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

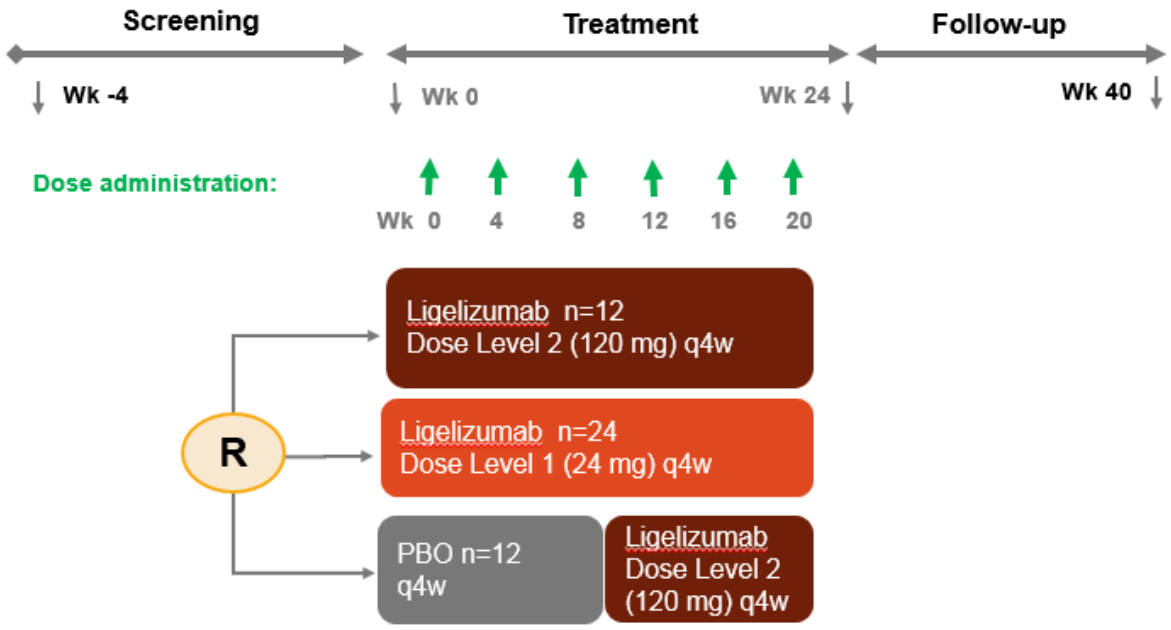
[redacted]

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) • 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]

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]

[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]													

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]

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]

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]

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]

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]

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

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]

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]

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]

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]

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]

- 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]

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]

[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]

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]

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]

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 Note: Dependent on normal hydration status- 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 For height in cm and sCr in mg/dL: eGFR (mL/min/1.73 m^2) = 0.413 x (height/sCr) 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. [2] When assessing DIN renal events, also consider other causes of renal events and/or altered serum creatinine and BUN:	
• Hypovolemia • Major operations • Severe infections and sepsis • Co-medications affecting creatinine secretion (e.g., trimethoprim, cimetidine) • Change of antihypertensive treatment regimens • Acute or worsening heart failure • Rhabdomyolysis (monitor for increase in CPK) Cr : Creatinine, sCr: : Serum Creatinine, CPK : creatinine phosphokinase	