.73[1] $m^2$ compared to baseline<br>Note: Dependent on normal hydration status-<br>See list below[2] | Confirm finding after 24 h but within 5 days |
| [1] Calculate the eGFR with "Schwartz formula" for use in children 1-18 years old<br>For height in cm and sCr in mg/dL: eGFR (mL/min/1.73 $m^2$) = 0.413 x (height/sCr)<br>For height in cm and sCr in µmol/L: eGFR (mL/min/1.73 $m^2$) = 36.5 x (height/sCr) | |
| **Urine Event** | |
| Protein-creatinine ratio (PCR)≥1g/g Cr | Confirm finding after 24h but within 5 days |
| New dipstick glycosuria ≥3+ | |
| New dipstick hematuria ≥3+ | |
| Proteinuria is very common in children in a condition called benign orthostatic (postural) proteinuria. Thus, whenever assessing a positive dipstick for proteinuria in children, where feasible a first morning sample should be used to eliminate this potentially complicating variable.<br><br>[2] When assessing DIN renal events, also consider other causes of renal events and/or altered serum creatinine and BUN: | |
| • Hypovolemia<br>• Major operations<br>• Severe infections and sepsis<br>• Co-medications affecting creatinine secretion (e.g., trimethoprim, cimetidine)<br>• Change of antihypertensive treatment regimens<br>• Acute or worsening heart failure<br>• Rhabdomyolysis (monitor for increase in CPK)<br><br>Cr : Creatinine, sCr: : Serum Creatinine, CPK : creatinine phosphokinase | |

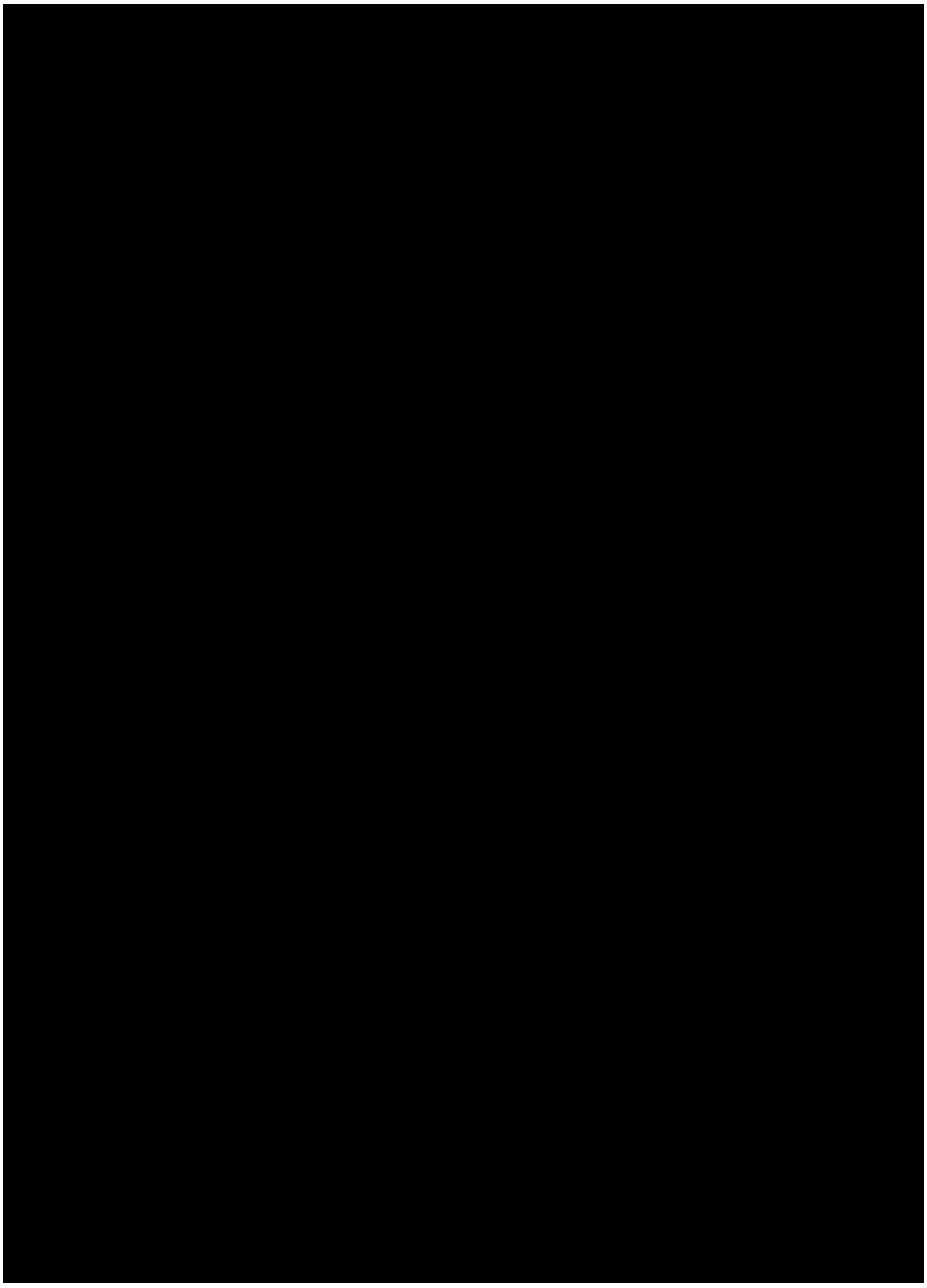
## 13.4 Appendix 4 PRO tools

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



[redacted]





## 13.5 Appendix 5 PK/PD/ADA [redacted] log

| Analyte | | Visit | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 110 | 120 | 130 | 140 | 150 | 160 | 170 | 180 | 190 | 200 | 210 |
| | | Days | | | | | | | | | | | | |
| | | -28/-14 | -7 | 1 | 29 | 57 | 85 | 113 | 141 | 169 | 197 | 225 | 253 | 281 |
| PK | | | | x | x | x | x | x | x | x | | x | | x |
| | Dose ref ID | | | 1 | 2 | 3 | 4 | 5 | 6 | 6 | | 6 | | 6 |
| | Sample No | | | 101 | 102 | 103 | 104 | 105 | 106 | 107 | | 108 | | 109 |
| Total IgE | | | | x | x | x | x | x | x | x | | x | | x |
| | Sample no | | | 201 | 202 | 203 | 204 | 205 | 206 | 207 | | 208 | | 209 |
| Anti-drug/ QGE031 antibodies | | | | x | | x | | x | | x | | x | | x |
| | Sample no | | | 401 | | 402 | | 403 | | 404 | | 405 | | 406 |

[redacted]

[redacted]

## 13.6 Appendix 6 World allergy organization grading system